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13/742,694 | DEXCOM.217A:

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

PUBLIC VIEW

Application #	Confirmation #	Attorney Docket #	Patent #
13/742,694	6142	DEXCOM.217A	9,119,528 Download PDF Issued - 09/01/2015

Filing or 371 (c) date	Status
01/16/2013	Patented Case 08/12/2015

Documents & transaction history

Documents | Transactions

Showing 1 to 142 of 142 entries

Mail room date	Doc code	Doc description	Pages		Quick download	File size (KB)	
01/16/2013	ADS	Application Data Sheet	8			480	
01/16/2013	DRW	Drawings-only black and white line drawings	18			1080	
01/16/2013	SPEC	Specification	72			272 / 4320	
01/16/2013	CLM	Claims	5			21 / 300	
01/16/2013	ABST	Abstract	1			2 / 60	
01/16/2013	WFEE	Fee Worksheet (SB06)	2			120	
01/16/2013	N417	Electronic Filing System Acknowledgment Receipt	3			180	
02/11/2013	APP.FILE.REC	Filing Receipt	3			180	
02/11/2013	WFEE	Fee Worksheet (SB06)	1			60	
02/11/2013	NTC.MISS.PRT	Notice to File Missing Parts	2			120	
04/04/2013	PEFR	Applicant Response to Pre-Exam Formalities Notice	1			60	
04/04/2013	OATH	Oath or Declaration filed	10			600	

Mail room date	Doc code	Doc description	Pages		Quick download	File size (KB)	
04/04/2013	R3.73	Assignee showing of ownership per 37 CFR 3.73	2			120	
04/04/2013	PA..	Power of Attorney	1			60	
04/04/2013	LET.	Miscellaneous Incoming Letter	2			120	
04/04/2013	WFEE	Fee Worksheet (SB06)	2			120	
04/04/2013	N417	Electronic Filing System Acknowledgment Receipt	2			120	
04/16/2013	APP.FILE.REC	Filing Receipt	3			180	
04/16/2013	WFEE	Fee Worksheet (SB06)	1			60	
04/16/2013	N570	Communication - Re: Power of Attorney (PTOL-308)	1			60	
09/11/2013	IDS	Information Disclosure Statement (IDS) Form (SB08)	10			600	
09/11/2013	N417	Electronic Filing System Acknowledgment Receipt	8			480	
09/11/2013	FOR	Foreign Reference	26			1560	
09/11/2013	FOR	Foreign Reference	28			1680	
09/11/2013	FOR	Foreign Reference	56			3360	
09/11/2013	FOR	Foreign Reference	168			10080	
09/11/2013	FOR	Foreign Reference	46			2760	
09/11/2013	FOR	Foreign Reference	30			1800	
09/11/2013	FOR	Foreign Reference	36			2160	
09/11/2013	FOR	Foreign Reference	36			2160	
09/11/2013	FOR	Foreign Reference	16			960	
09/11/2013	FOR	Foreign Reference	41			2460	
09/11/2013	FOR	Foreign Reference	44			2640	
09/11/2013	FOR	Foreign Reference	56			3360	
09/11/2013	FOR	Foreign Reference	16			960	
09/11/2013	FOR	Foreign Reference	37			2220	
09/11/2013	FOR	Foreign Reference	14			840	
09/11/2013	FOR	Foreign Reference	16			960	
09/11/2013	FOR	Foreign Reference	17			1020	
09/11/2013	FOR	Foreign Reference	88			5280	
09/11/2013	FOR	Foreign Reference	46			2760	
09/11/2013	FOR	Foreign Reference	95			5700	
09/11/2013	FOR	Foreign Reference	97			5820	

Mail room date	Doc code	Doc description	Pages		Quick download	File size (KB)	
09/11/2013	FOR	Foreign Reference	35			2100	
09/11/2013	FOR	Foreign Reference	29			1740	
09/11/2013	NPL	Non Patent Literature	10			600	
09/11/2013	NPL	Non Patent Literature	6			360	
09/11/2013	NPL	Non Patent Literature	8			480	
09/11/2013	NPL	Non Patent Literature	15			900	
09/11/2013	NPL	Non Patent Literature	6			360	
09/11/2013	NPL	Non Patent Literature	20			1200	
09/11/2013	NPL	Non Patent Literature	12			720	
09/11/2013	NPL	Non Patent Literature	9			540	
09/11/2013	NPL	Non Patent Literature	8			480	
09/11/2013	NPL	Non Patent Literature	9			540	
09/11/2013	NPL	Non Patent Literature	13			780	
09/11/2013	NPL	Non Patent Literature	9			540	
09/11/2013	NPL	Non Patent Literature	9			540	
09/11/2013	NPL	Non Patent Literature	10			600	
09/11/2013	NPL	Non Patent Literature	10			600	
09/11/2013	NPL	Non Patent Literature	8			480	
09/11/2013	NPL	Non Patent Literature	6			360	
09/11/2013	NPL	Non Patent Literature	10			600	
09/11/2013	NPL	Non Patent Literature	13			780	
09/11/2013	NPL	Non Patent Literature	8			480	
09/11/2013	NPL	Non Patent Literature	10			600	
09/11/2013	NPL	Non Patent Literature	22			1320	
09/11/2013	NPL	Non Patent Literature	14			840	
09/11/2013	NPL	Non Patent Literature	12			720	
09/11/2013	NPL	Non Patent Literature	9			540	
09/11/2013	NPL	Non Patent Literature	7			420	
09/11/2013	NPL	Non Patent Literature	18			1080	
09/11/2013	NPL	Non Patent Literature	9			540	
09/11/2013	NPL	Non Patent Literature	5			300	
09/11/2013	TRAN.LET	Transmittal Letter	1			60	
09/13/2013	IDS	Information Disclosure Statement (IDS) Form (SB08)	1			60	

Mail room date	Doc code	Doc description	Pages		Quick download	File size (KB)	
09/13/2013	NPL	Non Patent Literature	7			420	
09/13/2013	N417	Electronic Filing System Acknowledgment Receipt	2			120	
09/13/2013	TRAN.LET	Transmittal Letter	1			60	
03/03/2014	IDS	Information Disclosure Statement (IDS) Form (SB08)	2			120	
03/03/2014	NPL	Non Patent Literature	6			360	
03/03/2014	NPL	Non Patent Literature	4			240	
03/03/2014	NPL	Non Patent Literature	7			420	
03/03/2014	N417	Electronic Filing System Acknowledgment Receipt	2			120	
03/03/2014	TRAN.LET	Transmittal Letter	2			120	
05/01/2014	NTC.PUB	Notice of Publication	1			60	
09/03/2014	SRNT	Examiner's search strategy and results	1			60	
10/02/2014	CTNF	Non-Final Rejection	17			33 / 55 / 1020	
10/02/2014	892	List of references cited by examiner	1			60	
10/02/2014	BIB	Bibliographic Data Sheet	1			60	
10/02/2014	FWCLM	Index of Claims	2			120	
10/02/2014	SRFW	Search information including classification, databases and other search related notes	1			60	
10/02/2014	1449	List of References cited by applicant and considered by examiner	10			600	
10/02/2014	1449	List of References cited by applicant and considered by examiner	2			120	
10/02/2014	SRNT	Examiner's search strategy and results	11			660	
10/02/2014	1449	List of References cited by applicant and considered by examiner	1			60	
01/02/2015	A...	Amendment/Request for Reconsideration-After Non-Final Rejection	1			60	
01/02/2015	CLM	Claims	6			34 / 360	
01/02/2015	REM	Applicant Arguments/Remarks Made in an Amendment	6			21 / 360	
01/02/2015	WFEE	Fee Worksheet (SB06)	2			120	
01/02/2015	N417	Electronic Filing System Acknowledgment Receipt	2			120	

Mail room date	Doc code	Doc description	Pages		Quick download	File size (KB)	
01/02/2015	WFEE	Fee Worksheet (SB06)	1			60	
01/05/2015	IDS	Information Disclosure Statement (IDS) Form (SB08)	1			39 / 60	
01/05/2015	WFEE	Fee Worksheet (SB06)	2			120	
01/05/2015	N417	Electronic Filing System Acknowledgment Receipt	2			120	
01/05/2015	TRAN.LET	Transmittal Letter	2			120	
01/09/2015	SA..	Supplemental Response or Supplemental Amendment	1			60	
01/09/2015	CLM	Claims	7			34 / 420	
01/09/2015	INTRVIEW.APP	Applicant summary of interview with examiner	1			60	
01/09/2015	REM	Applicant Arguments/Remarks Made in an Amendment	2			4 / 120	
01/09/2015	WFEE	Fee Worksheet (SB06)	2			120	
01/09/2015	N417	Electronic Filing System Acknowledgment Receipt	2			120	
01/09/2015	WFEE	Fee Worksheet (SB06)	1			60	
01/13/2015	INTV.SUM.APP	Applicant Initiated Interview Summary (PTOL-413)	3			180	
01/28/2015	CTNF	Non-Final Rejection	30			41 / 94 / 1800	
01/28/2015	INTV.SUM.EX	Examiner initiated interview summary (PTOL-413B)	1			60	
01/28/2015	892	List of references cited by examiner	1			60	
01/28/2015	FWCLM	Index of Claims	2			120	
01/28/2015	SRNT	Examiner's search strategy and results	7			420	
01/28/2015	1449	List of References cited by applicant and considered by examiner	1			60	
01/28/2015	SRFW	Search information including classification, databases and other search related notes	1			60	
04/23/2015	A...	Amendment/Request for Reconsideration-After Non-Final Rejection	1			60	
04/23/2015	CLM	Claims	7			35 / 420	
04/23/2015	INTRVIEW.APP	Applicant summary of interview with examiner	1			60	
04/23/2015	REM	Applicant Arguments/Remarks Made in an Amendment	7			420	

Abbott Ex. 1002 - 5/1438

Mail room date	Doc code	Doc description	Pages		Quick download	File size (KB)	
04/23/2015	AF/D.132	Affidavit-traversing rejections or objections rule 132	5			300	
04/23/2015	N417	Electronic Filing System Acknowledgment Receipt	2			120	
04/23/2015	WFEE	Fee Worksheet (SB06)	1			60	
05/04/2015	NOA	Notice of Allowance and Fees Due (PTOL-85)	7			23 / 9 / 420	
05/04/2015	IIFW	Issue Information including classification, examiner, name, claim, renumbering, etc.	3			180	
05/04/2015	SRNT	Examiner's search strategy and results	1			60	
05/04/2015	SRFW	Search information including classification, databases and other search related notes	1			60	
07/29/2015	IFEE	Issue Fee Payment (PTO-85B)	1			60	
07/29/2015	WFEE	Fee Worksheet (SB06)	2			120	
07/29/2015	N417	Electronic Filing System Acknowledgment Receipt	2			120	
08/05/2015	1449	List of References cited by applicant and considered by examiner	3			180	
08/12/2015	ISSUE.NTF	Issue Notification	1			60	
02/19/2016	COCIN	Request for Certificate of Correction	2			120	
02/19/2016	WFEE	Fee Worksheet (SB06)	2			120	
02/19/2016	N417	Electronic Filing System Acknowledgment Receipt	2			120	
02/19/2016	COCIN	Request for Certificate of Correction	1			60	
04/19/2016	COCOUT	Certificate of Correction - Post Issue Communication	2			120	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	DEXCOM.217A
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

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Inventor 3 Remove

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	DEXCOM.217A
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Andrea		Facchinetti	

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Inventor 5 Remove

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	Anna Leigh		Rack-Gomer	

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Title of Invention	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS	

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	Chiara		Zecchin	

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Inventor 8 Remove

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	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS	

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☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	68851		
Email Address	efiling@knobbe.com	Add Email	Remove Email

Application Information:

Title of the Invention	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS		
Attorney Docket Number	DEXCOM.217A	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	18	**Suggested Figure for Publication (if any)**	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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	Application Number	
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Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
Present	non provisional of	61720286	2012-10-30

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Priority Claimed
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	DEXCOM.217A
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS	

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

◉ Assignee	○ Legal Representative under 35 U.S.C. 117
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Assignee is an Organization check here. ☒

Organization Name	DexCom, Inc.		
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Address 2			
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Country	US	Postal Code	92121
Phone Number		Fax Number	
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Signature				Date (YYYY-MM-DD)	2013-01-16
First Name	Rose	Last Name	Thiessen	Registration Number	40202

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	DEXCOM.217A
	Application Number	
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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

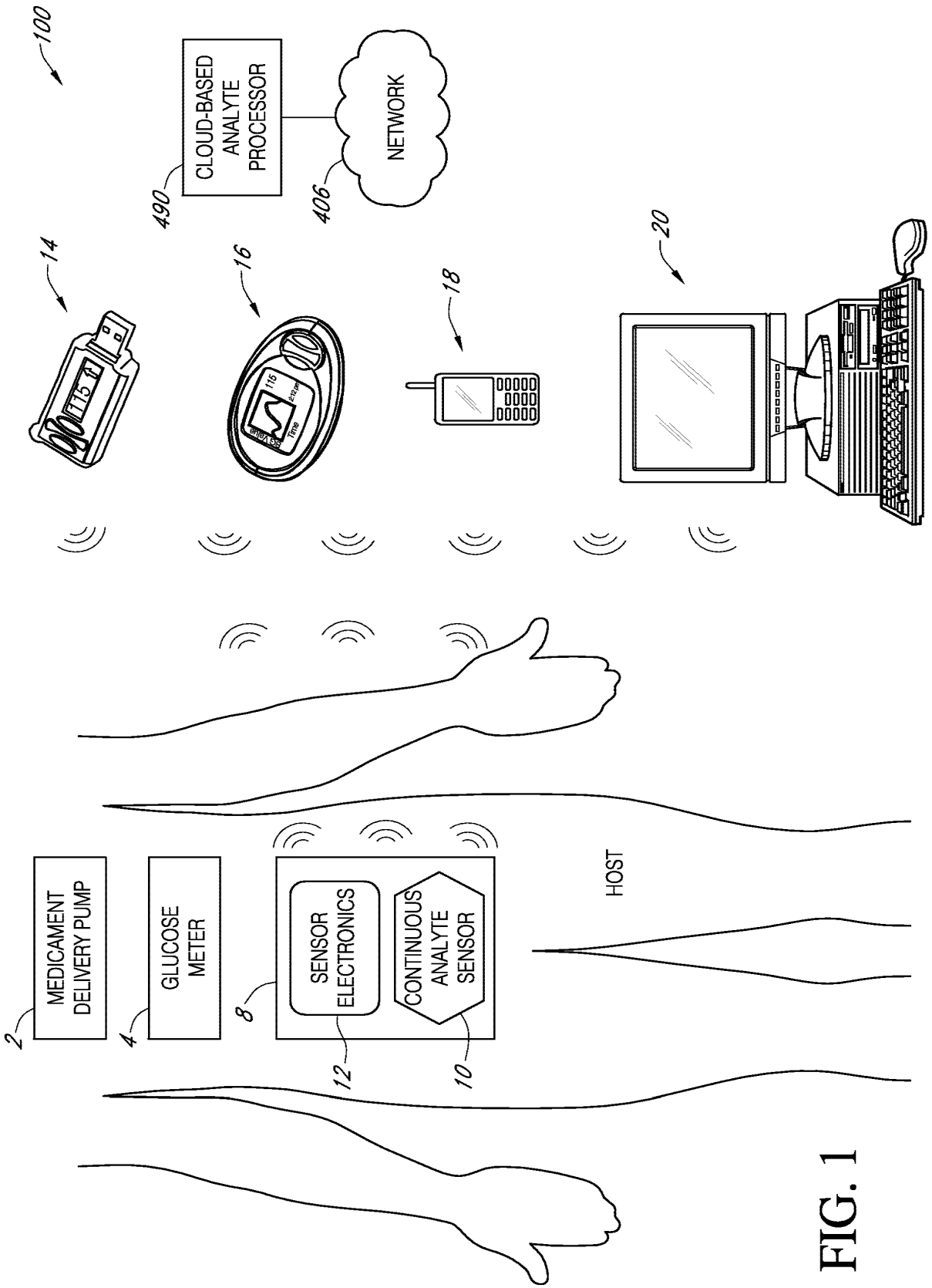

100
CLOUD-BASED ANALYTE PROCESSOR
490
NETWORK
406
14
16
18
20
MEDICAMENT DELIVERY PUMP
2
GLUCOSE METER
4
8
SENSOR ELECTRONICS
12
CONTINUOUS ANALYTE SENSOR
10
HOST

FIG. 1

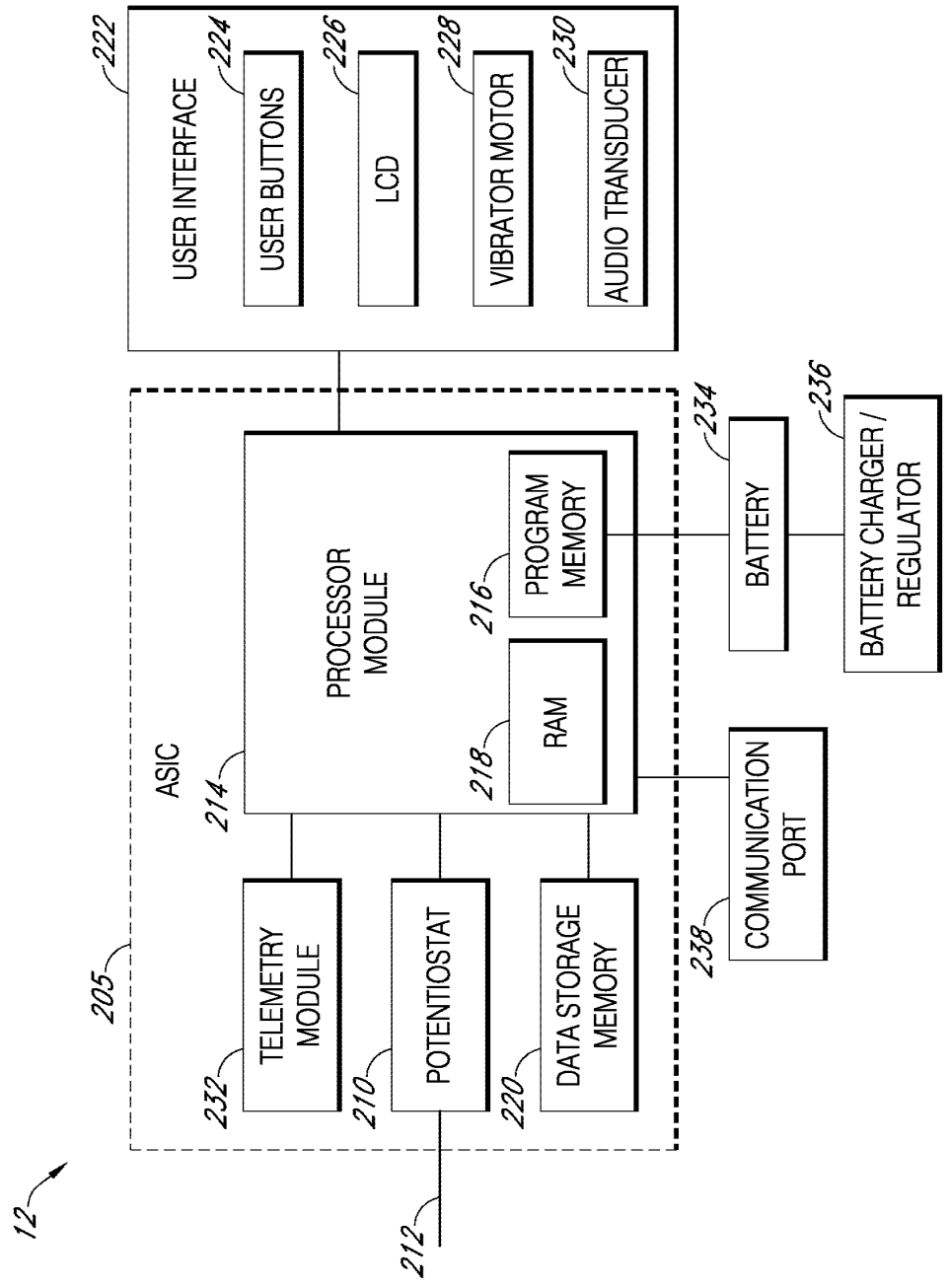

12
205
ASIC
214
PROCESSOR MODULE
216
PROGRAM MEMORY
218
RAM
232
TELEMETRY MODULE
210
POTENTIOSTAT
220
DATA STORAGE MEMORY
212
222
USER INTERFACE
224
USER BUTTONS
226
LCD
228
VIBRATOR MOTOR
230
AUDIO TRANSDUCER
234
BATTERY
236
BATTERY CHARGER / REGULATOR
238
COMMUNICATION PORT

FIG. 2

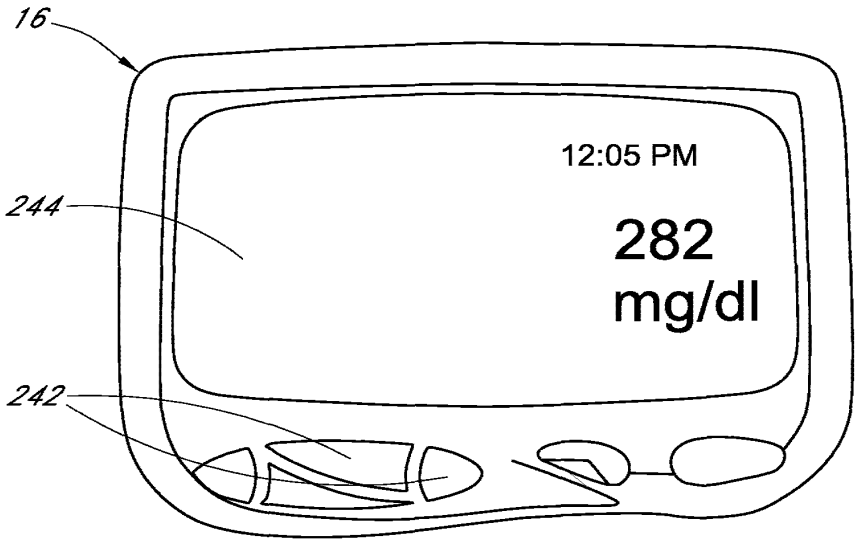

16
12:05 PM
244
282
mg/dl
242

FIG. 3A

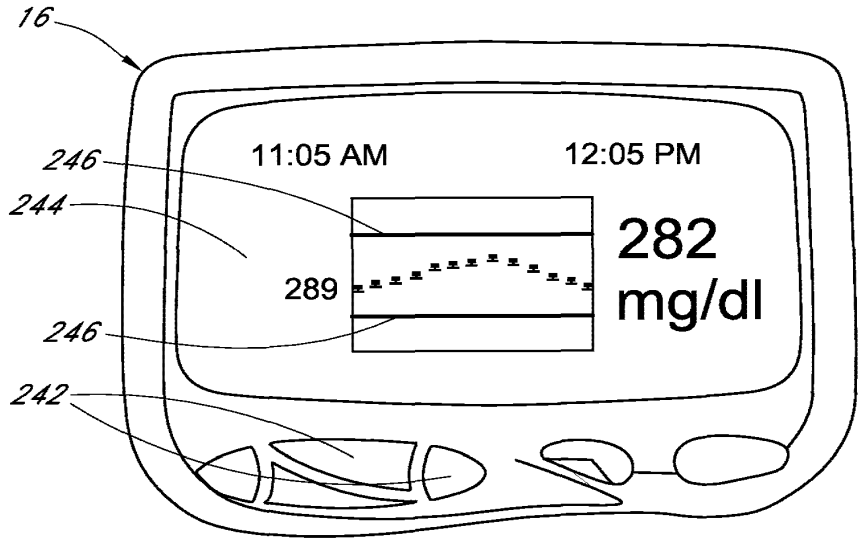

16
246
11:05 AM
12:05 PM
244
289
282
mg/dl
246
242

FIG. 3B

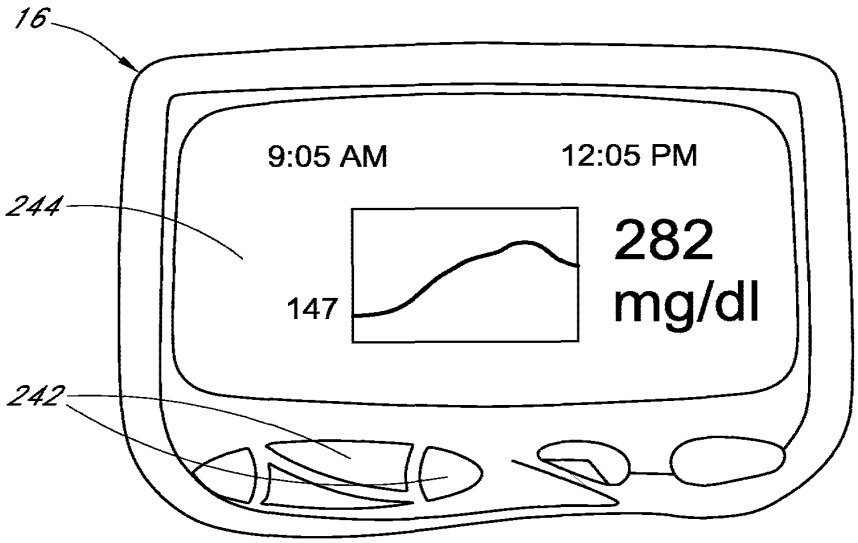

16
9:05 AM
12:05 PM
244
147
282
mg/dl
242

FIG. 3C

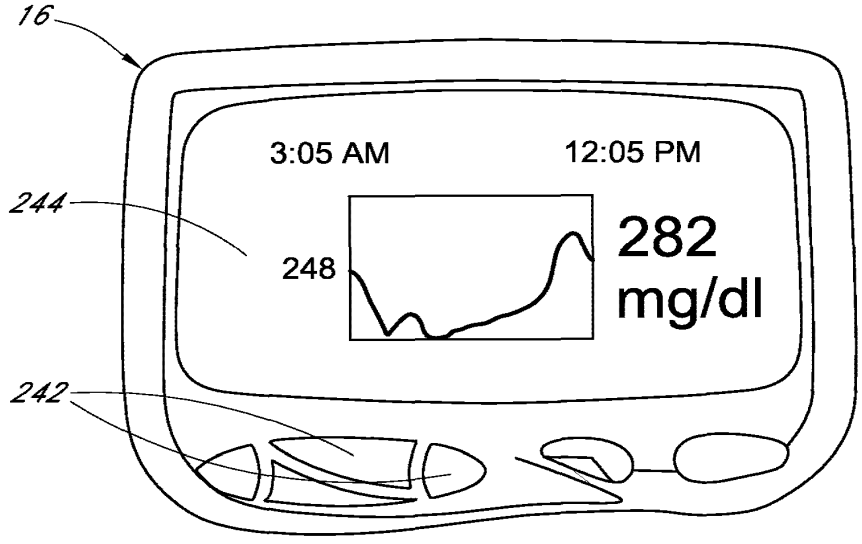

16
3:05 AM
12:05 PM
244
248
282
mg/dl
242

FIG. 3D

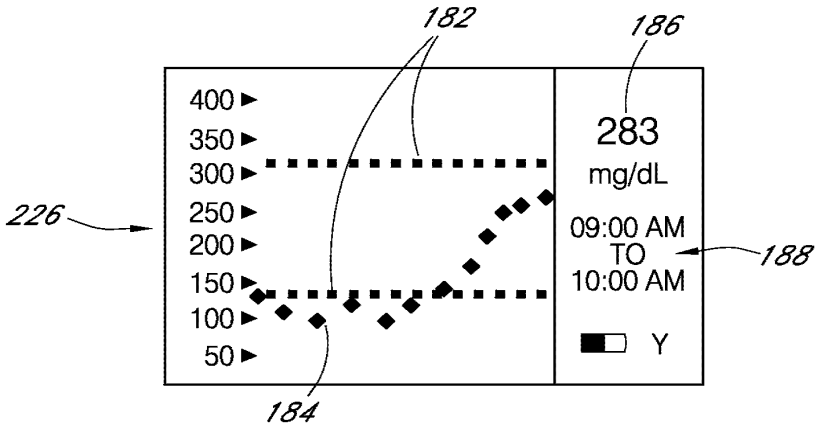


FIG. 4A



FIG. 4B

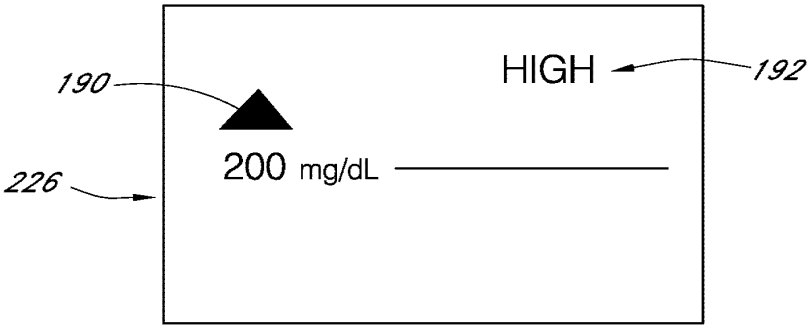


FIG. 4C

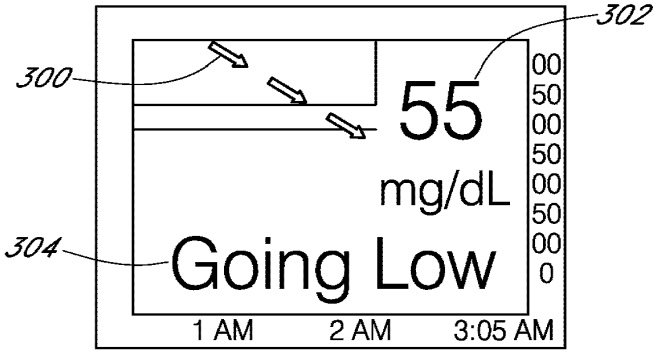


FIG. 4D

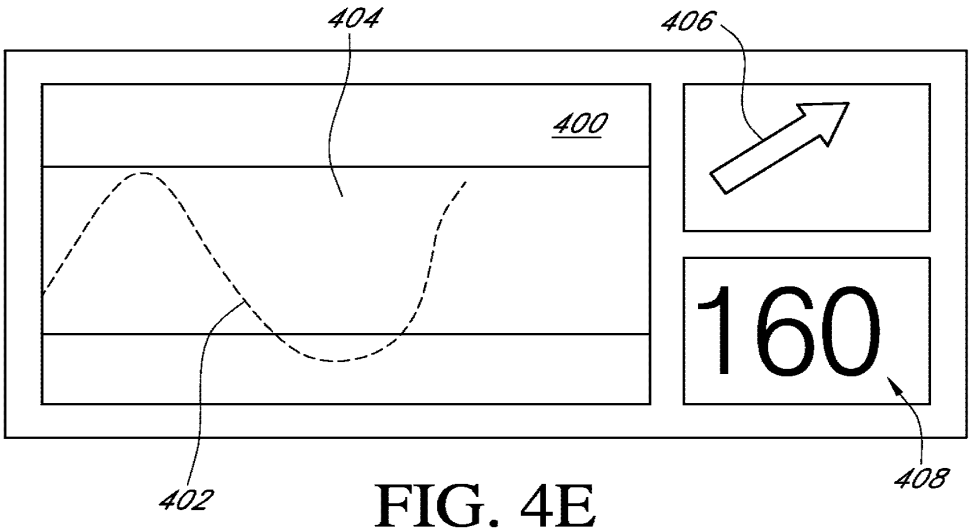


FIG. 4E

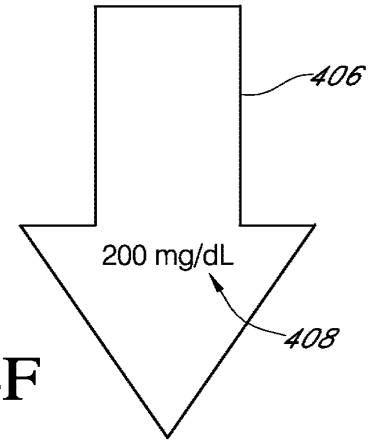


FIG. 4F

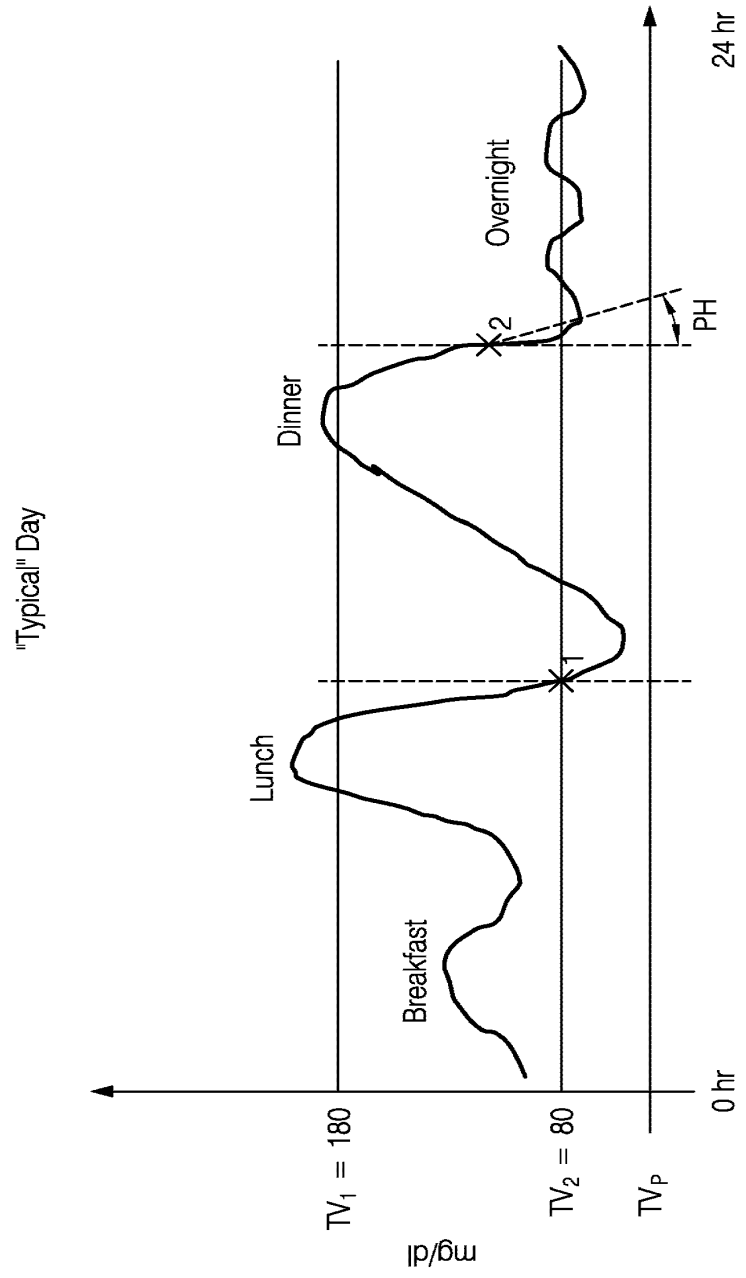

"Typical" Day
mg/dl
Time
24 hr
0 hr
TV_1 = 180
TV_2 = 80
TV_P
Breakfast
Lunch
Dinner
Overnight
1
2
PH

FIG. 5

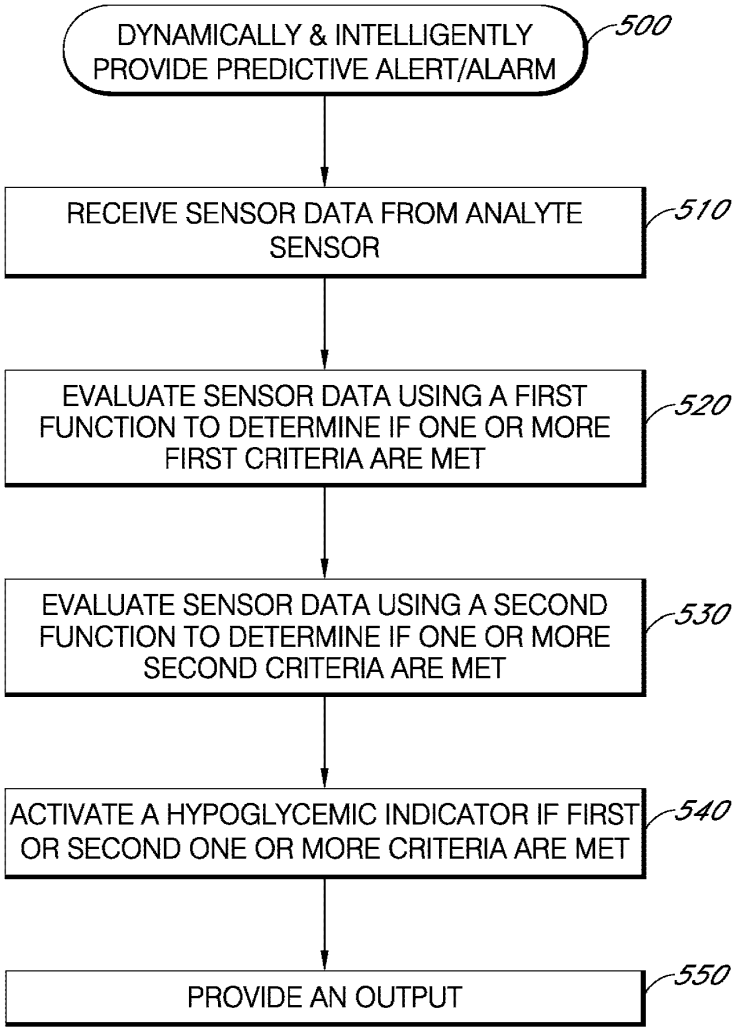

DYNAMICALLY & INTELLIGENTLY PROVIDE PREDICTIVE ALERT/ALARM
500
RECEIVE SENSOR DATA FROM ANALYTE SENSOR
510
EVALUATE SENSOR DATA USING A FIRST FUNCTION TO DETERMINE IF ONE OR MORE FIRST CRITERIA ARE MET
520
EVALUATE SENSOR DATA USING A SECOND FUNCTION TO DETERMINE IF ONE OR MORE SECOND CRITERIA ARE MET
530
ACTIVATE A HYPOGLYCEMIC INDICATOR IF FIRST OR SECOND ONE OR MORE CRITERIA ARE MET
540
PROVIDE AN OUTPUT
550

FIG. 6

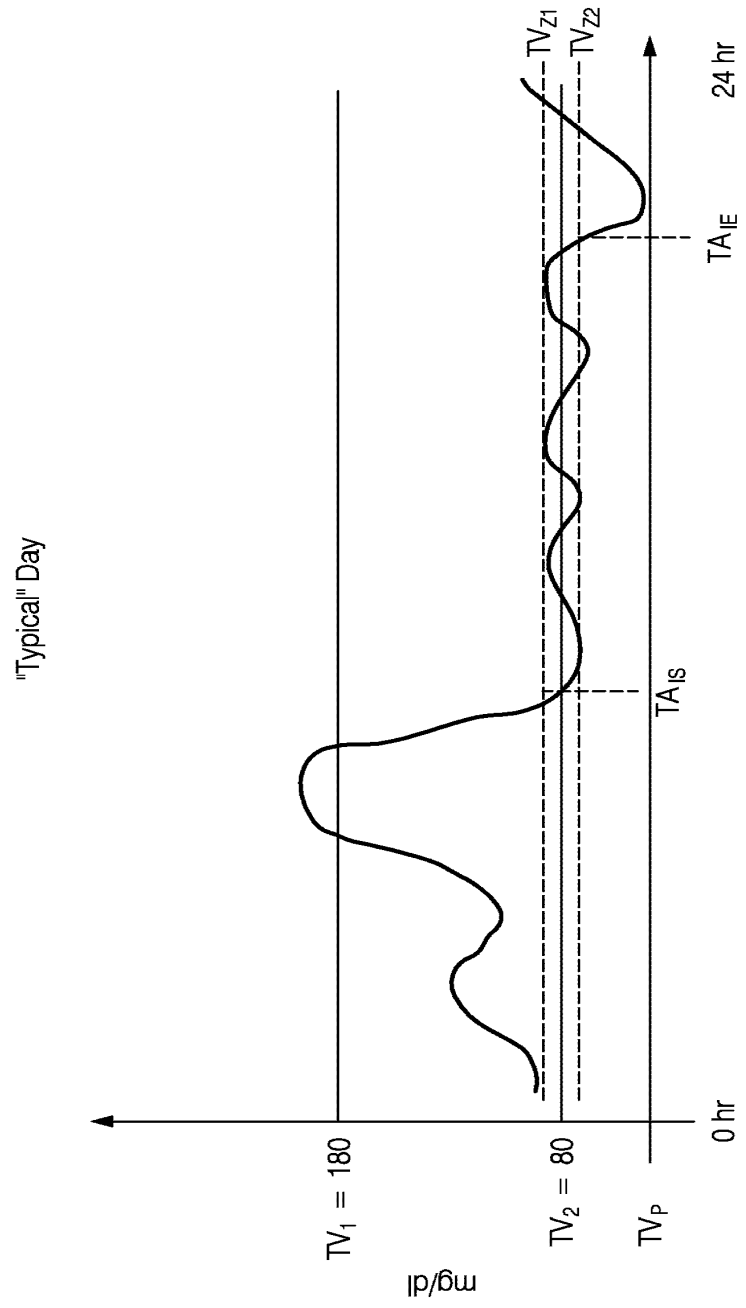

"Typical" Day
mg/dl
TV_1 = 180
TV_2 = 80
TV_P
TV_{Z1}
TV_{Z2}
TA_{IS}
TA_{IE}
0 hr
24 hr
Time

FIG. 7

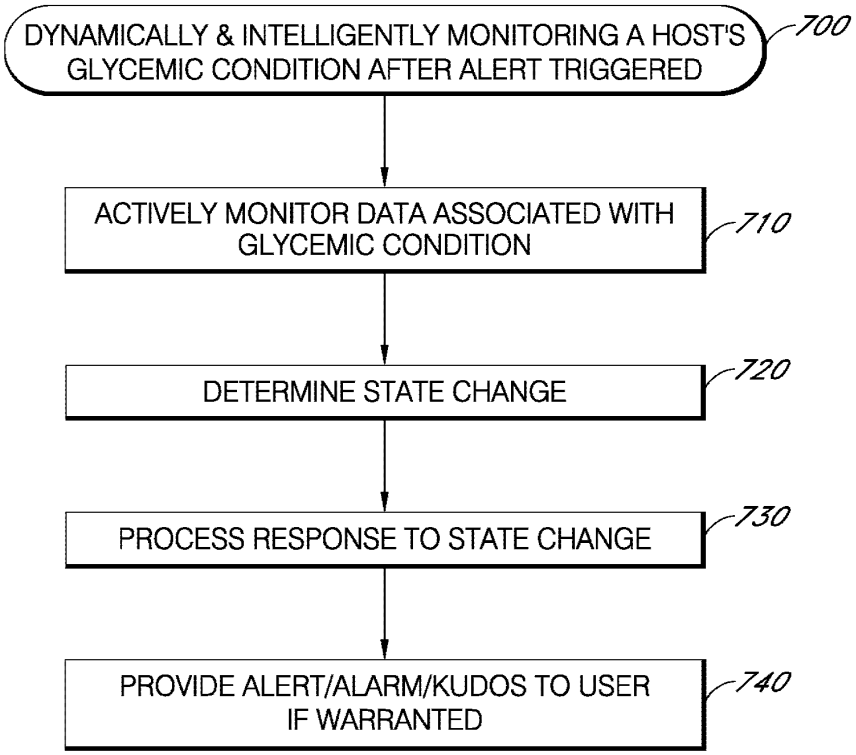

DYNAMICALLY & INTELLIGENTLY MONITORING A HOST'S GLYCEMIC CONDITION AFTER ALERT TRIGGERED
700
ACTIVELY MONITOR DATA ASSOCIATED WITH GLYCEMIC CONDITION
710
DETERMINE STATE CHANGE
720
PROCESS RESPONSE TO STATE CHANGE
730
PROVIDE ALERT/ALARM/KUDOS TO USER IF WARRANTED
740

FIG. 8

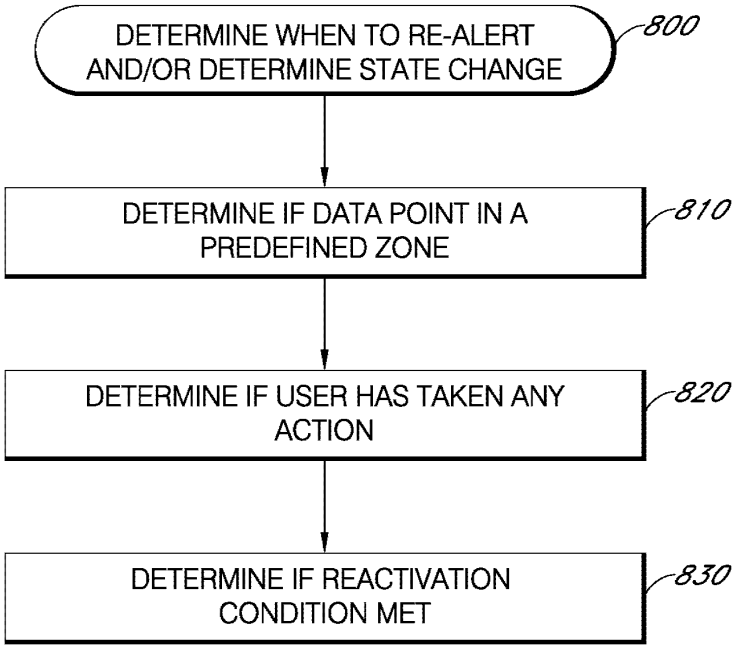

DETERMINE WHEN TO RE-ALERT AND/OR DETERMINE STATE CHANGE
800
DETERMINE IF DATA POINT IN A PREDEFINED ZONE
810
DETERMINE IF USER HAS TAKEN ANY ACTION
820
DETERMINE IF REACTIVATION CONDITION MET
830

FIG. 9

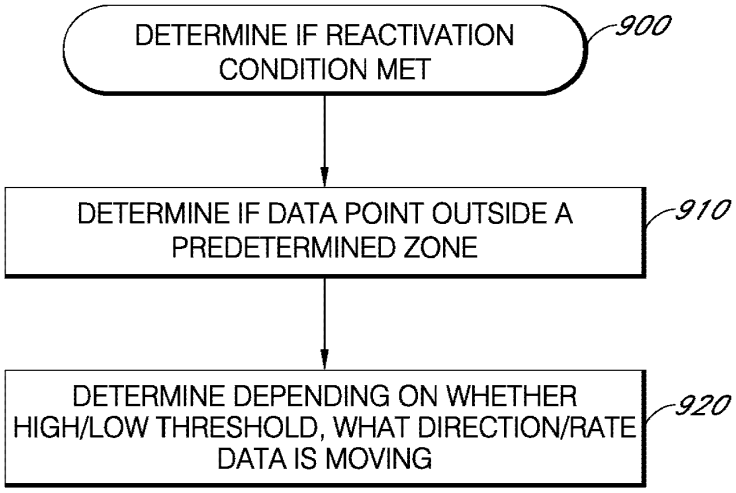

DETERMINE IF REACTIVATION CONDITION MET
900
DETERMINE IF DATA POINT OUTSIDE A PREDETERMINED ZONE
910
DETERMINE DEPENDING ON WHETHER HIGH/LOW THRESHOLD, WHAT DIRECTION/RATE DATA IS MOVING
920

FIG. 10

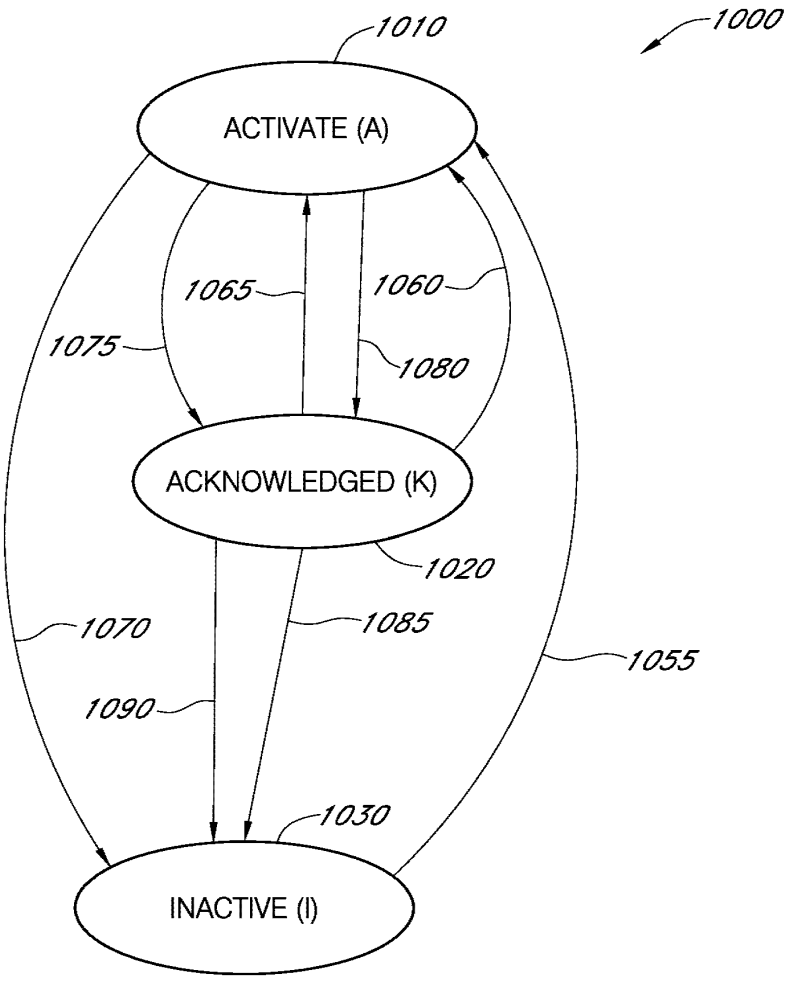

1010
1000
ACTIVATE (A)
1065
1060
1075
1080
ACKNOWLEDGED (K)
1020
1070
1085
1055
1090
1030
INACTIVE (I)

FIG. 11

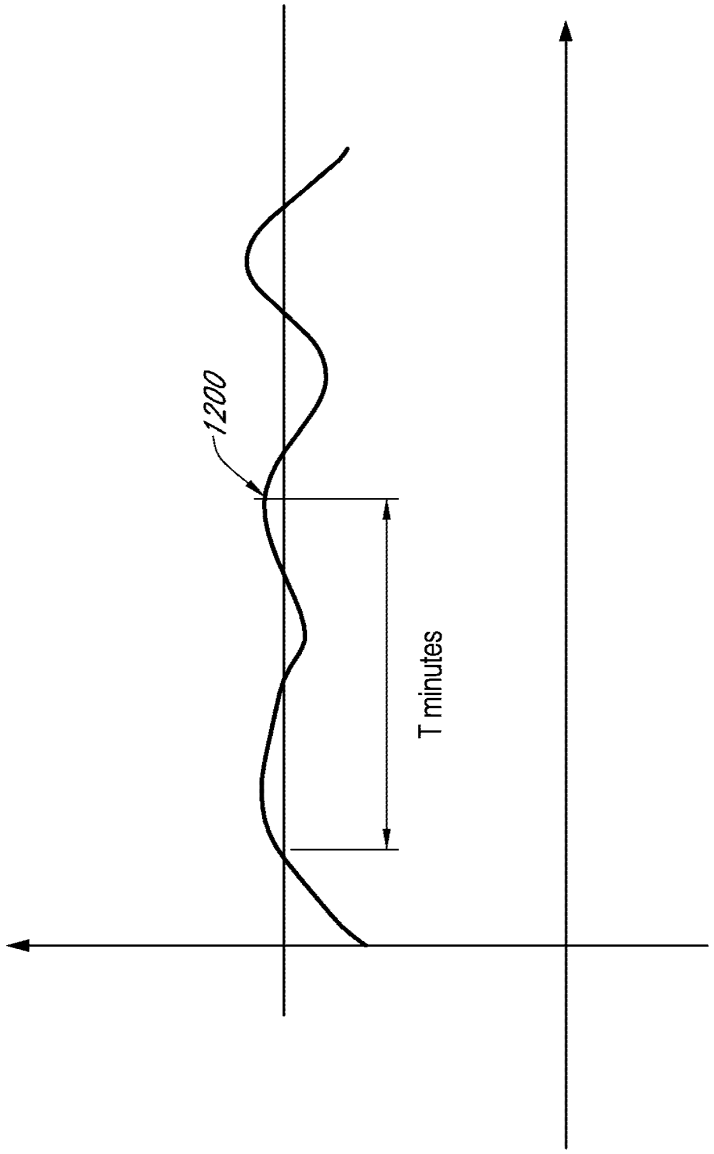


FIG. 12

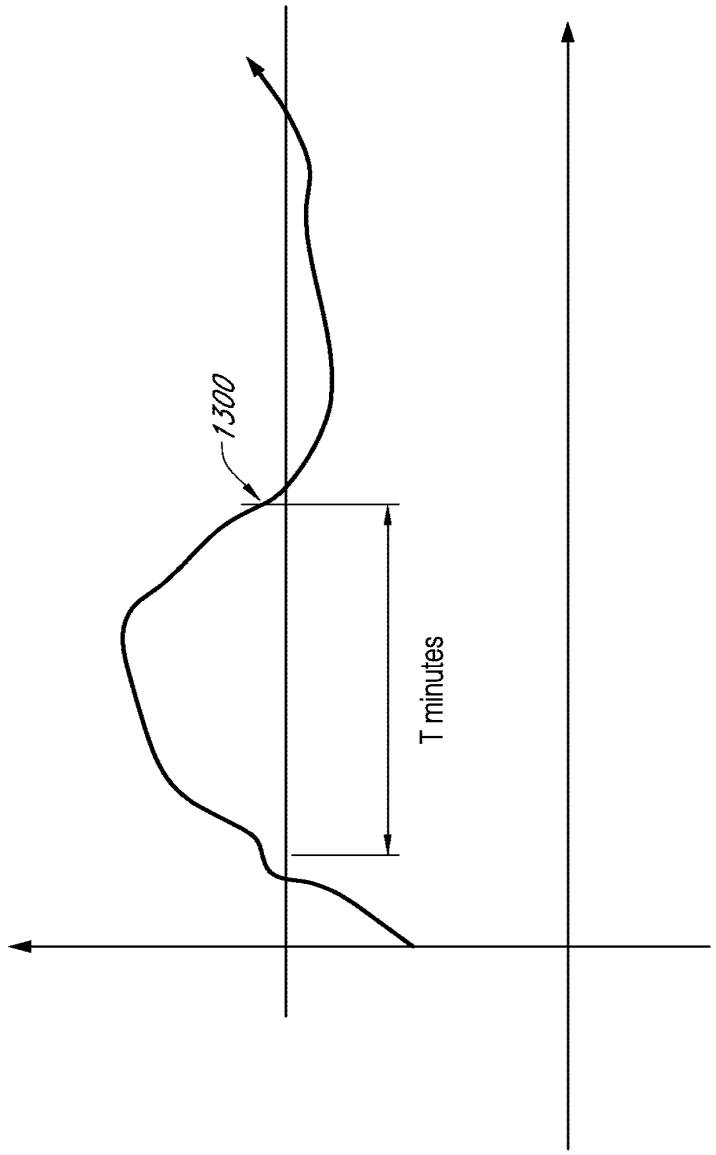


FIG. 13

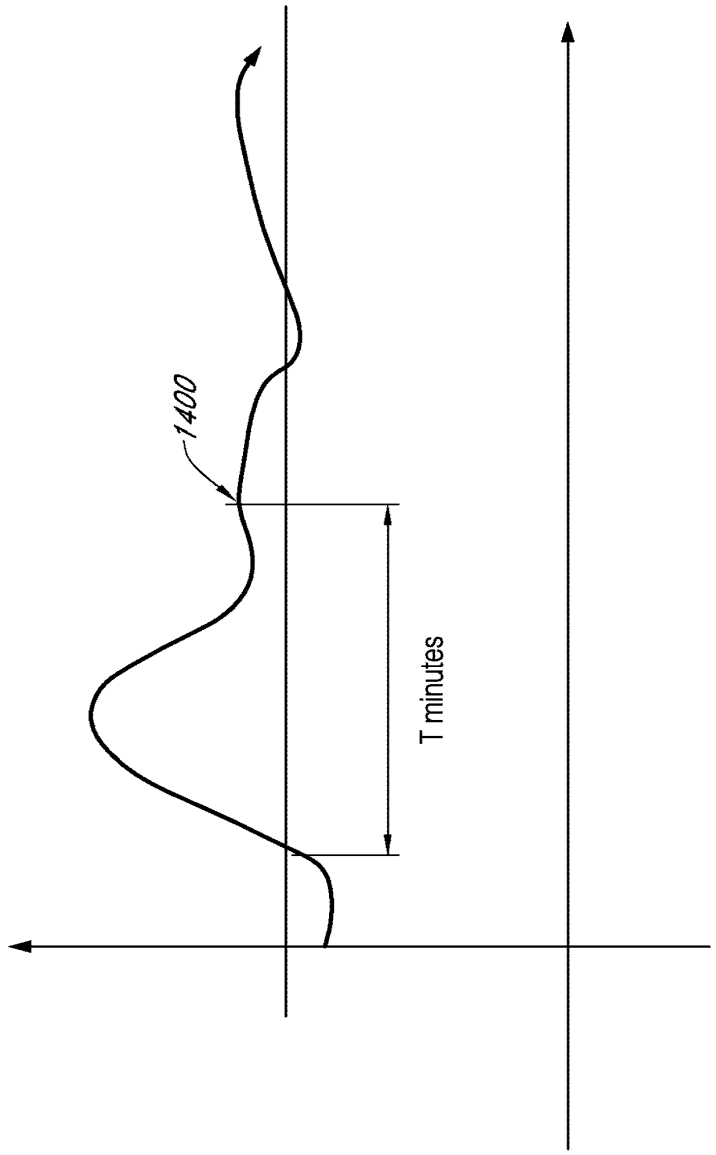


FIG. 14

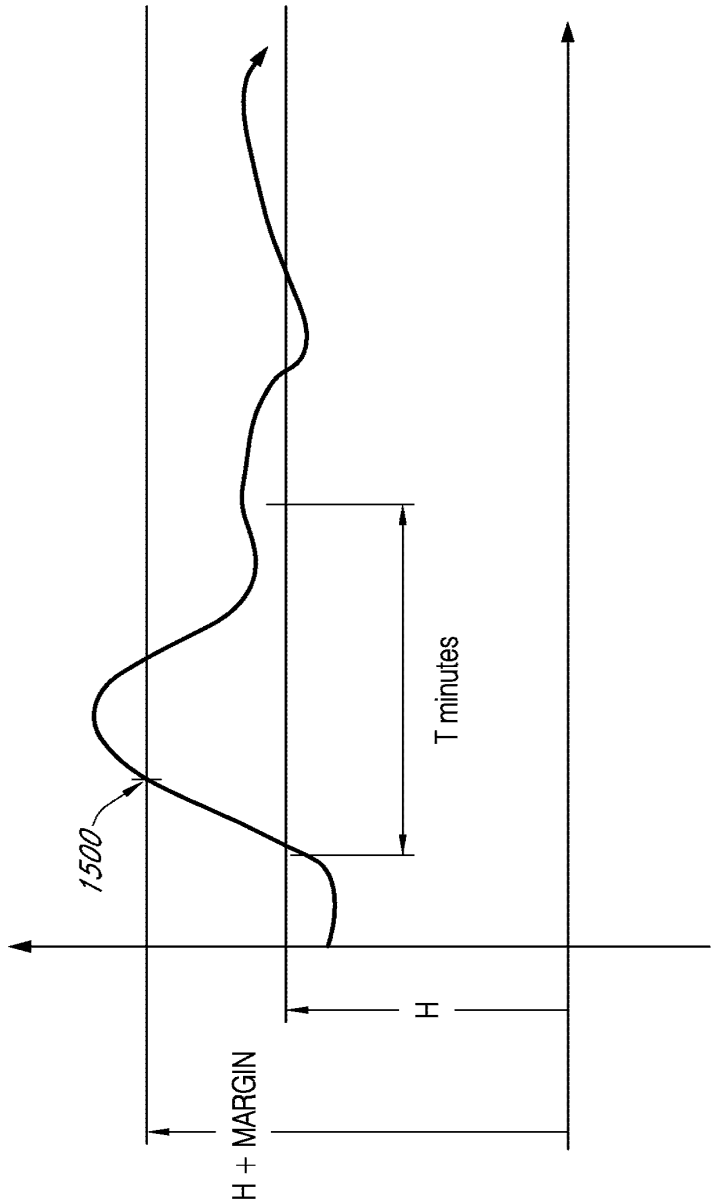


FIG. 15

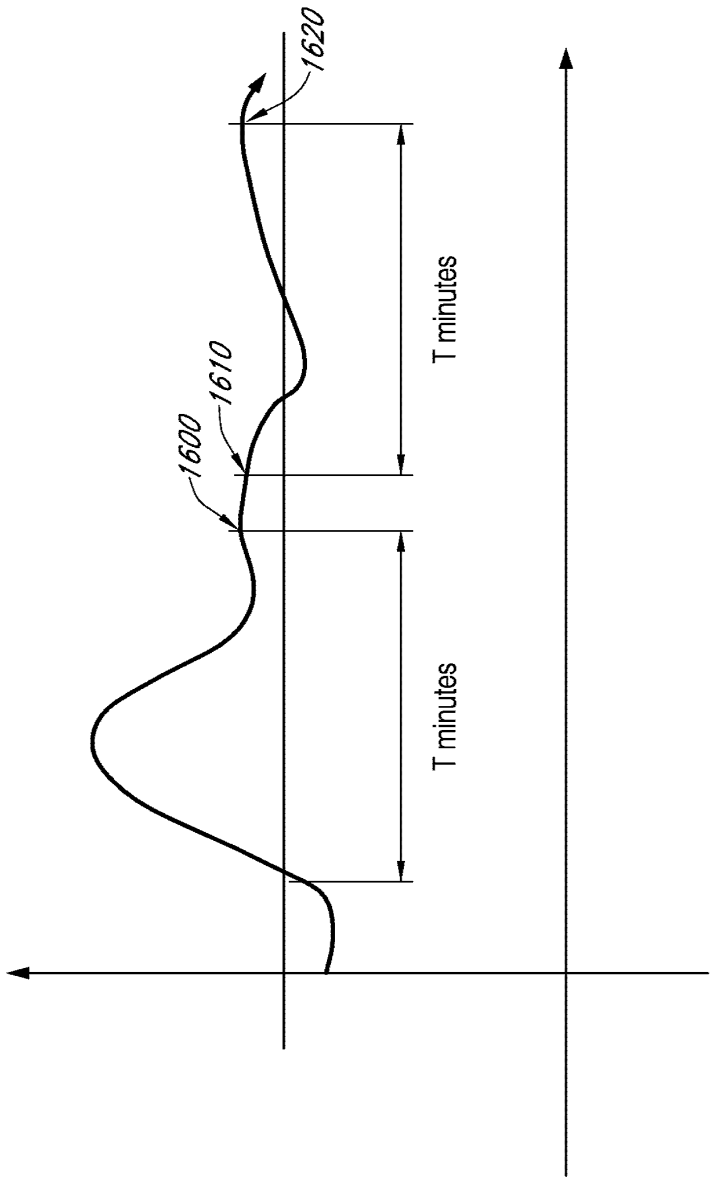


FIG. 16

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/720,286, filed October 30, 2012, the disclosure of which is hereby expressly incorporated by reference in its entirety and is hereby expressly made a portion of this application.

BACKGROUND

[0002] The present systems and methods relate to processing analyte sensor data from a continuous analyte sensor. More particularly, the present systems and methods relate to providing accurate predictive alarms to a user.

Description of Related Art

[0003] Diabetes mellitus is a disorder in which the pancreas cannot create sufficient insulin (Type I or insulin dependent) and/or in which insulin is not effective (Type 2 or non-insulin dependent). In the diabetic state, the victim suffers from high blood sugar, which can cause an array of physiological derangements associated with the deterioration of small blood vessels, for example, kidney failure, skin ulcers, or bleeding into the vitreous of the eye. A hypoglycemic reaction (low blood sugar) can be induced by an inadvertent overdose of insulin, or after a normal dose of insulin or glucose-lowering agent accompanied by extraordinary exercise or insufficient food intake.

[0004] Conventionally, a person with diabetes carries a self-monitoring blood glucose (SMBG) monitor, which typically requires uncomfortable finger pricks to obtain blood samples for measurement. Due to the lack of comfort and convenience associated with finger pricks, a person with diabetes normally only measures his or her glucose levels two to four times per day. Unfortunately, time intervals between measurements can be spread far enough apart that the person with diabetes finds out too late of a hyperglycemic or hypoglycemic condition, sometimes incurring dangerous side effects. It is not only unlikely that a person with diabetes will take a timely SMBG value, it is

also likely that he or she will not know if his or her blood glucose value is going up (higher) or down (lower) based on conventional methods. Diabetics thus may be inhibited from making educated insulin therapy decisions.

[0005] Another device that some diabetics use to monitor their blood glucose is a continuous analyte sensor. A continuous analyte sensor typically includes a sensor that is placed subcutaneously, transdermally (e.g., transcutaneously), or intravascularly. The sensor measures the concentration of a given analyte within the body, and generates a signal that is transmitted to electronics associated with the sensor.

[0006] One of the major perceived benefits of a continuous analyte sensor is the ability of these devices to have alarms to alert the diabetic user of hyperglycemic or hypoglycemic events before they occur. Additionally, it is desirable for these alarms to be accurate, so that a user does not become de-sensitized from their alarm going off, such that they ignore it because it has become a nuisance. The present disclosure addresses these needs.

SUMMARY

[0007] The present systems and methods relate to processing analyte sensor data. Provided herein are systems and methods that allow a user to receive alerts or alarms indicative of glycemic condition in a more accurate and useful way. Consequently, the user may have an improved user experience using such systems and methods.

[0008] In a first aspect, a method of activating a hypoglycemic indicator based on continuous glucose sensor data is provided, the method comprising: evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria; evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria; activating a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and providing an output based on the activated hypoglycemic indicator. In an embodiment of the first aspect, the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria comprises determining whether the real-time glucose value passes a glucose threshold. In an

Abbott Ex. 1002 - 35/1438

embodiment of the first aspect, the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion. In an embodiment of the first aspect, the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value. In an embodiment of the first aspect, the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value. In an embodiment of the first aspect, the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value. In an embodiment of the first aspect, the second function utilizes a first order autoregressive model to determine the predicted glucose value. In an embodiment of the first aspect, the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received. In an embodiment of the first aspect, the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone. In an embodiment of the first aspect, evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function. In an embodiment of the first aspect, the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose. In an embodiment of the first aspect, the one or more first criteria comprises a first threshold that is configured to be user settable. In an embodiment of the first aspect, the one or more second criteria comprises a second threshold that is not user settable. In an embodiment of the first aspect, the second function comprises a prediction horizon that is not user settable. In an embodiment of the first aspect, the one or more second criteria comprises a second

threshold that is adaptively set by the processor module based on the first threshold. In an embodiment of the first aspect, the second function comprises a prediction horizon that is adaptively set by the processor module based on the first threshold. In an embodiment of the first aspect, the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria. In an embodiment of the first aspect, the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria. In an embodiment of the first aspect, providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

[0009] In a second aspect, a system for processing data is provided, the system comprising: a continuous analyte sensor configured to be implanted within a body; and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to: evaluate sensor data using a first function to determine whether a real time glucose value meets one or more first criteria; evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria; activate a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and provide an output based on the activated hypoglycemic indicator. In an embodiment of the second aspect, the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria comprises determining whether the real-time glucose value passes a glucose threshold. In an embodiment of the second aspect, the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an

amplitude of rate of change or direction of rate of change meets a rate of change criterion. In an embodiment of the second aspect, the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value. In an embodiment of the second aspect, the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value. In an embodiment of the second aspect, the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value. In an embodiment of the second aspect, the second function utilizes a first order autoregressive model to determine the predicted glucose value. In an embodiment of the second aspect, the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received. In an embodiment of the second aspect, the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone. In an embodiment of the second aspect, evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function. In an embodiment of the second aspect, the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose. In an embodiment of the second aspect, the one or more first criteria comprises a first threshold that is configured to be user settable. In an embodiment of the second aspect, the one or more second criteria comprises a second threshold that is not user settable. In an embodiment of the second aspect, the second function comprises a prediction horizon that is not user settable. In an embodiment of the second aspect, the one or more second criteria comprises a second threshold that is adaptively set by the processor module based on the first threshold. In an embodiment of the second aspect, the second function comprises a prediction horizon that is adaptively

set by the processor module based on the first threshold. In an embodiment of the second aspect, the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria. In an embodiment of the second aspect, the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria. In an embodiment of the second aspect, providing output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

[0010] In a third aspect, a method of transitioning between states associated with a host's glycemic condition is provided, the method comprising: evaluating sensor data from a continuous glucose sensor and activating an alert state based on the sensor data meeting one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition; providing an output associated with the active alert state, wherein the output is indicative of the hypoglycemic condition or hyperglycemic condition; transitioning from the active state to an acknowledged state for a time period responsive to at least one of a user acknowledgment of the alert state or data indicative of the host's glucose trending toward euglycemia; actively monitoring data associated with the host's hypoglycemic or hyperglycemic condition for a time period in the acknowledged state; and transitioning from the acknowledged state to at least one of an inactive state or active state responsive to the data associated with the host's hypoglycemic or hyperglycemic condition meeting one or more predetermined criteria. In an embodiment of the third aspect, the transitioning from the active state to an acknowledged state comprises transitioning from the active state to the acknowledged state based on the data indicative of the host's glucose trending toward euglycemia,

wherein the data is selected from the group consisting of a) sensor data indicative of a change in glucose trend or b) insulin information associated with a correction of the condition. In an embodiment of the third aspect, the transitioning from the active state to an acknowledged state comprises transitioning from the active state to the acknowledged state based on the a user acknowledgment, wherein the data is selected from the group consisting of a) a user acknowledgement of the alert on a user interface or b) user input insulin information or c) user input of meal information. In an embodiment of the third aspect, the actively monitoring comprises monitoring at least one of the sensor data, sensor diagnostic information, meal information, insulin information, or event information. In an embodiment of the third aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the inactive state based on the sensor data no longer meeting the one or more criteria associated with a hypoglycemic condition or hyperglycemic condition. In an embodiment of the third aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the inactive state based on the sensor data meeting one or more inactive transition criteria, wherein the inactivation criteria are different from the one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition. In an embodiment of the third aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the inactive state based on insulin data and/or meal information. In an embodiment of the third aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the active state based on the one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition being met and based on an expiration of a predetermined time period. In an embodiment of the third aspect, after receiving the user acknowledgement of the alert state and determining data is indicative of the host's glucose trending toward euglycemia, further comprising transitioning from the acknowledged state to the active state based on the host's glucose trending away from euglycemia during the active monitoring time period. In an embodiment of the third aspect, the method further comprises selectively outputting information associated with the state transition. In an embodiment of the third aspect, the

output associated with a transition to the active state is different from the output association with a transition from the acknowledged state to the inactive state.

[0011] In a fourth aspect, a system for processing data is provided, the system comprising: a continuous analyte sensor configured to be implanted within a body; and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to: evaluate sensor data from a continuous glucose sensor and activating an alert state based on the sensor data meeting one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition; provide an output associated with the active alert state, wherein the output is indicative of the hypoglycemic condition or hyperglycemic condition; transition from the active state to an acknowledged state for a time period responsive to at least one of a user acknowledgment of the alert state or data indicative of the host's glucose trending toward euglycemia; actively monitor data associated with the host's hypoglycemic or hyperglycemic condition for a time period in the acknowledged state; and transition from the acknowledged state to at least one of an inactive state or active state responsive to the data associated with the host's hypoglycemic or hyperglycemic condition meeting one or more predetermined criteria. In an embodiment of the fourth aspect, the transitioning from the active state to an acknowledged state comprises transitioning from the active state to the acknowledged state based on the data indicative of the host's glucose trending toward euglycemia, wherein the data is selected from the group consisting of a) sensor data indicative of a change in glucose trend or b) insulin information associated with a correction of the condition. In an embodiment of the fourth aspect, transitioning from the active state to an acknowledged state comprises transitioning from the active state to the acknowledged state based on the a user acknowledgment, wherein the data is selected from the group consisting of a) a user acknowledgement of the alert on a user interface or b) user input insulin information or c) user input of meal information. In an embodiment of the fourth aspect, the actively monitoring comprises monitoring at least one of the sensor data, sensor diagnostic information, meal information, insulin information, or event information. In an embodiment of the fourth aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the inactive state based on the sensor data

no longer meeting the one or more criteria associated with a hypoglycemic condition or hyperglycemic condition. In an embodiment of the fourth aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the inactive state based on the sensor data meeting one or more inactive transition criteria, wherein the inactivation criteria are different from the one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition. In an embodiment of the fourth aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the inactive state based on insulin data and/or meal information. In an embodiment of the fourth aspect, transitioning from the acknowledged state comprises transitioning from the acknowledged state to the active state based on the one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition being met and based on an expiration of a predetermined time period. In an embodiment of the fourth aspect, after receiving the user acknowledgement of the alert state and determining data is indicative of the host's glucose trending toward euglycemia, further comprising transitioning from the acknowledged state to the active state based on the host's glucose trending away from euglycemia during the active monitoring time period. In an embodiment of the fourth aspect, the system further comprises selectively outputting information associated with the state transition. In an embodiment of the fourth aspect, the output associated with a transition to the active state is different from the output association with a transition from the acknowledged state to the inactive state.

[0012] In a fifth aspect, a method of determining when to re-alert a user based after a user has acknowledged a first alert is provided, the method comprising: initially activating an alert state based on one or more criteria based on data associated with a hypoglycemic or hyperglycemic condition being met; transitioning to an acknowledged state for an predetermined active monitoring time period responsive to at least one of a user acknowledgment or data indicative of the host's glucose trending toward euglycemia; actively monitoring, by a processor module, data associated with the host's hypoglycemic or hyperglycemic condition during the active monitoring time period; and reactivating the first alert state during the acknowledgement time period initiated by the data associated with the host's hypoglycemic or hyperglycemic condition meeting one or

more second criteria. In an embodiment of the fifth aspect, the second one or more criteria are different from the first one or more criteria. In an embodiment of the fifth aspect, the method further comprises providing a first output associated with the initially activating and providing a second output associated with the reactivating. In an embodiment of the fifth aspect, the first output and the second output are different. In an embodiment of the fifth aspect, the second criteria comprise conditions indicative of the host's glucose trending toward euglycemia and further comprise conditions indicative of the host's glucose trending away from euglycemia after trending toward euglycemia during the active monitoring time period. In an embodiment of the fifth aspect, the one or more second criteria associated with reactivation comprise a change in a real-time glucose value as compared to the real-time glucose value associated with the initially activating.

[0013] In a sixth aspect, a system for processing data is provided, the system comprising: a continuous analyte sensor configured to be implanted within a body; and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to: initially activate an alert state based on one or more criteria based on data associated with a hypoglycemic or hyperglycemic condition being met; transition to an acknowledged state for an predetermined active monitoring time period responsive to at least one of a user acknowledgment or data indicative of the host's glucose trending toward euglycemia; actively monitor data associated with the host's hypoglycemic or hyperglycemic condition during the active monitoring time period; and reactivate the first alert state during the acknowledgement time period initiated by the data associated with the host's hypoglycemic or hyperglycemic condition meeting one or more second criteria. In an embodiment of the sixth aspect, the second one or more criteria are different from the first one or more criteria. In an embodiment of the sixth aspect, the system further comprises providing a first output associated with the initially activating and providing a second output associated with the reactivating. In an embodiment of the sixth aspect, the first output and the second output are different. In an embodiment of the sixth aspect, the second criteria comprise conditions indicative of the host's glucose trending toward euglycemia and further comprise conditions indicative of the host's glucose trending

away from euglycemia after trending toward euglycemia during the active monitoring time period. In an embodiment of the sixth aspect, the one or more second criteria associated with reactivation comprise a change in a real-time glucose value as compared to the real-time glucose value associated with the initially activating.

[0014] In a seventh aspect, a method of avoiding unnecessary hyperglycemic alerts is provided, the method comprising: initially activating a first alert state based on one or more first criteria associated with a hyperglycemic condition; waiting a time period before providing an output associated with the first alert state; actively monitoring, by a processor module, data associated with the host's hyperglycemic condition during the waiting time period; and providing an output associated with the first alert state after the waiting time period based on the data associated with the host's hyperglycemic condition meeting one or more second criteria. In an embodiment of the seventh aspect, the actively monitoring comprises determining an average glucose over a window of time. In an embodiment of the seventh aspect, the actively monitoring comprises determining an amplitude and/or direction of rate of change. In an embodiment of the seventh aspect, the actively monitoring comprises determining an amplitude and/or direction of rate of acceleration. In an embodiment of the seventh aspect, the actively monitoring comprises evaluating insulin information. In an embodiment of the seventh aspect, the actively monitoring comprises evaluating meal information or timing. In an embodiment of the seventh aspect, the waiting time period is user selectable. In an embodiment of the seventh aspect, the method further comprises not providing output associated with the first alert state after the waiting time period based on the data associated with the host's hyperglycemic condition not meeting the one or more second criteria. In an embodiment of the seventh aspect, the one or more first criteria and the one or more second criteria are the same. In an embodiment of the seventh aspect, the one or more first criteria and the one or more second criteria are different. In an embodiment of the seventh aspect, the method further comprises transitioning from the first alert state to an inactive alert state based on the data associated with the host's hyperglycemic condition meeting one or more third criteria. In an embodiment of the seventh aspect, the one or more first criteria and the one or more third criteria are the

same. In an embodiment of the seventh aspect, the one or more first criteria and the one or more third criteria are different.

[0015] In an eighth aspect, a system for processing data is provided, the system comprising: a continuous analyte sensor configured to be implanted within a body; and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to: initially activate a first alert state based on one or more first criteria associated with a hyperglycemic condition; wait a time period before providing an output associated with the first alert state; actively monitor data associated with the host's hyperglycemic condition during the waiting time period; and provide an output associated with the first alert state after the waiting time period based on the data associated with the host's hyperglycemic condition meeting one or more second criteria. In an embodiment of the eighth aspect, the actively monitoring comprises determining an average glucose over a window of time. In an embodiment of the eighth aspect, the actively monitoring comprises determining an amplitude and/or direction of rate of change. In an embodiment of the eighth aspect, the actively monitoring comprises determining an amplitude and/or direction of rate of acceleration. In an embodiment of the eighth aspect, the actively monitoring comprises evaluating insulin information. In an embodiment of the eighth aspect, the actively monitoring comprises evaluating meal information or timing. In an embodiment of the eighth aspect, the waiting time period is user selectable. In an embodiment of the eighth aspect, the system further comprises not providing output associated with the first alert state after the waiting time period based on the data associated with the host's hyperglycemic condition not meeting the one or more second criteria. In an embodiment of the eighth aspect, the one or more first criteria and the one or more second criteria are the same. In an embodiment of the eighth aspect, the one or more first criteria and the one or more second criteria are different. In an embodiment of the eighth aspect, the system further comprises transitioning from the first alert state to an inactive alert state based on the data associated with the host's hyperglycemic condition meeting one or more third criteria. In an embodiment of the eighth aspect, the one or more first criteria and the one or more third criteria are the same. In an embodiment of the eighth aspect, the one or more first criteria and the one or more third criteria are different.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The details of the present disclosure, both as to its structure and operation, may be understood in part by study of the accompanying drawings, in which like reference numerals refer to like parts. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the disclosure.

[0017] Figure 1 is a schematic view of a continuous analyte sensor system attached to a host and communicating with a plurality of example devices.

[0018] Figure 2 is a block diagram that illustrates electronics associated with the sensor system of Figure 1.

[0019] Figure 3A illustrates an embodiment, where the receiver of Figure 1 shows a numeric representation of the estimated analyte value on its user interface.

[0020] Figure 3B illustrates an embodiment, where the receiver of Figure 1 shows an estimated glucose value and one hour of historical data trend on its user interface.

[0021] Figure 3C illustrates an embodiment, where the receiver of Figure 1 shows an estimated glucose value and three hours of historical trend data on its user interface.

[0022] Figure 3D illustrates an embodiment, where the receiver of Figure 1 shows and estimated glucose value and nine hours of historical trend data on its user interface.

[0023] Figures 4A, 4B and 4C are illustrations of receiver liquid crystal displays showing embodiments of screen displays.

[0024] Figure 4D is a screenshot of a smartphone display illustrating one embodiment of an alert indicting that the user's blood glucose is dropping and will soon be in a low range.

[0025] Figure 4E is a screenshot of a smartphone display illustrating one embodiment of a blood glucose trend graph.

[0026] Figure 4F is an embodiment of a blood glucose trend arrow.

[0027] Figure 5 is an illustration of a continuous trace of glucose values measured during a time frame in accordance with an embodiment of the disclosure.

Abbott Ex. 1002 - 46/1438

[0028] Figure 6 is a flowchart illustrating a process for dynamically and intelligently providing a prediction alert/alarm in accordance with an embodiment of the disclosure.

[0029] Figure 7 is an illustration of a continuous trace of glucose values measured during a time frame in accordance with an embodiment of the disclosure.

[0030] Figure 8 is a flowchart illustrating a process for dynamically and intelligently monitoring the status after an alert/alarm has been triggered in accordance with an embodiment of the disclosure.

[0031] Figure 9 is a flowchart illustrating a process for determining a status change in accordance with an embodiment of the disclosure.

[0032] Figure 10 is a flowchart illustrating a process for determining if a reactivation condition is met in accordance with an embodiment of the disclosure.

[0033] Figure 11 is an illustration of a state diagram showing the transitions from various states in accordance with an embodiment of the disclosure.

[0034] Figures 12-16 are example graphs showing estimated glucose values ("EGVs") and when alerts would be expected to be provided for the EGVs in accordance with embodiments of the disclosure.

DETAILED DESCRIPTION

[0035] The following detailed description describes the present embodiments with reference to the drawings. In the drawings, reference numbers label elements of the present embodiments. These reference numbers are reproduced below in connection with the discussion of the corresponding drawing features.

Sensor System and Applicator

[0036] Figure 1 depicts an example system 100, in accordance with some example implementations. The system 100 includes a continuous analyte sensor system 8 including sensor electronics 12 and a continuous analyte sensor 10. The system 100 may include other devices and/or sensors, such as medicament delivery pump 2 and glucose meter 4. The continuous analyte sensor 10 may be physically connected to sensor electronics 12 and may be integral with (e.g., non-releasably attached to) or

Abbott Ex. 1002 - 47/1438

releasably attachable to the continuous analyte sensor 10. The sensor electronics 12, medicament delivery pump 2, and/or glucose meter 4 may couple with one or more devices, such as display devices 14, 16, 18, and/or 20.

[0037] In some example implementations, the system 100 may include a cloud-based analyte processor 490 configured to analyze analyte data (and/or other patient related data) provided via network 406 (e.g., via wired, wireless, or a combination thereof) from sensor system 8 and other devices, such as display devices 14-20 and the like, associated with the host (also referred to as a patient) and generate reports providing high-level information, such as statistics, regarding the measured analyte over a certain time frame. A full discussion of using a cloud-based analyte processing system may be found in U.S. Patent Application No. 61/655,991, entitled "Cloud-Based Processing of Analyte Data" and filed on June 5, 2012, herein incorporated by reference in its entirety.

[0038] In some example implementations, the sensor electronics 12 may include electronic circuitry associated with measuring and processing data generated by the continuous analyte sensor 10. This generated continuous analyte sensor data may also include algorithms, which can be used to process and calibrate the continuous analyte sensor data, although these algorithms may be provided in other ways as well. The sensor electronics 12 may include hardware, firmware, software, or a combination thereof to provide measurement of levels of the analyte via a continuous analyte sensor, such as a continuous glucose sensor. An example implementation of the sensor electronics 12 is described further below with respect to Figure 2.

[0039] The term "sensor data", as used herein is a broad term and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and furthermore refers without limitation to any data associated with a sensor, such as a continuous analyte sensor. Sensor data includes a raw data stream, or simply a data stream, of analog or digital signal related to a measured analyte from an analyte sensor (or other signal received from another sensor), as well as calibrated and/or filtered raw data. In one example, the sensor data comprises digital data in "counts" converted by an A/D converter from an analog signal (e.g., voltage or amps) and includes one or more data points representative of a glucose concentration. Thus, the terms "sensor data point" and "data point" refer generally to a

digital representation of sensor data at a particular time. The term broadly encompasses a plurality of time spaced data points from a sensor, such as from a substantially continuous glucose sensor, which includes individual measurements taken at time intervals ranging from fractions of a second up to, e.g., 1, 2, or 5 minutes or longer. In another example, the sensor data includes an integrated digital value representative of one or more data points averaged over a time period. In some embodiments, sensor data may include calibrated data, smoothed data, filtered data, transformed data, and/or any other data associated with a sensor.

[0040] The sensor electronics 12 may, as noted, couple (e.g., wirelessly and the like) with one or more devices, such as display devices 14, 16, 18, and/or 20. The display devices 14, 16, 18, and/or 20 may be configured for presenting information (and/or alarming), such as sensor information transmitted by the sensor electronics 12 for display at the display devices 14, 16, 18, and/or 20.

[0041] The display devices may include a relatively small, key fob-like display device 14, a relatively large, hand-held display device 16, a cellular phone 18 (e.g., a smart phone, a tablet, and the like), a computer 20, and/or any other user equipment configured to at least present information (e.g., medicament delivery information, discrete self-monitoring glucose readings, heart rate monitor, caloric intake monitor, and the like).

[0042] In some example implementations, the relatively small, key fob-like display device 14 may comprise a wrist watch, a belt, a necklace, a pendent, a piece of jewelry, an adhesive patch, a pager, a key fob, a plastic card (e.g., credit card), an identification (ID) card, and/or the like. This small display device 14 may include a relatively small display (e.g., smaller than the large display device 16) and may be configured to display certain types of displayable sensor information, such as a numerical value and an arrow.

[0043] In some example implementations, the relatively large, hand-held display device 16 may comprise a hand-held receiver device, a palm-top computer, and/or the like. This large display device may include a relatively larger display (e.g., larger than the small display device 14) and may be configured to display information,

such as a graphical representation of the continuous sensor data including current and historic sensor data output by sensor system 8.

[0044] In some example implementations, the continuous analyte sensor 10 comprises a sensor for detecting and/or measuring analytes, and the continuous analyte sensor 10 may be configured to continuously detect and/or measure analytes as a non-invasive device, a subcutaneous device, a transdermal device, and/or an intravascular device. In some example implementations, the continuous analyte sensor 10 may analyze a plurality of intermittent blood samples, although other analytes may be used as well.

[0045] In some example implementations, the continuous analyte sensor 10 may comprise a glucose sensor configured to measure glucose in the blood using one or more measurement techniques, such as enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, radiometric, immunochemical, and the like. In implementations in which the continuous analyte sensor 10 includes a glucose sensor, the glucose sensor may be comprise any device capable of measuring the concentration of glucose and may use a variety of techniques to measure glucose including invasive, minimally invasive, and non-invasive sensing techniques (e.g., fluorescence monitoring), to provide a data, such as a data stream, indicative of the concentration of glucose in a host. The data stream may be raw data signal, which is converted into a calibrated and/or filtered data stream used to provide a value of glucose to a host, such as a user, a patient, or a caretaker (e.g., a parent, a relative, a guardian, a teacher, a doctor, a nurse, or any other individual that has an interest in the wellbeing of the host). Moreover, the continuous analyte sensor 10 may be implanted as at least one of the following types of sensors: an implantable glucose sensor, a transcutaneous glucose sensor, implanted in a host vessel or extracorporeally, a subcutaneous sensor, a refillable subcutaneous sensor, an intravascular sensor.

[0046] Although the disclosure herein refers to some implementations that include a continuous analyte sensor 10 comprising a glucose sensor, the continuous analyte sensor 10 may comprises other types of analyte sensors as well. Moreover, although some implementations refer to the glucose sensor as an implantable glucose sensor, other types of devices capable of detecting a concentration of glucose and providing an output signal representative of glucose concentration may be used as well.

Abbott Ex. 1002 - 50/1438

Furthermore, although the description herein refers to glucose as the analyte being measured, processed, and the like, other analytes may be used as well including, for example, ketone bodies (e.g., acetone, acetoacetic acid and beta hydroxybutyric acid, lactate, etc.), glucagon, Acetyl Co A, triglycerides, fatty acids, intermediaries in the citric acid cycle, choline, insulin, cortisol, testosterone, and the like.

[0047] Figure 2 depicts an example of sensor electronics 12, in accordance with some example implementations. The sensor electronics 12 may include sensor electronics that are configured to process sensor information, such as sensor data, and generate transformed sensor data and displayable sensor information, e.g., via a processor module. For example, the processor module may transform sensor data into one or more of the following: filtered sensor data (e.g., one or more filtered analyte concentration values), raw sensor data, calibrated sensor data (e.g., one or more calibrated analyte concentration values), rate of change information, trend information, rate of acceleration/deceleration information, sensor diagnostic information, location information, alarm/alert information, calibration information, smoothing and/or filtering algorithms of sensor data, and/or the like.

[0048] In some embodiments, a processor module 214 is configured to achieve a substantial portion, if not all, of the data processing. Processor module 214 may be integral to sensor electronics 12 and/or may be located remotely, such as in one or more of devices 14, 16, 18, and/or 20 and/or cloud 490. In some embodiments, processor module 214 may comprise a plurality of smaller subcomponents or submodules. For example, processor module 214 may include an alert module (not shown) or prediction module (not shown), or any other suitable module that may be utilized to efficiently process data. When processor module 214 is made up of a plurality of submodules, the submodules may be located within processor module 214, including within the sensor electronic 12 or other associated devices (e.g., 14, 16, 18, 20 and/or 490). For example, in some embodiments, processor module 214 may be located at least partially within cloud-based analyte processor 490 or elsewhere in network 406.

[0049] In some example implementations, the processor module 214 may be configured to calibrate the sensor data, and the data storage memory 220 may store the calibrated sensor data points as transformed sensor data. Moreover, the processor module

214 may be configured, in some example implementations, to wirelessly receive calibration information from a display device, such as devices 14, 16, 18, and/or 20, to enable calibration of the sensor data from sensor 12. Furthermore, the processor module 214 may be configured to perform additional algorithmic processing on the sensor data (e.g., calibrated and/or filtered data and/or other sensor information), and the data storage memory 220 may be configured to store the transformed sensor data and/or sensor diagnostic information associated with the algorithms.

[0050] In some example implementations, the sensor electronics 12 may comprise an application-specific integrated circuit (ASIC) 205 coupled to a user interface 222. The ASIC 205 may further include a potentiostat 210, a telemetry module 232 for transmitting data from the sensor electronics 12 to one or more devices, such devices 14, 16, 18, and/or 20, and/or other components for signal processing and data storage (e.g., processor module 214 and data storage memory 220). Although Figure 2 depicts ASIC 205, other types of circuitry may be used as well, including field programmable gate arrays (FPGA), one or more microprocessors configured to provide some (if not all of) the processing performed by the sensor electronics 12, analog circuitry, digital circuitry, or a combination thereof.

[0051] In the example depicted at Figure 2, the potentiostat 210 is coupled to a continuous analyte sensor 10, such as a glucose sensor to generate sensor data from the analyte. The potentiostat 210 may also provide via data line 212 a voltage to the continuous analyte sensor 10 to bias the sensor for measurement of a value (e.g., a current and the like) indicative of the analyte concentration in a host (also referred to as the analog portion of the sensor). The potentiostat 210 may have one or more channels depending on the number of working electrodes at the continuous analyte sensor 10.

[0052] In some example implementations, the potentiostat 210 may include a resistor that translates a current value from the sensor 10 into a voltage value, while in some example implementations, a current-to-frequency converter (not shown) may also be configured to integrate continuously a measured current value from the sensor 10 using, for example, a charge-counting device. In some example implementations, an analog-to-digital converter (not shown) may digitize the analog signal from the sensor 10 into so-called "counts" to allow processing by the processor module 214. The resulting

counts may be directly related to the current measured by the potentiostat 210, which may be directly related to an analyte level, such as a glucose level, in the host.

[0053] The telemetry module 232 may be operably connected to processor module 214 and may provide the hardware, firmware, and/or software that enable wireless communication between the sensor electronics 12 and one or more other devices, such as display devices, processors, network access devices, and the like. A variety of wireless radio technologies that can be implemented in the telemetry module 232 include Bluetooth, Bluetooth Low-Energy, ANT, ANT+, ZigBee, IEEE 802.11, IEEE 802.16, cellular radio access technologies, radio frequency (RF), infrared (IR), paging network communication, magnetic induction, satellite data communication, spread spectrum communication, frequency hopping communication, near field communications, and/or the like. In some example implementations, the telemetry module 232 comprises a Bluetooth chip, although the Bluetooth technology may also be implemented in a combination of the telemetry module 232 and the processor module 214.

[0054] The processor module 214 may control the processing performed by the sensor electronics 12. For example, the processor module 214 may be configured to process data (e.g., counts), from the sensor, filter the data, calibrate the data, perform fail-safe checking, and/or the like.

[0055] In some example implementations, the processor module 214 may comprise a digital filter, such as for example an infinite impulse response (IIR) or a finite impulse response (FIR) filter. This digital filter may smooth a raw data stream received from sensor 10. Generally, digital filters are programmed to filter data sampled at a predetermined time interval (also referred to as a sample rate). In some example implementations, such as when the potentiostat 210 is configured to measure the analyte (e.g., glucose and/or the like) at discrete time intervals, these time intervals determine the sampling rate of the digital filter. In some example implementations, the potentiostat 210 may be configured to measure continuously the analyte, for example, using a current-to-frequency converter. In these current-to-frequency converter implementations, the processor module 214 may be programmed to request, at predetermined time intervals (acquisition time), digital values from the integrator of the current-to-frequency

converter. These digital values obtained by the processor module 214 from the integrator may be averaged over the acquisition time due to the continuity of the current measurement. As such, the acquisition time may be determined by the sampling rate of the digital filter.

[0056] The processor module 214 may further include a data generator (not shown) configured to generate data packages for transmission to devices, such as the display devices 14, 16, 18, and/or 20. Furthermore, the processor module 214 may generate data packets for transmission to these outside sources via telemetry module 232. In some example implementations, the data packages may, as noted, be customizable for each display device, and/or may include any available data, such as a time stamp, displayable sensor information, transformed sensor data, an identifier code for the sensor and/or sensor electronics 12, raw data, filtered data, calibrated data, rate of change information, trend information, error detection or correction, and/or the like.

[0057] The processor module 214 may also include a program memory 216 and other memory 218. The processor module 214 may be coupled to a communications interface, such as a communication port 238, and a source of power, such as a battery 234. Moreover, the battery 234 may be further coupled to a battery charger and/or regulator 236 to provide power to sensor electronics 12 and/or charge the battery 234.

[0058] The program memory 216 may be implemented as a semi-static memory for storing data, such as an identifier for a coupled sensor 10 (e.g., a sensor identifier (ID)) and for storing code (also referred to as program code) to configure the ASIC 205 to perform one or more of the operations/functions described herein. For example, the program code may configure processor module 214 to process data streams or counts, filter, calibrate, perform fail-safe checking, and the like.

[0059] The memory 218 may also be used to store information. For example, the processor module 214 including memory 218 may be used as the system's cache memory, where temporary storage is provided for recent sensor data received from the sensor. In some example implementations, the memory may comprise memory storage components, such as read-only memory (ROM), random-access memory (RAM), dynamic-RAM, static-RAM, non-static RAM, easily erasable programmable read only memory (EEPROM), rewritable ROMs, flash memory, and the like.

Abbott Ex. 1002 - 54/1438

[0060] The data storage memory 220 may be coupled to the processor module 214 and may be configured to store a variety of sensor information. In some example implementations, the data storage memory 220 stores one or more days of continuous analyte sensor data. For example, the data storage memory may store 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, and/or 30 (or more days) of continuous analyte sensor data received from sensor 10. The stored sensor information may include one or more of the following: a time stamp, raw sensor data (one or more raw analyte concentration values), calibrated data, filtered data, transformed sensor data, and/or any other displayable sensor information, calibration information (e.g., reference BG values and/or prior calibration information), sensor diagnostic information, and the like.

[0061] The user interface 222 may include a variety of interfaces, such as one or more buttons 224, a liquid crystal display (LCD) 226, a vibrator 228, an audio transducer (e.g., speaker) 230, a backlight (not shown), and/or the like. The components that comprise the user interface 222 may provide controls to interact with the user (e.g., the host). One or more buttons 224 may allow, for example, toggle, menu selection, option selection, status selection, yes/no response to on-screen questions, a "turn off" function (e.g., for an alarm), an "acknowledged" function (e.g., for an alarm), a reset, and/or the like. The LCD 226 may provide the user with, for example, visual data output. The audio transducer 230 (e.g., speaker) may provide audible signals in response to triggering of certain alerts, such as present and/or predicted hyperglycemic and hypoglycemic conditions. In some example implementations, audible signals may be differentiated by tone, volume, duty cycle, pattern, duration, and/or the like. In some example implementations, the audible signal may be configured to be silenced (e.g., acknowledged or turned off) by pressing one or more buttons 224 on the sensor electronics 12 and/or by signaling the sensor electronics 12 using a button or selection on a display device (e.g., key fob, cell phone, and/or the like).

[0062] Although audio and vibratory alarms are described with respect to Figure 2, other alarming mechanisms may be used as well. For example, in some example implementations, a tactile alarm is provided including a poking mechanism configured to "poke" or physically contact the patient in response to one or more alarm conditions.

Abbott Ex. 1002 - 55/1438

[0063] The battery 234 may be operatively connected to the processor module 214 (and possibly other components of the sensor electronics 12) and provide the necessary power for the sensor electronics 12. In some example implementations, the battery is a Lithium Manganese Dioxide battery, however any appropriately sized and powered battery can be used (e.g., AAA, Nickel-cadmium, Zinc-carbon, Alkaline, Lithium, Nickel-metal hydride, Lithium-ion, Zinc-air, Zinc-mercury oxide, Silver-zinc, or hermetically-sealed). In some example implementations, the battery is rechargeable. In some example implementations, a plurality of batteries can be used to power the system. In yet other implementations, the receiver can be transcutaneously powered via an inductive coupling, for example.

[0064] A battery charger and/or regulator 236 may be configured to receive energy from an internal and/or external charger. In some example implementations, a battery regulator (or balancer) 236 regulates the recharging process by bleeding off excess charge current to allow all cells or batteries in the sensor electronics 12 to be fully charged without overcharging other cells or batteries. In some example implementations, the battery 234 (or batteries) is configured to be charged via an inductive and/or wireless charging pad, although any other charging and/or power mechanism may be used as well.

[0065] One or more communication ports 238, also referred to as external connector(s), may be provided to allow communication with other devices, for example a PC communication (com) port can be provided to enable communication with systems that are separate from, or integral with, the sensor electronics 12. The communication port, for example, may comprise a serial (e.g., universal serial bus or "USB") communication port, and allow for communicating with another computer system (e.g., PC, personal digital assistant or "PDA," server, or the like). In some example implementations, the sensor electronics 12 is able to transmit historical data to a PC or other computing device (e.g., an analyte processor as disclosed herein) for retrospective analysis by a patient and/or physician.

[0066] In some continuous analyte sensor systems, an on-skin portion of the sensor electronics may be simplified to minimize complexity and/or size of on-skin electronics, for example, providing only raw, calibrated, and/or filtered data to a display device configured to run calibration and other algorithms required for displaying the

sensor data. However, the sensor electronics 12 (e.g., via processor module 214) may be implemented to execute prospective algorithms used to generate transformed sensor data and/or displayable sensor information, including, for example, algorithms that: evaluate a clinical acceptability of reference and/or sensor data, evaluate calibration data for best calibration based on inclusion criteria, evaluate a quality of the calibration, compare estimated analyte values with time corresponding measured analyte values, analyze a variation of estimated analyte values, evaluate a stability of the sensor and/or sensor data, detect signal artifacts (noise), replace signal artifacts, determine a rate of change and/or trend of the sensor data, perform dynamic and intelligent analyte value estimation, perform diagnostics on the sensor and/or sensor data, set modes of operation, evaluate the data for aberrancies, and/or the like.

[0067] Although separate data storage and program memories are shown in Figure 2, a variety of configurations may be used as well. For example, one or more memories may be used to provide storage space to support data processing and storage requirements at sensor electronics 12.

[0068] Referring now to Figures 3A to 3D, more detailed schematic views of hand-held receiver 16 is shown. Hand-held receiver 16 may comprise systems necessary to receive, process, and display sensor data from an analyte sensor, such as described elsewhere herein. Particularly, the hand-held receiver 16 can be a pager-sized device, for example, and comprise a user interface that has a plurality of buttons 242 and a liquid crystal display (LCD) screen 244, and which can include a backlight. In some embodiments, the user interface can also include a keyboard, a speaker, and a vibrator.

[0069] In some embodiments, a user is able to toggle through some or all of the screens shown in Figures 3A to 3D using a toggle button on the hand-held receiver. In some embodiments, the user is able to interactively select the type of output displayed on their user interface. In some embodiments, the sensor output can have alternative configurations.

[0070] In some embodiments, analyte values are displayed on e.g., a display of medical device received. In some embodiments, prompts or messages can be displayed on the display device to convey information to the user, such as reference outlier values, requests for reference analyte values, therapy recommendations, deviation of the

measured analyte values from the estimated analyte values, providing predictive alert/alarm, monitoring the glycemic alert state after the alert/alarm is triggered, determining state changes, or the like. Additionally, prompts can be displayed to guide the user through calibration or troubleshooting of the calibration.

[0071] Figures 4A to 4C illustrate some additional visual displays that can be provided on the user interface 222. While these visual displays may include the same or similar output to the ones shown on hand-held device 16 in Figure 3, and the visual displays of Figure 4 can be provided on any suitable user interface 222, such as those on devices 14, 16, 18, 20. In some embodiments, the LCD 226 is a touch-activated screen, enabling each selection by a user, for example, from a menu on the screen. Buttons can provide for toggle, menu selection, option selection, mode selection, and reset, for example. In some alternative embodiments, a microphone can be provided to allow for voice-activated control.

[0072] Figure 4A is an illustration of an LCD screen 226 showing continuous and single point glucose information in the form of a trend graph 184 and a single numerical value 186. The trend graph shows upper and lower boundaries 182 representing a target range between which the host should maintain his/her glucose values. Preferably, the receiver is configured such that these boundaries 182 can be configured or customized by a user, such as the host or a care provider. By providing visual boundaries 182, in combination with continuous analyte values over time (e.g., a trend graph 184), a user can better learn how to control his/her analyte concentration (e.g., a person with diabetes can better learn how to control his/her glucose concentration) as compared to single point (e.g., single numerical value 186) alone. Although Figure 4A illustrates a 1-hour trend graph (e.g., depicted with a time range 188 of 1-hour), a variety of time ranges can be represented on the screen 226, for example, 3-hour, 9-hour, 1-day, and the like.

[0073] Figure 4B is an illustration of an LCD screen 226 showing a low alert screen that can be displayed responsive to a host's analyte concentration falling below a lower boundary (see boundaries 182). In this example screen, a host's glucose concentration has fallen to 55 mg/dL, which is below the lower boundary set in FIG. 4A, for example. The arrow 190 represents the direction of the analyte trend, for example,

Abbott Ex. 1002 - 58/1438

indicating that the glucose concentration is continuing to drop. The annotation 192 ("LOW") is helpful in immediately and clearly alerting the host that his/her glucose concentration has dropped below a preset limit, and what may be considered to be a clinically safe value, for example.

[0074] In contrast, Figure 4C is an illustration of an LCD screen 226 showing a high alert screen that can be displayed responsive to a host's analyte concentration rising above an upper boundary (see boundaries 182). In this example screen, a host's glucose concentration has risen to 200 mg/dL, which is above a boundary set by the host, thereby triggering the high alert screen. The arrow 190 represents the direction of the analyte trend, for example, indicating that the glucose concentration is continuing to rise. The annotation 192 ("HIGH") is helpful in immediately and clearly alerting the host that his/her glucose concentration has above a preset limit, and what may be considered to be a clinically safe value, for example.

[0075] Although a few example screens are depicted herein, a variety of screens can be provided for illustrating any of the information described in the provided embodiments, as well as additional information. A user can toggle between these screens and/or the screens can be automatically displayed responsive to programming within the e.g., hand-held receiver 16, and can be simultaneously accompanied by another type of alert (e.g., audible or tactile).

[0076] For example, Figure 4D is a screenshot of a smartphone 18 display illustrating one embodiment of an alert indicting that the user's blood glucose is dropping and will soon be in a low range. Figure 4E is a screenshot of a smartphone 18 display illustrating one embodiment of a blood glucose trend graph. Figure 4F is an embodiment of a blood glucose trend arrow.

[0077] In some embodiments, the processor module 214 may provide a predictive alert on a smartphone 18 display or user interface 222 when a severe hypoglycemic event is predicted to occur in the near future. For example, the predictive alert may be shown when a severe hypoglycemic event is predicted to occur within 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, etc. With reference to Figure 4D, an arrow 300 may be displayed on a trend screen pointing towards a BG value 302 that indicates a severe hypoglycemic event, such as 55 mg/dL. The arrow 300 may

Abbott Ex. 1002 - 59/1438

change color as it transitions from euglycemia to hypoglycemia, to emphasize the change in glucose levels that is expected. Furthermore, the arrow 300 may be animated to flash to emphasize the seriousness of the alert. The display may also show text 304, such as Going LOW. This predictive alert may be configured to be prioritized over (override) whatever mode or application the smartphone 18 is in at the time the processor module 214 determines that a severe hypoglycemic event is predicted to occur. In other words, the alert may interrupt whatever is currently on the smartphone's user interface 222.

[0078] In these embodiments, the processor module 214 may be programmed with a blood glucose value corresponding to a threshold below which the user is considered to be hypoglycemic. As the processor module 214 receives as inputs multiple EGV's at time-spaced intervals, it processes the inputs by comparing each one to the programmed value, and also to previously received EGV's. If the user's blood glucose shows a downward trend, and is approaching the programmed value, the processor module 214 outputs an alert such as the one shown in Figure 4D to the smartphone's user interface 222. The user thus receives an advance warning of a potential hypoglycemic event, so that he or she can take appropriate action to avoid the hypoglycemic event.

[0079] In various other embodiments, the processor module 214 may change the color of the user interface 222 to reflect the user's current blood glucose level. For example, the user's EGV may be displayed on the screen as a number, as a trend graph, a horizontal bar graph, etc. The text and/or background on the user interface 222 may change when the user's current blood glucose level transitions from one state to another. For example, the text/background may show a first color, such as green, if the user's blood glucose is within a healthy range, and a second color, such as red, if the user's blood glucose is low or high. Alternatively, a first color may be used for the healthy range, a second color for low, and a third color for high. Further, when in the low or high range, as the user's blood glucose becomes increasingly lower or higher, the intensity of the color may increase. The text/background may also flash, with the frequency of the flashing increasing as the user's blood glucose becomes increasingly lower or higher.

[0080] In these embodiments, the processor module 214 may be programmed with blood glucose values corresponding to low and high threshold BG values. As the processor module 214 receives as inputs multiple EGV's at time-spaced intervals, it

Abbott Ex. 1002 - 60/1438

processes the inputs by comparing each one to the programmed values. If the user's blood glucose value crosses one of the thresholds, the processor module 214 outputs an alert to the smartphone's user interface 222 in the form of changing the color of the text and/or background. If the user's blood glucose value continues to become increasingly low or high, the processor module 214 produces additional outputs, such as increasing the intensity of the color and/or causing the text/background to flash. These additional outputs may be generated in response to the processor module 214 comparing input EGV's to additional programmed threshold values.

[0081] In various other embodiments, the processor module 214 may use iconography and/or alert symbols that reflect real time data. For example, the user's blood glucose becomes low, an icon on the smartphone 18 may show an image of the user's BG trend graph using e.g., actual data points from EGV's. The input-processing-output for this embodiment would be substantially the same as that for the previous embodiment.

[0082] With extremely low blood glucose, a person can lose consciousness. Thus, in certain of the present embodiments, at a predetermined level or event (low glucose level, no button pressing after alert, etc.) that might signify a loss of consciousness, the processor module 214 may go into an emergency response instruction mode. This mode may include an alarm to alert others in close proximity to the user that something is wrong. For example, step-by-step instructions on how to assist the unconscious user may be shown on the smartphone's user interface 222, such as administering glucose tabs or another form of carbohydrates, calling an ambulance, etc.

[0083] In these embodiments, the processor module 214 may receive an input from a CGM, which is the user's EGV. The processor module 214 may process the input by comparing it to one or more threshold values, and determine that the user's blood glucose is low. The processor module 214 may produce an output in the form of an alert. If the user does not respond to the alert by pressing a button or an area on a touchscreen user interface 222, for example, the processor module 214 may determine that the user may be unconscious, and produces another output in the form of the emergency response instruction mode described herein.

[0084] In various other embodiments, the processor module 214 may provide differentiated visual high/low thresholds versus alert thresholds. For example, the processor module 214 may be programmed with low and high blood glucose thresholds. These thresholds may be shown on a blood glucose trend graph on the user interface 222 as horizontal lines that the user should strive not to cross. Ordinarily, crossing either of the lines might generate an alert. However, excessive alerts can be annoying to the user, and can decrease patient compliance. Thus, in some embodiments, the visual high/low target range boundaries shown on the graph may be different from boundaries that generate an alert. For example, the boundaries that generate an alert might be wider than the visual target range threshold boundaries on the user interface 222, and the boundaries that generate an alert may be hidden from view. This configuration gives the user a little bit of a buffer zone to cross either of the visual boundaries without generating an alert. Alternatively, the boundaries that generate an alert might be visible, but distinguishable from the target range boundaries. Examples of visual distinctions include different colors, flashing vs. static, solid vs. dashed, different line weights, an alarm icon adjacent the alarm lines, etc. In some embodiments, the high/low target boundaries may always be displayed, but the alert boundaries may be shown or not based on a user setting, a mode (e.g. silent), thresholds, etc.

[0085] In various other embodiments, a user interface of the processor module 214 may be the first thing that the user sees when he or she activates the smartphone's user interface 222. For example, many smartphones 18 automatically put the user interface 222 to sleep (e.g., in a sleep mode) when no activity is detected for a predetermined amount of time. This measure saves battery power. To reactivate the user interface 222, the user must press a button on the smartphone 18. In certain embodiments, when the user reactivates the user interface 222, the first thing he or she sees is the user interface of the processor module 214. In these embodiments, the processor module 214 receives as an input a notification that the user interface 222 has entered sleep mode, followed by a later notification that the user interface 222 has been reactivated. The processor module 214 may process these inputs and produce as an output a display of the user interface 222 of the processor module 214 on the smartphone 18.

Abbott Ex. 1002 - 62/1438

[0086] In various other embodiments, a trend graph displayed by the processor module 214 is color coded. For example, with reference to Figure 4E, the color of the graph 400 (either the trend line 402 or the background 404) may be green if within a target range, yellow if ± 10% outside the target range, orange if ± 15% outside the target range, and red if ± 20% outside the target range. A trend arrow 406 may be similarly color coded, and the angle at which the trend arrow 406 is oriented may correspond to the actual rate of change of the user's glucose, e.g. a more horizontal arrow indicates a low rate of change, while a steeply sloping arrow indicates a high rate of change. In these embodiments, the processor module 214 may receive as inputs continuous EGV's from a sensor system 8. In some embodiments, the rate of change is calculated by the sensor system 8 and sent to the processor module 214 for display (e.g., determination of how to display and resulting display), although the processor module 214 may also perform rate of change calculations. The rate of change based on a linear or non-linear function is applied to a window of recent sensor data. In some embodiments, the rate of change calculation comprises calculating at least two point-to-point rate of change calculations, and wherein the rate of change calculation further comprises adaptively selecting a filter to apply to the point-to-point rate of change calculation based at least in part on a level of noise determined. The processor module 214 may output these values as data points on the trend graph 400 on the user interface 222 and also updates the value 408 shown in the box containing the user's most recent EGV. If the user's blood glucose is dropping, the processor module 214 outputs this information by orienting the arrow 406 downward, while if the user's blood glucose is rising the processor module 214 outputs this information by orienting the arrow 406 upward. In some embodiments, the trend arrow is located on the end of the trend graph (e.g., rather an in a separate box/area).

[0087] In certain embodiments, a size of the value 408 shown in the box containing the user's most recent EGV may change size depending on how far off the user is from their target zone. For example, as the user's glucose gets farther and farther away from the target zone, the number could get bigger and bigger. This amplification could be one directional or either direction, meaning the EGV displayed on the trend graph could get bigger and bigger if it's outside the target range in either direction or only get bigger and bigger if it's outside the target range on the low side (e.g., hypo). The

Abbott Ex. 1002 - 63/1438

same applies to the trend arrow 406. With reference to Figure 4F, the trend arrow 406 could be drawn large enough to fit the EGV 408 inside the arrow 406. The layout of the trend arrow 406 / EGV 408 in Figure 4F may be used independently of the foregoing embodiment in which the size of the trend arrow 406 / EGV 408 changes dynamically as the user's glucose changes.

[0088] In various other embodiments related to that of Figure 4E, rather than using a hard threshold for the transition from one color to the next, the display could instead show a gradient type of trend graph. That is, rather than transitioning directly from green to yellow as soon as the user's glucose hits the threshold of, say ± 10% outside the target range, the display would instead gradually transition from green to yellow as the user's glucose moves away from the target range toward the established threshold. Thus, at ± 5% outside the target range, the display would show a color between green and yellow, with the color becoming gradually more yellow as the user's glucose moves through± 6% outside the target range, ± 7% outside the target range, ± 8% outside the target range, etc.

Predictive Alerts/Alarms

[0089] In some embodiments, the sensor outputs a signal in the form of electrical current; however any output signal from any measurement technique may be used for the predictive alerts/alarms described herein. In general, a conversion function is applied to the sensor signal in order to produce a user output that the user understands as representative of a concentration of analyte in his or her bloodstream. Such a proper conversion function may take into account numerous variables, e.g., sensitivity (slope), baseline (intercept), drift, temperature correction, factory-derived information or other calibrations or adjustment to the data. After a suitable conversion function is applied, the user may see an output similar to that shown in e.g., Figures 3A to 3D.

[0090] In the scope of preventing the consequences of diabetes, it is desirable to prevent hypoglycemia and/or hyperglycemia episodes instead of simply generating alerts when such episodes occur. For example, an alert generated to indicate that without intervention a hypoglycemia episode will occur within 20 minutes would allow the host or patient to ingest and absorb sugar in time.

Abbott Ex. 1002 - 64/1438

[0091] Referring now to Figure 5, an example of a continuous trace of glucose values measured during a time frame and having a threshold flag x_1 and a predictive flag x_2 located thereon is shown. As presented in Figure 5, the example glucose trace embodies a graph having a glucose level e.g., mg/dl, compared against a time frame e.g., 24 hours.

[0092] As shown, there are three threshold values or limits used in the monitoring of the glucose values in some embodiments: TV_1, TV_2 and TV_P. TV_1 may be settable by the user and generally defines the upper limit or upper glucose value that a user may operate at before being alerted by the monitor. Similarly, TV_2 may be settable by the user and generally defines the lower limit or lower glucose value that a user may operate at before being alerted by the monitor. TV_P is the predictive threshold, e.g., the threshold against which a predicted value is compared. It should be appreciated that although the illustrated embodiment envisions a threshold value, threshold ranges or other criteria (e.g., glycemic states) may alternatively be used.

[0093] As shown, TV_P does not have a particular glucose value given. This is because TV_P may not be settable by the user; it may be a fixed value or permanent value set during factory settings. In some embodiments, TV_P may represent a dangerously low glucose value e.g., be indicative of a serious hypoglycemic event. In some embodiments, TV_P may represent a value at or around 55 mg/dL.

[0094] In some embodiments, TV_P may be adaptively determined based on TV_2. For example, if the user sets TV_2 to be a relative high value, e.g., 90 mg/dL, an algorithm or function may determine that TV_P should be set at 65 mg/dL. Conversely, if the user sets TV_2 to be a relative low value, e.g., 70 mg/dL, an algorithm or function may determine that TV_P should be set at 55 mg/dL. Additionally or alternatively, the prediction horizon, PH, may be preset or adaptively selected based on another parameter associated with prediction, for example, based on TV_2 selected and/or TV_P.

[0095] Still referring to Figure 5, there are shown two flags x_1 and x_2. Flag x_1 may generally be considered a threshold flag, and may be configured to alert the user that a first threshold, e.g., TV_2, has been met. In some embodiments, threshold flag x_1 operates to notify the user in real time, or approximately real time (e.g., may take into account processing delay, etc.) when a threshold has been met or crossed. An example of

Abbott Ex. 1002 - 65/1438

using threshold flag x_1 is when the user wants to be notified of when his glucose level hits a certain value, high or low. When the user's glucose value is determined to meet that predetermined user set value, the user may be notified via an alert or alarm. Additional rate of change conditions may be added (e.g. TV_1 and rate of change increasing at > 0.5 mg/dL/min or TV_2 and rate of change decreasing at > 0.5 mg/dL/min).

[0096] Flag x_2 may generally be considered a predictive flag, and may be configured to alert the user that a second threshold, e.g., TV_P, is predicted to be met within a predetermined or predefined time frame or time horizon PH. In some embodiments, predictive flag x_2 operates to notify the user in real time that a threshold is predicted to be crossed or met in a predefined time frame, e.g., 20 minutes.

[0097] An advantage of the glucose monitoring profile shown in Figure 5 is that prediction may be paired with a threshold alert that is settable by the user, where an alert will sound for whichever condition is met first (threshold or prediction) Use of prediction algorithm parameters (e.g., reliance on modeled versus measured data, time-sensitive weighting of past data, prediction horizon PH, and prediction threshold TV_P) tuned in advance may increase or optimize warning time for patients before a severe event occurs and may minimize the number of nuisance/false alarms heard by user.

[0098] In some embodiments, the prediction parameters (TV_P and PH) may be invisible to the user and preset or fixed. In some embodiments the prediction parameters are determined from the sensor manufacturer using a variety of historical data using e.g., the user's historical data, a population historical data, the particular sensor's historical data, etc.

[0099] Referring back to Figure 3A, an example glucose trace of a user's day is shown. From looking at the trace, it can be appreciated that the glucose trace generally falls within a shaded or bound region 246. This region may be generally referred to as a "target zone", and the user is encouraged to "stay between the lines". This region is generally viewable to a user on their monitor or device with a viewing screen as can serve as a quick check on how a user's glucose looked for a particular time period. Another example of the bound region is shown in Figure 4A and designated as reference numeral 182.

Abbott Ex. 1002 - 66/1438

[00100] In some embodiments, this shaded "target zone" differs from the region defined by TV_1 and TV_2, hereinafter referred to as the "alert boundary". In some embodiments, TV_1 and TV_2 are not viewable by a user, but are rather internal values used by appropriate algorithms or functions to e.g., alert the user when necessary.

[00101] In other embodiments, the alert boundary may be viewable to the user. It should be appreciated that values, pictures or icons, or simple designations such as "HIGH" and "LOW" may be associated with TV_1 and TV_2, respectively. Additionally, TV_P may be shown, as a simple alarm icon, for example.

[00102] In some embodiments, the predictive alerts may be activated using a simple on/off button. Additionally, in some embodiments, there may be one or more general settings for prediction such as "sensitive", "normal", "non-annoying" for different user needs. For example, a sensitive prediction setting may use a PH = 30 minutes and TV_P = 70 mg/dL; a normal prediction setting may set values at PH = 20 min and TV_P = 55 mg/dL; and a non-annoying prediction setting may set values at PH = 10 min and TV_P = 55 mg/dL.

[00103] It should be noted that, although the disclosure focuses on prediction horizon and criteria associated with prediction at low glucose (hypoglycemia), all of the principles applied to hypoglycemic alarms/alerts may be implemented for high glucose (hyperglycemia) as may be appreciated by one skilled in the art.

[00104] Figure 6 is a flowchart 500 illustrating a process for dynamically and intelligently providing a prediction alert/alarm in accordance with an embodiment of the disclosure. As explained above, providing a predictive alert/alarm is highly desirable as it may minimize and/or prevent the number of hypoglycemia and/or hyperglycemia episodes a user experiences.

[00105] At block 510, processor module 214 may be configured to receive sensor data (e.g., a data stream), including one or more time-spaced sensor data points, from the sensor 10. The sensor data point(s) can be averaged, smoothed, and/or filtered in certain embodiments using a filter, for example, a finite impulse response (FIR) or infinite impulse response (IIR) filter.

[00106] At block 520, processor module 214 may be configured to evaluate the sensor data using a first set of instructions or criteria. The first set of instructions or

Abbott Ex. 1002 - 67/1438

criteria may include any algorithm suitable for determining if a data point has met one or more first predetermined criteria associated with hypoglycemia or hyperglycemia. Such predetermined criteria may be input by the user using e.g., a menu for inputting various alert thresholds. Alternatively, the predetermined criteria may be set according to factory settings and may be fixed, such that the user cannot change, e.g., the alert threshold. In some embodiments, the predetermined threshold is saved in e.g., a lookup table, and may depend on other parameters such as time of day (e.g., more or less sensitive at nighttime), historical patient information, or the like. In other embodiments, more complex algorithms may be used to define a user's current glycemic state, rather than static thresholds, such as static risk or dynamic risk models, where the criteria would be defined based on the output of these complex algorithms or instructions (e.g., gradients, yes/no indicators, percentages, probabilities, or the like).

[00107] In some embodiments, the sensor data comprises real time glucose values (e.g. blood glucose values (BGs)), calibrated glucose values (e.g., estimated glucose values (EGVs)), rate of change of glucose values, direction of change of glucose values, acceleration or deceleration of glucose values, insulin information, event information, historical trend analysis results, and the like. Consequently, in some embodiments, the processor module 214 may be configured to evaluate sensor data using a first function to determine whether a real time glucose value meets one or more first predetermined criteria.

[00108] In some embodiments, the criteria may be thought of as including at least one component. For example, the criteria may be representative of a singular or absolute value. In some embodiments, the criteria may comprise two or more components. For example, the threshold may be representative of a range of values. Alternatively, the threshold may be representative of a singular value associated with a time component. In other embodiments, the threshold may be representative of a singular value associated with a direction or rate of direction.

[00109] As mentioned above, the one or more criteria may be a first threshold value set by a user. For example, the user may decide that he wants to be alerted whenever his glucose reading drops to 70 mg/dL or 70 mg/dL and rate of change is negative (indicative of decreasing glucose level). In other cases, the user may decide that

Abbott Ex. 1002 - 68/1438

70 mg/dL might be to too low of a reading, and wants to be alerted whenever his glucose drops below 80 mg/dL. As understood by those of skill in the art, there is a fine balance between being alerted too often, e.g., nuisance alarms, and being adequately alerted when there is a real event. Consequently, the user may be allowed to have some input on how often he is alerted, based on selecting the first threshold value. The higher the selected value, the more sensitive the alert trigger, e.g., the more often a user is going to be alerted.

[00110] In some embodiments, the first threshold may be a user settable number or a qualitatively sensitive indication for the threshold being crossed. The qualitatively sensitive indication may include settings such as "sensitive", "normal", "non-annoying", etc., as described above. For example, the analyte monitoring system 8 may detect a high number of alerts (e.g., > 2 a day) and prompt the user with a question to determine if settings should be adjusted to avoid unnecessary annoyances. For example, system 8 may suggest to the user to change the qualitatively sensitive indication from sensitive to normal or from normal to non-annoying if a higher than usual number of alerts (e.g., twice as usual) are being provided.

[00111] In some embodiments, the first set of instructions or criteria may include any algorithm suitable for determining if a data point has met or crossed a predetermined threshold. In some embodiments the first set of instructions or criteria may include a more complex assessment of glycemic state, including for example, other parameters such as amplitude and/or direction of rate of change of glucose, rate of acceleration/deceleration of glucose, insulin and/or meal consumption. In some embodiments, the first set of instructions or criteria may use a measure of risk, such as the static risk and/or dynamic risk models for continuous glucose monitoring data to generate and determine whether a particular criterion has been met. In some embodiments, the algorithm performs its calculations on uncalibrated sensor data, after which the results are converted into calibrated data and compared to the criteria and/or threshold. Performing some or all of the algorithmic processing on uncalibrated data may be advantageous to reduce negative impacts of error or bias associated with calibration; however in some embodiments, the algorithmic processing may be performed on calibrated data.

[00112] In other embodiments, more complex algorithms may be used to define a user's predicted glycemic state, rather than static thresholds, such as static risk or dynamic risk models, where the input could include real-time or predicted values and where the criteria would be defined based on the output of these complex algorithms (gradients, yes/no indicators, percentages, probabilities, or the like).

[00113] At block 530, processor module 214 may be configured to evaluate the sensor data using a second set of instructions or criteria. In some embodiments, the first set of instructions from block 520 is different than the second set of instructions from block 530.

[00114] Similar to block 520, in block 530, the second set of instructions or criteria may include any algorithm or algorithms suitable for evaluating sensor data to determine whether a glycemic state (hyper- or hypo-gylcemia) is predicted, for example, by determining if a data point is predicted or projected to cross a predetermined threshold. Suitable algorithms include algorithms based on polynomial and auto-regressive models, algorithms based on Kalman Filtering (KF), artificial neural networks, statistical and numerical logical algorithms, and machine learning.

[00115] In some embodiments, the second set of instructions may use utilize an artificial neural network that can consider other relevant information, if available, such as food, exercise, stress, illness or surgery to predict a future glucose value. The architecture may include three layers, with a first layer gathering the inputs, a hidden layer that transforms the inputs using polynomial or non-linear functions, e.g. squaring, sigmoidal, thresholding, and a third output layer that combines the outputs of hidden layer into output or predicted value(s). Neurons may be totally connected and feedforward. One useful artificial neural network implementation is described by W. A Sandham, D. Nikoletou. D. J. Hamilton, K. Patterson. A Japp and C. MacGregor, in "Blood glucose prediction for diabetes therapy using a recurrent artificial neural network," in *IX European Signal Processing Conference (EUSIPCO), Rhodes,* 1998, pp. 673-676. Each neuron in second and third layers takes as input a weight combination of outputs from the previous layer. These weights are tuned to give the best predicted value through a process called training. That is, a neural network starts with an initial guess and using training and testing data sets with known input and outputs, finds the best

Abbott Ex. 1002 - 70/1438

possible weights to give optimal outputs. Once the training process is complete, the network may be used to predict outputs for any new data. The network input information may be the current glucose measurement and its timestamps together with a limited number of previous glucose samples from the CGM system. The NNM (neural network model) may take into account the glucose measurements up to 20 minutes before the current time. Since the sampling rate varies from one CGM system to another, the number of the NNM inputs may be different for each dataset. The output of the network may be the glucose prediction at the prediction horizon time.

[00116] In some embodiments, the second set of instructions may use an autoregressive model (first order, second order or third order, for example) to predict a future glucose value. One useful first-order autoregressive model implementation is described by G. Sparacino, F. Zanderigo. S. Corazza, A. Maran, A. Facchinetti and C. Cobelli, in "Glucose Concentration can be Predicted. Ahead in Time From Continuous Glucose Monitoring Sensor Time-Series." Biomedical Engineering. IEEE Transactions 011. 2007, voL 54, pp. 931-937. This algorithm predicts the future glucose value by taking the current glucose value y(n) and multiplying the previous glucose value y(n-1) by some coefficient α. When glucose is rising, α will be some value slightly larger than 1 and when it is falling α will be a little less than 1. In this algorithm, the model parameter (α) may be estimated recursively (e.g., updated every 5 minutes to account for glucose dynamics) to minimize the sum of squared residuals for all pairs of predicted and current glucose values. An estimate of alpha may be updated (e.g., using a weighted least squares regression) every time a new sensor data point is received (e.g., every 5 minutes). Prediction parameters (e.g., forgetting factor, prediction horizon, and prediction threshold) may be tuned in advance to optimize warning time for patients before a severe hypo event occurs (e.g., 55 mg/dL), and to minimize the number of nuisance/false alerts heard by patient. For example, the direction of glucose changes over time, so a forgetting factor μ may be used to weight the most recent data more heavily with a value between 0 and 1. Prediction horizon and/or prediction thresholds may be predetermined by the system and/or user selectable as described in more detail elsewhere herein.

[00117] In some embodiments, the first order autoregressive model includes a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone. In some embodiments, this is at least partially achieved by monitoring the user's qualitatively sensitive indication and prompting or urging the user to select the appropriate setting.

[00118] In some embodiments, the second set of instructions may use a Kalman filter (an optimal estimation method) to predict a future glucose value. The Kalman filter trades off the probability that a measured glucose change is due to sensor noise versus an actual change in glucose, to obtain the maximum likelihood estimate of glucose (and its first and second derivatives). One useful Kalman Filter implementation is described by Palerm, C. and Bequette, W. in "Hypoglycemia Detection and Prediction Using Continuous Glucose Monitoring—A Study on Hypoglycemic Clamp Data," J Diabetes Sci Technol. 2007 September; 1(5): 624–629. The states are the blood glucose concentration (g_k), its rate of change (d_k, e.g., the velocity), and the rate of change of the rate of change (f_k, e.g., the acceleration). The latter is assumed to vary in a random fashion, driven by input noise w_k (with covariance matrix $\boldsymbol{Q}$), which describes changes to the process. The sensor glucose measurements are assumed to contain noise, described by υ_k (with covariance matrix $\boldsymbol{R}$). Prediction model parameters (e.g., Q/R ratio, prediction horizon, and prediction threshold) may be tuned in advance and/or user selectable.

[00119] In some embodiments, the second set of instructions or function may optionally include a mechanism to include user input, such as insulin, exercise, meals, stress, illness, historical patient information (e.g., patterns or trends), etc.

[00120] In some embodiments, the sensor data comprises real time glucose values, (e.g. blood glucose values (BGs)), calibrated glucose values (e.g., estimated glucose values (EGVs)), rate of change of glucose values, direction of change of glucose values, acceleration or deceleration of glucose values, insulin information, event information, historical trend analysis results, and the like Consequently, in some embodiments, the processor module 214 may be configured to evaluate sensor data using

Abbott Ex. 1002 - 72/1438

a second function to determine whether a predicted glucose value meets one or more predictive alarm criteria.

[00121] The second predetermined criteria may include a single value, a range of values, a direction associated with the value, a rate of direction, etc. In some embodiments, the second criteria include a predetermined threshold, which is a fixed value set as part of factory settings. For example, it may be desirable to have a second threshold that the user cannot manipulate or change because of the importance associated with the threshold. For example, in some embodiments, the second predetermined threshold may represent a value that is indicative of a severe hypoglycemic event, e.g., 55 mg/dL.

[00122] In some embodiments, the second predetermined criteria is determined based on a probability of hypoglycemia within a particular time frame, which may account for the rate at which sensor data is changing, the direction the sensor data is going, the current glucose level, past history of glucose change, insulin information, meal information, exercise information, etc. An example of applying additional criteria to the processor module 214 is that if hypoglycemia is predicted in the near future but the current glucose level is 200 mg/dL then that prediction is not probable or likely, thus, limits on glucose value, rates of changes, and the like, may be applied. Another example, this time of using meal information, is that if the user indicated that they recently ate a meal, then it may be the glucose will quickly turn around and it is not necessary to alert them at this time.

[00123] In some embodiments, the second predetermined criteria may be at least partially or adaptively based on the first predetermined threshold. For example, a suitable set of algorithms or functions may base e.g., the prediction horizon and/or the second predetermined threshold on the first predetermined threshold.

[00124] In some embodiments, the second set of instructions is completely predictive, meaning that the instructions use past and/or current data to determine if a user will meet or cross through the second predetermined threshold in a predetermined time frame or horizon. The predetermined time frame or horizon is preferably long enough for a user to take action to turn around a predicted event. For example, the

Abbott Ex. 1002 - 73/1438

predetermined horizon may be at least 15 minutes in some embodiments, at least 20 minutes in some embodiments, and at least 30 minutes in some embodiments.

[00125] In some embodiments, the predetermined time frame or horizon may have addition capabilities or take additional information into consideration when setting the time frame. For example, as is known by those of skill in the art, some continuous glucose monitoring systems sense glucose in the interstitial fluid, rather than blood (e.g., capillary blood from which finger stick measurements are traditionally derived). Consequently, there may be a time lag between the value measured and the actual blood glucose value, e.g. 5 minutes or more. In some examples the time lag can be as small as 0 minutes, where in other examples the time lag is as large as 15 minutes or more. There may also be variability in the time lag, which may be represented by a standard deviation in the measurement, e.g., 10 minutes for a 5 minute lag.

[00126] As sensors become more accurate through improved sensor design, the inaccuracy due to time lag may become a more substantial contributor to the total error. While not wishing to be bound by any particular theory, it is suspected that physiology, time since the sensor was inserted, glucose state (hypo- or hyper-), glucose rate of change, knowledge of filtering performed, and other variables may influence the amount of time lag a sensor will experience. Consequently, in some embodiments, a time lag adjustment algorithm or set of instructions may be used in determining or in conjunction with setting the predetermined time frame or time horizon. In some embodiments, the time lag adjustment set of instructions uses near time prediction to predict and display the estimated glucose value at a future point in time, e.g. from about 2.5 minutes to about 15 minutes, depending on additional information e.g., obtained through algorithmic or alternate detection means. For example, information that may influence the prediction horizon include: time since the sensor was inserted, glucose state or rate of change, adaptive learning algorithms that can learn what each individual's average time lag is and apply a unique setting, etc. Consequently, in some embodiments, a time adjustment lag algorithm may use as one or more inputs, one or more of the following variables: time since the sensor was inserted, glucose state or rate of change, user a priori information. In some embodiments, additional sensors may be implemented to directly or indirectly measure time lag. An example sensor could be the use of impedance data between the

working and reference electrodes that are separated in space or between an electrode at the sensing area and a secondary electrode on the surface of the skin.

[00127] In some embodiments, blocks 520 and/or 530 may be iteratively repeated with the receipt of any new data, including data derived from the sensor, another medical device (e.g., insulin delivery device) and/or the user or host (via user input) prior to the activation of a hypoglycemic indicator.

[00128] At block 540, processor module 214 may be configured to activate a hypoglycemic indicator if either the first criteria is met or if the second criteria is predicted to be met. In some embodiments, the processor module 214 is configured to determine which set of instructions has met its criteria (e.g., 520 or 530 where x_1 or x_2 is flagged). For example, the first set of instructions may determine first threshold has been met at 8:47 pm in block 520, using real time data. In the same example, the second set of instructions may determine second threshold is predicted to be met at 9:00 pm in block 530, using the 20 minute prediction horizon. In this example then, where both the first and second evaluations have met their criteria, either or both may be used in subsequent processing.

[00129] As described above, the hypoglycemic indicator may comprise a single indicator representative of whichever function determines or predicts that a threshold will be crossed first in time. In some embodiments, the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it, depending on whether the first evaluation using the first criteria (x_1) or the second evaluation using the second criteria (x_2) were met. The responses to the first or second evaluations may also be differentiated in processing and/or output differently. In some embodiments, where both evaluations show criteria being met, there is unique processing and output indicating both actual and prediction-based criteria were met. Alternatively, rules may be provided to determine which criteria were met.

[00130] For example, in some embodiments, the x_1 and x_2 flags may be differentiated on the user display or user interface 222. In some embodiments, the user interface 222 may be configured to show the simultaneous display or both criteria (x_1 and x_2), such as "x_1 is at 76 mg/dL" and "x_2 is predicted to be at 55 mg/dL in 20 minutes."

Abbott Ex. 1002 - 75/1438

[00131] At block 550, processor module 214 may be configured to provide an alert or alarm if warranted by the detection of a threshold being met or predicted to be met, as represented by the hypoglycemic indicator. In some embodiments, the processor module 214 provides an alarm or alert based on the detection of the threshold that is met or predicted to be met at an earliest time point. In some embodiments, providing an alert based on the earliest detected or predicted threshold is desirable because it may provide a user more time to turn around an actual or predicted a hypoglycemic and/or hyperglycemic event.

[00132] In addition to sending any of the above-described sensor data to an insulin delivery device, in some embodiments, the processor module 214 may send a message to an insulin delivery device including at least one of: a) suspend insulin delivery (e.g. configured to suspend a basal or bolus delivery of glucose in an insulin delivery device responsive to sensor data meeting a predetermined criterion), b) initiate a hypoglycemia and/or hyperglycemia minimizer algorithm (e.g. an algorithm configured to control a user's blood glucose to a target range using an automatic insulin delivery device), c) control insulin delivery responsive thereto or d) information associated with the alert (e.g., hypoglycemia indicator). Sensor data and/or messages may be sent directly to a dedicated insulin delivery device or indirectly through a controller, such as in a smart phone or via the cloud. Some embodiments provide the necessary sensor data useful for a hypoglycemic hypo-avoidance system to be sent to the insulin delivery device, for example, a hypoglycemic indicator may include information useful for determining when and for how long to suspend or reduce basal insulin delivery (e.g., predicted glucose value and prediction horizon, rate of change of glucose, static risk, dynamic risk) or may send the actual instructions (e.g., suspend basal delivery for 20 minutes).

[00133] In some embodiments, the alert and/or alert settings may be manipulated by a user or set one or more thresholds (e.g., from about 60-100 mg/dL). In some embodiments, the user can disable/enable the first and/or second functions. In some embodiments, a single message indicating an "early warning" or alert may be provided to the user. In some embodiments, particularly in the context of a closed loop or semi-

Abbott Ex. 1002 - 76/1438

closed loop systems, the settings are configured based on a control algorithm, which may be programmable or downloadable by a user.

[00134] In some embodiments, the alert may be selected from the group including: audible, tactile, visual and/or data transmissions (e.g., to a remote monitoring site) to subsequent audible, tactile and/or visual output to a user interface 222. For example, if a child host's alarm is activated, the data may be transmitted to a parent's smartphone (and the same or different alarm information may be provided). In such an example, the child host may receive an audible alarm, while the parent may receive a detailed glucose log. In some embodiments, if the first function determines that the first threshold is met first, an alert is provided to a user. In other embodiments, if the second function predicts that the second threshold will be met first, an alarm is provided to a user.

[00135] In some embodiments, a prediction alarm could trump a threshold alert to give a greater sense of urgency. For example, if the prediction alarm is associated with a reading of 55 mg/dL having a 20 minute prediction horizon, and the threshold alert is associated with a reading of 70 mg/dL, the prediction alarm indicator would be configured to control the alert screens and output.

[00136] In some embodiments, prediction alarm sounds/screens may convey a greater sense of urgency than the settable threshold alert. A rationale for having a differing sound/screen for alarms and alerts is to assist the user in understanding the difference between the two thresholds, e.g., that one may be a routine alert, while the other is indicative of a serious event. In some embodiments, whichever alert is met or predicted to be met first in time, is the alert conveyed to the user. It should be appreciated that these predictive and threshold alerts are different than target alerts, which may be used to "keep a user between the lines", such as described above with respect to Figures 3B and 4A. In some embodiments, information from the results of both the first and second sets of instructions may be combined and relayed on a user interface, whether or not they both met certain criteria. For example, a combined alert screen would include both a predictive alarm (e.g., an indication that the host is below the alert threshold (TV_2) and is predicted to be below predicted threshold TV_P within 20 minutes or an indication that the host is below the alert threshold (TV_2) but is not

Abbott Ex. 1002 - 77/1438

predicted to be below predicted threshold TV_P within 20 minutes). In some embodiments, additional information, such as therapy recommendations or requests for additional information may be displayed.

[00137] Once a hypoglycemic alert or alarm has been triggered, the processor module 214 may continue onto the post-alert monitoring, described in more detail below. Additionally or alternatively, where a system includes remote monitoring (e.g., a remote electronic device receiving and tracking a user, such as a parent's cell phone or a caretaker's personal computer), once a hypoglycemic alert has been triggered, and sent to the remote device, an increase in communication, data transmission, or the like, may be initiated to allow the caretaker or parent to more closely monitor the patient during hypoglycemic or predicted hypoglycemic events. The increase in communication or data transmission can include more frequent pushing and pulling of sensor data, additional input from or messaging to or from the remote device, or the like. The request for additional information may originate at the remote device and processor module 214 may be configured to receive and process such requests for additional information directly from the remote device.

Post-Alert Monitoring

[00138] Another issue commonly confronted with continuous glucose monitors, is that once an alert or alarm is triggered, the user may remain at or about the threshold value that triggered the alert, and may thereafter continue to trigger repeat or redundant alerts. Such alerts may be a nuisance to the user, causing them to suspend (e.g., snooze) alert/alarm feature of the monitor. A snooze that considers only time (e.g., rather than additional sensor data) may be undesirable, as there may be situations following the initial trigger of an alarm that would require an additional alarm to be provided to the user. If the user has suspended the alert/alarm feature, and suspend or "snooze" feature is solely time-based, the user may not be aware that they are in danger of approaching a hypoglycemic and/or hyperglycemic event during suspend or snooze time period.

[00139] Referring now to Figure 7, an example of a continuous trace of glucose values measured during a time frame showing different scenarios that may cause an alert/alarm to be repeated is shown. Similar to Figure 5, in Figure 7, the example

Abbott Ex. 1002 - 78/1438

continuous glucose trace may embody a graph having a glucose level e.g., mg/dL, compared against a time frame e.g., 24 hours.

[00140] As shown, there are three threshold values or limits used in the monitoring of the glucose values: TV_1, TV_2 and TV_P. These values have already been discussed in the Figure 5 discussion above.

[00141] In Figure 7, there is a region or zone defined between a first and second time point TA_{1S} and TA_{1E}. Time point TA_{1S} may generally be referred to as a time that the first alert begins or starts. Assuming the user has acknowledged the alert soon after Time point TA_{1S}, Time point TA_{1E} may generally be referred to as the time that the user's glycemic state changes. As shown, at TA_{1S}, a user may first be provided an alert that a threshold value TV_2 has been met. In the time interval following TA_{1S}, the user's glucose value generally hovers or oscillates around the same glucose level that triggered the initial alert, during which time re-alerts should not occur, and after which re-alerts should occur.

[00142] In some conventional systems, each time a user's glucose value would cross a threshold such as TV_1 and TV_2, the user would be alerted again that a threshold had been crossed. This would be annoying at best, and may even influence a user to turn off the alarms of the sensor following the first alert TA_{1S}. Further, if the user turned off or even "snoozed" or the one or more threshold alerts (e.g., at 80 mg/dl) using a simple time-based snooze, the user may not be aware of the worsening condition after TA_{1E}.

[00143] Still referring to Figure 7, the region or zone where the glucose value oscillates may be further defined by a first and/or second glucose threshold TV_{Z1} and TV_{Z2}. First glucose threshold value TV_{Z1} may generally be referred to as the upper region or zone limit for a value that oscillates around e.g., TV_2. Second glucose threshold value TV_{Z2} may generally be referred to as the lower region or zone limit for a value that oscillates around e.g., TV_2. In some embodiments, taken together, TV_{Z1} and TV_{Z2} provide a buffer zone, which also may be referred to as a margin (e.g., +/- 5, 10, 15% or +/- 5, 10, 15, 20 mg/dL) above and below a threshold value that would trigger an initial alert by which few, if any, repeat alerts are provided to the user. In other words, after the initial alert is provided to the user at TA_{1S} and the user acknowledges the alert, the user may not be re-alerted until after $TA_{1E,}$ e.g., when the glucose value exits the

Abbott Ex. 1002 - 79/1438

buffer zone (e.g., change in glycemic state). In some embodiments, TV_{Z1} and TV_{Z2} may have asymmetrical bounds and/or no lower bound (no TV_{Z2}). For at least the reason that the glucose trace scenario suggests, more intelligent and dynamic decision making may be advantageous such that a user is not overly alarmed in certain situations (e.g., between TA_{1S} and TA_{1E}), but sufficiently alarmed in other situations (e.g., after TA_{1E}). Such a buffer zone, also referred to as margins or deltas herein, may be bidirectional and/or asymmetrical depending on the condition.

[00144] Figure 8 is a flowchart illustrating a process 700 for dynamically and intelligently monitoring the hosts' glycemic condition after activating an alert state based on the sensor data meeting one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition, for example, as described with reference to block 540. Additionally, post alert monitoring may be applied for any alarm or alert, whether evaluating against multiple criteria as in blocks 520 and 530, or simply compared against a single threshold (e.g., hypoglycemic or hyperglycemic threshold). In some embodiments, the triggering of an alert or alarm is merely the flagging or marking of the alert or alarm, for example, some hyperglycemic alert conditions include a wait time (e.g., 0 to 120 minutes), for example, an "enable wait before first alert" option that the user can set/enable. When this input enabled, the wait time will be applied before alerting the user for the first time, as described in more detail elsewhere herein, unless the actively monitoring determines a worsening condition.

[00145] In some embodiments, the triggering of an alert or alarm includes providing the alert or alarm to the user. In general, the processor module may be configured to provide an output associated with the active alert state, wherein the output is indicative of the hypoglycemic condition or hyperglycemic condition. In some embodiments, the post-alert monitoring will begin regardless of whether a user has acknowledged the alert, where the acknowledgement will alter the post-alert state as described elsewhere herein. In some embodiments, post-alert monitoring begins with a transition from the active state to the acknowledged state.

[00146] Criteria for triggering an alert, also referred to as transitioning from an inactive state to active state or activation criteria, may be any criteria or threshold associated with hypoglycemia or hyperglycemia. Activation criteria may include glucose

Abbott Ex. 1002 - 80/1438

value, predicted glucose value, rate of change of glucose (direction and/or amplitude), rate of acceleration of glucose (direction and/or amplitude), static risk models, dynamic risk models, or the like. Additionally or alternatively, activation criteria disclosed for transitioning 1055 from inactive state 1030 to active state 1010 may initiate the dynamic and intelligent monitoring the hosts' glycemic condition after activating an alert state associated with hypoglycemia or hyperglycemia.

[00147] At block 710, processor module 214 may be configured to actively monitor data associated with the host's hypoglycemic or hyperglycemic condition for a time period following the triggering or an alert/alarm to the user (e.g., as described in Fig. 6 and associated text) and/or user acknowledgement. In some embodiments, the user or host has acknowledged the initial alert. As described in more detail elsewhere herein, acknowledgement of an alarm may include a user interaction with the system ("user action"), such as a button or menu selection, or other data input (e.g., meal or insulin information entered). Additionally or alternatively, acknowledgement of an alarm may be based on monitoring of data associated with the glycemic state, including sensor data, insulin data, meal data, or the like. In some embodiments, the acknowledgement may come from a remote monitor, such as a parent's cell phone, or the like. Acknowledgement of an alarm may cause the processor module 214 to transition from the active state to the acknowledged state, during which active monitoring may occur.

[00148] In some embodiments, processor module 214 actively monitors data associated with the host's hypoglycemic or hyperglycemic condition for a time period in the acknowledged state or continuously while in the acknowledged state until a state transition to inactive (e.g. based on inactivation criteria). In some embodiments, processor module 214 monitors sensor data or other data received post-alert activation. For example, the data may include information such as: sensor data (e.g., glucose levels, trends, distances between peaks and valleys indicative of meal timing, etc), sensor diagnostic information (noise indicators), meal information (e.g., caloric intake and time of intake), insulin information, or other event information. In some embodiments, actively monitoring data includes determining an average glucose over a window of time, an amplitude and/or direction of rate of change of glucose or an amplitude and/or direction of rate of acceleration of glucose.

[00149] In some embodiments, processor module 214 tracks how quickly and/or how often the user acknowledges the alarms to determine further processing. For example, patterns that evaluate timing of user acknowledgement, information about the type of alert that was triggered and/or resulting recovery from the condition may be evaluated and future acknowledgements or alerts modified based thereon. In general, however, the processor module 214 may process alarms based on the assumption that a user acknowledgement of the alert/alarm indicates the user is aware of the conditions. Accordingly, re-alert conditions may be different, e.g., more stringent, in some embodiments, as described herein.

[00150] In some embodiments, the sensor data is actively monitored during the acknowledgement time period, also referred to as the active monitoring time period. Suitable time periods include, for example, 20 minute, 40 minute, 60 minute, etc., time periods, and may be user settable. Such time periods may commence or begin at the first data point following the alert or alarm triggering data point. In some embodiments, the user may be allowed to select the time period. In some embodiments, the post-alert sensor data monitoring continues until the alert is inactivated, as described in more detail elsewhere herein.

[00151] At block 720, processor module 214 is configured to transition from the acknowledged state to at least one of an inactive state or active state responsive to the data associated with the host's hypoglycemic or hyperglycemic condition meeting one or more predetermined criteria. The processor module 214 may determine if there has been a change in state based on the sensor data or other data associated with the host's glycemic condition. In some embodiments, the change in state may be indicative of a change in the host's glycemic condition.

[00152] In some embodiments, a change in state may be a positive event, such as an indication that a user has safely turned around a predicted hypoglycemic event, which may trigger the acknowledged state to recognize a sub-state of recovery and/or inactive state, as described in more detail elsewhere herein. In other embodiments, a change in status may be a negative event, such as an indication that a user has dropped further toward a hypoglycemic event (e.g., acceleration/deceleration analysis of the sensor data) for a particular time period (e.g., 20 minutes), with or without a sub-state of recovery

being determined. In this second example discussing the negative event, it may be desirable to reactivate the alert, even when a user has acknowledged the alert. This second alert or alarm may be valuable in warning the user that his condition is declining – that whatever action he took following the first alarm, if any, was insufficient to turn around or improve his glucose reading. In some embodiments, a status change indicative of such a negative event may override an acknowledged state (described elsewhere herein), causing the system to transition back into an active alert state (also referred to as re-alert or reactivation). However, if the system was already in an active alert state (e.g., unacknowledged by a user), the resulting output may escalate, e.g., louder and more frequent, and/or may result in a communication with 911, a care taker, or the like.

[00153] In some embodiments, processor module 214 may be configured to determine no change has occurred over the last x minutes, for example 15, 30, 45 or 60 minutes, such as described with reference to conditions associated with remaining in a particular state (e.g., active state) and/or reactivation conditions as described in more detail elsewhere herein. No change may occur, for example, in situations where the data points are hovering around the threshold value that triggered the initial alert (e.g., with low rates of change). It may be appreciated that in such situations, each time a data point crosses the threshold in an undesirable direction, e.g., below a threshold for a hypoglycemic event or above a threshold for a hyperglycemic event, an alert or alarm would be triggered in conventional systems. This is typically thought of as a nuisance, and may be a reason a user would act to turn off his alerts or become desensitized to the alerts. In these situations, the intelligent post-alert monitoring algorithms would likely avoid these annoying alerts (e.g., as long as a user remains in the same state and/or reactivation conditions have not been met, which are described in more detail elsewhere herein).

[00154] As used herein, the user may be in different monitoring "states" such that processor module 214 can detect when the user transitions from one state to another. Examples of such states include, for example, "active", "inactive" and "acknowledged".

[00155] The active state is herein defined as an alert state post-alert trigger, where data is being monitored to determine whether to change the alert state to "acknowledged" or "inactive." The active state may be entered from an inactive and/or

acknowledged state by comparing data (sensor, glucose, insulin, user provided information, etc.) against different criteria, respectively for each state transition. Re-alerts and/or reactivation of the alerts may occur in this state, which escalate the initial alert, even when an acknowledgement has not occurred.

[00156] The inactive state is herein defined as an alert state post-alert trigger, where evaluation of data indicates the glycemic state is in a safe or target zone. The inactive state may be entered from an active and/or acknowledged state by comparing data (sensor, insulin, user provided information, etc.) against different criteria, respectively for each state transition.

[00157] The acknowledged state is herein defined as an alert state post-alert trigger, where the user has acknowledged an alert and/or alarm and where no additional alerts/alarms will be provided for a predetermined time period, unless certain re-activation criteria are met (wherein the reactivation criteria are different and/or more stringent that the initial activation criteria, for example, which is described in more detail elsewhere herein). The acknowledged state may be entered from the active state based on user interaction and/or data indicative of a recovery from the hyper- or hypoglycemic condition. It should be appreciated that the terms used herein for the states and/or functions are merely descriptive and may go by other names, provided the functions remain substantially the same.

[00158] In some embodiments, a user may acknowledge an alert by pressing a button, selecting a menu screen, or the like. In some embodiments, a timer is set for a predetermined time period when the system enters the acknowledged state, after which predetermined time period the state may automatically transition into active and/or inactive based on selected conditions.

[00159] In some embodiments, the acknowledged state evaluates data associated with the hosts' glycemic condition (including glucose, meal and/or insulin information) and may transition into the acknowledged state based on the evaluation indicating the host's recovery from the glycemic condition that triggered the alert. The host's recovery may be also considered as a sub-state of acknowledged and may be determined by comparing data (sensor, glucose, insulin, user provided information, etc.) against different criteria, respectively for each state transition. Re-alerts may be suspended for

Abbott Ex. 1002 - 84/1438

some time period, when in the acknowledged state and/or acknowledged and recovering sub-state.

[00160] In some embodiments, if the user does not acknowledge the alert, the alert remains in active state. In some embodiments, if the user does not acknowledge the alert after X minutes (e.g., 5, 10, 15 minutes), the alert may be escalated via output to a secondary display device, a remote monitor, emergency contact, etc. Similarly, if the conditions worsens during active monitoring (e.g., in acknowledged state), the alert may be escalated via output to a secondary display device, remote monitor, emergency contact, etc.

[00161] An example showing the various transitions from one state to another is provided in the discussion of Figure 11 below. It should be appreciated that using different states to describe that user or host's glycemic condition is useful in tracking the user's condition after an alert or alarm has been triggered. Thus, certain trends, such as a user's glycemic condition improving or just hovering about a non-serious alert may be reason enough to discontinue alerting the user. However, other trends, such as a user's rapid decline in glycemic condition or even hovering about a serious alert, may be reason to continue to warn or alarm the user. A number of suitable responses (e.g., associated with reactivation of an active alert) may be saved in an e.g., lookup table, depending on the state transition and other known information.

[00162] Referring now to Figure 11, a state diagram 1000 is provided that shows the transitions between the following states: active (A) 1010, acknowledged (K) 1020, and inactive (I) 1030. These states and their transitions may be described as follows:

[00163] Upon activation of an alert, the processor module transitions (1055) from an inactive state (1030) to an active state (1010). Conditions for activation include various criteria or thresholds, hereinafter referred to as "activation criteria" or "activation conditions", useful for detecting actual or upcoming hyperglycemia or hypoglycemia, such as described in more detail elsewhere herein (e.g., Fig. 6). Alert conditions are met as designated by reference numeral 1055. In addition to sensor data (glucose values, derivatives (rate of change) and double derivatives thereof (acceleration)), alert conditions may relate to other data including insulin data and/or user input (meal information, exercise information, etc.). Additionally, embodiments discussed herein

with respect to reactivation may be applied here (e.g., analysis of static risk and/or dynamic risk). However, regardless of the detection method for an active hypoglycemic or hyperglycemic condition, the disclosed active monitoring and state transitions may apply.

[00164] In some embodiments, certain of the following activation conditions may apply for a state transition from inactive to active based on a hyperglycemic condition: the glucose level exceeds a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); the average glucose level over a predetermined time period (e.g., 10, 20, 30, 40 minutes) is more than a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); the current glucose level is more than a predetermined threshold plus a predetermined margin (e.g., 25, 50, 75 mg/dL); and/or the rate of change of glucose is greater than a predetermined threshold (e.g., - 0.5 mg/dL).

[00165] In some embodiments, the following activation conditions may apply for a state transition from inactive to active based on a hypoglycemic condition: glucose level is less than a predetermined threshold (e.g., 80, 60, 60 mg/dL); glucose level is less than a predetermined threshold and rate of change is less than is a predetermined rate (1.0 mg/dL/min, e.g., not rising rapidly); or glucose level is predicted to go below a second threshold (e.g., 55 mg/dL) within a prediction horizon (e.g., 10, 15, 20 minutes).

[00166] In some embodiments, transitioning (1080) from the active state (1010) to an acknowledged state (1020) is based on data or acknowledgement criteria indicative of the host's glucose trending toward euglycemia, wherein the data may include sensor data indicative of a change in glucose trend and/or insulin information associated with a correction of the condition.

[00167] For example, upon activation of an alert indicative of hyper- or hypoglycemia, sensor data indicative of a change in glucose trend may include evaluating sensor data whereby a direction and/or amplitude of glucose level, rate of change of glucose level or acceleration/deceleration of glucose level indicative of a trend back toward euglycemia (e.g., change in direction or trend) is sufficient to automatically transition from active to acknowledged state (with or without user interaction with a user interface). A trend back toward euglycemia may also flag or trigger a "recovering" sub-state, which is a status within the acknowledged state indicative of trend back toward

Abbott Ex. 1002 - 86/1438

euglycemia. In one example, after an active transition associated with a hyperglycemic condition, a state transition to acknowledged, but recovering sub-state, may be based on an acknowledgement criteria or condition such as the glucose level (or average glucose level over a predetermined time period) is less than a predetermined threshold minus a delta (e.g., 10, 15, 20 mg/dL), and in some examples with a condition on rate of change trending toward euglycemia (e.g., decreasing faster than about 1 mg/dL/min). Similarly, after an active transition associated with a hypoglycemic condition, a state transition to acknowledged, but recovering sub-state, may be based on an acknowledgement criteria or condition such as the glucose level (or average glucose level over a predetermined time period) is greater than a predetermined threshold plus a delta (e.g., 10, 15, 20 mg/dL), and in some examples with a condition on rate of change trending toward euglycemia (e.g., increasing faster than about 1 mg/dL/min).

[00168] In some embodiments, transitioning (1075) from the active state (1010) to an acknowledged state (1020) is based on acknowledgement criteria indicative of a user acknowledgement of the alert on a user interface, user input insulin information and/or user input of meal information. For example, the user may hit a touch screen "button" to acknowledge the alert. Additionally or alternatively, when the continuous glucose sensor is operably connected to an insulin delivery device (including a remote programmer associated therewith), changes associated with basal or bolus delivery profiles or amounts may be considered as user input, particularly when the change was initiated by user interaction. Similarly, when the continuous glucose sensor is operably connected to an electronic device (or integral with the electronic device) capable of receiving meal information (e.g., carbohydrates and timing of consumption), such meal information may be considered as user input. In some embodiments, user input may come from another electronic device (e.g., via remote monitoring from a parents' smart phone, or the like).

[00169] In some embodiments, transitioning (1085) from the acknowledged state (1020) to the inactive state (1030) is based on the sensor data no longer meeting one or more active transition criteria associated with a hypoglycemic condition or hyperglycemic condition and/or based one or more inactive transition criteria (e.g., that may be different from the one or more active transition criteria associated with the a

Abbott Ex. 1002 - 87/1438

hypoglycemic condition or hyperglycemic condition (e.g., associated with the initial alert). Additionally or alternatively, transitioning (1080) from the acknowledged state to the inactive state may be based on insulin data and/or meal information. In some embodiments, transitioning (1090) includes a time element, for example, after the expiration of an acknowledgement (active monitoring) time period, which may be fixed and/or user settable.

[00170] Inactivation criteria for transitioning from acknowledged to inactive may be similar to or the same as conditions for inactive to active (except that acknowledged state would be entered when the one or more first or second criteria (e.g., see Figure 6) were not met and/or for transitioning from active to inactive. In some embodiments, certain of the following inactivation criteria or conditions may apply for a state transition from acknowledged to inactive based on a hyperglycemic condition: the average glucose level over a predetermined time period (e.g., 10, 20, 30, 40 minutes) is less than a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); minus a predetermined delta (e.g., 10, 15, 20 mg/dL); the acknowledge time period has expired and the glucose level is less than a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); and/or the rate of change of glucose is dropping at a predetermined rate.

[00171] Alternatively, the inactivation criteria for transitioning from acknowledged to inactive may be different (e.g., more stringent). In addition to sensor data, other data including insulin data and/or user input may be considered for the state transition criteria. In some embodiments, the following inactivation criteria or conditions may apply for a state transition from acknowledged to inactive based on a hypoglycemic condition may include determining whether the glucose value has increased by more than a predetermined amount (e.g., 10, 15, 20 mg/dL, which may be indicative of some user action) and whether the glucose value has risen above the threshold condition (e.g., from the first function). Inactivation conditions for the real-time alert (first function) and predictive alert (second function) may be the same or different. In some embodiments, a positive glucose rate of change (increasing rise rate) exceeding a certain value may be used as a condition because it may be assumed that the rise rate is indicative of the user taking some preventive action. In some embodiments, the rise rate condition may be

Abbott Ex. 1002 - 88/1438

combined with a glucose value threshold condition. In some embodiments, the glucose value rise rate condition is 0.25, 0.5, or 1 mg/dL/min.

[00172] In some embodiments, in cases where a hypoglycemic condition has triggered an active state, and active monitoring after user acknowledgement, the state may transition from acknowledged state to inactive state prior to the expiration of the acknowledgement time period based on inactivation criteria or data indicative of hypoglycemic conditions significantly improving for example, a determination that the host's glucose level is greater than the low threshold plus a delta and the predicted glucose level for the prediction horizon is more than some predetermined limit (which may be the same or different from that prediction horizon or threshold of initial activation).

[00173] In some embodiments, transitioning (1060) from the acknowledged state (1020) to the active state (1010) is based on the one or more activation criteria associated with a hypoglycemic condition or hyperglycemic condition being met and based on an expiration of a predetermined time period. Activation criteria for transitioning from acknowledged to active may be any of the same conditions for initially alerting or may be different (e.g., based on glucose trending away from euglycemia). In addition to sensor data, other data including insulin data and/or user input may be considered for the state transition criteria. Additionally embodiments discussed herein with respect to reactivation may be applied here.

[00174] In some embodiments, reactivation criteria for transitioning (1065) from acknowledged state (1020) to active state (1010) may be different than criteria for initially transitioning to active state. For example, even when the user has acknowledged the alert (during the active monitoring and/or acknowledged time period), a worsening condition may indicate a need for a re-alert based on sensor data indicative of worsening glycemic conditions, such as the second function meeting one or more criteria and/or the sensor data indicative of glucose further trending away from euglycemia based one or more criteria indicative of worsening.

[00175] In some embodiments, the following reactivation criteria or conditions may apply for a state transition from acknowledged to active based on a hypoglycemic condition after acknowledged time has expired: glucose level is less than a predetermined

threshold (e.g., 80, 60, 60 mg/dL); glucose level is than a predetermined threshold and rate of change is less than is a predetermined rate (e.g., 1.0 mg/dL/min, e.g., not rising rapidly); or glucose level is predicted to go below a second threshold (e.g., 55 mg/dL) within a prediction horizon (e.g., 10, 15, 20 minutes). However, in some embodiments, reactivation criteria indicative of a worsening hypoglycemic condition may case a state transition from acknowledged to active prior to expiration of the acknowledged time period (re-activation or re-alert) based on one or more re-alert criteria (e.g., different from criteria for initial alert), some of which are described in more detail elsewhere herein. In some embodiments, an alert activated by the first function (at 520) may trigger a re-alert or re-activation during the acknowledgement time period (transition to active prior to expiration of time period) if the second function meets the second criteria (at 530).

[00176] In some embodiments, the activation criteria associated with a hyperglycemic condition to transition from acknowledged to active may include a determination of whether: the glucose level exceeds a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); the average glucose level over a predetermined time period (e.g., 10, 20, 30, 40 minutes) is more than a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); the current glucose level is more than a predetermined threshold plus a predetermined margin (e.g., 25, 50, 75 mg/dL); and/or the rate of change of glucose is greater than a predetermined threshold (e.g., - 0.5 mg/dL per minute).

[00177] In some embodiments, transitioning (1065) from the acknowledged state (1020) to the active state (1010), also referred to as reactivation, occurs after determining data is indicative of the host's glucose trending toward euglycemia, also referred to as the recovering sub-state, and the subsequently trending away from euglycemia during the active monitoring time period (based on one or more criteria). In other words, a rebound situation may occur, after an active alert, when a user's glycemic condition initially trends towards euglycemia (recovering), but subsequently trends back towards the hyper- or hypoglycemic condition. Accordingly, reactivating the first alert state during the acknowledgement time period may be by the data associated with the host's hypoglycemic or hyperglycemic condition meeting one or more rebound (e.g., reactivation) criteria indicative of a rebound situation. In general, criteria for transitioning from recovering to active may be any of the same conditions for initially

Abbott Ex. 1002 - 90/1438

alerting or may be different (e.g., a reversing trend of glucose value, rate of change or acceleration). In some embodiments, the one or more rebound criteria include conditions indicative of the host's glucose trending toward euglycemia (e.g., recovering sub-state) and subsequent conditions indicative of the host's glucose trending away from euglycemia during the active monitoring time period. In addition to sensor data, other data including insulin data and/or user input may be considered for the state transition criteria. Additionally embodiments discussed herein with respect to reactivation may be applied here.

[00178] In some embodiments, transitioning (1070) from active state (1010) to inactive state (1050) may be any of the same conditions for initially alerting (except that inactive state would be entered when the one or more first or second criteria (of Figure 6) were not met). Alternatively, the inactivation criteria for transitioning from active to inactive may be different (e.g., different thresholds). In addition to sensor data, other data including insulin data and/or user input may be considered for the state transition criteria. In one example, a transition from active to inactive is based on the alert conditions no longer being met, e.g., EGV and delta EGV as described in more detail elsewhere herein.

[00179] In some embodiments, certain of the following inactivation criteria or conditions may apply for a state transition from active to inactive based on a hyperglycemic condition: the average glucose level over a predetermined time period (e.g., 10, 15, 30, 45 minutes) is less than a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL) minus a predetermined delta (e.g., 10, 15, 20 mg/dL); the glucose level over a predetermined time period (e.g., 10, 15, 30, 45 minutes) goes below a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL) minus a predetermined delta (e.g., 10, 15, 20 mg/dL); the average glucose level over a predetermined time period is less than a predetermined threshold; and/or the rate of change of glucose is falling (negative) at greater than a predetermined rate (e.g., 1 mg/dL/min).

[00180] In some embodiments, certain of the following inactivation criteria or conditions may apply for a state transition from active to inactive based on a hypoglycemic condition: the average glucose level over a predetermined time period (e.g., 10, 15, 30, 45 minutes) is greater than a predetermined threshold (e.g., 60, 70, 80 mg/dL) plus a predetermined delta (e.g., 10, 15, 20 mg/dL); the glucose level over a

Abbott Ex. 1002 - 91/1438

predetermined time period (e.g., 10, 15, 30, 45 minutes) goes above a predetermined threshold (e.g., 60, 70, 80 mg/dL) plus a predetermined delta (e.g., 10, 15, 20 mg/dL); the average glucose level over a predetermined time period is more than a predetermined threshold; and/or the rate of change of glucose is increase (positive) at greater than a predetermined rate (e.g., 1 mg/dL/min).

[00181] For example, in some embodiments, the criteria to get out of the acknowledged state, where the acknowledgement is based on data user acknowledgement (e.g., pressing button), to either an inactive state or active state (e.g., reactivation) are different from the criteria to get out of acknowledged state, wherein the acknowledgement is based on user action detected (e.g., recovery detected by monitoring of data). This acknowledgement based on user action detected is described in more detail below in the acknowledgement sub-state recovery discussion. For example, to go from the acknowledged state, where the acknowledgement is based on data user acknowledgement, to the inactive state, certain first criteria may apply (e.g., criteria that allow for oscillations around the threshold without inactivation occurring, or, in other words, criteria that ensure the user is not merely oscillating around the threshold). In contrast, to go from the acknowledged state, where the acknowledgement is based on user action detected (recovery sub-state), to the inactive state, certain second criteria may apply (e.g., the second criteria do not consider oscillations, but rather consider the data confirming the user's detected successfully recovered into euglycemia.

[00182] As mentioned above, the conditions or criteria for reactivation may be more stringent than for the initial activation. Similarly, the reactivation criteria to get out of the acknowledged state, where the acknowledgement is based on user acknowledgement (e.g., pressing a button), to the active state may be different from the reactivation criteria to get out of acknowledged state, wherein the acknowledgement is based on user action detected (e.g., recovery detected by monitoring of data). In some embodiments, the reactivation criteria for the transition from acknowledged (based on user acknowledgement) to active, may be time-based or could include a stringent second set of criteria (e.g., change greater than 200 mg/dL). In contrast, the reactivation criteria for the transition from acknowledged (based on user action detected, recovery sub-state) to active, may include recognizing a reversing trend or a worsening, etc. indicative of

rebound conditions, based on monitoring of the sensor data. Example worsening of conditions may include or be based on a strong change in glucose away from a target, and could be based on glucose level (g), amount of glucose change (Δg), rate of glucose change ($\Delta g/t$), rate of acceleration, or combinations thereof.

[00183] Referring back to Fig. 8, at block 730, processor module 214 may be configured to process a response to an alert state change or transition. In some embodiments, processor module 214 may include instructions or criteria on how to process an appropriate response for a status change. In some embodiments, such responses may be stored in e.g., a lookup table, or the like. In some embodiments, the output associated with a transition to the active state is different from the output associated with a transition from the acknowledged state to the active state and/or different from a transition from the acknowledged state to an inactive state.

[00184] It should be appreciated that depending on the status change there may be one or more possible and/or appropriate responses. For example, if sensor data indicates that a user has stabilized his glucose value and come down sufficiently from a hyperglycemic event (e.g., active to inactive state transition), a particular type of alert indicating a positive status change or kudos may be provided. The kudos may have a particular sound, e.g., particular pitch or number of chimes. In some embodiments, the user may be able to customize or select the alert signature, similar to that currently available to smart phone users.

[00185] In other embodiments, a particular type of alert indicating a negative status change or warning may be provided (e.g., transitioning back to active state). The warning may also have a particular sound and may, in some instances, be customizable by the user. In some embodiments, the severity of the warning may be reflected by the sound itself of the warning, e.g., the warning may be louder or more intense or maybe sound similar to a recognizable distress sound. In some embodiments, a re-alert or follow up alarm may be different than the initial alert.

[00186] State transitions are described in more detail elsewhere herein; however, it should be appreciated that any of a variety of indicators may be provided audibly, tactilely, visually and/or communicated via data transfer, based on preset or user selectable options.

Abbott Ex. 1002 - 93/1438

[00187] At block 740, processor module 214 is optionally configured to output information associated with the state transition, for example, to provide an alert or alarm or kudos if warranted by the detection of a state or status change. In some embodiments, wherein the output associated with a transition to the active state is different from the output associated with a transition from the acknowledged state to the inactive state and/or active (reactivation) state. In some embodiments, the alert or alarm or kudos may be subject to a time restriction, e.g., such as if the user has pushed an acknowledgement on alerts. This may disable the user from receiving alerts/alarms/kudos in all but a handful of situations, such as where the alarm is characterized as a reactivation condition, as described in more detail with reference to Figure 9.

[00188] Some use cases arise, wherein immediate notification of an alert may not be advantageous. For example, post-prandial glycemic excursions are normal for people with diabetes, even with insulin injections, or people without diabetes. In some circumstances, alerting a user about glycemic excursions of which they are already aware may lead to frustration and desensitization of the alarms. It may be preferable to wait and determine whether the host's glycemic excursion follows a normal course of recovery before alerting them. Accordingly, in some embodiments, the processor module may be configured to provide output associated with a first alert state after waiting a predetermined time period, wherein the output is based on the data associated with the host's hyperglycemic condition meeting one or more second criteria after the predetermined waiting time period. Thus, it would follow that the processor module 214 may be configured to not provide output associated with the first alert state after the waiting time period based on the data associated with the host's hyperglycemic condition not meeting the one or more second criteria, thereby allowing the state to transition to the active state and back to the inactive state without alerting and/or otherwise providing output to a user. In these embodiments, the one or more first criteria and the one or more second criteria may be the same may be different and the waiting time period may be fixed or user selectable. For example, the one or more second criteria may include determine whether: the glucose level exceeds a predetermined threshold (e.g., 160, 180, 200, 220 mg/dL); the average glucose level over a predetermined time period (e.g., 10, 20, 30, 40 minutes) is more than a predetermined threshold (e.g., 160, 180, 200, 220

mg/dL); the current glucose level is more than a predetermined threshold plus a predetermined margin (e.g., 25, 50, 75 mg/dL); estimated time to a threshold (e.g., based on rate of change of glucose) and/or the rate of change of glucose is greater than a predetermined threshold (e.g., - 0.5 mg/dL per minute).

[00189] Figure 9 is a flowchart 800 illustrating an example process for determining when to re-alert and/or for determining a state transition post-alert activation from acknowledged back into an active state, also referred to as reactivation conditions, in accordance with an embodiment of the disclosure. In some embodiments, reactivation conditions have different criteria for going into an active alert state (providing alert output) as compared to an initial trigger of the active alert state, e.g., as described with reference to Figure 6, in order to avoid unnecessary "flickering" re-alerts.

[00190] At block 810, processor module 214 may be configured to determine if one or more sensor data points is within a predetermined or predefined zone during a predetermined time period post-alert trigger, in one example embodiment. Such predetermined or predefined zone may include a region above and/or below the threshold that triggered the initial alert provided to the user. For example, referring back to Figure 7, TV_{Z1} and TV_{Z2} may provide a buffer zone or envelope above and below a threshold value. In some embodiments, the predefined zone is a zone that defines a range surrounding a value that triggered the first alert. For example, the predefined zone may be 10 mg/dL above the value that triggered the first alert and/or 10 mg/dL below the value that triggered the first alert.

[00191] In some embodiments, a data point in a predefined zone is indicative of no status change. In such embodiments, no further action is performed. In embodiments utilizing state transitions, assuming the user has acknowledged the alert/alarm (or based on data analysis), the acknowledged alert state remains and no transitions to either inactive or active will occur. In contrast, if a sensor data point moves outside the zone, the state remains in acknowledged and may be actively monitored (e.g., for recovery or worsening based on certain criteria indicative of the host's glucose level trending towards or away from euglycemia), or for transition to inactive if the sensor data moves towards euglycemia based on a second (more stringent that first) one or more criteria, or transitions to active (e.g., reactivation if the sensor data moves away from euglycemia

based on additional one or more reactivation criteria). For example, if the user transitions from the acknowledged state to the active state, the user may be re-alerted.

[00192] At block 820, processor module 214 also may be optionally configured to determine if a user has acknowledged an alert, as described in more detail elsewhere herein, whereby alerts or alarms are not provided to a user for a set time period, e.g. 30 minutes. In some embodiments, processor module 214 may be configured to determine if a user has taken some sort of action independent of the sensor during the predetermined time period post-alert trigger. For example, the user may have eaten or increased insulin since the initial alarm, which would likely lead to a noticeable change in glucose levels. The user may or may not input this type of information on the sensor. However, certain types of changes, e.g., insulin update, may have identifiable patterns that the processor module 214 may be able to determine was a user action, such as a change in glucose level, direction, rate of change, or acceleration/deceleration.

[00193] At block 830, processor module 214 may be configured to determine if a reactivation condition has been met by one or more sensor data points. As used herein, a "reactivation condition" refers to a condition that would cause an alert or alarm to be provided to the user after the initial alert, during the "acknowledged time period" when a user isn't expected to receive additional unnecessary alerts (e.g., a state transition from the acknowledged state to active state). Generally speaking, the reactivation condition will more likely than not relate to alarms for events considered to be dangerous to a user's health, e.g., a severe hypoglycemic event. In some embodiments, a reactivation condition may be thought of as a condition or event that would cause a host or user to change from acknowledged into an active state, as discussed with respect to Figure 11.

[00194] Additionally, because the reactivation may have been unexpected or responsive to an attempt to suppress, the output associated with the reactivation may be more noticeable or different from other alarms, for example, by displaying explanatory information or questions of actions taken and/or by escalating the alarms as may be appreciated by one skilled in the art.

[00195] Figure 10 is a flowchart 900 illustrating an example process for determining if a reactivation condition is met in accordance with an example embodiment of the disclosure. At block 910, processor module 214 may be configured to determine if

one or more sensor data points is outside a predetermined or predefined zone. For example, as shown in Figure 7, there may be regions or zones that data points seem to oscillate around after an alert has been provided to a user. Once a data point is determined to fall outside this predefined zone, it may be indicative of a user's glucose level moving toward an undesirable value or in an undesirable trend (e.g., trending away from euglycemia).

[00196] At block 920, processor module 214 may be configured to determine, depending on whether the data point has a high or low value, e.g. is within a range of the high or low threshold indicative of a hyperglycemic event or a hypoglycemic event, respectively, what direction and/or rate the data is moving or trending. Additionally, in some embodiments, the processor module 214 may be further configured to consider user input and/or insulin information as variables in assessing whether or not a reactivation condition has been met.

[00197] As may be appreciated, having a reactivation condition may also be thought of as intelligent acknowledged conditions, because it limits the number of alerts that may be provided to the user following a first alert. This can help ensure that a user is not annoyed by a series of additional alerts going off after the first alert, but allows for more intelligence and safety than a simple time-based snooze. In some embodiments, data points that may be considered to qualify as reactivation conditions may be predetermined by or fixed by factory settings. Such reactivation conditions may be stored, for example, in a lookup table.

[00198] In some embodiments, reactivation is intended to re-alert users when they have taken an action that is inadequate and returned to a dangerous zone. For example, after a low threshold alert the user may eat something that starts to increase their glucose but it is not enough so their glucose drops again. It is desirable to alert the user again in this situation, but it should be distinguishable from oscillating/annoying alarms. This may be achieved by e.g., setting criteria of glucose rising some distance above the low threshold and then falling below, or rate of change increasing to e.g., above 1 mg/dL/min and then going negative again.

[00199] In some embodiments, following the first or initial alert to the user, the user may suspend additional alerts by acknowledging the initial alert. For example, when

Abbott Ex. 1002 - 97/1438

a user or host acknowledges the initial alert, additional alerts are suspended for a time period, except for re-alert conditions. In other words, following a threshold or predictive alert, the user would not hear another threshold or predictive alert immediately after, but would instead wait for a time period, e.g., 30 minutes. In some embodiments, the suspend time is user settable. In some embodiments, the user may have a default of 30 minutes and a maximum of e.g., 2 hours for safety.

[00200] In some embodiments, a post-alert set of instructions or algorithms may be used to detect the end of a hypoglycemic and/or hyperglycemic event transition to a recovering sub-state such that re-alert only occurs if another event occurs (e.g., rise of 5 mg/dL about threshold, upward slope greater than 1 mg/dL/min, etc.). In such embodiments, this can help prevent an annoying situation of stable glucose oscillating around 80 mg/dL and setting off threshold alert over and over, as described above.

[00201] In some embodiments, alerts may be generated if the user remains in the same condition, e.g., just below 70 mg/dL, for a long period of time because the length of time hypoglycemic may also be considered a health risk.

EXAMPLES

[00202] A number of examples are provided below. When referring to a "low" threshold, it should be understood that the low threshold relates generally to a low glucose value that may be indicative of a hypoglycemic event. Similarly, when referring to a "high" threshold, it should be understood that the high threshold relates generally to a high glucose value that may be indicative of a hyperglycemic event. As used herein, the glucose values may be estimated glucose values (EGVs) or any known type of glucose indicator or sensor data.

[00203] It should be appreciated that the following examples may be implemented according to the flow charts described above. The examples relate to specific implementations and are provided for a more in-depth understanding of how the disclosed processes can operate. The examples should not be construed as limiting, but rather as a general guide on how certain aspects may be performed.

Example 1: Low threshold alert

Abbott Ex. 1002 - 98/1438

[00204] In this example, the processor module may be configured to receive sensor data (510) and evaluate the sensor data using a first function (520) to determine whether the "real-time" glucose value has crossed a first threshold (80 mg/dL) and using a second function (530) to determine whether the predicted glucose value will cross a second threshold (55 mg/dL) within 15 minutes (PH). The processor module may be configured to actively monitor data (710) associated with glycemic condition after a hypoglycemic indicator has been triggered based on the first or second function to determine whether a state change transition should occur. In this example, the following three inactivation conditions exist (to transition from active or acknowledged to inactive): 1) if the glucose value increases by more than a predetermined amount (15 mg/dL) and the glucose value is above the first threshold (80 mg/dL) since activation of the hypoglycemic indicator; 2) the rate of change of glucose is increasing at a rate greater than a predetermined value (1 mg/dL/min); and 3) the acknowledged time period is over (30 minutes).

Scenario A- glucose level is more than a low threshold

[00205] In this scenario, a hypoglycemic indicator is triggered based on the first function (host's glucose goes below 80 mg/dL), and the user is alerted via a user interface (visually and audibly). The user acknowledges the alert by pressing a button and the state transitions to the acknowledged state. In the acknowledged state, the processor module actively monitors the host's glycemic condition as the glucose value goes down to 65 mg/dL, then starts coming back up and reaches 75 mg/dL, but then starts falling again. In this example, the acknowledged state will remain for 30 minutes during which the user will not receive any additional alerts, during active monitoring the processor module determined the user's glucose to be recovering (coming back up and reaching 75 mg/dL), which triggered the recovering sub-state of acknowledged. The user will not be alerted until his/her glucose reaches a reactivation or inactivation condition. In the acknowledged state, recovering sub-state, criteria for re-alert may include any condition indicative of a glucose "rebound." Advantageously, the recovering sub-state takes advantage of the fact that some user interaction was detected, thus it can be assumed that the user has attempted to treat him/herself and should be re-alerted only if the user's action was not sufficient and a rebound (e.g., predetermined reversal of trend or

Abbott Ex. 1002 - 99/1438

worsening of glucose) is detected. In this scenario, the state transitioned back to active when the glucose started falling again (i.e., based on reactivation conditions), and the user was re-alerted.

Scenario B- glucose level oscillating around the threshold

[00206] In this scenario, a hypoglycemic indicator is triggered based on the first function (host's glucose goes below 80 mg/dL), and the user is alerted via a user interface (visually and audibly), but this time the host's glucose stays in the range 70-90 mg/dL going above and below 80 mg/dL several times. Once the user acknowledges the alert, the acknowledged state is maintained and the user will not get any alerts until the acknowledged time is over. In other words, the states do not transition back and forth from active to inactive, causing re-alerts as the user oscillates above and below 80 mg/dL. Advantageously, this avoids annoying alerts by allowing for some buffer to avoid flickering of the alert off and on. If the user does not acknowledge, there may be re-alerts every 5 minutes (maintains in active state until acknowledged by the user). However, it is important to note that the alert is not a conventional "threshold" alert. Instead, it is an "early warning" alert and as a result warning the user of the condition is reasonable. After the acknowledged time is expired, the state will transition to either or active or inactive depending on whether the alert conditions are still met. The state will transition to active and the alert may be shown only if the EGV is still below the threshold of 80 mg/dL (e.g., if the acknowledged time is 30 minutes and after 30 minutes, the EGV is 75 mg/dL, the user will get an alert). The state will transition to inactive and the user will not get an alert if the EGV is 85 mg/dL (unless the fall rate predicted is enough to trigger the alert).

Scenario C – Prediction followed by crossing the threshold

[00207] In this case, the user's glucose value is 100 mg/dL, and is predicted to reach 55 mg/dL in 15 minutes as determined by the second function (530). The active state is triggered and the alert is displayed to the user (according to block 550). Once the user acknowledges, the acknowledged state is maintained until the glucose value falls to 80 mg/dL (the low threshold) in 10 minutes, at which time the state remain as acknowledged as the host's glucose remains around 80 mg/dL for 20 minutes. Notably,

Abbott Ex. 1002 - 100/1438

no alert will be triggered when 80 mg/dL is reached (acknowledged state maintained), the state will transition back to active after 30 min if the threshold condition is met.

Example 2: Actionable alerts associated with hyperglycemic conditions

[00208] Advantageously, the user may be alerted only when it is likely that a user action is necessary. In one such example, the user may still be alerted as soon as the glucose value crosses an alert threshold. However, a user may also select to enable the wait time under certain conditions, for example, when a hyperglycemic excursion is correlated with known meal ingestion. In some embodiments, whether or not the wait time is enabled, annoying repeated alerts when the glucose value oscillates around the threshold may be minimized or eliminated, while ensuring that if the glucose value crosses the threshold twice due to reasons that are likely not related, then the user is alerted. For example, the user may be alerted once after the glucose value goes high due to carbohydrate intake (hyperglycemic alert) or not at all. Then the user takes insufficient amount of insulin, which causes the glucose value to go down a little bit, but comes back up once more.

[00209] Figure 12 is an example graph showing average EGV is high over last T minutes. Notably, the user's glucose level crossed the predetermined hyperglycemic threshold at the beginning of T minutes, and the processor module transitioned to the active state 700 based on the (first) active transition criteria of the glucose level exceeding a first predetermined hyperglycemic threshold level of 180 mg/dL, thereby triggering the dynamic and intelligent monitoring of the host's glycemic condition. However, the user was not alerted because the user had enabled a predetermined wait time period (T) of 60 minutes before high alert. During the 60 minutes, the processor module actively monitored the host's glycemic condition using one or more hyperglycemic (second) criteria based on the average glucose over the predetermined wait time period, after which the glucose level was determined to be greater than the predetermined threshold level (180 mg/dL), resulting in output associated with the alert at 1200. In this case, the active state was initiated based on the first criteria (glucose level exceeding a threshold), but the alert was not provided to the user until the second criteria was met (based on average glucose level over the wait time exceeding a threshold).

Abbott Ex. 1002 - 101/1438

[00210] Figure 13 is example graph showing average glucose is high, but falling rapidly, thus no alert is provided to the user or host because, although the average glucose level is high, the glucose level is falling rapidly. Notably, the user's glucose level crossed the predetermined hyperglycemic threshold at the beginning of T minutes, and the processor module transitioned to the active state 700 based on the (first) active transition criteria of the glucose level exceeding a first predetermined hyperglycemic threshold level of 180 mg/dL, thereby triggering the dynamic and intelligent monitoring of the host's glycemic condition. However, the user was not alerted because the user had enabled a predetermined wait time period (T) of 60 minutes before high alert. During the 60 minutes, the processor module actively monitored the host's glycemic condition using one or more hyperglycemic (second) criteria based on the rate of change of the glucose level, which was determined to be dropping a rate greater than the predetermined value (1 mg/dL/min), resulting in no output at 1300. In this case, the active state was initiated based on the first criteria (glucose level exceeding a threshold), but the processor module determined a state transition to inactive at 1300.

[00211] In some embodiments, the activation condition may include a time criteria or time component, meaning that a user's glucose has to exceed a threshold on average over a predetermined period of time, e.g., 60 minutes. As applied to the example shown in Figure 13, , the processor module may actively monitor the host's glycemic condition continuously using one or more hyperglycemic criteria based on the average glucose level and rate of change of the glucose level. In this scenario at 1300, the average glucose over 60 minutes was found to be above a predetermined threshold, however the rate of change of the glucose was determined to be dropping a rate greater than the predetermined value (1 mg/dL/min), resulting in no output at 1300. Consequently, the active state is not entered in this circumstance and no output is provided to the user.

[00212] Figure 14 is an example graph showing a high glucose level, followed by a rapid rate of change down, but then a steady glucose level still above the predetermined threshold. Notably, the user's glucose level crossed the predetermined hyperglycemic threshold at the beginning of T minutes, and the processor module transitioned to the active state 700 based on the (first) active transition criteria of the

Abbott Ex. 1002 - 102/1438

glucose level exceeding a first predetermined hyperglycemic threshold level of 180 mg/dL, thereby triggering the dynamic and intelligent monitoring of the host's glycemic condition. However, the user was not alerted because the user had enabled a predetermined wait time period (T) of 60 minutes before high alert. During the 60 minutes, the processor module actively monitored the host's glycemic condition using one or more hyperglycemic (second) criteria based on the glucose level and the rate of change of the glucose level, which at the end of the waiting period, was determined to still exceed the predetermined threshold and to have a rate of change that was not dropping faster than a predetermined rate, resulting in output at 1400. In this case, at reference numeral 1400, the user or host should be alerted here because although the glucose level fell for some time, the glucose level was steady and high (e.g., above a threshold) at the end of the wait time.

[00213] Figure 15 is an example graph showing a host's glucose level that goes beyond the threshold plus a margin even before the wait time expires. Notably, the user's glucose level crossed the predetermined hyperglycemic threshold at the beginning of T minutes, and the processor module transitioned to the active state 700 based on the (first) active transition criteria of the glucose level exceeding a first predetermined hyperglycemic threshold level of 180 mg/dL, thereby triggering the dynamic and intelligent monitoring of the host's glycemic condition. However, the user was not alerted because the user had enabled a predetermined wait time period (T) of 60 minutes before high alert. During the 60 minutes, the processor module actively monitored the host's glycemic condition using one or more hyperglycemic (second) criteria based on the glucose level plus a margin (180 mg/dL + 50 mg/dL = 230 mg/dL), which occurred prior to the end of the waiting period, resulting in output at 1500 prior to the 60 minute expiration. In this case, the user or host should be alerted at 1500 because the glucose level has risen to such an extent that the no-alert waiting period should be overridden.

[00214] Figure 16 is an example graph showing after user acknowledgement of an alert in a scenario similar to Figure 14, because although the glucose level fell for some time, the glucose level was steady and high (e.g., above a threshold) at the end of the wait time. After the alert was output at 1600, the user acknowledged the alert at 1610, transitioning into the acknowledged state, which has a 60 minute active monitoring

Abbott Ex. 1002 - 103/1438

period. Notably, the user's glucose level crossed below the predetermined hyperglycemic threshold soon after the user acknowledged the alert, however not sufficiently low to inactive the alert (because the inactivation conditions included threshold plus delta criteria). Accordingly, the processor module continued to actively monitor the host's glycemic condition based on average glucose, which determined the average glucose level at something above the predetermined threshold at the end of 60 minutes. In this case, the user or host is re-alerted or provided a subsequent alert because the average EGV is still high after the acknowledgment time period1620.

[00215] The scenarios above assume that "enable wait before alert" is turned on, however, any of those scenarios would have functioned similarly if the wait time was not enabled, but the acknowledged time period was selected by the user to be 60 minutes, in which case user would have a first alert after the first criteria were met (at the beginning of time period T) and then another one after the second criteria were met, for example at 1200, 1400, 1500 or 1600 (but not at other times in between when the user's glucose level oscillated up and down around the predetermined threshold).

[00216] This example further describes how the processor module actively monitors the host's glycemic condition after the user acknowledges a hyperglycemic alert (e.g., triggered with the host's glucose meeting one or more first or second criteria). Subsequent to the hyperglycemic alert output, the user acknowledges the alert, thus it may be assumed that the user is either watching or taking some action. The processor module transitions to acknowledged state. The processor module then actively monitors the host's glycemic condition, such that if the host's average glucose level since activation of the alert is less than the threshold (180 mg/dL) minus a delta (15 mg/dL); the host's actual (real-time) glucose level is less than the threshold minus the delta (165 mg/dL); average glucose level since activation of the alert is less than the predetermined threshold and the acknowledged time has expired; or rate of change of the host's glucose level falls faster than a predetermined rate (e.g., 1.0 mg/dL/min) and the glucose level is less than a threshold, predetermined meal information is received or confirmed; or predetermined insulin delivery information is received or confirmed, then the processor module would transition to inactive based on those inactivation criteria.

Abbott Ex. 1002 - 104/1438

[00217] The disclosure presents the best mode contemplated for carrying out the present systems and methods for processing analyte sensor data, and of the manner and process of practicing them, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which they pertain to practice these systems and methods. These systems and methods are, however, susceptible to modifications and alternate constructions from those discussed above that are fully equivalent.

[00218] For example, it should further be appreciated that the implementation and/or execution of all methods and processes may be performed by any suitable devices or systems, whether local or remote. Further, any combination of devices or systems may be used to implement the present methods and processes. Additionally, in some embodiments, the methods and processes described herein may reside in a non-transitory computer-readable storage medium including code which when executed by at least one processor causes operations of the present disclosure to be realized.

[00219] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it is apparent to those skilled in the art that certain changes and modifications may be practiced. The functions, steps and/or actions of the method claims in accordance with the embodiments of the invention described herein need not be performed in any particular order. Furthermore, although elements of the invention may be described or claimed in the singular, the plural is contemplated unless limitation to the singular is explicitly stated. Therefore, the description and examples should not be construed as limiting the scope of the disclosure to the specific embodiments and examples described herein, but rather to also cover all modification and alternatives coming with the true scope and spirit of the disclosure.

Abbott Ex. 1002 - 105/1438

WHAT IS CLAIMED IS:

1. A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria;

activating a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

2. The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

3. The method of Claim 2, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

4. The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value.

5. The method of Claim 1, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value.

6. The method of Claim 1, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

7. The method of Claim 1, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

8. The method of Claim 7, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

Abbott Ex. 1002 - 106/1438

9. The method of Claim 7, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone.

10. The method of Claim 1, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

11. The method of Claim 1, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

12. The method of Claim 1, wherein the one or more first criteria comprises a first threshold that is configured to be user settable.

13. The method of Claim 12, wherein the one or more second criteria comprises a second threshold that is not user settable.

14. The method of Claim 12, wherein the second function comprises a prediction horizon that is not user settable.

15. The method of Claim 12, wherein the one or more second criteria comprises a second threshold that is adaptively set by the processor module based on the first threshold.

16. The method of Claim 12, wherein the second function comprises a prediction horizon that is adaptively set by the processor module based on the first threshold.

17. The method of Claim 1, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria.

Abbott Ex. 1002 - 107/1438

18. The method of Claim 1, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria.

19. The method of Claim 1, wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

20. A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria;

activate a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

21. The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

22. The system of Claim 21, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

23. The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value.

24. The system of Claim 20, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value.

25. The system of Claim 20, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

26. The system of Claim 20, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

27. The system of Claim 26, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

28. The system of Claim 26, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone.

29. The system of Claim 20, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

30. The system of Claim 20, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

31. The system of Claim 20, wherein the one or more first criteria comprises a first threshold that is configured to be user settable.

32. The system of Claim 31, wherein the one or more second criteria comprises a second threshold that is not user settable.

Abbott Ex. 1002 - 109/1438

33. The system of Claim 31, wherein the second function comprises a prediction horizon that is not user settable.

34. The system of Claim 31, wherein the one or more second criteria comprises a second threshold that is adaptively set by the processor module based on the first threshold.

35. The system of Claim 31, wherein the second function comprises a prediction horizon that is adaptively set by the processor module based on the first threshold.

36. The system of Claim 20, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria.

37. The system of Claim 20, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria.

38. The system of Claim 20, wherein providing output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

Abbott Ex. 1002 - 110/1438

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

ABSTRACT OF THE DISCLOSURE

Systems and methods for providing sensitive and specific alarms indicative of glycemic condition are provided herein. In an embodiment, a method of processing sensor data by a continuous analyte sensor includes: evaluating sensor data using a first function to determine whether a real time glucose value meets a first threshold; evaluating sensor data using a second function to determine whether a predicted glucose value meets a second threshold; activating a hypoglycemic indicator if either the first threshold is met or if the second threshold is predicted to be met; and providing an output based on the activated hypoglycemic indicator.

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Abbott Ex. 1002 - 111/1438

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First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Rose M. Thiessen/Jennifer Jung
Attorney Docket Number:	DEXCOM.217A

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Basic Filing:				
Utility application filing	1011	1	390	390
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Claims in excess of 20	1202	18	62	1116
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
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First Named Inventor/Applicant Name:	Claudio Cobelli
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1	Application Data Sheet	20130116104129.pdf	449154 b43727b69614846ca170a1e67d8f47011a764f1a	no	8
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2	Drawings-only black and white line drawings	DEXCOM_217A_Figs.pdf	386614 688586dd316e69d9ed75fbbd42e42ec816f05ab0	no	18
Warnings:					
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3		DEXCOM_217A_Spec.pdf	356303 eb495b20b5644249917553e1f676a92bd053fb21	yes	78

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	72
	Claims	73	77
	Abstract	78	78

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4	Fee Worksheet (SB06)	fee-info.pdf	36814 984f784e8eab73057776821e36b0e509b3456b46	no	2
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68851
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Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

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Assignment For Published Patent Application

DexCom, Inc., San Diego, CA

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Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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Abbott Ex. 1002 - 117/1438

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Title

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

Preliminary Class

514

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Abbott Ex. 1002 - 118/1438

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/742,694

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	390
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	38 minus 20 =	* 18			OR	x 62 =	1116
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 250 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2376

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A

CONFIRMATION NO. 6142

68851
KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

FORMALITIES LETTER

OC000000059193828

Date Mailed: 02/11/2013

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing.

Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **130** for a non-small entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **130** for a non-small entity
- $ **130** Surcharge.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  All
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Abbott Ex. 1002 - 121/1438

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/wtsige/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Abbott Ex. 1002 - 122/1438

Please Direct All Correspondence to Customer Number 68851

RESPONSE TO FORMALITIES NOTICE

Inventor	:	Claudio Cobelli, et al.
App. No.	:	13/742,694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Art Unit	:	1629
Conf No.	:	6142

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The above-captioned application was filed without a Declaration and/or filing fees. Enclosed in compliance with 37 CFR 1.53(f) are the following.

(X) A Declaration in 10 pages.

(X) Power of Attorney by Assignee and Statement Under 37 CFR 3.73(b).

(X) Fees will be paid via EFS Web. Extension of time is requested by payment of any extension fee.

The Commissioner is hereby authorized to charge any additional fees which may be required, now or in the future, or credit any overpayment, to Account No. 11-1410.

4/4/13

Rose M. Thiessen
Registration No. 40,202
Attorney of Record
Customer No. 68851
(858) 707-4000

15160163:JSJ

Document Description: Oath or declaration filed

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing OR ■ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required)

Attorney Docket Number	DEXCOM.217A
First Named Inventor	Claudio Cobelli
COMPLETE IF KNOWN	
Application Number	13/742694
Filing Date	January 16, 2013
Art Unit	1629
Examiner Name	Unassigned

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

(Title of the Invention)

As a below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application,

OR

■ United States Application Number or PCT International application number 13/742694 filed on January 16, 2013.

The above-identified application was made or authorized to be made by me.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Authorization To Permit Access To Application by Participating Office

☑ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	■	The address associated with Customer Number:	68851	OR ☐	Correspondence address below

Name		
Address		
City	State	Zip
Country	Telephone	Email

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

LEGAL NAME OF SOLE OR FIRST INVENTOR:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Claudio Cobelli

Inventor's Signature	Date (Optional) 1/2, 2013

Residence: City Padova	State	Country Italy
Mailing Address Via S. Eufemia 3		
City Padova	State	Zip 35121 / Country Italy

■ Additional inventors are being named on the 3 supplemental sheet(s) PTO/AIA/10 attached hereto

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SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)**
Supplemental Sheet (for PTO/AIA/08,09) Page 3 of 5

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Giovanni Sparacino

Inventor's Signature: Giovanni Sparacino | Date (Optional): January, 30, 2013

Residence: City: Padova | State: | Country: Italy

Mailing Address: Via Forcellini 209/B

City: Padova | State: | Zip: 35128 | Country: Italy

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Andrea Facchinetti

Inventor's Signature: Andrea Facchinetti | Date (Optional): 30/1/2013

Residence: City: Padova | State: | Country: Italy

Mailing Address: Via Saetta 3

City: Padova | State: | Zip: 35131 | Country: Italy

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Hari Hampapuram

Inventor's Signature: | Date (Optional):

Residence: City: San Diego | State: CA | Country: US

Mailing Address: 13152 Chambord Way

City: San Diego | State: CA | Zip: 92130 | Country: US

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)** Supplemental Sheet (for PTO/AIA/08,09) Page 4 of 5

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Anna Leigh Rack-Gomer

Inventor's Signature	Date (Optional)

Residence: City	State	Country
San Diego	CA	US

Mailing Address: 3502 1st Avenue, #2

City	State	Zip	Country
San Diego	CA	92103	US

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Chiara Zecchin

Inventor's Signature	Date (Optional)
Chiara Zecchin	30/01/2013

Residence: City	State	Country
Pernumia		Italy

Mailing Address: Via della Pria 1/A

City	State	Zip	Country
Pernumia		35020	Italy

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Naresh C. Bhavaraju

Inventor's Signature	Date (Optional)

Residence: City	State	Country
San Diego	CA	US

Mailing Address: 13128 Sierra Mesa Court

City	State	Zip	Country
San Diego	CA	92129	US

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SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)**
Supplemental Sheet (for PTO/AIA/08,09)

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Apurv Ullas Kamath

Inventor's Signature	Date (Optional)

Residence: City	State	Country
San Diego	CA	US

Mailing Address: 3524 Chasewood Drive

City	State	Zip	Country
San Diego	CA	92111	US

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Inventor's Signature	Date (Optional)

Residence: City	State	Country

Mailing Address

City	State	Zip	Country

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Inventor's Signature	Date (Optional)

Residence: City	State	Country

Mailing Address

City	State	Zip	Country

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Doc Code: Oath
Document Description: Oath or declaration filed

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing OR ■ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required)

Attorney Docket Number	DEXCOM.217A
First Named Inventor	Claudio Cobelli
COMPLETE IF KNOWN	
Application Number	13/742694
Filing Date	January 16, 2013
Art Unit	1629
Examiner Name	Unassigned

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

(Title of the Invention)

As a below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application,

OR

■ United States Application Number or PCT International application number 13/742694 filed on January 16, 2013.

The above-identified application was made or authorized to be made by me.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Authorization To Permit Access To Application by Participating Office

☑ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to: ■ The address associated with Customer Number: 68851	OR	☐ Correspondence address below

Name		
Address		
City	State	Zip
Country	Telephone	Email

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

LEGAL NAME OF SOLE OR FIRST INVENTOR:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Claudio Cobelli

Inventor's Signature	Date (Optional)

Residence: City	State	Country
Padova		Italy

Mailing Address

Via S. Eufemia 3

City	State	Zip	Country
Padova		35121	Italy

■ Additional Inventors are being named on the 3 supplemental sheet(s) PTO/AIA/10 attached hereto

Abbott Ex. 1002 - 130/1438

PTO/AIA/10 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)**
Supplemental Sheet (for PTO/AIA/08,09) Page 3 of 5

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Giovanni Sparacino

Inventor's Signature | Date (Optional)

Residence: City: Padova | State | Country: Italy

Mailing Address: Via Forcellini 209/B

City: Padova | State | Zip: 35128 | Country: Italy

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Andrea Facchinetti

Inventor's Signature | Date (Optional)

Residence: City: Padova | State | Country: Italy

Mailing Address: Via Saetta 3

City: Padova | State | Zip: 35131 | Country: Italy

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Hari Hampapuram

Inventor's Signature: Hampapuram | Date (Optional): 1/29/2013

Residence: City: San Diego | State: CA | Country: US

Mailing Address: 13152 Chambord Way

City: San Diego | State: CA | Zip: 92130 | Country: US

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/AIA/10 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)** Supplemental Sheet (for PTO/AIA/08,09) Page 4 of 5

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Anna Leigh Rack-Gomer

Inventor's Signature: Anna Leigh Rack-Gomer | Date (Optional): 1/29/13

Residence: City: San Diego | State: CA | Country: US

Mailing Address: 3502 1st Avenue, #2

City: San Diego | State: CA | Zip: 92103 | Country: US

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Chiara Zecchin

Inventor's Signature | Date (Optional)

Residence: City: Pernumia | State | Country: Italy

Mailing Address: Via della Pria 1/A

City: Pernumia | State | Zip: 35020 | Country: Italy

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Naresh C. Bhavaraju

Inventor's Signature: Naresh C. Bhavaraju | Date (Optional): 1/29/20

Residence: City: San Diego | State: CA | Country: US

Mailing Address: 13128 Sierra Mesa Court

City: San Diego | State: CA | Zip: 92129 | Country: US

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)**
Supplemental Sheet (for PTO/AIA/08,09) Page 5 of 5

Legal Name of Additional Joint Inventor, if any:
(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)
Apurv Ullas Kamath

Inventor's Signature: Apurv Kamath — Date (Optional): 1/29/13

Residence: City: San Diego | State: CA | Country: US

Mailing Address: 3524 Chasewood Drive

City: San Diego | State: CA | Zip: 92111 | Country: US

Legal Name of Additional Joint Inventor, if any:
(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Inventor's Signature | Date (Optional)

Residence: City | State | Country

Mailing Address

City | State | Zip | Country

Legal Name of Additional Joint Inventor, if any:
(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Inventor's Signature | Date (Optional)

Residence: City | State | Country

Mailing Address

City | State | Zip | Country

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Docket No.: DEXCOM.217A **Customer No. 68851**

STATEMENT UNDER 37 CFR § 3.73
ESTABLISHMENT OF ASSIGNEE

Applicant	:	Cobelli, et al.
App. No.	:	13/742,694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	Unassigned
Group Art Unit	:	1629

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This document is being filed with a copy of a Power of Attorney signed by the Assignee. This Statement sets forth the chain of title of the above-identified application.

DexCom, Inc., a Corporation, is the Assignee of the entire right, title, and interest of the above-referenced application by virtue of:

A chain of title, in reverse order, from the inventors to the current Assignee as shown by the following recorded assignments:

1. Assignment from Universita Degli Studi Di Padova to DexCom, Inc. recorded in the United States Patent and Trademark Office on March 6, 2013, at Reel 029935, and Frame 0826.
2. Assignment from Naresh C. Bhavaraju, Hari Hampapuram, Apurv Ullas Kamath, and Anna Leigh Rack-Gomer to DexCom, Inc. recorded in the United States Patent and Trademark Office on March 6, 2013, at Reel 029935, and Frame 0689.
3. Assignment from Claudio Cobelli, Andrea Facchinetti, Giovanni Sparacino, and Chiara Zecchin to Universita Degli Studi Di Padova recorded in the United States Patent and Trademark Office on March 6, 2013, at Reel 029934, and Frame 0821.

The undersigned is an agent of Customer No. 68851 and is authorized to act on behalf of the Assignee. Please recognize or change the correspondence address for the above-identified application to **Customer No. 68851.**

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/4/13

By: _____

Rose M. Thiessen
Registration No. 40,202
Attorney of Record
Customer No. 68851
(858) 707-4000

15160215:JSJ

Abbott Ex. 1002 - 135/1438

REVOCATION & GENERAL POWER OF ATTORNEY
and
CHANGE IN CORRESPONDENCE ADDRESS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The undersigned is an empowered representative of the Assignee and hereby appoints the registrants of Knobbe, Martens, Olson & Bear, LLP, **Customer No. 68,851**, as attorneys and agents to represent the Assignee before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned to the Assignee according to the USPTO assignment records or assignment documents supplied with an accompanying Statement Under 37 CFR § 3.73(b). This appointment is to be to the exclusion of the inventor(s) and his attorney(s) in accordance with the provisions of 37 CFR § 3.71.

Submission of this paper in connection with any matter of the below named assignee, together with a statement under 37 CFR 3.73(b), shall serve to revoke any previous powers of attorney in that matter.

Attached is a Statement Under 37 CFR § 3.73(b), signed by a registrant of Knobbe, Martens, Olson & Bear, LLP, setting forth a full chain of title for the subject application owned by the Assignee named below.

Please recognize or change the correspondence address for the application identified in the attached Statement to **Customer No. 68,851.**

By: _____ Date: March 6 2012

Name: Laura Johnson Title: Vice President of Intellectual Property

Assignee: DexCom, Inc.
Address: 6340 Sequence Drive
San Diego, CA 92121

GENPOA

12886529
030612

Abbott Ex. 1002 - 136/1438

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A

CONFIRMATION NO. 6142

68851
KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

FORMALITIES LETTER

OC000000059193828

Date Mailed: 02/11/2013

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing.

Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **130** for a non-small entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **130** for a non-small entity
- $ **130** Surcharge.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  All
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Abbott Ex. 1002 - 137/1438

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/wtsige/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Abbott Ex. 1002 - 138/1438

Electronic Patent Application Fee Transmittal

Application Number:	13742694
Filing Date:	16-Jan-2013
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**140**

Electronic Acknowledgement Receipt

EFS ID:	15432200
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Rose M. Thiessen/Tony Do
Filer Authorized By:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	04-APR-2013
Filing Date:	16-JAN-2013
Time Stamp:	16:07:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$140
RAM confirmation Number	2950
Deposit Account	111410
Authorized User	KNOBBE MARTENS OLSON AND BEAR

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MP_DEXCOM_217A.pdf	1005433 3b4bf1c5e96474822b8ed08663bbdc8b7e63b98e	yes	16

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Response to Pre-Exam Formalities Notice	1	1
Oath or Declaration filed	2	11
Assignee showing of ownership per 37 CFR 3.73.	12	13
Power of Attorney	14	14
Miscellaneous Incoming Letter	15	16

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30121 b04fb90578dbff0c51da4674f919540d3681e97f	no	2

Warnings:

Information:

Total Files Size (in bytes):	1035554

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/742,694	01/16/2013	1629	2516	DEXCOM.217A	38	2

CONFIRMATION NO. 6142

68851
KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

UPDATED FILING RECEIPT

OC000000060350663

Date Mailed: 04/16/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Claudio Cobelli, Padova, ITALY;
Giovanni Sparacino, Padova, ITALY;
Andrea Facchinetti, Padova, ITALY;
Hari Hampapuram, San Diego, CA;
Anna Leigh Rack-Gomer, San Diego, CA;
Chiara Zecchin, Pernumia, ITALY;
Naresh C. Bhavaraju, San Diego, CA;
Apurv Ullas Kamath, San Diego, CA;

Applicant(s)

DexCom, Inc., San Diego, CA

Assignment For Published Patent Application

DexCom, Inc., San Diego, CA

Power of Attorney: The patent practitioners associated with Customer Number 68851

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/720,286 10/30/2012

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

Abbott Ex. 1002 - 143/1438

If Required, Foreign Filing License Granted: 02/08/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/742,694**

Projected Publication Date: 05/01/2014

Non-Publication Request: No

Early Publication Request: No

Title

SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

Abbott Ex. 1002 - 144/1438

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/742,694

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	38 minus 20 =	* 18			OR	x 80 =	1440
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	3040

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A

CONFIRMATION NO. 6142

68851
KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

POA ACCEPTANCE LETTER

OC000000060350633

Date Mailed: 04/16/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/04/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/tchaka/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 5299571	4/5/1994	Mastrototaro, John J.	
	2	US- 5390671	2/21/1995	Lord et al.	
	3	US- 5568806	10/29/1996	Cheney et al.	
	4	US- 5586553	12/24/1996	Halili et al.	
	5	US- 5680858	10/28/1997	Henrik-Egesborg et al.	
	6	US- 5851197	12/22/1998	Marano et al.	
	7	US- 5971922	10/26/1999	Arita et al.	
	8	US- 5993411	11/30/1999	Choi, Soo Bong	
	9	US- 6093172	7/25/2000	Funderburk et al.	
	10	US- 6180416	1/30/2001	Kurnik et al.	
	11	US- 6197001	3/6/2001	Wilson et al.	
	12	US- 6212424	4/3/2001	Robinson, Mak Ries	
	13	US- 6236872	5/22/2001	Diab et al.	
	14	US- 6254586	7/3/2001	Mann et al.	
	15	US- 6272364	8/7/2001	Kurnik, Ronald T.	
	16	US- 6293925	9/25/2001	Safabash et al.	
	17	US- 6424847	7/23/2002	Mastrototaro et al.	
	18	US- 6544212	4/8/2003	Galley et al.	
	19	US- 6546269	4/8/2003	Kurnik, Ronald T.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	1	EP 1077634-B1	2003-07-30	Cygnus, Inc.		
	2	EP 1078258-B1	2003-07-30	Cygnus, Inc.		
	3	EP 1102559-B1	2003-06-04	Cygnus, Inc.		
	4	EP 1119637-B1	2004-03-24	Therasense, Inc.		
	5	EP 1144028-B1	2004-06-23	Novo Nordisk A/S		
	6	EP 1437674-B1	2008-08-13	Novo Nordisk A/S		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	20	US- 6553244	4/22/2003	Lesho et al.	
	21	US- 6558351	5/6/2003	Steil et al.	
	22	US- 6560471	5/6/2003	Heller et al.	
	23	US- 6572545	6/3/2003	Knobbe et al.	
	24	US- 6574490	6/3/2003	Abbink et al.	
	25	US- 6575905	6/10/2003	Knobbe et al.	
	26	US- 6577899	6/10/2003	Lebel et al.	
	27	US- 6479690	6/17/2003	Bonnecaze et al.	
	28	US- 6607509	8/19/2003	Bobroff et al.	
	29	US- 6653091	11/25/2003	Dunn et al.	
	30	US- 6656114	12/2/2003	Poulsen et al.	
	31	US- 6695860	2/24/2004	Ward et al.	
	32	US- 6740518	5/25/2004	Duong et al.	
	33	US- 6882940	4/19/2005	Potts et al.	
	34	US- 6895263	5/17/2005	Shin et al.	
	35	US- 6990366	1/24/2006	Say et al.	
	36	US- 6991619	1/31/2006	Marano-Ford et al.	
	37	US- 6991620	1/31/2006	Marano-Ford et al.	
	38	US- 6997907	2/14/2006	Safabash et al.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	7	EP 1473050-B1	2009-12-09	Medtronic MiniMed, Inc.		
	8	EP 1503660-B1	2007-01-17	Medtronic Minimed, Inc.		
	9	EP 1518495-B1	2010-03-31	Roche Diagnostics GmbH		
	10	EP 1703839-B1	2012-02-08	Medtronic MiniMed, Inc.		
	11	EP 1706022-B1	2008-10-29	Medtronic MiniMed, Inc.		
	12	EP 1759201-B1	2010-10-13	Medtronic Minimed, Inc.		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	39	US- 7003336	2/21/2006	Holker et al.	
	40	US- 7003341	2/21/2006	Say et al.	
	41	US- 7022072	4/4/2006	Fox et al.	
	42	US- 7022108	4/4/2006	Marano-Ford et al.	
	43	US- 7029444	4/18/2006	Shin et al.	
	44	US- 7190988	3/13/2007	Say et al.	
	45	US- 7207974	4/24/2007	Safabash et al.	
	46	US- 7228162	6/5/2007	Ward et al.	
	47	US- 7282029	10/16/2007	Poulsen et al.	
	48	US- 7299082	11/20/2007	Feldman et al.	
	49	US- 7310544	12/18/2007	Brister et al.	
	50	US- 7318816	1/15/2008	Bobroff et al.	
	51	US- 7343188	3/11/2008	Sohrab, Borzu	
	52	US- 7361184	6/3/2008	Funderburk et al.	
	53	US- 7384397	6/10/2008	Zhang et al.	
	54	US- 7389133	6/17/2008	Kotulla et al.	
	55	US- 7399277	7/15/2008	Saidara et al.	
	56	US- 7402153	7/22/2008	Steil et al.	
	57	US- 7494465	2/24/2009	Brister et al.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	13	EP 1890597-B1	2012-02-22	Abbott Diabetes Care, Inc		
	14	EP 1927602-B1	2012-01-11	Abbott Diabetes Care, Inc		
	15	EP 1931253-B1	2012-02-22	Abbott Diabetes Care, Inc		
	16	EP 2051620-B1	2010-04-28	Koninklijke Philips Elect		
	17	EP 2069771-B1	2011-11-02	Abbott Diabetes Care, Inc		
	18	WO 1999/058051	1999-11-18	Cygnus, Inc		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	58	US- 7582059	9/1/2009	Funderburk et al.	
	59	US- 7602310	10/13/2009	Mann et al.	
	60	US- 7618369	11/17/2009	Hayter et al.	
	61	US- 7630748	12/8/2009	Budiman, Erwin S.	
	62	US- 7647237	1/12/2010	Malave et al.	
	63	US- 7653425	1/26/2010	Hayter et al.	
	64	US- 7654956	2/2/2010	Brister et al.	
	65	US- 7660615	2/9/2010	Van Antwerp et al.	
	66	US- 7670288	3/2/2010	Sher, Philip M.	
	67	US- 7682338	3/23/2010	Griffin, Christopher G.	
	68	US- 7686787	3/30/2010	Moberg et al.	
	69	US- 7695434	4/13/2010	Malecha, Michael	
	70	US- 7697967	4/13/2010	Stafford, Gary Ashley	
	71	US- 7699807	4/20/2010	Faust et al.	
	72	US- 7704229	4/27/2010	Moberg et al.	
	73	US- 7729737	6/1/2010	Ward, W. Kenneth	
	74	US- 7731657	6/8/2010	Stafford, Gary Ashley	
	75	US- 7731659	6/8/2010	Malecha, Michael	
	76	US- 7736310	6/15/2010	Taub, Mark B.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	19	WO 2002/082989	2002-10-24	Abbott Laboratories		
	20	WO 2008/042918	2008-04-10	Dexcom, Inc.		
	21	WO 2009/136372	2009-12-12	Universita Degli Studi Pa		
	22	WO 2011/051922	2011-05-05	Universita Degli Studi di		

Examiner Signature		Date Considered	

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Sheet 5 of 10

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Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
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	77	US- 7736338	6/15/2010	Kavazov et al.	
	78	US- 7736344	6/15/2010	Moberg et al.	
	79	US- 7740613	6/22/2010	Yokoi et al.	
	80	US- 7744589	6/29/2010	Mounce et al.	
	81	US- 7762793	7/27/2010	Gray et al.	
	82	US- 7766830	8/3/2010	Fox et al.	
	83	US- 7768386	8/3/2010	Hayter et al.	
	84	US- H2246-H	8/3/2010	Miller et al.	
	85	US- 7771393	8/10/2010	Liniger et al.	
	86	US- 7774038	8/10/2010	Wang et al.	
	87	US- 7783442	8/24/2010	Mueller et al.	
	88	US- 7785293	8/31/2010	Gray et al.	
	89	US- 7789857	9/7/2010	Moberg et al.	
	90	US- 7815569	10/19/2010	Kovatchev et al.	
	91	US- 7815607	10/19/2010	Rutti et al.	
	92	US- 7846132	12/7/2010	Gravesen et al.	
	93	US- 7850652	12/14/2010	Liniger et al.	
	94	US- 7860544	12/28/2010	Say et al.	
	95	US- 7866026	1/11/2011	Wang et al.	

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Examiner Signature		Date Considered	

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(Use as many sheets as necessary)

Sheet 6 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	96	US- 7869853	1/11/2011	Say et al.	
	97	US- 7871394	1/18/2011	Halbert et al.	
	98	US- 7878975	2/1/2011	Lilleryd et al.	
	99	US- 7885698	2/8/2011	Feldman, Benjamin J.	
	100	US- 7890295	2/15/2011	Shin et al.	
	101	US- 7895740	3/1/2011	Wang et al.	
	102	US- 7899545	3/1/2011	John, Michael Sasha	
	103	US- 7912655	3/22/2011	Power et al.	
	104	US- 7912674	3/22/2011	Killoren-Clark et al.	
	105	US- 7920907	4/5/2011	McGarraugh et al.	
	106	US- 7946985	5/24/2011	Mastrototaro et al.	
	107	US- 7970449	6/28/2011	Ward, W. Kenneth	
	108	US- 7976466	7/12/2011	Ward, W. Kenneth	
	109	US- 7981034	7/19/2011	Jennewine et al.	
	110	US- 7988630	8/2/2011	Osorio et al.	
	111	US- 7996158	8/9/2011	Hayter et al.	
	112	US- 8103456	1/24/2012	Doniger et al.	
	113	US- 8103471	1/24/2012	Hayter, Gary	
	114	US- 8129173	3/6/2012	Shapiro et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 10

Complete if Known	
Application Number	13/742694
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First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	115	US- 8135548	3/13/2012	Breton et al.	
	116	US- 8219173	7/10/2012	Budiman et al.	
	117	US- 8224415	7/17/2012	Budiman, Erwin Satrya	
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	125	US- 20100137699	6/3/2010	Sher, Philip Michael	
	126	US- 20110098548	4/28/2011	Budiman et al.	
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Sheet 8 of 10

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Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

NON PATENT LITERATURE DOCUMENTS

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	1	Arnold et al., IEEE Transactions on Biomedical Engineering 45(5):553-562 (1998): Adaptive AR Modeling of Nonstationary by Means of Kalman Filtering	
	2	Choleau et al., Biosensors & Bioelectronics 17:641-646 (2002): Calibration of a subcutaneous amperometric glucose sensor part 1: Effect of measurement of uncertainties on th	
	3	Choleau et al., Biosensors & Bioelectronics 17:647-654 (2002): Calibration of a subcutaneous amperometric glucose sensor implanted for 7 days in diabetic patients part 2: Su	
	4	Commenges, Daniel, IEEE Transactions on AUtomatic Control 29(3):229-243 (1984): The deconvolution problem: fast algorithms including the preconditioned conjugate-gradient to	
	5	Dassau et al, Diabetes Care 33(6):1249-1254 (June 2010): Real-Time Hypoglycemia Prediction Suite Using Continuous Glucose Monitoring	
	6	DiNicolao et al., Automatica 33(5):851-870 (1997): Nonparametric Input Estimation in Physiological Systems: Problems, Methods and Case Studies	
	7	Eren-Oruklu et al., Diabetes Technology & Therapeutics 11(4):243-253 (2009): Estimation of Future Glucose Concentrations with Subject-Specific Recursive Linear Models	
	8	Eren-Oruklu et al., Journal of Diabetes Science and Technology 4(1):25-33 (Jan 2010): Hypoglycemia Prediction with Subject-Specific Recursive Time-Series Models	
	9	Facchinetti et al., IEEE Transactions on Biomedical engineering 57(3):634 (2010): An online self-tunable method to denoise CGM sensor data	
	10	Facchinetti et al., IEEE Transactions on Biomedical Engineering 58(9):2664 (2011): Online denoising method to handle intraindividual variability of signal-to-noise ratio in c	

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Sheet 9 of 10

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Application Number	13742694
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Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	11	Freeland et al., Annals of Biomedical Engineering 27:525-537 (1999): Inference of blood glucose concentrations from subcutaneous glucose concentrations: applications to gluc	
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	15	Guerra et al., IEEE Transactions on Biomedical Engineering 59(6):1658-1669 (2012): Enhancing the accuracy of subcutaneous glucose sensors: a real-time devconvolution-based a	
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	17	King et al., J. Diab. Sci. Tech. 1(1):36 (2007): A prospective evaluation of insuling dosing recommendations in patients with type 1 diabetes at near normal glucose control:	
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	19	Leal et al., J. Diab. Sci. Tech. 4(2):391 (2010): Real-time glucose estimation algorithm for continuous glucose monitoring using autoregressive models	
	20	Lu et al., IEEE Transactions on Biomedical Engineering 57(8):1839-1846 (Aug 2010): The Importance of Different Frequency Bands in Predicting Subcutaneous Glucose Concentratio	

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Sheet 10 of 10

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Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	21	Panteleon et al., Diabetes Technology & Therapeutics 5(3):401-410 (2003): The role of the independent variable to glucose sensor calibration	
	22	Perez-Gandia et al., Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain (2007): Artificial Neural Network Algorithm for On	
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EFS ID:	16829974
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Kaare Douglas Larson/Renee Zavala
Filer Authorized By:	Kaare Douglas Larson
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	11-SEP-2013
Filing Date:	16-JAN-2013
Time Stamp:	20:11:55
Application Type:	Utility under 35 USC 111(a)

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1	Foreign Reference	X-EP-01077634-B1.pdf	427437 a43f175a09f8bfe5e557d49ea7bf90ef2af97dfe	no	26

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5	Foreign Reference	X-EP-1144028-B1-Assmul.pdf	943322 77b4a45019faa741745cf872f46a8e652c9ee537	no	46
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6	Foreign Reference	X-EP-1437674-B1.pdf	796013 8c9f944b064e62e4193639dcfb419edb6c9415d5	no	30
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23	Foreign Reference	X-WO-2011-051922-A2A3.pdf	3130115 3e9063231030f5a16a4cd197d3d3376162c32bc3	no	29
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24	Non Patent Literature	X-Arnold-IEEETxnsBiomedEng-1998.pdf	355339 6fcf322c257ae1207b3bcda73ad02400ab48dc4c	no	10
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27	Non Patent Literature	X-Commenges-IEEETxnsAutoControl-1984.pdf	2412348 2a53b5e74e63645db0cc286b93a5a4ae27cc81c3	no	15
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Information:					
28	Non Patent Literature	X-Dassau-DiabCare-2010.pdf	432466 a52e062e6e94a4aeaf0818b706bc6902b2eefb26	no	6
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29	Non Patent Literature	X-DiNicolao-Automatica-1997.pdf	5784819 0cbf9fb5252b8ae6ece766d16a356cc90fa82561	no	20
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30	Non Patent Literature	X-Eren-Oruklu-DiabTechTher-2009-Estimation.pdf	614522 7219b8e24e6b58f9d4867b0c72e200e714af0234	no	12
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38	Non Patent Literature	X-Guerra-IEEE-2011-MS.pdf	436840 deb7cd1c874e77893831d40986da39597f92d9c5	no	10
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39	Non Patent Literature	X-SpectralDensity-Wikipedia.pdf	1475578 a93e11a4209482be7ab41b2a96184f09edfe2955	no	8
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47	Non Patent Literature	X-Rebrin-JDiabSciTech-2010.pdf	1230174 c0d78ee44a7ac5de01433a793e3a439a915db801	no	12
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51	Non Patent Literature	X-Tarvainen-IEEETxnsBiomedEng-2004.pdf	1018518 9c7b2bc6f384996ddea3c2c52e370b3c473c6d6a	no	9
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52	Non Patent Literature	X-Tikhonov-SovietMethodDokl-1963.pdf	3335621 1b36b744ca48b21ad45d8e06436310a375f4d772	no	5
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53		2013-0911b-IDS-initial-217A.pdf	2397977 8e36774a79a541d592155ad19273e41c600401a1	yes	11

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(54) **MONITORING OF PHYSIOLOGICAL ANALYTES**

ÜBERWACHUNG PHYSIOLOGISCHER ANALYTE

CONTROLE D'ANALYTES PHYSIOLOGIQUES

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EP 1 077 634 B1

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Description

Field of the Invention

[0001] The invention relates generally to measuring the concentration of target chemical analytes present in a biological system. One important application of the invention involves monitoring blood glucose concentrations.

Background of the Invention

[0002] A number of diagnostic tests are routinely performed on humans to evaluate the amount or existence of substances present in blood or other body fluids. These diagnostic tests typically rely on physiological fluid samples removed from a subject, either using a syringe or by pricking the skin. One particular diagnostic test entails self-monitoring of blood glucose levels by diabetics.

[0003] Diabetes is a major health concern, and treatment of the more severe form of the condition, Type I (insulin-dependent) diabetes, requires one or more insulin injections per day. Insulin controls utilization of glucose or sugar in the blood and prevents hyperglycemia which, if left uncorrected, can lead to ketosis. On the other hand, improper administration of insulin therapy can result in hypoglycemic episodes, which can cause coma and death. Hyperglycemia in diabetics has been correlated with several long-term effects of diabetes, such as heart disease, atherosclerosis, blindness, stroke, hypertension and kidney failure.

[0004] The value of frequent monitoring of blood glucose as a means to avoid or at least minimize the complications of Type I diabetes is well established. Patients with Type II (non-insulin-dependent) diabetes can also benefit from blood glucose monitoring in the control of their condition by way of diet and exercise.

[0005] Conventional blood glucose monitoring methods generally require the drawing of a blood sample (e.g., by fingerprick) for each test, and a determination of the glucose level using an instrument that reads glucose concentrations by electrochemical or colorimetric methods. Type I diabetics must obtain several fingerprick blood glucose measurements each day in order to maintain tight glycemic control. However, the pain and inconvenience associated with this blood sampling, along with the fear of hypoglycemia, has led to poor patient compliance, despite strong evidence that tight control dramatically reduces long-term diabetic complications. In fact, these considerations can often lead to an abatement of the monitoring process by the diabetic. See, e.g., The Diabetes Control and Complications Trial Research Group (1993) *New Engl. J. Med.* 329:977-1036.

[0006] Recently, various methods for determining the concentration of blood analytes without drawing blood have been developed. For example, U.S. Patent No. 5,267,152 to Yang et al. describes a noninvasive technique of measuring blood glucose concentration using near-IR radiation diffuse-reflection laser spectroscopy. Similar near-IR spectrometric devices are also described in U.S. Patent No. 5,086,229 to Rosenthal et al. and U.S. Patent No. 4,975,581 to Robinson et al.

[0007] U.S. Patent No. 5,139,023 to Stanley describes a transdermal blood glucose monitoring apparatus that relies on a permeability enhancer (e.g., a bile salt) to facilitate transdermal movement of glucose along a concentration gradient established between interstitial fluid and a receiving medium. U.S. Patent No. 5,036,861 to Sembrowich describes a passive glucose monitor that collects perspiration through a skin patch, where a cholinergic agent is used to stimulate perspiration secretion from the eccrine sweat gland. Similar perspiration collection devices are described in U.S. Patent No. 5,076,273 to Schoendorfer and U.S. Patent No. 5,140,985 to Schroeder.

[0008] In addition, U.S. Patent No. 5,279,543 to Glikfeld describes the use of iontophoresis to noninvasively sample a substance through skin into a receptacle on the skin surface. Glikfeld teaches that this sampling procedure can be coupled with a glucose-specific biosensor or glucose-specific electrodes in order to monitor blood glucose. Finally, International Publication No. WO 96/00110 to Tamada describes an iontophoretic apparatus for transdermal monitoring of a target substance, wherein an iontophoretic electrode is used to move an analyte into a collection reservoir and a biosensor is used to detect the target analyte present in the reservoir.

Summary of the Invention

[0009] The present invention provides a sampling system for measuring the concentration of an analyte present in a biological system, as defined in claim 6 and a microprocessor programmed to measure the concentration of said analyte, as defined in claim 1. Use of the invention generally entails sampling and detecting an analyte from the biological system and deriving a detectable signal therefrom, wherein the signal is specifically related to the analyte. The signal can be correlated with a measurement value indicative of the concentration of analyte present in the biological system. Sampling system configurations and/or measurement techniques are used to minimize the effect of interfering species on a particular sensing means.

[0010] Analyte sampling is carried out using a transdermal sampling system that is placed in operative contact with

Abbott Ex. 1002 - 167/1438

a skin or mucosal surface. In preferred embodiments, the sampling system transdermally extracts the analyte from the biological system using iontophoresis. The transdermal sampling system can be maintained in operative contact with the skin or mucosal surface to provide for continual or continuous analyte measurement.

[0011] The analyte can be any specific substance or component that one is desirous of detecting and/or measuring in a chemical, physical, enzymatic, or optical analysis. Such analytes include, but are not limited to, amino acids, enzyme substrates or products indicating a disease state or condition, other markers of disease states or conditions, drugs of abuse, therapeutic and/or pharmacologic agents, electrolytes, physiological analytes of interest (e.g., calcium, potassium, sodium, chloride, bicarbonate (CO_2), glucose, urea (blood urea nitrogen), lactate, hematocrit, and hemoglobin), lipids, and the like. In preferred embodiments, the analyte is a physiological analyte of interest, for example glucose, or a chemical that has a physiological action, for example a drug or pharmacological agent.

[0012] Accordingly, the sampling system of the invention may be used in a method for measuring an analyte present in a biological system. The method entails a step for transdermally extracting the analyte from the biological system in an extraction step using a sampling system that is in operative contact with a skin or mucosal surface of the biological system; and a step for contacting the extracted analyte with a sensor means in a sensing step to obtain a detectable signal which is specifically related to the analyte. The extraction and sensing steps are conducted in a measurement cycle which selectively favors analyte-specific signal components over signal components due to interfering species.

[0013] The sampling system of the invention may be used in another method for measuring the concentration of an analyte present in a biological system. The method includes a measurement cycle which comprises an extraction step in which a sample containing the analyte is transdermally extracted from the biological system using a sampling system that is in operative contact with a skin or mucosal surface of the biological system. The method also entails a sensing step in which the extracted sample is contacted with sensor means to obtain a measurement signal that is related to analyte concentration. The measurement cycle further comprises a process for selectively favoring analyte-specific signal components over signal components due to interfering species. Such processes can include (a) a differential signal process which subtracts non-analyte signal components from the measurement signal, (b) a delay step which is performed between the extraction and sensing steps, (c) a selective electrochemical detection process which is performed during the sensing step, (d) a purge step which is performed after the sensing step, (e) a charge segregation step (as in Example 1), or any combination of the processes of (a)-(e).

[0014] The sampling system of the invention may also be used in another method for measuring the concentration of an analyte present in a biological system. The method includes a measurement cycle which comprises transdermally extracting the analyte from the biological system in an extraction step using an iontophoretic sampling system that is in operative contact with a skin or mucosal surface of the biological system, and contacting the extracted analyte with a sensor means in a sensing step to obtain a detectable signal which is specifically related to the analyte. In particular, the sampling system comprises (a) a first collection reservoir containing an ionically conductive medium, a first iontophoretic sampling means for extracting substances including the analyte from the biological system into the first collection reservoir to obtain a concentration of the analyte, and a first sensor element, wherein the first sampling means and the first sensor element are in operative contact with the first collection reservoir; and (b) a second collection reservoir containing an ionically conductive medium, a second iontophoretic sampling means for extracting substances including the analyte from the biological system into the second collection reservoir, and a second sensor element, wherein the second sampling means and the second sensor element are in operative contact with the second collection reservoir. The measurement cycle comprises (a) operating the first iontophoretic sampling means as an iontophoretic cathode during a first phase of the extraction step, (b) detecting substances extracted into the first reservoir with the first sensor element during a first phase of the sensing step to obtain a first signal, (c) purging residual signal from the sampling system in a purging step, (d) operating the second iontophoretic sampling means as an iontophoretic cathode during a second phase of the extraction step, and (e) detecting substances extracted into the second reservoir with the second sensor element during a second phase of the sensing step to obtain a second signal. At least one of the first and second signals comprises an analyte-specific signal component.

[0015] In one particular embodiment, one of the collection reservoirs includes an enzyme that reacts specifically with the extracted analyte, and the second reservoir does not contain the enzyme.

[0016] The sampling system of the invention may be used in yet another method for measuring the concentration of an analyte present in a biological system. The method includes transdermally extracting the analyte from the biological system in an extraction step using an iontophoretic sampling system that comprises first and second collection reservoirs which are respectively in operative contact with first and second iontophoretic sampling means and a skin or mucosal surface of the biological system. The first and second iontophoretic sampling means extract substances including the analyte from the biological system into the first and second collection reservoirs, and the first iontophoretic sampling means is operated as a cathode during the extraction step. The method further entails passively collecting substances which diffuse from, or are secreted by the biological system into a third collection reservoir using a passive transdermal sampling system that is in operative contact with a skin or mucosal surface of the biological system. The analyte that is extracted into the first collection reservoir is then contacted with a sensing means in a sensing step to

Abbott Ex. 1002 - 168/1438

obtain an active signal, and the substances collected into the third collection reservoir are contacted with the sensing means to obtain a blank signal. The blank signal is then subtracted from the active signal to provide an analyte-specific signal.

[0017] In one aspect of the devices of the present invention, a charge segregation step can be used to reduce the presence of interfering species at the sensing means. For example, the measurement cycle can include a charge segregation step wherein sensing takes place at the cathode and certain interfering species preferentially collect at the anode, or visa versa.

[0018] The sampling system of the invention may be used in a related method for measuring the concentration of an analyte present in a biological system. The method includes transdermally extracting the analyte from the biological system in an extraction step using an iontophoretic sampling system that comprises first, second, and third collection reservoirs which are respectively in operative contact with first, second, and third iontophoretic sampling means and a skin or mucosal surface of the biological system. The first, second, and third iontophoretic sampling means respectively extract substances including the analyte from the biological system into the first, second, and third collection reservoirs, and the first and second iontophoretic sampling means are operated as cathodes during the extraction step. The method further entails contacting the analyte extracted into the first collection reservoir with a sensing means in a sensing step to obtain an active signal, and contacting the substances extracted into the second collection reservoir with the sensing means to obtain a blank signal. An analyte-specific signal is then obtained by subtracting the blank signal from the active signal.

[0019] The sampling system of the invention may be used in a still further related method for measuring the concentration of an analyte present in a biological system. The method includes transdermally extracting the analyte from the biological system in an extraction step using an iontophoretic sampling system that comprises first, second, and third collection reservoirs which are respectively in operative contact with first, second, and third iontophoretic sampling means and a skin or mucosal surface of the biological system. The first, second, and third iontophoretic sampling means respectively extract substances including the analyte from the biological system into the first, second, and third collection reservoirs, and the first and second iontophoretic sampling means are operated as cathodes during the extraction step. The method further entails contacting the analyte extracted into the first and second collection reservoirs with a sensing means in a sensing step to obtain multiple analyte-specific signals.

[0020] It is another object of the invention to provide a sampling system for measuring an analyte present in a biological system. The sampling system comprises, in operative combination (a) a sampling means for extracting the analyte from the biological system, (b) a sensing means in operative contact with the analyte extracted by the sampling means, and (c) a microprocessor means in operative communication with the sampling and sensing means. The sampling means is adapted for extracting the analyte across a skin or mucosal surface of a biological system. In preferred embodiments, the sampling means is used to continually or continuously extract the analyte. The sensing means is used to obtain a detectable signal from the extracted analyte, wherein the signal is specifically related to the analyte. The microprocessor means is used to control the sampling means and the sensing means to provide for one or more measurement cycles.

[0021] In one aspect of the invention, the sampling system comprises (a) a first collection reservoir containing an ionically conductive medium, a first iontophoretic sampling means for extracting substances including the analyte from the biological system into the first collection reservoir, and a first sensor element, wherein the first sampling means and the first sensor element are in operative contact with the first collection reservoir; and (b) a second collection reservoir containing an ionically conductive medium, a second iontophoretic sampling means for extracting substances including the analyte from the biological system into the second collection reservoir, and a second sensor element, wherein the second sampling means and the second sensor element are in operative contact with the second collection reservoir. In the subject sampling system, the microprocessor controls a measurement cycle which entails (a) operating the first iontophoretic sampling means as an iontophoretic cathode during a first phase of the extraction step, (b) detecting substances extracted into the first reservoir with the first sensor element during a first phase of the sensing step to obtain a first signal, (c) purging residual signal from the sampling system in a purging step, (d) operating the second iontophoretic sampling means as an iontophoretic cathode during a second phase of the extraction step, and (e) detecting substances extracted into the second reservoir with the second sensor element during a second phase of the sensing step to obtain a second signal. At least one of the first and second signals comprises an analyte-specific signal component.

[0022] In a further aspect, the devices of the present invention can include enhancement of skin permeability by pricking the skin with micro-needles when the biological system includes skin, or, for example, a mucosal surface. Such pricking with micro-needles can facilitate extraction an analyte of interest from the biological system.

[0023] Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following disclosure, or may be learned by practice of the invention.

Abbott Ex. 1002 - 169/1438

Brief Description of the Drawings

[0024]

Figure 1A depicts a top plan view of an iontophoretic collection reservoir and electrode assembly for use in a transdermal sampling device constructed according to the present invention.
Figure 1B depicts the side view of the iontophoretic collection reservoir and electrode assembly shown in Figure 1A.
Figure 2 is a pictorial representation of an iontophoretic sampling device which includes the iontophoretic collection reservoir and electrode assembly of Figures 1A and 1B.
Figure 3 is an exploded pictorial representation of components from a preferred embodiment of the automatic sampling system of the present invention.
Figure 4 is a representation of one embodiment of a bimodal electrode design. The figure presents an overhead and schematic view of the electrode assembly **43.** In the figure, the bimodal electrode is shown at **40** and can be, for example, a Ag/AgCl iontophoretic/counter electrode. The sensing or working electrode (made from, for example, platinum) is shown at **41.** The reference electrode is shown at **42** and can be, for example, a Ag/AgCl electrode. The components are mounted on a suitable nonconductive substrate **44**, for example, plastic or ceramic. The conductive leads **47** leading to the connection pad **45** are covered by a second nonconductive piece **46** of similar or different material. In this example of such an electrode the working electrode area is approximately 1.35 cm^2. The dashed line in Figure 4 represents the plane of the cross-sectional schematic view presented in Figure 5.
Figure 5 is a representation of a cross-sectional schematic view of the bimodal electrodes as they may be used in conjunction with a reference electrode and a hydrogel pad. In the figure, the components are as follows: bimodal electrodes **50** and **51**; sensing electrodes **52** and **53**; reference electrodes **54** and **55**; a substrate **56**; and hydrogel pads **57** and **58.**

Detailed Description of the Preferred Embodiments

[0025] Before describing the present invention in detail, it is to be understood that this invention is not limited to particular compositions or biological systems as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0026] As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an interfering species" includes two or more such species, reference to "an analyte" includes mixtures of analytes, and the like.

[0027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein.

[0028] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

Definitions

[0029] The terms "analyte" and "target analyte" are used herein to denote any physiological analyte of interest that is a specific substance or component that is being detected and/or measured in a chemical, physical, enzymatic, or optical analysis. A detectable signal (e.g., a chemical signal or electrochemical signal) can be obtained, either directly or indirectly, from such an analyte or derivatives thereof. Furthermore, the terms "analyte" and "substance" are used interchangeably herein, and are intended to have the same meaning, and thus encompass any substance of interest. In preferred embodiments, the analyte is a physiological analyte of interest, for example, glucose, or a chemical that has a physiological action, for example, a drug or pharmacological agent.

[0030] A "sampling device" or "sampling system" refers to any device for obtaining a sample from a biological system for the purpose of determining the concentration of an analyte of interest. As used herein, the term "sampling" means invasive, minimally invasive or non-invasive extraction of a substance from the biological system, generally across a membrane such as skin or mucosa. The membrane can be natural or artificial, and can be of plant or animal nature, such as natural or artificial skin, blood vessel tissue, intestinal tissue, and the like. Typically, the sampling means are in operative contact with a "reservoir," or "collection reservoir," wherein the sampling means is used for extracting the analyte from the biological system into the reservoir to obtain the analyte in the reservoir. A "biological system" includes both living and artificially maintained systems. Examples of minimally invasive and noninvasive sampling techniques include iontophoresis, sonophoresis, suction, electroporation, thermal poration, passive diffusion, microfine (miniature) lances or cannulas, subcutaneous implants or insertions, and laser devices. Sonophoresis uses ultrasound to increase

Abbott Ex. 1002 - 170/1438

the permeability of the skin (see, e.g., Menon et al. (1994) *Skin Pharmacology* 7:130-139). Suitable sonophoresis sampling systems are described in International Publication No. WO 91/12772, published 5 September 1991. Passive diffusion sampling devices are described, for example, in International Publication Nos.: WO 97/38126 (published 16 October 1997); WO 97/42888, WO 97/42886, WO 97/42885, and WO 97/42882 (all published 20 November 1997); and WO 97/43962 (published 27 November 1997). Laser devices use a small laser beam to burn a hole through the upper layer of the patient's skin (see, e.g., Jacques et al. (1978) *J. Invest. Dermatology* 88:88-93). Examples of invasive sampling techniques include traditional needle and syringe or vacuum sample tube devices.

[0031] The term "collection reservoir" is used to describe any suitable containment means for containing a sample extracted from a biological system. For example, the collection reservoir can be a receptacle containing a material which is ionically conductive (e.g., water with ions therein), or alternatively, it can be a material, such as, a sponge-like material or hydrophilic polymer, used to keep the water in place. Such collection reservoirs can be in the form of a hydrogel (for example, in the form of a disk or pad). Hydrogels are typically referred to as "collection inserts." Other suitable collection reservoirs include, but are not limited to, tubes, vials, capillary collection devices, cannulas, and miniaturized etched, ablated or molded flow paths.

[0032] A "housing" for the sampling system can further include suitable electronics (e.g., microprocessor, memory, display and other circuit components) and power sources for operating the sampling system in an automatic fashion.

[0033] A "monitoring system," as used herein, refers to a system useful for continually or continuously measuring a physiological analyte present in a biological system. Such a system typically includes, but is not limited to, sampling means, sensing means, and a microprocessor means in operative communication with the sampling means and the sensing means.

[0034] The term "artificial," as used herein, refers to an aggregation of cells of monolayer thickness or greater which are grown or cultured *in vivo* or *in vitro*, and which function as a tissue of an organism but are not actually derived, or excised, from a pre-existing source or host.

[0035] The term "subject" encompasses any warm-blooded animal, particularly including a member of the class *Mammalia* such as, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

[0036] As used herein, the term "continual measurement" intends a series of two or more measurements obtained from a particular biological system, which measurements are obtained using a single device maintained in operative contact with the biological system over the time period in which the series of measurements is obtained. The term thus includes continuous measurements.

[0037] The term "transdermal," as used herein, includes both transdermal and transmucosal techniques, i.e., extraction of a target analyte across skin or mucosal tissue. Aspects of the invention which are described herein in the context of "transdermal," unless otherwise specified, are meant to apply to both transdermal and transmucosal techniques.

[0038] The term "transdermal extraction," or "transdermally extracted" intends any noninvasive, or at least minimally invasive sampling method, which entails extracting and/or transporting an analyte from beneath a tissue surface across skin or mucosal tissue. The term thus includes extraction of an analyte using iontophoresis (reverse iontophoresis), electroosmosis, sonophoresis, microdialysis, suction, and passive diffusion. These methods can, of course, be coupled with application of skin penetration enhancers or skin permeability enhancing technique such as tape stripping or pricking with micro-needles. The term "transdermally extracted" also encompasses extraction techniques which employ thermal poration, electroporation, microfine lances, microfine canulas, subcutaneous implants or insertions, and the like.

[0039] The term "iontophoresis" intends a method for transporting substances across tissue by way of an application of electrical energy to the tissue. In conventional iontophoresis, a reservoir is provided at the tissue surface to serve as a container of material to be transported. Iontophoresis can be carried out using standard methods known to those of skill in the art, for example, by establishing an electrical potential using a direct current (DC) between fixed anode and cathode "iontophoretic electrodes," alternating a direct current between anode and cathode iontophoretic electrodes, or using a more complex waveform such as applying a current with alternating polarity (AP) between iontophoretic electrodes (so that each electrode is alternately an anode or a cathode).

[0040] The term "reverse iontophoresis" refers to the movement of a substance from a biological fluid across a membrane by way of an applied electric potential or current. In reverse iontophoresis, a reservoir is provided at the tissue surface to receive the extracted material.

[0041] "Electroosmosis" refers to the movement of a substance through a membrane by way of an electric field-induced convective flow. The terms iontophoresis, reverse iontophoresis, and electroosmosis, will be used interchangeably herein to refer to movement of any ionically charged or uncharged substance across a membrane (e.g., an epithelial membrane) upon application of an electric potential to the membrane through an ionically conductive medium.

Abbott Ex. 1002 - 171/1438

[0042] The term "sensing device," "sensing means," or "biosensor device" encompasses any device that can be used to measure the concentration of an analyte, or derivative thereof, of interest. Preferred sensing devices for detecting blood analytes generally include electrochemical devices and chemical devices. Examples of electrochemical devices include the Clark electrode system (see, e.g., Updike, et al., (1967) *Nature* 214:986-988), and other amperometric, coulometric, or potentiometric electrochemical devices. Examples of chemical devices include conventional enzyme-based reactions as used in the Lifescan® glucose monitor (Johnson and Johnson, New Brunswick, NJ) (see, e.g., U.S. Patent 4,935,346 to Phillips, et al.).

[0043] A "biosensor" or "biosensor device" includes, but is not limited to, a "sensor element" which includes, but is not limited to, a "biosensor electrode" or "sensing electrode" or "working electrode" which refers to the electrode that is monitored to determine the amount of electrical signal at a point in time or over a given time period, which signal is then correlated with the concentration of a chemical compound. The sensing electrode comprises a reactive surface which converts the analyte, or a derivative thereof, to electrical signal. The reactive surface can be comprised of any electrically conductive material such as, but not limited to, platinum-group metals (including, platinum, palladium, rhodium, ruthenium, osmium, and iridium), nickel, copper, silver, and carbon, as well as, oxides, dioxides, combinations or alloys thereof. Some catalytic materials, membranes, and fabrication technologies suitable for the construction of amperometric biosensors were described by Newman, J.D., et al. (*Analytical Chemistry* **67**(24), 4594-4599, 1995).

[0044] The "sensor element" can include components in addition to a biosensor electrode, for example, it can include a "reference electrode," and a "counter electrode." The term "reference electrode" is used herein to mean an electrode that provides a reference potential, e.g., a potential can be established between a reference electrode and a working electrode. The term "counter electrode" is used herein to mean an electrode in an electrochemical circuit which acts as a current source or sink to complete the electrochemical circuit. Although it is not essential that a counter electrode be employed where a reference electrode is included in the circuit and the electrode is capable of performing the function of a counter electrode, it is preferred to have separate counter and reference electrodes because the reference potential provided by the reference electrode is most stable when it is at equilibrium. If the reference electrode is required to act further as a counter electrode, the current flowing through the reference electrode may disturb this equilibrium. Consequently, separate electrodes functioning as counter and reference electrodes are most preferred.

[0045] In one embodiment, the "counter electrode" of the "sensor element" comprises a "bimodal electrode." The term "bimodal electrode" as used herein typically refers to an electrode which is capable of functioning non-simultaneously as, for example, both the counter electrode (of the "sensor element") and the iontophoretic electrode (of the "sampling means").

[0046] The terms "reactive surface," and "reactive face" are used interchangeably herein to mean the surface of the sensing electrode that: (1) is in contact with the surface of an electrolyte containing material (e.g. gel) which contains an analyte or through which an analyte, or a derivative thereof, flows from a source thereof; (2) is comprised of a catalytic material (e.g., carbon, platinum, palladium, rhodium, ruthenium, or nickel and/or oxides, dioxides and combinations or alloys thereof) or a material that provides sites for electrochemical reaction; (3) converts a chemical signal (e.g. hydrogen peroxide) into an electrical signal (e.g., an electrical current); and (4) defines the electrode surface area that, when composed of a reactive material, is sufficient to drive the electrochemical reaction at a rate sufficient to generate a detectable, reproducibly measurable, electrical signal that is correlatable with the amount of analyte present in the electrolyte.

[0047] The term "collection reservoir" and "collection insert" are used to describe any suitable containment means for containing a sample extracted from a biological system. The reservoir can include a material which is ionically conductive (e.g., water with ions therein), wherein another material such as a sponge-like material or hydrophilic polymer is used to keep the water in place. Such collection reservoirs can be in the form of a hydrogel (for example, in the shape of a disk or pad). Other suitable collection reservoirs include, but are not limited to, tubes, vials, capillary collection devices, cannulas, and miniaturized etched, ablated or molded flow paths.

[0048] An "ionically conductive material" refers to any material that provides ionic conductivity, and through which electrochemically active species can diffuse. The ionically conductive material can be, for example, a solid, liquid, or semi-solid (e.g., in the form of a gel) material that contains an electrolyte, which can be composed primarily of water and ions (e.g., sodium chloride), and generally comprises 50% or more water by weight. The material can be in the form of a gel, a sponge or pad (e.g., soaked with an electrolytic solution), or any other material that can contain an electrolyte and allow passage therethrough of electrochemically active species, especially the analyte of interest.

[0049] The term "physiological effect" encompasses effects produced in the subject that achieve the intended purpose of a therapy. In preferred embodiments, a physiological effect means that the symptoms of the subject being treated are prevented or alleviated. For example, a physiological effect would be one that results in the prolongation of survival in a patient.

[0050] A "laminate" , as used herein, refers to structures comprised of at least two bonded layers. The layers may be bonded by welding or through the use of adhesives. Examples of welding include, but are not limited to, the following: ultrasonic welding, heat bonding, and inductively coupled localized heating followed by localized flow. Examples of

Abbott Ex. 1002 - 172/1438

common adhesives include, but are not limited to, pressure sensitive adhesives, thermoset adhesives, cyanocrylate adhesives, epoxies, contact adhesives, and heat sensitive adhesives.

[0051] A "collection assembly", as used herein, refers to structures comprised of several layers, where the assembly includes at least one collection insert, for example a hydrogel. An example of a collection assembly of the present invention is a mask layer, collection inserts, and a retaining layer where the layers are held in appropriate, functional relationship to each other but are not necessarily a laminate, i.e., the layers may not be bonded together. The layers may, for example, be held together by interlocking geometry or friction.

[0052] An "autosensor assembly", as used herein, refers to structures generally comprising a mask layer, collection inserts, a retaining layer, an electrode assembly, and a support tray. The autosensor assembly may also include liners. The layers of the assembly are held in appropriate, functional relationship to each other.

[0053] The mask and retaining layers are preferably composed of materials that are substantially impermeable to the analyte (chemical signal) to be detected (e.g., glucose); however, the material can be permeable to other substances. By "substantially impermeable" is meant that the material reduces or eliminates chemical signal transport (e.g., by diffusion). The material can allow for a low level of chemical signal transport, with the proviso that the chemical signal that passes through the material does not cause significant edge effects at the sensing electrode.

[0054] "Substantially planar" as used herein, includes a planar surface that contacts a slightly curved surface, for example, a forearm or upper arm of a subject. A "substantially planar" surface is, for example, a surface having a shape to which skin can conform, i.e., contacting contact between the skin and the surface.

[0055] By the term "printed" as used herein is meant a substantially uniform deposition of an electrode formulation onto one surface of a substrate (i.e., the base support). It will be appreciated by those skilled in the art that a variety of techniques may be used to effect substantially uniform deposition of a material onto a substrate, e.g., Gravure-type printing, extrusion coating, screen coating, spraying, painting, or the like.

[0056] The term "signal-to-noise ratio" describes the relationship between the actual signal intended to be measured and the variation in signal in the absence of the analyte. The terms "S/N" and "SNR" are also used to refer to the signal-to-noise ratio. "Noise," as used herein, refers to any undesirable signal which is measured along with the intended signal.

[0057] As used herein, an "interfering species" is broadly defined as any moiety in an extracted sample that gives rise to signal noise and which is not a target analyte. The term thus includes any component of an extracted sample that provides a signal not related to the target analyte.

[0058] The term "enzyme" intends any compound or material which catalyzes a reaction between molecules to produce one or more reaction products. The term thus includes protein enzymes, or enzymatically active portions (fragments) thereof, which proteins and/or protein fragments may be isolated from a natural source, or recombinantly or synthetically produced. The term also encompasses designed synthetic enzyme mimetics.

General Methods

[0059] The present invention relates to a device for transdermally extracting and measuring the concentration of a target analyte present in a biological system. In preferred embodiments, the sensing device comprises a biosensor. The sampling device is used to extract small amounts of a target analyte from the biological system, and then sense and/or quantify the concentration of the target analyte. Measurement with the biosensor and/or sampling with the sampling device can be carried out in a continual or continuous manner. In one particular embodiment, a biosensor is used which comprises an electrochemical sensing element.

[0060] The analyte can be any specific substance or component that one is desirous of detecting and/or measuring in a chemical, physical, enzymatic, or optical analysis. Such analytes include, but are not limited to, amino acids, enzyme substrates or products indicating a disease state or condition, other markers of disease states or conditions, drugs of abuse, therapeutic and/or pharmacologic agents (e.g., theophylline, anti-HIV drugs, lithium, anti-epileptic drugs, cyclosporin, chemotherapeutics), electrolytes, physiological analytes of interest (e.g., urate/uric acid, carbonate, calcium, potassium, sodium, chloride, bicarbonate (CO_2), glucose, urea (blood urea nitrogen), lactate/lactic acid, hydroxybutyrate, cholesterol, triglycerides, creatine, creatinine, insulin, hematocrit, and hemoglobin), blood gases (carbon dioxide, oxygen, pH), lipids, heavy metals (e.g., lead, copper), and the like. In preferred embodiments, the analyte is a physiological analyte of interest, for example glucose, or a chemical that has a physiological action, for example a drug or pharmacological agent.

[0061] In order to facilitate detection of the analyte, an enzyme can be disposed in the collection reservoir, or, if several collection reservoirs are used, the enzyme can be disposed in several or all of the reservoirs. The selected enzyme is capable of catalyzing a reaction with the extracted analyte (in this case glucose) to the extent that a product of this reaction can be sensed, e.g., can be detected electrochemically from the generation of a current which current is detectable and proportional to the concentration or amount of the analyte which is reacted. A suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide. The subsequent detection

Abbott Ex. 1002 - 173/1438

of hydrogen peroxide on an appropriate biosensor electrode generates two electrons per hydrogen peroxide molecule which create a current which can be detected and related to the amount of glucose entering the device. Glucose oxidase (GOx) is readily available commercially and has well known catalytic characteristics. However, other enzymes can also be used, so long as they specifically catalyze a reaction with an analyte or substance of interest to generate a detectable product in proportion to the amount of analyte so reacted.

[0062] In like manner, a number of other analyte-specific enzyme systems can be used in the invention, which enzyme systems operate on much the same general techniques. For example, a biosensor electrode that detects hydrogen peroxide can be used to detect ethanol using an alcohol oxidase enzyme system, or similarly uric acid with urate oxidase system, urea with a urease system, cholesterol with a cholesterol oxidase system, and theophylline with a xanthine oxidase system.

[0063] In addition, the oxidase enzyme (used for hydrogen peroxide-based detection) can be replaced with another redox system, for example, the dehydrogenase-enzyme NAD-NADH, which offers a separate route to detecting additional analytes. Dehydrogenase-based sensors can use working electrodes made of gold or carbon (via mediated chemistry). Examples of analytes suitable for this type of monitoring include, but are not limited to, cholesterol, ethanol, hydroxybutyrate, phenylalanine, triglycerides, and urea. Further, the enzyme can be eliminated and detection can rely on direct electrochemical or potentiometric detection of an analyte. Such analytes include, without limitation, heavy metals (e.g., cobalt, iron, lead, nickel, zinc), oxygen, carbonate/carbon dioxide, chloride, fluoride, lithium, pH, potassium, sodium, and urea. Also, the sampling system described herein can be used for therapeutic drug monitoring, for example, monitoring anti-epileptic drugs (e.g., phenytion), chemotherapy (e.g., adriamycin), hyperactivity (e.g., ritalin), and anti-organ-rejection (e.g., cyclosporin).

[0064] One problem related to the use of transdermal extraction techniques relates to the presence of interfering species within an extracted sample, which species may be extracted by the transdermal sampling process, diffuse through the skin passively, and/or be secreted in perspiration or sebum. These interfering species (that is, any species detected by a sensor which is not the analyte of interest, or any species which interferes with, or reduces an analyte-specific signal) can give rise to significant background interferences, decreasing the overall sensor signal-to-noise response.

In addition, since transdermal sampling techniques generally extract very small quantities of analyte, sensor devices which are used for sensing and/or quantitating the extracted analyte need to perform reliably and reproducibly using small analyte concentrations (e.g., sub-mM) which are well below those measured by conventional detection techniques (which are generally in the mM range). As used herein, "sub-mM" refers to any concentration that is less than 1 mM. Thus, background interferences which may not be problematic in other applications may produce critical interferences with transdermal sampling systems which measure sub-mM concentrations of extracted analyte. The present invention is concerned with the reduction of such interferences.

[0065] Accordingly, the sampling system of the invention may be used in a method for measuring the concentration of an analyte present in a biological system. The method includes a measurement cycle having an extraction step in which a sample containing the analyte is transdermally extracted from the biological system using a sampling system that is in operative contact with a skin or mucosal surface of said biological system. A sensing step is also carried out during the measurement cycle. In the sensing step, the extracted sample is contacted with a sensor to obtain a measurement signal that is related to analyte concentration. The measurement cycle further comprises a process for selectively favoring analyte-specific signal components over signal components due to interfering species, wherein the process can entail (a) a differential signal process which subtracts non-analyte signal components from the measurement signal, (b) a delay step which is performed between the extraction and sensing steps, (c) a selective electrochemical detection process which is performed during the sensing step, (d) a purge step which is performed after the sensing step, (e) a charge segregation step (e.g., uric acid migrates to the anode, and glucose to the cathode, as in Example 1), and (f) any combination of the processes of (a)-(e).

[0066] The transdermal sampling device used to extract the sample can employ any suitable minimally invasive or noninvasive sampling technique including, for example, iontophoresis, sonophoresis, suction, electroporation, thermal poration, passive diffusion, use of microfine (miniature) lances or cannulas, use of subcutaneous implants or insertions, and use of laser devices. The sensing step can be carried out using any suitable sensing methodology, for example, colormetric, chemical (e.g., enzyme-based reactions) or electrochemical (e.g., amperometric, coulometric, or potentiometric) methods.

[0067] The differential signal process can be carried out in several ways. For example, the extracted sample can be divided into two portions, wherein a first portion is contacted with the sensor to obtain a signal that predominantly contains signal components due to interfering species and background variations. The second portion is contacted with the sensor to obtain a measurement signal that contains analyte-specific signal components, and the first signal is then subtracted from the second in order to obtain a refined signal that is specifically related to the analyte. An analyte-specific signal can be readily obtained using an enzyme which reacts specifically with the analyte to produce a detectable signal. For example, if the analyte is glucose, the glucose oxidase enzyme can be contacted with the

Abbott Ex. 1002 - 174/1438

second sample portion. This enzyme catalyzes a reaction with glucose to generate hydrogen peroxide, which can then be detected using conventional electrochemical biosensors.

[0068] Alternatively, the differential signal process can be carried out by extracting two samples from the biological system, wherein at least one of the samples contains the target analyte. The samples are then contacted with a suitable sensor, whereby a first signal is obtained from one of the samples and contains predominantly signal components due to interfering species and background variations (e.g., a blank signal). A second signal is obtained from the other sample and contains analyte-specific signal components (e.g., an active signal). Subtraction of the first signal from the second provides a refined signal that is specifically related to the analyte. Here again, an analyte-specific signal can be readily obtained using a enzyme which reacts specifically with the analyte in the second sample to produce a detectable signal. The first sample can be obtained using any transdermal sampling technique, including both passive and active collection techniques, while the second sample is generally obtained using active sampling techniques, e. g., iontophoresis or sonophoresis. The sensor or sensors which are used to obtain the signals can, of course, be attached to, or be integral with the sampling device used in the extraction step, or can be part of a discrete sensing apparatus.

[0069] The selective electrochemical detection process can be carried out as follows. Electrochemical detection using biosensor electrodes allows for a variety of selective detection processes, wherein the electrodes can be operated at lowered or raised potentials in order to favor detection of analyte-specific electrochemical signal over signal due to interfering species or background variance. For example, operating an electrochemical biosensor electrode at a potential of about 0.5V or less allows one to avoid signal components due to common interfering species collected with transdermal sampling devices.

[0070] In each of the above methods, the sample or samples can be extracted into a suitable collection reservoir(s) placed in operative contact with the biological system (e.g., contacted with a skin or mucosal surface of a subject). In addition, a sensor can be included with each collection reservoir to detect extracted substances. In use, the transdermal sampling device is preferably maintained in contact with the biological system in order to provide for continual or continuous monitoring of the analyte concentration.

[0071] In the context of such continual or continuous monitoring of the analyte (e.g., where the sampling device is maintained in contact with the system to obtain two or more samples and analyte measurements), the method can further include a purge step wherein residual signal is reduced or substantially eliminated from the sampling system (e.g., from one or more collection reservoir) between measurements. If required, the purge step can be carried out using an electrochemical sensor electrode which is contacted with the reservoir during the sensing operation. Further, the electrode can be operated at a raised potential in order to ensure that residual signal components are removed from the sampling system. Exemplary purge techniques are described in detail herein below. An optional delay step can also be included between the extraction and sensing steps in order to improve the signal-to-noise ratio in detected signals.

[0072] Although all of the devices of the invention are broadly applicable to sampling any chemical analyte and/or substance, the invention is expressly exemplified hereafter for use in transdermal sampling and quantifying or qualifying glucose or a glucose metabolite.

[0073] Accordingly, an automatic sampling system may be used to monitor levels of glucose in a biological system. The method is carried out using a sampling system (device) which transdermally extracts glucose from the system, in this case, an animal subject. Transdermal extraction is carried out by applying an electrical current to a tissue surface at a collection site. The electrical current is used to extract small amounts of glucose from the subject into one or more collection reservoirs. At least one collection reservoir is in contact with a biosensor which provides for measurement of glucose concentration in the subject.

[0074] More particularly, a collection reservoir is contacted with a tissue surface, for example, the stratum corneum of a patient's skin. An electrical force is then applied to the tissue surface in order to extract glucose or a glucose metabolite from the tissue into the collection reservoir. Extraction is typically performed for a period of about 1-20 minutes. If desired, however, extraction can be carried out continually or continuously over a period of about 1-24 hours, or longer. After extraction, the collection reservoir is analyzed to measure the amount or concentration of glucose or glucose metabolite contained therein. The measured value correlates with the subject's blood glucose level. If continual or continuous sampling is desired, the collection reservoir is analyzed periodically or continuously to measure the glucose analyte.

[0075] In certain embodiments of the invention, one or more additional collection reservoirs are used in the transdermal sampling system. These additional collection reservoirs are also contacted with an electrode which generates a current sufficient to extract substances from the tissue into the collection reservoir.

[0076] The collection reservoirs which are used with the iontophoretic sampling system generally contain an ionically conductive liquid or liquid-containing medium. The conductive medium is preferably a hydrogel which can contain ionic substances in an amount sufficient to produce high ionic conductivity. The hydrogel is formed from a solid or liquid material (solute) which, when combined with water, forms a gel by the formation of a structure which holds water

Abbott Ex. 1002 - 175/1438

including interconnected cells and/or network structure formed by the solute. Suitable hydrogel formulations are described in International Publication Nos. WO 97/02811, published 30 January 1997, and WO 96/00110, published 4 January 1996.

[0077] Since the sampling system of the present invention is intended to be operated at very low (electrochemical) background noise levels, all components of the system which will be in contact with extracted sample (e.g., the collection reservoirs) preferably do not contain or contribute significant electrochemically sensitive components and/or contaminants. Thus, components of the system are generally formulated using a judicious selection of materials and reagents which do not add significant amounts of electrochemical contaminants to the final system.

[0078] In order to facilitate detection of the analyte, an enzyme can be disposed in the collection reservoir, or, if several collection reservoirs are used, the enzyme can be disposed in several or all of the reservoirs. The selected enzyme is capable of catalyzing a reaction with the extracted analyte (in this case glucose) to the extent that a product of this reaction can be sensed, e.g., can be detected electrochemically from the generation of a current which current is detectable and proportional to the concentration or amount of the analyte which is reacted. A suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide. The subsequent detection of hydrogen peroxide on an appropriate biosensor electrode generates two electrons per hydrogen peroxide molecule which create a current which can be detected and related to the amount of glucose entering the device. Glucose oxidase (GOx) is readily available commercially and has well known catalytic characteristics. However, other enzymes can also be used, so long as they specifically catalyze a reaction with an analyte or substance of interest to generate a detectable product in proportion to the amount of analyte so reacted.

[0079] In like manner, a number of other analyte-specific enzyme systems can be used in the invention, which enzyme systems operate on much the same general techniques. For example, a biosensor electrode that detects hydrogen peroxide can be used to detect ethanol using an alcohol oxidase enzyme system, or similarly uric acid with urate oxidase system, cholesterol with a cholesterol oxidase system, and theophylline with a xanthine oxidase system.

[0080] Referring again to the glucose sampling system exemplified herein, as the glucose analyte is transdermally extracted into the collection reservoir, it reacts with the GOx within the reservoir to produce hydrogen peroxide. The presence of hydrogen peroxide generates a current at the biosensor electrode that is directly proportional to the amount of hydrogen peroxide in the reservoir. This current provides a signal which can be detected and interpreted by an associated system controller to provide a glucose concentration value for display.

[0081] If desired, the detected current can be correlated with the subject's blood glucose concentration so that the system controller displays the subject's actual blood glucose concentration as measured by the sampling system. For example, the system can be calibrated to the subject's actual blood glucose concentration by sampling the subject's blood during a standard glucose tolerance test, and analyzing the blood glucose using both a standard blood glucose monitor and the sampling system of the present invention. In this manner, measurements obtained by the sampling system can be correlated to actual values using known statistical techniques.

[0082] Iontophoretic extraction can be carried out as follows. A first iontophoretic electrode is contacted with the collection reservoir (which is in contact with a target tissue surface), and a second iontophoretic electrode is contacted with either a second collection reservoir in contact with the tissue surface, or some other ionically conductive medium in contact with the tissue. A power source provides an electric potential between the two electrodes to perform reverse iontophoresis in a manner known in the art.

[0083] An electric potential (either direct current or a more complex waveform) is applied between the two iontophoresis electrodes such that current flows from the first electrode through the first conductive medium into the skin, and back out from the skin through the second conductive medium to the second electrode. This current flow extracts substances through the skin into the one or more collection reservoirs through the process of reverse iontophoresis or electroosmosis. The electric potential may be applied as described in International Publication No. WO 96/00110, published 4 January 1996. Any suitable iontophoretic electrode system can be employed, however it is preferred that a silver/silver chloride (Ag/AgCl) electrode system is used.

[0084] Referring now to Figures 1A and 1B, one particular iontophoretic collection reservoir and electrode assembly for use in such transdermal sensing devices is generally indicated at **2.** The assembly comprises two iontophoretic collection reservoirs, **4** and **6,** each having a conductive medium **8,** and **10** (preferably cylindrical hydrogel pads), respectively disposed therein. First (**12**) and second (**14**) ring-shaped iontophoretic electrodes are respectively contacted with conductive medium **8** and **10.** The first iontophoretic electrode **12** surrounds three biosensor electrodes which are also contacted with the conductive medium **8**, a working electrode **16**, a reference electrode **18**, and a counter electrode **20**. A guard ring **22** separates the biosensor electrodes from the iontophoretic electrode **12** to minimize noise from the iontophoretic circuit. Conductive contacts provide communication between the electrodes and an associated power source and control means as described in detail below. A similar biosensor electrode arrangement can be contacted with the conductive medium **10**, or the medium can not have a sensor means contacted therewith.

[0085] Referring now to Figure 2, the iontophoretic collection reservoir and electrode assembly **2** of Figures 1A and 1B is shown in exploded view in combination with a suitable iontophoretic sampling device housing **32**.

Abbott Ex. 1002 - 176/1438

The housing can be a plastic case or other suitable structure which preferably is configured to be worn on a subjects arm in a manner similar to a wrist watch. As can be seen, conductive media **8** and **10** (hydrogel pads) are separable from the assembly **2**; however, when the assembly **2** and the housing **32** are assembled to provide an operational iontophoretic sampling device **30**, the media are in contact with the electrodes to provide a electrical contact therewith.

[0086] Referring now to Figure 3, an exploded view of the key components from one embodiment of an iontophoretic sampling system is presented. The sampling system components include two biosensor/iontophoretic electrode assemblies, **304** and **306,** each of which have an annular iontophoretic electrode, respectively indicated at **308** and **310**, which encircles a biosensor **312** and **314**. The electrode assemblies **304** and **306** are printed onto a polymeric substrate **316** which is maintained within a sensor tray **318.** A collection reservoir assembly **320** is arranged over the electrode assemblies, wherein the collection reservoir assembly comprises two hydrogel inserts **322** and **324** retained by a gel retaining layer **326** and a mask layer **328**.

[0087] In one embodiment, the electrode assemblies can include bimodal electrodes as shown in Figure 4.

[0088] The components shown in exploded view in Figure 3 are intended for use in a automatic sampling device which is configured to be worn like an ordinary wristwatch. As described in International Publication No. WO 96/00110, published 4 January 1996, the wristwatch housing (not shown) contains conductive leads which communicate with the iontophoretic electrodes and the biosensor electrodes to control cycling and provide power to the iontophoretic electrodes, and to detect electrochemical signals produced at the biosensor electrode surfaces. The wristwatch housing can further include suitable electronics (e.g., microprocessor, memory, display and other circuit components) and power sources for operating the automatic sampling system.

[0089] Modifications and additions to the embodiment of Figure 3 will be apparent to those skilled in the art in light of the teachings of the present specification.

[0090] A power source (e.g., one or more rechargeable or nonrechargeable batteries can be disposed within the housing **32** or within the straps **34** which hold the device in contact with a skin or mucosal surface of a subject. In use, an electric potential (either direct current or a more complex waveform) is applied between the two iontophoretic electrodes **12** and **14** such that current flows from the first iontophoretic electrode **12**, through the first conductive medium **8** into the skin or mucosal surface, and then back out through the second conductive medium **10** to the second iontophoretic electrode **14**. The current flow is sufficient to extract substances including an analyte of interest through the skin into one or both of collection reservoirs **4** and **6**. -The electric potential may be applied using any suitable technique, for example, the applied current density may be in the range of about 0.01 to 0.5 mA/cm^2. In a preferred embodiment, the device is used for continual or continuous monitoring, and the polarity of iontophoretic electrodes **12** and **14** is alternated at a rate of about one switch every 10 seconds to about one switch every hour so that each electrode is alternately a cathode or an anode. The housing **32** can further include an optional temperature sensing element (e.g., a thermistor, thermometer, or thermocouple device) which monitors the temperature at the collection reservoirs to enable temperature correction of sensor signals. The housing can further include an optional conductance sensing element (e.g., an integrated pair of electrodes) which monitors conductance at the skin or mucosal surface to enable data screening correction or invalidation of sensor signals.

[0091] After a suitable iontophoretic extraction period, one or both of the sensor electrode sets can be activated in order to detect extracted substances including the analyte of interest.

[0092] Further, the sampling device can operate in an alternating polarity mode using first and second bimodal electrodes (Figure 5, **50** and **51**) and two collection reservoirs (Figure 5, **57** and **58**). Each bi-modal electrode (Figure 4, **40**; Figure 5, **50** and **51**) serves two functions depending on the phase of the operation: (1) an electro-osmotic electrode (or iontophoretic electrode) used to electrically draw analyte from a source into a collection reservoir comprising water and an electrolyte, and to the area of the electrode subassembly; and (2) as a counter electrode to the first sensing electrode at which the chemical compound is catalytically converted at the face of the sensing electrode to produce an electrical signal.

[0093] The reference (Figure 5, **54** and **55**; Figure 4, 42) and sensing electrodes (Figure 5, **52** and **53**; Figure 4, **41**), as well as, the bimodal electrode (Figure 5, **50** and **51;** Figure 4, **40**) are connected to a standard potentiostat circuit during sensing. In general, practical limitations of the system require that the bimodal electrode will not act as both a counter and iontophoretic electrode simultaneously.

[0094] The general operation of an iontophoretic sampling system in this embodiment is the cyclical repetition of two phases: (1) a reverse-iontophoretic phase, followed by a (2) sensing phase. During the reverse iontophoretic phase, the first bimodal electrode (Figure 5, **50**) acts as an iontophoretic cathode and the second bimodal electrode (Figure 5, **51**) acts as an iontophoretic anode to complete the circuit. Analyte is collected in the reservoirs, for example, a hydrogel (Figure 5, **57** and **58**). At the end of the reverse iontophoretic phase, the iontophoretic current is turned off. During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (Figure 5, **54**) and the sensing electrode (Figure 5, **52**). The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (Figure 5, **52**) producing an electrical current, while the first bi-modal electrode (Figure 5, **50**) acts as a counter electrode to complete the electrical circuit.

Abbott Ex. 1002 - 177/1438

[0095] The electrode described is particularly adapted for use in conjunction with a hydrogel collection reservoir system for monitoring glucose levels in a subject through the reaction of collected glucose with the enzyme glucose oxidase present in the hydrogel matrix.

[0096] The bi-modal electrode is preferably comprised of Ag/AgCl. The electrochemical reaction which occurs at the surface of this electrode serves as a facile source or sink for electrical current. This property is especially important for the iontophoresis function of the electrode. Lacking this reaction, the iontophoresis current could cause the hydrolysis of water to occur at the iontophoresis electrodes causing pH changes and possible gas bubble formation. The pH changes to acidic or basic pH could cause skin irritation or burns. The ability of an Ag/AgCl electrode to easily act as a source of sink current is also an advantage for its counter electrode function. For a three electrode electrochemical cell to function properly, the current generation capacity of the counter electrode should not limit the speed of the reaction at the sensing electrode. In the case of a large sensing electrode, the counter electrode should be able to source proportionately larger currents.

[0097] The design of the sampling system provides for a larger sensing electrode (see for example, Figure 4) than previously designed. Consequently, the size of the bimodal electrode should be sufficient so that when acting as a counter electrode with respect to the sensing electrode the counter electrode does not become limiting the rate of catalytic reaction at the sensing electrode catalytic surface.

[0098] Two methods exist to ensure that the counter electrode does not limit the current at the sensing electrode: (1) the bi-modal electrode is made much larger than the sensing electrode, or (2) a facile counter reaction is provided.

[0099] During the reverse iontophoretic phase, the power source provides a current flow to the first bi-modal electrode to facilitate the extraction of the chemical signal into the reservoir. During the sensing phase, the power source is used to provide voltage to the first sensing electrode to drive the conversion of chemical signal retained in the reservoir to electrical signal at the catalytic face of the sensing electrode. The power source also maintains a fixed potential at the electrode where, for example, hydrogen peroxide is converted to molecular oxygen, hydrogen ions, and electrons, which is compared with the potential of the reference electrode during the sensing phase. While one sensing electrode is operating in the sensing mode it is electrically connected to the adjacent bimodal electrode which acts as a counter electrode at which electrons generated at the sensing electrode are consumed.

[0100] The electrode sub-assembly can be operated by electrically connecting the bimodal electrodes such that each electrode is capable of functioning as both an iontophoretic electrode and counter electrode along with appropriate sensing electrode(s) and reference electrode(s), to create standard potentiostat circuitry.

[0101] A potentiostat is an electrical circuit used in electrochemical measurements in three electrode electrochemical cells. A potential is applied between the reference electrode and the sensing electrode. The current generated at the sensing electrode flows through circuitry to the counter electrode (i.e., no current flows through the reference electrode to alter its equilibrium potential). Two independent potentiostat circuits can be used to operate the two biosensors. For the purpose of the present sampling system, the electrical current measured at the sensing electrode subassembly is the current that is correlated with an amount of chemical signal.

[0102] With regard to continual operation for extended periods of time, Ag/AgCl electrodes are provided herein which are capable of repeatedly forming a reversible couple which operates without unwanted electrochemical side reactions (which could give rise to changes in pH, and liberation of hydrogen and oxygen due to water hydrolysis). The Ag/AgCl electrodes of the present sampling system are thus formulated to withstand repeated cycles of current passage in the range of about 0.01 to 1.0 mA per cm^2 of electrode area. With regard to high electrochemical purity, the Ag/AgCl components are dispersed within a suitable polymer binder to provide an electrode composition which is not susceptible to attack (e.g., plasticization) by components in the collection reservoir, e.g., the hydrogel composition. The electrode compositions are also formulated using analytical- or electronic-grade reagents and solvents, and the polymer binder composition is selected to be free of electrochemically active contaminants which could diffuse to the biosensor to produce a background current.

[0103] Because the Ag/AgCl iontophoretic electrodes must be capable of continual cycling over extended periods of time, the absolute amounts of Ag and AgCl available in the electrodes, and the overall Ag/AgCl availability ratio, can be adjusted to provide for the passage of high amounts of charge. Although not limiting in the sampling system described herein, the Ag/AgCl ratio can approach unity. In order to operate within the preferred system which uses a biosensor having a geometric area of 0.1 to 3 cm^2, the iontophoretic electrodes are configured to provide an approximate electrode area of 0.3 to 1.0 cm^2, preferably about 0.85 cm^2. These electrodes provide for reproducible, repeated cycles of charge passage at current densities ranging from about 0.01 to 1.0 mA/cm^2 of electrode area. More particularly, electrodes constructed according to the above formulation parameters, and having an approximate electrode area of 0.85 cm^2, are capable of a reproducible total charge passage (in both anodic and cathodic directions) of 270 mC, at a current of about 0.3 mA (current density of 0.35 mA/cm^2) for at least about 48 cycles in a 24 hour period.

[0104] Once formulated, the Ag/AgCl electrode composition is affixed to a suitable rigid or flexible nonconductive surface as described above with respect to the biosensor electrode composition. A silver (Ag) underlayer is first applied to the surface in order to provide uniform conduction. The Ag/AgCl electrode composition is then applied over the Ag

Abbott Ex. 1002 - 178/1438

underlayer in any suitable pattern or geometry using various thin film techniques, such as sputtering, evaporation, vapor phase deposition, or the like, or using various thick film techniques, such as film laminating, electroplating, or the like. Alternatively, the Ag/AgCl composition can be applied using screen printing, pad printing, inkjet methods, transfer roll printing, or similar techniques. Preferably, both the Ag underlayer and the Ag/AgCl electrode are applied using a low temperature screen print onto a polymeric substrate. This low temperature screen print can be carried out at about 125 to 160°C, and the screening can be carried out using a suitable mesh, ranging from about 100-400 mesh.

[0105] In one embodiment of the present invention, the sampling system can have two collection reservoirs which contain, for example, an active collection reservoir, having the GOx enzyme, and a blank collection reservoir (without the GOx enzyme); or, in an alternative, two active reservoirs, i.e., two reservoirs containing the GOx enzyme. In the case of an active collection reservoir and a blank collection reservoir signal can be adjusted by subtraction of the blank reservoir signal from the signal obtained from the active reservoir. In the case of two active collection reservoirs the signals can be summed and averaged, or a total of the two signals can be used. This signal, for example the detected current, is then used alone or in combination with other factors (for example, glucose concentration at a calibration point, skin temperature, conductivity, voltage, time since calibration of the system, etc.) to provide a glucose concentration value. The measurement cycle can further include a process for selectively favoring analyte-specific signal components over signal components due to interfering species (as described below). Such process can include, but are not limited to, (a) a differential signal process which subtracts non-analyte signal components from the measurement signal, (b) a delay step which is performed between the extraction and sensing steps, (c) a selective electrochemical detection process which is performed during the sensing step, (d) a purge step which is performed after the sensing step, (e) a charge segregation step (e.g., uric acid migrates to the anode, and glucose to the cathode, as in Example 1), and (f) any combinations of (a) to (e).

[0106] In particular embodiments, the detected current can be correlated with the subject's blood glucose concentration (typically using statistical algorithms associated with a microprocessor) so that the system controller may display the subject's actual blood glucose concentration as measured by the sampling system. For example, the system can be calibrated to the subject's actual blood glucose concentration by sampling the subject's blood during a standard glucose tolerance test, and analyzing the blood glucose using both a standard blood glucose monitor and the sampling system of the present invention. In addition or alternately, the sampling system can be calibrated at a calibration time point where the signal obtained from the sampling system at that time point is correlated to blood glucose concentration at that time point as determined by direct blood testing (for example, glucose concentration can be determined using a HemoCue® clinical analyzer (HemoCue AB, Sweden)). In this manner, measurements obtained by the sampling system can be correlated to actual values using known statistical techniques. Such statistical techniques can be formulated as algorithm(s) and incorporated in a microprocessor associated with the sampling system.

[0107] Operation of the iontophoretic sampling device **30** is optionally controlled by a controller **36** (e.g., a microprocessor), which interfaces with the iontophoretic electrodes, the sensor electrodes, the power supply, the optional temperature and/or conductance sensing elements, a display and other electronics. For example, the controller **36** can include a programmable controlled circuit source/sink drive for driving the iontophoretic electrodes. Power and reference voltage are provided to the sensor electrodes, and signal amplifiers can be used to process the signal from the working electrode or electrodes. In general, the controller discontinues the iontophoretic current drive during sensing periods. A sensor confidence loop can be provided for continually monitoring the sampling system to ensure proper operations.

[0108] User control can be carried out using push buttons located on the housing **32**, and an optional liquid crystalline display (LCD) can provide visual prompts, readouts and visual alarm indications. The microprocessor generally uses a series of programmed sequences to control the operations of the sampling device, which sequences can be stored in the microprocessor's read only memory (ROM). Embedded software (firmware) controls activation of measurement and display operations, calibration of analyte readings, setting and display of high and low analyte value alarms, display and setting of time and date functions, alarm time, and display of stored readings. Sensor signals obtained from the sensor electrodes can be processed before storage and display by one or more signal processing functions or algorithms provided by the embedded software. The microprocessor can also include an electronically erasable, programmable, read only memory (EEPROM) for storing calibration parameters, user settings and all downloadable sequences.

[0109] Further, the sampling system can be pre-programmed to begin execution of its signal measurements (or other functions) at a designated time. One application of this feature is to have the sampling system in contact with a subject and to program the sampling system to begin sequence execution during the night so that it is available for calibration immediately upon waking. One advantage of this feature is that it removes any need to wait for the sampling system to warm-up before calibrating it.

[0110] As discussed above, the sensitivity of such iontophoretic extraction and electrochemical detection methodologies can be affected by the presence of interfering species within an extracted sample. These interfering species may be extracted by the iontophoretic sampling process, diffuse through the skin passively, or may be extracted in perspiration or sebum, and can give rise to significant background interferences, decreasing the overall sensor re-

Abbott Ex. 1002 - 179/1438

sponse. For example, in the glucose-specific monitoring system exemplified herein, the GOx enzyme is highly specific for glucose. However, the biosensor electrode will oxidize any interfering species present in the extracted sample that is oxidizable at the applied potential, resulting in interference with the hydrogen peroxide signal.

[0111] In particular, a number of substances commonly found in iontophoretically extracted body fluids can interfere with the hydrogen peroxide signal. Several of these interfering species, such as ascorbic acid, uric acid, and certain amino acids (e.g., tryptophan and tyrosine) can react with the reactive surface of the biosensor and result in substantial signal interference. These major interfering species can be divided into two broad classes which will behave differently under an applied electric potential; that is, they are either charged (ionic) substances, or uncharged (substantially neutral) substances. Ascorbic acid and uric acid are negatively charged (anionic) substances. Tryptophan and tyrosine are substantially neutral substances. During iontophoretic sampling, negatively charged species are preferentially extracted toward the anodal electrode, while positively charged and neutral species are preferentially extracted toward the cathodal electrode. These and other interfering species will also be present in any transdermally extracted sample obtained from a subject.

[0112] In use of the invention, an iontophoretic sampling system is used to measure the concentration of the analyte in the biological system. The iontophoretic sampling system is configured to have two collection reservoirs, and provides for a selective extraction step as follows. Each reservoir is in contact with a single iontophoretic electrode, and a direct current is used to establish an electric potential between the two electrodes during iontophoretic extraction. Thus, the electrode in a first reservoir serves as the iontophoretic anode, and the electrode in the second reservoir serves as the iontophoretic cathode. Only the second (cathodic) collection reservoir also contains the biosensor electrode. Thus, analyte detection is carried out with an extracted sample that has a reduced amount of interfering species, since negatively charged species (e.g., ascorbic acid and uric acid) are preferentially extracted into the anodic collection reservoir.

[0113] The benefits provided by this selective extraction technique can be enhanced using any one, or a combination of the following optional techniques. In one embodiment, selective cathodic extraction is combined with a means for obtaining a "blank" signal which can be used to subtract a portion of the cathodic signal which is derived from the positively charged and/or neutral interfering species. More particularly, the above-described two-reservoir iontophoretic sampling device is used to carry out cathode-selective detection in a continual manner. Each reservoir is in contact with a single iontophoretic electrode, and a direct current is used to establish an electric potential between the two electrodes during iontophoretic extraction. Both reservoirs also contain a biosensor electrode; however, glucose detection is only carried out in the cathodic reservoir which contains the GOx enzyme. A number of measurement cycles are carried out in a continual or continuous manner over an operational period of about 1-24 hours or longer. In order to increase the operational lifetime of the collection reservoirs and iontophoretic electrodes during this continual or continuous sampling, the polarity of the reservoirs can be alternated such that each reservoir serves as the anode at least during a portion of a measurement cycle (i.e., after each iontophoretic half cycle).

[0114] In a preferred use of the above system, a detection cycle is carried out after each iontophoretic half cycle. For example, each measurement cycle entails the following: an iontophoretic extraction is carried out for a first phase of the extraction step using the first collection reservoir as the cathode; a detection step is then carried out during a first phase of the sensing step to detect substances extracted during the first phase of the extraction; an iontophoretic extraction is carried out for a second phase of the extraction step using the second reservoir as the cathode; and a second detection step-is then carried out during a second phase of the sensing step. Only biosensor measurements from the cathodes are recorded. However, activation of the biosensor electrodes in the anode reservoirs is effective to deplete (e.g., purge) the concentration of substances (including interfering species) collected therein by chemical reaction with the reactive surface of the electrode. In this manner, activation of the biosensor electrode in the anode reservoir helps purge the sampling system and substantially remove residual signal components therefrom.

[0115] Detection is carried out for a sufficient time to ensure that all of the glucose collected in the cathodic reservoir has been subjected to a reaction and is therefore no longer detectable, and the biosensor current generated in the cathode is related to the concentration of glucose in the subject at the approximate time of sample collection. In addition, the duration of each detection step should be sufficient to eliminate or substantially reduce the interfering species preferentially collected into the anodic reservoir. As will be understood by the ordinarily skilled artisan upon reading the instant disclosure, both the iontophoretic extraction phases (half cycles) and the sensing phases can be tailored to account for the various diffusion characteristics of both the analyte (glucose) and the major interfering species in a particular collection reservoir (e.g., reservoir composition and geometry), as well as for chemical equilibria associated with the analyte/enzyme system (e.g., mutarotation of the glucose molecule).

[0116] After the completion of each measurement cycle, the process is repeated and subsequent measurements are obtained. If desired, the biosensor electrodes can be activated before the initial measurement cycle, and in between subsequent measurement cycles, and/or in between sensing and extraction phases of a measurement cycle. Activation of the biosensors is maintained for a sufficient period of time to substantially reduce or eliminate background electrochemical signal and/or residual analyte and interfering species. The biosensor signal can be monitored during the activation phase and, after the device has been activated for a suitable period of time (as indicated by obtaining a

Abbott Ex. 1002 - 180/1438

stable signal), the measurement cycle can be initiated. Optionally, a measurement can be taken from the sensor after it reaches stasis, which measurement can then be used to establish a baseline background signal value. This background signal value can be subtracted from an actual cathode signal measurement value (which includes both analyte-specific and background components) to obtain a corrected measurement value.

[0117] In a related embodiment which uses the above alternating extraction/detection cycles, an additional purging step can be carried out during one or more of the measurement cycles, wherein the biosensor electrodes are activated in between a detection step and before a subsequent extraction step (e.g., in between a first phase of the detection step and a second phase of the extraction step) and in order to purge the sampling system of residual signal components (both analyte-specific and signal due to interfering species). As described above, activation of the biosensor electrode depletes both residual analyte signal and signal due to residual interfering species by chemical reaction with the reactive surface of the electrode. During the purge step, the biosensor electrode can be operated at a potential of about 0.6V or greater in order to ensure that the purge is substantially complete.

[0118] In one preferred use of the system, the iontophoretic sampling system is operated to provide a measurement cycle having the following components: a first phase of the extraction step wherein the first reservoir is operated as the iontophoretic cathode; a first phase of the sensing step wherein an electrochemical signal is obtained from the first reservoir; a purging step to remove residual signal from the sampling system; a second phase of the extraction step wherein the second reservoir is operated as the iontophoretic cathode; and a second phase of the sensing step wherein an electrochemical signal is obtained from the second reservoir. If desired, the first reservoir can have the enzyme excluded therefrom, such that the first signal predominantly contains signal components due to interfering species and background variations, and the second signal contains analyte-specific signal components. In this manner, a subtraction step can also be used to obtain a signal which is specifically related to the analyte, for example where the first signal is subtracted from the second signal.

[0119] Alternatively, both reservoirs can contain the enzyme such that cathodic signals can be obtained to provide two "active" analyte-specific signals. For continuous or continual monitoring applications, the purge step can performed once, or several times during the continual or continuous monitoring period. In one aspect, the purge step is performed between each sensing step and a subsequent extraction step. As will be understood by the ordinarily skilled artisan upon reading the instant specification, the preferential extraction techniques described herein which entail sensing extracted substances in the cathode to obtain analyte-specific information can be used to monitor any positively charged or neutral substance. If, however, the methods are used to monitor negatively charged substances, detection will be carried out at the anode, since such analytes will be preferentially extracted into the anode during iontophoretic extraction.

[0120] In another related aspect which uses the above alternating extraction/detection cycles, a delay period can also be used to maximize the detectable glucose signal. More particularly, a delay period is imposed between each iontophoretic half cycle extraction and its corresponding sensing step. During this delay period, the glucose analyte is converted to the hydrogen peroxide signal, and the effect of the rate-limiting process related to mutarotation of glucose is reduced. The delay can be for any suitable period of time, for example, from about 15 seconds to about 20 minutes, preferably about 1-7 minutes. Use of such a sensor delay allows for a reduction in biosensor detection time, where detection can be limited from about 10 seconds to about 30 minutes, preferably from about 30 seconds to about 10 minutes, and most preferably from about 90 seconds to about 5 minutes. The combination of the sensor delay and the shortened detection time reduces the overall noise obtained with the biosensor measurement, but provides for the same analyte signal, improving the signal-to-noise ratio of the analyte measurement. As described above, the biosensor electrode can optionally be kept on for a longer period (e.g., during a purging step) in order to substantially deplete signal due to residual analyte and/or interfering species in the collection reservoirs.

[0121] In yet a further aspect, preferential (selective cathodic) extraction is combined with a means for reducing the signal produced by the interfering tryptophan and tyrosine species collected in the cathodic reservoir. In this regard, the iontophoretic sampling systems described herein typically employ a biosensor having a platinum-containing electrode which is highly sensitive to the hydrogen peroxide signal produced by the GOx enzyme. The potential of such biosensor electrodes is generally set at about 0.6V, where the hydrogen peroxide current-voltage curve is at a plateau. However, at this operating potential, the signal from tryptophan and tyrosine cannot be differentiated from the hydrogen peroxide (glucose-specific) signal.

[0122] Accordingly, in the present aspect, the potential of the biosensor electrode is reduced in order to decrease the non-glucose signal. In particular, the potential can be reduced to about 0.5V or less, at which potentials the signal from tryptophan and tyrosine is greatly reduced without a concomitant reduction in the analyte-specific (hydrogen peroxide) signal. In one particular aspect, the potential is reduced to about 0.42V in order to substantially eliminate the signal component due to the tryptophan and tyrosine interfering species.

[0123] Each of the techniques used in the above-described two-reservoir iontophoretic sampling devices can be applied to sampling devices comprising three or more such reservoirs. Accordingly, the sampling device of the invention may be used in a method for measuring the concentration of an analyte present in a biological system which entails

Abbott Ex. 1002 - 181/1438

transdermally extracting the analyte from the biological system in an extraction step using an iontophoretic sampling system that comprises first and second iontophoretic collection reservoirs each of which are in operative contact with an iontophoretic electrode. When placed in contact with a skin or mucosal surface, the iontophoretic sampling system extracts substances including the analyte into the first and second collection reservoirs. The first iontophoretic electrode is operated as a cathode during the extraction step. The sampling system further comprises a means for passively collecting substances which diffuse from, or are secreted by the subject. Passively extracted substances are collected into a third collection reservoir that is in operative contact with a skin or mucosal surface of the subject. Suitable passive collection systems are known in the art, for example skin patches which collect perspiration (with or without the use of a cholinergic agent or permeation enhancing agent), and the like. The analyte which is extracted into the first collection reservoir is contacted with a sensor in a sensing step to obtain an active signal, and the substances collected into the third collection reservoir are contacted with the sensor to obtain a blank signal. An analyte-specific signal is then obtained by subtracting the blank signal from the active signal. If a negatively charged analyte is being monitored, the first iontophoretic electrode is operated as an anode during the extraction step.

[0124] In a related aspect, the analyte is extracted using an iontophoretic sampling system that comprises first, second, and third collection reservoirs which are respectively in operative contact with first, second, and third iontophoretic electrodes. When these reservoirs are contacted with a skin or mucosal surface of a subject, the sampling means is used to extract substances including the analyte from the biological system into the first, second, and third collection reservoirs. The first and second iontophoretic electrodes are operated as cathodes during the extraction step (i.e., the iontophoretic current is divided equally between the cathodes). Sensing is carried out at the cathodes only, wherein the analyte that is extracted into the first collection reservoir is contacted with a sensor to obtain an active signal and the substances extracted into the second collection reservoir are contacted with the sensor to obtain a blank signal. The blank signal is then subtracted from the active signal to provide an analyte-specific signal. If desired, the first collection reservoir can contain an analyte-specific enzyme (e.g., glucose oxidase if glucose is being monitored) to provide for the active signal, and the second reservoir can be substantially identical except that the enzyme is excluded therefrom in order to obtain the blank signal. Alternatively, both the first and second collection reservoirs can be used to obtain active signals (e.g., where both contain an analyte-specific enzyme) in order to obtain multiple analyte-specific signals. Furthermore, the first and second iontophoretic electrodes can be operated as anodes if the analyte of interest is negatively charged.

[0125] In a still further aspect, an iontophoretic sampling system is provided which can combine cathode-selective measurement with both active-blank subtraction and alternating polarity techniques to provide for a substantial reduction in the effect of interfering species on sensor sensitivity. More particularly, a two-reservoir collection system is used, wherein the collection reservoirs are prepared as an active/blank system and have identical components (iontophoretic electrode, biosensor electrode) except that one reservoir contains the GOx enzyme (the active reservoir), while the other does not contain the GOx enzyme (the blank reservoir). These two collection reservoirs are operated at alternating polarity during iontophoretic extraction.

[0126] A microprocessor is used to control the extraction and sensing operations of the device to provide a measurement cycle which can be carried out in at least a four step protocol as follows. A first phase of the extraction step is used to generate the blank signal. During this phase, the blank reservoir is used as the iontophoretic cathode, and glucose (along with positively charged and neutral interfering species) is preferentially collected into the blank reservoir. The negatively charged interfering species are preferentially collected into the active reservoir which is operated as the iontophoretic anode. After a suitable extraction time, the biosensor electrode in the blank reservoir is used to obtain a blank signal. A purge step is then carried out, wherein the active/blank biosensor electrodes are activated to consume residual glucose and/or residual interfering species, particularly the negatively charged interfering species that were preferentially collected into the active reservoir during anodic extraction. The polarity of the active/blank reservoirs is then switched, and cathodic collection is carried out in the active reservoir. After this second extraction, the glucose analyte is detected in the active reservoir to provide the active signal. If desired, a sensor delay can also be used between the cathodic extraction and cathodic detection steps of the collection and analysis phase in order to maximize the glucose signal. Of course these steps can be reversed, such as wherein it is desired to obtain the active signal first during the measurement cycle. Additional, a two active system (both reservoirs contain the GOx enzyme) can be used to obtain multiple active signals. Any of the above sampling systems can be operated continuously or continually, wherein additional purge steps are used to clear the reservoirs between sensing steps and subsequent extraction steps. Further, the methods (e.g., purging at an increased potential, detection at a reduced potential, and the like) can be used to further reduce the affect of interfering species.

[0127] Each of the above-described iontophoretic sampling system configurations and measurement techniques can be used alone, or in any combination, in order to reduce the effect of interfering species on biosensor sensitivity. These non-invasive glucose monitoring systems allow one to measure changes in analyte levels in a subject over a wide range of analyte concentrations. Further, the sampling systems can be contacted with the subject continuously, and automatically obtain samples in order to measure analyte concentration at preprogrammed intervals. Other modifica-

Abbott Ex. 1002 - 182/1438

tions and additions to the above embodiments will be apparent to those skilled in the art upon reading the present enabling disclosure.

Examples

[0128] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the devices and formulae of the present invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Selective Extraction to Reduce Interfering Species

[0129] In order to confirm that certain interfering species are preferentially collected at the anode of an anode/cathode collection system, the following study was carried out. Iontophoretic sampling was performed on a subject using a prototype iontophoretic sampling system. The iontophoretic sampling system has two iontophoretic collection reservoirs each having an iontophoretic electrode.

[0130] The subject ingested 250 mg of ascorbic acid at the following time points: (1) two hours prior to start of sample collection; (2) one hour prior to start of sample collection; and (3) at the time when sample collection was first initiated. Iontophoretic sampling (reverse iontophoresis) was performed for 15 minute extraction phases, which were followed by a 5 minute period during which buffer sample was removed from the iontophoretic collection chambers and replaced with fresh buffer. Samples were taken every 20 minutes for two hours. The iontophoresis current was run in a DC mode such that the iontophoretic anode and cathode were the same collection reservoir for each sample. Samples were analyzed immediately after collection using HPLC. The results of the study are reported below in Table 1, wherein the concentration of ascorbic acid, uric acid, tyrosine and tryptophan in both the anode and cathode reservoirs are provided for each of the six collection time points.

Table 1

Sample	Ascorbic Acid	Uric Acid	Tyrosine	Tryptophan
A1	5.1947	2.8066	4.0392	0.3481
A2	2.5519	2.8623	1.7218	0.1096
A3	2.0226	2.632	1.1308	0.0726
A4	1.7966	2.5704	1.1026	0.0766
A5	1.7094	2.5064	1.1184	0.0617
A6	1.6663	2.4746	1.349	0.067
C1	nd	0.392	6.2655	0.3161
C2	nd	0.0776	2.8673	0.1213
C3	nd	0.0311	3.2719	0.0954
C4	nd	0.0175	2.5316	0.1017
C5	nd	0.0215	2.2356	0.0932
C6	nd	0.0106	2.148	0.0838

* nd = not determined.

[0131] As can be seen in Table 1, ascorbic acid is collected solely at the anode (the ascorbic acid level in the cathode samples is undetectable in all samples). In like manner, uric acid is collected predominantly at the anode, although a low level of uric acid was detectable at the cathode. The anode-to-cathode ratio of ascorbic and uric acid collection is quite high, varying from about 7.16 to 233.45 to 1. Tyrosine and tryptophan are collected at substantially equal concentrations at the anode and cathode. However, the average flux at the cathode is greater than at the anode, as expected for a neutral species.

Abbott Ex. 1002 - 183/1438

Example 2

Reduced Sensitivity to Interferinq Species at Lower Biosensor Operating Potentials

[0132] In order to confirm that certain reduction in biosensor operating potential can reduce sensitivity to interfering species, the following study was carried out. Iontophoretic sampling was again performed using a prototype iontophoretic sampling system. Comparisons were carried out between signals obtained using a platinum biosensor electrode operated at either 0.6V or 0.5V. More particularly, signals for hydrogen peroxide, tyrosine and tryptophan were obtained at each operating potential. The results of the study are reported below in Table 2. The slope is for the linear relationship between detected current at 30 seconds, and the concentration of the reacting species.

Table 2

Species	30 sec slope @ 0.6V	30 sec slope @ 0.5V
Hydrogen Peroxide	112.9	115
Tyrosine	33.9	3.28
Tryptophan	15.23	0.39

[0133] As can be seen, operating the Pt electrode at a lower potential (0.5V) substantially reduces sensor signals arising from the interfering species (tyrosine and tryptophan), while the analyte-specific sensor signal (hydrogen peroxide) remains unaffected.

Claims

1. A microprocessor (36) programmed to measure the concentration of an analyte present in a biological system, wherein the microprocessor (36) is programmed to subject a measurement signal to a process for selectively favouring analyte-specific signal components over signal components due to interfering species, said process selected from the group consisting of (a) a differential signal process which subtracts non-analyte signal components from the measurement signal, (b) a delay step which is performed between the extraction and sensing steps, (c) a selective electrochemical detection process which is performed during the sensing step, (d) a purging step which is performed after the sensing step, (e) a charge segregation step, and (f) any combination thereof.

2. The microprocessor (36) of claim 1, wherein the differential signal process comprises subtracting a first signal, which predominantly comprises signal components due to interfering species and background variation, from a measurement signal, which comprises analyte-specific signal components, to obtain a signal which is specifically related to the analyte.

3. The microprocessor (36) of claim 1, wherein the purging step comprises operating a biosensor electrode for a sufficient period of time to substantially remove residual signal components from a collection reservoir (8, 10) after a sensing step has been carried out.

4. The microprocessor (36) of claim 1, wherein a blank signal, which is due to diffused or extracted substances, is subtracted from an active signal, which is due to extracted analyte, to provide an analyte-specific signal.

5. The microprocessor (36) of claim 1, wherein the microprocessor (36) is programmed to control a sampling means (8, 10, 12, 14) and a sensing means (16, 18, 20) to provide a measurement cycle in which analyte-specific signal components are detected in the absence of signal components due to interfering species.

6. A sampling system for measuring an analyte present in a biological system, said system comprising, in operative combination:

   (a) sampling means (8, 10, 12, 14) for transdermally extracting the analyte from the biological system across a skin or mucosal surface of said biological system; and
   (b) sensing means (16, 18, 20) in operative contact with the analyte extracted by the sampling means (8, 10, 12, 14), wherein said sensing means (16, 18, 20) obtains a detectable signal from the extracted analyte and said signal is specifically related to the analyte;

Abbott Ex. 1002 - 184/1438

(c) **characterised in that** said system further comprises the microprocessor (36) of claim 5 in operative communication with the sampling means (8, 10, 12, 14) and the sensing means (16, 18, 20).

7. The sampling system of claim 6, wherein:

(a) said sampling system is an iontophoretic sampling system comprising (i) a first collection reservoir (8) containing an ionically conductive medium, a first iontophoretic sampling means (12) for extracting substances including the analyte from the biological system into the first collection reservoir (8), and a first sensor element (16, 18, 20), wherein said first sampling means (12) and said first sensor element (16, 18, 20) are in operative contact with the first collection reservoir (8); and (ii) a second collection reservoir (10) containing an ionically conductive medium, a second iontophoretic sampling means (14) for extracting substances including the analyte from the biological system into the second collection reservoir (10), and a second sensor element, wherein said second sampling means (14) and said second sensor element are in operative contact with the second collection reservoir (10); and
(b) the microprocessor (36) controls a measurement cycle which entails (i) operating the first iontophoretic sampling means (12) as an iontophoretic cathode during a first phase of the extraction step, (ii) detecting substances extracted into the first reservoir (8) with the first sensor element (16, 18, 20) during a first phase of the sensing step to obtain a first signal, (iii) removing residual signal components from the sampling system in a purging step, (iv) operating the second iontophoretic sampling means (14) as an iontophoretic cathode during a second phase of the extraction step, and (v) detecting substances extracted into the second reservoir (10) with the second sensor element during a second phase of the sensing step to obtain a second signal, wherein at least one of said first and second signals comprises an analyte-specific signal component.

8. The sampling system of claim 7, wherein the first (16, 18, 20) and second sensor elements are respectively first and second electrochemical biosensor electrodes.

9. The sampling system of claim 8, wherein the second collection reservoir (10) contains an enzyme.

10. The sampling system of claim 8, wherein the first (8) and second (10) collection reservoirs contain an enzyme.

11. The sampling system of claim 9 or claim 10, wherein the enzyme is glucose oxidase.

12. The sampling system of claim 8, wherein the measurement cycle comprises a charge segregation step wherein sensing takes place at the cathode and certain interfering species preferentially collect at the anode.

Patentansprüche

1. Mikroprozessor (36), der programmiert ist, die Konzentration eines in einem biologischen System vorhandenen Analyten zu messen, wobei der Mikroprozessor (36) programmiert ist, ein Meßsignal einem Verfahren zum selektiven Favorisieren analytspezifischer Signalkomponenten gegenüber Signalkomponenten infolge von Störspezies zu unterziehen, wobei das Verfahren aus der Gruppe ausgewählt ist, die aus folgendem besteht: (a) einem Differenzsignalverfahren, das Nichtanalytsignalkomponenten vom Meßsignal subtrahiert, (b) einem Verzögerungsschritt, der zwischen dem Extraktions- und dem Meßschritt durchgeführt wird, (c) einem selektiven elektrochemischen Detektionsverfahren, das während des Meßschritts durchgeführt wird, (d) einem Spülschritt, der nach dem Meßschritt durchgeführt wird, (e) einem Ladungsentmischungsschritt und (f) einer Kombination daraus.

2. Mikroprozessor (36) nach Anspruch 1, wobei das Differenzsignalverfahren aufweist: Subtrahieren eines ersten Signals, das vorwiegend Signalkomponenten infolge von Störspezies und Hintergrundvariation aufweist, von einem Meßsignal, das analytspezifische Signalkomponenten aufweist, um ein Signal zu erhalten, das sich spezifisch auf den Analyt bezieht.

3. Mikroprozessor (36) nach Anspruch 1, wobei der Spülschritt aufweist: Betreiben einer Biosensorelektrode für eine ausreichende Zeitperiode, um Restsignalkomponenten aus einem Auffangreservoir (8, 10) im wesentlichen zu entfernen, nachdem ein Meßschritt durchgeführt wurde.

4. Mikroprozessor (36) nach Anspruch 1, wobei ein Leersignal, das Folge diffundierter oder extrahierter Stoffe ist, von einem aktiven Signal, das Folge von extrahiertem Analyt ist, subtrahiert wird, um ein analytspezifisches Signal

Abbott Ex. 1002 - 185/1438

zu bilden.

5. Mikroprozessor (36) nach Anspruch 1, wobei der Mikroprozessor (36) programmiert ist, eine Probenahmeeinrichtung (8, 10, 12, 14) und eine Meßeinrichtung (16, 18, 20) zu steuern, um einen Meßzyklus vorzusehen, in dem analytspezifische Signalkomponenten in Abwesenheit von Signalkomponenten infolge von Störspezies detektiert werden.

6. Probenahmesystem zum Messen eines in einem biologischen System vorhandenen Analyten, wobei das System in betrieblicher Kombination aufweist:

(a) eine Probenahmeeinrichtung (8, 10, 12, 14) zum transdermalen Extrahieren des Analyten aus dem biologischen System über eine Haut- oder Schleimhautoberfläche des biologischen Systems; und
(b) eine Meßeinrichtung (16, 18, 20) in betrieblichem Kontakt mit dem durch die Probenahmeeinrichtung (8, 10, 12, 14) extrahierten Analyt, wobei die Meßeinrichtung (16, 18, 20) ein detektierbares Signal aus dem extrahierten Analyt erhält und sich das Signal spezifisch auf den Analyt bezieht;
(c) **dadurch gekennzeichnet, daß** das System ferner den Mikroprozessor (36) nach Anspruch 5 in betrieblicher Kommunikation mit der Probenahmeeinrichtung (8, 10, 12, 14) und der Meßeinrichtung (16, 18, 20) aufweist.

7. Probenahmesystem nach Anspruch 6, wobei:

(a) das Probenahmesystem ein iontophoretisches Probenahmesystem ist, das aufweist: (i) ein erstes Auffangreservoir (8), das ein ionenleitfähiges Medium aufweist, eine erste iontophoretische Probenahmeeinrichtung (12) zum Extrahieren von Stoffen, u. a. des Analyten, aus dem biologischen System in das erste Auffangreservoir (8), und ein erstes Sensorelement (16, 18, 20), wobei die erste Probenahmeeinrichtung (12) und das erste Sensorelement (16, 18, 20) in betrieblichem Kontakt mit dem ersten Auffangreservoir (8) stehen; und (ii) ein zweites Auffangreservoir (10), das ein ionenleitfähiges Medium aufweist, eine zweite iontophoretische Probenahmeeinrichtung (14) zum Extrahieren von Stoffen, u. a. des Analyten, aus dem biologischen System in das zweite Auffangreservoir (10), und ein zweites Sensorelement, wobei die zweite Probenahmeeinrichtung (14) und das zweite Sensorelement in betrieblichem Kontakt mit dem zweiten Auffangreservoir (10) stehen; und
(b) der Mikroprozessor (36) einen Meßzyklus steuert, der aufweist: (i) Betreiben der ersten iontophoretischen Probenahmeeinrichtung (12) als iontophoretische Kathode während einer ersten Phase des Extraktionsschritts, (ii) Detektieren von in das erste Reservoir (8) extrahierten Stoffen mit dem ersten Sensorelement (16, 18, 20) während einer ersten Phase des Meßschritts, um ein erstes Signal zu erhalten, (iii) Entfernen von Restsignalkomponenten aus dem Probenahmesystem in einem Spülschritt, (iv) Betreiben der zweiten iontophoretischen Probenahmeeinrichtung (14) als iontophoretische Kathode während einer zweiten Phase des Extraktionsschritts, und (v) Detektieren von in das zweite Reservoir (10) extrahierten Stoffen mit dem zweiten Sensorelement während einer zweiten Phase des Meßschritts, um ein zweites Signal zu erhalten, wobei das erste und/oder das zweite Signal eine analytspezifische Signalkomponente aufweist.

8. Probenahmesystem nach Anspruch 7, wobei das erste (16, 18, 20) und zweite Sensorelement eine erste bzw. zweite elektrochemische Biosensorelektrode sind.

9. Probenahmesystem nach Anspruch 8, wobei das zweite Auffangreservoir (10) ein Enzym aufweist.

10. Probenahmesystem nach Anspruch 8, wobei das erste (8) und zweite (10) Auffangreservoir ein Enzym aufweisen.

11. Probenahmesystem nach Anspruch 9 oder Anspruch 10, wobei das Enzym Glucoseoxidase ist.

12. Probenahmesystem nach Anspruch 8, wobei der Meßzyklus einen Ladungsentmischungsschritt aufweist, wobei das Messen an der Kathode stattfindet und sich bestimmte Störspezies vorzugsweise an der Anode sammeln.

Revendications

1. Microprocesseur (36) programmé pour mesurer la concentration d'un analyte présent dans un système biologique, dans lequel le microprocesseur (36) est programmé de manière à soumettre un signal de mesure à un traitement

Abbott Ex. 1002 - 186/1438

afin de favoriser de manière sélective des composantes de signal spécifiques à l'analyte par rapport à des composantes de signal dues à des espèces en interférence, ledit traitement étant sélectionné à partir du groupe consistant en (a) un traitement de signal différentiel qui soustrait les composantes de signal non d'analyte du signal de mesure, (b) une étape d'application de retard qui est exécutée entre les étapes d'extraction et de détection, (c) un traitement de détection électrochimique sélectif qui est réalisé au cours de l'étape de détection, (d) une étape de purge qui est exécutée après l'étape de détection, (e) une étape de ségrégation de charge, et (f) une association quelconque de celles-ci.

2. Microprocesseur (36) selon la revendication 1, dans lequel le traitement de signal différentiel comprend la soustraction d'un premier signal, qui comprend de manière prédominante des composantes de signal dues à des espèces en interférence et à la variation de bruit de fond, du signal de mesure, qui comprend des composantes de signal spécifique à l'analyte, afin d'obtenir un signal qui est associé de manière spécifique à l'analyte.

3. Microprocesseur (36) selon la revendication 1, dans lequel l'étape de purge comprend l'activation d'une électrode de biocapteur pendant une durée suffisante pour éliminer sensiblement les composantes de signal résiduelles d'un réservoir de collecte (8, 10) après qu'une étape de détection a été réalisée.

4. Microprocesseur (36) selon la revendication 1, dans lequel un signal blanc, qui est dû à des substances diffusées ou extraites, est soustrait d'un signal actif, qui est dû à l'analyte extrait, afin de délivrer un signal spécifique à l'analyte.

5. Microprocesseur (36) selon la revendication 1, dans lequel le microprocesseur (36) est programmé afin de commander un moyen d'échantillonnage (8, 10, 12, 14) et un moyen de détection (16, 18, 20) de manière à assurer un cycle de mesure dans lequel des composantes de signal spécifiques à l'analyte sont détectées en l'absence de composantes de signal dues à des espèces en interférence.

6. Dispositif d'échantillonnage destiné à mesurer un analyte présent dans un système biologique, ledit dispositif comprenant, en association opérationnelle:

(a) un moyen d'échantillonnage (8, 10, 12, 14) destiné à extraire de manière transdermique l'analyte à partir du système biologique à travers la peau ou une surface de muqueuse dudit système biologique ; et
(b) un moyen de détection (16, 18, 20) en contact opérationnel avec l'analyte extrait par le moyen d'échantillonnage (8, 10, 12, 14), dans lequel ledit moyen de détection (16, 18, 20) permet d'obtenir un signal détectable à partir de l'analyte extrait et ledit signal est associé de manière spécifique à l'analyte ;
(c) **caractérisé en ce que** ledit dispositif comprend, en outre, le microprocesseur (36) selon la revendication 5 en communication opérationnelle avec le moyen d'échantillonnage (8, 10, 12, 14) et le moyen de détection (16, 18, 20).

7. Dispositif d'échantillonnage selon la revendication 6, dans lequel:

(a) ledit dispositif d'échantillonnage est un dispositif d'échantillonnage par iontophorèse comprenant (i) un premier réservoir de collecte (8) contenant un milieu ioniquement conducteur, un premier moyen d'échantillonnage par iontophorèse (12) destiné à extraire des substances comprenant l'analyte à partir du système biologique vers un premier réservoir de collecte (8), et un premier élément formant capteur (16, 18, 20), dans lequel ledit premier moyen d'échantillonnage (12) et le ledit premier élément de détection (16, 18, 20) sont en contact opérationnel avec le premier réservoir de collecte (8) ; et (ii) un second réservoir de collecte (10) contenant un milieu ioniquement conducteur, un second moyen d'échantillonnage par iontophorèse (14) destiné à extraire des substances comprenant l'analyte à partir du système biologique vers le second réservoir de collecte (10), et un second élément formant capteur, dans lequel ledit second moyen d'échantillonnage (14) et ledit second élément formant capteur sont en contact opérationnel avec le second réservoir de collecte (10) ; et
(b) le microprocesseur (36) commande un cycle de mesure qui implique (i) l'activation du premier moyen d'échantillonnage par iontophorèse (12) en tant que cathode de iontophorèse au cours d'une première phase de l'étape d'extraction, (ii) la détection de substances extraites dans le premier réservoir (8) avec le premier élément formant capteur (16, 18, 20) au cours d'une première phase de l'étape de détection afin d'obtenir un premier signal, (iii) l'élimination des composantes de signal résiduelles à partir du système d'échantillonnage en une étape de purge, (iv) l'activation du second moyen d'échantillonnage par iontophorèse (14) en tant que cathode d'iontophorèse au cours d'une seconde phase de l'étape d'extraction, et (v) la détection de substances

Abbott Ex. 1002 - 187/1438

extraites dans le second réservoir (10) avec le second élément formant capteur au cours d'une seconde phase de l'étape de détection afin d'obtenir un second signal, dans lequel, au moins l'un desdits premier et second signaux comporte une composante de signal spécifique à l'analyte.

8. Dispositif d'échantillonnage selon la revendication 7, dans lequel les premier (16, 18, 20) et second éléments formant capteurs sont respectivement des première et seconde électrodes de biocapteur électrochimique.

9. Dispositif d'échantillonnage selon la revendication 8, dans lequel le second réservoir de collecte (10) contient une enzyme.

10. Dispositif d'échantillonnage selon revendication 8, dans lequel le premier (8) et le second (10) réservoirs de collecte contiennent une enzyme.

11. Dispositif d'échantillonnage selon la revendication 9 ou la revendication 10, dans lequel l'enzyme est une oxydase glucose.

12. Dispositif d'échantillonnage selon la revendication 8, dans lequel le cycle de mesure comprend une étape de ségrégation de charge dans laquelle la détection est assurée sur la cathode et certaines espèces en interférence sont collectées de manière préférentielle sur l'anode.

Abbott Ex. 1002 - 188/1438

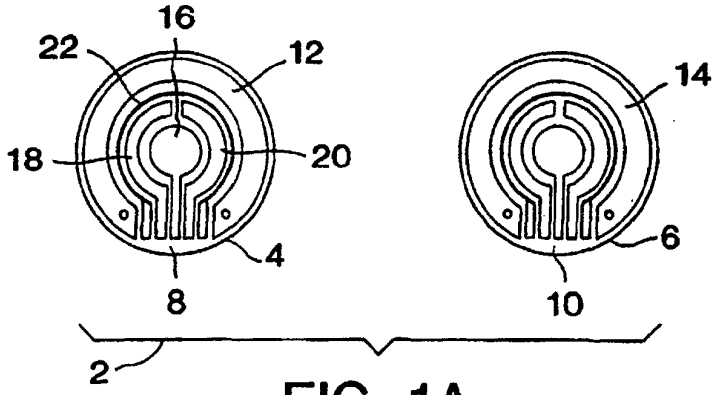


FIG. 1A

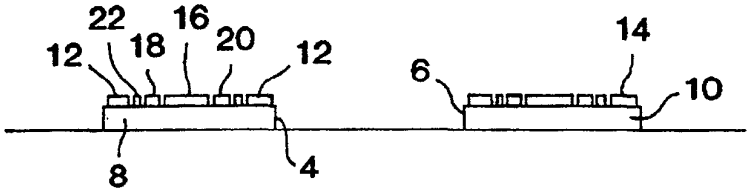


FIG. 1B

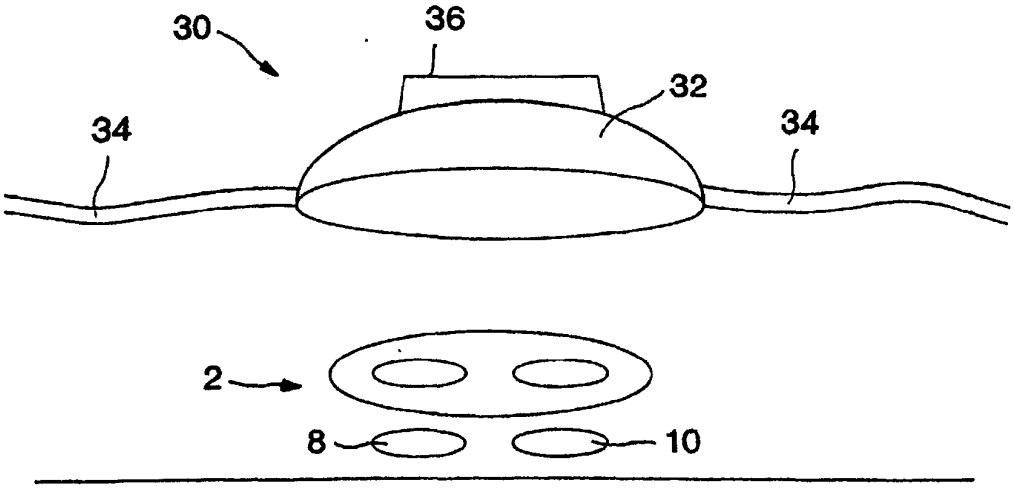


FIG. 2

Abbott Ex. 1002 - 189/1438

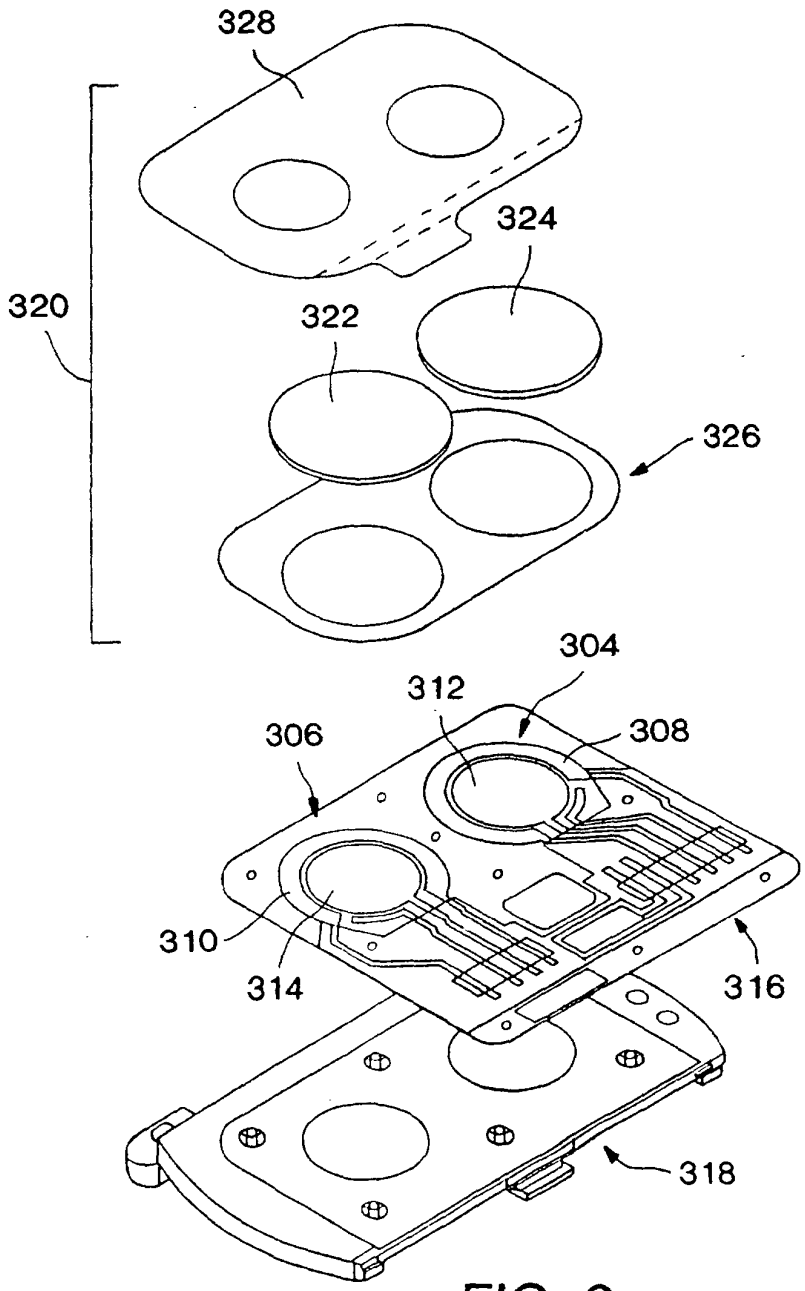


FIG. 3

Abbott Ex. 1002 - 190/1438

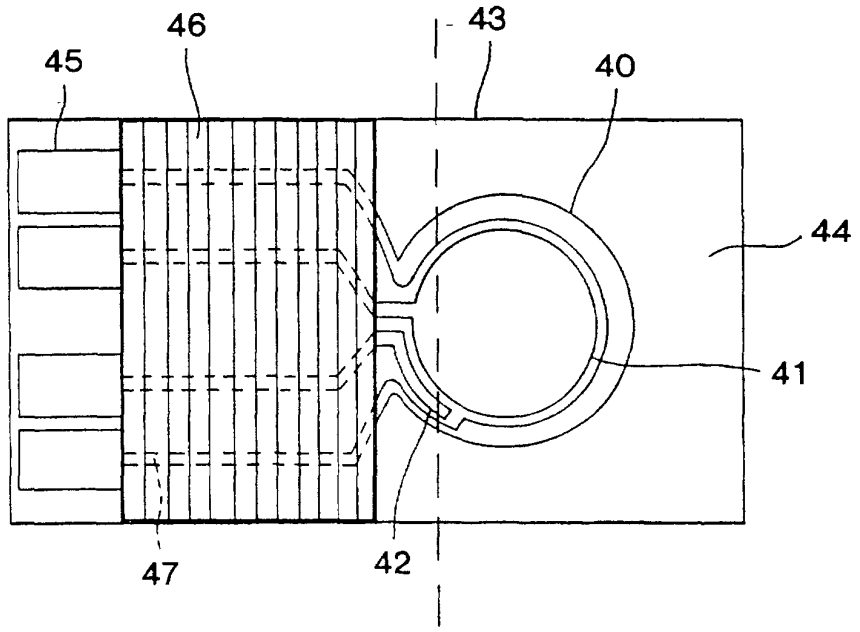


FIG. 4

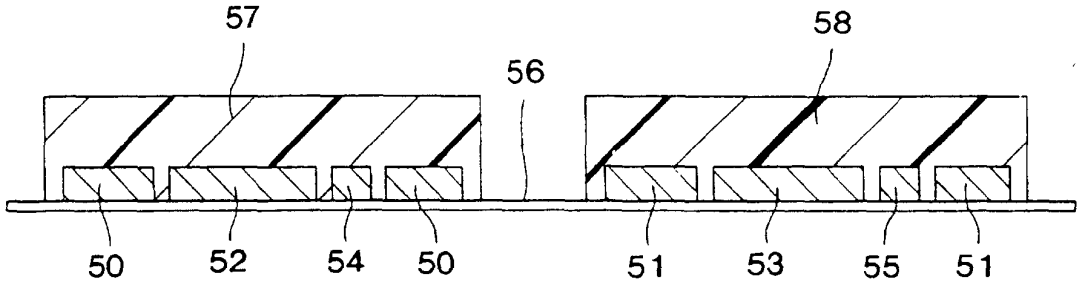


FIG. 5

Abbott Ex. 1002 - 191/1438

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(54) **DEVICE FOR PREDICTING PHYSIOLOGICAL VALUES**

VORRICHTUNG ZUM VORHERSAGEN VON PHYSIOLOGISCHEN MESSWERTEN

DISPOSITIF PERMETTANT DE PREVOIR DES VALEURS DE MESURES PHYSIOLOGIQUES

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US-A- 4 819 752
US-A- 5 730 714

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EP 1 078 258 B1

Description

Field of the Invention

[0001] The invention relates generally to a device for measuring the concentration of target chemical analytes present in a biological system. More particularly, the invention relates to a device for predicting a future or past concentration of an analyte using a series of measurements obtained from a monitoring system. One important application of the invention involves predicting future or past blood glucose concentrations.

Background of the Invention

[0002] The generally accepted methods for time series forecasting are: extrapolation of linear regression, extrapolation of polynomial regression, autoregressive moving average (ARMA), and exponential smoothing as discussed by Diggle, *Time Series: A Biostatistical Introduction*, Oxford University Press, Oxford, (1990). Linear regression models are an acceptable means of forecasting, provided that the data being analyzed are linear. In the case where the data in question are nonlinear, polynomial regression is often used to model the data.

[0003] Autoregressive (ARMA) methods have been used with success in forecasting where the underlying phenomena are stationary (or can be converted to stationary), with superimposed fluctuations expressible as random white noise. These two requirements can be met for some physiologic variables, but plasma glucose levels in diabetic patients generally do not fit these requirements. The method of exponential smoothing is a special case of the ARMA method. The above methods forecast the future value of a variable based on the value of that variable at previous time points. Information on the first and second derivative of the variable with respect to time is not included. Inclusion of these time derivatives can substantially increase the accuracy of the forecasting method in the situation where the future value of a variable depends on its time rate of change.

Summary of the Invention

[0004] The present invention provides a device for continually or continuously measuring the concentration of an analyte present in a biological system. Using the device entails continually or continuously detecting a raw signal from the biological system,
wherein the raw signal is specifically related to the analyte. As the raw signals are obtained, a calibration step is performed to correlate raw signal with a measurement value indicative of the concentration of analyte present in the biological system. These steps of detection and calibration are used to obtain a series of measurement values at selected time intervals. In a preferred embodiment, the selected time intervals are evenly spaced. Once the series of measurement values is obtained, this method provides for the prediction of a measurement value at a further time interval which occurs either one time interval before, or one time interval after, the series of measurement values is obtained.

[0005] In preferred embodiments of the invention, devices are used to extract samples from the biological sample using minimally invasive or non-invasive sampling techniques. The sensing apparatus used with any of the above-noted methods can employ any suitable sensing element to provide the raw signal including, but not limited to, physical, chemical, electrochemical, photochemical, spectrophotometric, polarimetric, colorimetric, radiometric, or like elements. In preferred embodiments of the invention, a biosensor is used which comprises an electrochemical sensing element.

[0006] The analyte can be any specific substance or component that one is desirous of detecting and/or measuring in a chemical, physical, enzymatic, or optical analysis. Such analytes include, but are not limited to, amino acids, enzyme substrates or products indicating a disease state or condition, other markers of disease states or conditions, drugs of abuse, therapeutic and/or pharmacologic agents, electrolytes, physiological analytes of interest (e.g., calcium, potassium, sodium, chloride, bicarbonate (CO_2), glucose, urea (blood urea nitrogen), lactate, hematocrit, and hemoglobin), lipids, and the like. In preferred embodiments, the analyte is a physiological analyte of interest, for example glucose, or a chemical that has a physiological action, for example a drug or pharmacological agent.

[0007] A wide variety of mathematical techniques can be used to predict the measurement value at the further time interval (e.g., to predict unmeasured values at future or past time intervals). However, in a preferred embodiment of the invention, a Taylor Series Exponential Smoothing (TSES) function is used to predict measurement values. The TSES function is represented by the following equation:

$$y_{n+1} = y_n + \alpha(y_n - y_{n-1}) + \frac{\alpha^2}{2}(y_n - 2y_{n-1} + y_{n-2})$$

Abbott Ex. 1002 - 193/1438

wherein: α is an optimizable variable which is a real number of between 0 and 1 and is adjusted based on the particular measurements obtained and the relationship between those measurements and actual results; *n* is a time interval; and *y* is an analyte concentration or signal converted to an analyte concentration which signal measurement is optimized to fit the results sought e.g., to correspond with a reference analyte concentration.

[0008] Accordingly, it is an object of the invention to obtain a series of measurement values taken at selected time intervals, and then use the TSES function of the invention to predict a future measurement value occurring one time interval after the series is taken. In one particular aspect of the invention, the predicted future value is used to eliminate or substantially reduce a lag time inherent in a transdermal extraction sampling system.

[0009] It is also an object of the invention to obtain a series of measurement values taken at evenly spaced time intervals, and then use the TSES function of the invention to predict a past measurement value occurring one time interval prior to the time when the series is taken. In one particular aspect of the invention, the predicted past value is used in a calibration step to calibrate a sampling device.

[0010] It is also an object of the invention to provide a monitoring system for continually or continuously measuring an analyte present in a biological system.

The monitoring system is formed from the operative combination of a sampling means, a sensing means, and a microprocessor means which controls the sampling means and the sensing means. The sampling means is used to continually or continuously extract the analyte from the biological system across a skin or mucosal surface of said biological system. The sensing means is arranged in operative contact with the analyte extracted by the sampling means, such that the sensing means can obtain a raw signal from the extracted analyte which signal is specifically related to the analyte. The microprocessor means communicates with the sampling means and the sensing means, and is used to: (a) control the sampling means and the sensing means to obtain a series of raw signals at selected time intervals during a continual or continuous measurement period; (b) correlate the raw signals with measurement values indicative of the concentration of analyte present in the biological system; and (c) predict a measurement value at a further time interval which occurs either one time interval before or one time interval after the series of measurement values is obtained. In one aspect, the monitoring system uses an iontophoretic current to extract the analyte from the biological system.

[0011] It is a further object of the invention to provide a monitoring system for measuring blood glucose in a subject. The monitoring system is formed from an operative combination of a sensing means and a microprocessor means. The sensing means is adapted for operative contact with the subject or with a glucose-containing sample extracted from the subject, and is used to obtain a raw signal specifically related to blood glucose in the subject. The microprocessor means communicates with the sensing means, and is used to: (a) control the sensing means to obtain a series of raw signals (specifically related to blood glucose) at selected time intervals; (b) correlate the raw signals with measurement values indicative of the concentration of blood glucose present in the subject; and (c) predict a measurement value at a further time interval which occurs either one time interval before or one time interval after the series of measurement values is obtained. In one aspect, the monitoring system comprises a biosensor having an electrochemical sensing element. In another aspect, the monitoring system comprises a near-IR spectrometer.

[0012] In a further aspect, the devices of the present invention can include enhancement of skin permeability by pricking the skin with micro-needles when the biological system includes skin, or, for example, a mucosal surface. Such pricking with micro-needles can facilitate extraction an analyte of interest from the biological system.

[0013] Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

Brief Description of the Drawings

[0014]

Figure 1A depicts a top plan view of an iontophoretic collection reservoir and electrode assembly for use in a transdermal sampling device constructed according to the present invention.

Figure 1B depicts the side view of the iontophoretic collection reservoir and electrode assembly shown in Figure 1A.

Figure 2 is a pictorial representation of an iontophoretic sampling device which includes the iontophoretic collection reservoir and electrode assembly of Figures 1A and 1B.

Figure 3 depicts a time series (times t_1, t_2, t_3, and t_4), and two corresponding series of measurements taken in this time series (y_{n-2}, y_{n-1} and y_n), and (y_n, y_{n-1} and y_{n-2}) which are respectively used to predict future or past measurements of the variable *y* at a time $n+1$ using the method described herein.

Figures 4, 5, and 6 depict experimental iontophoretic flux data compared with predicted values obtained using the method described herein.

Figure 7 is an expanded pictorial representation of components comprising one embodiment of an automatic sam-

Abbott Ex. 1002 - 194/1438

pling system for use in the practice of the present invention.

Figure 8 is a representation of one embodiment of a bimodal electrode design. The figure presents an overhead and schematic view of the electrode assembly **83**. In the figure, the bimodal electrode is shown at **80** and can be, for example, a Ag/AgCl iontophoretic/counter electrode. The sensing or working electrode (made from, for example, platinum) is shown at **81**. The reference electrode is shown at **82** and can be, for example, a Ag/AgCl electrode. The components are mounted on a nonconductive substrate **84**, for example, plastic or ceramic. The conductive leads **87** leading to the connection pad **85** are covered by a second nonconductive piece **86** of similar or different material. In this example of such an electrode the working electrode area is approximately 1.35 cm^2. The dashed line in Figure 8 represents the plane of the cross-sectional schematic view presented in Figure 9.

Figure 9 is a representation of a cross-sectional schematic view of the bimodal electrodes as they may be used in conjunction with a reference electrode and a hydrogel pad. In the figure, the components are as follows: bimodal electrodes **90** and **91**; sensing electrodes **92** and **93**; reference electrodes **94** and **95**; a substrate **96**; and hydrogel pads **97** and **98**.

Detailed Description of the Preferred Embodiments

[0015] Before describing the present invention in detail, it is to be understood that this invention is not limited to particular compositions or biological systems as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0016] As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an analyte" includes mixtures of analytes, and the like.

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein.

[0018] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

Definitions

[0019] The terms "analyte" and "target analyte" are used herein to denote any physiological analyte of interest that is a specific substance or component that is being detected and/or measured in a chemical, physical, enzymatic, or optical analysis. A detectable signal (e.g., a chemical signal or electrochemical signal) can be obtained, either directly or indirectly, from such an analyte or derivatives thereof. Furthermore, the terms "analyte" and "substance" are used interchangeably herein, and are intended to have the same meaning, and thus encompass any substance of interest. In preferred embodiments, the analyte is a physiological analyte of interest, for example, glucose, or a chemical that has a physiological action, for example, a drug or pharmacological agent.

[0020] A "sampling device" or "sampling system" refers to any device for obtaining a sample from a biological system for the purpose of determining the concentration of an analyte of interest. As used herein, the term "sampling" means invasive, minimally invasive or non-invasive extraction of a substance from the biological system, generally across a membrane such as skin or mucosa. The membrane can be natural or artificial, and can be of plant or animal nature, such as natural or artificial skin, blood vessel tissue, intestinal tissue, and the like. Typically, the sampling means are in operative contact with a "reservoir," or "collection reservoir," wherein the sampling means is used for extracting the analyte from the biological system into the reservoir to obtain the analyte in the reservoir. A "biological system" includes both living and artificially maintained systems. Examples of minimally invasive and noninvasive sampling techniques include iontophoresis, sonophoresis, suction, electroporation, thermal poration, passive diffusion, microfine (miniature) lances or cannulas, subcutaneous implants or insertions, and laser devices. Sonophoresis uses ultrasound to increase the permeability of the skin (see, e.g., Menon et al. (1994) *Skin Pharmacology* 7:130-139). Suitable sonophoresis sampling systems are described in International Publication No. WO 91/12772, published 5 September 1991. Passive diffusion sampling devices are described, for example, in International Publication Nos.: WO 97/38126 (published 16 October 1997); WO 97/42888, WO 97/42886, WO 97/42885, and WO 97/42882 (all published 20 November 1997); and WO 97/43962 (published 27 November 1997). Laser devices use a small laser beam to burn a hole through the upper layer of the patient's skin (see, e.g., Jacques et al. (1978) *J. Invest. Dermatology* 88:88-93). Examples of invasive sampling techniques include traditional needle and syringe or vacuum sample tube devices.

[0021] The term "collection reservoir" is used to describe any suitable containment means for containing a sample extracted from a biological system. For example, the collection reservoir can be a receptacle containing a material which is ionically conductive (e.g., water with ions therein), or alternatively, it can be a material, such as, a sponge-like

Abbott Ex. 1002 - 195/1438

material or hydrophilic polymer, used to keep the water in place. Such collection reservoirs can be in the form of a hydrogel (for example, in the form of a disk or pad). Hydrogels are typically referred to as "collection inserts." Other suitable collection reservoirs include, but are not limited to, tubes, vials, capillary collection devices, cannulas, and miniaturized etched, ablated or molded flow paths.

[0022] A "housing" for the sampling system can further include suitable electronics (e.g., microprocessor, memory, display and other circuit components) and power sources for operating the sampling system in an automatic fashion.

[0023] A "monitoring system," as used herein, refers to a system useful for continually or continuously measuring a physiological analyte present in a biological system. Such a system typically includes, but is not limited to, sampling means, sensing means, and a microprocessor means in operative communication with the sampling means and the sensing means.

[0024] The term "artificial," as used herein, refers to an aggregation of cells of monolayer thickness or greater which are grown or cultured *in vivo* or *in vitro,* and which function as a tissue of an organism but are not actually derived, or excised, from a pre-existing source or host.

[0025] The term "subject" encompasses any warm-blooded animal, particularly including a member of the class *Mammalia* such as, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

[0026] As used herein, the term "continual measurement" intends a series of two or more measurements obtained from a particular biological system, which measurements are obtained using a single device maintained in operative contact with the biological system over the time period in which the series of measurements is obtained. The term thus includes continuous measurements.

[0027] The term "transdermal," as used herein, includes both transdermal and transmucosal techniques, i.e., extraction of a target analyte across skin or mucosal tissue. Aspects of the invention which are described herein in the context of "transdermal," unless otherwise specified, are meant to apply to both transdermal and transmucosal techniques.

[0028] The term "transdermal extraction," or "transdermally extracted" intends any noninvasive, or at least minimally invasive sampling method, which entails extracting and/or transporting an analyte from beneath a tissue surface across skin or mucosal tissue. The term thus includes extraction of an analyte using iontophoresis (reverse iontophoresis), electroosmosis, sonophoresis, microdialysis, suction, and passive diffusion. These methods can, of course, be coupled with application of skin penetration enhancers or skin permeability enhancing technique such as tape stripping or pricking with micro-needles. Such methods do not constitute a portion of the invention and are merely described for the purpose of explanation. The term "transdermally extracted" also encompasses extraction techniques which employ thermal poration, electroporation, microfine lances, microfine canulas, subcutaneous implants or insertions, and the like.

[0029] The term "iontophoresis" intends a method for transporting substances across tissue (also not part of the invention) by way of an application of electrical energy to the tissue. In conventional iontophoresis, a reservoir is provided at the tissue surface to serve as a container of material to be transported. Iontophoresis can be carried out using standard methods known to those of skill in the art, for example, by establishing an electrical potential using a direct current (DC) between fixed anode and cathode "iontophoretic electrodes," alternating a direct current between anode and cathode iontophoretic electrodes, or using a more complex waveform such as applying a current with alternating polarity (AP) between iontophoretic electrodes (so that each electrode is alternately an anode or a cathode).

[0030] The term "reverse iontophoresis" refers to the movement of a substance from a biological fluid across a membrane by way of an applied electric potential or current. In reverse iontophoresis, a reservoir is provided at the tissue surface to receive the extracted material.

[0031] "Electroosmosis" refers to the movement of a substance through a membrane by way of an electric field-induced convective flow. The terms iontophoresis, reverse iontophoresis, and electroosmosis, will be used interchangeably herein to refer to movement of any ionically charged or uncharged substance across a membrane (e.g., an epithelial membrane) upon application of an electric potential to the membrane through an ionically conductive medium.

[0032] The term "sensing device," "sensing means," or "biosensor device" encompasses any device that can be used to measure the concentration of an analyte, or derivative thereof, of interest. Preferred sensing devices for detecting blood analytes generally include electrochemical devices and chemical devices. Examples of electrochemical devices include the Clark electrode system (see, e.g., Updike, et al., (1967) *Nature* 214:986-988), and other amperometric, coulometric, or potentiometric electrochemical devices. Examples of chemical devices include conventional enzyme-based reactions as used in the Lifescan® glucose monitor (Johnson and Johnson, New Brunswick, NJ) (see, e.g., U.S. Patent 4,935,346 to Phillips, et al.).

[0033] A "biosensor" or "biosensor device" includes, but is not limited to, a "sensor element" which includes, but is not limited to, a "biosensor electrode" or "sensing electrode" or "working electrode" which refers to the electrode that

Abbott Ex. 1002 - 196/1438

is monitored to determine the amount of electrical signal at a point in time or over a given time period, which signal is then correlated with the concentration of a chemical compound. The sensing electrode comprises a reactive surface which converts the analyte, or a derivative thereof, to electrical signal. The reactive surface can be comprised of any electrically conductive material such as, but not limited to, platinum-group metals (including, platinum, palladium, rhodium, ruthenium, osmium, and iridium), nickel, copper, silver, and carbon, as well as, oxides, dioxides, combinations or alloys thereof. Some catalytic materials, membranes, and fabrication technologies suitable for the construction of amperometric biosensors were described by Newman, J.D., et al. (*Analytical Chemistry* **67**(24), 4594-4599, 1995).

[0034] The "sensor element" can include components in addition to a biosensor electrode, for example, it can include a "reference electrode," and a "counter electrode." The term "reference electrode" is used herein to mean an electrode that provides a reference potential, e.g., a potential can be established between a reference electrode and a working electrode. The term "counter electrode" is used herein to mean an electrode in an electrochemical circuit which acts as a current source or sink to complete the electrochemical circuit. Although it is not essential that a counter electrode be employed where a reference electrode is included in the circuit and the electrode is capable of performing the function of a counter electrode, it is preferred to have separate counter and reference electrodes because the reference potential provided by the reference electrode is most stable when it is at equilibrium. If the reference electrode is required to act further as a counter electrode, the current flowing through the reference electrode may disturb this equilibrium. Consequently, separate electrodes functioning as counter and reference electrodes are most preferred.

[0035] In one embodiment, the "counter electrode" of the "sensor element" comprises a "bimodal electrode." The term "bimodal electrode" as used herein typically refers to an electrode which is capable of functioning non-simultaneously as, for example, both the counter electrode (of the "sensor element") and the iontophoretic electrode (of the "sampling means").

[0036] The terms "reactive surface," and "reactive face" are used interchangeably herein to mean the surface of the sensing electrode that: (1) is in contact with the surface of an electrolyte containing material (e.g. gel) which contains an analyte or through which an analyte, or a derivative thereof, flows from a source thereof; (2) is comprised of a catalytic material (e.g., carbon, platinum, palladium, rhodium, ruthenium, or nickel and/or oxides, dioxides and combinations or alloys thereof) or a material that provides sites for electrochemical reaction; (3) converts a chemical signal (e.g. hydrogen peroxide) into an electrical signal (e.g., an electrical current); and (4) defines the electrode surface area that, when composed of a reactive material, is sufficient to drive the electrochemical reaction at a rate sufficient to generate a detectable, reproducibly measurable, electrical signal that is correlatable with the amount of analyte present in the electrolyte.

[0037] The term "collection reservoir" and "collection insert" are used to describe any suitable containment means for containing a sample extracted from a biological system. The reservoir can include a material which is ionically conductive (e.g., water with ions therein), wherein another material such as a sponge-like material or hydrophilic polymer is used to keep the water in place. Such collection reservoirs can be in the form of a hydrogel (for example, in the shape of a disk or pad). Other suitable collection reservoirs include, but are not limited to, tubes, vials, capillary collection devices, cannulas, and miniaturized etched, ablated or molded flow paths.

[0038] An "ionically conductive material" refers to any material that provides ionic conductivity, and through which electrochemically active species can diffuse. The ionically conductive material can be, for example, a solid, liquid, or semi-solid (e.g., in the form of a gel) material that contains an electrolyte, which can be composed primarily of water and ions (e.g., sodium chloride), and generally comprises 50% or more water by weight. The material can be in the form of a gel, a sponge or pad (e.g., soaked with an electrolytic solution), or any other material that can contain an electrolyte and allow passage therethrough of electrochemically active species, especially the analyte of interest.

[0039] The term "physiological effect" encompasses effects produced in the subject that achieve the intended purpose of a therapy. In preferred embodiments, a physiological effect means that the symptoms of the subject being treated are prevented or alleviated. For example, a physiological effect would be one that results in the prolongation of survival in a patient.

[0040] A "laminate" , as used herein, refers to structures comprised of at least two bonded layers. The layers may be bonded by welding or through the use of adhesives. Examples of welding include, but are not limited to, the following: ultrasonic welding, heat bonding, and inductively coupled localized heating followed by localized flow. Examples of common adhesives include, but are not limited to, pressure sensitive adhesives, thermoset adhesives, cyanocrylate adhesives, epoxies, contact adhesives, and heat sensitive adhesives.

[0041] A "collection assembly", as used herein, refers to structures comprised of several layers, where the assembly includes at least one collection insert, for example a hydrogel. An example of a collection assembly of the present invention is a mask layer, collection inserts, and a retaining layer where the layers are held in appropriate, functional relationship to each other but are not necessarily a laminate, i.e., the layers may not be bonded together. The layers may, for example, be held together by interlocking geometry or friction.

[0042] An "autosensor assembly", as used herein, refers to structures generally comprising a mask layer, collection inserts, a retaining layer, an electrode assembly, and a support tray. The autosensor assembly may also include liners.

Abbott Ex. 1002 - 197/1438

The layers of the assembly are held in appropriate, functional relationship to each other.

[0043] The mask and retaining layers are preferably composed of materials that are substantially impermeable to the analyte (chemical signal) to be detected (e.g., glucose); however, the material can be permeable to other substances. By "substantially impermeable" is meant that the material reduces or eliminates chemical signal transport (e.g., by diffusion). The material can allow for a low level of chemical signal transport, with the proviso that chemical signal that passes through the material does not cause significant edge effects at the sensing electrode.

[0044] "Substantially planar" as used herein, includes a planar surface that contacts a slightly curved surface, for example, a forearm or upper arm of a subject. A "substantially planar" surface is, for example, a surface having a shape to which skin can conform, i.e., contacting contact between the skin and the surface.

[0045] By the term "printed" as used herein is meant a substantially uniform deposition of an electrode formulation onto one surface of a substrate (i.e., the base support). It will be appreciated by those skilled in the art that a variety of techniques may be used to effect substantially uniform deposition of a material onto a substrate, e.g., Gravure-type printing, extrusion coating, screen coating, spraying, painting, or the like.

[0046] The term "Taylor Series Exponential Smoothing Function ("TSES")" encompasses mathematical functions (algorithms) for predicting the behavior of a variable at a different point in time, which factors in the slope, and the rate of change of the slope. An example of a TSES function useful in connection with the present invention is a TSES function represented by:

$$y_{n+1} = y_n + \alpha(y_n - y_{n-1}) + \frac{\alpha^2}{2}(y_n - 2y_{n-1} + y_{n-2})$$

wherein: α is an optimizable variable which is a real number of between 0 and 1, and is adjusted based on the particular measurements obtained and the relationship between those measurements and actual results; n is an evenly spaced time interval; and y is an analyte concentration or signal converted to an analyte concentration which signal measurement is optimized to fit the results sought, e.g., to correspond with a reference analyte concentration.

[0047] A "future time point" refers to the time point in the future at which the concentration of the analyte of interest is predicted. In preferred embodiments, this term refers to a time point that is one time interval ahead, where a time interval is the amount of time between sampling and sensing events.

General Methods

[0048] The present invention relates to a sensing device for measuring the concentration of a target analyte present in a biological system. In preferred embodiments, the sensing device comprises a biosensor.

[0049] The analyte can be any specific substance or component that one is desirous of detecting and/or measuring in a chemical, physical, enzymatic, or optical analysis. Such analytes include, but are not limited to, amino acids, enzyme substrates or products indicating a disease state or condition, other markers of disease states or conditions, drugs of abuse, therapeutic and/or pharmacologic agents (e.g., theophylline, anti-HIV drugs, lithium, anti-epileptic drugs, cyclosporin, chemotherapeutics), electrolytes, physiological analytes of interest (e.g., urate/uric acid, carbonate, calcium, potassium, sodium, chloride, bicarbonate (CO_2), glucose, urea (blood urea nitrogen), lactate/lactic acid, hydroxybutyrate, cholesterol, triglycerides, creatine, creatinine, insulin, hematocrit, and hemoglobin), blood gases (carbon dioxide, oxygen, pH), lipids, heavy metals (e.g., lead, copper), and the like. In preferred embodiments, the analyte is a physiological analyte of interest, for example glucose, or a chemical that has a physiological action, for example a drug or pharmacological agent.

[0050] In order to facilitate detection of the analyte, an enzyme can be disposed in the collection reservoir, or, if several collection reservoirs are used, the enzyme can be disposed in several or all of the reservoirs.

The selected enzyme is capable of catalyzing a reaction with the extracted analyte (in this case glucose) to the extent that a product of this reaction can be sensed, e.g., can be detected electrochemically from the generation of a current which current is detectable and proportional to the concentration or amount of the analyte which is reacted. A suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide. The subsequent detection of hydrogen peroxide on an appropriate biosensor electrode generates two electrons per hydrogen peroxide molecule which create a current which can be detected and related to the amount of glucose entering the device. Glucose oxidase (GOx) is readily available commercially and has well known catalytic characteristics. However, other enzymes can also be used, so long as they specifically catalyze a reaction with an analyte or substance of interest to generate a detectable product in proportion to the amount of analyte so reacted.

[0051] In like manner, a number of other analyte-specific enzyme systems can be used in the invention, which enzyme systems operate on much the same general techniques. For example, a biosensor electrode that detects hydrogen peroxide can be used to detect ethanol using an alcohol oxidase enzyme system, or similarly uric acid with urate

Abbott Ex. 1002 - 198/1438

oxidase system, urea with a urease system, cholesterol with a cholesterol oxidase system, and theophylline with a xanthine oxidase system.

[0052] In addition, the oxidase enzyme (used for hydrogen peroxidase-based detection) can be replaced with another redox system, for example, the dehydrogenase-enzyme NAD-NADH, which offers a separate route to detecting additional analytes. Dehydrogenase-based sensors can use working electrodes made of gold or carbon (via mediated chemistry). Examples of analytes suitable for this type of monitoring include, but are not limited to, cholesterol, ethanol, hydroxybutyrate, phenylalanine, triglycerides, and urea. Further, the enzyme can be eliminated and detection can rely on direct electrochemical or potentiometric detection of an analyte. Such analytes include, without limitation, heavy metals (e.g., cobalt, iron, lead, nickel, zinc), oxygen, carbonate/carbon dioxide, chloride, fluoride, lithium, pH, potassium, sodium, and urea. Also, the sampling system described herein can be used for therapeutic drug monitoring, for example, monitoring anti-epileptic drugs (e.g., phenytion), chemotherapy (e.g., adriamycin), hyperactivity (e.g., ritalin), and anti-organ-rejection (e.g., cyclosporin).

[0053] In the general method described herein, a raw signal is obtained from a sensing device, which signal is related to a target analyte present in the biological system. The raw signal can be obtained using any suitable sensing methodology including, for example, methods which rely on direct contact of a sensing apparatus with the biological system; methods which rely on indirect contact of a sensing apparatus with the biological system; and the like. The sensing apparatus used with any of the above-noted methods can employ any suitable sensing element to provide the signal including, but not limited to, physical, chemical, electrochemical, photochemical, spectrophotometric, polarimetric, colorimetric, radiometric, or like elements. In preferred embodiments of the invention, a biosensor is used which comprises an electrochemical sensing element.

[0054] In another embodiment of the invention, a near-IR glucose sensing apparatus is used to detect blood glucose in a subject, and thus generate the raw signal. A number of near-IR glucose sensing devices suitable for use in the present method are known in the art and are readily available. For example, a near-IR radiation diffuse-reflection laser spectroscopy device is described in U.S. Patent No. 5,267,152 to Yang et al. Similar near-IR spectrometric devices are also described in U.S. Patent No. 5,086,229 to Rosenthal et al. and U.S. Patent No. 4,975,581 to Robinson et al. These near-IR devices use traditional methods of reflective or transmissive near infrared (near-IR) analysis to measure absorbance at one or more glucose-specific wavelengths, and can be contacted with the subject at an appropriate location, such as a finger-tip, skin fold, eyelid, or forearm surface to obtain the raw signal.

[0055] The raw signal obtained using any of the above-described methodologies is then converted into an analyte-specific value of known units to provide an interpretation of the signal obtained from the sensing device. The interpretation uses a mathematical transformation to model the relationship between a measured response in the sensing device and a corresponding analyte-specific value. Thus, a calibration step is used herein to relate, for example, an electrochemical signal (detected by a biosensor), or near-IR absorbance spectra (detected with a near-IR detector) with the concentration of a target analyte in a biological system.

[0056] Analyte-specific values are then used to predict future (time forecasting) or past (calibration) measurements of the target analyte concentration in the biological system. More particularly, a series of analyte-specific values are obtained, and this measurement series is then used to predict unmeasured analyte values at different points in time, e.g., future or past time points. In this manner, lag times inherent in certain sampling and/or sensing techniques can be eliminated to provide real-time measurement predictions.

[0057] The predicted analyte values can optionally be used in a subsequent step to control an aspect of the biological system. In one embodiment, predicted analyte values are used to determine when, and at what level, a constituent should be added to the biological system in order to control an aspect of the biological system. In a preferred embodiment, the analyte value can be used in a feedback control loop to control a physiological effect in the biological system.

[0058] The above general methods and devices can, of course, be used with a wide variety of biological systems, target analytes, and/or sensing techniques. The determination of particularly suitable combinations is within the skill of the ordinarily skilled artisan when directed by the instant disclosure. Although these devices are broadly applicable to measuring any chemical analyte and/or substance in a biological system, the invention is expressly exemplified for a non-invasive, transdermal sampling system which uses an electrochemical biosensor to quantify or qualify glucose or a glucose metabolite.

Obtaining the raw signal.

[0059] The raw signal can be obtained using any sensing device that is operatively contacted with the biological system. Such sensing devices can employ physical, chemical, electrochemical, spectrophotometric, polarimetric, colorimetric, radiometric, or like measurement techniques. In addition, the sensing device can be in direct or indirect contact with the biological system, or used with a sampling device which extracts samples from the biological system using invasive, minimally invasive or non-invasive sampling techniques. In preferred embodiments, a minimally invasive or non-invasive sampling device is used to obtain samples from the biological system, and the sensing device comprises

Abbott Ex. 1002 - 199/1438

a biosensor with an electrochemical sensing element. In particularly preferred embodiments, a sampling device is used to obtain continual transdermal or transmucosal samples from a biological system, and the analyte of interest is glucose.

[0060] More specifically, a non-invasive glucose monitoring device is used to measure changes in glucose levels in an animal subject over a wide range of glucose concentrations. The sampling means is based on transdermal glucose extraction and the sensing means is based on electrochemical detection technology. The monitoring device can be contacted with the biological system continuously, and automatically obtains glucose samples in order to measure glucose concentration at preprogrammed intervals.

[0061] Sampling is carried out continually by non-invasively extracting glucose through the skin of the patient using an iontophoretic current. More particularly, an iontophoretic current is applied to a surface of the skin of a subject. When the current is applied, ions or charged molecules pull along other uncharged molecules or particles such as glucose which are drawn into a collection reservoir placed on the surface of the skin. The collection reservoir may comprise any ionically conductive material and is preferably in the form of a hydrogel which is comprised of a hydrophilic material, water and an electrolyte. The collection reservoir may further contain an enzyme which catalyzes a reaction between glucose and oxygen. The enzyme is preferably glucose oxidase (GOx) which catalyzes the reaction between glucose and oxygen and results in the. production of hydrogen peroxide. The hydrogen peroxide reacts at a catalytic surface of a biosensor electrode, resulting in the generation of electrons which create a detectable biosensor current (raw signal). Based on the amount of biosensor current created over a given period of time, a measurement is taken, which measurement is related to the amount of glucose drawn into the collection reservoir over a given period of time. In a preferred embodiment the reaction is allowed to continue until substantially all of the glucose in the collection reservoir has been subjected to a reaction and is therefore no longer detectable, and the total biosensor current generated is related to the concentration of glucose in the subject.

[0062] When the reaction is complete, the process is repeated and a subsequent measurement is obtained. More specifically, the iontophoretic current is again applied, glucose is drawn through the skin surface into the collection reservoir, and the reaction is catalyzed in order to create a biosensor current. These sampling (extraction) and sensing operations are integrated such that glucose from interstitial fluid directly beneath the skin surface is extracted into the hydrogel collection pad where it contacts the GOx enzyme. The GOx enzyme converts glucose and oxygen in the hydrogel to hydrogen peroxide which diffuses to a Pt-based sensor and reacts with the sensor to regenerate oxygen and form electrons. The electrons generate an electrical signal that can be measured, analyzed, and correlated to blood glucose.

[0063] A generalized method for continual monitoring of a physiological analyte is disclosed in International Publication No. WO 97/24059, published 10 July 1997. As noted in that publication, the analyte is extracted into a reservoir containing a hydrogel which is preferably comprised of a hydrophilic material of the type described in International Publication No. WO 97/02811, published 30 January 1997. Suitable hydrogel materials include polyethylene oxide polyacrylic acid, polyvinylalcohol and related hydrophilic polymeric materials combined with water to form an aqueous gel.

[0064] In the above non-invasive glucose monitoring device, a biosensor electrode is positioned on a surface of the hydrogel opposite the surface contacting the skin. The sensor electrode acts as a detector which detects current generated by hydrogen peroxide in the redox reaction, or more specifically detects current which is generated by the electrons generated by the redox reaction catalyzed by the platinum surface of the electrode. The details of such electrode assemblies and devices for iontophoretic extraction of glucose are disclosed in International Publication No. WO 96/00110, published 4 January 1996, and International Publication No. WO 97/10499, published 2 March 1997.

[0065] Referring now to Figures 1A and 1B, an iontophoretic collection reservoir and electrode assembly for use in a transdermal sensing device is generally indicated at **2**. The assembly comprises two iontophoretic collection reservoirs, **4** and **6**, each having a conductive medium **8**, and **10** (preferably cylindrical hydrogel pads), respectively disposed therein. First (**12**) and second (**14**) ring-shaped iontophoretic electrodes are respectively contacted with conductive medium **8** and **10**. The first iontophoretic electrode **12** surrounds three biosensor electrodes which are also contacted with the conductive medium **8**, a working electrode **16**, a reference electrode **18**, and a counter electrode **20**. A guard ring **22** separates the biosensor electrodes from the iontophoretic electrode **12** to minimize noise from the iontophoretic circuit. Conductive contacts provide communication between the electrodes and an associated power source and control means as described in detail below. A similar biosensor electrode arrangement can be contacted with the conductive medium **10**, or the medium can not have a sensor means contacted therewith.

[0066] Referring now to Figure 2, the iontophoretic collection reservoir and electrode assembly **2** of Figures 1A and 1B is shown in exploded view in combination with a suitable iontophoretic sampling device housing **32**. The housing can be a plastic case or other suitable structure which preferably is configured to be worn on a subjects arm in a manner similar to a wrist watch. As can be seen, conductive media **8** and **10** (hydrogel pads) are separable from the assembly **2**; however, when the assembly **2** and the housing **32** are assembled to provide an operational iontophoretic sampling device **30**, the media are in contact with the electrodes to provide a electrical contact therewith.

[0067] Referring now to Figure 7, an exploded view of the key components from an embodiment of an iontophoretic

Abbott Ex. 1002 - 200/1438

sampling system is presented. The sampling system components include two biosensor/iontophoretic electrode assemblies, **704** and **706**, each of which have an annular iontophoretic electrode, respectively indicated at **708** and **710**, which encircles a biosensor **712** and **714**. The electrode assemblies **704** and **706** are printed onto a polymeric substrate **716** which is maintained within a sensor tray **718**. A collection reservoir assembly **720** is arranged over the electrode assemblies, wherein the collection reservoir assembly comprises two hydrogel inserts **722** and **724** retained by a gel retaining layer **726** and a mask layer **728**.

[0068] In one embodiment, the electrode assemblies can include bimodal electrodes as shown in Figure 8 and described below.

[0069] The components shown in exploded view in Figure 7 are intended for use in an automatic sampling device which is configured to be worn like an ordinary wristwatch. As described in International Publication No. WO 96/00110, published 4 January 1996, the wristwatch housing (not shown) contains conductive leads which communicate with the iontophoretic electrodes and the biosensor electrodes to control cycling and provide power to the iontophoretic electrodes, and to detect electrochemical signals produced at the biosensor electrode surfaces. The wristwatch housing can further include suitable electronics (e.g., microprocessor, memory, display and other circuit components) and power sources for operating the automatic sampling system.

[0070] Modifications and additions to the embodiment of Figure 7 will be apparent to those skilled in the art in light of the teachings of the present specification.

[0071] A power source (e.g., one or more rechargeable or nonrechargeable batteries) can be disposed within the housing **32** or within the straps **34** which hold the device in contact with a skin or mucosal surface of a subject. In use, an electric potential (either direct current or a more complex waveform) is applied between the two iontophoretic electrodes **12** and **14** such that current flows from the first iontophoretic electrode **12**, through the first conductive medium **8** into the skin or mucosal surface, and then back out through the second conductive medium **10** to the second iontophoretic electrode **14**. The current flow is sufficient to extract substances including an analyte of interest through the skin into one or both of collection reservoirs **4** and **6**. The electric potential may be applied using any suitable technique, for example, the applied current density may be in the range of about 0.01 to 0.5 mA/cm^2. In a preferred embodiment, the device is used for continual or continuous monitoring, and the polarity of iontophoretic electrodes **12** and **14** is alternated at a rate of about one switch every 10 seconds to about one switch every hour so that each electrode is alternately a cathode or an anode. The housing **32** can further include an optional temperature sensing element (e.g., a thermistor, thermometer, or thermocouple device) which monitors the temperature at the collection reservoirs to enable temperature correction of sensor signals. The housing can also include an optional conductance sensing element (e.g., an integrated pair of electrodes) which monitors conductance at the skin or mucosal surface to enable data screening correction or invalidation of sensor signals.

[0072] In a further aspect, the sampling device can operate in an alternating polarity mode using first and second bimodal electrodes (Figure 9, **90** and **91**) and two collection reservoirs (Figure 9, **97** and **98**). Each bi-modal electrode (Figure 8, **80**; Figure 9, **90** and **91**) serves two functions depending on the phase of the operation: (1) an electro-osmotic electrode (or iontophoretic electrode) used to electrically draw analyte from a source into a collection reservoir comprising water and an electrolyte, and to the area of the electrode subassembly; and (2) as a counter electrode to the first sensing electrode at which the chemical compound is catalytically converted at the face of the sensing electrode to produce an electrical signal.

[0073] The reference (Figure 9, **94** and **95**; Figure 8, **82**) and sensing electrodes (Figure 9, **92** and **93;** Figure 8, **81**), as well as, the bimodal electrode (Figure 9, **90** and **91**; Figure 8, **80**) are connected to a standard potentiostat circuit during sensing. In general, practical limitations of the system require that the bimodal electrode will not act as both a counter and iontophoretic electrode simultaneously.

[0074] The general operation of an iontophoretic sampling system in this embodiment is the cyclical repetition of two phases: (1) a reverse-iontophoretic phase, followed by a (2) sensing phase. During the reverse iontophoretic phase, the first bimodal electrode (Figure 9, **90**) acts as an iontophoretic cathode and the second bimodal electrode (Figure 9, **91**) acts as an iontophoretic anode to complete the circuit. Analyte is collected in the reservoirs, for example, a hydrogel (Figure 9, **97** and **98**). At the end of the reverse iontophoretic phase, the iontophoretic current is turned off. During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (Figure 9, **94**) and the sensing electrode (Figure 9, **92**). The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (Figure 9, **92**) producing an electrical current, while the first bi-modal electrode (Figure 9, **90**) acts as a counter electrode to complete the electrical circuit.

[0075] The electrode described is particularly adapted for use in conjunction with a hydrogel collection reservoir system for monitoring glucose levels in a subject through the reaction of collected glucose with the enzyme glucose oxidase present in the hydrogel matrix.

[0076] The bi-modal electrode is preferably comprised of Ag/AgCl. The electrochemical reaction which occurs at the surface of this electrode serves as a facile source or sink for electrical current. This property is especially important for the iontophoresis function of the electrode. Lacking this reaction, the iontophoresis current could cause the hydrol-

Abbott Ex. 1002 - 201/1438

ysis of water to occur at the iontophoresis electrodes causing pH changes and possible gas bubble formation. The pH changes to acidic or basic pH could cause skin irritation or burns. The ability of an Ag/AgCl electrode to easily act as a source of sink current is also an advantage for its counter electrode function. For a three electrode electrochenucal cell co function properly, the current generation capacity of the counter electrode should not limit the speed of the reaction at the sensing electrode. In the case of a large sensing electrode, the counter electrode should be able to source proportionately larger currents.

[0077] The design of the sampling system provides for a larger sensing electrode (see for example, Figure 8) than previously designed. Consequently, the size of the bimodal electrode should be sufficient so that when acting as a counter electrode with respect to the sensing electrode the counter electrode does not become limiting the rate of catalytic reaction at the sensing electrode catalytic surface.

[0078] Two methods exist to ensure that the counter electrode does not limit the current at the sensing electrode: (1) the bi-modal electrode is made much larger than the sensing electrode, or (2) a facile counter reaction is provided.

[0079] During the reverse iontophoretic phase, the power source provides a current flow to the first bi-modal electrode to facilitate the extraction of the chemical signal into the reservoir. During the sensing phase, the power source is used to provide voltage to the first sensing electrode to drive the conversion of chemical signal retained in the reservoir to electrical signal at the catalytic face of the sensing electrode. The power source also maintains a fixed potential at the electrode where, for example, hydrogen peroxide is converted to molecular oxygen, hydrogen ions, and electrons, which is compared with the potential of the reference electrode during the sensing phase. While one sensing electrode is operating in the sensing mode it is electrically connected to the adjacent bimodal electrode which acts as a counter electrode at which electrons generated at the sensing electrode are consumed.

[0080] The electrode sub-assembly can be operated by electrically connecting the bimodal electrodes such that each electrode is capable of functioning as both an iontophoretic electrode and counter electrode along with appropriate sensing electrode(s) and reference electrode(s), to create standard potentiostat circuitry.

[0081] A potentiostat is an electrical circuit used in electrochemical measurements in three electrode electrochemical cells. A potential is applied between the reference electrode and the sensing electrode. The current generated at the sensing electrode flows through circuitry to the counter electrode (i.e., no current flows through the reference electrode to alter its equilibrium potential). Two independent potentiostat circuits can be used to operate the two biosensors. For the purpose of the present sampling system, the electrical current measured at the sensing electrode subassembly is the current that is correlated with an amount of chemical signal.

[0082] With regard to continual operation for extended periods of time, Ag/AgCl electrodes are provided herein which are capable of repeatedly forming a reversible couple which operates without unwanted electrochemical side reactions (which could give rise to changes in pH, and liberation of hydrogen and oxygen due to water hydrolysis). The Ag/AgCl electrodes of the present sampling system are thus formulated to withstand repeated cycles of current passage in the range of about 0.01 to 1.0 mA per cm^2 of electrode area. With regard to high electrochemical purity, the Ag/AgCl components are dispersed within a suitable polymer binder to provide an electrode composition which is not susceptible to attack (e.g., plasticization) by components in the collection reservoir, e.g., the hydrogel composition. The electrode compositions are also formulated using analytical- or electronic-grade reagents and solvents, and the polymer binder composition is selected to be free of electrochemically active contaminants which could diffuse to the biosensor to produce a background current.

[0083] Since the Ag/AgCl iontophoretic electrodes must be capable of continual cycling over extended periods of time, the absolute amounts of Ag and AgCl available in the electrodes, and the overall Ag/AgCl availability ratio, can be adjusted to provide for the passage of high amounts of charge. Although not limiting in the sampling system described herein, the Ag/AgCl ratio can approach unity. In order to operate within the preferred system which uses a biosensor having a geometric area of 0.1 to 3 cm^2, the iontophoretic electrodes are configured to provide an approximate electrode area of 0.3 to 1.0 cm^2, preferably about 0.85 cm^2. These electrodes provide for reproducible, repeated cycles of charge passage at current densities ranging from about 0.01 to 1.0 mA/cm^2 of electrode area. More particularly, electrodes constructed according to the above formulation parameters, and having an approximate electrode area of 0.85 cm^2, are capable of a reproducible total charge passage (in both anodic and cathodic directions) of 270 mC, at a current of about 0.3 mA (current density of 0.35 mA/cm^2) for 48 cycles in a 24 hour period.

[0084] Once formulated, the Ag/AgCl electrode composition is affixed to a suitable rigid or flexible nonconductive surface as described above with respect to the biosensor electrode composition. A silver (Ag) underlayer is first applied to the surface in order to provide uniform conduction. The Ag/AgCl electrode composition is then applied over the Ag underlayer in any suitable pattern or geometry using various thin film techniques, such as sputtering, evaporation, vapor phase deposition, or the like, or using various thick film techniques, such as film laminating, electroplating, or the like. Alternatively, the Ag/AgCl composition can be applied using screen printing, pad printing, inkjet methods, transfer roll printing, or similar techniques. Preferably, both the Ag underlayer and the Ag/AgCl electrode are applied using a low temperature screen print onto a polymeric substrate. This low temperature screen print can be carried out at about 125 to 160°C, and the screening can be carried out using a suitable mesh, ranging from about 100-400 mesh.

Abbott Ex. 1002 - 202/1438

[0085] After a suitable iontophoretic extraction period, one or both of the sensor electrode sets can be activated in order to detect extracted substances including the analyte of interest. Operation of the iontophoretic sampling device **30** can be controlled by a controller **36** (e.g., a microprocessor), which interfaces with the iontophoretic electrodes, the sensor electrodes, the power supply, the optional temperature and/or conductance sensing elements, a display and other electronics. For example, the controller **36** can include a programmable controlled circuit source/sink drive for driving the iontophoretic electrodes. Power and reference voltage are provided to the sensor electrodes, and signal amplifiers can be used to process the signal from the working electrode or electrodes. In general, the controller discontinues the iontophoretic current drive during sensing periods. A sensor confidence loop can be provided for continually monitoring the sampling system to insure proper operations.

[0086] User control can be carried out using push buttons located on the housing **32**, and an optional liquid crystal display (LCD) can provide visual prompts, readouts and visual alarm indications. The microprocessor generally uses a series of program sequences to control the operations of the sampling device, which program sequences can be stored in the microprocessor's read only memory (ROM). Embedded software (firmware) controls activation of measurement and display operations, calibration of analyte readings, setting and display of high and low analyte value alarms, display and setting of time and date functions, alarm time, and display of stored readings. Sensor signals obtained from the sensor electrodes can be processed before storage and display by one or more signal processing functions or algorithms which are stored in the embedded software. The microprocessor can also include an electronically erasable, programmable, read only memory (EEPROM) for storing calibration parameters, user settings and all downloadable sequences. A serial communications port allows the device to communicate with associated electronics, for example, wherein the device is used in a feedback control application to control a pump for delivery of a medicament.

Converting to an analyte-specific value.

[0087] In one embodiment, one or more additional "active" collection reservoirs (e.g., each containing the GOx enzyme) can be used to obtain measurements, including raw signal. In one embodiment, two active collection reservoirs are used, and an average is taken between signals from the reservoirs for each measurement time point. Obtaining multiple signals, and then averaging reads from each signals, allows for signal smoothing of unusual data points from a sensor that otherwise may not have been detected by data screening techniques. Furthermore, skin site variability can be detected, and "lag" and/or "lead" differences in blood glucose changes relative to extracted glucose changes can be mitigated. In another embodiment, a second collection reservoir can be provided which serves as a blank (e.g., does not contain the GOx enzyme). This second reservoir can serve as an internal reference (blank) for the sensing device, where a biosensor is used to measure the "blank" signal from the reference reservoir which signal is then used in a blank subtraction step as described below.

[0088] A generalized method for continual monitoring of a physiological analyte is disclosed in International Publication No. WO 97/24059, published 10 July 1997.

[0089] The raw signal is then converted into an analyte-specific value using a calibration step which correlates the signal obtained from the sensing device with the concentration of the analyte present in the biological system. A wide variety of calibration techniques can be used to interpret such signals. These calibration techniques apply mathematical, statistical and/or pattern recognition techniques to the problem of signal processing in chemical analyses, for example, using neural networks, genetic algorithm signal processing, linear regression, multiple-linear regression, or principal components analysis of statistical (test) measurements.

[0090] One method of calibration involves estimation techniques. To calibrate an instrument using estimation techniques, it is necessary to have a set of exemplary measurements with known concentrations referred to as the calibration set (e.g., reference set). This set consists of m samples, each with n instrument variables contained in an m by n matrix (X), and an m by 1 vector (y) , containing the concentrations. If *a priori* information indicates the relationship between the measurement and concentration is linear, the calibration will attempt to determine an n by 1 transformation or mapping (b), such that

$$y = Xb$$

is an optimal estimate of y according to a predefined criteria. Numerous suitable estimation techniques useful in the practice of the invention are known in the art. These techniques can be used to provide correlation factors (e.g., constants), which correlation factors are then used in a mathematical transformation to obtain a measurement value indicative of the concentration of analyte present in the biological system at the times of measurement.

[0091] In one particular embodiment, the calibration step can be carried out using artificial neural networks or genetic algorithms. The structure of a particular neural network algorithm used in the practice of the invention can vary widely; however, the network should contain an input layer, one or more hidden layers, and one output layer. Such networks

Abbott Ex. 1002 - 203/1438

can be trained on a test data set, and then applied to a population. There are an infinite number of suitable network types, transfer functions, training criteria, testing and application methods which will occur to the ordinarily skilled artisan upon reading the instant specification.

[0092] In particular embodiments of the present invention, the detected current can be correlated with the subject's blood glucose concentration (typically using statistical algorithms associated with a microprocessor) so that the system controller may display the subject's actual blood glucose concentration as measured by the sampling system. For example, the system can be calibrated to the subject's actual blood glucose concentration by sampling the subject's blood during a standard glucose tolerance test, and analyzing the blood glucose using both a standard blood glucose monitor and the sampling system of the present invention. In addition or alternately, the sampling system can be calibrated at a calibration time point where the signal obtained from the sampling system at that time point is correlated to blood glucose concentration at that time point as determined by direct blood testing (for example, glucose concentration can be determined using a HemoCue® clinical analyzer (HemoCue AB, Sweden)). In this manner, measurements obtained by the sampling system can be correlated to actual values using known statistical techniques. Such statistical techniques can be formulated as algorithm(s) and incorporated in a microprocessor associated with the sampling system.

[0093] In the context of the iontophoretic glucose sampling device described hereinabove, a preferred neural network algorithm could use, for example, the following inputs to provide a blood glucose measurement: time; signal from the active reservoir/signal from the blank reservoir; signal from two active reservoirs (averaged or cumulative); calibration time; skin temperature; voltage; skin conductivity; and, when operating in the training mode, measured glucose.

[0094] For example, perspiration contains glucose, and perspiration occurring rapidly and in sufficient quantities may affect the detected signal either before or during biosensor measurement. Accordingly, a sensor can be used to monitor perspiration levels for a given measurement cycle at time points before, during, and/or after iontophoresis, and before, during, and/or after glucose sensing. Although a number of different mechanisms can be used, skin conductance can be readily measured with a device contacted with the skin. Skin conductivity is related to perspiration.

[0095] In a similar manner, a sensor can be used to measure skin temperature for a given measurement cycle at time points before, during, and/or after iontophoresis, and before, during, and/or after glucose sensing.

[0096] Further, the sampling system can be pre-programmed to begin execution of its signal measurements (or other functions) at a designated time. One application of this feature is to have the sampling system in contact with a subject and to program the sampling system to begin sequence execution during the night so that it is available for calibration immediately upon waking. One advantage of this feature is that it removes any need to wait for the sampling system to warm-up before calibrating it.

Predicting future or past measurements.

[0097] The analyte-specific values obtained using the above techniques are used herein to predict future (e.g., time forecasting) or past (e.g., calibration) target analyte concentrations in the biological system. In one preferred embodiment, a series of analyte values are obtained, and these measurements are then used to predict unmeasured analyte values at different points in time, future or past.

[0098] More particularly, the above-described iontophoretic sampling process is carried out in order to obtain three or more measurements of the target analyte. Using these measurements, an additional measurement can be calculated. The additional measurement is preferably calculated using a series function as described in greater detail below.

[0099] In the context of blood glucose monitoring, it has been found that the actual (real-time) glucose level in a subject differs from the measured glucose level obtained using a sampling device that extracts glucose from the subject using iontophoresis. The difference is due, in part, to a lag time between extracting the glucose analyte and obtaining a measurement from the extracted glucose. This lag time can vary depending on factors such as the particular subject using the device, the particular area of skin from which glucose is extracted, the type of collection reservoir used, and the amount of current applied. In order to compensate for this inherent lag time, the present invention utilizes data obtained from previous measurements and a mathematical function in order to predict what a future analyte concentration will be. In this case, the predicted future reading can be used as a "real-time value" of the analyte level.

[0100] In another embodiment, the described methods can be used to predict past measurements, such as in the context of making a calibration. More particularly, measurements obtained using the above-described transdermal sampling device can be calibrated against one or more reference measurements obtained by conventional (blood extraction) methods. In such calibration processes, actual blood glucose levels are determined using conventional methods (e.g., colorimetric methods, spectrophotometric methods, or the like) to analyze an extracted blood sample. These actual measurements are then compared with corresponding measurements obtained with the transdermal sampling device, and a conversion factor is then determined. In normal operations, the transdermal sampling device is generally first contacted with the biological system (placed on the surface of a subject's skin) upon waking. After the device is put in place, it is preferable to wait a period of time in order allow the device to attain normal operating

Abbott Ex. 1002 - 204/1438

parameters, after which time the device can be calibrated. However, if a blood sample is extracted at the time when the device is first applied (as would normally be most convenient), there may not be a corresponding glucose reading from the transdermal sampling system which can be compared with the reference value obtained from the extracted blood sample. The present method overcomes this problem by allowing one to perform a conventional blood glucose test (via a blood sample extraction) when the device is first applied, and then calibrate the device at a later time.

[0101] A number of mathematical methods for predicting future or past measurements can be used in the practice of the invention. For example, linear or polynomial regression analyses, time series analyses, or neural networks can be used to predict such measurements. However, it is preferred that a novel combination of exponential smoothing and a Taylor series analysis be used herein to predict the future or past measurement. This combination is referred to as a Taylor Series Exponential Smoothing (TSES) function.

[0102] The TSES function of the present invention was derived from an exponential smoothing function. The method of exponential smoothing calculates the predicted value of a variable (y) at time ($n+1$) as a function of that variable at the current time (n), as well as at two previous times ($n-1$) and ($n-2$). An exponential smoothing equation that is typically used for evenly spaced time points is shown in Equation (1) below,

$$y_{n+1} + \beta y_n + \beta(1 - \beta)y_{n-1} + \beta(1 - \beta)^2 y_{n-2} \tag{1}$$

wherein the variable (β) is an empirical parameter obtained from experimental data, and typically falls between 0 and 1. Adjustments in the value of variable β can be made by regressing experimental results and using Equation (1). An improvement to Equation (1) was then made as follows. Since there is a resemblance between Equation (1) and the following conventional Taylor Series expansion function (referred to as Equation (2)),

$$f(x) = f(a) + f'(a)(x - a) + \frac{f''(a)(x - a)^2}{2!} + \ldots + \frac{f^{(n-1)}(a)(x - a)^{(n-1)}}{(n - 1)!} \tag{2}$$

the variable (y_{n-1}) in Equation (1) was replaced with a variable (y'_n), which is the first derivative at y_n with respect to time, and the variable (y_{n-2}) was replaced by a variable ($y''_n/2$), which is the second derivative at y_n with respect to time. This resulted in Equation (3) below,

$$y_{n+1} = \beta y_n + \beta(1 - \beta)y'_n + \frac{\beta(1 - \beta)^2}{2} y''_n \tag{3}$$

where the derivatives are calculated by Equations (4) and (5) as follows:

$$y'_n = \frac{y_n - y_{n-1}}{\Delta t} \tag{4}$$

$$y''_n = \frac{y_n - 2y_{n-1} + y_{n-2}}{\Delta t} \tag{5}$$

and (Δt) is the equally spaced time interval.

[0103] The analogy between Equation (3) and the Taylor Series expansion function of Equation (2) was further improved by dividing the right hand side of Equation (3) by β to give Equation (6), where the definition $\alpha=1-\beta$ was used.

$$y_{n+1} = y_n + \alpha y'_n + \frac{\alpha^2}{2} y''_n \tag{6}$$

Finally, by substituting Equations (4) and (5) into Equation (6), the final expression of the TSES function was obtained as:

$$y_{n+1} = y_n + a(y_n - y_{n-1}) + \frac{\alpha^2}{2}(y_n - 2y_{n-1} + y_{n-2}) \tag{7}$$

Abbott Ex. 1002 - 205/1438

[0104] The TSES function of Equation (7) is essentially an exponentially smoothed moving average Taylor series expansion using the first two terms of the Taylor series. This function can be used to predict y_{n+1}, an unmeasured value of the variable y (e.g., blood glucose concentration) at time $n+1$. The prediction is based on y_n, y_{n-1}, and y_{n-2}, a series of three measurements for y preferably taken at equally spaced time intervals, Δt. The series of measurements used in the TSES function can be taken at any selected time intervals, and need not be taken at equally spaced time intervals. The function can, of course, be used with a larger series of measurements by using additional terms of the Taylor series. In the context of blood glucose monitoring with an iontophoretic sampling device, the TSES function allows for the accurate prediction of a future (e.g., a "real-time") glucose concentration. In this regard, during a typical iontophoretic measuring cycle, iontophoretic extraction of the analyte is carried out for a suitable amount of time, for example about 1 to 30 minutes, after which time the extracted analyte is detected for a suitable amount of time, for example about 1-30 minutes. These extraction and detection time periods create an inherent lag period of about 2 to 60 minutes between the time at which the analyte is first extracted, and a raw signal has been generated and correlated with the analyte concentration in the biological system.

[0105] This inherent lag period can be overcome as follows. In an exemplary iontophoretic measuring cycle, iontophoresis is carried out for a 5 minute interval to extract the glucose analyte through the skin, followed by a 10 minute interval for electrochemical detection of the glucose by the biosensor to obtain the raw signal. This results in a 15 minute lag period. However, by performing a series of these 15 minute measurement cycles, and then applying the TSES function of Equation (7) to the measurement series, the described method allows for an accurate prediction of a future, unmeasured value for y at time $n+1$ (y_{n+1}), substantially reducing or even eliminating the lag period inherent in such iontophoretic measurement periods (by using this future predicted value as the current, real-time value). In preferred applications of the invention, the data sampling interval (in the above example, 15 minutes) should be smaller than the period over which large changes in the value of y (e.g., blood glucose concentrations) are expected to occur, and the data should be sufficiently smooth so that first and second derivatives can be meaningfully calculated.

[0106] Using similar mathematical techniques, the TSES function of Equation (7) can be used to predict a past unmeasured value based on a series of evenly spaced measurements. In blood glucose monitoring using the above-described iontophoretic sampling device, a blood sample can conveniently be obtained at the same time at which the device is first contacted with the subject's skin, that is, at time zero. After a series of 3 measurements (corresponding to three measurement cycles) have been taken with the iontophoretic device, the TSES function can be solved for a past unmeasured value y_{n+1} (in this case, a time zero measurement) by inserting the measured values for y_n, y_{n-1}, and y_{n-2} (the series of three measurements) into Equation (7). The actual blood glucose concentration at time zero (obtained from the extracted blood sample) can then be used as a calibration reference value and compared against the predicted time zero measurement. Referring to Figure 3, time is used in the reverse direction in the TSES function of Equation (7) to predict the past value (y_{n+1}). This allows for accurate and reliable calibration of the sampling device using the measured and predicted time zero values.

[0107] A number of other physiological variables may be predicted using the above functions. For example, the TSES function of the invention can be used to time forecast those physiological variables that cannot be measured in real-time, or that demonstrate frequent fluctuations in their data. Examples of physiological functions and the variables that characterize them include, but are not limited to, cerebral blood flow (in the treatment of stroke patients) which is related to blood viscosity and the concentrations of plasma proteins and clotting factors in the blood stream (Hachinski, V. and Norris, J.W., "The Acute Stroke," Philadelphia, FA Davis, 1985); pulmonary function (in asthma patients) as measured by lung volumes in the different phases of respiration (Thurlbeck, W.M. (1990) *Clin.* Chest *Med.* 11:389); and heart activity (in recurrent cardiac arrest) as measured by electrical activity of the heart (Marriott, HJL, "Practical Electrocardiography", 8th Ed., Baltimore, Williams & Wilkins, 1983). Other examples of physiological variables that can be predicted using the described methods include renal dialysis, where the blood concentrations of urea and blood gases are followed (Warnock, D.G. (1988) *Kidney Int.* 34:278); and anesthesia treatment, where various parameters (e.g., heart rate, blood pressure, blood concentration of the anesthesia) are monitored to determine when the anesthesia will stop functioning (Vender, J.S., and Gilbert, H.C., "Monitoring the Anesthetized Patient," in Clinical Anesthesia, 3rd Ed., by Barash et al., Lippincott-Raven Publishers, Philadelphia, 1996).

Controlling a physiological effect.

[0108] Predicted analyte values obtained with the above techniques can also be used to control an aspect of the biological system. e.g., a physiological effect. In one embodiment, the predicted analyte value is used to determine when, and at what level, a constituent should be added to the biological system in order to control the concentration of the target analyte.

[0109] More particularly, in the context of blood glucose monitoring, use of the TSES function of Equation (7) allows for accurate predictions of either real-time or future blood glucose values. This is of particular value in predicting hypoglycemic episodes which can lead to diabetic shock, or even coma. Having a series of measurements obtained from

Abbott Ex. 1002 - 206/1438

the continual iontophoretic sampling device, and the capability to predict future values using Equation (7), allows a subject to detect blood glucose swings or trends indicative of hypoglycemic or hyperglycemic episodes prior to their reaching a critical level, and to compensate therefor by way of exercise, diet or insulin administration.

[0110] A feedback control application of the present invention entails using the TSES function of Equation (7) to predict real-time blood glucose levels, or measurement of future blood glucose levels, and then using these predicted signals to control a pump for insulin delivery to treat hyperglycemia.

EXAMPLES

[0111] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the devices and formulae of the present invention, and are not intended to limit the scope of what the inventor regards as his invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Prediction of Measurement Values

[0112] Iontophoretic extraction of glucose was carried out using a low-level iontophoretic current to extract glucose through patient's skin and an electrochemical biosensor to detect the extracted glucose.
Iontophoresis was carried out for 5 minute intervals and electrochemical detection was carried out for 10 minute intervals to result in 15 minute measurement cycles.

[0113] Iontophoretic flux data thus obtained are displayed in Figures 4-6. These measured data are represented by the (■) data points. Superimposed in these figures are the predicted iontophoretic flux at time n+1, represented by the (□) data points, wherein the predicted values were obtained using the TSES function of Equation (7). Also shown are predicted values obtained using the exponential smoothing function of Equation (1), represented by the (X) data points. The value of α used in the TSES function prediction was α=0.5, and the value β that was used in the exponential smoothing function was β=0.8. The average RMS error between predicted flux data obtained using the TSES function of Equation (7) and the actual flux data was found to be 10.2%, while the average RMS error between the predicted flux data obtained using the smoothing function of Equation (1) and the actual flux data was found to be 12.3%. These results indicate that the TSES function of the present invention provides a twenty-percent improvement in the accuracy of predicted analyte values when compared with conventional exponential smoothing techniques.

Claims

1. A microprocessor (36) for use in a monitoring system for obtaining a series of analyte measurement values from a biological system, wherein said microprocessor (36) is capable of being placed in operative communication with a sampling means (8, 10, 12, 14) and a sensing means (16, 18, 20), and wherein said microprocessor (36) (i) can be used to control the sampling means (8, 10, 12, 14) and the sensing means (16, 18, 20) to obtain a series of raw signals at selected time intervals during a continual or continuous measurement period, (ii) correlates the raw signals with measurement values indicative of the amount of analyte present in the sampling means (8, 10, 12, 14) or indicative of the concentration of analyte present in the biological system to obtain a series of measurement values, and (iii) predicts a measurement value at a further time interval which occurs either one time interval before or one time interval after the series of measurement values is obtained.

2. A monitoring system for continually or continuously measuring an analyte present in a biological system, said monitoring system comprising:

   (a) sensing means (16, 18, 20) to obtain a raw signal specifically related to the analyte in the biological system; and
   (b) the microprocessor (36) of claim 1, wherein said microprocessor (36) is in operative communication with the sensing means (16, 18, 20), and wherein said microprocessor (36) (i) controls the sensing means (16, 18, 20) to obtain a series of raw signals at selected time intervals during a continual or continuous measurement period, and (ii) correlates the raw signals with measurement values indicative of the amount of analyte present in the sampling means (8, 10, 12, 14) or indicative of the concentration of analyte present in the biological

Abbott Ex. 1002 - 207/1438

system to obtain a series of measurement values, **characterised in that** said microprocessor (36) (iii) predicts a measurement value at a further time interval which occurs either one time interval before or one time interval after the series of measurement values is obtained.

3. The monitoring system of claim 2, comprising:

(a) sampling means (8, 10, 12, 14) for continually or continuously extracting the analyte from the biological system, wherein said sampling means (8, 10, 12, 14) is adapted for extracting the analyte across a skin or mucosal surface of said biological system;
(b) the sensing means (16, 18, 20) of claim 2, wherein said sensing means (16, 18, 20) is in operative contact with the analyte extracted by the sampling means (8, 10, 12, 14), and wherein said sensing means (16, 18, 20) obtains a raw signal from the extracted analyte and said raw signal is specifically related to the analyte; and
(c) the microprocessor (36) of claim 2.

4. The monitoring system of claim 2 or claim 3, wherein the sensing means (16, 18, 20) comprises a biosensor having an electrochemical sensing element.

5. The monitoring system of claim 2 or claim 3, wherein the sensing means (16, 18, 20) comprises a near-IR spectrometer.

6. The monitoring system of claim 3, wherein the sampling means (8, 10, 12, 14) comprises one or more collection reservoirs (8, 10) for containing the extracted analyte.

7. The monitoring system of claim 6, wherein the collection reservoir (8, 10) comprises an enzyme that reacts with the extracted analyte to produce an electrochemically detectable signal.

8. The monitoring system of claim 7, wherein the analyte is glucose and the enzyme is glucose oxidase.

9. The monitoring system of claim 3, wherein the sampling means (8, 10, 12, 14) comprises an iontophoretic current to extract the analyte from the biological system.

10. The microprocessor (36) of claim 1 or the monitoring system of claim 2 or claim 3, wherein the selected time intervals are evenly spaced.

11. The microprocessor (36) of claim 1 or the monitoring system of claim 2 or claim 3, wherein the series of measurement values is comprised of three or more discrete values.

12. The microprocessor (36) of claim 1 or the monitoring system of claim 3, wherein the analyte is glucose.

13. The microprocessor (36) or monitoring system of claim 12, wherein the series of measurement values is comprised of three or more discrete blood glucose values.

14. The microprocessor (36) or monitoring system of claim 11 or claim 13, wherein the further time interval occurs one time interval after the series of measurement values.

15. The microprocessor (36) or monitoring system of claim 11 or claim 13, wherein the further time interval occurs one time interval before the series of measurement values.

16. The microprocessor (36) or monitoring system of claim 11 or claim 13, wherein the prediction of a measurement value at a further time interval is carried out using said series of three or more measurement values in a series function represented by:

$$y_{n+1} = y_n + \alpha(y_n - y_{n-1}) + \frac{\alpha^2}{2}(y_n - 2y_{n-1} + y_{n-2}) \quad (7)$$

wherein y is the measurement value of the analyte, n is the time interval between measurement values, and α is a real number between 0 and 1.

Abbott Ex. 1002 - 208/1438

17. The microprocessor (36) or monitoring system of claim 16, wherein the series function is used to predict the value of y_{n+1} and the time interval *n+1* occurs one time interval after the series of measurement values.

18. The microprocessor (36) or monitoring system of claim 16, wherein the series function is used to predict the value of y_{n+1} and the time interval *n+1* occurs one time interval before the series of measurement values.

19. The microprocessor (36) or monitoring system of claim 18, wherein a reference malyte measurement from the biological system is provided for the time interval *n+1.*

20. The microprocessor (36) or monitoring system of claim 19, wherein the reference analyte measurement is compared against the predicted value of y_{n+1} and used to calibrate the microprocessor (36) or monitoring system.

21. The microprocessor (36) or monitoring system of claim 18, wherein the analyte is glucose and a reference blood glucose measurement from the biological system is provided for the time interval *n+1*.

22. The microprocessor (36) or monitoring system of claim 21, wherein the reference blood glucose measurement is compared against the predicted value of y_{n+1} and used to calibrate the microprocessor (36) or monitoring system.

Revendications

1. Un microprocesseur (36) destiné à être utilisé dans un système de surveillance pour obtenir une série de mesures d'analyte sur un système biologique, dans lequel ledit microprocesseur (36) peut être placé en communication opérante avec des moyens d'échantillonnage (8, 10, 12, 14) et des moyens de détection (16, 18, 20) et dans lequel ledit microprocesseur 36 (i) peut être utilisé pour contrôler les moyens d'échantillonnage (8, 10, 12, 14) et les moyens de détection (16, 18, 20) pour obtenir une série de signaux bruts à intervalles de temps sélectionnés pendant une période de mesure continuelle ou continue, (ii) corrèle les signaux bruts avec des valeurs de mesure indicatives de la quantité d'analyte présent dans les moyens d'échantillonnage (8, 10, 12, 14) ou indicative de la concentration d'analyte présent dans le système biologique pour obtenir une série de valeurs de mesure, et (iii) prédit une valeur de mesure à un intervalle de temps ultérieur qui intervient un intervalle de temps avant ou un intervalle de temps après que la série de valeurs de mesures est obtenue.

2. Un système de surveillance pour mesurer continuellement ou continûment un analyte présent dans un système biologique, ledit système de surveillance comprenant :

   (a) des moyens de détection (16, 18, 20) pour obtenir un signal brut spécifiquement lié à l'analyte dans le système biologique ; et
   (b) le microprocesseur (36) de la revendication 1, dans lequel ledit microprocesseur (36) est en communication opérante avec les moyens de détection (16, 18, 20) et dans lequel ledit microprocesseur (36) (i) contrôle les moyens de détection (16, 18, 20) pour obtenir une série de signaux bruts à intervalles de temps sélectionnés pendant une période de mesure continuelle ou continue, et (ii) corrèle les signaux bruts avec des valeurs de mesures indicatives de la quantité d'analyte présent dans les moyens d'échantillonnage (8, 10, 12, 14) ou indicatives de la concentration d'analyte présent dans le système biologique pour obtenir une série de valeurs de mesure, **caractérisé en ce que** ledit microprocesseur (36) (iii) prédit une valeur de mesure à un intervalle de temps ultérieur qui intervient un intervalle de temps avant ou un intervalle de temps après que la série de valeurs de mesure est obtenue.

3. Le système de surveillance selon la revendication 2, comprenant :

   (a) des moyens d'échantillonnage (8, 10, 12, 14) pour extraire continuellement ou continûment l'analyte du système biologique, dans lequel lesdits moyens d'échantillonnage (8, 10, 12, 14) sont adaptés pour extraire l'analyte au travers d'une peau ou surface muqueuse dudit système biologique ;
   (b) les moyens de détection (16, 18, 20) selon la revendication 2, dans lequel lesdits moyens de détection (16, 18, 20) sont en contact opératoire avec l'analyte extrait par les moyens d'échantillonnage (8, 10, 12, 14), et dans lesquels lesdits moyens de détection (16, 18, 20) obtiennent un signal brut de l'analyte extrait et ledit signal brut est spécifiquement lié à l'analyte; et
   (c) le microprocesseur (36) selon la revendication 2.

Abbott Ex. 1002 - 209/1438

4. Le système de surveillance selon la revendication 2 ou la revendication 3, dans lequel les moyens de détection (16, 18, 20) comprennent un biocapteur ayant un élément de détection électrochimique.

5. Le système de surveillance selon la revendication 2 ou la revendication 3, dans lequel les moyens de détection (16, 18, 20) comprennent un spectromètre en proche IR.

6. Le système de surveillance selon la revendication 3, dans lequel les moyens d'échantillonnage (8, 10, 12, 14) comprennent un ou plusieurs réservoirs de collecte (8, 10) pour contenir l'analyte extrait.

7. Le système de surveillance selon la revendication 6, dans lequel le réservoir de collecte (8, 10) comprend une enzyme qui réagit avec l'analyte extrait pour produire un signal détectable électrochimiquement.

8. Le système de surveillance selon la revendication 7, dans lequel l'analyte est le glucose et l'enzyme est le glucose oxydase.

9. Le système de surveillance selon la revendication 3, dans lequel les moyens d'échantillonnage (8, 10, 12, 14) comprennent un courant iontophorétique pour extraire l'analyte du système biologique.

10. Le microprocesseur (36) selon la revendication 1 ou le système de surveillance selon la revendication 2 ou la revendication 3, dans lequel les intervalles de temps sélectionnés sont régulièrement espacés.

11. Le microprocesseur (36) selon la revendication 1 ou le système de surveillance selon la revendication 2 ou la revendication 3, dans lequel la série de valeurs de mesure est composée de trois valeurs discrètes ou plus.

12. Le microprocesseur (36) selon la revendication 1 ou le système de surveillance selon la revendication 3, dans lequel l'analyte est le glucose.

13. Le microprocesseur (36) ou système de surveillance selon la revendication 12, dans lequel la série de valeurs de mesure est composée de trois valeurs de glucose sanguin discrètes ou plus.

14. Le microprocesseur (36) ou système de surveillance selon la revendication 11 ou la revendication 13, dans lequel l'intervalle de temps ultérieur intervient un intervalle de temps après la série de valeurs de mesure.

15. Le microprocesseur (36) ou système de surveillance selon la revendication 11 ou la revendication 13, dans lequel l'intervalle de temps ultérieur intervient un intervalle de temps avant la série de valeurs de mesure.

16. Le microprocesseur (36) ou système de surveillance selon la revendication 11 ou la revendication 13, dans lequel la prédiction d'une valeur de mesure à un intervalle de temps ultérieur est effectuée à l'aide de ladite série de trois valeurs de mesure ou plus dans une fonction série représentée par :

$$y_{n+1} = y_n + \alpha(y_n - y_{n-1}) + \frac{\alpha^2}{2}(y_n - 2y_{n-1} + y_{n-2}) \quad (7)$$

où y est la valeur de mesure de l'analyte, n est l'intervalle de temps entre les valeurs de mesure et α est un nombre réel entre 0 et 1.

17. Le microprocesseur (36) ou système de surveillance selon la revendication 16, dans lequel la fonction série est utilisée pour prédire la valeur de y_{n+1} et l'intervalle de temps $n+1$ intervient un intervalle de temps après la série de valeurs de mesure.

18. Le microprocesseur (36) ou système de surveillance selon la revendication 16, dans lequel la fonction série est utilisée pour prédire la valeur de y_{n+1} et l'intervalle de temps $n+1$ intervient un intervalle de temps après la série de valeurs de mesure.

19. Le microprocesseur (36) ou système de surveillance selon la revendication 18, dans lequel une mesure de l'analyte de référence du système biologique est fournie pour l'intervalle de temps $n+1$.

Abbott Ex. 1002 - 210/1438

20. Le microprocesseur (36) ou système de surveillance selon la revendication 19, dans lequel la mesure d'analyte de référence est comparée à la valeur prédite de y_{n+1}et utilisée pour étalonner le microprocesseur (36) ou le système de surveillance.

21. Le microprocesseur (36) ou le système de surveillance selon la revendication 18, dans lequel l'analyte est le glucose et où une mesure de glucose sanguin de référence du système biologique est fournie pour l'intervalle de temps *n+1.*

22. Le microprocesseur (36) ou système de surveillance selon la revendication 21, dans lequel la mesure de glucose sanguin de référence est comparée à la valeur prédite de y_{n+1} et utilisée pour étalonner le microprocesseur (36) ou système de surveillance.

Patentansprüche

1. Mikroprozessor (36) zur Verwendung in einem Überwachungssystem zur Gewinnung einer Serie von Analytmeßwerten aus einem biologischen System, wobei der Mikroprozessor (36) in betriebsfähige Kommunikation mit einer Probenahmeeinrichtung (8, 10, 12, 14) und einer Erfassungseinrichtung (16, 18, 20) versetzt werden kann und wobei der Mikroprozessor (36) (i) verwendet werden kann, um die Probenahmeeinrichtung (8, 10, 12, 14) und die Erfassungseinrichtung (16, 18, 20) zu steuern, um in gewählten Zeitintervallen während einer dauernden oder kontinuierlichen Meßperiode eine Serie von Rohsignalen zu gewinnen, (ii) die Rohsignale mit Meßwerten korreliert, die die Analytmenge, die in der Probenahmeeinrichtung (8, 10, 12, 14) vorliegt, oder die Analytkonzentration, die im biologischen System vorliegt, anzeigen, um eine Serie von Meßwerten zu gewinnen, und (iii) in einem weiteren Zeitintervall, das entweder ein Zeitintervall vor oder ein Zeitintervall nach der Gewinnung die Serie von Meßwerten auftritt, einen Meßwert vorhersagt.

2. Überwachungssystem zur dauernden oder kontinuierlichen Messung eines Analyts, das in einem biologischen System vorhanden ist, wobei das Überwachungssystem aufweist:

(a) eine Erfassungseinrichtung (16, 18, 20) zur Gewinnung eines Rohsignals, das sich spezifisch auf den Analyt im biologischen System bezieht; und
(b) den Mikroprozessor (36) nach Anspruch 1, wobei der Mikroprozessor (36) in betriebsfähiger Kommunikation mit der Erfassungseinrichtung (16, 18, 20) ist und wobei der Mikroprozessor (36) (i) die Erfassungseinrichtung (16, 18, 20) steuert, um in gewählten Zeitintervallen während einer dauernden oder kontinuierlichen Meßperiode eine Serie von Rohsignalen zu gewinnen, und (ii) die Rohsignale mit Meßwerten korreliert, die die Analytmenge, die in der Probenahmeeinrichtung (8, 10, 12, 14) vorliegt, oder die Analytkonzentration, die im biologischen System vorliegt, anzeigen, um eine Serie von Meßwerten zu gewinnen, **dadurch gekennzeichnet**, das der Mikroprozessor (36) (iii) in einem weiteren Zeitintervall, daß entweder ein Zeitintervall vor oder ein Zeitintervall nach der Gewinnung der Serie von Meßwerten auftritt, einen Meßwert vorhersagt.

3. Überwachungssystem nach Anspruch 2, mit:

(a) einer Probenahmeeinrichtung (8, 10, 12, 14) zum dauernden oder kontinuierlichen Extrahieren des Analyts aus dem biologischen System, wobei die Probenahmeeinrichtung (8, 10, 12, 14) zum Extrahieren des Analyts durch eine Haut- oder Schleimhautoberfläche des biologischen Systems geeignet ist;
(b) der Erfassungseinrichtung (16, 18, 20) nach Anspruch 2, wobei die Erfassungseinrichtung (16, 18, 20) in betriebsfähigem Kontakt mit dem von der Probenahmeeinrichtung (8, 10, 12, 14) extrahierten Analyt ist und wobei die Erfassungseinrichtung (16, 18, 20) ein Rohsignal aus dem extrahierten Analyt gewinnt und das Rohsignal sich spezifisch auf den Analyt bezieht;
(c) dem Mikroprozessor (36) nach Anspruch 2.

4. Überwachungssystem nach Anspruch 2 oder 3, wobei die Erfassungseinrichtung (16, 18, 20) einen Biosensor mit einem elektrochemischen Erfassungselement aufweist.

5. Überwachungssystem nach Anspruch 2 oder 3, wobei die Erfassungseinrichtung (16, 18, 20) ein Spektrometer für den nahen Infrarotbereich aufweist.

6. Überwachungssystem nach Anspruch 3, wobei die Probenahmeeinrichtung (8, 10, 12, 14) ein oder mehrere Auf-

Abbott Ex. 1002 - 211/1438

nahmereservoire (8, 10) zum Aufnehmen des extrahierten Analyts aufweist.

7. Überwachungssystem nach Anspruch 6, wobei das Aufnahmereservoir (8, 10) ein Enzym aufweist, das mit dem extrahierten Analyt reagiert, um ein elektrochemisch detektierbares Signal zu erzeugen.

8. Überwachungssystem nach Anspruch 7, wobei der Analyt Glucose und das Enzym Glucoseoxidase ist.

9. Überwachungssystem nach Anspruch 3, wobei die Probenahmeeinrichtung (8, 10, 12, 14) einen iontophorischen Strom zum Extrahieren des Analyts aus dem biologischen System aufweist.

10. Mikroprozessor (36) nach Anspruch 1 oder Überwachungssystem nach Anspruch 2 oder 3, wobei die gewählten Zeitintervalle gleichmäßig beabstandet sind.

11. Mikroprozessor (36) nach Anspruch 1 oder Überwachungssystem nach Anspruch 2 oder 3, wobei die Serie von Meßwerten drei oder mehr diskrete Werte umfaßt.

12. Mikroprozessor (36) nach Anspruch 1 oder Überwachungssystem nach Anspruch 3, wobei der Analyt Glucose ist.

13. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 12, wobei die Serie von Meßwerten drei oder mehr diskrete Blutzuckerwerte umfaßt.

14. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 11 oder 13, wobei das weitere Zeitintervall ein Zeitintervall nach der Serie von Meßwerten auftritt.

15. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 11 oder 13, wobei das weitere Zeitintervall ein Zeitintervall vor der Serie von Meßwerten auftritt.

16. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 11 oder 13, wobei die Vorhersage eines Meßwertes in einem weiteren Zeitintervall unter Verwendung der Serie von drei oder mehr Meßwerten in einer Serienfunktion erfolgt, die wie folgt dargestellt ist:

$$y_{n+1} = y_n + \alpha(y_n - y_{n-1}) + \frac{\alpha^2}{2}(y_n - 2y_{n-1} + y_{n-2}) \quad (7)$$

wobei y der Meßwert des Analyts, n das Zeitintervall zwischen den Meßwerten und α eine reelle Zahl zwischen 0 und 1 ist.

17. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 16, wobei die Serienfunktion verwendet wird, um den Wert y_{n+1} vorherzusagen, und das Zeitintervall n+1 ein Zeitintervall nach der Serie von Meßwerten auftritt.

18. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 16, wobei die Serienfunktion verwendet wird, um den Wert y_{n+1} vorherzusagen, und das Zeitintervall n+1 ein Zeitintervall vor der Serie von Meßwerten auftritt.

19. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 18, wobei ein Referenzanalytmeßergebnis aus dem biologischen System für das Zeitintervall n+1 bereitgestellt wird.

20. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 19, wobei das Referenzanalytmeßergebnis mit dem vorhergesagten Wert y_{n+1} verglichen wird und verwendet wird, um den Mikroprozessor (36) oder das Überwachungssystem zu kalibrieren.

21. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 18, wobei der Analyt Glucose ist und ein Referenzblutzuckermeßergebnis aus dem biologischen System für das Zeitintervall n+1 durchgeführt wird.

22. Mikroprozessor (36) oder Überwachungssystem nach Anspruch 21, wobei das Referenzblutzuckermeßergebnis mit dem vorhergesagten Wert y_{n+1} verglichen wird und verwendet wird, um den Mikroprozessor (36) oder das Überwachungssystem zu kalibrieren.

Abbott Ex. 1002 - 212/1438

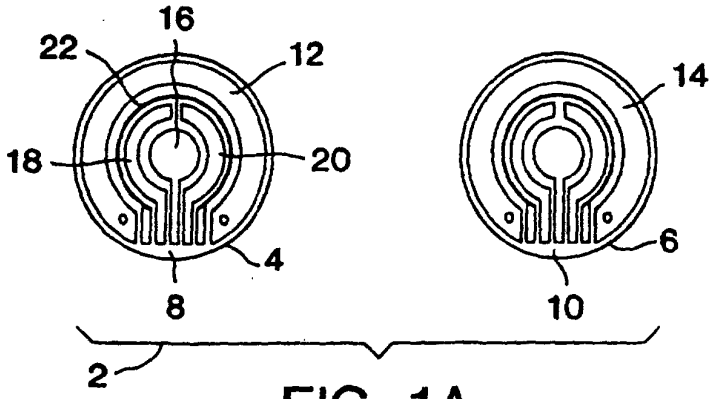


FIG. 1A

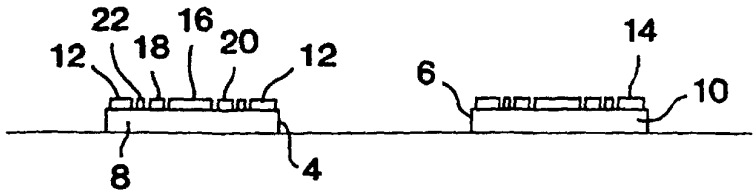


FIG. 1B

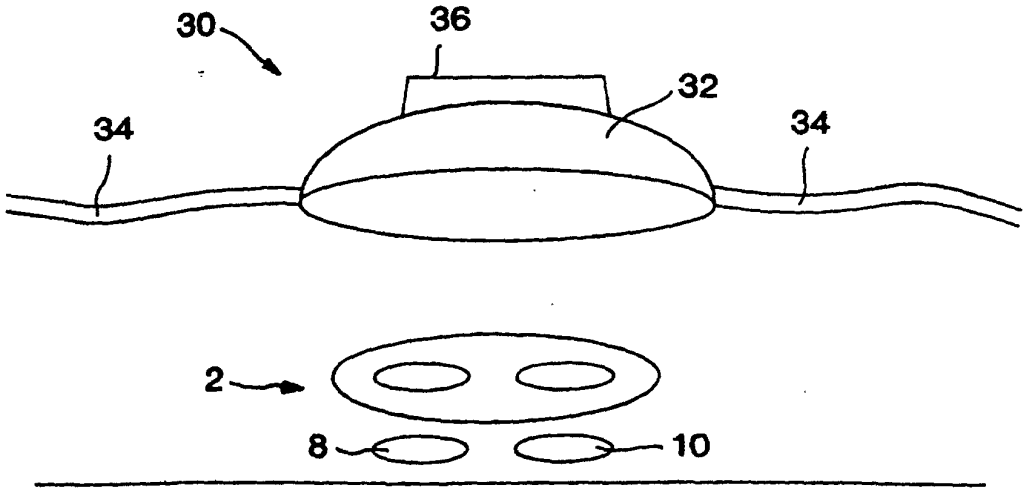


FIG. 2

Abbott Ex. 1002 - 213/1438

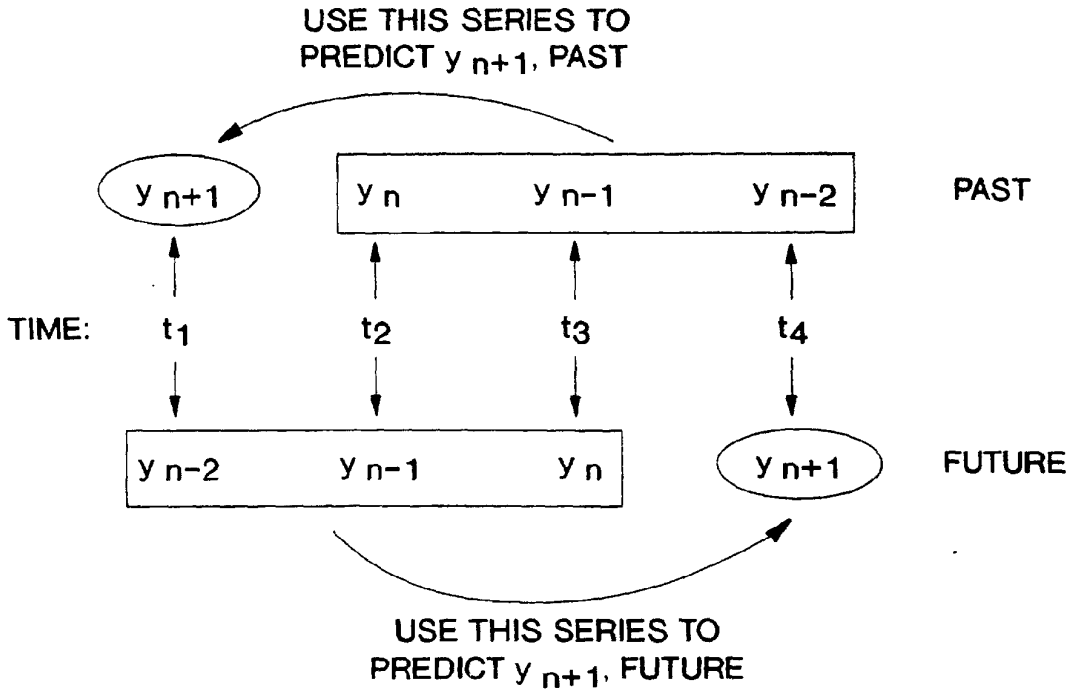


FIG. 3

Abbott Ex. 1002 - 214/1438

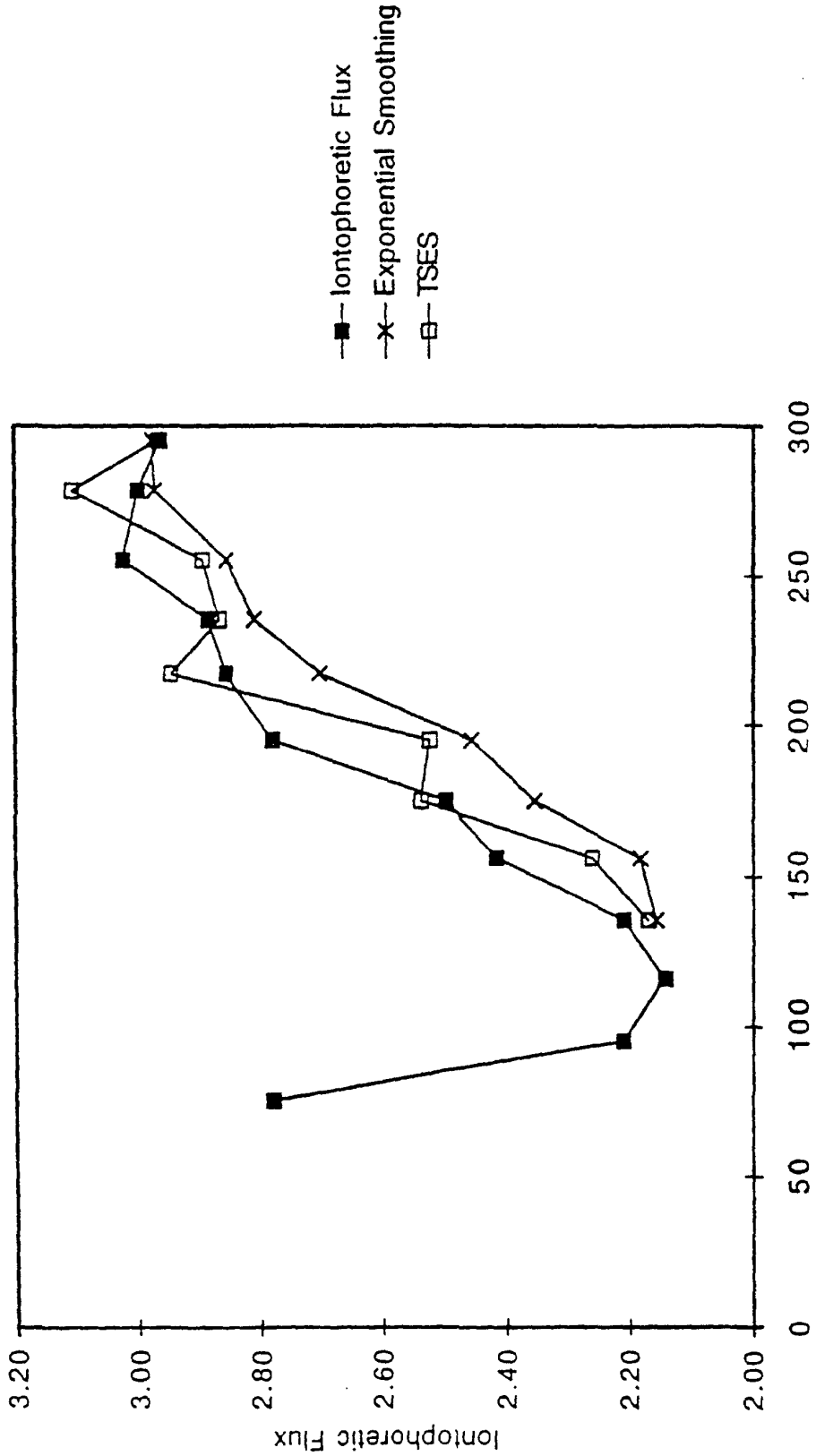


FIG. 4

Abbott Ex. 1002 - 215/1438

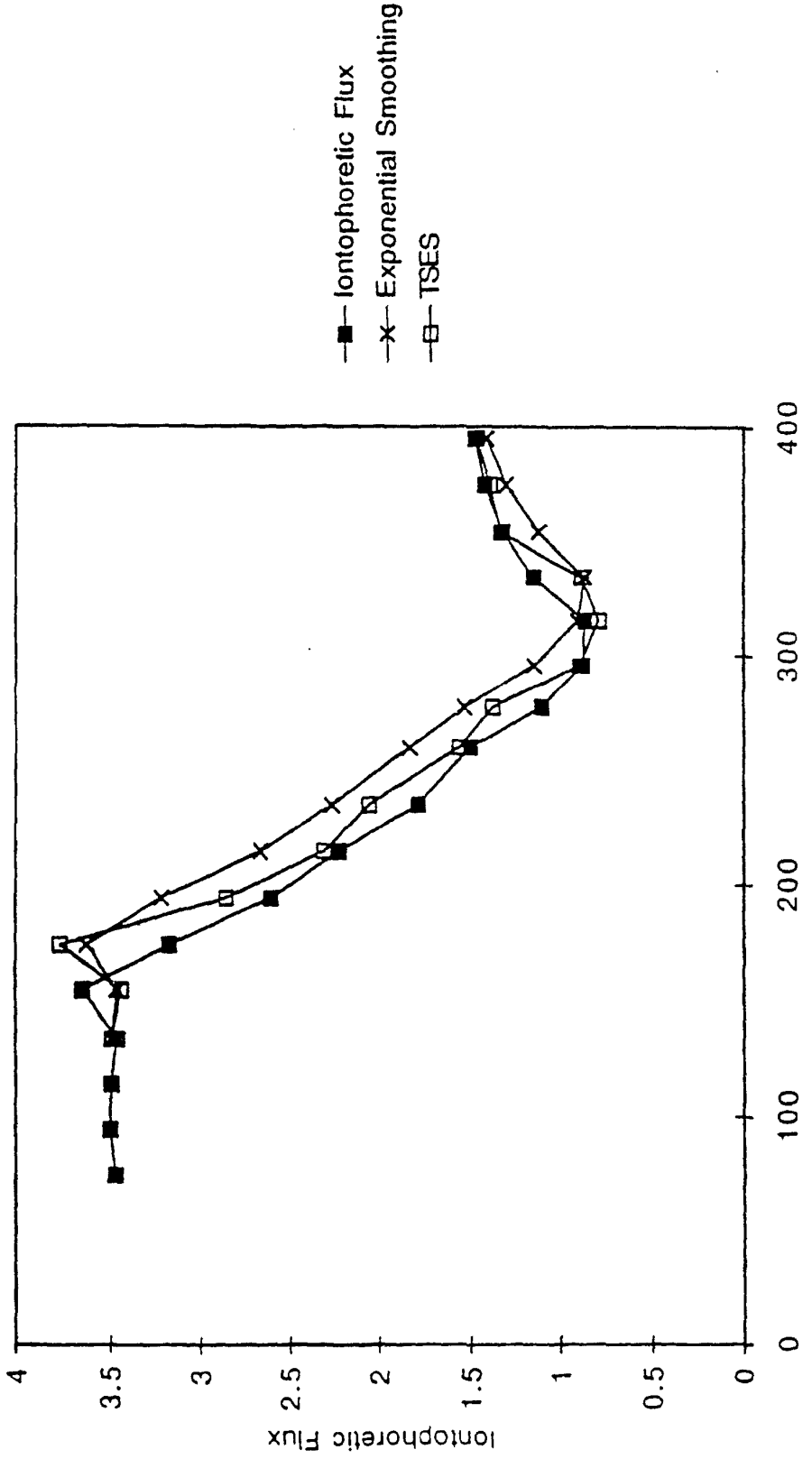


FIG. 5

Abbott Ex. 1002 - 216/1438

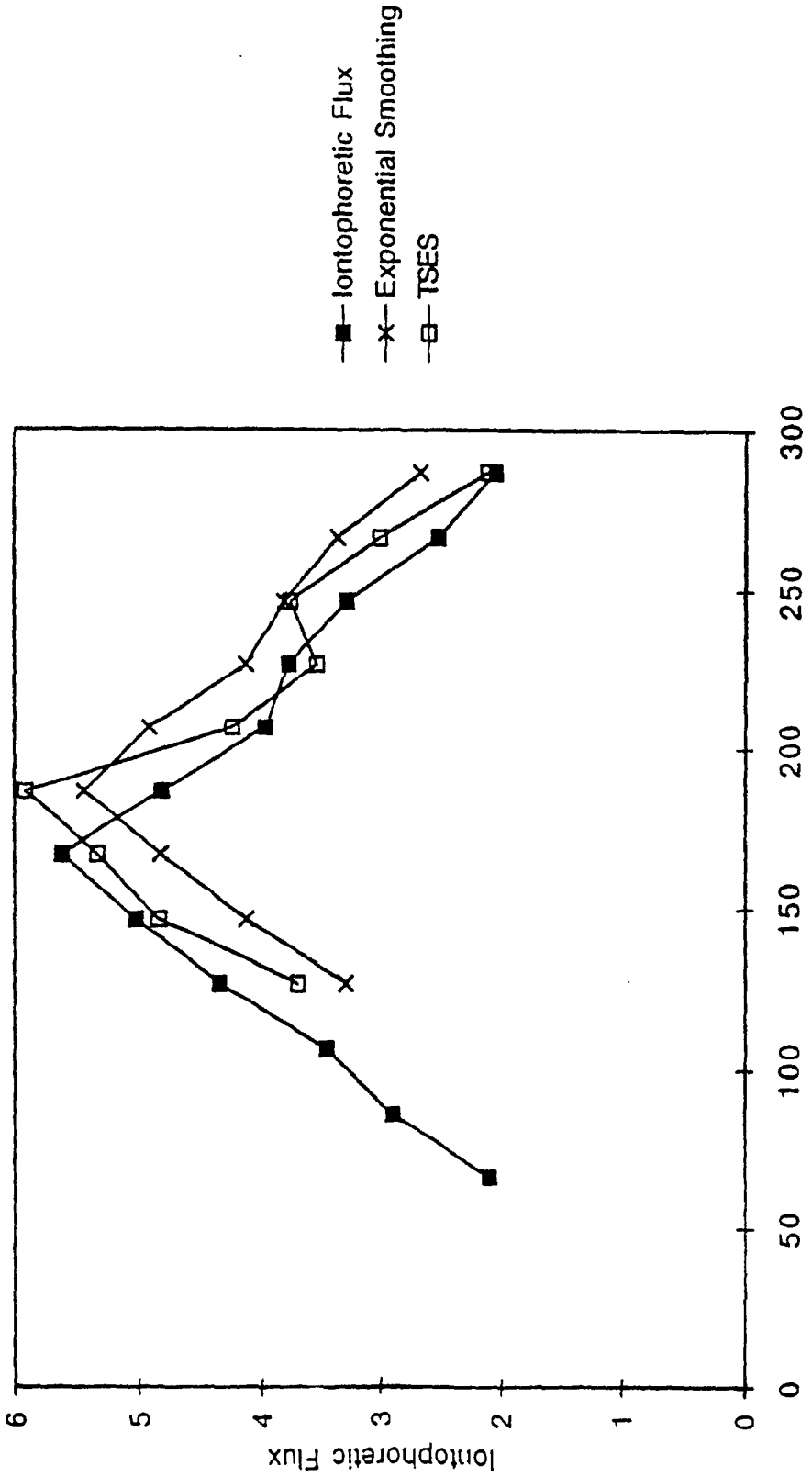


FIG. 6

Abbott Ex. 1002 - 217/1438

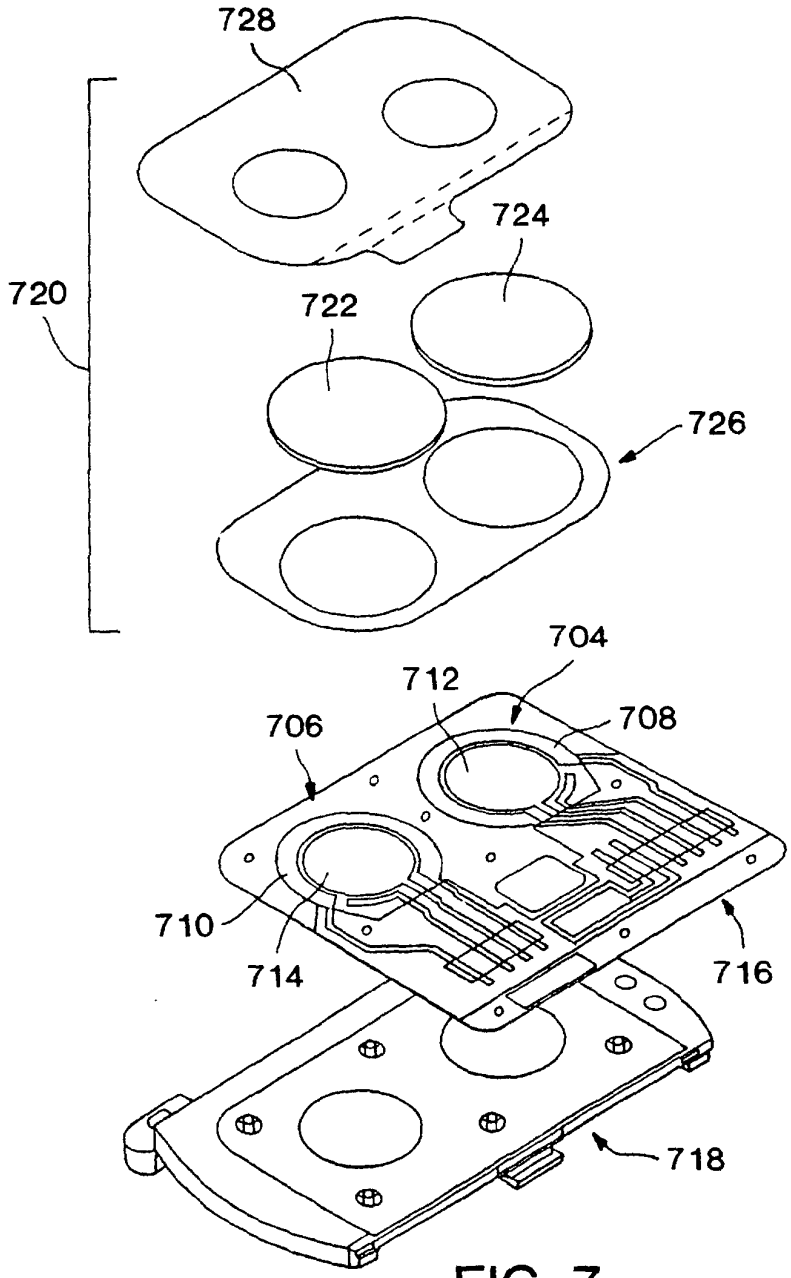


FIG. 7

Abbott Ex. 1002 - 218/1438

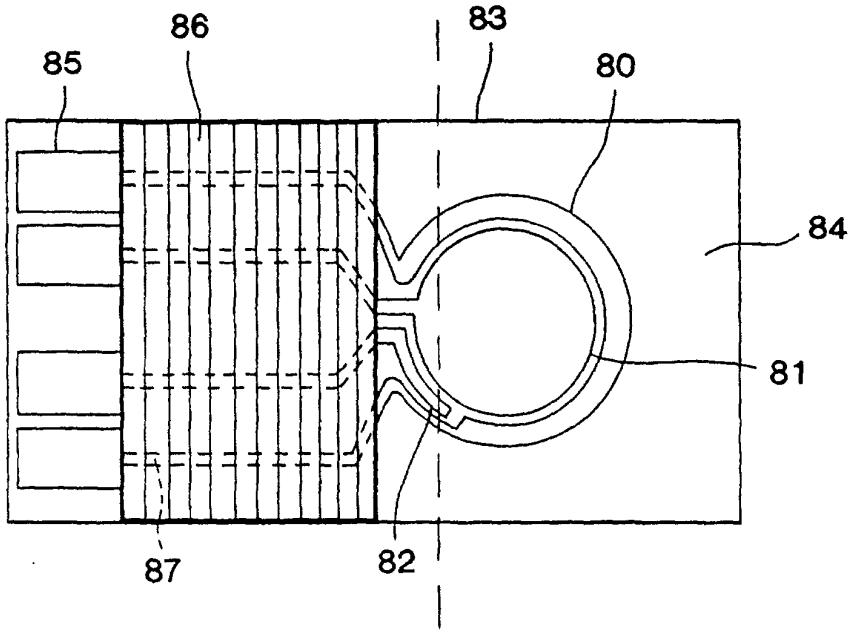


FIG. 8

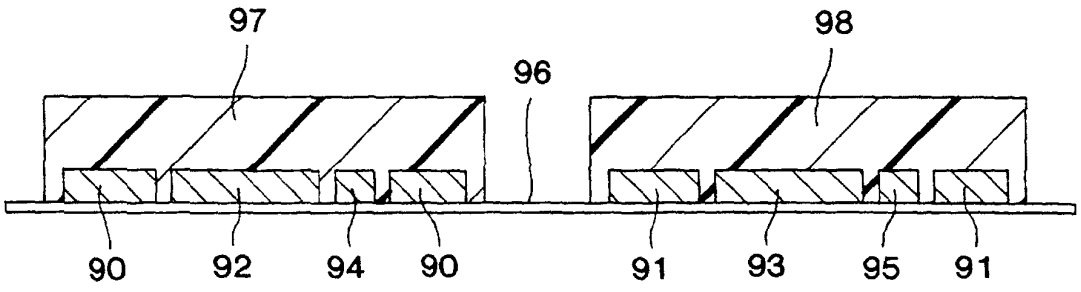


FIG. 9

Abbott Ex. 1002 - 219/1438

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(54) **METHOD AND DEVICE FOR PREDICTING PHYSIOLOGICAL VALUES**

VERFAHREN UND VORRICHTUNG ZUM VORHERSAGEN VON PHYSIOLOGISCHEN MESSWERTEN

PROCEDE ET DISPOSITIF DE PREDICTION DE VALEURS PHYSIOLOGIQUES

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EP 1 102 559 B1

Description

FIELD OF THE INVENTION

[0001] The invention relates generally to a method and device for measuring the concentration of target chemical analytes present in a biological system. More particularly, the invention relates to a method and monitoring systems for predicting a concentration of an analyte using a series of measurements obtained from a monitoring system and a Mixtures of Experts (MOE) algorithm.

BACKGROUND OF THE INVENTION

[0002] The Mixtures of Experts model is a statistical method for classification and regression (Waterhouse, S., *"Classification and Regression Using Mixtures of Experts,* October 1997, Ph.D. Thesis, Cambridge University). Waterhouse discusses Mixtures of Experts models from a theoretical perspective and compares them with other models, such as, trees, switching regression models, modular networks. The first extension described in Waterhouse's thesis is a constructive algorithm for learning model architecture and parameters, which is inspired by recursive partitioning. The second extension described in Waterhouse's thesis uses Bayesian methods for learning the parameters of the model. These extensions are compared empirically with the standard Mixtures of Experts model and with other statistical models on small to medium sized data sets. Waterhouse also describes the application of the Mixtures of Experts framework to acoustic modeling within a large vocabulary speech recognition system.

[0003] The Mixtures of Experts model has been employed in protein secondary structure prediction (Barlow, T.W., *Journal Of Molecular Graphics,* **13**(3), p. 175-183, 1995). In this method input data were clustered and used to train a series different networks. Application of a Hierarchical Mixtures of Experts to the prediction of protein secondary structure was shown to provide no advantages over a single network.

[0004] Mixtures of Experts algorithms have also been applied to the analysis of a variety of different kinds of data sets including the following: human motor systems (Ghahramani, Z. and Wolpert, D.M., *Nature,* **386**(6623) : 392-395, 1997); and economic analysis (Hamilton, J.D. and Susmel, R., *Journal* of *Econometrics,* **64**(1-2) : 307-333, 1994).

SUMMARY OF THE INVENTION

[0005] The present invention provides a method and device (for example, a monitoring or sampling system) for continually or continuously measuring the concentration of an analyte present in a biological system. The method entails continually or continuously detecting a raw signal from the biological system, wherein the raw signal is specifically related to the analyte. A calibration step is performed to correlate the raw signal with a measurement value indicative of the concentration of analyte present in the biological system. These steps of detection and calibration are used to obtain a series of measurement values at selected time intervals. Once the series of measurement values is obtained, the method of the invention provides for the prediction of a measurement value using a Mixtures of Experts (MOE) algorithm.

[0006] The raw signal can be obtained using any suitable sensing methodology including, for example, methods which rely on direct contact of a sensing apparatus with the biological system; methods which extract samples from the biological system by invasive, minimally invasive, and non-invasive sampling techniques, wherein the sensing apparatus is contacted with the extracted sample; methods which rely on indirect contact of a sensing apparatus with the biological system; and the like. Methods may be used to extract samples from the biological sample using minimally invasive or non-invasive sampling techniques. The sensing apparatus used with any of the above-noted methods can employ any suitable sensing element to provide the raw signal including, but not limited to, physical, chemical, electrochemical, photochemical, spectrophotometric, polarimetric, colorimetric, radiometric, or like elements. In preferred embodiments of the invention, a biosensor is used which comprises an electrochemical sensing element.

[0007] In one particular embodiment of the invention, the raw signal is obtained using a transdermal sampling system that is placed in operative contact with a skin or mucosal surface of the biological system. The sampling system transdermally extracts the analyte from the biological system using any appropriate sampling technique, for example, iontophoresis. The transdermal sampling system is maintained in operative contact with the skin or mucosal surface of the biological system to provide for continual or continuous analyte measurement.

[0008] A Mixtures of Experts algorithm is used to predict measurement values. The general Mixtures of Experts algorithm is represented by the following series of equations: where the individual experts have a linear form:

Abbott Ex. 1002 - 221/1438

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

wherein (*An*) is an analyte of interest, *n* is the number of experts, An_i is the analyte predicted by Expert *i*; and w_i is a parameter, and the individual experts An_i are further defined by the expression shown as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wherein, An_i is the analyte predicted by Expert *i* ; P_j is one of *m* parameters, *m* is typically less than 100; a_{ij} are coefficients; and z_i is a constant; and further where the weighting value, w_i, is defined by the formula shown as Equation (3).

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

where *e* refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i. The d_k are given by Equation 4.

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of m parameters, and where ω_k is a constant.

[0009] It is an object of the invention to use the Mixtures of Experts algorithm of the invention to predict blood glucose values. In one aspect, the method of the invention is used in conjunction with an iontophoretic sampling device that provides continual or continuous blood glucose measurements. In one embodiment the Mixtures of Experts algorithm is essentially as follows: where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (*BG*) is blood glucose, there are three experts (n=3) and BG_i is the analyte predicted by Expert *i*; w_i is a parameter, and the individual Experts BG_i are further defined by the expression shown as Equations 6, 7, and 8

$$BG_1 = p_1(time) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \qquad (6)$$

$$BG_2 = p_2(time) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \qquad (7)$$

$$BG_3 = p_3(time) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \qquad (8)$$

wherein, BG_i is the analyte predicted by Expert *i*; parameters include, time (elapsed time since the sampling system was placed in operative contact with said biological system), active (active signal), signal (calibrated signal), and *BG/cp* (blood glucose value at a calibration point); p_i, q_i, r_i, and s_i are coefficients; and t_i is a constant; and further where

Abbott Ex. 1002 - 222/1438

the weighting value, w_i, is defined by the formulas shown as Equations 9, 10, and 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that is used to determine the weights w_i, given by Equations 9, 10, and 11, and

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + \varepsilon_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where ε_i is a constant.

[0010] In another embodiment for the prediction of blood glucose values, the Mixtures of Experts algorithm is essentially as follows: where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \quad (15)$$

wherein (BG) is blood glucose, there are three experts (n=3) and BG_i is the analyte predicted by Expert i; w_i is a parameter, and the individual Experts BG_i are further defined by the expression shown as Equations 16, 17, and 18

$$BG_1 = p_1(time_c) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \quad (16)$$

$$BG_2 = p_2(time_c) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \quad (17)$$

$$BG_3 = p_3(time_c) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \quad (18)$$

wherein, BG_i is the analyte predicted by Expert i; parameters include, $time_c$ (elapsed time since calibration of said sampling system), *active* (active signal), *signal* (calibrated signal), and *BG/cp* (blood glucose value at a calibration point) ; p_i, q_i, r_i, and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 19, 20, and 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

Abbott Ex. 1002 - 223/1438

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that is used to determine the weights w_i, given by Equations 19, 20, and 21, and

$$d_1 = \tau_1(time_c) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \varepsilon_1 \quad (22)$$

$$d_2 = \tau_2(time_c) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \varepsilon_2 \quad (23)$$

$$d_3 = \tau_3(time_c) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + \varepsilon_3 \quad (24)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where ε_i is a constant.

[0011] Parameters can be substituted, and/or other parameters can be included in these calculations, for example, time parameters can be varied (e.g., as described above, elapsed time since the sampling system was placed in contact with a biological system, or elapsed time since the sampling system was calibrated) or multiple time parameters can be used in the same equation where these parameters are appropriately weighted. Further parameters include, but are not limited to, temperature, ionophoretic voltage, and skin conductivity. In addition, a calibration check can be used to ensure an efficacious calibration.

[0012] A further object of the invention is to provide a method for measuring an analyte, for example, blood glucose, in a subject. In one embodiment, the method entails operatively contacting a glucose sensing apparatus with the subject to detect blood glucose and thus obtain a raw signal from the sensing apparatus. The raw signal is specifically related to the glucose, and is converted into a measurement value indicative of the subject's blood glucose concentration using a calibration step. In one aspect of the invention, the sensing apparatus is a near-IR spectrometer. In another aspect of the invention, the sensing means comprises a biosensor having an electrochemical sensing element.

[0013] It is also an object of the invention to provide a monitoring system for continually or continuously measuring an analyte present in a biological system. The monitoring system is formed from the operative combination of a sampling means, a sensing means, and a microprocessor means which controls the sampling means and the sensing means. The sampling means is used to continually or continuously extract the analyte from the biological system across a skin or mucosal surface of said biological system. The sensing means is arranged in operative contact with the analyte extracted by the sampling means, such that the sensing means can obtain a raw signal from the extracted analyte which signal is specifically related to the analyte. The microprocessor means communicates with the sampling means and the sensing means, and is used to: (a) control the sampling means and the sensing means to obtain a series of raw signals at selected time intervals during a continual or continuous measurement period; (b) correlate the raw signals with measurement values indicative of the concentration of analyte present in the biological system; and (c) predict a measurement value using the Mixtures of Experts algorithm. In one aspect, the monitoring system uses an iontophoretic current to extract the analyte from the biological system.

[0014] It is a further object of the invention to provide a monitoring system for measuring blood glucose in a subject. The monitoring system is formed from an operative combination of a sensing means and a microprocessor means. The sensing means is adapted for operative contact with the subject or with a glucose-containing sample extracted from the subject, and is used to obtain a raw signal specifically related to blood glucose in the subject. The microprocessor means communicates with the sensing means, and is used to: (a) control the sensing means to obtain a series of raw signals (specifically related to blood glucose) at selected time intervals; (b) correlate the raw signals with measurement values indicative of the concentration of blood glucose present in the subject; and (c) predict a measurement value using the Mixtures of Experts algorithm.

[0015] In a further aspect, the monitoring system comprises a biosensor having an electrochemical sensing element. In another aspect, the monitoring system comprises a near-IR spectrometer.

[0016] Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

Abbott Ex. 1002 - 224/1438

BRIEF DESCRIPTION OF THE DRAWINGS

[0017]

Figure 1A depicts a top plan view of an iontophoretic collection reservoir and electrode assembly for use in a transdermal sampling device constructed according to the present invention.

Figure 1B depicts the side view of the iontophoretic collection reservoir and electrode assembly shown in Figure 1A.

Figure 2 is a pictorial representation of an iontophoretic sampling device which includes the iontophoretic collection reservoir and electrode assembly of Figures 1A and 1B.

Figure 3 is an exploded pictorial representation of components from a preferred embodiment of the automatic sampling system of the present invention.

Figure 4 is a representation of one embodiment of a bimodal electrode design. The figure presents an overhead and schematic view of the electrode assembly **433**. In the figure, the bimodal electrode is shown at **430** and can be, for example, a Ag/AgCl iontophoretic/counter electrode. The sensing or working electrode (made from, for example, platinum) is shown at **431**. The reference electrode is shown at **432** and can be, for example, a Ag/AgCl electrode. The components are mounted on a suitable nonconductive substrate **434**, for example, plastic or ceramic. The conductive leads **437** (represented by dotted lines) leading to the connection pad **435** are covered by a second nonconductive piece **436** (the area represented by vertical striping) of similar or different material (e.g., plastic or ceramic). In this example of such an electrode the working electrode area is approximately 1.35 cm^2. The dashed line in Figure 4 represents the plane of the cross-sectional schematic view presented in Figure 5.

Figure 5 is a representation of a cross-sectional schematic view of the bimodal electrodes as they may be used in conjunction with a reference electrode and a hydrogel pad. In the figure, the components are as follows: bimodal electrodes **540** and **541**; sensing electrodes **542** and **543**; reference electrodes **544** and **545**; a substrate **546**; and hydrogel pads **547** and **548**.

Figure 6 depicts predicted blood glucose data (using the Mixtures of Experts algorithm) versus measured blood glucose data, as described in Example 2.

Figure 7 depicts predicted blood glucose data (using the Mixtures of Experts algorithm) versus measured blood glucose data, as described in Example 4.

Figure 8 presents a graph of the measured and predicted blood glucose levels vs. time, as described in Example 4.

Figure 9 depicts an exploded view of an embodiment of an autosensor.

Figures 10A and 10B graphically illustrate the method of the present invention used for decreasing the bias of a data set.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0018] Before describing the present invention in detail, it is to be understood that this invention is not limited to particular compositions or biological systems, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0019] It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an analyte" includes mixtures of analytes, and the like.

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein.

[0021] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

1.0.0 DEFINITIONS

[0022] The terms "analyte" and "target analyte" are used herein to denote any physiological analyte of interest that is a specific substance or component that is being detected and/or measured in a chemical, physical, enzymatic, or optical analysis. A detectable signal (e.g., a chemical signal or electrochemical signal) can be obtained, either directly or indirectly, from such an analyte or derivatives thereof. Furthermore, the terms "analyte" and "substance" are used interchangeably herein, and are intended to have the same meaning, and thus encompass any substance of interest. In preferred embodiments, the analyte is a physiological analyte of interest, for example, glucose, or a chemical that has a physiological action, for example, a drug or pharmacological agent.

[0023] A "sampling device" or "sampling system" refers to any device for obtaining a sample from a biological system

Abbott Ex. 1002 - 225/1438

for the purpose of determining the concentration of an analyte of interest. As used herein, the term "sampling" means invasive, minimally invasive or non-invasive extraction of a substance from the biological system, generally across a membrane such as skin or mucosa. The membrane can be natural or artificial, and can be of plant or animal nature, such as natural or artificial skin, blood vessel tissue, intestinal tissue, and the like. Typically, the sampling means are in operative contact with a "reservoir," or "collection reservoir," wherein the sampling means is used for extracting the analyte from the biological system into the reservoir to obtain the analyte in the reservoir. A "biological system" includes both living and artificially maintained systems. Examples of minimally invasive and noninvasive sampling techniques include iontophoresis, sonophoresis, suction, electroporation, thermal poration, passive diffusion, microfine (miniature) lances or cannulas, subcutaneous implants or insertions, and laser devices. Sonophoresis uses ultrasound to increase the permeability of the skin (see, e.g., Menon et al. (1994) *Skin Pharmacology* 7:130-139). Suitable sonophoresis sampling systems are described in International Publication No. WO 91/12772, published 5 September 1991. Passive diffusion sampling devices are described, for example, in International Publication Nos.: WO 97/38126 (published 16 October 1997); WO 97/42888, WO 97/42886, WO 97/42885, and WO 97/42882 (all published 20 November 1997); and WO 97/43962 (published 27 November 1997). Laser devices use a small laser beam to burn a hole through the upper layer of the patient's skin (see, e.g., Jacques et al. (1978) *J. Invest. Dermatology* 88 : 88-93). Examples of invasive sampling techniques include traditional needle and syringe or vacuum sample tube devices.

[0024] The term "collection reservoir" is used to describe any suitable containment means for containing a sample extracted from a biological system. For example, the collection reservoir can be a receptacle containing a material which is ionically conductive (e.g., water with ions therein), or alternatively, it can be a material, such as, a sponge-like material or hydrophilic polymer, used to keep the water in place. Such collection reservoirs can be in the form of a hydrogel (for example, in the form of a disk or pad). Hydrogels are typically referred to as "collection inserts." Other suitable collection reservoirs include, but are not limited to, tubes, vials, capillary collection devices, cannulas, and miniaturized etched, ablated or molded flow paths.

[0025] A "housing" for the sampling system can further include suitable electronics (e.g., microprocessor, memory, display and other circuit components) and power sources for operating the sampling system in an automatic fashion.

[0026] A "monitoring system," as used herein, refers to a system useful for continually or continuously measuring a physiological analyte present in a biological system. Such a system typically includes, but is not limited to, sampling means, sensing means, and a microprocessor means in operative communication with the sampling means and the sensing means.

[0027] The term "artificial," as used herein, refers to an aggregation of cells of monolayer thickness or greater which are grown or cultured *in vivo* or *in vitro,* and which function as a tissue of an organism but are not actually derived, or excised, from a pre-existing source or host.

[0028] The term "subject" encompasses any warm-blooded animal, particularly including a member of the class *Mammalia* such as, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

[0029] As used herein, the term "continual measurement" intends a series of two or more measurements obtained from a particular biological system, which measurements are obtained using a single device maintained in operative contact with the biological system over the time period in which the series of measurements is obtained. The term thus includes continuous measurements.

[0030] The term "transdermal," as used herein, includes both transdermal and transmucosal techniques, i.e., extraction of a target analyte across skin or mucosal tissue. Aspects of the invention which are described herein in the context of "transdermal," unless otherwise specified, are meant to apply to both transdermal and transmucosal techniques.

[0031] The term "transdermal extraction," or "transdermally extracted" intends any noninvasive, or at least minimally invasive sampling method, which entails extracting and/or transporting an analyte from beneath a tissue surface across skin or mucosal tissue. The term thus includes extraction of an analyte using iontophoresis (reverse iontophoresis), electroosmosis, sonophoresis, microdialysis, suction, and passive diffusion. These methods can, of course, be coupled with application of skin penetration enhancers or skin permeability enhancing technique such as tape stripping or pricking with micro-needles. The term "transdermally extracted" also encompasses extraction techniques which employ thermal poration, electroporation, microfine lances, microfine canulas, subcutaneous implants or insertions, and the like.

[0032] The term "iontophoresis" intends a method for transporting substances across tissue by way of an application of electrical energy to the tissue. In conventional iontophoresis, a reservoir is provided at the tissue surface to serve as a container of material to be transported. Iontophoresis can be carried out using standard methods known to those of skill in the art, for example, by establishing an electrical potential using a direct current (DC) between fixed anode and cathode "iontophoretic electrodes," alternating a direct current between anode and cathode iontophoretic elec-

Abbott Ex. 1002 - 226/1438

trodes, or using a more complex waveform such as applying a current with alternating polarity (AP) between iontophoretic electrodes (so that each electrode is alternately an anode or a cathode).

[0033] The term "reverse iontophoresis" refers to the movement of a substance from a biological fluid across a membrane by way of an applied electric potential or current. In reverse iontophoresis, a reservoir is provided at the tissue surface to receive the extracted material.

[0034] "Electroosmosis" refers to the movement of a substance through a membrane by way of an electric field-induced convective flow. The terms iontophoresis, reverse iontophoresis, and electroosmosis, will be used interchangeably herein to refer to movement of any ionically charged or uncharged substance across a membrane (e.g., an epithelial membrane) upon application of an electric potential to the membrane through an ionically conductive medium.

[0035] The term "sensing device," "sensing means," or "biosensor device" encompasses any device that can be used to measure the concentration of an analyte, or derivative thereof, of interest. Preferred sensing devices for detecting blood analytes generally include electrochemical devices and chemical devices. Examples of electrochemical devices include the Clark electrode system (see, e.g., Updike, et al., (1967) *Nature* 214:986-988), and other amperometric, coulometric, or potentiometric electrochemical devices. Examples of chemical devices include conventional enzyme-based reactions as used in the Lifescan® glucose monitor (Johnson and Johnson, New Brunswick, NJ) (see, e.g., U.S. Patent 4,935,346 to Phillips, et al.).

[0036] A "biosensor" or "biosensor device" includes, but is not limited to, a "sensor element" which includes, but is not limited to, a "biosensor electrode" or "sensing electrode" or "working electrode" which refers to the electrode that is monitored to determine the amount of electrical signal at a point in time or over a given time period, which signal is then correlated with the concentration of a chemical compound. The sensing electrode comprises a reactive surface which converts the analyte, or a derivative thereof, to electrical signal. The reactive surface can be comprised of any electrically conductive material such as, but not limited to, platinum-group metals (including, platinum, palladium, rhodium, ruthenium, osmium, and iridium), nickel, copper, silver, and carbon, as well as, oxides, dioxides, combinations or alloys thereof. Some catalytic materials, membranes, and fabrication technologies suitable for the construction of amperometric biosensors were described by Newman, J.D., et al.(Analytical *Chemistry* **67**(24), 4594-4599, 1995).

[0037] The "sensor element" can include components in addition to a biosensor electrode, for example, it can include a "reference electrode," and a "counter electrode." The term "reference electrode" is used herein to mean an electrode that provides a reference potential, e.g., a potential that can be established between a reference electrode and a working electrode. The term "counter electrode" is used herein to mean an electrode in an electrochemical circuit which acts as a current source or sink to complete the electrochemical circuit. Although it is not essential that a counter electrode be employed where a reference electrode is included in the circuit and the electrode is capable of performing the function of a counter electrode, it is preferred to have separate counter and reference electrodes because the reference potential provided by the reference electrode is most stable when it is at equilibrium. If the reference electrode is required to act further as a counter electrode, the current flowing through the reference electrode may disturb this equilibrium. Consequently, separate electrodes functioning as counter and reference electrodes are most preferred.

[0038] In one embodiment, the "counter electrode" of the "sensor element" comprises a "bimodal electrode." The term "bimodal electrode" as used herein typically refers to an electrode which is capable of functioning non-simultaneously as, for example, both the counter electrode (of the "sensor element") and the iontophoretic electrode (of the "sampling means").

[0039] The terms "reactive surface," and "reactive face" are used interchangeably herein to mean the surface of the sensing electrode that: (1) is in contact with the surface of an electrolyte containing material (e.g. gel) which contains an analyte or through which an analyte, or a derivative thereof, flows from a source thereof; (2) is comprised of a catalytic material (e.g., carbon, platinum, palladium, rhodium, ruthenium, or nickel and/or oxides, dioxides and combinations or alloys thereof) or a material that provides sites for electrochemical reaction; (3) converts a chemical signal (e.g. hydrogen peroxide) into an electrical signal (e.g., an electrical current); and (4) defines the electrode surface area that, when composed of a reactive material, is sufficient to drive the electrochemical reaction at a rate sufficient to generate a detectable, reproducibly measurable, electrical signal that is correlatable with the amount of analyte present in the electrolyte.

[0040] An "ionically conductive material" refers to any material that provides ionic conductivity, and through which electrochemically active species can diffuse. The ionically conductive material can be, for example, a solid, liquid, or semi-solid (e.g., in the form of a gel) material that contains an electrolyte, which can be composed primarily of water and ions (e.g., sodium chloride), and generally comprises 50% or more water by weight. The material can be in the form of a gel, a sponge or pad (e.g., soaked with an electrolytic solution), or any other material that can contain an electrolyte and allow passage therethrough of electrochemically active species, especially the analyte of interest.

[0041] The term "physiological effect" encompasses effects produced in the subject that achieve the intended purpose of a therapy. In preferred embodiments, a physiological effect means that the symptoms of the subject being treated are prevented or alleviated. For example, a physiological effect would be one that results in the prolongation of survival in a patient.

Abbott Ex. 1002 - 227/1438

[0042] A "laminate" , as used herein, refers to structures comprised of at least two bonded layers. The layers may be bonded by welding or through the use of adhesives. Examples of welding include, but are not limited to, the following: ultrasonic welding, heat bonding, and inductively coupled localized heating followed by localized flow. Examples of common adhesives include, but are not limited to, pressure sensitive adhesives, thermoset adhesives, cyanocrylate adhesives, epoxies, contact adhesives, and heat sensitive adhesives.

[0043] A "collection assembly", as used herein, refers to structures comprised of several layers, where the assembly includes at least one collection insert, for example a hydrogel. An example of a collection assembly of the present invention is a mask layer, collection inserts, and a retaining layer where the layers are held in appropriate, functional relationship to each other but are not necessarily a laminate, i.e., the layers may not be bonded together. The layers may, for example, be held together by interlocking geometry or friction.

[0044] An "autosensor assembly", as used herein, refers to structures generally comprising a mask layer, collection inserts, a retaining layer, an electrode assembly, and a support tray. The autosensor assembly may also include liners. The layers of the assembly are held in appropriate, functional relationship to each other.

[0045] The mask and retaining layers are preferably composed of materials that are substantially impermeable to the analyte (chemical signal) to be detected (e.g., glucose); however, the material can be permeable to other substances. By "substantially impermeable" is meant that the material reduces or eliminates chemical signal transport (e.g., by diffusion). The material can allow for a low level of chemical signal transport, with the proviso that chemical signal that passes through the material does not cause significant edge effects at the sensing electrode.

[0046] "Substantially planar" as used herein, includes a planar surface that contacts a slightly curved surface, for example, a forearm or upper arm of a subject. A "substantially planar" surface is, for example, a surface having a shape to which skin can conform, i.e., contacting contact between the skin and the surface.

[0047] A "Mixtures of Experts (MOE)" algorithm is used in the practice of the present invention. An example of a Mixtures of Experts algorithm useful in connection with the present invention is represented by the following equations, where the individual experts have a linear form:

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

wherein (*An*) is an analyte of interest, *n* is the number of experts, An_i is the analyte predicted by Expert *i*; and w_i is a parameter, and the individual experts An_i are further defined by the expression shown as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wherein, An_i is the analyte predicted by Expert *i*; P_j is one of *m* parameters, *m* is typically less than 100; a_{ij} are coefficients; and z_i is a constant; and further where the weighting value, w_i, is defined by the formula shown as Equation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

where *e* refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i. The d_k are given by Equation 4

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of *m* parameters, and where ω_k is a constant.

[0048] The Mixtures of Experts algorithm is a generalized predictive technology for data analysis. This method uses

Abbott Ex. 1002 - 228/1438

a superposition of multiple linear regressions, along with a switching algorithm, to predict outcomes. Any number of input/output variables are possible. The unknown coefficients in this method are determined by a maximum posterior probability technique.

[0049] The method is typically implemented as follows. An experimental data set of input/output pairs is assembled that spans the expected ranges of all variables. These variables are then used to train the Mixtures of Experts (that is, used to determine the unknown coefficients). These coefficients are determined using, for example, the Expectation Maximization method (Dempster, A.P., N.M. Laird, and D.B. Rubin, J. *Royal Statistical Society* (Series B-Methodological) **39**:(1), 1977). Once these coefficients are known, the Mixtures of Experts is easily applied to a new data set.

[0050] "Parameter" as used herein refers to an arbitrary constant or variable so appearing in a mathematical expression that changing it gives various cases of the phenomenon represented (*McGraw-Hill Dictionary of Scientific and Technical Terms,* S.P. Parker, ed., Fifth Edition, McGraw-Hill Inc., 1994). In the context of the GlucoWatch® monitor (Cygnus, Inc., Redwood City, CA), a parameter is a variable that influences the value of the blood glucose level as calculated by an algorithm. For the Mixtures of Experts algorithm, these parameters include, but are not limited to, the following: time (e.g., elapsed time since the monitor was applied to a subject; and/or elapsed time since calibration); the active signal; the calibrated signal; the blood glucose value at the calibration point; the skin temperature; the skin conductivity; and the iontophoretic voltage. Changes in the values of any of these parameters can be expected to change the value of the calculated blood glucose value. Parameters can be substituted, and/or other parameters can be included in these calculations, for example, time parameters can be varied (e.g., elapsed time since the sampling system was placed in contact with a biological system, or elapsed time since the sampling system was calibrated) or multiple time parameters can be used in the same equation where these parameters are appropriately weighted.

[0051] By the term "printed" as used herein is meant a substantially uniform deposition of an electrode formulation onto one surface of a substrate (i.e., the base support). It will be appreciated by those skilled in the art that a variety of techniques may be used to effect substantially uniform deposition of a material onto a substrate, e.g., Gravure-type printing, extrusion coating, screen coating, spraying, painting, or the like.

[0052] "Bias" as used herein refers to the difference between the expected value of an estimator and the true value of a parameter. "Bias" is used in a statistical context, in particular, in estimating the value of a parameter of a probability distribution. For example, in the case of a linear regression wherein

$$y = mx + b, \text{ for } x = a,$$

the bias at "a" equals (ma + b) - a.

"Decay" as used herein refers to a gradual reduction in the magnitude of a quantity, for example, a current detected using a sensor electrode where the current is correlated to the concentration of a particular analyte and where the detected current gradually reduces but the concentration of the analyte does not.

2.0.0 GENERAL METHODS

[0053] The present invention relates to the analysis of data obtained by use of a sensing device for measuring the concentration of a target analyte present in a biological system. In preferred embodiments, the sensing device comprises a biosensor. In other preferred embodiments, a sampling device is used to extract small amounts of a target analyte from the biological system, and then sense and/or quantify the concentration of the target analyte. Measurement with the biosensor and/or sampling with the sampling device can be carried out in a continual manner. Continual measurement allows for closer monitoring of target analyte concentration fluctuations.

[0054] In the general method of the invention, a raw signal is obtained from a sensing device, which signal is related to a target analyte present in the biological system. The raw signal can be obtained using any suitable sensing methodology including, for example, methods which rely on direct contact of a sensing apparatus with the biological system; methods which extract samples from the biological system by invasive, minimally invasive, and non-invasive sampling techniques, wherein the sensing apparatus is contacted with the extracted sample; methods which rely on indirect contact of a sensing apparatus with the biological system; and the like. Methods may be used to extract samples from the biological sample using minimally invasive or non-invasive sampling techniques. The sensing apparatus used with any of the above-noted methods can employ any suitable sensing element to provide the signal including, but not limited to, physical, chemical, electrochemical, photochemical, spectrophotometric, polarimetric, colorimetric, radiometric, or like elements. In preferred embodiments of the invention, a biosensor is used which comprises an electrochemical sensing element.

[0055] In another embodiment of the invention, a near-IR glucose sensing apparatus is used to detect blood glucose in a subject, and thus generate the raw signal. A number of near-IR glucose sensing devices suitable for use in the present method are known in the art and are readily available. For example, a near-IR radiation diffuse-reflection laser

Abbott Ex. 1002 - 229/1438

spectroscopy device is described in U.S. Patent No. 5,267,152 to Yang et al. Similar near-IR spectrometric devices are also described in U.S. Patent No. 5,086,229 to Rosenthal et al. and U.S. Patent No. 4,975,581 to Robinson et al. These near-IR devices use traditional methods of reflective or transmissive near infrared (near-IR) analysis to measure absorbance at one or more glucose-specific wavelengths, and can be contacted with the subject at an appropriate location, such as a finger-tip, skin fold, eyelid, or forearm surface to obtain the raw signal.

[0056] The raw signal obtained using any of the above-described methodologies is then converted into an analyte-specific value of known units to provide an interpretation of the signal obtained from the sensing device. The interpretation uses a mathematical transformation to model the relationship between a measured response in the sensing device and a corresponding analyte-specific value (in the present invention, a Mixtures of Experts algorithm). Thus, a calibration step is used herein to relate, for example, an electrochemical signal (detected by a biosensor), or near-IR absorbance spectra (detected with a near-IR detector) with the concentration of a target analyte in a biological system.

[0057] The predicted analyte values can optionally be used in a subsequent step to control an aspect of the biological system. In one embodiment, predicted analyte values are used to determine when, and at what level, a constituent should be added to the biological system in order to control an aspect of the biological system. In a preferred embodiment, the analyte value can be used in a feedback control loop to control a physiological effect in the biological system.

[0058] The above general methods can, of course, be used with a wide variety of biological systems, target analytes, and/or sensing techniques. The determination of particularly suitable combinations is within the skill of the ordinarily skilled artisan when directed by the instant disclosure. Although these methods are broadly applicable to measuring any chemical analyte and/or substance in a biological system, the invention is expressly exemplified for use in a non-invasive, transdermal sampling system which uses an electrochemical biosensor to quantify or qualify glucose or a glucose metabolite.

2.1.0 OBTAINING THE RAW SIGNAL.

[0059] The raw signal can be obtained using any sensing device that is operatively contacted with the biological system. Such sensing devices can employ physical, chemical, electrochemical, spectrophotometric, polarimetric, colorimetric, radiometric, or like measurement techniques. In addition, the sensing device can be in direct or indirect contact with the biological system, or used with a sampling device which extracts samples from the biological system using invasive, minimally invasive or non-invasive sampling techniques. In preferred embodiments, a minimally invasive or non-invasive sampling device is used to obtain samples from the biological system, and the sensing device comprises a biosensor with an electrochemical sensing element.

[0060] The analyte can be any specific substance or component in a biological system that one is desirous of detecting and/or measuring in a chemical, physical, enzymatic, or optical analysis. In the embodiment, of the invention, the analyte is glucose.

[0061] In order to facilitate detection of the analyte, an enzyme can be disposed in the collection reservoir, or, if several collection reservoirs are used, the enzyme can be disposed in several or all of the reservoirs. The selected enzyme is capable of catalyzing a reaction with the extracted analyte (e.g., glucose) to the extent that a product of this reaction can be sensed, e.g., can be detected electrochemically from the generation of a current which current is detectable and proportional to the concentration or amount of the analyte which is reacted. A suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide. The subsequent detection of hydrogen peroxide on an appropriate biosensor electrode generates two electrons per hydrogen peroxide molecule which create a current which can be detected and related to the amount of glucose entering the device. Glucose oxidase (GOx) is readily available commercially and has well known catalytic characteristics. However, other enzymes can also be used, so long as they specifically catalyze a reaction with an analyte or substance of interest to generate a detectable product in proportion to the amount of analyte so reacted.

[0062] In like manner, a number of other analyte-specific enzyme systems can be used, which enzyme systems operate on much the same general techniques but which do not form part of this invention. For example, a biosensor electrode that detects hydrogen peroxide can be used to detect ethanol using an alcohol oxidase enzyme system, or similarly uric acid with urate oxidase system, urea with a urease system, cholesterol with a cholesterol oxidase system, and theophylline with a xanthine oxidase system.

[0063] In addition, the oxidase enzyme (used for hydrogen peroxidase-based detection) can be replaced with another redox system, for example, the dehydrogenase-enzyme NAD-NADH, which offers a separate route to detecting additional analytes. Dehydrogenase-based sensors can use working electrodes made of gold or carbon (via mediated chemistry). Examples of analytes suitable for this type of monitoring include, but are not limited to, cholesterol, ethanol, hydroxybutyrate, phenylalanine, triglycerides, and urea. Further, the enzyme can be eliminated and detection can rely on direct electrochemical or potentiometric detection of an analyte. Such analytes include, without limitation, heavy metals (e.g., cobalt, iron, lead, nickel, zinc), oxygen, carbonate/carbon dioxide, chloride, fluoride, lithium, pH, potassium, sodium, and urea. Also, the sampling system described herein can be used for therapeutic drug monitoring, for

Abbott Ex. 1002 - 230/1438

example, monitoring anti-epileptic drugs (e.g., phenytion), chemotherapy (e.g., adriamycin), hyperactivity (e.g., ritalin), and anti-organ-rejection (e.g., cyclosporin).

[0064] In particularly preferred embodiments, a sampling device is used to obtain continual transdermal or transmucosal samples from a biological system, and the analyte of interest is glucose. More specifically, a non-invasive glucose monitoring device is used to measure changes in glucose levels in an animal subject over a wide range of glucose concentrations. The sampling method is based on transdermal glucose extraction and the sensing method is based on electrochemical detection technology. The device can be contacted with the biological system continuously, and automatically obtains glucose samples in order to measure glucose concentration at preprogrammed intervals.

[0065] Sampling is carried out continually by non-invasively extracting glucose through the skin of the patient using an iontophoretic current. More particularly, an iontophoretic current is applied to a surface of the skin of a subject. When the current is applied, ions or charged molecules pull along other uncharged molecules or particles such as glucose which are drawn into a collection reservoir placed on the surface of the skin. The collection reservoir may comprise any ionically conductive material and is preferably in the form of a hydrogel which is comprised of a hydrophilic material, water and an electrolyte. The collection reservoir may further contain an enzyme which catalyzes a reaction between glucose and oxygen. The enzyme is preferably glucose oxidase (GOx) which catalyzes the reaction between glucose and oxygen and results in the production of hydrogen peroxide. The hydrogen peroxide reacts at a catalytic surface of a biosensor electrode, resulting in the generation of electrons which create a detectable biosensor current (raw signal). Based on the amount of biosensor current created over a given period of time, a measurement is taken, which measurement is related to the amount of glucose drawn into the collection reservoir over a given period of time. In a preferred embodiment the reaction is allowed to continue until substantially all of the glucose in the collection reservoir has been subjected to a reaction and is therefore no longer detectable, and the total biosensor current generated is related to the concentration of glucose in the subject.

[0066] When the reaction is complete, the process is repeated and a subsequent measurement is obtained. More specifically, the iontophoretic current is again applied, glucose is drawn through the skin surface into the collection reservoir, and the reaction is catalyzed in order to create a biosensor current. These sampling (extraction) and sensing operations are integrated such that glucose from interstitial fluid directly beneath the skin surface is extracted into the hydrogel collection pad where it contacts the GOx enzyme. The GOx enzyme converts glucose and oxygen in the hydrogel to hydrogen peroxide which diffuses to a Pt-based sensor and reacts with the sensor to regenerate oxygen and form electrons. The electrons generate an electrical signal that can be measured, analyzed, and correlated to blood glucose.

[0067] A generalized method for continual monitoring of a physiological analyte is disclosed in International Publication No. WO 97/24059, published 10 July 1997. As noted in that publication, the analyte is extracted into a reservoir containing a hydrogel which is preferably comprised of a hydrophilic material of the type described in International Publication No. WO 97/02811, published 30 January 1997. Suitable hydrogel materials include polyethylene oxide, polyacrylic acid, polyvinylalcohol and related hydrophilic polymeric materials combined with water to form an aqueous gel.

[0068] In the above non-invasive glucose monitoring device, a biosensor electrode is positioned on a surface of the hydrogel opposite the surface contacting the skin. The sensor electrode acts as a detector which detects current generated by hydrogen peroxide in the redox reaction, or more specifically detects current which is generated by the electrons generated by the redox reaction catalyzed by the platinum surface of the electrode. The details of such electrode assemblies and devices for iontophoretic extraction of glucose are disclosed in International Publication No. WO 96/00110, published 4 January 1996, and International Publication No. WO 97/10499, published 2 March 1997.

[0069] Referring now to Figures 1A and 1B, one example of an iontophoretic collection reservoir and electrode assembly for use in a transdermal sensing device is generally indicated at **2**. The assembly comprises two iontophoretic collection reservoirs, **4** and **6**, each having a conductive medium **8**, and **10** (preferably hydrogel pads), respectively disposed therein. First (**12**) and second (**14**) ring-shaped iontophoretic electrodes are respectively contacted with conductive medium **8** and **10**. The first iontophoretic electrode **12** surrounds three biosensor electrodes which are also contacted with the conductive medium **8**, a working electrode **16**, a reference electrode **18**, and a counter electrode **20**. A guard ring **22** separates the biosensor electrodes from the iontophoretic electrode **12** to minimize noise from the iontophoretic circuit. Conductive contacts provide communication between the electrodes and an associated power source and control means as described in detail below. A similar biosensor electrode arrangement can be contacted with the conductive medium **10**, or the medium can not have a sensor means contacted therewith.

[0070] Referring now to Figure 2, the iontophoretic collection reservoir and electrode assembly **2** of Figures 1A and 1B is shown in exploded view in combination with a suitable iontophoretic sampling device housing **32**. The housing can be a plastic case or other suitable structure which preferably is configured to be worn on a subjects arm in a manner similar to a wrist watch. As can be seen, conductive media **8** and **10** (hydrogel pads) are separable from the assembly **2**; however, when the assembly **2** and the housing **32** are assembled to provide an operational iontophoretic sampling device **30**, the media are in contact with the electrodes to provide a electrical contact therewith.

Abbott Ex. 1002 - 231/1438

[0071] A power source (e.g., one or more rechargeable or nonrechargeable batteries) can be disposed within the housing **32** or within the straps **34** which hold the device in contact with a skin or mucosal surface of a subject. In use, an electric potential (either direct current or a more complex waveform) is applied between the two iontophoretic electrodes **12** and **14** such that current flows from the first iontophoretic electrode **12**, through the first conductive medium **8** into the skin or mucosal surface, and then back out through the second conductive medium **10** to the second iontophoretic electrode **14**. The current flow is sufficient to extract substances including an analyte of interest through the skin into one or both of collection reservoirs **4** and **6**. The electric potential may be applied using any suitable technique, for example, the applied current density may be in the range of about 0.01 to 0.5 mA/cm^2. In a preferred embodiment, the device is used for continual or continuous monitoring, and the polarity of iontophoretic electrodes **12** and **14** is alternated at a rate of about one switch every 10 seconds to about one switch every hour so that each electrode is alternately a cathode or an anode. The housing **32** can further include an optional temperature sensing element (e.g., a thermistor, thermometer, or thermocouple device) which monitors the temperature at the collection reservoirs to enable temperature correction of sensor signals. The housing can also include an optional conductance sensing element (e.g., an integrated pair of electrodes) which monitors conductance at the skin or mucosal surface to enable data screening correction or invalidation of sensor signals.

[0072] After a suitable iontophoretic extraction period, one or both of the sensor electrode sets can be activated in order to detect extracted substances including the analyte of interest. Operation of the iontophoretic sampling device **30** can be controlled by a controller **36** (e.g., a microprocessor), which interfaces with the iontophoretic electrodes, the sensor electrodes, the power supply, the optional temperature and/or conductance sensing elements, a display and other electronics. For example, the controller **36** can include a programmable controlled circuit source/sink drive for driving the iontophoretic electrodes. Power and reference voltage are provided to the sensor electrodes, and signal amplifiers can be used to process the signal from the working electrode or electrodes. In general, the controller discontinues the iontophoretic current drive during sensing periods. A sensor confidence loop can be provided for continually monitoring the sampling system to insure proper operations.

[0073] User control can be carried out using push buttons located on the housing **32**, and an optional liquid crystal display (LCD) can provide visual prompts, readouts and visual alarm indications. The microprocessor generally uses a series of program sequences to control the operations of the sampling device, which program sequences can be stored in the microprocessor's read only memory (ROM). Embedded software (firmware) controls activation of measurement and display operations, calibration of analyte readings, setting and display of high and low analyte value alarms, display and setting of time and date functions, alarm time, and display of stored readings. Sensor signals obtained from the sensor electrodes can be processed before storage and display by one or more signal processing functions or algorithms which are stored in the embedded software. The microprocessor can also include an electronically erasable, programmable, read only memory (EEPROM) for storing calibration parameters, user settings and all downloadable sequences. A serial communications port allows the device to communicate with associated electronics, for example, wherein the device is used in a feedback control application to control a pump for delivery of a medicament.

[0074] Further, the sampling system can be pre-programmed to begin execution of its signal measurements (or other functions) at a designated time. One application of this feature is to have the sampling system in contact with a subject and to program the sampling system to begin sequence execution during the night so that it is available for calibration immediately upon waking. One advantage of this feature is that it removes any need to wait for the sampling system to warm-up before calibrating it.

2.1.1 EXEMPLARY EMBODIMENTS OF THE SAMPLING SYSTEM

[0075] An exemplary apparatus for sampling small amounts of an analyte via transdermal methods is described below in further detail. The apparatus is used to detect and/or quantify the concentration of a target analyte present in a biological system. This sampling is carried out in a continual manner, and quantification is possible even when the target analyte is extracted in sub-millimolar concentrations. Although the apparatus is broadly applicable to sampling any chemical analyte and/or substance, the sampling system is expressly exemplified for use in transdermal sampling and quantifying or qualifying glucose or a glucose metabolite.

[0076] Accordingly, in one aspect, an automatic sampling system is used to monitor levels of glucose in a biological system. A method can be practiced using a sampling system (device) which transdermally extracts glucose from the system, in this case, an animal subject. Transdermal extraction is carried out by applying an electrical current or ultrasonic radiation to a tissue surface at a collection site. The electrical current or ultrasonic radiation is used to extract small amounts of glucose from the subject into a collection reservoir. The collection reservoir is in contact with a biosensor which provides for measurement of glucose concentration in the subject.

[0077] In the practice, a collection reservoir is contacted with a tissue surface, for example, on the stratum corneum of a patient's skin. An electrical or ultrasonic force is then applied to the tissue surface in order to extract glucose from the tissue into the collection reservoir. Extraction is carried out continually over a period of about 1-24 hours, or longer.

Abbott Ex. 1002 - 232/1438

The collection reservoir is analyzed, at least periodically, to measure glucose concentration therein. The measured value correlates with the subject's blood glucose level.

[0078] More particularly, one or more collection reservoirs are placed in contact with a tissue surface on a subject. The collection reservoirs are also contacted with an electrode which generates a current (for reverse iontophoretic extraction) or with a source of ultrasonic radiation such as a transducer (for sonophoretic extraction) sufficient to extract glucose from the tissue into the collection reservoir.

[0079] The collection reservoir contains an ionically conductive liquid or liquid-containing medium. The conductive medium is preferably a hydrogel which can contain ionic substances in an amount sufficient to produce high ionic conductivity. The hydrogel is formed from a solid material (solute) which, when combined with water, forms a gel by the formation of a structure which holds water including interconnected cells and/or a network structure formed by the solute. The solute may be a naturally occurring material such as the solute of natural gelatin which includes a mixture of proteins obtained by the hydrolysis of collagen by boiling skin, ligaments, tendons and the like. However, the solute or gel forming material is more preferably a polymer material (including, but not limited to, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polyacrylamidomethylpropanesulfonate and copolymers thereof, and polyvinyl pyrrolidone) present in an amount in the range of more than 0.5% and less than 40% by weight, preferably 8 to 12% by weight when a humectant is also added, and preferably about 15 to 20% by weight when no humectant is added. Additional materials may be added to the hydrogel, including, without limitation, electrolyte (e.g., a salt), buffer, tackifier, humectant, biocides, preservatives and enzyme stabilizers. Suitable hydrogel formulations are described in International Publication Nos. WO 97/02811, published 30 January 1997, and WO 96/00110, published 4 January 1996.

[0080] Since the sampling system must be operated at very low (electrochemical) background noise levels, the collection reservoir must contain an ionically conductive medium that does not include significant electrochemically sensitive components and/or contaminants. Thus, the preferred hydrogel composition described hereinabove is formulated using a judicious selection of materials and reagents which do not add significant amounts of electrochemical contaminants to the final composition.

[0081] In order to facilitate detection of the analyte, an enzyme is disposed within the one or more collection reservoirs. The enzyme is capable of catalyzing a reaction with the extracted analyte (in this case glucose) to the extent that a product of this reaction can be sensed, e.g., can be detected electrochemically from the generation of a current which current is detectable and proportional to the amount of the analyte which is reacted. A suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide. The subsequent detection of hydrogen peroxide on an appropriate biosensor electrode generates two electrons per hydrogen peroxide molecule which create a current which can be detected and related to the amount of glucose entering the device (see Fig. 1). Glucose oxidase (GOx) is readily available commercially and has well known catalytic characteristics. However, other enzymes can also be used, so long as they specifically catalyze a reaction with an analyte, or derivative thereof (or substance of interest), to generate a detectable product in proportion to the amount of analyte so reacted.

[0082] In like manner, a number of other analyte-specific enzyme systems can be used in the sampling system, which enzyme systems operate on much the same general techniques. For example, a biosensor electrode that detects hydrogen peroxide can be used to detect ethanol using an alcohol oxidase enzyme system, or similarly uric acid with urate oxidase system, cholesterol with a cholesterol oxidase system, and theophylline with a xanthine oxidase system.

[0083] The biosensor electrode must be able to detect the glucose analyte extracted into the one or more collection reservoirs even when present at nominal concentration levels. In this regard, conventional electrochemical detection systems which utilize glucose oxidase (GOx) to specifically convert glucose to hydrogen peroxide, and then detect the hydrogen peroxide with an appropriate electrode, are only capable of detecting the analyte when present in a sample in at least mM concentrations. In contrast, the sampling system of the present invention allows sampling and detection of small amounts of analyte from the subject, wherein the analyte is detected at concentrations on the order of 2 to 4 orders of magnitude lower (e.g., μM concentration in the reservoir) than presently detectable with conventional systems.

[0084] Accordingly, the biosensor electrode must exhibit substantially reduced background current relative to prior such electrodes. In one particularly preferred embodiment, an electrode is provided which contains platinum (Pt) and graphite dispersed within a polymer matrix. The electrode exhibits the following features, each of which are essential to the effective operation of the biosensor: background current in the electrode due to changes in the Pt oxidation state and electrochemically sensitive contaminants in the electrode formulation is substantially reduced; and catalytic activity (e.g., non-electrochemical hydrogen peroxide decomposition) by the Pt in the electrode is reduced.

[0085] The Pt-containing electrode is configured to provide a geometric surface area of about 0.1 to 3 cm^2, preferably about 0.5 to 2 cm^2, and more preferably about 1 cm^2. This particular configuration is scaled in proportion to the collection area of the collection reservoir used in the sampling system, throughout which the extracted analyte and/or its reaction products will be present. The electrode is specially formulated to provide a high signal-to-noise ratio (S/N ratio) for this geometric surface area not heretofore available with prior Pt-containing electrodes. For example, a Pt-containing electrode constructed for use in the sampling system and having a geometric area of about 1 cm^2 preferably has a background current in the order of about 20 nA or less (when measured with buffer solution at 0.6V), and has high sensitivity

Abbott Ex. 1002 - 233/1438

(e.g., at least about 60 nA/μM of H_2O_2 in buffer at 0.6V). In like manner, an electrode having a geometric area of about 0.1 cm^2 preferably has a background current of about 2 nA or less and sensitivity of at least about 6 nA/μM of H_2O_2; and an electrode having a geometric area of about 3 cm^2 preferably has a background current of about 60 nA or less and sensitivity of at least about 180 nA/μM of H_2O_2, both as measured in buffer at 0.6V. These features provide for a high S/N ratio, for example a S/N ratio of about 3 or greater. The electrode composition is formulated using analytical- or electronic-grade reagents and solvents which ensure that electrochemical and/or other residual contaminants are avoided in the final composition, significantly reducing the background noise inherent in the resultant electrode. In particular, the reagents and solvents used in the formulation of the electrode are selected so as to be substantially free of electrochemically active contaminants (e.g., anti-oxidants), and the solvents in particular are selected for high volatility in order to reduce washing and cure times.

[0086] The Pt powder used to formulate the electrode composition is also substantially free from impurities, and the Pt/graphite powders are evenly distributed within the polymer matrix using, for example, co-milling or sequential milling of the Pt and graphite. Alternatively, prior to incorporation into the polymer matrix, the Pt can be sputtered onto the graphite powder, colloidal Pt can be precipitated onto the graphite powder (see, e.g., U.K. patent application number GB 2,221,300, published 31 January 1990, and references cited therein), or the Pt can be adsorbed onto the graphite powder to provide an even distribution of Pt in contact with the conductive graphite. In order to improve the S/N ratio of the electrode, the Pt content in the electrode is lower relative to prior Pt or Pt-based electrodes. In a preferred embodiment, the overall Pt content is about 3-7% by weight. Although decreasing the overall amount of Pt may reduce the sensitivity of the electrode, the inventors have found that an even greater reduction in background noise is also achieved, resulting in a net improvement in signal-to-noise quality.

[0087] The Pt/graphite matrix is supported by a suitable binder, such as an electrochemically inert polymer or resin binder, which is selected for good adhesion and suitable coating integrity. The binder is also selected for high purity, and for absence of components with electrochemical background. In this manner, no electrochemically sensitive contaminants are introduced into the electrode composition by way of the binder. A large number of suitable such binders are known in the art and are commercially available, including, without limitation, vinyl, acrylic, epoxy, phenoxy and polyester polymers, provided that the binder or binders selected for the formulation are adequately free of electroactive impurities.

[0088] The Pt/graphite biosensor electrodes formulated above exhibit reduced catalytic activity (e.g., passive or non-electrochemical hydrogen peroxide degradation) relative to prior Pt-based electrode systems, and thus have substantially improved signal-to-noise quality. In preferred Pt/graphite electrode compositions, the biosensor exhibits about 10-25% passive hydrogen peroxide degradation.

[0089] Once formulated, the electrode composition is affixed to a suitable nonconductive surface which may be any rigid or flexible material having appropriate insulating and/or dielectric properties. The electrode composition can be affixed to the surface in any suitable pattern or geometry, and can be applied using various thin film techniques, such as sputtering, evaporation, vapor phase deposition, or the like; or using various thick film techniques, such as film laminating, electroplating, or the like. Alternatively, the composition can be applied using screen printing, pad printing, inkjet methods, transfer roll printing, or similar techniques. Preferably, the electrode is applied using a low temperature screen print onto a polymeric substrate. The screening can be carried out using a suitable mesh, ranging from about 100-400 mesh.

[0090] As glucose is transdermally extracted into the collection reservoir, the analyte reacts with the glucose oxidase within the reservoir to produce hydrogen peroxide. The presence of hydrogen peroxide generates a current at the biosensor electrode that is directly proportional to the amount of hydrogen peroxide in the reservoir. This current provides a signal which can be detected and interpreted by an associated system controller to provide a glucose concentration value for display. In particular embodiments, the detected current can be correlated with the subject's blood glucose concentration so that the system controller may display the subject's actual blood glucose concentration as measured by the sampling system. For example, the system can be calibrated to the subject's actual blood glucose concentration by sampling the subject's blood during a standard glucose tolerance test, and analyzing the blood glucose using both a standard blood glucose monitor and the sampling system. In this manner, measurements obtained by the sampling system can be correlated to actual values using known statistical techniques.

[0091] In one preferred embodiment, the automatic sampling system transdermally extracts the sample in a continual manner over the course of a 1-24 hour period, or longer, using reverse iontophoresis. More particularly, the collection reservoir contains an ionically conductive medium, preferably the hydrogel medium described hereinabove. A first iontophoresis electrode is contacted with the collection reservoir (which is in contact with a target tissue surface), and a second iontophoresis electrode is contacted with either a second collection reservoir in contact with the tissue surface, or some other ionically conductive medium in contact with the tissue. A power source provides an electric potential between the two electrodes to perform reverse iontophoresis in a manner known in the art. As discussed above, the biosensor selected to detect the presence, and possibly the level, of the target analyte (glucose) within a reservoir is also in contact with the reservoir.

Abbott Ex. 1002 - 234/1438

[0092] In practice, an electric potential (either direct current or a more complex waveform) is applied between the two iontophoresis electrodes such that current flows from the first electrode through the first conductive medium into the skin, and back out from the skin through the second conductive medium to the second electrode. This current flow extracts substances through the skin into the one or more collection reservoirs through the process of reverse iontophoresis or electroosmosis. The electric potential may be applied as described in International Publication No. WO 96/00110, published 4 January 1996.

[0093] As an example, to extract glucose, the applied electrical current density on the skin or tissue is preferably in the range of about 0.01 to about 2 mA/cm^2. In a preferred embodiment, in order to facilitate the extraction of glucose, electrical energy is applied to the electrodes, and the polarity of the electrodes is alternated at a rate of about one switch every 7.5 minutes (for a 15 minute extraction period), so that each electrode is alternately a cathode or an anode. The polarity switching can be manual or automatic.

[0094] Any suitable iontophoretic electrode system can be employed, however it is preferred that a silver/silver chloride (Ag/AgCl) electrode system is used. The iontophoretic electrodes are formulated using two critical performance parameters: (1) the electrodes are capable of continual operation for extended periods, preferably periods of up to 24 hours or longer; and (2) the electrodes are formulated to have high electrochemical purity in order to operate within the present system which requires extremely low background noise levels. The electrodes must also be capable of passing a large amount of charge over the life of the electrodes.

[0095] In an alternative embodiment, the sampling device can operate in an alternating polarity mode necessitating the presence of a first and second bimodal electrode (Figure 5, **540** and **541**) and two collection reservoirs (Figure 5, **547** and **548**). Each bi-modal electrode (Figure 4, **430**; Figure 5, **540** and **541**) serves two functions depending on the phase of the operation: (1) an electro-osmotic electrode (or iontophoretic electrode) used to electrically draw analyte from a source into a collection reservoir comprising water and an electrolyte, and to the area of the electrode subassembly; and (2) as a counter electrode to the first sensing electrode at which the chemical compound is catalytically converted at the face of the sensing electrode to produce an electrical signal.

[0096] The reference (Figure 5, **544** and **545**; Figure 4, **432**) and sensing electrodes (Figure 5, **542** and **543**; Figure 4, **431**), as well as, the bimodal electrode (Figure 5, **540** and **541**; Figure 4, **430**) are connected to a standard potentiostat circuit during sensing. In general, practical limitations of the system require that the bimodal electrode will not act as both a counter and iontophoretic electrode simultaneously.

[0097] The general operation of an iontophoretic sampling system is the cyclical repetition of two phases: (1) a reverse-iontophoretic phase, followed by a (2) sensing phase. During the reverse iontophoretic phase, the first bimodal electrode (Figure 5, **540**) acts as an iontophoretic cathode and the second bimodal electrode (Figure 5, **541**) acts as an iontophoretic anode to complete the circuit. Analyte is collected in the reservoirs, for example, a hydrogel (Figure 5, **547** and **548**). At the end of the reverse iontophoretic phase, the iontophoretic current is turned off. During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (Figure 5, **544**) and the sensing electrode (Figure 5, **542**). The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (Figure 5, **542**) producing an electrical current, while the first bi-modal electrode (Figure 5, **540**) acts as a counter electrode to complete the electrical circuit.

[0098] At the end of the sensing phase, the next iontophoresis phase begins. The polarity of the iontophoresis current is reversed in this cycle relative to the previous cycle, so that the first bi-modal electrode (Figure 5, **540**) acts as an iontophoretic anode and the second bi-modal electrode (Figure 5, **541**) acts as an iontophoretic cathode to complete the circuit. At the end of the iontophoretic phase, the sensor is activated. The chemical signal reacts catalytically on the catalytic face of the second sensing electrode (Figure 5, **543**) producing an electrical current, while the second bimodal electrode (Figure 5, **541**) acts as a counter electrode to complete the electrical circuit.

[0099] The iontophoretic and sensing phases repeat cyclically with the polarity of the iontophoretic current alternating between each cycle. This results in pairs of readings for the signal, that is, one signal obtained from a first iontophoretic and sensing phase and a second signal obtained from the second phase. These two values can be used (i) independently as two signals, (ii) as a cumulative (additive) signal, or (iii) the signal values can be added and averaged.

[0100] If two active reservoirs are used for analyte detection (for example, where both hydrogels contain the GOx enzyme), a sensor consistency check can be employed that detects whether the signals from the reservoirs are changing in concert with one another. This check compares the percentage change from the calibration signal for each reservoir, then calculates the difference in percentage change of the signal between the two reservoirs. If this difference is greater than a predetermined threshold value (which is commonly empirically determined), then the signals are said not to be tracking one another and the data point related to the two signals can be, for example, ignored.

[0101] The electrode described is particularly adapted for use in conjunction with a hydrogel collection reservoir system for monitoring glucose levels in a subject through the reaction of collected glucose with the enzyme glucose oxidase present in the hydrogel matrix.

[0102] The bi-modal electrode is preferably comprised of Ag/AgCl. The electrochemical reaction which occurs at the surface of this electrode serves as a facile source or sink for electrical current. This property is especially important

Abbott Ex. 1002 - 235/1438

for the iontophoresis function of the electrode. Lacking this reaction, the iontophoresis current could cause the hydrolysis of water to occur at the iontophoresis electrodes causing pH changes and possible gas bubble formation. The pH changes to acidic or basic pH could cause skin irritation or burns. The ability of an Ag/AgCl electrode to easily act as a source or sink current is also an advantage for its counter electrode function. For a three electrode electrochemical cell to function properly, the current generation capacity of the counter electrode must not limit the speed of the reaction at the sensing electrode. In the case of a large sensing electrode, the ability of the counter electrode to source proportionately larger currents is required.

[0103] The design of the sampling system provides for a larger sensing electrode (see for example, Figure 4) than previously designed. Consequently, the size of the bimodal electrode must be sufficient so that when acting as a counter electrode with respect to the sensing electrode the counter electrode does not become limiting for the rate of catalytic reaction at the sensing electrode catalytic surface.

[0104] Two methods exist to ensure that the counter electrode does not limit the current at the sensing electrode: (1) the bi-modal electrode is made much larger than the sensing electrode, or (2) a facile counter reaction is provided.

[0105] During the reverse iontophoretic phase, the power source provides a current flow to the first bi-modal electrode to facilitate the extraction of the chemical signal into the reservoir. During the sensing phase, the power source is used to provide voltage to the first sensing electrode to drive the conversion of chemical signal retained in the reservoir to electrical signal at the catalytic face of the sensing electrode. The power source also maintains a fixed potential at the electrode where, for example hydrogen peroxide is converted to molecular oxygen, hydrogen ions, and electrons, which is compared with the potential of the reference electrode during the sensing phase. While one sensing electrode is operating in the sensing mode it is electrically connected to the adjacent bimodal electrode which acts as a counter electrode, at which electrons generated at the sensing electrode are consumed.

[0106] The electrode sub-assembly can be operated by electrically connecting the bimodal electrodes such that each electrode is capable of functioning as both an iontophoretic electrode and counter electrode along with appropriate sensing electrode(s) and reference electrode(s), to create standard potentiostat circuitry.

[0107] A potentiostat is an electrical circuit used in electrochemical measurements in three electrode electrochemical cells. A potential is applied between the reference electrode and the sensing electrode. The current generated at the sensing electrode flows through circuitry to the counter electrode (i.e., no current flows through the reference electrode to alter its equilibrium potential). Two independent potentiostat circuits can be used to operate the two biosensors. For the purpose of the present sampling system, the electrical current measured at the sensing electrode subassembly is the current that is correlated with an amount of chemical signal.

[0108] With regard to continual operation for extended periods of time, Ag/AgCl electrodes are provided herein which are capable of repeatedly forming a reversible couple which operates without unwanted electrochemical side reactions (which could give rise to changes in pH, and liberation of hydrogen and oxygen due to water hydrolysis). The Ag/AgCl electrodes of the present sampling system are thus formulated to withstand repeated cycles of current passage in the range of about 0.01 to 1.0 mA per cm^2 of electrode area. With regard to high electrochemical purity, the Ag/AgCl components are dispersed within a suitable polymer binder to provide an electrode composition which is not susceptible to attack (e.g., plasticization) by components in the collection reservoir, e.g., the hydrogel composition. The electrode compositions are also formulated using analytical- or electronic-grade reagents and solvents, and the polymer binder composition is selected to be free of electrochemically active contaminants which could diffuse to the biosensor to produce a background current.

[0109] Since the Ag/AgCl iontophoretic electrodes must be capable of continual cycling over extended periods of time, the absolute amounts of Ag and AgCl available in the electrodes, and the overall Ag/AgCl availability ratio, can be adjusted to provide for the passage of high amounts of charge. Although not limiting in the sampling system described herein, the Ag/AgCl ratio can approach unity. In order to operate within the preferred system which uses a biosensor having a geometric area of 0.1 to 3 cm^2, the iontophoretic electrodes are configured to provide an approximate electrode area of 0.3 to 1.0 cm^2, preferably about 0.85 cm^2. These electrodes provide for reproducible, repeated cycles of charge passage at current densities ranging from about 0.01 to 1.0 mA/cm^2 of electrode area. More particularly, electrodes constructed according to the above formulation parameters, and having an approximate electrode area of 0.85 cm^2, are capable of a reproducible total charge passage (in both anodic and cathodic directions) of 270 mC, at a current of about 0.3 mA (current density of 0.35 mA/cm^2) for 48 cycles in a 24 hour period.

[0110] Once formulated, the Ag/AgCl electrode composition is affixed to a suitable rigid or flexible nonconductive surface as described above with respect to the biosensor electrode composition. A silver (Ag) underlayer is first applied to the surface in order to provide uniform conduction. The Ag/AgCl electrode composition is then applied over the Ag underlayer in any suitable pattern or geometry using various thin film techniques, such as sputtering, evaporation, vapor phase deposition, or the like, or using various thick film techniques, such as film laminating, electroplating, or the like. Alternatively, the Ag/AgCl composition can be applied using screen printing, pad printing, inkjet methods, transfer roll printing, or similar techniques. Preferably, both the Ag underlayer and the Ag/AgCl electrode are applied using a low temperature screen print onto a polymeric substrate. This low temperature screen print can be carried out

Abbott Ex. 1002 - 236/1438

at about 125 to 160°C, and the screening can be carried out using a suitable mesh, ranging from about 100-400 mesh.

[0111] In another preferred embodiment, the automatic sampling system transdermally extracts the sample in a continual manner over the course of a 1-24 hour period, or longer, using sonophoresis. More particularly, a source of ultrasonic radiation is coupled to the collection reservoir and used to provide sufficient perturbation of the target tissue surface to allow passage of the analyte (glucose) across the tissue surface. The source of ultrasonic radiation provides ultrasound frequencies of greater than about 10 MHz, preferably in the range of about 10 to 50 MHz, most preferably in the range of about 15 to 25 MHz. It should be emphasized that these ranges are intended to be merely illustrative of the preferred embodiment; in some cases higher or lower frequencies may be used.

[0112] The ultrasound may be pulsed or continuous, but is preferably continuous when lower frequencies are used. At very high frequencies, pulsed application will generally be preferred so as to enable dissipation of generated heat. The preferred intensity of the applied ultrasound is less than about 5.0 W/cm^2, more preferably is in the range of about 0.01 to 5.0 W/cm^2, and most preferably is in the range of 0.05 to 3.0 W/cm^2.

[0113] Virtually any type of device may be used to administer the ultrasound, providing that the device is capable of producing the suitable frequency ultrasonic waves required by the sampling system. An ultrasound device will typically have a power source such as a small battery, a transducer, and a means to attach the system to the sampling system collection reservoir. Suitable sonophoresis sampling systems are described in International Publication No. WO 91/12772, published 5 September 1991.

[0114] As ultrasound does not transmit well in air, a liquid medium is generally needed in the collection reservoir to efficiently and rapidly transmit ultrasound between the ultrasound applicator and the tissue surface.

[0115] Referring now to Figure 3, an exploded view of the key components from a preferred embodiment of an autosensor is presented. The sampling system components include two biosensor/iontophoretic electrode assemblies, **304** and **306**, each of which have an annular iontophoretic electrode, respectively indicated at **308** and **310**, which encircles a biosensor **312** and **314**. The electrode assemblies **304** and **306** are printed onto a polymeric substrate **316** which is maintained within a sensor tray **318**. A collection reservoir assembly **320** is arranged over the electrode assemblies, wherein the collection reservoir assembly comprises two hydrogel inserts **322** and **324** retained by a gel retaining layer **326**.

[0116] Referring now to Figure 9, an exploded view of the key components from another embodiment of an autosensor for use in an iontophoretic sampling device is presented. The sampling system components include, but are not limited to, the following: a sensor-to-tray assembly comprising two bimodal electrode assemblies and a support tray **904**; two holes **906** to insure proper alignment of the support tray in the sampling device; a plowfold liner **908** used to separate the sensors from the hydrogels **912** (for example, during storage); a gel retaining layer **910**; a mask layer **914** (where the gel retaining layer, hydrogels, and mask layer form a collection assembly, which can, for example, be a laminate); and a patient liner **916**.

[0117] The components shown in exploded view in Figures 3 and 9 are intended for use in, for example, an automatic sampling device which is configured to be worn like an ordinary wristwatch. As described in International Publication No. WO 96/00110, published 4 January 1996, the wristwatch housing (not shown) contains conductive leads which communicate with the iontophoretic electrodes and the biosensor electrodes to control cycling and provide power to the iontophoretic electrodes, and to detect electrochemical signals produced at the biosensor electrode surfaces. The wristwatch housing can further include suitable electronics (e.g., microprocessor, memory, display and other circuit components) and power sources for operating the automatic sampling system.

[0118] Modifications and additions to the embodiments of Figures 3 and 9 will be apparent to those skilled in the art in light of the teachings of the present specification. The laminates and collection assemblies described herein are suitable for use as consumable components in an iontophoretic sampling device.

[0119] In one aspect, the electrode assemblies can include bimodal electrodes as shown in Figure 4 and described above.

[0120] Modifications and additions to the embodiments shown in Figures 3 and 9 will be apparent to those skilled in the art.

2.2.0 CONVERTING TO AN ANALYTE-SPECIFIC VALUE.

[0121] The raw signal is then converted into an analyte-specific value using a calibration step which correlates the signal obtained from the sensing device with the concentration of the analyte present in the biological system. A wide variety of calibration techniques can be used to interpret such signals. These calibration techniques apply mathematical, statistical and/or pattern recognition techniques to the problem of signal processing in chemical analyses, for example, using neural networks, genetic algorithm signal processing, linear regression, multiple-linear regression, or principal components analysis of statistical (test) measurements.

[0122] One method of calibration involves estimation techniques. To calibrate an instrument using estimation techniques, it is necessary to have a set of exemplary measurements with known concentrations referred to as the cali-

Abbott Ex. 1002 - 237/1438

bration set (e.g., reference set). This set consists of *S* samples, each with *m* instrument variables contained in an *S* by *m* matrix (*X*), and an *S* by 1 vector (*y*), containing the concentrations. If a priori information indicates the relationship between the measurement and concentration is linear, the calibration will attempt to determine an *S* by 1 transformation or mapping (*b*), such that $y = Xb$ is an optimal estimate of *y* according to a predefined criteria. Numerous suitable estimation techniques useful in the practice of the invention are known in the art. These techniques can be used to provide correlation factors (e.g., constants), which correlation factors are then used in a mathematical transformation to obtain a measurement value indicative of the concentration of analyte present in the biological system at the times of measurement.

[0123] In one particular embodiment, the calibration step can be carried out using artificial neural networks or genetic algorithms. The structure of a particular neural network algorithm used in the practice of the invention can vary widely; however, the network should contain an input layer, one or more hidden layers, and one output layer. Such networks can be trained on a test data set, and then applied to a population. There are an infinite number of suitable network types, transfer functions, training criteria, testing and application methods which will occur to the ordinarily skilled artisan upon reading the instant specification.

[0124] The iontophoretic glucose sampling device described hereinabove typically uses one or more "active" collection reservoirs (e.g., each containing the GOx enzyme) to obtain measurements. In one embodiment, two active collection reservoirs are used. An input value can be obtained from these reserviors by, for example, taking an average between signals from the reservoirs for each measurement time point or using a summed value. Such inputs are discussed in greater detail below. In another embodiment, a second collection reservoir can be provided which does not contain, for example, the GOx enzyme. This second reservoir can serve as an internal reference (blank) for the sensing device, where a biosensor is used to measure the "blank" signal from the reference reservoir which signal can then be used in, for example, a blank subtraction step.

[0125] In the context of such a sampling device an algorithm, in a preferred embodiment a Mixtures of Experts algorithm, could use the following inputs to provide a blood glucose measurement: time (for example, time since monitor was applied to a subject, and/or time since calibration); signal from an active reservoir; signal from a blank reservoir; averaged (or a cumulative) signal from two active reservoirs; calibration time; skin temperature; voltage; normalized background; raw data current; peak or minimum value of a selected input, e.g., current, averged signal, calibrated signal; discrete value points of a selected input, e.g., current, averged signal, calibrated signal; integral avgerage temperature, initial temperature, or any discrete time temperature; skin conductivity, including, but not limited to, sweat value, iontophoretic voltage, baseline value, normalized baseline value, other background values; relative change in biosensor current or iontophoretic voltage (relative to calibration) as an indicator of decay; alternate integration ranges for calculating nanocoulomb (nC) values, e.g., using an entire biosensor time interval, or alternative ranges of integration (for example, using discrete time points instead of ranges, break out intervals from the total sampling time interval, or full integration of the interval plus partial integration of selected portions of the interval); and, when operating in the training mode, measured glucose (use of exemplary inputs are presented in Examples 1 and 2). Further, a calibration ratio check is described in Example 4 that is useful to insure that the calibration has been efficacious, and that the calibration demonstrates a desired level of sensitivity of the sampling system.

2.3.0 PREDICTING MEASUREMENTS

[0126] The analyte-specific values obtained using the above techniques are used herein to predict target analyte concentrations in a biological system using a Mixtures of Experts (MOE) analysis.

[0127] The Mixtures of Experts algorithm breaks up a non-linear prediction equation into several linear prediction equations ("Experts"). An "Expert" routine is then used to switch between the different linear equations. In the equations presented below, the *w* (weighting) factor determines the switch by weighting the different Experts with a number between 0 and 1, with the restriction that:

$$\sum_{i=1}^{n} w_i = 1$$

[0128] The Mixtures of Experts algorithm of the present invention is based on the ideal case presented in Equation 1, where the individual experts have a linear form:

Abbott Ex. 1002 - 238/1438

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

wherein (*An*) is an analyte of interest, *n* is the number of experts, An_i is the analyte predicted by Expert *i*; and w_i is a parameter. The number of experts is chosen based on the quality of the fit of the model, subject to the requirement that it is desirable to use the least number of experts possible. The number of experts is preferably less than 100, and more preferably less than 30. In most cases, selection of the fewest possible experts is desirable.

[0129] The individual Experts An_i are further defined by the expression shown as Equation (2).

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wherein, An_i is the analyte predicted by Expert *i*; P_j is one of *m* parameters, *m* is typically less than 100; a_{ij} are coefficients; and z_i is a constant.

[0130] The weighting value, w_i, is defined by the formula shown as Equation (3).

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

where *e* refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i. The d_k are given by Equation 4.

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of *m* parameters, and where ω_k is a constant.

[0131] The Mixtures of Experts method described by the above equations is supplied with a large data base of empirically obtained information about the parameters defined by the equations. By employing a linear regression function, the equations are simultaneously solved for the values of all coefficients and constants. In other words, the algorithm is trained to be predictive for the value of *An* (the analyte) given a particular set of data. A preferred optimization method to determine the coefficients and constants is the Expectation Maximization method (Dempster, A.P., N.M. Laird, and D.B. Rubin, *J. Royal Statistical Society* (Series B-Methodological) **39**: (1), 1977). Other optimization methods include the Levenburg-Marquardt algorithm (Marquardt, D.W., *J. Soc. Ind.* Appl. *Math.* **11**:p431-441, 1963) and the Simplex algorithm (Nelder, J.A., and Mead, *R., Computer Journal* 7:p308, 1965).

[0132] In the context of blood glucose monitoring with an iontophoretic sampling device, the MOE algorithm allows for the accurate prediction of glucose concentration. In this regard, during a typical iontophoretic measuring cycle, iontophoretic extraction of the analyte is carried out for a suitable amount of time, for example about 1 to 30 minutes, after which time the extracted analyte is detected for a suitable amount of time, for example about 1-30 minutes. An application of the Mixtures of Experts algorithm to a specific set of parameters for glucose monitoring is presented in Example 1.

[0133] In the context of blood glucose monitoring with an iontophoretic sampling device, the Mixtures of Experts algorithm allows for the accurate prediction of blood glucose concentrations.

Abbott Ex. 1002 - 239/1438

2.4.0 ALGORITHM MODIFICATIONS

[0134] A further aspect of the present invention is the modification of the Mixtures of Experts (MOE) algorithm. The MOE can be modified in a number of ways including, but not limited to, the following modifications: using different groups of selected inputs (see above); adapting the algorithm by modifying the training set; using different algorithms or modifications of the MOE for different ranges of analyte detection; using different statistical distributions in the Mixtures of Experts; rejection of selected expert(s); and, switching algorithms.

2.4.1 ADAPTING THE ALGORITHM

[0135] The Mixtures of Experts (MOE) is trained using sets of data that contain patterns. Those patterns, represented in a training data set, typically give good performance. Accordingly, training MOE with a wide variety of patterns improves the predictive performance of MOE, for example, using a variety of blood glucose patterns that occur in diabetic patients to obtain parameters that represent the patterns. In this case the selected patterns are used to develop an appropriate training set for MOE and then the parameters generated from that training set are used to test data representing a variety of patterns. In one embodiment, a "global" training set may be augmented by providing a training data set developed from an individual subject's blood glucose data taken over several (or many) days. Such an individual pattern is potentially useful to customize the algorithm to that subject. The parameters generated from using a training set including such an individual patterns is then tested in the same individual to determine whether the expanded training data set provides better predicted values. In an alternative embodiment, a selected percentage of the global training set can be used with the individual's training set (rather than using the entire global training set).

[0136] Further, the data comprising a training data set can be specifically chosen to optimize performance of the MOE under specific conditions. Such optimization may include, for example, using diverse data sets or selecting the best data to represent a specific condition. For example, different training data sets based on data obtained from a variety of races can be used to train the MOE to optimize predictive performance for individual members of the different races represented by different data sets.

[0137] Finally, MOE is typically trained with values chosen in a selected range (e.g., blood glucose values in the range of 40-400 mg/dl). However, the MOE can be trained with data sets that fall outside of the selected range.

2.4.2 ALGORITHM OPTIMIZED FOR DIFFERENT RANGES

[0138] The MOE can be optimized for predictive performance in selected ranges of data. Depending on the range different MOEs may be invoked for prediction of analyte values (see "Switching Algorithms" below). Alternatively, different algorithms can be used for prediction of values in selected ranges of analyte detection. For example, MOE may be used for prediction of glucose values in a range of 40-400 mg/dl; however, at low and high ends of glucose values a specifically defined function can be applied to the data in order to get preferred values. Such preferred values may, for example, be useful in the situation where under-prediction is more desirable than over-prediction (e.g., at low blood glucose values). In this case a modification of MOE may be used or a specific algorithm may be optimized for prediction in the selected range using, for example, a non-linear distribution function that emphasizes predicting low blood glucose (BG) in the range $BG \leq 100$.

2.4.3 EMPLOYING DIFFERENT DISTRIBUTION FUNCTIONS

[0139] When calculating the weights used in the MOE algorithm a selected distribution is used. One exemplary distribution is a Gaussian distribution (Example 3) that weighs deviations relative to the square of difference from the mean. However, other distributions can be used to improve predictive function of the algorithm. For example, a Laplacian distribution function was used in the calculations presented in Example 4. The Laplacian distribution has longer tails than a Gaussian distribution, and weighs deviations relative to the absolute difference from the mean. Other distribution functions can be used as well including, but not limited to, Cauchy distribution or a specific distribution function devised (or calculated) based on specific data sets obtained, for example, from different individuals or different groups of individuals (e.g., different races).

2.4.4 REJECTING EXPERTS

[0140] When multiple experts are used in the MOE each expert can be inspected to determine if, for example, one or more of the experts is providing incongruous values. When such an expert is identified (e.g., in the calculation of a particular data point) the expert may be eliminated for that calculation and the weights of the remaining experts readjusted appropriately. Inspection of the experts can be carried out by a separate algorithm and can, for example, be

Abbott Ex. 1002 - 240/1438

based on whether the value predicted by the expert falls outside of a designated range. If the value falls outside of a designated range, the expert may be eliminated in that calculation. For example, Example 3 describes the use of three experts (BG_1, BG_2, and BG_3) in an MOE for prediction of blood glucose values, wherein a weighted average is used to calculate the final blood glucose value. However, each of these three experts can be inspected to determine if one (or more) of them does not make sense (e.g., is providing a stochastic or out-lying value significantly different from the other two experts). The expert providing the incongruous value is disregarded and the weights of the other two experts are readjusted accordingly.

2.4.5 SWITCHING ALGORITHMS

[0141] In yet another aspect of the present invention, prediction of the concentration of an analyte can be accomplished using specialized algorithms, where the specialized algorithms are useful for predictions in particular situations (e.g., particular data sets or ranges of predicted values) and where the algorithm used for performing the calculations is determined based on the situation. In this case a "switch" can be used to employ one (or more) algorithm rather than another (or more) algorithm. For example, a global MOE algorithm can be the switch used to select one of three different MOE algorithms. In one embodiment such a global MOE algorithm may be used to determine a blood glucose value. The blood glucose value is determined, by the algorithm, to fall into one of three ranges (for example, low, normal, and high). For each range there is a separate MOE algorithm that optimizes the prediction for values in the particular range. The global MOE algorithm then selects the appropriate MOE algorithm based on the value and the selected MOE performs a new prediction of blood glucose values based on the original input values but optimized for the range into which the value was predicted (by the global MOE) to fall. As a further illustration, inputs to determine a blood glucose value are provided to a global MOE which determines that the value is a low-value. The inputs are then directed to a Low-Value Optimized MOE to generate a more accurate predicted blood glucose value.

[0142] Specialized algorithms may be developed to be used in different parts of a range of analyte signal spectrum or other input values (e.g., high signal / low signal; high BGCal / low BGCal; high/low calratio; high/low temp; etc., for all variables used in the prediction). A global algorithm can be used to decide which region of the spectrum the analyte signal is in, and then the global algorithm switches the data to the appropriate specialized algorithm.

[0143] In another embodiment, an algorithm other than the MOE can be used as the switch to choose among a set of MOE algorithms, or an MOE can be used as the switch to choose among a set of other algorithms. Further, there can be multiple levels of specialized switching (which can be graphically represented for instance by branched tree-diagrams).

[0144] Following here are several specific, non-limiting examples, of the uses of switching in the practice of the present invention when blood glucose values are being determined.

[0145] In one embodiment, variables are identified that explicitly represent signal decay, for example, a switch based on elapsed time since calibration (early or late) or the value of Calratio at CAL (high or low). An exemplary switch of this type is represented by elapsed time since calibration where, for example, the algorithm described in Example 3 may be trained independently with inputs from an early phase of sensor use and inputs from a late phase sensor use (e.g., the total useful life of a sensor element may be split into two halves -- early and late). Then, depending on the time since calibration that selected input values are being obtained (an exemplary switch), the input values are directed to an MOE algorithm that was trained on data from the appropriate phase (i.e., either early or late). Such a switch is useful to help correct for error based in sensor decay.

[0146] Another exemplary switch of this type is represented by the value of Calratio at the calibration point. Calratio is described in Example 4. The Calratio is a measure of sensor sensitivity. Accordingly, if desired the Calratio range can be divided into two halves (high and low ranges). The algorithm described in Example 3 may be trained independently with inputs from the high and low ranges of the Calratio. A switch is then based on the Calratio values to direct the inputs to the MOE algorithm that is trained with the appropriate data set (i.e., data sets corresponding to inputs from high and low Calratio ranges).

2.5.0 DECREASING THE BIAS OF A DATA SET

[0147] In addition to the MOE algorithm described in the present specification, following here is a description of a method to alter data used to generate a training data set so as to correct slope, intercept (and resultant bias) introduced by the limited range of data input. This invention provides a useful correction for any asymmetric data input that gives a bias to resultant predictions. In this method, the values of a data set are used to create a second data set that mirrors the first, i.e., positive values become negative values (opposite signs). The two data sets are then used as the training data set. This transformation of the asymmetrical data set results in a forced symmetry of the data comprising the training set.

[0148] The following is a non-limiting example of this method for the correction of bias using blood glucose level

Abbott Ex. 1002 - 241/1438

determination. In the blood glucose value determinations described herein there is an inherent bias (manifested by a slope of <1 and a positive intercept, e.g., Figure 10A; in the figure, pBG is predicted blood glucose and mBG is directly measured blood glucose -- measured, for example, using a HemoCue® meter) introduced into the prediction function. This is in part due to the fact that there are no blood glucose levels of < 40 mg/dl used in the data input training set. The data input for training the MOE algorithm, used to predict blood glucose levels, uses, for example, the following variables: elapsed time since calibration, average signal, calibrated signal, and the blood glucose at the calibration point (see, e.g., Examples 3 and 4). The value that these inputs predict and try to match is directly measured blood glucose. The allowed range for blood glucose is 40-400 mg/dl.

Due to this limited range of blood glucose, the resultant function predictions (i.e., via the MOE) result in an inherent bias, slope <1 and positive intercept when plotting predicted blood glucose (y-axis variable, pBG, Figure 10A) versus directly measured blood glucose (x-axis variable, mBG, Figure 10A).

[0149] The method of the present invention circumvents this problem by augmenting the original input data set with a data set comprising the same elapsed time since calibration, but with values of the average signal (in nanocoulombs) and directly measured blood glucose both of the opposite sign relative to the original, real data set. The calibrated signal is then calculated using the opposite sign data. In this way the input data is doubled and is now symmetric around the origin (Figure 10B; in the figure, pBG is predicted blood glucose and mBG is directly measured blood glucose -- measured, for example, using a HemoCue® meter). In Figure 10B the dotted lines represent the slopes predicted from the single data set with which they are associated. The solid line between the two dashed lines represents the corrected slope based on use of the original data set and the opposite sign data set to train the algorithm.

[0150] The value of this approach when plotting predicted blood glucose(using MOE) versus measured blood glucose can be seen by examining the results presented in the following table.

	Original Data Set	Original Data Set & Opposite Sign Data Set
Deming Slope*	0.932	1.042
Deming Intercept*	12.04	-5.63
Bias 50 mg/dl	8.64	-3.53
Bias 80 mg/dl	6.6	-2.27
Bias 100 mg/dl	5.24	-1.43
Bias 150 mg/dl	1.84	0.67
Bias 200 mg/dl	-1.56	2.77

* Based on orthogonal regression with a variance ratio equal to two.

[0151] As the results in this table demonstrate, the bias reducing method of the present invention has a slope closer to 1, an intercept closer to zero, and the bias values are, in general, closer to zero.

[0152] Accordingly, one aspect of the present invention is a method for decreasing the bias of a data set. The method involves generating a second data set that has values opposite in sign of the original data set and using this first and second data set as a combined data set to train the algorithm (e.g., MOE).

EXAMPLES

[0153] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the devices, methods, and formulae of the present invention, and are not intended to limit the scope of what the inventor regards as the invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Application of the "Mixtures of Experts" to Glucose Monitoring

[0154] This example describes the use of a Mixtures of Experts (MOE) algorithm to predict blood glucose data from

Abbott Ex. 1002 - 242/1438

a series of signals.

[0155] In the present example, a GlucoWatch® monitor was used to collect data and the following variables were chosen to generate data sets for the MOE algorithm:

1) elapsed time (*time*), elapsed time since the GlucoWatch® monitor was applied to the subject, i.e., elapsed time since the sampling system was placed in operative contact with the biological system;
2) active signal (*active*), in this example, the value of the active parameter corresponded to the nanoamp signal that was integrated over the sensing time-interval to give the *active* parameter in nanocoulombs (nC);
3) calibrated signal (*signal*), in this example was obtained by multiplying an *active* by a constant, where the constant was defined as the blood glucose level at the calibration point divided by the *active* value at the calibration point. For example, as follows:

$$signal = \frac{BG/cp}{active/cp}\,(active)$$

where the slope of the line *active* versus blood glucose had a non-zero intercept and the offset took into account that the intercept was not zero. In the alternative, the constant could be as follows:

$$signal = \frac{BG/cp}{(active/cp + offset)}\,(active + offset)$$

where the *offset* takes into account the intercept value.
4) blood glucose value at the calibration point (*BG/cp*) was determined by direct blood testing.

[0156] Other possible variables include, but are not limited to, temperature, iontophoretic voltage (which is inversely proportional to skin resistance), and skin conductivity.

[0157] Large data sets were generated by collecting signals using a transdermal sampling system that was placed in operative contact with the skin. The sampling system transdermally extracted the analyte from the biological system using an appropriate sampling technique (in this case, iontophoresis). The transdermal sampling system was maintained in operative contact with the skin to provide a near continual or continuous stream of signals.

[0158] The basis of the Mixtures of Experts was to break up a non-linear prediction equation (Equation 5, below) into several Expert prediction equations, and then to have a routine to switch between the different linear equations. For predicting blood glucose levels, three separate linear equations (Equations 6, 7, and 8) were used to represent blood glucose, with the independent variables discussed above of *time, active, signal,* blood glucose at a calibration point (*BG/cp),* and a constant (t_i).

[0159] The switching between equations 6, 7, and 8 was determined by the parameters w_1, w_2, and w_3 in equation 5, which was further determined by the parameters d_1, d_2, and d_3 as given by equations 9-14, where the individual experts had a linear form:

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (*BG*) was blood glucose, there are three experts (n=3) ; BG_i was the analyte predicted by Expert *i*; and w_i was a parameter, and the individual Experts BG_i were further defined by the expression shown as Equations 6, 7, and 8

$$BG_1 = p_1(time) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \qquad (6)$$

$$BG_2 = p_2(time) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \qquad (7)$$

$$BG_3 = p_3(time) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \qquad (8)$$

wherein, BG_i was the analyte predicted by Expert *i*;
parameters include, time (elapsed time), active (active signal), signal (calibrated signal), and *BG/cp* (blood glucose value at a calibration point); p_i, q_i, r_i, and s_i were coefficients; and t_i was a constant; and further where the weighting

Abbott Ex. 1002 - 243/1438

value, w_i, was defined by the formulas shown as Equations 9, 10, and 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

where e referred to the exponential function and d_i was a parameter set (analogous to Equations 6, 7, and 8) that was used to determine the weights w_i, given by Equations 9, 10, and 11, and

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + \varepsilon_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i were coefficients, and where ε_i is a constant.

[0160] To calculate the above parameters an optimization method was applied to the algorithm (Equations 5-14) and the large data set. The optimization method used was the Expectation Maximization method (Dempster, A.P., N.M. Laird, and D.B. Rubin, J. Royal Statistical Society (Series B-Methodological) **39**:(1), 1977), but other methods may be used as well.

[0161] The parameters in these equations were determined such that the posterior probability of the actual glucose was maximized.

Example 2

Prediction of Measurement Values I

[0162] Iontophoretic extraction of glucose was carried out using a GlucoWatch® monitor which employs (i) a low-level iontophoretic current to extract glucose through patient's skin, and (ii) an electrochemical biosensor to detect the extracted glucose. Iontophoresis was carried out for 3 minute intervals and electrochemical detection was carried out for 7 minute intervals to result in 10 minute measurement cycles -- thus generating collections of data (data sets) as described in Example 1.

[0163] The data that were used for this analysis were obtained by diabetic subjects each wearing a GlucoWatch® monitor over a 14 hour period. The MOE inputs consisted of the following parameters (described in Example 1): *time, active, signal,* blood glucose at a calibration point (*BG/cp*). These training data were used to determine the unknown parameters in the MOE using the Expectation Maximization Method. The output of the MOE algorithm was the measured value of blood glucose.

Using a three hour time point for calibrating the GlucoWatch® monitor, the mean percentage error (MPE) between the actual blood glucose and the calculated (MOE predicted) blood glucose was 13%.

[0164] In a diabetic study consisting of 61 patients, the diabetic subjects' blood glucose ranged from 23-389 mg/dl. A protocol was followed whereby a subject (who had fasted since the previous midnight) came to a test site where the GlucoWatch® monitor was applied to the subject, started, and calibrated. Over the next 14 hours, the subject had normal meals and a finger prick blood sample was taken every 20 minutes for glucose determination ("actual glucose"). Blood glucose levels were measured using the HemoCue® meter (HemoCue AB, Sweden), which has an accuracy of ±10%.

[0165] A plot of the glucose levels predicted by the Mixtures of Experts algorithm (based on the data described

Abbott Ex. 1002 - 244/1438

above) versus the actual blood glucose levels is presented in Figure 6 (a Correlation Plot). Analysis of the data shown in Figure 6 showed a slope of 0.88, an intercept of 14, and a correlation coefficient of R=0.93. There were N=1,348 points comprising the Correlation Plot.

[0166] These statistical results, along with the MPE=0.13 (discussed above), show the excellent predictive capabilities of the GlucoWatch® monitor and the Mixtures of Experts algorithm.

Example 3

Another Application of the "Mixtures of Experts" to Glucose Monitoring

[0167] This example describes the use of a Mixtures of Experts (MOE) algorithm to predict blood glucose data from a series of signals.

[0168] In the present example, a GlucoWatch® monitor was used to collect data and the following variables were chosen to generate data sets for the MOE algorithm:

1) time since calibration ($time_c$), the elapsed time since the calibration step was carried out for the GlucoWatch® monitor (in hours);
2) active signal (*active*), in this example, the value of the active parameter corresponded to the averaged signal from two active reservoirs, where each reservoir provided a nanoamp signal that was integrated over the sensing time-interval, the two values were then added and averaged to give the *active* parameter in nanocoulombs (nC) ;
3) calibrated signal (*signal*), in this example was obtained as follows:

$$signal = \frac{BG/cp}{(active/cp + offset)}\,(active + offset)$$

where the *offset* takes into account the intercept value.
4) blood glucose value at the calibration point (*BG*/*cp*), in mg/dl, was determined by direct blood testing.

[0169] Other possible variables include, but are not limited to, temperature, iontophoretic voltage (which is inversely proportional to skin resistance), and skin conductivity.

[0170] Large data sets were generated by collecting signals using a transdermal sampling system that was placed in operative contact with the skin. The sampling system transdermally extracted the analyte from the biological system using an appropriate sampling technique (in this case, iontophoresis). The transdermal sampling system was maintained in operative contact with the skin to provide a near continual or continuous stream of signals.

[0171] The basis of the Mixtures of Experts was to break up a non-linear prediction equation (Equation 15, below) into several Expert prediction equations, and then to have a routine to switch between the different linear equations. For predicting blood glucose levels, three separate linear equations (Equations 16, 17, and 18) were used to represent blood glucose, with the independent variables discussed above of *time, active, signal,* blood glucose at a calibration point (*BG*/*cp*) , and a constant (t_i).

[0172] The switching between Equations 16, 17, and 18 was determined by the parameters w_1, w_2, and w_3 in equation 5, which was further determined by the parameters d_1, d_2, and d_3 as given by equations 9-14, where the individual experts had a linear form:

$$BG = w_1BG_1 + w_2BG_2 + w_3BG_3 \qquad (15)$$

wherein (*BG*) was blood glucose, there are three experts (n=3); BG_i was the analyte predicted by Expert *i*; and w_i was a parameter, and the individual Experts BG_i were further defined by the expression shown as Equations 16, 17, and 18

$$BG_1 = p_1(time_c) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \qquad (16)$$

$$BG_2 = p_2(time_c) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \qquad (17)$$

$$BG_3 = p_3(time_c) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \qquad (18)$$

Abbott Ex. 1002 - 245/1438

wherein, BG_i was the analyte predicted by Expert *i;* parameters include, $time_c$ (elapsed time since calibration), *active* (active signal), *signal* (calibrated signal), and *BG/cp* (blood glucose value at a calibration point) ; p_i, q_i, r_i, and s_i were coefficients; and t_i was a constant; and further where the weighting value, w_i, was defined by the formulas shown as Equations 19, 20, and 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \tag{19}$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \tag{20}$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \tag{21}$$

where *e* referred to the exponential function and d_i was a parameter set (analogous to Equations 16, 17, and 18) that was used to determine the weights w_i, given by Equations 19, 20, and 21, and

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG/cp) + \varepsilon_1 \tag{22}$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \varepsilon_2 \tag{23}$$

$$d_3 = \tau_3(time_c) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG/cp) + \varepsilon_3 \tag{24}$$

where τ_i, β_i, γ_i and δ_i were coefficients, and where ε_i is a constant.

[0173] To calculate the above parameters an optimization method was applied to the algorithm (Equations 15-24) and the large data set. The optimization method used was the Expectation Maximization method (Dempster, A.P., N. M. Laird, and D.B. Rubin, *J. Royal Statistical Society* (Series B-Methodological) 39: (1), 1977), but other methods may be used as well.

[0174] The parameters in these equations were determined such that the posterior probability of the actual glucose was maximized.

Example 4

Prediction of Measurement Values II

A. Calibration Ratio Check

[0175] In order to insure an efficacious calibration of the sampling system, the value of the following ratio was found to fall in a selected range:

$$CalRatio = \frac{BG/cp}{(active/cp + offset)}$$

where the *offset* takes into account the intercept value. The range is established using standard error minimization routines to evaluate a large population of calibration points, and thereby determine the *CalRatio* values which result in accurate blood glucose predictions. In one embodiment, the preferred *CalRatio* range of values was between 0.00039 and 0.01. In the *CalRatio, BG/cp* was the blood glucose concentration at the calibration point (or calibration time), *active* was the input prediction at the calibration point, and *offset* was a constant offset. The offset value was established empirically using standard error minimization routines to evaluate a number of potential offset values for a large data set, and thereby select the one that results in the most accurate prediction of blood glucose.

[0176] The *CalRatio* check provides a screen for valid or efficacious calibration readings. If the *CalRatio* falls outside

Abbott Ex. 1002 - 246/1438

of the range of selected values, then the calibration was rejected and the calibration was redone. Low values of this ratio indicated low sensitivity of glucose detection.

B. Prediction of Values

[0177] GlucoWatch® monitors (Cygnus, Inc., Redwood City, CA, USA) were applied to the lower forearm of human subjects with diabetes (requiring insulin injection). Iontophoretic extraction of glucose was carried out using the GlucoWatch® monitor which employs (i) a low-level iontophoretic current to extract glucose through patient's skin, and (ii) an electrochemical biosensor to detect the extracted glucose.

[0178] The subjects were 18 years of age, or older, and consisted of both males and females from a broad ethnic cross-section. Iontophoresis was carried out for 3 minute intervals and electrochemical detection was carried out for 7 minute intervals to result in 10 minute measurement cycles -- thus generating collections of data (data sets) as described in Example 3. As described in Example 3, the *active* measurement was the averaged signal from two active reservoirs, for example, a first electrode acts as the cathode during the first 10 minute cycle (3 minutes of iontophoresis, followed by 7 minutes of sensing) and a second electrode acts as the cathode during the second 10 minute cycle. The combined cycle requires 20 minutes, and the combined cathode sensor data is used as a measure of the glucose extracted (an averaged "active signal", see Example 3). This 20 minute cycle is repeated throughout operation of the GlucoWatch® monitor.

[0179] In addition, subjects obtained two capillary blood samples per hour, and the glucose concentration was determined using a HemoCue® clinical analyzer (HemoCue AB, Sweden). The blood glucose measurement obtained at three hours was used as a single point calibration, which was used to calculate the extracted blood glucose for all subsequent GlucoWatch® monitor measurements.

[0180] The data that were used for this analysis were obtained by diabetic subjects each wearing two GlucoWatch® monitors over a 14 hour period. The MOE inputs consisted of the following parameters (described in Example 3): $time_c$, *active, signal,* blood glucose at a calibration point (*BG/cp*). For the calibrated signal:

$$signal = \frac{BG/cp\ (active + offset)}{(active/cp) + offset)}$$

where (i) *active/cp* was the input prediction at the calibration point, and (ii) the *offset* takes into account the fact that when predicted blood glucose is plotted vs. *active,* there is a non-zero y-intercept. The optimized value of the offset that was used was a constant value of 1000 nC. The *signal* that is used in the Mixtures of Experts algorithm is temperature compensated by applying an Arrhenius type correction to the raw signal data to account for skin temperature fluctuations.

[0181] Finally, in order to eliminate potential outlier points, various screens were applied to the raw and integrated sensor signals. The purpose of these screens was to determine whether certain environmental, physiological or technical conditions existed during a measurement cycle that could result in an erroneous reading. The screens that were used measured the averaged signal (active), iontophoretic voltage, temperature, and skin surface conductance. If any of these measurements deviated sufficiently from predefined behavior during a measurement, then the entire measurement was excluded. For example, if the skin surface conductance exceeded a set threshold, which indicated excessive sweating (sweat contains glucose), then this potentially erroneous measurement was excluded. These screens enable very noisy data to be removed, while enabling the vast majority of points (> 87%) to be accepted.

[0182] The Mixtures of Experts was further customized in the following way. When the weights were updated using equations 19-24 (Example 3), a Laplacian distribution function was used. The Laplacian distribution has longer tails than a Gaussian distribution, and weighs deviations relative to the absolute difference from the mean, whereas a Gaussian distribution weighs deviations relative to the square of difference from the mean (P. McCullagh and J.A. Nelder, Generalized *Linear Models,* Chapman and Hall, 1989; and W.H. Press, S.A. Teukolsky, W.T. Vetterling and B. P. Flannery, *Numerical Recipes* in C. Cambridge University Press, Cambridge, 1992). In addition, the individual blood glucose values were weighted by the inverse of the value of the blood glucose at the calibration point. Both of these modifications result in increased accuracy of predictions, especially at low blood glucose levels.

[0183] The training data were used to determine the unknown parameters in the Mixtures of Experts using the Expectation Maximization Method. The Mixtures of Experts algorithm was trained until convergence of the weights was achieved. The output of the MOE algorithm was the measured value of blood glucose. Using a three hour time point for calibrating the GlucoWatch® monitor, the mean percentage error (MPE) between the actual blood glucose and the calculated (MOE predicted) blood glucose was 14.4%.

[0184] In a diabetic study consisting of 91 GlucoWatch® monitors, the diabetic subjects' blood glucose ranged from 40-360 mg/dl. A protocol was followed whereby a subject (who had fasted since the previous midnight) came to a test site where two GlucoWatch® monitors were applied to the subject, started, and calibrated. Over the next 14 hours, the

Abbott Ex. 1002 - 247/1438

subject had normal meals and a finger prick blood sample was taken every 20 minutes for glucose determination ("actual glucose"). Blood glucose levels were measured using the HemoCue® meter (HemoCue AB, Sweden), which has an accuracy of ±10%.

[0185] A plot of the glucose levels predicted by the Mixtures of Experts algorithm (based on the data described above) versus the actual blood glucose levels is presented in Figure 7 (a Correlation Plot). Also shown in Figure 7 is the orthogonal least squares line (A. Madansky, *The Fitting of Straight Lines When both Variables are Subject to Error, J.* American Statistical Association **54**:173-206, 1959; D. York, *Least-Squares Fitting* of *a Straight Line,* Canadian Journal of Physics **44**:1079-1986, 1966; W.A. Fuller, *Measurement Error Models,* Wiley, New York, 1987; and W.H. Press, S.A. Teukolsky, W.T. Vetterling and B.P. Flannery, *Numerical Recipes* in C. Cambridge University Press, Cambridge, 1992) with an error variance ratio (defined as the error in the dependent variable divided by the error of the independent variable) of 2.05. This variance error ratio corrects the linear regression line (which assumes zero error in the independent variable) for the true error in both independent and dependent variables.

[0186] The variance ratio was determined as follows. Each subject was required to wear two GlucoWatch® monitors. Then, at each time point, the difference between the two watches was determined, squared and divided by 2. The resulting values were averaged over the total number of time points used. Fifty pairs of watches, each with 42 time points, were used for this calculation. The error variance for the HemoCue® was obtained from clinical data published in the literature. The GlucoWatch® monitor error variance was calculated to be 150 (standard deviation = 12 mg/dl) and the HemoCue® error variance was calculated to be 73 (standard deviation = 8.5 mg/dl), giving the error ratio of 2.05.

[0187] Analysis of the data shown, in Figure 7 showed a slope of 1.04, an intercept of approximately -10.7 mg/dl, and a correlation coefficient of R=0.89.

[0188] It is also instructive to examine graphs of the measured and predicted blood glucose levels vs. time. One such graph is shown in Figure 8 (in the legend of Figure 8: solid diamonds are measurements obtained using the GlucoWatch® monitor; open circles are blood glucose concentrations as determined using HemoCue®; and the "star" symbol represents blood glucose concentration at the calibration point). Figure 8 indicates the excellent capabilities of the GlucoWatch® monitor and the Mixtures of Experts algorithm in calibrating the device.

[0189] These statistical results, along with the MPE=14.4% (discussed above), show the excellent predictive capabilities of the GlucoWatch® monitor and the Mixtures of Experts algorithm.

[0190] Although preferred embodiments of the subject invention have been described in some detail, it is understood that obvious variations can be made without departing from the scope of the invention as defined by the appended claims.

Claims

1. A method for continually or continuously measuring blood glucose in a subject, said method comprising:

   (a) obtaining a raw signal from extracted blood glucose, wherein said raw signal is specifically related to the blood glucose;
   (b) performing a calibration step which correlates the raw signal obtained in step (a) with a measurement value indicative of the concentration of blood glucose present in the subject at the time of extraction;
   (c) repeating step (a) to obtain a series of measurement values at selected time intervals; and
   (d) predicting a measurement value based on the series of measurement values using the Mixtures of Experts algorithm, where the individual experts have a linear form

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

   wherein (*An*) is blood glucose, the analyte of interest; *n* is the number of experts; An_i is the analyte predicted by Expert *i*; and w_i is a parameter; and the individual experts An_i are further defined by the expression shown as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

Abbott Ex. 1002 - 248/1438

wherein An_i is the analyte predicted by Expert i; P_j is one of m parameters; m is typically less than 100; α_{ij} are coefficients; and z_i is a constant; and further where the weighting value, w_i, is defined by the formula shown as Equation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

where e refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i; the d_k being given by Equation 4

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of m parameters, and where ω_k is a constant.

2. The method of claim 1, wherein in step (a) an enzyme is reacted with the extracted blood glucose to produce an electrochemically detectable raw signal.

3. The method of claim 2, wherein the enzyme is glucose oxidase.

4. The method of claim 1, wherein the prediction of step (d) is carried out using said series of two or more measurement values in an algorithm represented by the Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (BG) is blood glucose; there are three experts (n=3) and BG_i is the blood glucose predicted by Expert i; w_i is a parameter; and the individual Experts BG_i are further defined by the expression shown as Equations 6, 7 and 8

$$BG_1 = p_1\,(time) + q_1\,(active) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \qquad (6)$$

$$BG_2 = p_2\,(time) + q_2\,(active) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \qquad (7)$$

$$BG_3 = p_3\,(time) + q_3\,(active) + r_3\,(signal) + s_3\,(BG/cp) + t_3 \qquad (8)$$

wherein BG_i is the blood glucose predicted by Expert i; parameters include *time* (elapsed time since the sampling system was placed in operative contact with said subject), *active* (active signal), *signal* (calibrated signal), and *BG/cp* (blood glucose value at a calibration point); p_i, q_i, r_i and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 9, 10 and 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (9)$$

Abbott Ex. 1002 - 249/1438

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7 and 8) that is used to determine the weights w_i, given by Equations 9, 10 and 11, and

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG/cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG/cp) + \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG/cp) + \varepsilon_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i are coefficients; and where ε_i is a constant.

5. The method of claim 1, wherein the prediction of step (d) is carried out using said series of two or more measurement values in an algorithm represented by the Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1BG_1 + w_2BG_2 + w_3BG_3 \quad (15)$$

wherein *(BG)* is blood glucose; there are three experts (n=3) and BG_i is the blood glucose predicted by Expert *i*; w_i is a parameter; and the individual Experts BG_i are further defined by the expression shown as Equations 16, 17 and 18

$$BG_1 = p_1\,(time_c) + q_1\,(active) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \quad (16)$$

$$BG_2 = p_2\,(time_c) + q_2\,(active) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \quad (17)$$

$$BG_3 = p_3\,(time_c) + q_3\,(active) + r_3\,(signal) + s_3\,(BG/cp) + t_3 \quad (18)$$

wherein BG_i is the blood glucose predicted by Expert *i*; parameters include $time_c$ (elapsed time from a calibration of said sampling system), *active* (active signal), *signal* (calibrated signal), and *BG/cp* (blood glucose value at a calibration point); p_i, q_i, r_i and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 19, 20 and 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

Abbott Ex. 1002 - 250/1438

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7 and 8) that is used to determine the weights w_i, given by Equations 19, 20 and 21, and

$$d_1 = \tau_1(time_c) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG/cp) + \varepsilon_1 \quad (22)$$

$$d_2 = \tau_2(time_c) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG/cp) + \varepsilon_2 \quad (23)$$

$$d_3 = \tau_3(time_c) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG/cp) + \varepsilon_3 \quad (24)$$

where τ_i, β_i, γ_i and δ_i are coefficients; and where ε_i is a constant.

6. The method of either of claim 4 or claim 5, which includes further parameters for measurement values selected from the group consisting of temperature, ionophoretic voltage and skin conductivity.

7. The method of either of claim 1, claim 4 or claim 5, wherein in step (a) the raw signal is obtained from a sensing apparatus (16, 18, 20), wherein said raw signal is specifically related to the glucose detected by the sensing apparatus (16, 18, 20).

8. The method of claim 7, wherein the sensing apparatus (16, 18, 20) is a near-IR spectrometer.

9. The method of claim 7, wherein the sensing apparatus (16, 18, 20) comprises a biosensor having an electrochemical sensing element.

10. A monitoring system for continually or continuously measuring blood glucose in a subject, said system comprising, in operative combination:

sensing means (16, 18, 20) in operative contact with extracted blood glucose, wherein said sensing means (16, 18, 20) obtains a raw signal from the extracted blood glucose and said raw signal is specifically related to the blood glucose; and
microprocessor means (36) in operative communication with the sensing means (16, 18, 20), wherein said microprocessor means (36) (i) is used to control the sensing means (16, 18, 20) to obtain a series of raw signals at selected time intervals during a continual or continuous measurement period, (ii) correlate the raw signals with measurement values indicative of the concentration of blood glucose present in the subject, and (iii) predict a measurement value based on a series of measurement values using the Mixtures of Experts algorithm, where the individual experts have a linear form

$$An = \sum_{i=1}^{n} An_i w_i \quad (1)$$

wherein *(An)* is blood glucose, the analyte of interest; n is the number of experts; An_i is the analyte predicted by Expert i; and w_i is a parameter; and the individual experts An_i are further defined by the expression shown as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \quad (2)$$

Abbott Ex. 1002 - 251/1438

wherein An_i is the analyte predicted by Expert i; P_j is one of m parameters; m is typically less than 100; a_{ij} are coefficients; and z_i is a constant; and further where the weighting value, w_i, is defined by the formula shown as Equation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

where e refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_1; the d_k being given by Equation 4

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a *coefficient;* P_j is one of m parameters; and where ω_k is a constant.

11. The monitoring system of claim 10, wherein the prediction of the measurement value is carried out using said series of measurement values in an algorithm represented by the Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (BG) is blood glucose; there are three experts (n=3) and BG_i is the blood glucose predicted by Expert i; w_i is a parameter; and the individual Experts BG_i are further defined by the expression shown as Equations 6, 7 and 8

$$BG_1 = p_1(time) + q_1(active) + r_1(signal) + s_1(BG/cp) + t_1 \qquad (6)$$

$$BG_2 = p_2(time) + q_2(active) + r_2(signal) + s_2(BG/cp) + t_2 \qquad (7)$$

$$BG_3 = p_3(time) + q_3(active) + r_3(signal) + s_3(BG/cp) + t_3 \qquad (8)$$

wherein BG_i is the blood glucose predicted by Expert i; parameters include *time* (elapsed time since the sampling system was placed in operative contact with said subject), *active* (active signal), *signal* (calibrated signal), and *BG/cp* (blood glucose value at a calibration point); p_i, q_i, r_i and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 9, 10 and 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (10)$$

Abbott Ex. 1002 - 252/1438

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7 and 8) that is used to determine the weights w_i, given by Equations 9, 10 and 11, and

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG/cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG/cp) + \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG/cp) + \varepsilon_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i are coefficients; and where ε_i is a constant.

12. The monitoring system of claim 10, wherein the prediction of the measurement value is carried out using said series of measurement values in an algorithm represented by the Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1BG_1 + w_2BG_2 + w_3BG_3 \quad (15)$$

wherein *(BG)* is blood glucose; there are three experts (n=3) and BG_i is the blood glucose predicted by Expert *i;* w_i is a parameter; and the individual Experts BG_i are further defined by the expression shown as Equations 16, 17 and 18

$$BG_1 = p_1\,(time_c) + q_1\,(active) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \quad (16)$$

$$BG_2 = p_2\,(time_c) + q_2\,(active) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \quad (17)$$

$$BG_3 = p_3\,(time_c) + q_3\,(active) + r_3\,(signal) + s_3\,(BG/cp) + t_3 \quad (18)$$

wherein BG_i is the blood glucose predicted by Expert *i*; parameters include $time_c$ (elapsed time from a calibration of said sampling system), *active* (active signal), *signal* (calibrated signal), and *BG/cp* (blood glucose value at a calibration point); p_i, q_i, r_i and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 19, 20 and 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7 and 8) that is used to determine the weights w_i, given by Equations 19, 20 and 21, and

Abbott Ex. 1002 - 253/1438

$$d_1 = \tau_1 (time_c) + \beta_1 (active) + \gamma_1 (signal) + \delta_1 (BG/cp) + \varepsilon_1 \quad (22)$$

$$d_2 = \tau_2 (time_c) + \beta_2 (active) + \gamma_2 (signal) + \delta_2 (BG/cp) + \varepsilon_2 \quad (23)$$

$$d_3 = \tau_3 (time_c) + \beta_3 (active) + \gamma_3 (signal) + \delta_3 (BG/cp) + \varepsilon_3 \quad (24)$$

where τ_i, β_i, γ_i and δ_i are coefficients; and where ε_i is a constant.

13. The monitoring system of any one of claims 10 to 12, which includes further parameters for raw signals selected from the group consisting of temperature, ionophoretic voltage and skin conductivity.

14. The monitoring system of any one of claims 10 to 12, wherein the sensing means (16, 18, 20) comprises a biosensor having an electrochemical sensing element.

15. The monitoring system of any one of claims 10 to 12, wherein the sensing means (16, 18, 20) comprises a near-IR spectrometer.

16. The monitoring system of any one of claims 10 to 12, further comprising
sampling means (8, 10, 12, 14) for continually or continuously extracting the blood glucose from the subject, wherein said sampling means (8, 10, 12, 14) is adapted for extracting the blood glucose across a skin or mucosal surface of said subject, and wherein the microprocessor means (36) is in operative communication with said sampling means (8, 10, 12, 14) and is used to control said sampling means (8, 10, 12, 14).

17. The monitoring system of claim 16, wherein the sampling means (8, 10, 12, 14) includes one or more collection reservoirs (8, 10) for containing the extracted blood glucose.

18. The monitoring system of claim 17, wherein the sampling means (8, 10, 12, 14) uses an iontophoretic current to extract the blood glucose from the subject.

19. The monitoring system of claim 18, wherein the collection reservoir (8, 10) contains an enzyme that reacts with the extracted blood glucose to produce an electrochemically detectable signal.

20. The monitoring system of claim 19, wherein the enzyme is glucose oxidase.

Patentansprüche

1. Verfahren zur ständigen oder kontinuierlichen Messung des Blutzuckers bei einem Patienten, wobei das Verfahren aufweist:

(a) Gewinnen eines Rohsignals aus extrahiertem Blutzukker, wobei sich das Rohsignal spezifisch auf den Blutzucker bezieht;
(b) Durchführen eines Kalibrierschritts, der das im Schritt (a) gewonnene Rohsignal mit einem Meßwert korreliert, der die Konzentration des Blutzuckers anzeigt, die bei dem Patienten zur Zeit der Extraktion vorliegt;
(c) Wiederholen des Schritts (a), um in gewählten Zeitintervallen eine Serie von Meßwerten zu gewinnen; und
(d) Vorhersage eines Meßwerts auf der Grundlage der Serie von Meßwerten unter Verwendung des Expertenmischalgorithmus, wobei die einzelnen Experten eine lineare Form haben, nämlich

$$An = \sum_{i=1}^{n} An_i w_i \quad (1)$$

wobei (*An*) der Blutzucker, der in Betracht kommende Analyt; *n* die Anzahl der Experten; An_i der vom Experten *i*

Abbott Ex. 1002 - 254/1438

vorhergesagte Analyt; und w_i ein Parameter ist; und die einzelnen Experten An_i in der in Gleichung (2) gezeigte Formel weiter definiert werden, nämlich

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wobei An_i der vom Experten i vorhergesagte Analyt ist; P_j einer von m Parametern; m normalerweise kleiner als 100; α_{ij} Koeffizienten; und z_i eine Konstante ist; und ferner wobei der Wichtungswert w_i durch die in Gleichung (3) gezeigte Formel definiert ist, nämlich

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

wobei e die Exponentialfunktion bezeichnet und die d_k (man beachte, daß d_i im Zähler der Gleichung 3 einer von den d_k ist) eine Parametergruppe analog zur Gleichung 2 sind, die verwendet wird, um die Gewichte w_i zu bestimmen; wobei die d_k in der Gleichung 4 gegeben sind, nämlich

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

wobei α_{jk} ein Koeffizient, P_j einer von m Parametern und ω_k eine Konstante ist.

2. Verfahren nach Anspruch 1, wobei im Schritt (a) ein Enzym mit dem extrahierten Blutzucker zur Reaktion gebracht wird, um ein elektromagnetisch detektierbares Rohsignal zu erzeugen.

3. Verfahren nach Anspruch 2, wobei das Enzym Glucoseoxidase ist.

4. Verfahren nach Anspruch 1, wobei die Vorhersage im Schritt (d) unter Verwendung der Serie von zwei oder mehr Meßwerten in einem Algorithmus erfolgt, der dem Expertenmischalgorithmus entspricht, wobei die einzelnen Experten eine lineare Form haben, nämlich

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wobei (BG) der Blutzucker ist; drei Experten (n=3) vorhanden sind und BG_i der vom Experten i vorhergesagte Blutzucker ist; w_i ein Parameter; und die einzelnen Experten BG_i durch die in den Gleichungen 6, 7 und 8 gezeigten Formel weiter definiert sind, nämlich

$$BG_1 = p_1\,(time) + q_1\,(active) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \qquad (6)$$

$$BG_2 = p_2\,(time) + q_2\,(active) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \qquad (7)$$

$$BG_1 = p_3\,(time) + q_3\,(active) + r_3\,(signal) + s_3\,(BG/cp) + t_3 \qquad (8)$$

wobei BG_i der vom Experten i vorhergesagte Blutzucker ist; die Parameter folgende sind: *time* (Zeit, die vergangen ist, seit das Probenahmesystem in betriebsfähigen Kontakt mit dem Patienten gebracht worden ist), *active* (aktives

Abbott Ex. 1002 - 255/1438

Signal), *signal* (kalibriertes Signal) und *BG/cp* (Blutzuckerwert an einem Kalibrierpunkt); p_i, q_i, r_i und s_i Koeffizienten sind; und t_i eine Konstante ist; und ferner wobei der Wichtungswert w_i durch die in den Gleichungen 9, 10 und 11 gezeigten Formeln definiert ist, nämlich

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

wobei *e* die Exponentialfunktion bezeichnet und d_i eine Parametergruppe ist (analog zu den Gleichungen 6, 7 und 8), die verwendet wird, um die Gewichte w_i zu bestimmen, die in den Gleichungen 9, 10 und 11 gegeben sind, und

$$d_1 = \tau_1 (time) + \beta_1 (active) + \gamma_1 (signal) + \delta_1 (BG/cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2 (time) + \beta_2 (active) + \gamma_2 (signal) + \delta_2 (BG/cp) + \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3 (time) + \beta_3 (active) + \gamma_3 (signal) + \delta_3 (BG/cp) + \varepsilon_3 \quad (14)$$

wobei τ_i, β_i, γ_i und δ_i Koeffizienten sind und ε_i eine Konstante ist.

5. Verfahren nach Anspruch 1, wobei die Vorhersage im Schritt (d) unter Verwendung der Serie von zwei oder mehr Meßwerten in einem Algorithmus erfolgt, der dem Expertenmischalgorithmus entspricht, wobei die einzelnen Experten eine lineare Form haben, nämlich

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \quad (15)$$

wobei *(BG)* der Blutzucker ist; drei Experten (n=3) vorhanden sind und BG_i der vom Experten *i* vorhergesagte Blutzucker ist; w_i ein Parameter ist; und die einzelnen Experten BG_i von den in den Gleichungen 16, 17 und 18 gezeigten Formeln weiter definiert sind, nämlich

$$BG_1 = p_1 (time_c) + q_1 (active) + r_1 (signal) + s_1 (BG/cp) + t_1 \quad (16)$$

$$BG_2 = p_2 (time_c) + q_2 (active) + r_2 (signal) + s_2 (BG/cp) + t_2 \quad (17)$$

$$BG_3 = p_3 (time_c) + q_3 (active) + r_3 (signal) + s_3 (BG/cp) + t_3 \quad (18)$$

wobei BG_i der vom Experten *i* vorhergesagte Blutzucker ist; die Parameter folgende sind: $time_c$ (die seit einer Kalibrierung des Probenahmesystems vergangene Zeit), *active* (aktives Signal), *signal* (kalibriertes Signal) und *BG/cp* (Blutzuckerwert an einem Kalibrierpunkt); p_i, q_i, r_i und s_i Koeffizienten sind; und t_i eine Konstante ist; und ferner wobei der Wichtungswert w_i durch die in den Gleichungen 19, 20 und 21 gezeigten Formeln definiert ist, nämlich

Abbott Ex. 1002 - 256/1438

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

wobei e die Exponentialfunktion bezeichnet und d_i eine Parametergruppe ist (analog den Gleichungen 6, 7 und 8), die verwendet wird, um die Gewichte w_i zu bestimmen, die in den Gleichungen 19, 20 und 21 gegeben sind, und

$$d_1 = \tau_1\ (time_c) + \beta_1(active) + \gamma_1\ (signal) + \delta_1\ (BG/cp) + \varepsilon_1 \quad (22)$$

$$d_2 = \tau_2\ (time_c) + \beta_2\ (active) + \gamma_2\ (signal) + \delta_2\ (BG/cp) + \varepsilon_2 \quad (23)$$

$$d_3 = \tau_3\ (time_c) + \beta_3\ (active) + \gamma_3\ (signal) + \delta_3\ (BG/cp) + \varepsilon_3 \quad (24)$$

wobei τ_i, β_i, γ_i und δ_i Koeffizienten sind; and ε_i eine Konstante ist.

6. Verfahren nach Anspruch 4 oder 5, das weitere Parameter für Meßwerte aufweist, die aus der Gruppe gewählt sind, die aus Temperatur, iontophoretischer Spannung und Hautleitfähigkeit besteht.

7. Verfahren nach Anspruch 1, 4 oder 5, wobei im Schritt (a) das Rohsignal von einer Erfassungsvorrichtung (16, 18, 20) bezogen wird, wobei sich das Rohsignal spezifisch auf die von der Erfassungsvorrichtung (16, 18, 20) detektierte Glucose bezieht.

8. Verfahren nach Anspruch 7, wobei die Erfassungsvorrichtung (16, 18, 20) ein Spektrometer für den nahen Infrarotbereich ist.

9. Verfahren nach Anspruch 7, wobei die Erfassungsvorrichtung (16, 18, 20) einen Biosensor mit einem elektrochemischen Erfassungselement aufweist.

10. Überwachungssystem zur ständigen oder kontinuierlichen Messung des Blutzuckers bei einem Patienten, wobei das System in betriebsfähiger Kombination aufweist:

eine Erfassungseinrichtung (16, 18, 20) in betriebsfähigem Kontakt mit extrahiertem Blutzucker, wobei die Erfassungseinrichtung (16, 18, 20) ein Rohsignal aus dem extrahierten Blutzucker gewinnt und das Rohsignal sich spezifisch auf den Blutzucker bezieht; und
eine Mikroprozessoreinrichtung (36) in betriebsfähiger Kommunikation mit der Erfassungseinrichtung (16, 18, 20), wobei die Mikroprozessoreinrichtung (36) (i) verwendet wird, um die Erfassungseinrichtung (16, 18, 20) zu steuern, um in gewählten Zeitintervallen während einer dauernden oder kontinuierlichen Meßperiode eine Serie von Rohsignalen zu gewinnen, (ii) die Rohsignale mit Meßwerten korreliert, die die Konzentration des Blutzuckers anzeigen, die beim Patienten vorliegt, und (iii) einen Meßwert auf der Grundlage einer Serie von Meßwerten unter Verwendung des Expertenmischalgorithmus vorhersagt, wobei die einzelnen Experten eine lineare Form haben, nämlich

$$An = \sum_{i=1}^{n} An_i w_i \quad (1)$$

Abbott Ex. 1002 - 257/1438

wobei (*An*) der Blutzucker, der in Betracht kommende Analyt; *n* die Anzahl der Experten; An_i der vom Experten *i* vorhergesagte Analyt; und w_i ein Parameter; und die einzelnen Experten An_i durch die in der Gleichung (2) gezeigte Formel weiter definiert sind, nämlich

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wobei An_i der vom Experten *i* vorhergesagte Analyt; P_j einer von *m* Parametern; *m* normalerweise kleiner als 100 ist; α_{ij} Koeffizienten sind; und z_i eine Konstante ist; und ferner wobei der Wichtungswert w_i durch die in der Gleichung (3) gezeigte Formel definiert ist, nämlich

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

wobei *e* die Exponentialfunktion bezeichnet und die d_k (man beachte, daß d_i im Zähler der Gleichung 3 einer von den d_k ist) eine Parametergruppe analog zur Gleichung 2 ist, die verwendet wird, um die Gewichte w_1 zu bestimmen; wobei die d_k in der Gleichung 4 gegeben sind, nämlich

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

wobei α_{jk} ein Koeffizient; P_j einer von *m* Parametern; und ω_k eine Konstante ist.

11. Überwachungssystem nach Anspruch 10, wobei die Vorhersage des Meßwerts unter Verwendung der Serie von Meßwerten in einem Algorithmus erfolgt, der dem Expertenmischalgorithmus entspricht, wobei die einzelnen Experten eine lineare Form haben, nämlich

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wobei (*BG*) der Blutzucker ist; drei Experten (n=3) vorhanden sind und BG_i der vom Experten *i* vorhergesagte Blutzucker ist; w_i ein Parameter ist; und die einzelnen Experten BG_i durch die in den Gleichungen 6, 7 und 8 gezeigte Formel weiter definiert sind, nämlich

$$BG_1 = p_1\,(time) + q_1\,(active) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \qquad (6)$$

$$BG_2 = p_2\,(time) + q_2\,(active) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \qquad (7)$$

$$BG_3 = p_3\,(time) + q_3\,(active) + r_3\,(signal) + s_3\,(BG/cp) + t_3 \qquad (8)$$

wobei BG_i der vom Experten *i* vorhergesagte Blutzucker ist; die Parameter folgende sind: time (Zeit, die vergangen ist, seit das Probenahmesystem in betriebsfähigen Kontakt mit dem Patienten gebracht wurde), *active* (aktives Signal), *signal* (kalibriertes Signal) und *BG/cp* (Blutzuckerwert an einem Kalibrierpunkt) ; p_i, q_i, r_i und s_i Koeffizienten sind; und t_i eine Konstante ist; und ferner wobei der Wichtungswert w_i durch die in den Gleichungen 9, 10 und 11 gezeigten Formeln definiert ist, nämlich

Abbott Ex. 1002 - 258/1438

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

wobei e die Exponentialfunktion bezeichnet und d_i eine Parametergruppe ist (analog zu den Gleichungen 6, 7 und 8), die verwendet wird, um die Gewichte w_i zu bestimmen, die in den Gleichungen 9, 10 und 11 gegeben sind, und

$$d_1 = \tau_i(\ time) + \beta_1\ (active) + \gamma_1\ (signal) + \delta_1\ (BG/cp) + \varepsilon_1 \quad (12)$$

$$d_1 = \tau_2\ (time) + \beta_2\ (active) + \gamma_2\ (signal + \delta_2\ (BG/cp) + \varepsilon_2 \quad (13)$$

$$d_1 = \tau_3\ (time) + \beta_3\ (active) + \gamma_3\ (signal) + \delta_3\ (BG/cp) + \varepsilon_3 \quad (14)$$

wobei τ_i, β_i, γ_i und δ_i Koeffizienten sind; und wobei ε_i eine Konstante ist.

12. Überwachungssystem nach Anspruch 10, wobei die Vorhersage des Meßwerts unter Verwendung der Serie von Meßwerten in einem Algorithmus erfolgt, der dem Expertenmischalgorithmus entspricht, wobei die einzelnen Experten eine lineare Form haben, nämlich

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \quad (15)$$

wobei (BG) der Blutzucker ist; drei Experten (n=3) vorhanden sind und BG_i der vom Experten i vorhergesagte Blutzucker ist; w_i ein Parameter ist; und die einzelnen Experten BG_i durch die in den Gleichungen 16, 17 und 18 gezeigte Formel weiter definiert sind, nämlich

$$BG_1 = p_1\ (time_c) + q_1\ (active) + r_1\ (signal) + s_2\ (BG/cp) + t_1 \quad (16)$$

$$BG_2 = p_2\ (time_c) + q_2\ (active) + r_2\ (signal) + s_2\ (BG/cp) + t_2 \quad (17)$$

$$BG_3 = p_3\ (time_c) + q_3\ (active) + r_3\ (signal) + s_3\ (BG/cp) + t_3 \quad (18)$$

wobei BG_i der vom Experten i vorhergesagte Blutzucker ist; die Parameter folgende sind: $time_c$ (die seit einer Kalibrierung des Probenahmesystems vergangene Zeit), *active* (aktives Signal), *signal* (kalibriertes Signal) und *BG/cp* (Blutzuckerwert an einem Kalibrierpunkt) ; p_i, q_i, r_i und s_i Koeffizienten sind; und t_i eine Konstante ist; und ferner wobei der Wichtungswert w_i durch die in den Gleichungen 19, 20 und 21 gezeigten Formeln definiert ist, nämlich

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

Abbott Ex. 1002 - 259/1438

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

wobei e die Exponentialfunktion bezeichnet und d_i eine Parametergruppe ist (analog zu den Gleichungen 6, 7 und 8), die verwendet wird, um die Gewichte w_i zu bestimmen, die in den Gleichjungen 19, 20 und 21 gegeben sind, und

$$d_1 = \tau_1 (time_c) + \beta_1 (active) + \gamma_1 (signal) + \delta_1 (BG/cp) + \varepsilon_1 \quad (22)$$

$$d_1 = \tau_2 (time_c) + \beta_2 (active) + \gamma_2 (signal) + \delta_2 (BG/Cp) + \varepsilon_2 \quad (23)$$

$$d_1 = \tau_3 (time_c) + \beta_3 (active) + \gamma_3 (signal) + \delta_3 (BG/cp)\ \varepsilon_3 \quad (24)$$

wobei τ_i, β_i, γ_i und β_i Koeffizienten sind und ε_i eine Konstante ist.

13. Überwachungssystem nach einem der Ansprüche 10 bis 12, das weitere Parameter für Rohsignale aufweist, die aus der Gruppe gewählt sind, die aus Temperatur, iontophoretischer Spannung und Hautleitfähigkeit besteht.

14. Überwachungssystem nach einem der Ansprüche 10 bis 12, wobei die Erfassungseinrichtung (16, 18, 20) einen Biosensor mit einem elektrochemischen Erfassungsmaterial aufweist.

15. Überwachungssystem nach einem der Ansprüche 10 bis 12, wobei die Erfassungseinrichtung (16, 18, 20) ein Spektrometer für den nahen Infrarotbereich aufweist.

16. Überwachungssystem nach einem der Ansprüche 10 bis 12, ferner mit
einer Probenahmeeinrichtung (8, 10, 12, 14) zum dauernden oder kontinuierlichen Extrahieren des Blutzukkers aus dem Patienten, wobei die Probenahmeeinrichtung (8, 10, 12, 14) zum Extrahieren des Blutzuckers durch eine Haut- oder Schleimhautoberfläche des Patienten geeignet ist und wobei die Mikroprozessoreinrichtung (36) in betriebsfähiger Kommunikation mit der Probenahmeeinrichtung (8, 10, 12, 14) ist und verwendet wird, um die Probenahmeeinrichtung (8, 10, 12, 14) zu steuern.

17. Überwachungssystem nach Anspruch 16, wobei die Probenahmeeinrichtung (8, 10, 12, 14) ein oder mehrere Aufnahmereservoire (8, 10) zum Aufnehmen des extrahierten Blutzuckers aufweist.

18. Überwachungssystem nach Anspruch 17, wobei die Probenahmeeinrichtung (8, 10, 12, 14) einen iontophoretischen Strom verwendet, um den Blutzucker aus dem Patienten zu extrahieren.

19. Überwachungssystem nach Anspruch 18, wobei das Aufnahmereservoir (8, 10) ein Enzym enthält, das mit dem extrahierten Blutzucker reagiert, um ein elektrochemisch detektierbares Signal zu erzeugen.

20. Überwachungssystem nach Anspruch 19, wobei das Enzym Glucoseoxidase ist.

Revendications

1. Procédé de mesure continuellement ou en continu du glucose sanguin chez un sujet, ledit procédé comprenant les étapes suivantes :

(a) obtenir un signal brut à partir de glucose sanguin extrait, où ledit signal brut se rapporte spécifiquement au glucose sanguin ;

Abbott Ex. 1002 - 260/1438

(b) effectuer une étape d'étalonnage qui corrèle le signal brut obtenu dans l'étape (a) avec une valeur de mesure indicative de la concentration du glucose sanguin présent chez le sujet au moment de l'extraction ;
(c) répéter l'étape (a) pour obtenir une série de valeurs de mesure à des intervalles de temps choisis ; et
(d) prévoir une valeur de mesure fondée sur la série de valeurs de mesure en utilisant l'algorithme des Mélanges d'Experts, où les experts individuels ont une forme linéaire

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

dans laquelle (*An*) est le glucose sanguin, l'analyte en question; *n* est le nombre d'experts ; An_i est l'analyte prévu par l'expert *i* ; et w_i est un paramètre ; et les experts individuels An_i sont en outre définis par les expressions données par l'équation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

dans laquelle An_i est l'analyte prévu par l'export *i* : P_j est un des *m* paramètres ; *m* est typiquement inférieur à 100 ; α_{ij} sont des coefficients ; et z_i est une constante ; et en outre dans laquelle la valeur de poids, w_i, est définie par la formule donnée par l'équation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

dans laquelle *e* fait référence à la fonction exponentielle et les d_k (noter que le d_i dans le numérateur de l'équation 3 est un des d_k) sont un ensemble de paramètres analogues à l'équation 2 qui est utilisée pour déterminer les poids w_i ; les d_k étant donnés par l'équation (4)

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

dans laquelle α_{jk} est un coefficient, P_j est un des paramètres *m,* et ω_k est une constante.

2. Procédé selon la revendication 1, dans lequel dans l'étape (a) on fait réagir une enzyme avec le glucose sanguin extrait pour produire un signal brut détectable électrochimiquement.

3. Procédé selon la revendication 2, dans lequel l'enzyme est la glucose oxydase.

4. Procédé selon la revendication 1, dans lequel on effectue la prévision de l'étape (d) en utilisant ladite série de deux valeurs de mesure ou plus dans un algorithme représenté par l'algorithme des Mélanges d'Experts, où les experts individuels ont une forme linéaire

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

dans laquelle *(BG)* est le glucose sanguin ; il y a trois experts *(n* = 3) et BG_i est le glucose sanguin prévu par l'expert *i* ; w_i est un paramètre ; et les experts individuels BG_i sont en outre définis par les expressions données par les équations 6, 7 et 8 :

Abbott Ex. 1002 - 261/1438

$$BG_1 = p_1\,(temps) + +q_1\,(actif) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \quad (6)$$

$$BG_2 = p_2\,(temps) + q_2\,(actif) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \quad (7)$$

$$BG_3 = p_3\,(temps) + q_3\,(actif) + r_3\,(signal) + s_3\,(BG/cp) + t_3 \quad (8)$$

dans lesquelles BG_i est le glucose sanguin prévu par l'expert i ; les paramètres comprennent le *temps* (temps passé depuis que le système d'échantillonnage a été placé en contact actif avec ledit sujet), *actif* (signal actif), *signal* (signal étalonné), et *BG/cp* (valeur de glucose sanguin à un point d'étalonnage) ; p_i, q_i, r_i et s_i sont des coefficients ; et t_i est une constante ; et en outre dans lesquelles la valeur de poids, w_i, est définie par les équations 9, 10 et 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

dans lesquelles e fait référence à la fonction exponentielle et d_i est un ensemble de paramètres (analogues aux équations 6, 7 et 8) qui est utilisé pour déterminer les poids w_i donnés par les équations 9, 10 et 11, et

$$d_1 = \tau_1\,(temps) + \beta_1\,(actif) + \gamma_1\,(signal) + \delta_1\,(BG/cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2\,(temps) + \beta_2\,(actif) + \gamma_2\,(signal) + \delta_2\,(BG/cp) = \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3\,(temps) + \beta_3\,(actif) + \gamma_3\,(signal) + \delta_3\,(BG/cp) + \varepsilon_3 \quad (14)$$

dans lesquelles τ_i, β_i, γ_i et δ_i sont des coefficients ; et ε_i est une constante.

5. Procédé selon la revendication 1, dans lequel on effectue la prévision de l'étape (d) en utilisant ladite série de deux valeurs de mesure ou plus dans un algorithme représenté par l'algorithme des Mélanges d'Experts, où les experts individuels ont une forme linéaire

$$BG = w_1 BG_1 + W_2 BG_2 + w_3 BG_3 \quad (15)$$

dans laquelle *(BG)* est le glucose sanguin ; il y a trois experts (n = 3) et BG_i est le glucose sanguin prévu par l'export i ; w_i est un paramètre ; et les experts individuels BG_i sont en outre définis par les expressions données par les équations 16, 17 et 18 :

$$BG_1 = p_1\,(temps_c) + q_1\,(actif) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \quad (16)$$

$$BG_2 = p_2\,(temps_c) + q_2\,(actif) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \quad (17)$$

Abbott Ex. 1002 - 262/1438

$$BG_3 = p_3\ (temps_c) + q_3\ (actif) + r_3\ (signal) + s_3\ (BG/cp) + t_3 \quad (18)$$

dans lesquelles BG_i est le glucose sanguin prévu par l'expert *i*; les paramètres comprennent le $temps_c$ (temps passé à partir de l'étalonnage dudit système d'échantillonnage), *actif* (signal actif), *signal* (signal étalonné), et *BG/cp* (valeur de glucose sanguin à un point d'étalonnage) ; p_i, q_i, r_i et s_i sont des coefficients ; et t_i est une constante ; et en outre dans lesquelles la valeur de poids, w_i, est définie par les équations 19, 20 et 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

dans lesquelles *e* fait référence à la fonction exponentielle et d_i est un ensemble de paramètres (analogues aux équations 6, 7 et 8) qui est utilisé pour déterminer les poids w_i donnés par les équations 19, 20 et 21, et

$$d_1 = \tau_1\ (temps_c) + \beta_1\ (actif) + \gamma_1\ (signal) + \delta_1\ (BG/cp) + \varepsilon_1 \quad (22)$$

$$d_2 = \tau_2\ (temps_c) + \beta_2\ (actif) + \gamma_2\ (signal) + \delta_2\ (BG/cp) + \varepsilon_2 \quad (23)$$

$$d_3 = \tau_3\ (temps_c) + \beta_3\ (actif) + \gamma_3\ (signal) + \delta_3\ (BG/cp) + \varepsilon_3 \quad (24)$$

dans lesquelles τ_i, β_i, γ_i et δ_i sont des coefficients ; et ε_i est une constante.

6. Procédé selon l'une de la revendication 4 ou de la revendication 5, qui comprend en outre des paramètres pour les valeurs de mesure choisies dans le groupe constitué par la température, la tension ionophorétique et la conductivité de la peau.

7. Procédé selon l'une de la revendication 1, la revendication 4 ou la revendication 5, dans lequel dans l'étape (a) on obtient le signal brut à partir d'un appareil capteur (16, 18, 20), dans lequel ledit signal brut est en liaison spécifique avec le glucose détecté par l'appareil capteur (16, 18, 20).

8. Procédé selon la revendication 7, dans lequel l'appareil capteur (16, 18, 20) est un spectromètre dans le proche IR.

9. Procédé selon la revendication 7, dans lequel l'appareil capteur (16, 18, 20) comprend un bio-capteur ayant un élément capteur électrochimique.

10. Système de contrôle pour mesurer continuellement ou en continu du glucose sanguin chez un sujet, ledit système comprenant, en combinaison active:

des moyens capteurs (16, 18, 20) en contact actif avec du glucose sanguin extrait, dans lequel lesdits moyens capteurs (16, 18, 20) obtiennent un signal brut provenant du glucose sanguin extrait et ledit signal brut se rapporte spécifiquement au glucose sanguin ; et
des moyens de microprocesseur (36) en communication active avec les moyens capteurs (16, 18, 20), dans lequel lesdits moyens de microprocesseur (36) (i) sont utilisés pour commander les moyens capteurs (16, 18, 20) pour obtenir une série de signaux bruts à des intervalles de temps choisis pendant une période de mesure continuelle ou en continu, (ii) corrèlent les signaux bruts avec des valeurs de mesure indicatives de la con-

Abbott Ex. 1002 - 263/1438

centration de glucose sanguin présent chez le sujet, et (iii) prévoient une valeur de mesure fondée sur une série de valeurs de mesure en utilisant l'algorithme des Mélanges d'Experts, où les experts individuels ont une forme linéaire

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

dans laquelle (*An*) est le glucose sanguin, l'analyte en question; *n* est le nombre d'experts ; An_i est l'analyte prévu par l'Expert *i* ; et w_i est un paramètre ; et les experts individuels An_i sont en outre définis par les expressions données par l'équation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

dans laquelle An_i est l'analyte prévu par l'export *i* : P_j est un des *m* paramètres ; *m* est typiquement inférieur à 100 ; α_{ij} sont des coefficients ; et z_i est une constante ; et en outre dans laquelle la valeur de poids, w_i, est définie par la formule donnée par l'équation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

dans laquelle e fait référence à la fonction exponentielle et les d_k (noter que le d_i dans le numérateur de l'équation 3 est un des d_k) sont un ensemble de paramètres analogues à l'équation 2 qui est utilisée pour déterminer les poids w_i; les d_k étant donnés par l'équation (4)

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

dans laquelle α_{jk} est un coefficient, P_j est un des paramètre *m,* et ω_k est une constante.

11. Système de contrôle de la revendication 10, dans lequel on effectue la prévision de la valeur de mesure en utilisant ladite série de valeurs de mesures dans un algorithme représenté par l'algorithme des mélanges des experts, où les experts individuels ont une forme linéaire

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

dans laquelle (*BG*) est le glucose sanguin ; il y a trois experts ($n = 3$) et BG_i est le glucose sanguin prévu par l'expert *i* ; w_i est un paramètre ; et les experts individuels BG_i sont en outre définis par les expressions données par les équations 6, 7 et 8 :

$$BG_1 = p_1\,(temps) + q_1\,(actif) + r_1\,(signal) + s_1\,(BG/cp) + t_1 \qquad (6)$$

$$BG_2 = p_2\,(temps) + q_2\,(actif) + r_2\,(signal) + s_2\,(BG/cp) + t_2 \qquad (7)$$

Abbott Ex. 1002 - 264/1438

$$BG_3 = p_3\ (temps) + q_3\ (actif) + r_3\ (signal) + s_3\ (BG/cp) + t_3 \quad (8)$$

dans lesquelles BG_i est le glucose sanguin prévu par l'expert i ; les paramètres comprennent le *temps* (temps passé depuis que le système d'échantillonnage a été placé en contact actif avec ledit sujet), *actif* (signal actif), *signal* (signal étalonné), et *BG/cp* (valeur de glucose sanguin à un point d'étalonnage) ; p_i, q_i, r_i et s_i sont des coefficients ; et t_i est une constante ; et en outre dans lesquelles la valeur de poids, w_i, est définie par les équations 9, 10 et 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

dans lesquelles e fait référence à la fonction exponentielle et d_i est un ensemble de paramètres (analogues aux équations 6, 7 et 8) qui est utilisé pour déterminer les poids w_i donnés par les équations 9, 10 et 11, et

$$d_1 = \tau_1\ (temps) + \beta_1\ (actif) + \gamma_1\ (signal) + \delta_1\ (BG/cp) + \varepsilon_1 \quad (12)$$

$$d_2 = \tau_2\ (temps) + \beta_2\ (actif) + \gamma_2\ (signal) + \delta_2\ (BG/cp) + \varepsilon_2 \quad (13)$$

$$d_3 = \tau_3\ (temps) + \beta_3\ (actif) + \gamma_3\ (signal) + \delta_3\ (BG/cp) + \varepsilon_3 \quad (14)$$

dans lesquelles τ_i, β_i, γ_i et δ_i sont des coefficients ; et ε_i est une constante.

12. Système de contrôle de la revendication 10, dans lequel on effectue la prévision de la valeur de mesure en utilisant ladite série de valeurs de mesures dans un algorithme représenté par l'algorithme des Mélanges d'Experts, où les experts individuels ont une forme linéaire

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \quad (15)$$

dans laquelle (*BG*) est le glucose sanguin ; il y a trois experts (n = 3) et BG_i est le glucose sanguin prévu par l'expert i ; w_i est un paramètre ; et les experts individuels BG_i sont en outre définis par les expressions données par les équations 16, 17 et 18:

$$BG_1 = p_1\ (temps_c) + q_1\ (actif) + r_1\ (signal) + s_1\ (BG/cp) + t_1 \quad (16)$$

$$BG_2 = p_2\ (temps_c) + q_2\ (actif) + r_2\ (signal) + s_2\ (BG/cp) + t_2 \quad (17)$$

$$BG_3 = p_3\ (temps_c) + q_3\ (actif) + r_3\ (signal) + s_3\ (BG/cp) + t_3 \quad (18)$$

dans lesquelles BG_i est le glucose sanguin prévu par l'expert i ; les paramètres comprennent le $temps_c$ (temps passé à partir de l'étalonnage dudit système d'échantillonnage), *actif (signal* actif), *signal* (signal étalonné), et *BG/*

Abbott Ex. 1002 - 265/1438

cp (valeur de glucose sanguin à un point d'étalonnage) ; p_i, q_i, r_i et s_i sont des coefficients ; et t_i est une constante ; et en outre dans lesquelles la valeur de poids, w_i, est définie par les équations 19, 20 et 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

dans lesquelles *e* fait référence à la fonction exponentielle et d_i est un ensemble de paramètres (analogues aux équations 6, 7 et 8) qui est utilisé pour déterminer les poids w_i donnés par les équations 19, 20 et 21, et

$$d_1 = \tau_1 (temps_c) + \beta_1 (actif) + \gamma_1 (signal) + \delta_1 (BG/cp) + \varepsilon_1 \quad (22)$$

$$d_2 = \tau_2 (temps_c) + \beta_2 (actif) + \gamma_2 (signal) + \delta_2 (BG/cp) + \varepsilon_2 \quad (23)$$

$$d_3 = \tau_3 (temps_c) + \beta_3 (actif) + \gamma_3 (signal) + \delta_3 (BG/cp) + \varepsilon_3 \quad (24)$$

dans lesquelles τ_i, β_i, γ_i et δ_i sont des coefficients ; et ε_i est une constante.

13. Système de contrôle selon l'une quelconque des revendications 10 à 12, qui comprend en outre des paramètres pour des signaux bruts choisis dans le groupe constitué par la température, la tension ionophorétique et la conductivité de la peau.

14. Système de contrôle selon l'une quelconque des revendications 10 à 12, dans lequel les moyens capteurs (16, 18, 20) comprennent un bio-capteur ayant un élément capteur électrochimique.

15. Système de contrôle selon l'une quelconque des revendications 10 à 12, dans lequel les moyens capteurs (16, 18, 20) comprennent un spectromètre dans le proche IR.

16. Système de contrôle selon l'une quelconque des revendications 10 à 12, comprenant en outre des moyens d'échantillonnage (8, 10, 12, 14) pour extraire continuellement ou en continu le glucose sanguin chez le sujet, dans lequel lesdits moyens d'échantillonnage (8, 10, 12, 14) sont adaptés pour extraire le glucose sanguin à travers la peau ou la surface de la muqueuse dudit sujet, et dans lequel les moyens de microprocesseur (36) sont en communication active avec lesdits moyens d'échantillonnage (8, 10, 12, 14) et sont utilisés pour contrôler lesdits moyens d'échantillonnage (8, 10, 12, 14).

17. Système de contrôle selon la revendication 16, dans lequel les moyens d'échantillonnage (8, 10, 12, 14) comprennent un ou plusieurs réservoirs collecteurs (8, 10) pour contenir le glucose sanguin extrait.

18. Système de contrôle selon la revendication 17, dans lequel les moyens d'échantillonnage (8, 10, 12, 14) utilisent un courant ionophore pour extraire le glucose sanguin du sujet.

19. Système de contrôle selon la revendication 18, dans lequel le réservoir collecteur (8, 10) contient une enzyme qui réagit avec le glucose sanguin extrait pour produire un signal détectable électrochimiquement.

20. Système de contrôle selon la revendication 19, dans lequel l'enzyme est la glucose oxydase.

Abbott Ex. 1002 - 266/1438

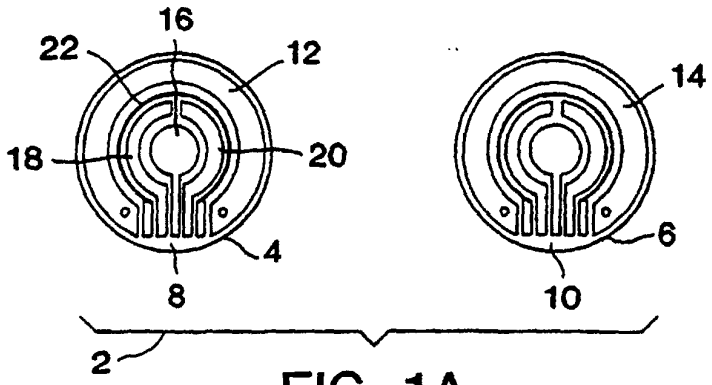


FIG. 1A

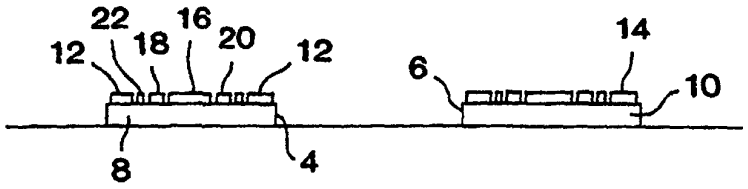


FIG. 1B

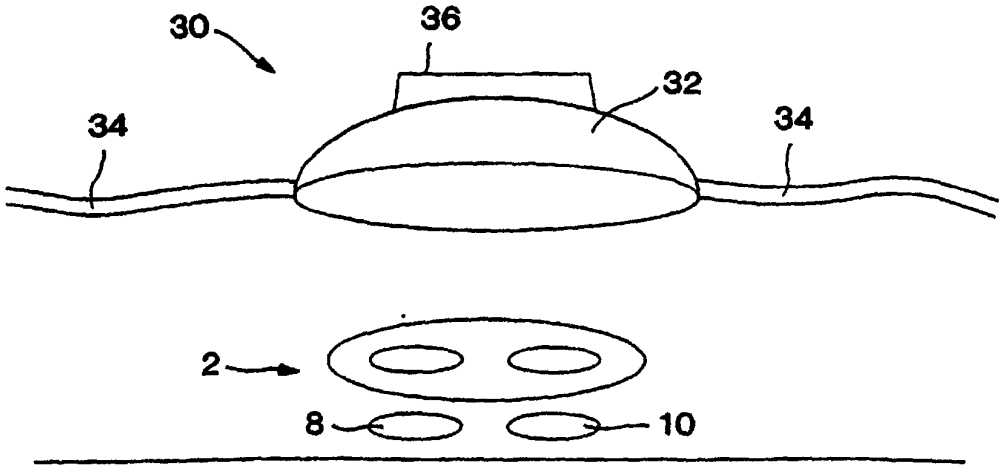


FIG. 2

Abbott Ex. 1002 - 267/1438

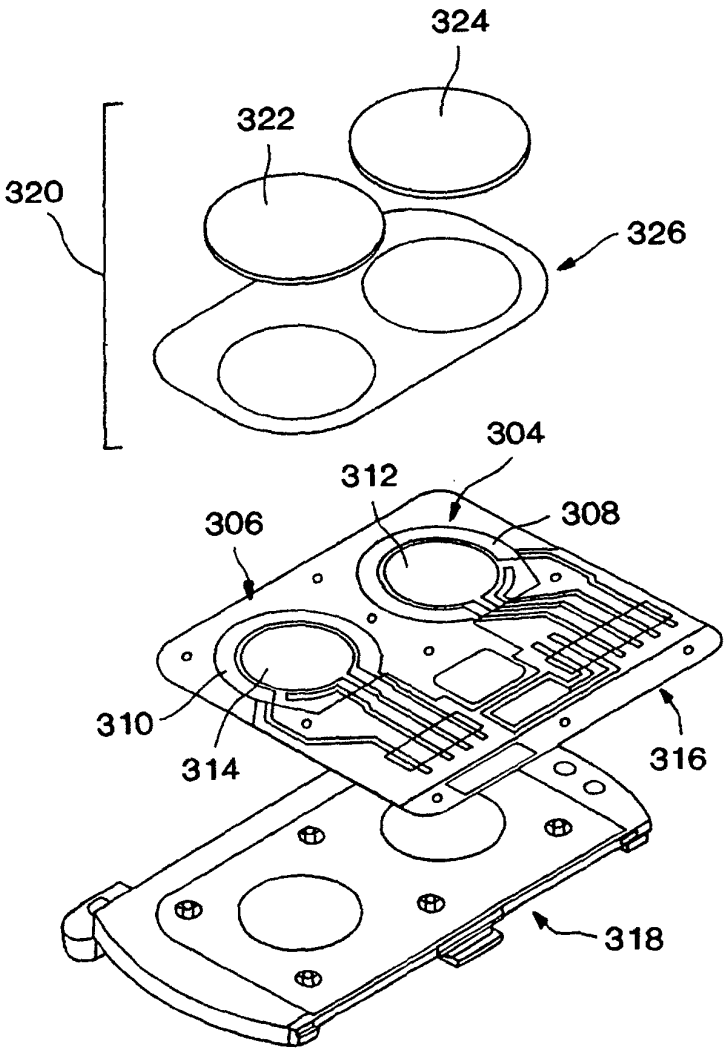


FIG. 3

Abbott Ex. 1002 - 268/1438

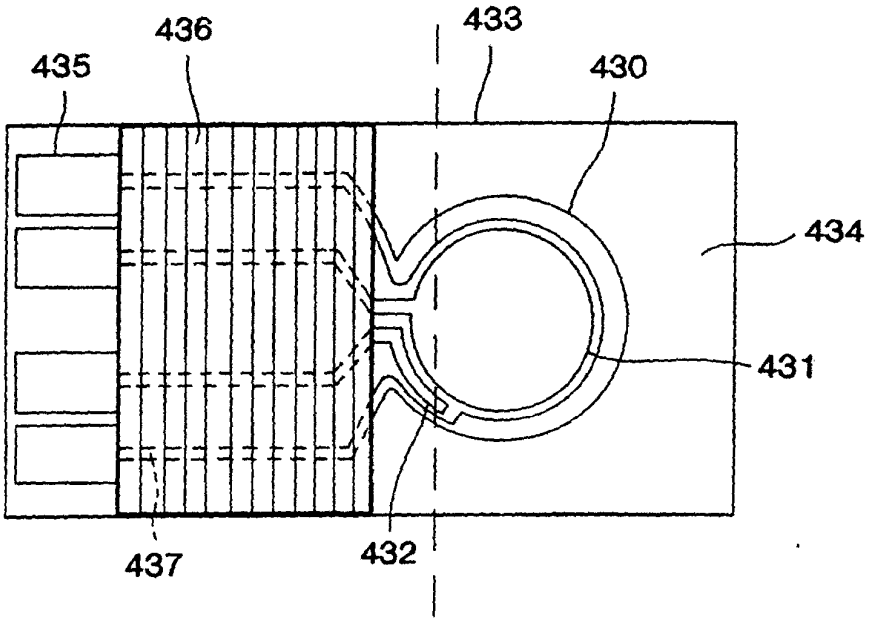


FIG. 4

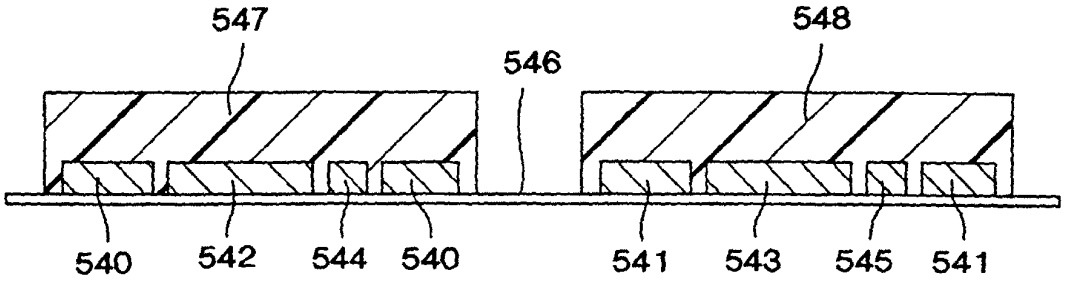


FIG. 5

Abbott Ex. 1002 - 269/1438

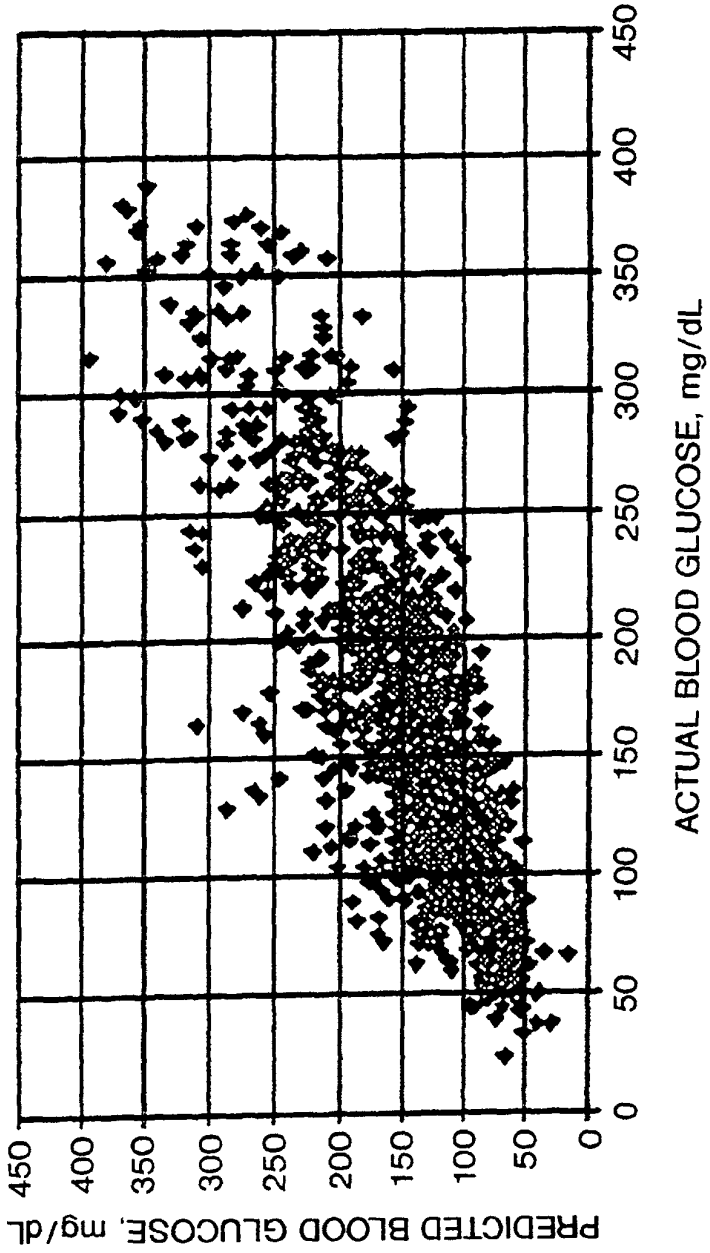


FIG. 6

Abbott Ex. 1002 - 270/1438

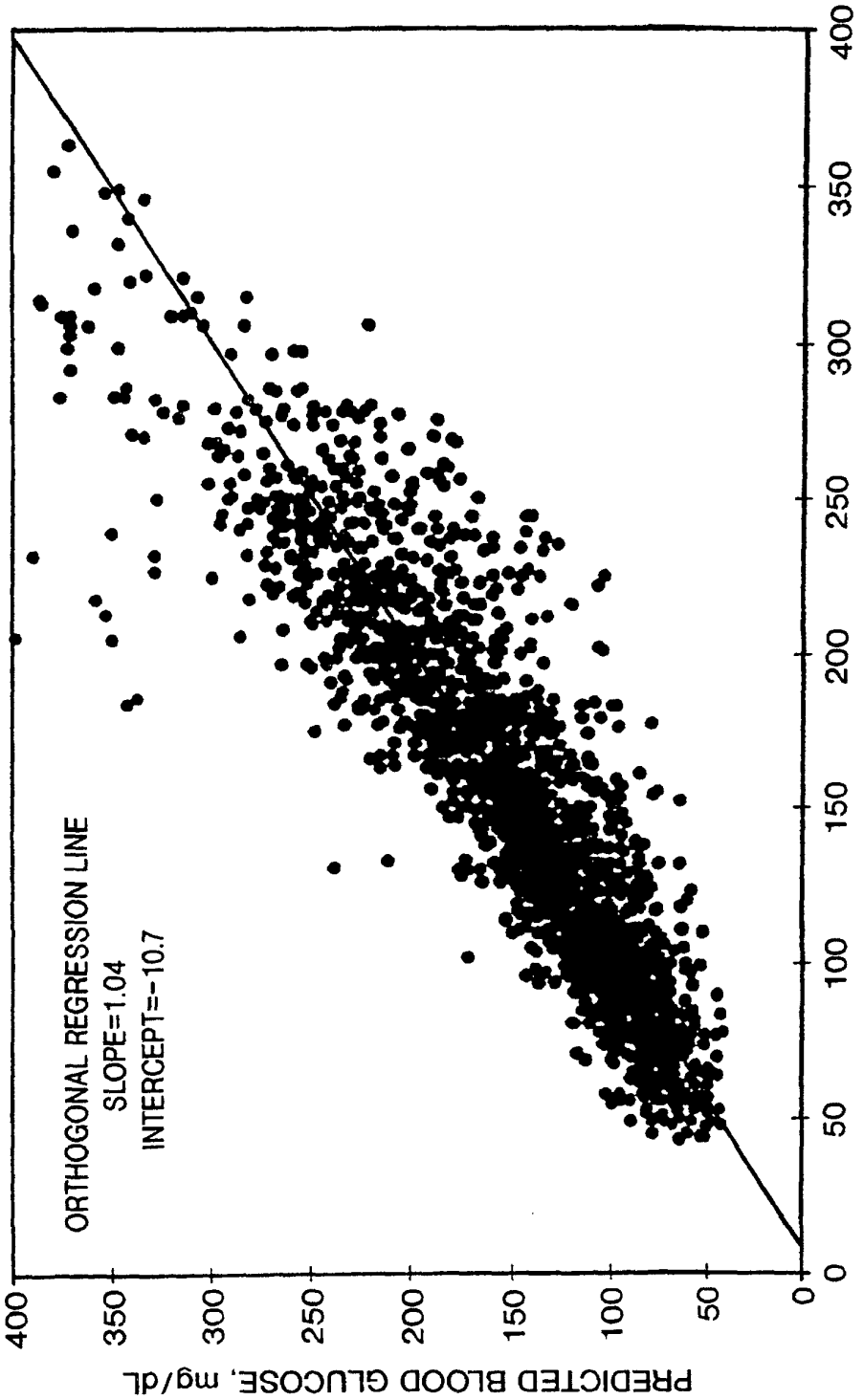


FIG. 7

Abbott Ex. 1002 - 271/1438

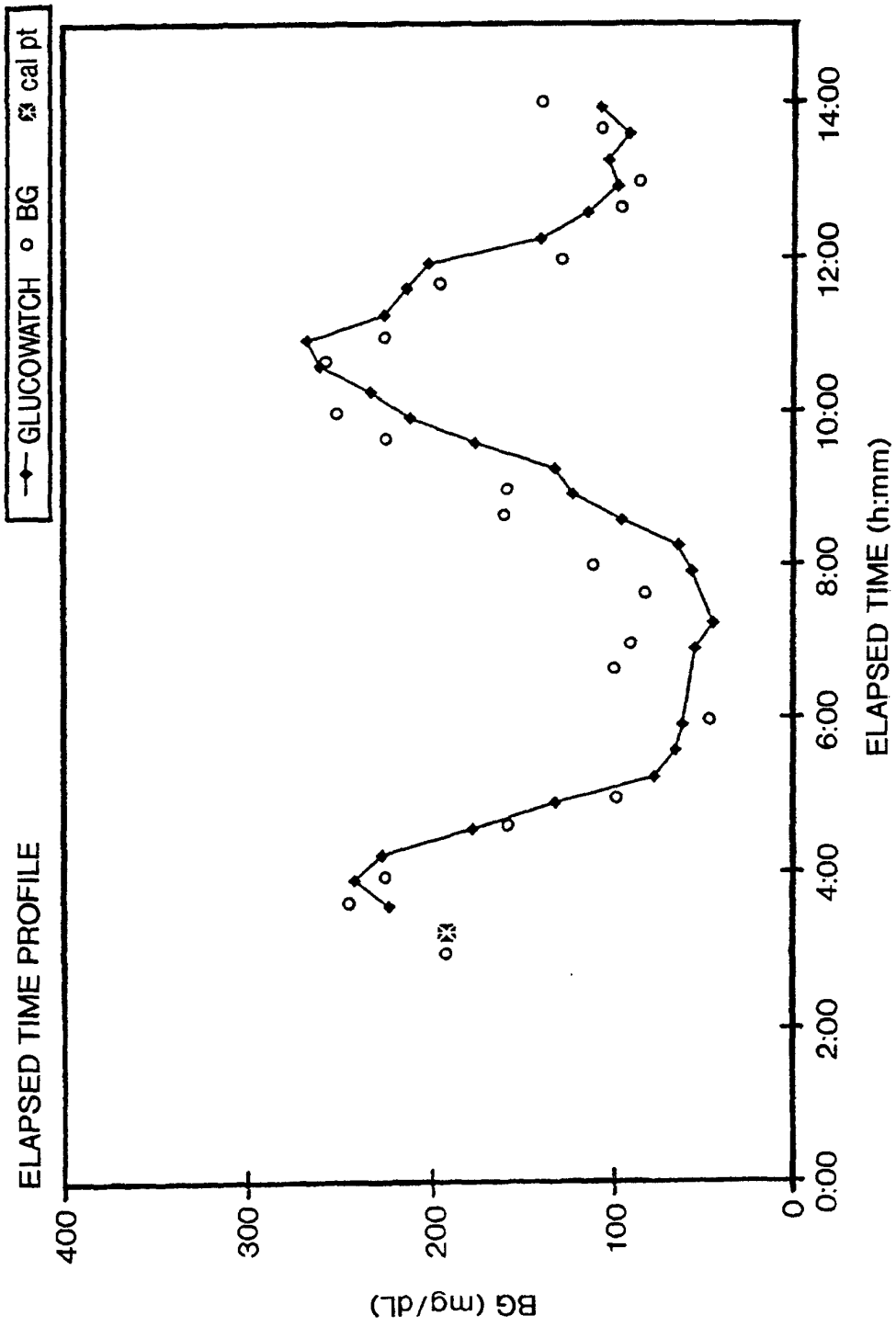


FIG. 8

Abbott Ex. 1002 - 272/1438

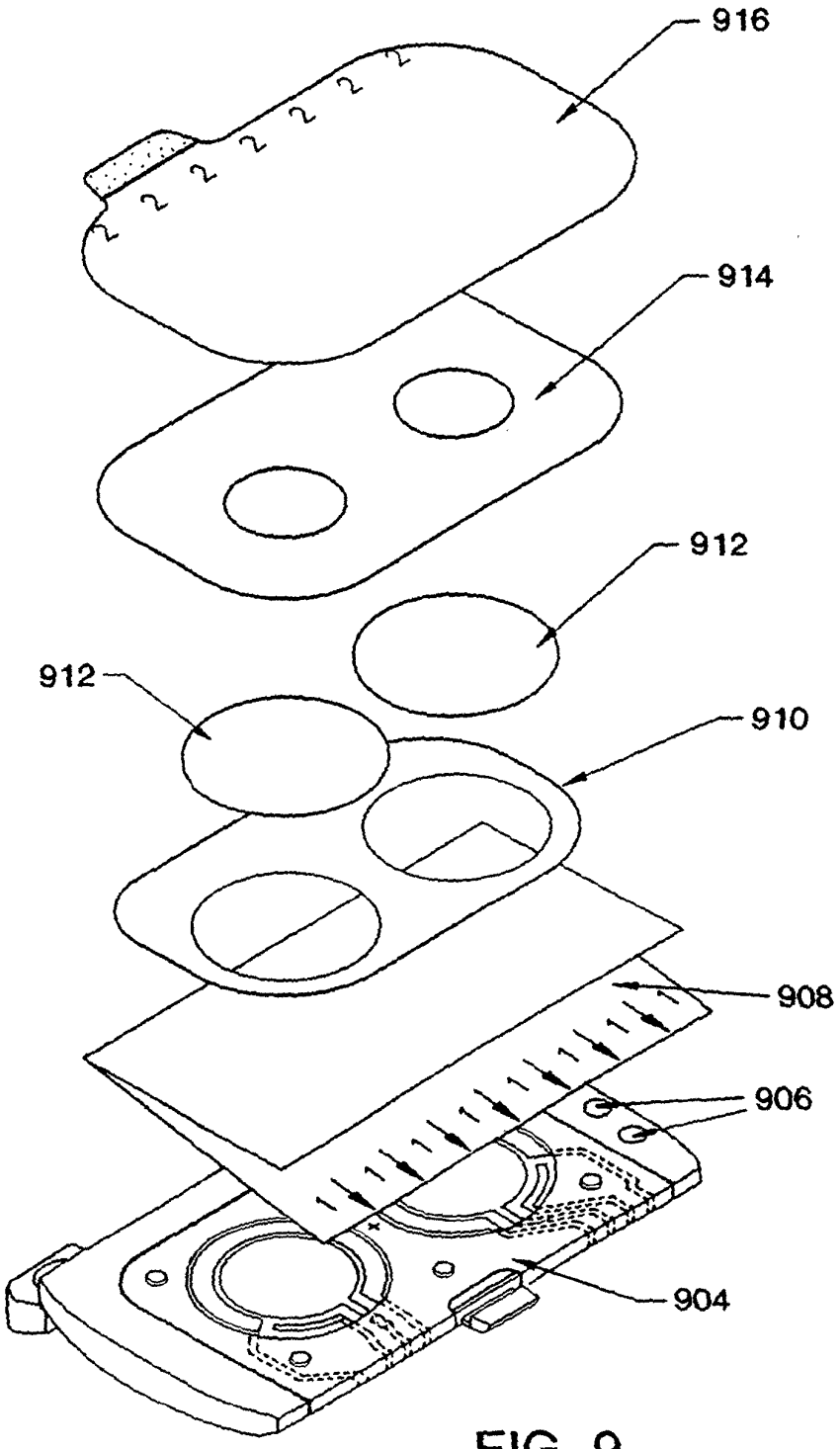


FIG. 9

Abbott Ex. 1002 - 273/1438

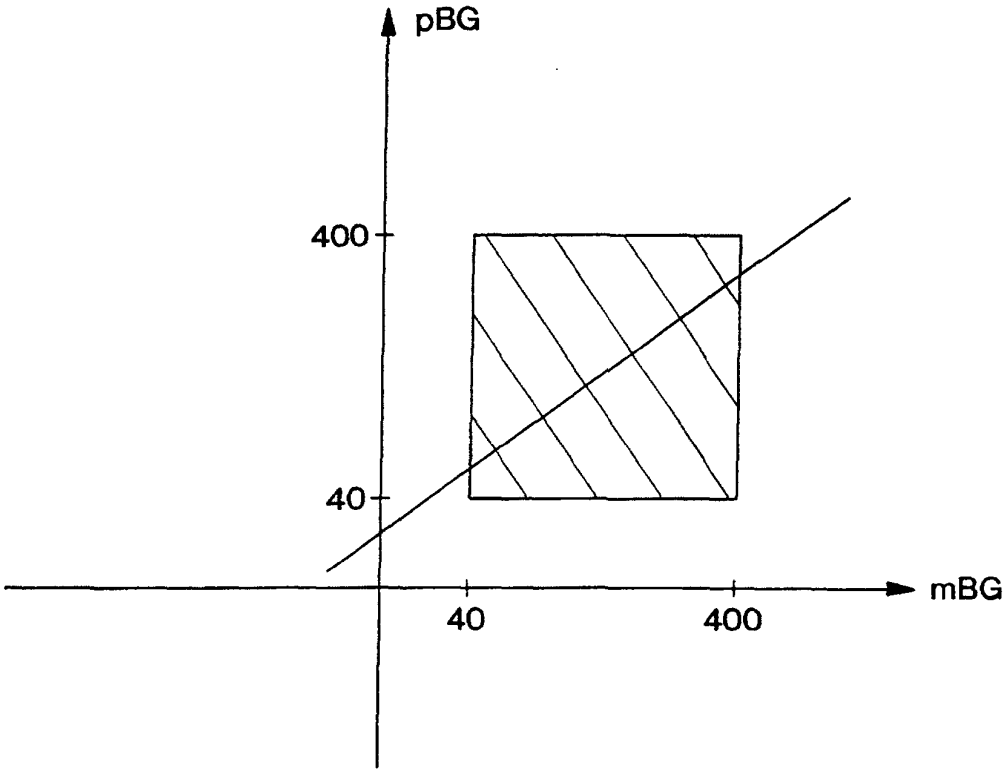


FIG. 10A

Abbott Ex. 1002 - 274/1438

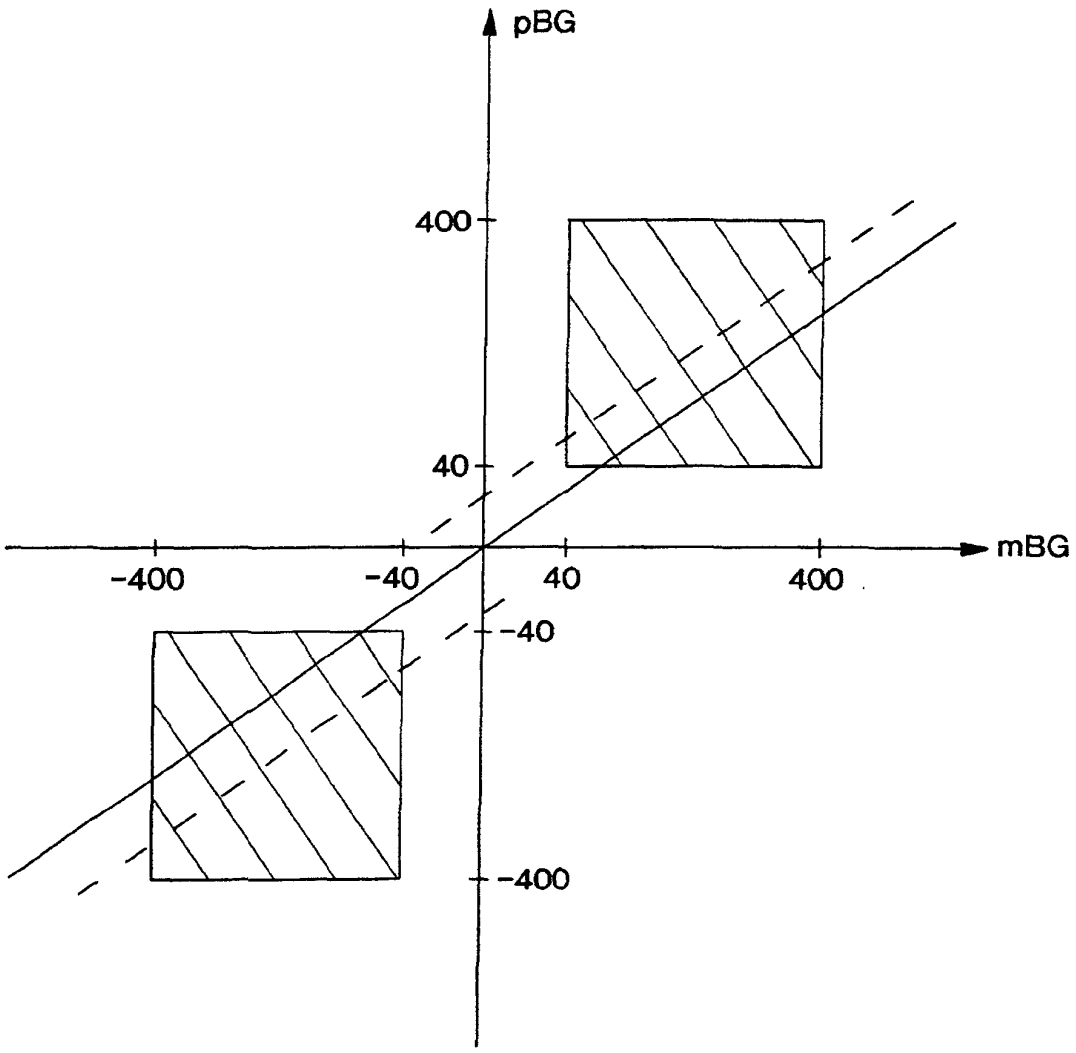


FIG. 10B

Abbott Ex. 1002 - 275/1438

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(54) **SMALL VOLUME IN VITRO ANALYTE SENSOR WITH DIFFUSIBLE OR NON-LEACHABLE REDOX MEDIATOR**

KLEINVOLUMIGER IN VITRO SENSOR MIT DIFFUSIONSFÄHIGEM ODER NICHTAUSWASCHBAREM REDOXVERMITTLER

DETECTEUR D'ANALYTES IN VITRO DANS DES PETITS VOLUMES UTILISANT UN MEDIATEUR DIFFUSIBLE OU NON LIXIVIABLE

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- **VIDAL J C ET AL: "A chronoamperometric sensor for hydrogen peroxide based on electron transfer between immobilized horseradish peroxidase on a glassy carbon electrode and a diffusing ferrocene mediator" SENSORS AND ACTUATORS B,CH,ELSEVIER SEQUOIA S.A., LAUSANNE, vol. 21, no. 2, 1 August 1994 (1994-08-01), pages 135-141, XP004012315 ISSN: 0925-4005**

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EP 1 119 637 B1

Description

[0001] This invention relates to analytical sensors for the detection of bioanalytes in a small volume sample.

Background of the Invention

[0002] Analytical sensors are useful in chemistry and medicine to determine the presence and concentration of a biological analyte. Such sensors are needed, for example, to monitor glucose in diabetic patients and lactate during critical care events.

[0003] Currently available technology measures bioanalytes in relatively large sample volumes, e.g., generally requiring 3 microliters or more of blood or other biological fluid. These fluid samples are obtained from a patient, for example, using a needle and syringe, or by lancing a portion of the skin such as the fingertip and "milking" the area to obtain a useful sample volume. These procedures are inconvenient for the patient, and often painful, particularly when frequent samples are required. Less painful methods for obtaining a sample are known such as lancing the arm or thigh, which have a lower nerve ending density. However, lancing the body in the preferred regions typically produces submicroliter samples of blood, because these regions are not heavily supplied with near-surface capillary vessels.

[0004] It would therefore be desirable and very useful to develop a relatively painless, easy to use blood analyte sensor, capable of performing an accurate and sensitive analysis of the concentration of analytes in a small volume of sample. Sensors capable of electrochemically measuring an analyte in a sample are known in the art. Some sensors known in the art use at least two electrodes and may contain a redox mediator to aid in the electrochemical reaction. However, the use of an electrochemical sensor for measuring analyte in a small volume introduces error into the measurements. One type of inaccuracy arises from the use of a diffusible redox mediator. Because the electrodes are so close together in a small volume sensor, diffusible redox mediator may shuttle between the working and counter electrode and add to the signal measured for analyte. Another source of inaccuracy in a small volume sensor is the difficulty in determining the volume of the small sample or in determining whether the sample chamber is filled. It would therefore be desirable to develop a small volume electrochemical sensor capable of decreasing the errors that arise from the size of the sensor and the sample.

[0005] WO 98/35225 discloses a sensor having a working electrode, a counter electrode, and a sample chamber for receiving a sample having the analyte to be measured. The sample chamber includes a measurement zone having a volume of less than about 1 μl. A non-leachable redox mediator, which acts as an electron transfer agent between the analyte and the working electrode, is present on a portion of the working electrode.

Summary of the Invention

[0006] The sensors of the present invention provide a method for the detection and quantification of an analyte in submicroliter samples. In general, the invention includes a method and sensor for analysis of an analyte in a small volume of sample by, for example, coulometry, amperometry and/or potentiometry. A sensor of the invention utilizes a non-leachable or diffusible redox mediator. The sensor also includes a sample chamber to hold the sample in electrolytic contact with the working electrode. In many instances, the sensor also contains a non-leachable or diffusible second electron transfer agent.

[0007] In a preferred embodiment, the working electrode faces a counter electrode, forming a measurement zone within the sample chamber, between the two electrodes, that is sized to contain no more than about 1 μL of sample, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL of sample. A sorbent material is optionally positioned in the sample chamber and measurement zone to reduce the volume of sample needed to fill the sample chamber and measurement zone.

[0008] In one embodiment of the invention, a biosensor is provided which combines coulometric electrochemical sensing with a non-leachable or diffusible redox mediator to accurately and efficiently measure a bioanalyte in a submicroliter volume of sample. The preferred sensor includes an electrode, a non-leachable or diffusible redox mediator on the electrode, a sample chamber for holding the sample in electrical contact with the electrode and, preferably, sorbent material disposed within the sample chamber to reduce the volume of the chamber. The sample chamber, together with any sorbent material, is sized to provide for analysis of a sample volume that is typically no more than about 1 μL, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL. In some instances, the sensor also contains a non-leachable or diffusible second electron transfer agent.

[0009] One embodiment of the invention includes a method for determining the concentration of an analyte in a sample by, first, contacting the sample with an electrochemical sensor and then determining the concentration of the analyte. The electrochemical sensor includes a facing electrode pair with a working electrode and a counter electrode and a sample chamber, including a measurement zone, positioned between the two electrodes. The measurement

Abbott Ex. 1002 - 277/1438

zone is sized to contain no more than about 1 μL of sample.

[0010] The invention also includes an electrochemical sensor with two or more facing electrode pairs. Each electrode pair has a working electrode, a counter electrode, and a measurement zone between the two electrodes, the measurement zone being sized to hold no more than about 1 μL of sample. In addition, the sensor also includes a non-leachable redox mediator on the working electrode of at least one of the electrode pairs or a diffusible redox mediator on a surface in the sample chamber or in the sample.

[0011] One aspect of the invention is a method of determining the concentration of an analyte in a sample by contacting the sample with an electrochemical sensor and determining the concentration of the analyte by coulometry. The electrochemical sensor includes an electrode pair with a working electrode and a counter electrode. The sensor also includes a sample chamber for holding a sample in electrolytic contact with the working electrode. Within the sample chamber is sorbent material to reduce the volume sample needed to fill the sample chamber so that the sample chamber is sized to contain no more than about 1 μL of sample. The sample chamber also contains a non-leachable or diffusible redox mediator and optionally contains a non-leachable or diffusible second electron transfer agent.

[0012] The sensors may also include a fill indicator, such as an indicator electrode or a second electrode pair, that can be used to determine when the measurement zone or sample chamber has been filled. An indicator electrode or a second electrode pair may also be used to increase accuracy of the measurement of analyte concentration. The sensors may also include a heating element to heat the measurement zone or sample chamber to increase the rate of oxidation or reduction of the analyte.

[0013] Sensors can be configured for side-filling or tip-filling. In addition, in some embodiments, the sensor may be part of an integrated sample acquisition and analyte measurement device. The integrated sample acquisition and analyte measurement device may include the sensor and a skin piercing member, so that the device can be used to pierce the skin of a user to cause flow of a fluid sample, such as blood, that can then be collected by the sensor. In at least some embodiments, the fluid sample can be collected without moving the integrated sample acquisition and analyte measurement device.

[0014] One method of forming a sensor, as described above, includes forming at least one working electrode on a first substrate and forming at least one counter or counter/reference electrode on a second substrate. A spacer layer is disposed on either the first or second substrates. The spacer layer defines a channel into which a sample can be drawn and held when the sensor is completed. A redox mediator and/or second electron transfer agent are disposed on the first or second substrate in a region that will be exposed within the channel when the sensor is completed. The first and second substrates are then brought together and spaced apart by the spacer layer with the channel providing access to the at least one working electrode and the at least one counter or counter/reference electrode. In some embodiments, the first and second substrates are portions of a single sheet or continuous web of material.

[0015] These and various other features which characterize the invention are pointed out with particularity in the attached claims. For a better understanding of the invention, its advantages, and objectives obtained by its use, reference should be made to the drawings and to the accompanying description, in which there is illustrated and described preferred embodiments of the invention.

Brief Description of the Drawings

[0016] Referring now to the drawings, wherein like reference numerals and letters indicate corresponding structure throughout the several views:

Figure 1 is a schematic view of a first embodiment of an electrochemical sensor in accordance with the principles of the present invention having a working electrode and a counter electrode facing each other;

Figure 2 is a schematic view of a second embodiment of an electrochemical sensor in accordance with the principles of the present invention having a working electrode and a counter electrode in a coplanar configuration;

Figure 3 is a schematic view of a third embodiment of an electrochemical sensor in accordance with the principles of the present invention having a working electrode and a counter electrode facing each other and having an extended sample chamber;

Figure 4 is a not-to-scale side-sectional drawing of a portion of the sensor of Figures 1 or 3 showing the relative positions of the redox mediator, the sample chamber, and the electrodes;

Figure 5 is a top view of a fourth embodiment of an electrochemical sensor in accordance with the principles of the present invention, this sensor includes multiple working electrodes;

Figure 6 is a perspective view of an embodiment of an analyte measurement device, in accordance with the principles of the present invention, having a sample acquisition means and the sensor of Figure 4;

Figure 7 is a graph of the charge required to electrooxidize a known quantity of glucose in an electrolyte buffered solution (filled circles) or serum solution (open circles) using the sensor of Figure 1 with glucose oxidase as the second electron transfer agent;

Abbott Ex. 1002 - 278/1438

Figure 8 is a graph of the average glucose concentrations for the data of Figure 7 (buffered solutions only) with calibration curves calculated to fit the averages; a linear calibration curve was calculated for the 10-20 mM concentrations and a second order polynomial calibration curve was calculated for the 0-10 mM concentrations;
Figure 9 is a Clarke-type clinical grid analyzing the clinical relevance of the glucose measurements of Figure 7;
Figure 10 is a graph of the charge required to electrooxidize a known quantity of glucose in an electrolyte buffered solution using the sensor of Figure 1 with glucose dehydrogenase as the second electron transfer agent;
Figures 11A, 11B, and 11C are top views of three configurations for overlapping working and counter electrodes according to the present invention;
Figures 12A and 12B are cross-sectional views of one embodiment of an electrode pair formed using a recess of a base material, according to the invention;
Figures 13A and 13B are cross-sectional views of yet another embodiment of an electrode pair of the present invention formed in a recess of a base material;
Figures 14A and 14B are cross-sectional views of a further embodiment of an electrode pair of the present invention formed using a recess of a base material and a sorbent material;
Figure 15 is a graph of charge delivered by a sensor having a diffusible redox mediator over time for several concentrations of glucose;
Figure 16 is a graph of charge delivered by a sensor having a diffusible redox mediator for several glucose concentrations;
Figure 17 is a graph of charge delivered by sensors with different amounts of diffusible redox mediator over time.
Figure 18A illustrates a top view of a first film with a working electrode for use in a fifth embodiment of a sensor according to the invention;
Figure 18B illustrates a top view of a spacer for placement on the first film of Figure 18A;
Figure 18C illustrates a bottom view of a second film (inverted with respect to Figures 18A and 18B) with counter electrodes placement over the spacer of Figure 18B and first film of Figure 18A;
Figure 19A illustrates a top view of a first film with a working electrode for use in a sixth embodiment of a sensor according to the invention;
Figure 19B illustrates a top view of a spacer for placement on the first film of Figure 19A;
Figure 19C illustrates a bottom view of a second film (inverted with respect to Figures 19A and 19B) with counter electrodes placement over the spacer of Figure 19B and first film of Figure 19A;
Figure 20A illustrates a top view of a first film with a working electrode for use in a seventh embodiment of a sensor according to the invention;
Figure 20B illustrates a top view of a spacer for placement on the first film of Figure 20A;
Figure 20C illustrates a bottom view of a second film (inverted with respect to Figures 20A and 20B) with counter electrodes placement over the spacer of Figure 20B and first film of Figure 20A;
Figure 21A illustrates a top view of a first film with a working electrode for use in a eighth embodiment of a sensor according to the invention;
Figure 21B illustrates a top view of a spacer for placement on the first film of Figure 21A;
Figure 21C illustrates a bottom view of a second film (inverted with respect to Figures 21A and 21B) with counter electrodes placement over the spacer of Figure 21B and first film of Figure 21A;
Figure 22A illustrates a top view of a first film with a working electrode for use in a ninth embodiment of a sensor according to the invention;
Figure 22B illustrates a top view of a spacer for placement on the first film of Figure 22A;
Figure 22C illustrates a bottom view of a second film (inverted with respect to Figures 22A and 22B) with counter electrodes placement over the spacer of Figure 22B and first film of Figure 22A;
Figure 23A illustrates a top view of a first film with a working electrode for use in a tenth embodiment of a sensor according to the invention;
Figure 23B illustrates a top view of a spacer for placement on the first film of Figure 23A;
Figure 23C illustrates a bottom view of a second film (inverted with respect to Figures 23A and 23B) with counter electrodes placement over the spacer of Figure 23B and first film of Figure 23A;
Figure 24A illustrates a top view of a first film with a working electrode for use in a eleventh embodiment of a sensor according to the invention;
Figure 24B illustrates a top view of a spacer for placement on the first film of Figure 24A;
Figure 24C illustrates a bottom view of a second film (inverted with respect to Figures 24A and 24B) with counter electrodes placement over the spacer of Figure 24B and first film of Figure 24A;
Figure 25 illustrates a top view of a twelfth embodiment of an electrochemical sensor, according to the invention;
Figure 26 illustrates a perspective view of one embodiment of an integrated analyte acquisition and sensor device;
Figure 27 illustrates a cross-sectional view of a thirteenth embodiment of a sensor, according to the invention;
Figure 28 illustrates a graph comparing measurements of analyte concentration in blood samples collected from

Abbott Ex. 1002 - 279/1438

a subject's arm made by a sensor of the invention with those determined by a standard blood test;
Figure 29 illustrates a graph comparing measurements of analyte concentration in blood samples collected from a subject's finger made by a sensor of the invention with those determined by a standard blood test;
Figure 30 illustrates a graph comparing measurements of analyte concentration in venous samples made by a sensor of the invention with those determined by a standard blood test;
Figure 31A illustrates a top view of one embodiment of a sheet of sensor components, according to the invention;
Figure 31B illustrates a top view of another embodiment of a sheet of sensor components, according to the invention; and
Figure 32 illustrates a cross-sectional view looking from inside the meter to a sensor of the invention disposed in a meter.

Detailed Description of the Preferred Embodiment

[0017] When used herein, the following definitions define the stated term:

[0018] An "air-oxidizable mediator" is a redox mediator that is oxidized by air, preferably so that at least 90% of the mediator is in an oxidized state upon storage in air either as a solid or as a liquid during a period of time, for example, one month or less, and, preferably, one week or less, and, more preferably, one day or less.

[0019] "Amperometry" includes steady-state amperometry, chronoamperometry, and Cottrell-type measurements.

[0020] A "biological fluid" is any body fluid in which the analyte can be measured, for example, blood, interstitial fluid, dermal fluid, sweat, and tears.

[0021] The term "blood" in the context of the invention includes whole blood and its cell-free components, such as, plasma and serum.

[0022] "Coulometry" is the determination of charge passed or projected to pass during complete or nearly complete electrolysis of the analyte, either directly on the electrode or through one or more electron transfer agents. The charge is determined by measurement of charge passed during partial or nearly complete electrolysis of the analyte or, more often, by multiple measurements during the electrolysis of a decaying current and elapsed time. The decaying current results from the decline in the concentration of the electrolyzed species caused by the electrolysis.

[0023] A "counter electrode" refers to one or more electrodes paired with the working electrode, through which passes an electrochemical current equal in magnitude and opposite in sign to the current passed through the working electrode. The term "counter electrode" is meant to include counter electrodes which also function as reference electrodes (i.e. a counter/reference electrode) unless the description provides that a "counter electrode" excludes a reference or counter/reference electrode.

[0024] An "effective diffusion coefficient" is the diffusion coefficient characterizing transport of a substance, for example, an analyte, an enzyme, or a redox mediator, in the volume between the electrodes of the electrochemical cell. In at least some instances, the cell volume may be occupied by more than one medium (e.g., the sample fluid and a polymer film). Diffusion of a substance through each medium may occur at a different rate. The effective diffusion coefficient corresponds to a diffusion rate through this multiple-media volume and is typically different than the diffusion coefficient for the substance in a cell filled solely with sample fluid.

[0025] An "electrochemical sensor" is a device configured to detect the presence of and/or measure the concentration of an analyte via electrochemical oxidation and reduction reactions. These reactions are transduced to an electrical signal that can be correlated to an amount or concentration of analyte.

[0026] "Electrolysis" is the electrooxidation or electroreduction of a compound either directly at an electrode or via one or more electron transfer agents (e.g., redox mediators and/or enzymes).

[0027] The term "facing electrodes" refers to a configuration of the working and counter electrodes in which the working surface of the working electrode is disposed in approximate opposition to a surface of the counter electrode. In at least some instances, the distance between the working and counter electrodes is less than the width of the working surface of the working electrode.

[0028] A compound is "immobilized" on a surface when it is entrapped on or chemically bound to the surface.

[0029] An "indicator electrode" includes one or more electrodes that detect partial or complete filling of a sample chamber and/or measurement zone.

[0030] A "layer" includes one or more layers.

[0031] The "measurement zone" is defined herein as a region of the sample chamber sized to contain only that portion of the sample that is to be interrogated during an analyte assay.

[0032] A "non-diffusible," "non-leachable," or "non-releasable" compound is a compound which does not substantially diffuse away from the working surface of the working electrode for the duration of the analyte assay.

[0033] The "potential of the counter/reference electrode" is the half cell potential of the reference electrode or counter/reference electrode of the cell when the solution in the cell is 0.1 M NaCl solution at pH7.

[0034] "Potentiometry" and "chronopotentiometry" refer to taking a potentiometric measurement at one or more points

Abbott Ex. 1002 - 280/1438

in time.

[0035] A "redox mediator" is an electron transfer agent for carrying electrons between the analyte and the working electrode, either directly, or via a second electron transfer agent.

[0036] A "reference electrode" includes a reference electrode that also functions as a counter electrode (i.e., a counter/reference electrode) unless the description provides that a "reference electrode" excludes a counter/reference electrode.

[0037] A "second electron transfer agent" is a molecule that carries electrons between a redox mediator and the analyte.

[0038] "Sorbent material" is material that wicks, retains, and/or is wetted by a fluid sample and which typically does not substantially prevent diffusion of the analyte to the electrode.

[0039] A "surface in the sample chamber" includes a surface of a working electrode, counter electrode, counter/reference electrode, reference electrode, indicator electrode, a spacer, or any other surface bounding the sample chamber.

[0040] A "working electrode" is an electrode at which analyte is electrooxidized or electroreduced with or without the agency of a redox mediator.

[0041] A "working surface" is the portion of a working electrode that is covered with non-leachable redox mediator and exposed to the sample, or, if the redox mediator is diffusible, a "working surface" is the portion of the working electrode that is exposed to the sample.

[0042] The small volume, *in vitro* analyte sensors of the present invention are designed to measure the concentration of an analyte in a portion of a sample having a volume no more than about 1 μL, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL. The analyte of interest is typically provided in a solution or biological fluid, such as blood or serum. Referring to the Drawings in general and Figures 1- 4 in particular, a small volume, *in vitro* electrochemical sensor 20 of the invention generally includes a working electrode 22, a counter (or counter/reference) electrode 24, and a sample chamber 26 (see Figure 4). The sample chamber 26 is configured so that when a sample is provided in the chamber the sample is in electrolytic contact with both the working electrode 22 and the counter electrode 24. This allows electrical current to flow between the electrodes to effect the electrolysis (electrooxidation or electroreduction) of the analyte.

Working Electrode

[0043] The working electrode 22 may be formed from a molded carbon fiber composite or it may consist of an inert non-conducting base material, such as polyester, upon which a suitable conducting layer is deposited. The conducting layer typically has relatively low electrical resistance and is typically electrochemically inert over the potential range of the sensor during operation. Suitable conducting layers include gold, carbon, platinum, ruthenium dioxide, palladium, and conductive epoxies, such as, for example, ECCOCOAT CT5079-3 Carbon-Filled Conductive Epoxy Coating (available from W.R. Grace Company, Woburn, Massachusetts), as well as other non-corroding materials known to those skilled in the art. The electrode (e.g., the conducting layer) is deposited on the surface of the inert material by methods such as vapor deposition or printing.

[0044] A tab 23 may be provided on the end of the working electrode 22 for easy connection of the electrode to external electronics (not shown) such as a voltage source or current measuring equipment. Other known methods or structures (such as contact pads) may be used to connect the working electrode 22 to the external electronics.

[0045] To prevent electrochemical reactions from occurring on portions of the working electrode not coated by the mediator, when a non-leachable mediator is used, a dielectric 40 may be deposited on the electrode over, under, or surrounding the region with the redox mediator, as shown in Figure 4. Suitable dielectric materials include waxes and non-conducting organic polymers such as polyethylene. Dielectric 40 may also cover a portion of the redox mediator on the electrode. The covered portion of the redox mediator will not contact the sample, and, therefore, will not be a part of the electrode's working surface.

Sensing Chemistry

[0046] In addition to the working electrode 22, sensing chemistry materials are provided in the sample chamber 26 for the analysis of the analyte. This sensing chemistry preferably includes a redox mediator and a second electron transfer mediator, although in some instances, one or the other may be used alone. The redox mediator and second electron transfer agent can be independently diffusible or non-leachable (i.e., non-diffusible) such that either or both may be diffusible or non-leachable. Placement of sensor chemistry components may depend on whether they are diffusible or non-leachable. For example, non-leachable and/or diffusible component(s) typically form a sensing layer on the working electrode.

Alternatively, one or more diffusible components may be disposed on any surface in the sample chamber prior to the

Abbott Ex. 1002 - 281/1438

introduction of the sample. As another example, one or more diffusible component(s) may be placed in the sample prior to introduction of the sample into the sensor.

[0047] If the redox mediator is non-leachable, then the non-leachable redox mediator is typically disposed on the working electrode 22 as a sensing layer 32. In an embodiment having a redox mediator and a second electron transfer agent, if the redox mediator and second electron transfer agent are both non-leachable, then both of the non-leachable components are disposed on the working electrode 22 as a sensing layer 32.

[0048] If, for example, the second electron transfer agent is diffusible and the redox mediator is non-leachable, then at least the redox mediator is disposed on the working electrode 22 as a sensing layer 32. The diffusible second electron transfer agent need not be disposed on a sensing layer of the working electrode, but may be disposed on any surface of the sample chamber, including within the redox mediator sensing layer, or may be placed in the sample. If the redox mediator is diffusible, then the redox mediator may be disposed on any surface of the sample chamber or may be placed in the sample.

[0049] If both the redox mediator and second electron transfer agent are diffusible, then the diffusible components may be independently or jointly disposed on any surface of the sample chamber and/or placed in the sample (i.e., each diffusible component need not be disposed on the same surface of the sample chamber or placed in the sample).

[0050] The redox mediator, whether it is diffusible or non-leachable, mediates a current between the working electrode 22 and the analyte and enables the electrochemical analysis of molecules which may not be suited for direct electrochemical reaction on an electrode. The mediator functions as an electron transfer agent between the electrode and the analyte.

[0051] In one embodiment, the redox mediator and second electron transfer agent are diffusible and disposed on the same surface of the sample chamber, such as, for example, on the working electrode. In this same vein, both can be disposed on, for example, the counter electrode, counter/reference electrode, reference electrode, or indicator electrode. In other instances, the redox mediator and second electron transfer agent are both diffusible and independently placed on a surface of the sample chamber and/or in the sample. For example, the redox mediator may be placed on the working electrode while the second electron transfer agent is placed on any surface, except for the working electrode, or is placed in the sample. Similarly, the reverse situation in which the second electron transfer agent is disposed on the working electrode and the redox mediator is disposed on any surface, except for the working electrode, or is placed in the sample is also a suitable embodiment. As another example, the redox mediator may be disposed on the counter electrode and the second electron transfer agent is placed on any surface except for the counter electrode or is placed in the sample. The reverse situation is also suitable.

[0052] The diffusible redox mediator and/or second electron transfer agent may diffuse rapidly into the sample or diffusion may occur over a period of time. Similarly, the diffusible redox mediator and/or second electron transfer agent may first dissolve from the surface on which it was placed as a solid and then the diffusible redox mediator and/or second electron transfer agent may diffuse into the sample, either rapidly or over a period of time. If the redox mediator and/or second electron transfer agent diffuse over a period of time, a user may be directed to wait a period of time before measuring the analyte concentration to allow for diffusion of the redox mediator and/or second electron transfer agent.

Background Signal

[0053] In at least some instances, a diffusible redox mediator may shuttle back and forth from the working electrode to the counter electrode even in the absence of analyte. This typically creates a background signal. For coulometric measurements, this background signal is referred to herein as "Q_{Back}." The background signal corresponds to the charge passed in an electrochemical assay in the absence of the analyte. The background signal typically has both a transient component and a steady-state component. At least a portion of the transient component may result, for example, from the establishment of a concentration gradient of the mediator in a particular oxidation state. At least a portion of the steady-state component may result, for example, from the redox mediator shuttling between the working electrode and counter or counter/reference electrode. Shuttling refers to the redox mediator being electrooxidized (or electroreduced) at the working electrode and then being electroreduced (or electrooxidized) at the counter or counter/reference electrode, thereby making the redox mediator available to be electrooxidized (or electroreduced) again at the working electrode so that the redox mediator is cycling between electrooxidation and electroreduction.

[0054] The amount of shuttling of the redox mediator, and therefore, the steady-state component of the background signal varies with, for example, the effective diffusion coefficient of the redox mediator, the viscosity of the sample, the temperature of the sample, the dimensions of the electrochemical cell, the distance between the working electrode and the counter or counter/reference electrode, and the angle between the working electrode and the counter or counter/reference electrode.

[0055] In some instances, the steady-state component of the background signal may contain noise associated with (a) variability in, for example, the temperature of the sample, the sample viscosity, or any other parameter on which

Abbott Ex. 1002 - 282/1438

the background signal depends during the duration of the assay, or (b) imperfections in the electrochemical cell, such as, for example, non-uniform separation between the working electrode and the counter or counter/reference electrode, variations in electrode geometry, or protrusions from the working electrode, the counter electrode, and/or the counter/reference electrode.

[0056] Although the steady-state component of the background signal may be reproducible, any noise inherently is not reproducible. As a result, the noise adversely affects accuracy. In some cases, the background signal and noise are related. As a result, the noise, and the error it introduces, can be reduced by reducing the background signal. For example, reducing the shuttling of the mediator between the working electrode and counter electrode or counter/reference electrode will likely reduce the noise associated with changes in sample temperature and viscosity which affect diffusion of the redox mediator.

[0057] Thus, to increase the accuracy of the measurements or to decrease error in the measurements in those instances when reducing a background signal also reduces noise, a moderate to near-zero level of background signal is desirable. In at least some instances, the sensor is constructed so that the background signal is at most five times the size of a signal generated by electrolysis of an amount of analyte. Preferably, the background signal is at most 200%, 100%, 50%, 25%, 10%, or 5% of the signal generated by electrolysis of the analyte. In the case of amperometry, this comparison may be made by determining the ratio of the current from the shuttling of the redox mediator to the current generated by the electrolysis of the analyte. In the case of potentiometry, this comparison may be made by determining the potential measurement from the shuttling of the redox mediator and the potential measurement generated by electrolysis of the analyte. In the case of coulometry, this comparison may be made by determining the charge transferred at the working electrode by the shuttling of the redox mediator and the charge transferred at the working electrode by the electrolysis of the analyte.

[0058] The size of the background signal may be compared to a predetermined amount of analyte. The predetermined amount of analyte in a sample may be, for example, an expected or average molar amount of analyte. The expected or average molar amount of analyte may be determined as, for example, the average value for users or individuals; an average value for a population; a maximum, minimum, or average of a normal physiological range; a maximum or minimum physiological value for a population; a maximum or minimum physiological value for users or individuals; an average, maximum, or minimum deviation outside a normal physiological range value for users, individuals, or a population; a deviation above or below an average value for a population; or an average, maximum, or minimum deviation above or below an average normal physiological value for users or individuals. A population may be defined by, for example, health, sex, or age, such as, for example, a normal adult, child, or newborn population. If a population is defined by health, the population may include people lacking a particular condition or alternatively, having a particular condition, such as, for example, diabetes. Reference intervals pertaining to average or expected values, such as, for example, those provided in Tietz Textbook of Clinical Chemistry, Appendix (pp. 2175-2217) (2nd Ed., Carl A. Burtis and Edward R. Ashwood, eds., W.D. Saunders Co., Philadelphia 1994) may be used as guidelines, but a physical examination or blood chemistry determination by a skilled physician may also be used to determine an average or expected value for an individual. For example, an adult may have glucose in a concentration of 65 to 95 mg/dL in whole blood or L-lactate in a concentration of 8.1 to 15.3 mg/dL in venous whole blood after fasting, according to Tietz Textbook of Clinical Chemistry. An average normal physiological concentration for an adult, for example, may then correspond to 80 mg/dL for glucose or 12.7 mg/dL for lactate. Other examples include a person having juvenile onset diabetes, yet good glycemic control, and a glucose concentration between about 50 mg/dL and 400 mg/dL, thereby having an average molar amount of 225 mg/dL. In another instance, a non-diabetic adult may have a glucose concentration between about 80 mg/dL (after fasting) and 140 mg/dL (after consuming food), thereby having an average molar amount of 110 mg/dL.

[0059] Additional analytes that may be determined include, for example, acetyl choline, amylase, bilirubin, cholesterol, chorionic gonadotropin, creatine kinase (e.g., CK-MB), creatine, DNA, fructosamine, glucose, glutamine, growth hormones, hormones, ketones, lactate, peroxide, prostate-specific antigen, prothrombin, RNA, thyroid stimulating hormone, and troponin. The concentration of drugs, such as, for example, antibiotics (e.g., gentamicin, vancomycin, and the like), digitoxin, digoxin, drugs of abuse, theophylline, and warfarin, may also be determined.

[0060] To construct a sensor having a particular ratio of background signal to analyte signal from electrolysis, several parameters relating to current and/or charge from the redox mediator shuttling background signal and/or from the signal generated by electrolysis of the analyte may be considered and chosen to obtain a desired ratio. Typically, the signal determined for a coulometric assay is the charge; whereas the signal determined for an amperometric assay is the current at the time when the measurement is taken. Because the current and charge depend on several parameters, the desired ratio for background signal generated by shuttling of the redox mediator to signal generated by electrolysis of the analyte may be accomplished by a variety of sensor configurations and methods for operating a sensor.

Abbott Ex. 1002 - 283/1438

Controlling Background Signal

[0061] One method of controlling background signal includes using a redox mediator that a) oxidizes the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no more than about +100 mV relative to the potential of a reference or counter/reference electrode or b) reduces the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no less than about -100 mV relative to the potential of a reference or counter/reference electrode. A suitable reference or counter/reference electrode (e.g., a silver/silver chloride electrode) may be chosen. Preferably, the redox mediator a) oxidizes the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no more than about +50 mV, +25 mV, 0 mV, - 25 mV, -50 mV, -100 mV, or -150 mV relative to the potential of the reference or counter/reference electrode or b) reduces the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no less than about -50 mV, -25 mV, 0 mV, +25 mV, +50 mV, +100 mV, +150 mV, or +200 mV relative to the potential of the reference or counter/reference electrode. Alternatively, in the case of reduction of the redox mediator by the counter electrode, the sensor is operated at an applied potential of no more than about +100 mV, +50 mV, +25 mV, 0 mV, -25 mV, -50 mV, -100 mV, or -150 mV between the working electrode and the counter or counter/reference electrode. In the case of oxidation of the redox mediator at the counter electrode, the sensor is operated at an applied potential of no less than about -100 mV, -50 mV, -25 mV, 0 mV, +25 mV, +50 mV, +100 mV, +150 mV, or +200 mV between the working electrode and the counter or counter/reference electrode.

[0062] Another method includes controlling the applied potential such that for an electrooxidative assay the redox mediator is not readily reduced at the counter or counter/reference electrode or for an electroreductive assay the redox mediator is not readily oxidized at the counter or counter/reference electrode. This can be accomplished, for example, in an electrooxidative assay by using a sensor having a diffusible redox mediator with a potential, relative to a reference or counter/reference electrode, that is negative with respect to the potential of the counter electrode (relative to a reference electrode) or the counter/reference electrode. The potential (relative to a reference or counter/reference electrode) of the working electrode is chosen to be positive with respect to the redox mediator and may be negative with respect to the counter or counter/reference electrode, so that the redox mediator is oxidized at the working electrode. For example, when the electrooxidation of an analyte is mediated by a diffusible redox mediator with a potential of -200 mV versus the reference or counter/reference electrode, and the potential at which the working electrode is poised is -150 mV relative to the reference or counter/reference electrode, then the redox mediator is substantially oxidized at the working electrode and will oxidize the analyte. Further, if some of the oxidized redox mediator reaches the counter or counter/reference electrode, the redox mediator will not be readily reduced at the counter or counter/reference electrode because the counter or counter/reference electrode is poised well positive (i.e., 150 mV) of the potential of the redox mediator.

[0063] In an electroreductive assay, a sensor is provided having a diffusible redox mediator with a formal potential, relative to a reference or counter/reference electrode, that is positive with respect to the potential of the counter or counter/reference electrode. The potential, relative to the reference or counter/reference electrode, of the working electrode is chosen to be negative with respect to the redox mediator and may be poised positive with respect to the counter or counter/reference electrode, so that the redox mediator is reduced at the working electrode.

[0064] Still another method of limiting background current includes having the redox mediator become immobilized when reacted on the counter electrode or counter/reference electrode by, for example, precipitation or polymerization. For example, the mediator may be cationic in the oxidized state, but neutral and much less soluble in the reduced state. Reduction at the counter/reference electrode leads to precipitation of the reduced, neutral mediator on the counter/reference electrode.

[0065] Another sensor configuration suitable for controlling background signal includes a sensor having a molar amount of redox mediator that is stoichiometrically the same as or less than an expected or average molar amount of analyte. The expected or average molar amount of analyte may be determined as already explained above. The expected or average molar amount of analyte may be determined as, for example, the average value for users or individuals; an average value for a population; a maximum, minimum, or average of a normal physiological range; a maximum or minimum physiological value for a population; a maximum or minimum physiological value for users or individuals; an average, maximum, or minimum deviation outside a normal physiological range value for users, individuals, or a population; a deviation above or below an average value for a population; or an average, maximum, or minimum deviation above or below an average normal physiological value for users or individuals. A population may be defined by, for example, health, sex, or age, such as, for example, a normal adult, child, or newborn population. If a population is defined by health, the population may include people lacking a particular condition or alternatively, having a particular condition, such as, for example, diabetes. Reference intervals pertaining to average or expected values, such as, for example, those provided in Tietz Textbook of Clinical Chemistry, *supra*, may be used as guidelines, but a physical examination or blood chemistry determination may also determine an average or expected value. For example, the physiological average molar amount of analyte may depend on the health or age of the person from whom the sample

Abbott Ex. 1002 - 284/1438

is obtained. This determination is within the knowledge of a skilled physician.

[0066] By reducing the concentration of the redox mediator relative to the concentration of the analyte, the signal attributable to the analyte relative to the signal attributable to the shuttling of the redox mediator is increased. In implementation of this method, the molar amount of redox mediator may be no more than 50%, 20%, 10%, or 5%, on a stoichiometric basis, of the expected or average molar amount of analyte.

[0067] The amount of redox mediator used in such a sensor configuration should fall within a range. The upper limit of the range may be determined based on, for example, the acceptable maximum signal due to shuttling of the redox mediator; the design of the electrochemical cell, including, for example, the dimensions of the cell and the position of the electrodes; the effective diffusion coefficient of the redox mediator; and the length of time needed for the assay. Moreover, the acceptable maximum signal due to redox mediator shuttling may vary from assay to assay as a result of one or more assay parameters, such as, for example, whether the assay is intended to be qualitative, semi-quantitative, or quantitative; whether small differences in analyte concentration serve as a basis to modify therapy; and the expected concentration of the analyte.

[0068] Although it is advantageous to minimize the amount of redox mediator used, the range for the acceptable amount of redox mediator does typically have a lower limit. The minimum amount of redox mediator that may be used is the concentration of redox mediator that is necessary to accomplish the assay within a desirable measurement time period, for example, no more than about 5 minutes or no more than about 1 minute. The time required to accomplish an assay depends on, for example, the distance between the working electrode and the counter or counter/reference electrode, the effective diffusion coefficient of the redox mediator, and the concentration of the analyte. In some instances, for example, when no kinetic limitations are present, i.e., shuttling of the redox mediator depends only on diffusion, the minimum concentration of redox mediator may be determined by the following formula:

$$C_m = (d^2 C_A) / D_m t$$

where C_m is the minimum concentration of mediator required; d is the distance between a working electrode and a counter or counter/reference electrode in a facing arrangement; C_A is the average analyte concentration in the sample; D_m is the effective diffusion coefficient of the mediator in the sample; and t is the desired measurement time.

[0069] For example, when the distance between the facing electrode pair is 50 μm, the analyte being measured is 5mM glucose, the redox mediator effective diffusion coefficient is 10^{-6} cm^2/sec and the desirable response time is no more than about 1 minute, then the minimum redox mediator concentration is 2.08mM. Under these conditions the background signal will be less than the signal from the electrooxidation of the analyte.

[0070] Yet another sensor configuration for limiting the background current generated by a diffusible redox mediator includes having a barrier to the flow of the diffusible mediator to the counter electrode. The barrier can be, for example, a film through which the redox mediator can not diffuse or through which the redox mediator diffuses slowly. Examples of suitable films include polycarbonate, polyvinyl alcohol, and regenerated cellulose or cellulose ester membranes. Alternatively, the barrier can include charged or polar particles, compounds, or functional groups to prevent or reduce the flow of a charged redox mediator relative to the flow of a charge neutral or less charged analyte. If the redox mediator is positively charged, as are many of the osmium redox mediators described below, the barrier can be a positively charged or polar film, such as a methylated poly(1-vinyl imidazole). If the redox mediator is negatively charged, the barrier can be a negatively charged or polar film, such as Nafion®. Examples of suitable polar matrices include a bipolar membrane, a membrane having a cationic polymer cross-linked with an anionic polymer, and the like. In some instances, the barrier reduces the oxidation or reduction of the diffusible redox mediator at the counter electrode by at least 25%, 50%, or 90%.

[0071] Still another sensor configuration for limiting the background current includes a sensor having a redox mediator that is more readily oxidized or reduced on the working electrode than reduced or oxidized on the counter electrode. The rate of reaction of the redox mediator at an electrode can be a function of the material of the electrode. For example, some redox mediators may react faster at a carbon electrode than at a Ag/AgCl electrode. Appropriate selection of the electrodes may provide a reaction rate at one electrode that is significantly slower than the rate at the other electrode. In some instances, the rate of oxidation or reduction of the diffusible redox mediator at the counter electrode is reduced by at least 25%, 50%, or 90%, as compared to the working electrode. In some instances the rate of reaction for the redox mediator at the counter or counter/reference electrode is controlled by, for example, choosing a material for the counter or counter/reference electrode that would require an overpotential or a potential higher than the applied potential to increase the reaction rate at the counter or counter/reference electrode.

[0072] Another sensor configuration for limiting background current includes elements suitable for reducing the diffusion of the redox mediator. Diffusion can be reduced by, for example, using a redox mediator with a relatively low diffusion coefficient or increasing the viscosity of the sample in the measurement zone. In another embodiment, the diffusion of the redox mediator may be decreased by choosing a redox mediator with high molecular weight, such as,

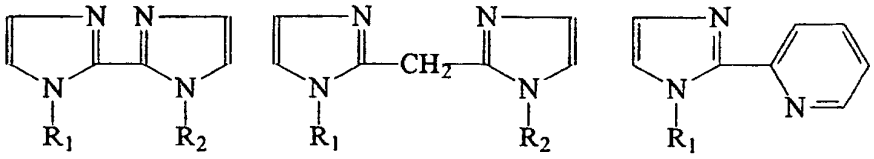
Abbott Ex. 1002 - 285/1438

for example, greater than 5,000 daltons, preferably greater than 25,000 daltons, and more preferably greater than 100,000 daltons.

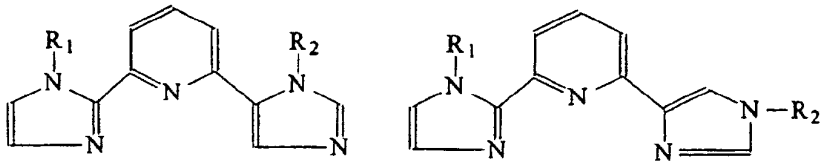
Redox Mediators

[0073] Although any organic or organometallic redox species can be used as a redox mediator, one type of suitable redox mediator is a transition metal compound or complex. Examples of suitable transition metal compounds or complexes include osmium, ruthenium, iron, and cobalt compounds or complexes. In these complexes, the transition metal is coordinatively bound to one or more ligands. The ligands are typically mono-, di-, tri-, or tetradentate. The most preferred ligands are heterocyclic nitrogen compounds, such as, for example, pyridine and/or imidazole derivatives. Multidentate ligands may include multiple pyridine and/or imidazole rings. Alternatively, metallocene derivatives, such as, for example, ferrocene, can be used.

[0074] Suitable redox mediators include osmium or ruthenium transition metal complexes with one or more ligands, each ligand having one or more nitrogen-containing heterocycles. Examples of such ligands include pyridine and imidazole rings and ligands having two or more pyridine and/or imidazole rings such as, for example, 2,2'-bipyridine; 2,2':6',2"-terpyridine; 1,10-phenanthroline; and ligands having the following structures:



(I) (II) (III)



(IV) (V)

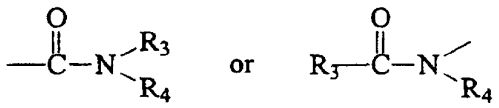
and derivatives thereof, wherein R_1 and R_2 are each independently hydrogen, hydroxy, alkyl, alkoxy, alkenyl, vinyl, allyl, amido, amino, vinylketone, keto, or sulfur-containing groups.

[0075] The term "alkyl" includes a straight or branched saturated aliphatic hydrocarbon chain having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl isopropyl (1-methylethyl), butyl, *tert*-butyl (1,1-dimethylethyl), and the like. Preferably the hydrocarbon chain has from 1 to 3 carbon atoms.

[0076] The term "alkoxy" includes an alkyl as defined above joined to the remainder of the structure by an oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy (1-methylethoxy), butoxy, *tert*-butoxy, and the like.

[0077] The term "alkenyl" includes an unsaturated aliphatic hydrocarbon chain having from 2 to 6 carbon atoms, such as, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-methy-1-propenyl, and the like. Preferably the hydrocarbon chain has from 2 to 3 carbon atoms.

[0078] The term "amido" includes groups having a nitrogen atom bonded to the carbon atom of a carbonyl group and includes groups having the following formulas:



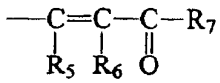
wherein R_3 and R_4 are each independently hydrogen, alkyl, alkoxy, or alkenyl.

[0079] The term "amino" as used herein includes alkylamino, such as methylamino, diethylamino, N,N-methylethyl-

Abbott Ex. 1002 - 286/1438

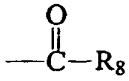
amino and the like; alkoxyalkylamino, such as N-(ethoxyethyl)amino, N,N-di(methoxyethyl)amino, N,N-(methoxyethyl) (ethoxyethyl)amino, and the like; and nitrogen-containing rings, such as piperidino, piperazino, morpholino, and the like.

[0080] The term "vinylketone" includes a group having the formula:



wherein R_5, R_6, and R_7 are each independently hydrogen, alkyl, alkoxy, or alkenyl.

[0081] The term "keto" includes a group having the formula:

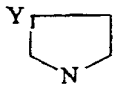


wherein R_8 is hydrogen, alkyl, alkoxy, or alkenyl.

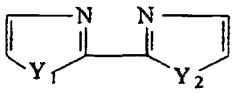
[0082] The term "sulfur-containing group" includes mercapto, alkylmercapto (such as methylmercapto, ethylmercapto, and the like), alkoxyalkylmercapto (such as methoxyethylmercapto and the like), alkylsulfoxide (such as methylsulfoxide and propylsulfoxide and the like), alkoxyalkylsulfoxide (such as ethoxyethylsulfoxide and the like), alkylsulfone (such as methylsulfone and propylsulfone and the like), and alkoxyalkylsulfone (such as methoxyethylsulfone and the like). Preferably, the sulfur-containing group is a mercapto group.

[0083] Other suitable redox mediators include osmium or ruthenium transition metal complexes with one or more ligands, each ligand having one or more nitrogen-containing heterocycles and each nitrogen-containing heterocycle having a second heteroatom selected from the group consisting of nitrogen, oxygen, sulfur, and selenium.

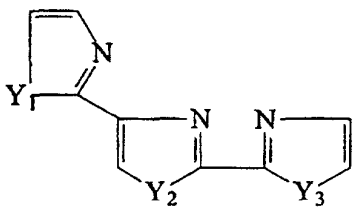
[0084] Examples of ligands having one or more nitrogen-containing heterocycles and in which each heterocycle has a second heteroatom include ligands having the following structures:



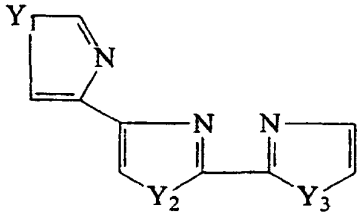
(VI)



(VII)

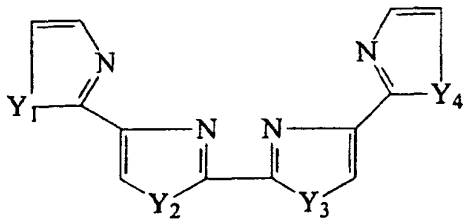


(VIII)

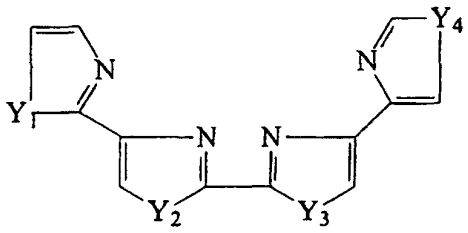


(IX)

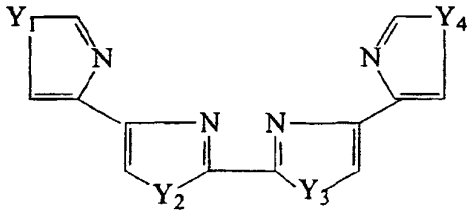
Abbott Ex. 1002 - 287/1438



(X)



(XI)



(XII)

wherein Y_1, Y_2, Y_3, and Y_4 are each independently an oxygen atom, a sulfur atom, a selenium atom, or a substituted nitrogen atom having the formula NR_9 wherein R_9 is hydrogen, hydroxy, alkyl, alkoxy, alkenyl, amido, amino, vinylketone, keto, or sulfur-containing group. The terms "alkyl," "alkoxy," "alkenyl," "amido," "amino," "vinylketone," "keto," and "sulfur-containing group" are as defined above.

[0085] Suitable derivatives of these ligands include, for example, the addition of alkyl, alkoxy, alkenyl, vinylester, and amido functional groups to any of the available sites on the heterocyclic ring, including, for example, on the 4-position (i.e., para to nitrogen) of the pyridine rings or on one of the nitrogen atoms of the imidazole ring.

[0086] Suitable derivatives of 2,2'-bipyridine for complexation with the osmium cation include, for example, mono-, di-, and polyalkyl-2,2'-bipyridines, such as 4,4'-dimethyl-2,2'-bipyridine; mono-, di-, and polyalkoxy-2,2'-bipyridines, such as 4,4'-dimethoxy-2,2'-bipyridine and 2,6'-dimethoxy-2,2'-bipyridine; mono-, di-, and polyacetamido-2,2'-bipyridines, such as 4,4'-di(acetamido)-2,2'-bipyridine; mono-, di-, and polyalkylaminoalkoxy-2,2'-bipyridines, such as 4,4'-di(N,N-dimethylaminoethoxy)-2,2'-bipyridine; and substituted mono-, di-, and polypyrazolyl-2,2'-bipyridines, such as 4,4'-dimethoxy-6-(N-pyrazolyl)-2,2'-bipyridine and 4,4'-dimethoxy-6-(N-pyrazolylmethyl)-2,2'-bipyridine.

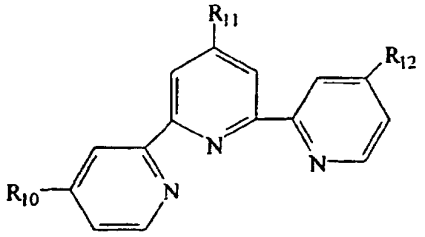
[0087] Suitable derivatives of 1,10-phenanthroline for complexation with the osmium cation include, for example, mono-, di-, and polyalkyl-1,10-phenanthrolines, such as 4,7-dimethyl-1,10-phenanthroline, and mono, di-, and polyalkoxy-1,10-phenanthrolines, such as 4,7-dimethoxy-1,10-phenanthroline and 5-methoxy-1,10-phenanthroline.

[0088] Suitable derivatives for 2,2':6',2"-terpyridine include, for example, mono-, di-, tri-, and polyalkyl-2,2':6',2"-terpyridines, such as 4,4',4"-trimethyl-2,2':6',2"-terpyridine, 4,4',4"-triethyl-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyalkoxy-2,2':6',2"-terpyridines, such as 4,4',4"-trimethoxy-2,2':6',2"-terpyridine and 4'-methoxy-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyamino-2,2':6',2"-terpyridine, such as 4'-amino-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyalkylamino-2,2':6',2"-terpyridine, such as 4'-dimethylamino-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyalkylthio-2,2':6',2"-terpyridine such as 4'-methylthio-2,2':6',2"-terpyridine and 4-methylthio-4'-ethylthio-2,2':6',2"-terpyridine.

[0089] Suitable derivatives for pyridine include, for example, mono-, di-, tri-, and polysubstituted pyridines, such as 2,6-bis(N-pyrazolyl)pyridine, 2,6-bis(3-methyl-N-pyrazolyl)pyridine, 2,6-bis(2-imidazolyl)pyridine, 2,6-bis(1-methyl-2-imidazolyl)pyridine, and 2,6-bis(1-vinyl-2-imidazolyl)pyridine, and mono-, di-, tri-, and polyaminopyridines, such as 4-aminopyridine, 4,4'-diaminobipyridine, 4,4'-di(dimethylamino)bipyridine, and 4,4',4"-triamino terpyridine.

[0090] Other suitable derivatives include compounds comprising three heterocyclic rings. For example, one suitable derivative includes a compound of the formula:

Abbott Ex. 1002 - 288/1438

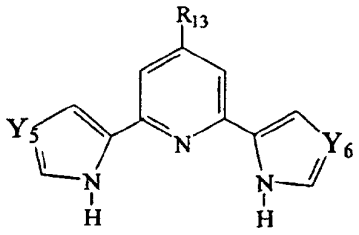


(XIII)

wherein R_{10}, R_{11}, and R_{12} are each independently hydrogen, hydroxy, alkyl, alkoxy, alkenyl, vinyl, allyl, amido, amino, vinylketone, keto, or sulfur-containing group.

[0091] The terms "alkyl," "alkoxy," "alkenyl," "amido," "amino," "vinylketone," "keto," and "sulfur-containing group" are as defined above.

[0092] Other suitable redox mediator derivatives include compounds of the formula:

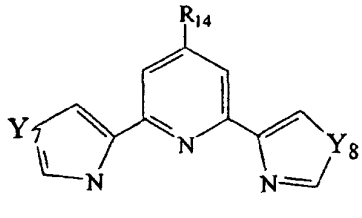


(XIV)

wherein R_{13} is hydrogen, hydroxy, alkyl, alkoxy, alkenyl, vinyl, allyl, vinylketone, keto, amido, amino, or sulfur-containing group; and Y_5 and Y_6 are each independently a nitrogen or carbon atom.

[0093] The terms "alkyl," "alkoxy," "alkenyl," "amido," "amino," "vinylketone," "keto," and "sulfur-containing group" are as defined above.

[0094] Still other suitable derivatives include compounds of the formula:



(XV)

wherein R_{14} is as defined above and Y_7 and Y_8 are each independently a sulfur or oxygen atom.

[0095] Examples of suitable redox mediators also include, for example, osmium cations complexed with (a) two bidentate ligands, such as 2,2'-bipyridine, 1,10-phenanthroline, or derivatives thereof (the two ligands not necessarily being the same), (b) one tridentate ligand, such as 2,2',2"-terpyridine and 2,6-di(imidazol-2-yl)-pyridine, or (c) one bidentate ligand and one tridentate ligand. Suitable osmium transition metal complexes include, for example, $[(bpy)_2OsLX]^{+/2+}$, $[(dimet)_2OsLX]^{+/2+}$, $[(dmo)_2OsLX]^{+/2+}$, $[terOsLX_2]^{0/+}$, $[trimetOsLX_2]^{0/+}$, and $[(ter)(bpy)LOs]^{2+/3+}$ where bpy is 2,2'-bipyridine, dimet is 4,4'-dimethyl-2,2'-bipyridine, dmo is 4,4'-dimethoxy-2,2'-bipyridine, ter is 2,2':6', 2"-terpyridine, trimet is 4,4',4"-trimethyl-2,2':6',2"-terpyridine, L is a nitrogen-containing heterocyclic ligand, and X is a halogen, such as fluorine, chlorine, or bromine.

[0096] The redox mediators often exchange electrons rapidly with each other and with the electrode so that the complex can be rapidly oxidized and/or reduced. In general, iron complexes are more oxidizing than ruthenium complexes, which, in turn, are more oxidizing than osmium complexes. In addition, the redox potential generally increases with the number of coordinating heterocyclic rings; six-membered heterocyclic rings increase the potential more than five membered rings, except when the nitrogen coordinating the metal is formally an anion. This is the case only if the nitrogen in the ring is bound to both of its neighboring carbon atoms by single bonds. If the nitrogen is formally an anion

Abbott Ex. 1002 - 289/1438

then the redox potential generally increases more upon coordination of the metal ion.

[0097] At least some diffusible redox mediators include one or more pyridine or imidazole functional groups. The imidazole functional group can also include other substituents and can be, for example, vinyl imidazole, e.g., 1-vinyl imidazole, or methylimidazole, e.g., 1-methylimidazole. Examples of suitable diffusible mediators may include $[Os(dmo)_2(1\text{-vinyl imidazole})X]X$, $[Os(dmo)_2(1\text{-vinyl imidazole})X]X_2$, $[Os(dmo)_2(imidazole)X]X$, $[Os(dmo)_2(imidazole)X]X_2$, $[Os(dmo)_2(1\text{-methylimidazole})X]X_2$, and $[Os(dmo)_2(methylimidazole)X]X_2$, where dmo is 4,4'-dimethoxy-2,2'-bipyridine, and X is halogen as described above.

[0098] Other osmium-containing redox mediators include $[Os((methoxy)_2phenanthroline)_2(N\text{-methylimidazole})X]^{+/2+}$; $[Os((acetamido)_2bipyridine)_2(L)X]^{+/2+}$, where L is a monodentate nitrogen-containing compound (including, but not limited to, an imidazole derivative) chosen to refine the potential; and $Os(terpyridine)(L)_2Cl$, where L is an aminopyridine, such as a dialkylaminopyridine; an N-substituted imidazole, such as N-methyl imidazole; an oxazole; a thiazole; or an alkoxypyridine, such as methoxypyridine. X is halogen as described above.

[0099] Osmium-free diffusible redox mediators include, for example, phenoxazines, such as, 7-dimethylamino-1,2-benzophenoxazine (Meldola Blue), 1,2-benzophenoxazine, and Nile Blue; 3-β-naphthoyl (Brilliant Cresyl Blue); tetramethylphenylenediamine (TMPD); dichlorophenolindophenol (DCIP); N-methyl phenazonium salts, for example, phenazine methosulfate (PMS), N-methylphenazine methosulfate and methoxyphenazine methosulfate; tetrazolium salts, for example, tetrazolium blue or nitrotetrazolium blue; and phenothiazines, for example, toluidine blue O.

[0100] Examples of other redox species include stable quinones and species that in their oxidized state have quinoid structures, such as Nile Blue and indophenol. Examples of suitable quinones include, for example, derivatives of naphthoquinone, phenoquinone, benzoquinone, naphthenequinone, and the like. Examples of naphthoquinone derivatives include juglone (i.e., 5-hydroxy-1,4-naphthoquinone) and derivatives thereof, such as, for example, 2,3-dichloro-5,8-dihydroxy-1,4-naphthoquinone, 2,3-dimethyl-5,8-dihydroxy-1,4-naphthoquinone, 2-chloro-5,8-dihydroxy-1,4-naphthoquinone, 2,3-methoxy-5-hydroxy-1,4-naphthoquinone, and the like. Other examples include aminonaphthoquinones, such as, for example, morpholino-naphthoquinones, such as 2-chloro-3-morpholino-1,4-naphthoquinone; piperidino-naphthoquinones, such as 2-methyl-3-peperidino-1,4-naphthoquinone; piperazino-naphthoquinones, such as 2-ethoxy-3-piperazino-1,4-naphthoquinone; and the like.

[0101] Suitable phenoquinone derivatives include, for example, coerulignone (i.e., 3,3',5,5'-tetramethoxydiphenoquinone) and derivatives thereof, such as, for example, 3,3',5,5'-tetramethyldiphenoquinone, 3,3',5,5'-tetrahydroxydiphenoquinone, and the like.

[0102] Suitable benzoquinone derivatives include, for example, coenzyme Q_0 (i.e., 2,3-dimethoxy-5-methyl-1,4-benzoquinone) and derivatives thereof, such as, for example, 2,3,5-trimethyl-1,4-benzoquinone, 2,3-dimethyl-5-methoxy-1,4-benzoquinone, 2,3-dimethyl-5-hydroxy-1,4-benzoquinone, and the like.

[0103] Other suitable quinone derivatives include, for example, acenaphthenequinone and ubiquinones, such as, for example, coenzyme Q, including Q_1, Q_2, Q_6, Q_7, Q_9, and Q_{10}.

[0104] Still other suitable osmium-free diffusible redox mediators include, for example, Taylor's blue (i.e., 1,9-dimethylmethylene blue), N,N'-diethylthiacyanine iodide, and thionine.

[0105] In another method, a sensing layer 32 contains a non-leachable (i.e., non-releasable) redox mediator and is disposed on a portion of the working electrode 22. The non-leachable redox mediator can be, for example, a redox polymer (i.e., a polymer having one or more redox species). Preferably, there is little or no leaching of the non-leachable redox mediator away from the working electrode 22 into the sample during the measurement period, which is typically less than about 5 minutes. The redox mediators of this embodiment can be bound or otherwise immobilized on the working electrode 22 to prevent leaching of the mediator into the sample. The redox mediator can be bound or otherwise immobilized on the working electrode by known methods, for example, formation of multiple ion bridges with a countercharged polyelectrolyte, covalent attachment of the redox mediator to a polymer on the working electrode, entrapment of the redox mediator in a matrix that has a high affinity for the redox mediator, or bioconjugation of the redox mediator with a compound bound to the working electrode. In one embodiment, a cationic exchange membrane may be used to entrap an anionic redox compound. Similarly, in another embodiment, an anionic exchange membrane may be used to entrap a cationic redox compound. In still another embodiment involving bioconjugation, a biotin-bound redox mediator can conjugate with avidin or straptavidin in a matrix near or immobilized on the working electrode. Still another embodiment includes having a digoxin or digoxigenin redox mediator react with antidigoxin in a matrix near or immobilized on a working electrode.

[0106] Preferred non-leachable redox mediators are redox polymers, such as polymeric transition metal compounds or complexes. Typically, the polymers used to form a redox polymer have nitrogen-containing heterocycles, such as pyridine, imidazole, or derivatives thereof for binding as ligands to the redox species. Suitable polymers for complexation with redox species, such as the transition metal complexes, described above, include, for example, polymers and copolymers of poly(1-vinyl imidazole) (referred to as "PVI") and poly(4-vinyl pyridine) (referred to as "PVP"), as well as polymers and copolymers ofpoly(acrylic acid) or polyacrylamide that have been modified by the addition of pendant nitrogen-containing heterocycles, such as pyridine and imidazole. Modification of poly(acrylic acid) may be

Abbott Ex. 1002 - 290/1438

performed by reaction of at least a portion of the carboxylic acid functionalities with an aminoalkylpyridine or aminoalkylimidazole, such as 4-ethylaminopyridine, to form amides. Suitable copolymer substituents of PVI, PVP, and poly (acrylic acid) include acrylonitrile, acrylamide, acrylhydrazide, and substituted or quatemized 1-vinyl imidazole. The copolymers can be random or block copolymers.

[0107] The transition metal complexes of non-leachable redox polymers are typically covalently or coordinatively bound with the nitrogen-containing heterocycles (e.g., imidazole and/or pyridine rings) of the polymer. The transition metal complexes may have vinyl functional groups through which the complexes can be co-polymerized. Suitable vinyl functional groups include, for example, vinylic heterocycles, amides, nitriles, carboxylic acids, sulfonic acids, or other polar vinylic compounds. An example of a redox polymer of this type is poly(vinyl ferrocene) or a derivative of poly (vinyl ferrocene) functionalized to increase swelling of the redox polymer in water.

[0108] Another type of redox polymer contains an ionically-bound redox species, by forming multiple ion-bridges. Typically, this type of mediator includes a charged polymer coupled to an oppositely charged redox species. Examples of this type of redox polymer include a negatively charged polymer such as Nafion® (DuPont) coupled to multiple positively charged redox species such as an osmium or ruthenium polypyridyl cation. Another example of an ionically-bound mediator is a positively charged polymer such as quaternized poly(4-vinyl pyridine) or poly(1-vinyl imidazole) coupled to a negatively charged redox species such as ferricyanide or ferrocyanide. The preferred ionically-bound redox species is a multiply charged, often polyanionic, redox species bound within an oppositely charged polymer.

[0109] Another suitable redox polymer includes a redox species coordinatively bound to a polymer. For example, the mediator may be formed by coordination of an osmium, ruthenium, or cobalt 2, 2'-bipyridyl complex to poly(1-vinyl imidazole) or poly(4-vinyl pyridine) or by co-polymerization of, for example, a 4-vinyl-2,2'-bipyridyl osmium, ruthenium, or cobalt complex with 1-vinyl imidazole or 4-vinyl pyridine.

[0110] Typically, the ratio of osmium or ruthenium transition metal complexes to imidazole and/or pyridine groups of the non-leachable redox polymers ranges from 1:20 to 1:1, preferably from 1:15 to 1:2, and more preferably from 1: 10 to 1:4. Generally, the redox potentials depend, at least in part, on the polymer with the order of redox potentials being poly(acrylic acid) < PVI < PVP.

[0111] A variety of methods may be used to immobilize a redox polymer on an electrode surface. One method is adsorptive immobilization. This method is particularly useful for redox polymers with relatively high molecular weights. The molecular weight of a polymer may be increased, for example, by cross-linking. The polymer of the redox polymer may contain functional groups, such as, for example, hydrazide, amine, alcohol, heterocyclic nitrogen, vinyl, allyl, and carboxylic acid groups, that can be crosslinked using a crosslinking agent. These functional groups may be provided on the polymer or one or more of the copolymers. Alternatively or additionally, the functional groups may be added by a reaction, such as, for example, quaternization. One example is the quaternization of PVP with bromoethylamine groups.

[0112] Suitable cross-linking agents include, for example, molecules having two or more epoxide (e.g., poly(ethylene glycol) diglycidyl ether (PEGDGE)), aldehyde, aziridine, alkyl halide, and azide functional groups or combinations thereof. When a polymer has multiple acrylate functions, it can be crosslinked with a di- or polythiol; when it has multiple thiol functions it can be crosslinked with a di- or polyacrylate. Other examples of cross-linking agents include compounds that activate carboxylic acid or other acid functional groups for condensation with amines or other nitrogen compounds. These cross-linking agents include carbodiimides or compounds with active N-hydroxysuccinimide or imidate functional groups. Yet other examples of cross-linking agents are quinones (e.g., tetrachlorobenzoquinone and tetracyanoquinodimethane) and cyanuric chloride. Other cross-linking agents may also be used. In some embodiments, an additional cross-linking agent is not required. Further discussion and examples of cross-linking and cross-linking agents are found in U.S. Patents Nos. 5,262,035; 5,262,305; 5,320,725; 5,264,104; 5,264,105; 5,356,786; and 5,593,852.

[0113] In another embodiment, the redox polymer is immobilized by the functionalization of the electrode surface and then the chemical bonding, often covalently, of the redox polymer to the functional groups on the electrode surface. One example of this type of immobilization begins with a poly(4-vinyl pyridine). The polymer's pyridine rings are, in part, complexed with a reducible/oxidizable species, such as $[Os(bpy)_2Cl]^{+/2+}$ where bpy is 2,2'-bipyridine. Part of the pyridine rings are quatemized by reaction with 2-bromoethylamine. The polymer is then crosslinked, for example, using a diepoxide, such as poly(ethylene glycol) diglycidyl ether.

[0114] Carbon surfaces can be modified for attachment of a redox polymer, for example, by electroreduction of a diazonium salt. As an illustration, reduction of a diazonium salt formed upon diazotization of p-aminobenzoic acid modifies a carbon surface with phenylcarboxylic acid functional groups. These functional groups can be activated by a carbodiimide, such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC). The activated functional groups are bound with an amine-functionalized redox couple, such as, for example, the quatemized osmium-containing redox polymer described above or 2-aminoethylferrocene, to form the redox couple.

[0115] Similarly, gold and other metal surfaces can be functionalized by, for example, an amine, such as cystamine, or by a carboxylic acid, such as thioctic acid. A redox couple, such as, for example, $[Os(bpy)_2$(pyridine-4-carboxylate) $Cl]^{0/+}$, is activated by 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) to form a reactive O-acyl-

Abbott Ex. 1002 - 291/1438

isourea which reacts with the gold-bound amine to form an amide. The carboxylic acid functional group of thioctic acid can be activated with EDC to bind a polymer or protein amine to form an amide.

[0116] When the enzyme used is PQQ glucose dehydrogenase or glucose oxidase, the preferred non-leachable redox mediators have a redox potential between about -300 mV to about +400 mV versus the standard calomel electrode (SCE). The most preferred non-leachable redox mediators have osmium redox centers and a redox potential more negative than +100 mV versus SCE, more preferably the redox potential is more negative than 0 mV versus SCE, and most preferably is near -150 mV versus SCE.

[0117] In at least some instances, the redox mediators of the sensors are air-oxidizable. This means that the redox mediator is oxidized by air, preferably, so that at least 90% of the mediator is in an oxidized state prior to introduction of sample into the sensor. Air-oxidizable redox mediators include osmium cations complexed with two mono-, di-, or polyalkoxy-2,2'-bipyridine or mono-, di-, or polyalkoxy-1,10-phenanthroline ligands, the two ligands not necessarily being the same, and further complexed with polymers or other ligands having pyridine and imidazole functional groups. In particular, $Os[4,4'\text{-dimethoxy-}2,2'\text{-bipyridine}]_2Cl^{+/+2}$ complexed with poly(4-vinyl pyridine) or poly(1-vinyl imidazole) attains approximately 90% or more oxidation in air. The air oxidation of the redox mediator may take place while the redox mediator is a solid, such as, for example, when it is coated on the sensor in a dry state and stored. Alternatively, the air oxidation of the redox mediator may take place while the redox mediator is in solution, such as, for example, prior to the solution being applied onto the sensor and dried. In the case in which the redox mediator is air oxidized in solution, the solution containing the redox mediator may be kept in storage for a period of time sufficient to air oxidize the mediator prior to use of the solution in the manufacturing process.

Second Electron Transfer Agent

[0118] In a preferred embodiment of the invention, the sensor includes a redox mediator and a second electron transfer agent which is capable of transferring electrons to or from the redox mediator and the analyte. The second electron transfer agent may be diffusible or may be non-leachable (e.g., entrapped in or coordinatively, covalently, or ionically bound to the redox polymer). One example of a suitable second electron transfer agent is an enzyme which catalyzes a reaction of the analyte. For example, a glucose oxidase or glucose dehydrogenase, such as pyrroloquinoline quinone glucose dehydrogenase (PQQ), is used when the analyte is glucose. A lactate oxidase fills this role when the analyte is lactate. Other enzymes can be used for other analytes. These enzymes catalyze the electrolysis of an analyte by transferring electrons between the analyte and the electrode via the redox mediator. In some embodiments, the second electron transfer agent is non-leachable, and more preferably immobilized on the working electrode, to prevent unwanted leaching of the agent into the sample. This is accomplished, for example, by cross-linking the non-leachable second electron transfer agent with the non-leachable redox mediator, thereby providing a sensing layer with non-leachable components on the working electrode. In other embodiments, the second electron transfer agent is diffusible (and may be disposed on any surface of the sample chamber or placed in the sample).

Counter Electrode

[0119] Counter electrode 24, as illustrated in Figures 1-4, may be constructed in a manner similar to working electrode 22. Counter electrode 24 may also be a counter/reference electrode. Alternatively, a separate reference electrode may be provided in contact with the sample chamber. Suitable materials for the counter/reference or reference electrode include Ag/AgCl or Ag/AgBr printed on a non-conducting base material or silver chloride on a silver metal base. The same materials and methods may be used to make the counter electrode as are available for constructing the working electrode 22, although different materials and methods may also be used. A tab 25 may be provided on the electrode for convenient connection to the external electronics (not shown), such as a coulometer, potentiostat, or other measuring device.

Electrode Configuration

[0120] In one embodiment of the invention, working electrode 22 and counter electrode 24 are disposed opposite to and facing each other to form a facing electrode pair as depicted in Figures 1 and 3. In this preferred configuration, the sample chamber 26 is typically disposed between the two electrodes. For this facing electrode configuration, it is preferred that the electrodes are separated by a distance of no more than about 0.2 mm (i.e., at least one portion of the working electrode is separated from one portion of the counter electrode by no more than 200 μm), preferably no more than 100 μm, and most preferably no more than 50 μm.

[0121] The electrodes need not be directly opposing each other; they may be slightly offset. Furthermore, the two electrodes need not be the same size. Preferably, the counter electrode 24 is at least as large as the working surface of the working electrode 22. The counter electrode 22 can also be formed with tines in a comb shape. Other configu-

Abbott Ex. 1002 - 292/1438

rations of both the counter electrode and working electrode are within the scope of the invention. However, for this particular embodiment, the separation distance between at least one portion of the working electrode and some portion of the counter electrode preferably does not exceed the limits specified hereinabove.

[0122] Figures 11A, 11B, and 11C illustrate different embodiments of pairs of facing electrodes 22, 24, as described above. A region 21 of overlap between the two electrodes 22, 24 typically corresponds to the measurement zone in which the sample will be interrogated. Each of the electrodes 22, 24 is a conducting surface and acts as a plate of a capacitor. The measurement zone between the electrodes 22, 24 acts as a dielectric layer between the plates. Thus, there is a capacitance between the two electrodes 22, 24. This capacitance is a function of the size of the overlapping electrodes 22, 24, the separation between the electrodes 22, 24, and the dielectric constant of the material between the electrodes 22, 24. Thus, if the size of the region 21 of the overlapping electrodes 22, 24 and the dielectric constant of the material between the electrodes (e.g., air or a sorbent material) are known, then the separation between the electrodes can be calculated to determine the volume of the measurement zone.

[0123] Figure 11A illustrates one embodiment of the invention in which the electrodes 22, 24 are positioned in a facing arrangement. For the capacitance to be uniform among similarly constructed analyte sensors having this particular sensor configuration, the registration (i.e., the positioning of the two electrodes relative to one another) should be uniform. If the position of either of the electrodes is shifted in the x-y plane from the position shown in Figure 11A, the size of the overlap, and therefore, of the capacitance, will change. The same principle holds for the volume of the measurement zone.

[0124] Figures 11B and 11C illustrate other embodiments of the invention with electrodes 22, 24 in a facing arrangement. In these particular arrangements, the position of either of the electrodes may be shifted, by at least some minimum distance, in the x-y plane relative to the other electrode without a change in the capacitance or the volume of the measurement zone. In these electrode arrangements, each electrode 22, 24 includes an arm 122, 124, respectively, which overlaps with the corresponding arm of the other electrode. The two arms 122, 124 are not parallel to each other (such as illustrated in Figure 11A); rather, the arms 122, 124 are disposed at an angle 123, which is greater than zero, relative to each other. In addition, the two arms 122, 124 extend beyond the region 21 of overlap (i.e., each arm has extra length corresponding to the difference between the length of the arm 222, 224, respectively, and the width 121 of the overlap 21). With these electrode arrangements, there can be a certain amount of allowed imprecision in the registration of the electrodes 22, 24 which does not change the capacitance of the electrode arrangement. A desired amount of allowed imprecision in the registration can be designed into the electrode arrangement by varying the angle 123 at which the arms 122, 124 overlap and the size of the extra length of each arm 122, 124 relative to the width 121 of the region 21 of overlap. Typically, the closer that the arms 122, 124 are to being perpendicular (i.e., angle 123 is 90°), the greater the allowed imprecision. Also, the greater the extra length of each arm 122, 124 (which may both be the same length or different lengths) relative to the width 121 of the region 21 of overlap, the greater the allowed imprecision. Conversely, the greater the amount of allowed imprecision, the larger the size of the electrodes (for a given electrode width, thickness, and angle 123 of intersection with the other electrode). Thus, the minimum distance that one electrode can be shifted relative to the other is balanced against the amount of material needed for the electrodes. Typically, the angle 123 of intersection ranges from 5 to 90 degrees, preferably, 30 to 90 degrees, and more preferably 60 to 90 degrees. Typically, the ratio of the extra length of an arm 122, 124 (corresponding to the difference between the arm length 222, 224 and the width 121 of the region 21 of overlap) versus the width 121 of the region 21 of overlap ranges from 0.1:1 to 50:1, preferably 1:1 to 15:1, and more preferably 4:1 to 10:1.

[0125] In another embodiment of the invention, the two electrodes 22, 24 are coplanar as shown in Figure 2. In this case, the sample chamber 26 is in contact with both electrodes and is bounded on the side opposite the electrodes by a non-conducting inert base 30. Suitable materials for the inert base include non-conducting materials such as polyester.

[0126] Other configurations of the inventive sensors are also possible. For example, the two electrodes may be formed on surfaces that make an angle to each other. One such configuration would have the electrodes on surfaces that form a right angle. Another possible configuration has the electrodes on a curved surface such as the interior of a tube. The working and counter electrodes may be arranged so that they face each other from opposite sides of the tube. This is another example of a facing electrode pair. Alternatively, the electrodes may be placed near each other on the tube wall (e.g., one on top of the other or side-by-side).

[0127] In any configuration, the two electrodes must be configured so that they do not make direct electrical contact with each other, to prevent shorting of the electrochemical sensor. This may be difficult to avoid when the facing electrodes are separated, over the average, by no more than about 100μm.

[0128] A spacer 28 can be used to keep the electrodes apart when the electrodes face each other as depicted in Figures 1 and 3. The spacer is typically constructed from an inert non-conducting material such as pressure-sensitive adhesive, polyester, Mylar™, Kevlar™ or any other strong, thin polymer film, or, alternatively, a thin polymer film such as a Teflon™ film, chosen for its chemical inertness. In addition to preventing contact between the electrodes, the spacer 28 often functions as a portion of the boundary for the sample chamber 26 as shown in Figures 1- 4. Other

Abbott Ex. 1002 - 293/1438

spacers include layers of adhesive and double-sided adhesive tape (e.g., a carrier film with adhesive on opposing sides of the film).

Sample Chamber

[0129] The sample chamber 26 is typically defined by a combination of the electrodes 22, 24, an inert base 30, and a spacer 28 as shown in Figures 1-4. A measurement zone is contained within this sample chamber and is the region of the sample chamber that contains only that portion of the sample that is interrogated during the analyte assay. In the embodiment of the invention illustrated in Figures 1 and 2, sample chamber 26 is the space between the two electrodes 22, 24 and/or the inert base 30. In this embodiment, the sample chamber has a volume that is preferably no more than about 1 μL, more preferably no more than about 0.5 μL, and most preferably no more than about 0.25 μL. In the embodiment of the invention depicted in Figures 1 and 2, the measurement zone has a volume that is approximately equal to the volume of the sample chamber. In a preferred embodiment the measurement zone includes 80% of the sample chamber, 90% in a more preferred embodiment, and about 100% in a most preferred embodiment.

[0130] In another embodiment of the invention, shown in Figure 3, sample chamber 26 includes much more space than the region proximate electrodes 22, 24. This configuration makes it possible to provide multiple electrodes in contact with one or more sample chambers, as shown in Figure 5. In this embodiment, sample chamber 26 is preferably sized to contain a volume of no more than about 1 μL, more preferably no more than about 0.5 μL, and most preferably no more than about 0.25 μL. The measurement zone (i.e., the region containing the volume of sample to be interrogated) is generally sized to contain a volume of sample of no more than about 1 μL, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL. One particularly useful configuration of this embodiment positions working electrode 22 and counter electrode 24 facing each other, as shown in Figure 3. In this embodiment, the measurement zone, corresponding to the region containing the portion of the sample which will be interrogated, is the portion of sample chamber 26 bounded by the working surface of the working electrode and disposed between the two facing electrodes.

[0131] In both of the embodiments discussed above, the thickness of the sample chamber and of the measurement zone correspond typically to the thickness of spacer 28 (e.g., the distance between the electrodes in Figures 1 and 3, or the distance between the electrodes and the inert base in Figure 2). The spacer may be, for example, an adhesive or double-sided adhesive tape or film. Preferably, this thickness is small to promote rapid electrolysis of the analyte, as more of the sample will be in contact with the electrode surface for a given sample volume. In addition, a thin sample chamber helps to reduce errors from diffusion of analyte into the measurement zone from other portions of the sample chamber during the analyte assay, because diffusion time is long relative to the measurement time. Typically, the thickness of the sample chamber is no more than about 0.2 mm. Preferably, the thickness of the sample chamber is no more than about 0.1 mm and, more preferably, the thickness of the sample chamber is about 0.05 mm or less.

[0132] The sample chamber may be formed by other methods. Exemplary methods include embossing, indenting, or otherwise forming a recess in a substrate within which either the working electrode 22 or counter electrode 24 is formed. Figures 12A and 12B illustrate one embodiment of this structure. First, a conducting layer 100 is formed on an inert non-conducting base material 102. As described above, the conducting layer 100 can include gold, carbon, platinum, ruthenium dioxide, palladium, or other non-corroding materials. The inert non-conducting base material 102 can be made using a polyester, other polymers, or other non-conducting, deformable materials. A recess 104 is then formed in a region of the non-conducting base material 102 so that at least a portion of the conducting layer 100 is included in the recess 104. The recess 104 may be formed using a variety of techniques including indenting, deforming, or otherwise pushing in the base material 102. One additional exemplary method for forming the recess includes embossing the base material 102. For example, the base material 102 may be brought into contact with an embossing roll or stamp having raised portions, such as punch members or channels, to form the recess 104. In some embodiments, the base material 102 may be heated to soften the material.

[0133] The recess 104 may be circular, oval, rectangular, or any other regular or irregular shape. Alternatively, the recess 104 may be formed as a channel which extends along a portion of the base material 102. The conducting layer 100 may extend along the entire channel or only a portion of the channel. The measurement zone may be restricted to a particular region within the channel by, for example, depositing the sensing layer 32 on only that portion of the conducting layer 100 within the particular region of the channel. Alternatively, the measurement zone may be defined by placing a second electrode 107 over only the desired region of the first electrode 105.

[0134] At least a portion, and in some cases, all, of the conducting layer 100 is situated in the recess 104. This portion of the conducting layer 100 may act as a first electrode 105 (a counter electrode or a working electrode). If the conducting layer 100 forms the working electrode, then a sensing layer 32 may be formed over a portion of the conducting layer 100 by depositing a non-leachable redox mediator and/or second electron transfer agent in the recess 104, as shown in Figure 12B. If a diffusible redox mediator or second electron transfer agent is used, then the diffusible material may be disposed on any surface in the sample chamber or in the sample.

Abbott Ex. 1002 - 294/1438

[0135] A second electrode 107 is then formed by depositing a second conducting layer on a second base material 106. This second electrode 107 is then positioned over the first electrode 105 in a facing arrangement. Although not illustrated, if the redox mediator is non-leachable it will be understood that if the first electrode 105 were to function as a counter electrode, then the sensing layer 32 would be deposited on the second electrode 107 which would then function as the working electrode. If the redox mediator is diffusible, however, the redox mediator may be disposed on any surface of the sample chamber or may be placed in the sample.

[0136] In one embodiment, the second base material 106 rests on a portion of the first base material 102 and/or the-conducting layer 100 which is not depressed, so that the second electrode 107 extends into the recess. In another embodiment, there is a spacer (not shown) between the first and second base materials 102, 106. In this embodiment, the second electrode 107 may or may not extend into the recess. In any case, the first and second electrodes 105, 107 do not make contact, otherwise the two electrodes would be shorted.

[0137] The depth of the recess 104 and the volume of the conductive layer 100, sensing layer 32, and the portion, if any, of the second electrode 107 in the recess 104 determines the volume of the measurement zone. Thus, the predictability of the volume of the measurement zone relies on the extent to which the formation of the recess 104 is uniform.

[0138] In addition to the conducting layer 100, a sorbent layer 103, described in detail below, may be deposited on the base material 102 prior to forming the recess 104, as shown in Figure 14A. The sorbent material 103 may be indented, embossed, or otherwise deformed with the conducting layer 100 and base material 102, as shown in Figure 14B. Alternatively, the sorbent material 103 may be deposited after the conducting layer 100 and base material 102 are indented, embossed, or otherwise deformed to make the recess 104.

[0139] In another exemplary method for forming the analyte sensor, a recess 114 is formed in a first base material 112, as shown in Figures 13A and 13B. The recess may be formed by indenting, embossing, etching (e.g., using photolithographic methods or laser removal of a portion of the base material), or otherwise deforming or removing a portion of the base material 112. Then a first conducting layer 110 is formed in the recess 114. Any of the conductive materials discussed above may be used. A preferred material is a conductive ink, such as a conductive carbon ink available, for example, from Ercon, Inc. (Wareham, MA). The conductive ink typically contains metal or carbon dissolved or dispersed in a solvent or dispersant. When the solvent or dispersant is removed, the metal or carbon forms a conductive layer 110 that can then be used as a first electrode 115. A second electrode 117 can be formed on a second base material 116 and positioned over the recess 114, as described above. In embodiments having a non-leachable redox mediator, a sensing layer 32 is formed on the first electrode 115 to form a working electrode, as shown in Figure 13B. In other embodiments having a non-leachable redox mediator, the sensing layer 32 may be formed on the second electrode 117 to form a working electrode. Alternatively, if a diffusible redox mediator is used, then the working electrode need not include the sensing layer disposed thereon. In fact, no sensing layer is required because the redox mediator may be placed in the sample and likewise for a diffusible second electron transfer agent, if one is present. Any diffusible components may be independently disposed on any surface of the sample chamber or placed in the sample. Furthermore, a sorbent material (not shown) may be formed within the recess, for example, on the first electrode 115.

[0140] A binder, such as a polyurethane resin, cellulose derivative, elastomer (e.g., silicones, polymeric dienes, or acrylonitrile-butadiene-styrene (ABS) resins), highly fluorinated polymer, or the like, may also be included in the conductive ink. Curing the binder may increase the conductivity of the conductive layer 110, however, curing is not necessary. The method of curing the binder may depend on the nature of the particular binder that is used. Some binders are cured by heat and/or ultraviolet light.

[0141] These structures allow for the formation of electrochemical sensors in which the volume of the measurement zone depends, at least in part, on the accuracy and reproducibility of the recess 104. Embossing, laser etching, photolithographic etching and other methods can be used to make reproducible recesses 104, even on the scale of 200 μm or less.

Sorbent Material

[0142] The sample chamber may be empty before the sample is placed in the chamber. Alternatively, the sample chamber may include a sorbent material 34 to sorb and hold a fluid sample during the measurement process. Suitable sorbent materials include polyester, nylon, cellulose, and cellulose derivatives such as nitrocellulose. The sorbent material facilitates the uptake of small volume samples by a wicking action which may complement or, preferably, replace any capillary action of the sample chamber. In addition or alternatively, a portion or the entirety of the wall of the sample chamber may be covered by a surfactant, such as, for example, Zonyl FSO.

[0143] In some embodiments, the sorbent material is deposited using a liquid or slurry in which the sorbent material is dissolved or dispersed. The solvent or dispersant in the liquid or slurry may then be driven off by heating or evaporation processes. Suitable sorbent materials include, for example, cellulose or nylon powders dissolved or dispersed in a suitable solvent or dispersant, such as water. The particular solvent or dispersant should also be compatible with the

Abbott Ex. 1002 - 295/1438

material of the working electrode 22 (e.g., the solvent or dispersant should not dissolve the electrode).

[0144] One of the most important functions of the sorbent material is to reduce the volume of fluid needed to fill the sample chamber and corresponding measurement zone of the sensor. The actual volume of sample within the measurement zone is partially determined by the amount of void space within the sorbent material. Typically, suitable sorbents consist of about 5% to about 50% void space. Preferably, the sorbent material consists of about 10% to about 25% void space.

[0145] The displacement of fluid by the sorbent material is advantageous. By addition of a sorbent, less sample is needed to fill sample chamber 26. This reduces the volume of sample that is required to obtain a measurement and also reduces the time required to electrolyze the sample.

[0146] The sorbent material 34 may include a tab 33 which is made of the same material as the sorbent and which extends from the sensor, or from an opening in the sensor, so that a sample may be brought into contact with tab 33, sorbed by the tab, and conveyed into the sample chamber 26 by the wicking action of the sorbent material 34. This provides a preferred method for directing the sample into the sample chamber 26. For example, the sensor may be brought into contact with a region of an animal (including human) that has been pierced with a lancet to draw blood. The blood is brought in contact with tab 33 and drawn into sample chamber 26 by the wicking action of the sorbent 34. The direct transfer of the sample to the sensor is especially important when the sample is very small, such as when the lancet is used to pierce a portion of the animal that is not heavily supplied with near-surface capillary vessels and furnishes a blood sample volume of 1 μL or less.

[0147] Methods other than the wicking action of a sorbent may be used to transport the sample into the sample chamber or measurement zone. Examples of such methods for transport include the application of pressure on a sample to push it into the sample chamber, the creation of a vacuum by a pump or other vacuum-producing method in the sample chamber to pull the sample into the chamber, capillary action due to interfacial tension of the sample with the walls of a thin sample chamber, as well as the wicking action of a sorbent material.

[0148] The sensor can also be used in conjunction with a flowing sample stream. In this configuration, the sample stream is made to flow through a sample chamber. The flow is stopped periodically and the concentration of the analyte is determined by an electrochemical method, such as coulometry. After the measurement, the flow is resumed, thereby removing the sample from the sensor. Alternatively, sample may flow through the chamber at a very slow rate, such that all of the analyte is electrolyzed in transit, yielding a current dependent only upon analyte concentration and flow rate.

[0149] Other filler materials may be used to fill the measurement zone and reduce the sample volume. For example, glass beads can be deposited in the measurement zone to occupy space. Preferably, these filler materials are hydrophilic so that the body fluid can easily flow into the measurement zone. In some cases, such as glass beads with a high surface area, these filler materials may also wick the body fluid into the measurement zone due to their high surface area and hydrophilicity.

[0150] The entire sensor assembly is held firmly together to ensure that the sample remains in contact with the electrodes and that the sample chamber and measurement zone maintain the same volume. This is an important consideration in the coulometric analysis of a sample, where measurement of a defined sample volume is needed. One method of holding the sensor together is depicted in Figures 1 and 2. Two plates 38 are provided at opposite ends of the sensor. These plates are typically constructed of non-conducting materials such as plastics. The plates are designed so that they can be held together with the sensor between the two plates. Suitable holding devices include adhesives, clamps, nuts and bolts, screws, and the like.

Alternative Sensor Designs

[0151] Figures 18A to 18C illustrate one alternative sensor design for formation of thin film sensors. The sensor includes a first substrate 500 upon which a working electrode 502 is formed. The working electrode 502 includes a contact region 503 for connection with external electronics. A spacer 504 (Figure 18B), such as, for example, a layer of adhesive or a double-sided tape defines a channel 506 to produce a sample chamber for the sensor. Two counter (or counter/reference) electrodes 510, 512 are formed on a second substrate 508, as shown in Figure 18C (inverted with respect to Figures 18A and 18B to show the electrode side up). This multiple counter electrode arrangement may provide a fill indicator function, as described below. Each counter electrode 510, 512 has a contact region 511, 513 for connection with external electronics. The second substrate 508 is inverted and placed over the first substrate 500, with the spacer 504 between, so that the working electrode 502 and the two counter electrodes 510, 512 are facing in the region of the channel 506.

[0152] In some instances, the counter electrode 510 nearest an entrance 514 of the channel 506 has a surface area within the sample chamber that is at least two times larger than the other counter electrode 512, and may be at least five or ten times larger. The non-leachable or diffusible redox mediator and/or second electron transfer agent can be provided on either the first or second substrates 500, 508 in a region corresponding to the channel 506, as described

Abbott Ex. 1002 - 296/1438

above.

[0153] The working electrode and counter electrodes can be formed to cover the entire channel region (except for a small space between the two counter electrodes). In this embodiment, the sample chamber and measurement zone are effectively the same and have the same volume. In other embodiments, the measurement zone has, for example, 80% or 90% of the volume of the sample chamber. It will be understood that similar sensors could be made using one counter electrode or three or more counter electrodes. It will also be understood that multiple working electrodes may also be provided on the sensor.

[0154] One example of a method for making the thin film sensors is described with respect to the sensor arrangement displayed in Figures 18A to 18C and can be used to make a variety of other sensor arrangements, including those described before. A substrate, such as a plastic substrate, is provided. The substrate can be an individual sheet or a continuous roll on a web. This substrate can be used to make a single sensor or to make multiple sensors. The multiple sensors can be formed on a substrate 1000 as working electrodes 1010 and counter electrode(s) 1020. In some embodiments, the substrate can be scored and folded to bring the working electrodes 1010 and counter electrodes 1020 together to form the sensor. In some embodiments, as illustrated in Figure 31A, the individual working electrodes 1010 (and, in a separate section, the counter electrode(s) 1020) can be formed next to each other on the substrate 1000, to reduce waste material, as illustrated in Figure 31A. In other embodiments, the individual working electrodes 1010 (and, in a separate section, the counter electrode(s) 1020) can be spaced apart, as illustrated in Figure 31B. The remainder of the process is described for the manufacture of multiple sensors, but can be readily modified to form individual sensors.

[0155] Carbon or other electrode material (e.g., metal, such as gold or platinum) is formed on the substrate to provide a working electrode for each sensor. The carbon or other electrode material can be deposited by a variety of methods including printing a carbon or metal ink, vapor deposition, and other methods.

[0156] Optionally, a non-conductive material, such as a non-conductive ink, can be formed adjacent the working electrode to provide a planar surface along the path of travel of the sample fluid. The non-conductive material is suitable for creating a smooth surface to facilitate filling by capillary action and/or for reducing the likelihood that air bubbles will become entrapped near the working electrode. This non-conductive material can be colored or colorless and may be formed on the substrate by printing or other techniques. The non-conductive material may be deposited prior to or subsequent to the formation of the working electrode.

[0157] The counter electrode or counter electrodes are formed on the substrate. The counter electrode(s) are formed by depositing carbon or other electrode material onto the substrate. In one embodiment, the material of the counter electrode(s) is a Ag/AgCl ink. The material of the counter electrode(s) may be deposited by a variety of methods including printing or vapor deposition. In some embodiments, the counter electrodes are formed using different materials and/or one electrode is a counter or counter/reference electrode and the other electrode is a reference or counter/reference electrode. In one embodiment, the working electrodes are formed on a first half of a polymer sheet or web and the counter electrodes are formed on a second half of the polymer sheet or web so that the sheet or web can be folded to superimpose the working and counter electrodes in a facing arrangement.

[0158] A second non-conductive material may be deposited adjacent and/or between the counter electrode(s) to provide a planar surface along the path of travel of the sample fluid. This may be particularly desirable in the region between the counter electrodes that will be part of the sample chamber to planarize the surface of the sample chamber. The non-conductive material is suitable for creating a smooth surface to faciliate filling by capillary action and/or for reducing the likelihood that air bubbles will become entrapped between or near the counter electrode(s). This non-conductive material can be colored or colorless and may be formed on the by printing or other techniques. The non-conductive material may be deposited prior to or subsequent to the formation of the counter electrode(s).

[0159] An adhesive spacer is formed over at least one of the substrate/working electrode and substrate/counter electrode(s). The adhesive spacer may be a single layer of adhesive or a double-sided adhesive tape (e.g., a polymer carrier film with adhesive disposed on opposing surfaces). To form the channel, the spacer, optionally provided with one or more release liners, may be cut (e.g., die-cut) to remove the portion of the adhesive corresponding to the channel prior to disposing the spacer on the substrate. Alternatively, the adhesive may be printed or otherwise disposed on the substrate according to a pattern which defines the channel region. The thickness of the spacer typically determines the spacing between the working and counter electrodes. When the uniformity of this spacing among sensors is necessary (e.g., for coulometric measurements), uniformity in the thickness of the spacer is important. Preferably, the thickness does not vary more than ± 5% over the individual sensor and/or among individual sensors in a batch.

[0160] The non-leachable or diffusible redox mediator and/or second electron transfer agent are disposed onto the substrate in at least the sample chamber region. If either or both of these components is non-leachable, that component or components must be disposed on the working electrode. If either or both of these components is diffusible, that component or components can be disposed on any surface of the substrate in the channel region. The redox mediator and/or second electrode transfer agent can be disposed independently or together on the substrate prior to or after disposition of the spacer. The redox mediator and/or second electrode transfer agent may be disposed by a variety of

Abbott Ex. 1002 - 297/1438

methods including, for example, screen printing, ink jet printing, spraying, painting, striping along a row or column of aligned and/or adjacent electrodes, and the like. Other components may be deposited separately or with the redox mediator and/or second electrode transfer agent including, for example, surfactants, polymers, polymer films, preservatives, binders, buffers, and cross-linkers.

[0161] After disposing the spacer, redox mediator, and second electron transfer agent, the substrate can be folded to form the sensor. The faces of the substrate are joined by the adhesive of the spacer. After bringing the faces together, the sensor can be cut out using a variety of methods including, for example, die cutting, slitting, or otherwise cutting away the excess substrate material and separating the individual sensors. In some embodiments, a combination of methods may be used. For example, some features may be die cut, while the remainder of the sensor is cut by slitting. As another alternative, the sensor components (e.g., the components illustrated in Figures 18A and 18C) may first be cut out of the substrates and then brought together to form the sensor by adhesively joining the two components using the spacer adhesive.

[0162] The embodiment of a sensor illustrated in Figures 18A to 18C is an example of a tip-fill sensor. An alternative sensor construction is illustrated in Figures 19A to 19C. This is a side-fill sensor. Figure 19A illustrates a first substrate 520 with a working electrode 522. Figure 19B illustrates a spacer 524 defining a channel 526. Figure 19C (inverted with respect to Figures 19A and 19B to illustrate the electrodes) illustrates a second substrate 528 with three counter (or counter/reference) electrodes 530, 532, 534.

[0163] This sensor can be manufactured as described above. The symmetric disposition of the counter electrodes allow the sensor to be filled from either the left or right side for convenience of left-handed and right-handed people. It will be understood, however, that similar sensor arrangements can be formed using one, two, or four or more counter electrode(s) and/or two or more working electrodes. The scalloped regions 536, 538 may be formed, for example, by die cutting and may, at least in some instances, be precisely controlled to provide a reproducible channel length. As an alternative arrangement, the sides of the sensor may be straight to allow the sensor to be cut out from the remainder of the substrate and/or from other sensors by slitting the substrate in parallel directions using, for example, a gang arbor blade system. As illustrated in Figures 19A, 19B, and 19C, the edges of the sensor can define edges of the sample chamber and/or measurement zone. By accurately controlling the distance between cuts, variability in sample chamber volume can often be reduced. In some instances, these cuts are preferably parallel to each other, as parallel cuts may be the easiest to make reproducibly.

[0164] Figures 20A, 20B, and 20C illustrate another example of a side-filling sensor arrangement. Figure 20A illustrates a first substrate 540 with a working electrode 542. Figure 20B illustrates a spacer 544 defining a channel 546. Figure 20C (inverted with respect to Figures 20A and 20B) illustrates a second substrate 548 with three counter (or counter/reference) electrodes 550, 552, 554.

[0165] Figures 21A, 21B, and 21C illustrate another example of a tip-filling sensor arrangement. Figure 21A illustrates a first substrate 560 with a working electrode 562. Figure 21B illustrates a spacer 564 defining a channel 566. Figure 21C (inverted with respect to Figures 21A and 21B) illustrates a second thin film substrate 568 with two counter (or counter/reference) electrodes 570, 572. A vent hole 574 (indicated as a shaded region in Figure 21C) is provided through the second substrate. In the illustrated embodiment, this vent hole 574 is made through only the substrate 568 that carries the counter electrode(s) and, optionally, the spacer 564. In this embodiment, the vent hole may be formed by, for example, die cutting a portion of the substrate. This die cut may remove a portion of at least one counter electrode, but a sufficient amount of the counter electrode should remain for contact with the sample in the channel and for electrical connection to a contact at the other end of the sensor. In another embodiment, the vent hole 574 may be made through all of the layers or through the first substrate and not the second substrate.

[0166] Another embodiment is illustrated in Figures 22A, 22B, and 22C, with a different shape. This sensor includes a first substrate 579 with at least one working electrode 580, as illustrated in Figure 22A. The sensor also includes a spacer 581 with a channel 582 formed in the spacer 581, as shown in Figure 22B. The sensor further includes a second substrate 583 with two counter electrodes 584, 585, as shown in Figure 22C (inverted with respect to Figures 22A and 22B). A venting aperture 586 is cut typically through all of the layers and extends from a side of the sensor. In some embodiments, the venting aperture and the front portion 587 of the sensor are simultaneously cut with a reproducible distance between the venting aperture and the front portion 587 of the sensor to provide a reproducible length for the channel 582 and the working electrode 580. Figures 22A, 22B, and 22C also illustrate another feature that can be used with any sensor arrangement. An indentation 588 may be formed at the filling opening of the channel 582 to facilitate the drawing of fluid into the sensor. In this configuration, the fluid is not provided with a flat face, but rather an indented face that may aid in wicking or capillary filling of the channel (i.e., sample chamber). This configuration may also reduce the likelihood that the user of the sensor will block the channel during collection of the sample. A flat faced sensor might be blocked by pressing the tip of the sensor edgewise against the skin.

[0167] Figures 23A, 23B, and 23C illustrate another example of a side-filling sensor arrangement. Figure 23A illustrates a first substrate 640 with a working electrode 642. Figure 23B illustrates a spacer 644 defining a channel 646. Figure 23C (inverted with respect to Figures 23A and 23B) illustrates a second substrate 648 with three counter (or

Abbott Ex. 1002 - 298/1438

counter/reference) electrodes 650, 652, 654. This sensor can be formed by making straight cuts of the substrates. The sensors can be made adjacent to one another, as illustrated in Figure 31A, which may produce less waste material. The length of the channel 646 is typically defined by the two parallel cuts along the sides 656, 658 of the sensors. Another optional processing advantage, particularly if the sensor are formed adjacent to each other, is that the redox mediator and/or second electron transfer agent can be disposed in the channel by striping a continuous stream of these components along a row or column of adjacent sensors. This may result in better efficiency and less waste of the redox mediator and/or second electron transfer agent, as compared to other techniques, such as individually placing these components within the individual channels.

[0168] Figures 24A, 24B, and 24C illustrate another sensor configuration. This sensor includes a first substrate 600 with at least one working electrode 602, as illustrated in Figure 24A. The sensor also includes a spacer 604 with a channel 606 formed in the spacer 604, as shown in Figure 24B. The sensor further includes a second substrate 608 with two counter electrodes 610, 612, as shown in Figure 24C (inverted with respect to Figures 24A and 24B). The sensor may also include, for example, an indicator, such as a slot 614 or an extension 616 from the body of the sensor that indicates to the user which side should be placed adjacent to the sample. This may be particularly important where the sensor reading is only correct when sample enters from a particular side.

[0169] Figure 24B also illustrates another optional feature that may be used in any of the sensor configurations. In this illustration, the sample chamber 606 is not formed using straight lines, but there is an expanded region 618 within the sample chamber. This permits larger sample chambers without forming larger openings. This expanded region can be formed as any shape including circular, square, rectangular, and other regular and irregular shapes.

[0170] Figure 25 is an example of an assembled sensor illustrating another alternative sensor arrangement for a side-fill sensor 620. This sensor includes extensions 622 from the sensor body 624 to indicate to a user where the openings for the sample chamber 626 are provided.

[0171] One optional feature is illustrated in Figure 32 which is an edge-on view of the sensor from the inside of the meter. Figure 32 illustrates a first substrate 1120 and a second substrate 1130 that extend into the meter from the remainder of the sensor 1100 (i.e., portion 1140 is recessed with respect to substrates 1120 and 1130 in Figure 32). Examples of this configuration are illustrated in Figures 18A-18C and 24A-24C. Typically, the sensor 1100 is coupled to a meter 1110 that includes contact pads (not shown) that contact the contact regions (e.g., regions 503, 511, and 513 in Figures 18A and 18C) of the electrodes of the sensor 1100. The end of the sensor 1100 which contains the contact regions can be slid into the meter 1110. It is typically important that the contact pads of the meter 1110 make contact with the correct contact regions of the sensor so that the working electrode and counter electrode(s) are correctly coupled to the meter. In some instances, the sensor is configured so that the contact region for the working electrode on the first substrate 1120 has a different width, w1, than width, w2, for the contact region of the second substrate 1130 carrying the counter electrode(s). Examples of electrode configurations with this structure are provided in Figures 18A-18C and 24A-24C. To ensure proper insertion of the sensor 1100 into the meter 1110, the meter 1110 may include a raised area 1140 that prevents or hinders the insertion of the sensor in an improper direction. For example, the width, w2, of the contact region of the second substrate 1130 may be wider than the width, w1, of the contact region of the first substrate 1120, as illustrated in Figure 32. In this instance, the raised area 1140 is positioned to allow sensor 1100 to be slid into the meter so that the first substrate 1120 is next to the surface 1150 from which the raised area 1140 protrudes, but would prevent or hinder having the second substrate 1130 next to the surface 1150 from which the raised area 1140 protrudes. Objects other than a raised area can also be used to guide the user in correct introduction of the sensor into the meter.

Integrated Sample Acquisition and Analyte Measurement Device

[0172] Many approaches are known in the art for acquiring and/or transporting a small sample from the body to a sensor. These include, for example, U.S. Patent Numbers 5,746,217; 5,820,570; 5857983; and 5879311. Any of these sample acquisition and/or transporting methods may be employed with the sensor of the current invention.

[0173] In a preferred embodiment of the invention, an analyte measurement device 52 constructed according to the principles of the present invention includes a sensor 20, as described hereinabove, combined with a sample acquisition apparatus 50 to provide an integrated sampling and measurement device. The sample acquisition apparatus 50 illustrated in Figure 6, includes, for example, a skin piercing member 54, such as a lancet, attached to a resilient deflectable strip 56 (or other similar device, such as a spring) which may be pushed to inject the lancet into a patient's skin to cause blood flow.

[0174] The resilient strip 56 is then released and the skin piercing member 54 retracts. Blood flowing from the area of skin pierced by member 54 can then be transported, for example, by the wicking action of sorbent material 34, into sensor 20 for analysis of the analyte. The analyte measurement device 52 may then be placed in a reader, not shown, which connects a coulometer or other electrochemical analysis equipment to the electrode tabs 23, 25 to determine the concentration of the analyte by electroanalytical means. Preferably, the analyte measurement device is enclosed

Abbott Ex. 1002 - 299/1438

within the reader when connected to the coulometer or other electrochemical analysis equipment.

[0175] In a preferred embodiment, the integrated sample acquisition and analyte measurement device comprises a lancing instrument that holds a lancet and measurement strip. The lancing instrument preferably requires active cocking. By requiring the user to cock the device prior to use, the risk of inadvertently triggering the lancet is minimized.

[0176] Preferably, the lancing instrument is automatically triggered when the lancing instrument is pressed firmly against the skin with an adequate amount of pressure. As is already known in the art, a larger sample of body fluid such as blood or interstitial fluid is expressed when pressure is applied around a site where a hole has been created the skin. For example, see the above-mentioned U.S. patents to Integ and Amira as well as the tip design of the lancing instruments sold by Becton Dickenson. All of these lancing devices have a protruding ring that surrounds the lancing site to create pressure that forces sample out of the wound. However, all of these devices require the user to apply adequate pressure to the wound site to express the sample, and all of the lancing instruments are triggered by a button push by the user. Design of an appropriate pressure trigger is well-known to one skilled in the art.

[0177] Preferably, the lancing instrument will also permit the user to adjust the depth of penetration of the lancet into the skin. Such devices are already commercially available from companies such as Boehringer Mannheim and Palco. This feature allows users to adjust the lancing device for differences in skin thickness, skin durability, and pain sensitivity across different sites on the body and across different users.

[0178] In a more preferred embodiment, the lancing instrument and the test reader are integrated into a single device. To operate the device the user need only insert a disposable cartridge containing a measurement strip and lancing device into the integrated device, cock the lancing instrument, press it against the skin to activate it, and read the result of the measurement. Such an integrated lancing instrument and test reader simplifies the testing procedure for the user and minimizes the handling of body fluids.

[0179] Figure 26 illustrates another example of an integrated sample acquisition and sensor device 700. The integrated sample acquisition and sensor device 700 includes a housing 702, a skin piercing member (e.g., a lancet) 704, a piercing/collecting aperture 706, an optionally removable sensor 708, a sensor guide 710, and a retraction mechanism 714 for the skin piercing member. This device 700 can be designed for reuse (e.g., by making the skin piercing member 704 and sensor 708 removable) or for single use.

[0180] The housing 702 may be formed of a variety of materials including metal and plastic. The housing 702 may include a hinge 716 or other configuration (e.g., adhesive or interlocking parts) for holding portions of the housing together.

[0181] The piercing/collecting aperture 706 is provided in the housing 702 to allow the skin piercing member 704 to extend through the aperture 706 and pierce the skin of a user, thereby causing blood (or other body fluid) flow. The sensor 708 also extends to the edge or out of the aperture 706 to collect the blood (or other body fluid) through an opening (not shown) in the tip of the sensor. This may allow the user to pierce the skin and collect the fluid sample without moving the device 700. Alternatively, separate apertures may be provided for the skin piercing member 704 and sensor 708. The sensor guide may be formed in the housing 702 or added to the housing to guide the sensor 708 into place if the sensor is inserted into and through the housing and/or to support the sensor within the housing and during sample collection.

[0182] The skin piercing member 704 may include an actuator (not shown) that includes a mechanism that allows for cocking and releasing the skin piercing member 704 or the skin piercing member may be actuated externally. For example, a sensor reader (not shown) or other device may be coupled to the sample acquisition and sensor device, the sensor reader or other device including a mechanism that cocks and/or releases the skin piercing member 704.

[0183] The retraction mechanism 714 of the device 700 may be, for example, a spring or resilient metal strip that retracts the skin piercing member 704 back into the housing after piercing the skin of the user. This may allow for unobstructed collection of the sample and/or prevent further piercing of the skin of the user or others to reduce or prevent contamination or infection caused by transfer of body fluids or other harmful agents. Alternatively, retraction of the skin piercing member may be accomplished using an external device or apparatus.

[0184] One example of operation includes cocking the skin piercing member 704 and then releasing the skin piercing member 704 so that it extends out of the housing 702 through the piercing/collecting aperture 706 and pierces the skin of the user. The skin piercing element 704 optionally pushes the sensor out of the way while extending out of the housing. The skin piercing element 704 is retracted back within the housing 702 using the retraction mechanism 714. Upon retraction of the skin piercing element, the sensor collects a sample fluid from the pierced skin through an opening in the sensor 708.

[0185] If a sensor reader is used, the sensor reader may also be configured to couple with a contact end of the sensor. The sensor reader may include a potentiostat or other component to provide a potential and/or current for the electrodes of the sensor. The sensor reader may also include a processor (e.g., a microprocessor or hardware) for determining analyte concentration from the sensor signals. The sensor reader may include a display or a port for coupling a display to the sensor. The display may display the sensor signals and/or results determined from the sensor signals including, for example, analyte concentration, rate of change of analyte concentration, and/or the exceeding

Abbott Ex. 1002 - 300/1438

of a threshold analyte concentration (indicating, for example, hypo- or hyperglycemia). This sensor reader may be used in conjunction with the integrated sample acquisition and sensor device or the sensor reader may be used with the sensor alone, the contacts of the sensor making connection with contacts in the sensor reader.

Operation of the Sensor

[0186] An electrochemical sensor of the invention may be operated with or without applying a potential. In one embodiment, the electrochemical reaction occurs spontaneously and a potential need not be applied between the working and counter electrodes.

[0187] In another embodiment, a potential is applied between the working and counter electrodes. Yet the potential does not need to remain constant. The magnitude of the required potential is dependent on the redox mediator. The potential at which the electrode poises itself, or where it is poised by applying an external bias, and where the analyte is electrolyzed is typically such that the electrochemical reaction is driven to or near completion, but it is, preferably, not oxidizing enough to result in significant electrochemical reaction of interferents, such as urate, ascorbate, and acetaminophen, that may affect the signal measured. For non-leachable redox mediators, the potential is typically between about -350 mV and about +400 mV versus the standard calomel electrode (SCE). Preferably, the potential of the redox mediator is more negative than +100 mV, more preferably the potential is more negative than 0 mV, and most preferably the potential is about -150 mV versus SCE.

[0188] When an external potential is applied, it may be applied either before or after the sample has been placed in the sample chamber. If the measurement zone comprises only a portion of the sample chamber then the potential is preferably applied after the sample has come to rest in the sample chamber to prevent electrolysis of sample passing through the measurement zone as the sample chamber is filling. Alternatively, in the case where the measurement zone comprises most or all of the sample chamber, the potential, optionally, may be applied before or during the filling of the sample chamber without affecting the accuracy of the assay. When the potential is applied and the sample is in the measurement zone, an electrical current will flow between the working electrode and the counter electrode. The current is a result, at least in part, of the electrolysis of the analyte in the sample. This electrochemical reaction occurs via the redox mediator and the optional second electron transfer agent. For many biomolecules, B, the process is described by the following reaction equations:

$$nA(ox) + B \xrightarrow{\text{enzyme}} nA(red) + C \qquad (1)$$

$$nA(red) \rightarrow nA(ox) + ne^- \qquad (2)$$

Biochemical B is oxidized to C by redox mediator species A in the presence of an appropriate enzyme. Then the redox mediator A is oxidized at the electrode. Electrons are collected by the electrode and the resulting current is measured. The measured current may also include a background current resulting in a measured background charge, due, at least in part, to the shuttling of a diffusible redox mediator between the working electrode and the counter electrode. This background current can be minimized or accounted for, as described above.

[0189] As an example, one sensor of the present invention is based on the reaction of a glucose molecule with two $[Os(dmo\text{-}phen)_2(NMI)Cl]^{2+}$ cations, where dmo-phen is 4,8-dimethoxy phenanthroline and NMI is N-methyl-imidazole, in the presence of glucose oxidase to produce two $[Os(dmo\text{-}phen)_2(NMI)Cl]^{+}$ cations, two protons, and an oxidation product of glucose, for example, gluconolactone or another ketone. The amount of glucose present is assayed by electrooxidizing the $[Os(dmo\text{-}phen)_2(NMI)Cl]^{+}$ cations to $[Os(dmo\text{-}phen)_2(NMI)Cl]^{2+}$ cations and measuring the total charge passed.

[0190] Those skilled in the art will recognize that there are many different reactions that will provide the same result; namely the electrolysis of an analyte through a reaction pathway incorporating a redox mediator. Equations (1) and (2) are a non-limiting example of such a reaction.

Coulometry

[0191] In a preferred embodiment of the invention, coulometry is used to determine the concentration of the analyte. This measurement technique utilizes current measurements obtained at intervals over the course of the assay, to determine analyte concentration. These current measurements are integrated over time to obtain the amount of charge, Q, passed to or from the electrode. Q is then used to calculate the concentration of the analyte (C_A) by the following

Abbott Ex. 1002 - 301/1438

equation (when the redox mediator is non-leachable):

$$C_A = Q/nFV \quad (3a)$$

where n is the number of electron equivalents required to electrolyze the analyte, F is Faraday's constant (approximately 96,500 coulombs per equivalent), and V is the volume of sample in the measurement zone. When using a diffusible mediator, the concentration of the analyte can be obtained from the following equation:

$$C_A = (Q_{tot} - Q_{back})/nFV \quad (3b)$$

where Q_{tot} is the total charge transferred during the measurement and Q_{back} is the amount of charge transferred that was not due to the analyte, e.g., charge transferred by the shuttling of the diffusible mediator between the working electrode and the counter electrode. In at least some instances, the sensor is constructed so that the background charge is at most 5 times the size of the charge generated by electrolysis of an amount of analyte. Preferably, the background signal is at most 200%, 100%, 50%, 25%, 10%, or 5% of the charge generated by electrolysis of the analyte.

[0192] One example of a method for determining the ratio of background signal to signal generated by electrolysis of the analyte is described as follows for the facing electrode pairs. If the shuttling of the redox mediator is not disabled by the applied potential, the charge that results from the shuttling of the redox mediator may be represented by the following formula:

$$Q_{back} = (A\ F\ D_M\ C_M / d)\ (t\ n_M)$$

where A is the area of the working electrode; F is Faraday's constant (96,500 coulombs/equivalent); D_M is the effective diffusion coefficient of the redox mediator; C_M is the concentration of the redox mediator in the measurement zone; d is the distance separating facing electrodes; t is the amount of time for the measurement; and n_M is the number of electrons gained or lost by the redox mediator.

[0193] Additionally, the charge of the analyte, for example, glucose, when the analyte is electrooxidized to about 90% completion in the measurement period may be represented by the following formula:

$$Q_G = A\ d(0.90)\ C_G\ n_G\ F$$

where A is the area of the working electrode; d is the distance separating facing electrodes; C_G is the concentration of glucose; n is the number of electrons needed to electrolyze the analyte (e.g., 2 electrons per glucose molecule); and F is Faraday's constant. When C_G is 5 mM (or 5×10^{-6} moles/cm^3), t is 60 seconds, n_G is 2, and n_M is 1, the ratio of charge from the redox mediator to the charge from electrooxidation of the analyte may be represented by the following formula:

$$Q_{Back}/Q_G = (D_M C_M/d^2)(t\ n_M/(0.9\ n_G\ C_G)) = (D_M\ C_M\ /\ d^2) \times (6.7 \times 10^6)$$

For example, if the ratio of Q_{Back}/Q_G is 5, then $(D_M\ C_M)/\ d^2$ is 7.5×10^{-7} moles/(cm^3 sec). Also for example, if the ratio of Q_{Back}/Q_G is 1, then $(D_M\ C_M)/\ d^2$ is $1{:}5 \times 10^{-7}$ moles/(cm^3 sec). Still another example, if the ratio is 0.1, then $(D_M\ C_M)\ /\ d^2$ is 1.5×10^{-8} moles/(cm^3 sec). Thus, depending on the ratio desired, a sensor may be configured to have the desired ratio by choosing D_M, C_M, and d accordingly. For example, the concentration of the redox mediator may be reduced (i.e., C_M may be reduced). Alternatively, or additionally, the diffusion of the redox mediator may be reduced by, for example, having a barrier to the flow of the diffusible mediator to the counter electrode (i.e., reduce the effective diffusion coefficient of the redox mediator—D_M). Other sensor configurations are also suitable for controlling the ratio of background signal to signal generated by the analyte and will be described below.

[0194] The background charge, Q_{back}, can be accounted for in a variety of ways. Q_{back} can be made small, for example, by using only limited amounts of diffusible redox mediator; by providing a membrane over the counter electrode that limits diffusion of the redox mediator to the counter electrode; or by having a relatively small potential difference between the working electrode and the counter electrode. Other examples of sensor configurations and methods suitable for reducing Q_{back} include those already described such as sensors having a redox mediator reaction rate at

Abbott Ex. 1002 - 302/1438

the working electrode that is significantly faster than that at the counter electrode; immobilizing the redox mediator on the working electrode; having the redox mediator become immobilized on the counter or counter/reference electrode upon its reaction at the counter or counter/reference electrode; or slowing the diffusion of the redox mediator.

[0195] Alternatively, the sensor may be calibrated individually or by batch to determine a calibration curve or a value for Q_{back}. Another option is to include a second electrode pair that is missing an item necessary for electrolysis of the analyte, such as, for example, the second electron transfer agent, so that the entire signal from this second electrode pair corresponds to Q_{back}.

[0196] For coulometric measurements, at least 20% of the analyte is electrolyzed. Preferably at least 50%, more preferably at least 80%, and even more preferably at least 90% of the analyte is electrolyzed. In one embodiment of the invention, the analyte is completely or nearly completely electrolyzed. The charge can then be calculated from current measurements made during the electrochemical reaction, and the concentration of the analyte is determined using equation (3a) or (3b). The completion of the electrochemical reaction is typically signaled when the current reaches a steady-state value. This indicates that all or nearly all of the analyte has been electrolyzed. For this type of measurement, at least 90% of the analyte is typically electrolyzed, preferably, at least 95% of the analyte is electrolyzed and, more preferably, at least 99% of the analyte is electrolyzed.

[0197] For coulometry, it is typically desirable that the analyte be electrolyzed quickly. The speed of the electrochemical reaction depends on several factors, including the potential that is applied between the electrodes and the kinetics of reactions (1) and (2). (Other significant factors include the size of the measurement zone and the presence of sorbent in the measurement zone.) In general, the larger the potential, the larger the current through the cell (up to a transport limited maximum) and therefore, the faster the reaction will typically occur. However, if the potential is too large, other electrochemical reactions may introduce significant error in the measurement. Typically, the potential between the electrodes as well as the specific redox mediator and optional second electron transfer agent are chosen so that the analyte will be almost completely electrolyzed in less than 5 minutes, based on the expected concentration of the analyte in the sample. Preferably, the analyte will be almost completely electrolyzed within about 2 minutes and, more preferably, within about 1 minute.

[0198] In another embodiment of the invention, the analyte is only partially electrolyzed. The current is measured during the partial reaction and then extrapolated using mathematical techniques known to those skilled in the art to determine the current curve for the complete or nearly complete electrolysis of the analyte. Integration of this curve yields the amount of charge that would be passed if the analyte were completely or nearly completely electrolyzed and, using equation (3a) or (3b), the concentration of the analyte is calculated.

[0199] Although coulometry has the disadvantage of requiring the volume of the measured sample be known, coulometry is a preferred technique for the analysis of the small sample because it has the advantages of, for example, no temperature dependence for the measurement, no enzyme activity dependence for the measurement, no redox-mediator activity dependence for the measurement, and no error in the measurement from depletion of analyte in the sample. As already described above, coulometry is a method for determining the amount of charge passed or projected to pass during complete or nearly complete electrolysis of the analyte. One coulometric technique involves electrolyzing the analyte on a working electrode and measuring the resulting current between the working electrode and a counter electrode at two or more times during the electrolysis. The electrolysis is complete when the current reaches a steady state. The charge used to electrolyze the sample is then calculated by integrating the measured currents over time and accounting for any background signal. Because the charge is directly related to the amount of analyte in the sample there is no temperature dependence of the measurement. In addition, the activity of the enzyme does not affect the value of the measurement, but only the time required to obtain the measurement (i.e., less active enzyme requires a longer time to achieve complete electrolysis of the sample) so that decay of the enzyme over time will not render the analyte concentration determination inaccurate. And finally, the depletion of the analyte in the sample by electrolysis is not a source of error, but rather the objective of the technique. (However, the analyte need not be completely electrolyzed if the electrolysis curve is extrapolated from the partial electrolysis curve based on well-known electrochemical principles.)

Non-Coulometric Assays

[0200] Although coulometric assays are useful, those skilled in the art will recognize that a sensor of the invention may also utilize potentiometric, amperometric, voltammetric, and other electrochemical techniques to determine the concentration of an analyte in a sample. The measurements obtained by these non-coulometric methods may not be temperature independent as are coulometric measurements.

[0201] In addition, the measurements obtained by these non-coulometric electrochemical techniques may be sensitive to the amount of active enzyme provided in the sensor. If the enzyme deactivates or decays over time, the resulting measurements may be affected. This may limit the shelf life of such sensors unless the enzyme is very stable.

[0202] Finally, the measurements obtained by non-coulometric electrochemical techniques, such as steady-state

Abbott Ex. 1002 - 303/1438

amperometry, may be negatively affected if a substantial portion of the analyte and/or redox mediator is electrolyzed during the measurement period. An accurate steady-state measurement may not be obtainable unless there is sufficient analyte and/or redox mediator so that only a relatively small portion of the analyte and/or redox mediator is electrolyzed during the measurement process. This may be challenging in a sample size of no more than 1 μl.

[0203] It may be desirable in some instances to utilize non-coulometric assays, such as amperometric or potentiometric measurement techniques. For example, coulometry requires that the volume of the measured sample be known. And, the volume of the sample in the measurement zone of a small volume sensor (i.e., no more than one microliter) may be difficult to accurately reproduce if the manufacturing tolerances of one or more dimensions of the measurement zone have significant variances.

[0204] As described for coulometric measurements, the background signal resulting from the shuttling of the redox mediator between the electrodes can be a source of measurement error in amperometric or potentiometric assays of samples of no more than 1 μL in thin layer electrochemical cells. In general, it is desirable that the mediator does not shuttle between a pair of electrodes more than ten times in the period of the measurement, preferably not more than once, and more preferably not more than 0.1 times, on average. To decrease error arising from background signal, methods and sensor configurations similar to, and in some cases identical to, those used for coulometric measurements may be used. Examples include all of the methods and structures described above, such as performing the electrochemical assay at relatively low applied potential, electrooxidizing the analyte at negative applied potentials or electroreducing the analyte at positive applied potentials, using a counter electrode at which the redox mediator reacts relatively slowly (particularly as compared to the reaction of the redox mediator at the working electrode), and/or using a redox mediator that undergoes an irreversible reaction at the counter electrode. Other examples are discussed below.

[0205] As described for coulometric measurements, it is preferred that the sensor be designed and operated so that the background signal is at most five times the size of the signal generated by electrolysis of the analyte. Preferably, the background signal is at most 200%, 100%, 50%, 25%, 10%, or 5% of the signal generated by electrolysis of an amount of analyte. The amount of analyte against which the background signal is compared is described above in the section entitled "Background Signal." In the case of amperometry, the signal generated by electrolysis of an amount of analyte is the current at the time or times at which the measurement is taken. In the case of potentiometry, the signal generated by electrolysis of an amount of analyte is the potential at the time or times at which the measurement is taken.

[0206] Under a given set of operating conditions, for example, temperature, cell geometry, and electrode size, the magnitude of the background current, I_{back}, is given by the following expression:

$$i_{back} = KC_M D_M / d$$

where: K is a proportionality constant; C_M is the concentration of the mediator in the measurement zone; D_m is the effective diffusion coefficient of the mediator in the measurement zone under normal operating conditions; and d is the distance between the electrodes.

[0207] It is desirable to reduce background current for non-coulometric assays. The sensor configurations and methods described above are generally useful and include, for example, using low concentrations of the redox mediator and/or the second electron transfer agent (e.g., enzyme) relative to the concentration of the analyte and/or using a large redox mediator having a relatively low effective diffusion constant. Other useful methods described above include methods for reducing the diffusion of the redox mediator by, for example, having a barrier (e.g., a charged or polar barrier) to the flow of the diffusible mediator or using a redox mediator having a relatively low effective diffusion constant.

[0208] In some instances, the effective diffusion coefficient is no more than about 1×10^{-6} cm^2/sec, no more than about 1×10^{-7} cm^2/sec, or no more than about 1×10^{-8} cm^2/sec. Moreover, in some cases, the product of $C_M D_M$ (the concentration of redox mediator times the effective diffusion coefficient) is no more than about 1×10^{-12} moles/cm·sec, no more than about 1×10^{-13} moles/cm·sec, or no more than about 1×10^{-14} moles/cm·sec.

[0209] The following provides a specific example for the case of an amperometric measurement of glucose carried out for 60 seconds during which time 10% of the glucose is electrolyzed in a 1 microliter cell with facing electrodes separated by a distance of d = 0.01 cm. If the measurement was carried out under the following conditions: a glucose concentration of, C_G = 5 mM (or 5×10^{-6} moles/cm^3), an area of A = 0.1 cm^2, a number of electrons from the redox mediator of n_M = 1, and a number of electrons from glucose n_G = 2, then the background current generated by the redox mediator and by the glucose is determined as follows.

$$i_{back} = A\,F\,n_M\,D_M\,C_M/d$$

$$= (0.1)\,(96{,}500)\,(1)\,D_M\,C_M/(0.01)$$

Abbott Ex. 1002 - 304/1438

$$= 9.65 \times 10^5 \, C_M \, D_M$$

$$i_G = n_G \, A \, d(0.1) \, F \, C_G/t$$

$$= (2)\,(0.01)\,(0.1)\,(96{,}500)\,(5 \times 10^{-6})/60 = 1.61 \text{ } \mu\text{amps}$$

[0210] Thus if $i_{back}/i_G = 5$, the value of $C_M D_M$ equal 8.34×10^{-12} moles/cm^2 sec. As another example, if $i_{back}/i_G = 0.5$, the value of $C_M D_M$ equal 8.34×10^{-13} moles/cm^2 sec. Additionally if $i_{back}/i_G = 0.05$, the value of $C_M D_M$ equal 8.34×10^{-14} moles/cm^2 sec.

[0211] In some amperometric or potentiometric embodiments, the redox mediator circulation is decreased by separating the working electrode from the counter or counter/reference electrode such that the distance through which the redox mediator would diffuse during the measurement period is no greater than, for example, the distance between the electrodes. A redox mediator can diffuse a distance equal to $(D_m t)^{1/2}$, where D_m is the effective diffusion coefficient for the medium between the electrodes and t is time. For a measurement time period of 30 seconds and a redox mediator with effective diffusion coefficient between 10^{-5} and 10^{-6} cm^2/second, the electrodes should be separated by at least 100μm, preferably at least 200μm, and even more preferably at least 400μm.

[0212] One method of separating the working and counter electrodes is to use a thicker spacer between the electrodes. One alternative method is illustrated in Figure 27. In this embodiment, the working electrode 740 is disposed on a first substrate 742 and the counter electrode 744 is disposed on a second substrate 746 (alternatively, the electrodes may be disposed on the same substrate). The working electrode 742 and the counter electrode 744 are offset so that the effective distance, d, between the two electrodes is greater than the thickness, w, of the spacer layer 748. In one embodiment, the distance between the electrodes, d, is selected to be in the range of 25 to 1000 μm, 50 to 500 μm, or 100 to 250 μm.

[0213] Additionally or alternatively, in the case of steady-state amperometry and potentiometry, background signal may be controlled by limiting the rate of electrolysis such that the rate is slow enough to prevent the analyte concentration from decreasing by more than about 20%, 10%, or 5% or less, during a measurement period, e.g., 30 second, 1 minute, 5 minutes, or 10 minutes. In some instances, to control the rate of electrolysis the concentration or activity of the second electron transfer agent may be reduced and/or the working electrode area may be reduced.

[0214] For example, the second electron transfer agent can be an enzyme and the enzyme activity can be a limiting factor for the electrolysis rate. If, for example, the analyte concentration is 5mM glucose (i.e., 5×10^{-9} moles of glucose in 1 μl) and no more than 10% of the glucose (5×10^{-10} moles) is to be electrooxidized during a 30-second measurement period, the current should not exceed 3.3×10^{-6} amperes for 1μL. One unit of an enzyme is that amount of the enzyme which catalyzes electrolysis of 1 μmole of its substrate in 60 seconds at pH of 7.4 at 37° C in HEPES buffer. Accordingly, for glucose, a current of up to 3.3×10^{-3} amperes in 1 cm^3 (i.e., 1 mL) can be generated. Therefore, the maximum amount of enzyme used in a sensor that limits the amount of electrolysis by controlling the amount of enzyme should be 1 unit/cm^3 or less.

[0215] The rate of electrolysis may also be limited by using a relatively small working electrode area. When the working electrode area is sufficiently small (e.g., no more than about 0.01 cm^2, no more than about 0.0025 cm^2, or no more than about 0.001 cm^2), then radial diffusion of analyte to the electrode may result in a steady-state current, at a constant applied potential, that is representative of the analyte concentration. For circular electrodes, the appropriate surface area may be achieved using an electrode with a radius of no more than 60μm, no more than 30μ m, or no more than 20μm. Radial diffusion of the analyte includes transport of analyte from all directions and not just from the direction normal to the electrode surface and can, therefore, reduce or prevent depletion of analyte near the electrode surface. A small electrode on a planar surface permits radial diffusion. In a sensor having a larger surface area electrodes, the transport of analyte to the electrode may be modeled as semi-infinite linear diffusion instead of radial diffusion. Thus, the transport of the analyte to the electrode is dominated by diffusion from the direction normal to the electrode surface. As a result, the reduced transport rate is typically unable to overcome the depletion of analyte near the electrode surface, and at constant applied potential the current decreases with time, t, according to $t^{1/2}$.

[0216] For a potentiometric assay of the type proposed by Yarnitzky and Heller, J. Phys. Chem., 102:10057-61 (1998), in which the potential varies linearly with the analyte concentration, the concentration of the analyte and/or redox mediator in a particular oxidation state should vary no more than about 20% during the assay. If the concentration varies by more than 20%, then the diffusion of the analyte or redox mediator should be controlled by, for example, controlling temperature and/or volume of the sample chamber and/or measurement zone.

[0217] While this description has described electrolysis of an analyte, one skilled in the art would recognize that the same devices and techniques would also be suitable for measurements of the average oxidation state of the mediator, such as, for example, in Cottrell types of reactions.

Abbott Ex. 1002 - 305/1438

Air-oxidizable Redox Mediators

[0218] In a sensor having a redox mediator, a potential source of measurement error is the presence of redox mediator in an unknown mixed oxidation state (i.e., mediator not reproducibly in a known oxidation state). The charge passed when the redox mediator is electrooxidized or electroreduced at the working electrode is affected by its initial oxidation state. Referring to equations (1) and (2) discussed above under the section entitled "Operation of the Sensor," the current not attributable to the oxidation of biochemical B will flow because of electrooxidation of that portion of the redox mediator, A, that is in its reduced form prior to the addition of the sample. Thus, it may be important to know the oxidation state of the analyte prior to introduction of the sample into the sensor. Furthermore, it is desirable that all or nearly all of the redox mediator have the same state or extent of oxidation prior to the introduction of the sample into the sensor.

[0219] Each redox mediator has a reduced form or state and an oxidized form or state. It is preferred that the amount of redox mediator in the reduced form prior to the introduction of sample be significantly smaller than the expected amount of analyte in a sample in order to avoid a significant background contribution to the measured current. In this embodiment of the invention, the molar amount of redox mediator in the reduced form prior to the introduction of the analyte is preferably no more than, on a stoichiometric basis, about 10%, and more preferably no more than about 5%, and most preferably no more than 1%, of the molar amount of analyte for expected analyte concentrations. (The relative molar amounts of analyte and redox mediator are compared based on the stoichiometry of the applicable redox reaction. If, for example, two moles of redox mediator are needed to electrolyze one mole of analyte, then the molar amount of redox mediator in the reduced form prior to introduction of the analyte is preferably no more than 20% and more preferably no more than about 10% and most preferably no more than about 2% of the molar amount of analyte for expected analyte concentrations.) Methods for controlling the amount of reduced mediator are discussed below.

[0220] In another aspect of the invention, it is preferred that the ratio of the amounts of oxidized redox mediator to reduced redox mediator, prior to introduction of the sample in the sensor, be relatively constant between similarly constructed sensors. Any deviation from holding the ratio relatively constant may increase the scatter of the results obtained for the same sample with multiple similarly made sensors. For this aspect of the invention, the percentage of the redox mediator in the reduced form prior to introduction of the sample in the sensor varies by no more than about 20% and preferably no more than about 10% between similarly constructed sensors.

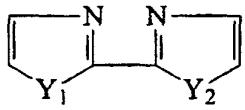
[0221] One method of controlling the amount of reduced redox mediator prior to the introduction of the sample in the sensor is to provide an oxidizer to oxidize the reduced form of the mediator. One of the most convenient oxidizers is O_2. Oxygen is usually readily available to perform this oxidizing function. Oxygen can be supplied by exposing the sensor to air. In addition, most polymers and fluids absorb O_2 from the air unless special precautions are taken. Typically, at least 90% of an air-oxidizable (i.e., O_2 oxidizable) mediator in the solid state is in the oxidized state upon storage or exposure to air for a useful period of time, e.g., one month or less, and preferably, one week or less, and, more preferably, one day or less. The air oxidation may take place in either the solid state or as a solution stored for a time period sufficient to air oxidize the mediator before deposition on the sensor. In the case of air oxidizable redox mediators in solution, it is desirable that the time required to achieve at least 80%, preferably at least 90%, oxidation of the redox mediator is at least 10 times the expected duration of the assay and is also less than the pot life of the solution. Preferably, at least 80%, more preferably at least 90%, of the redox mediator is air oxidized in less than 1 week, preferably, in less than 1 day, more preferably, in less than 8 hours, and even more preferably, in less than 1 hour.

[0222] While it is desirable to bring the mediators of the sensors manufactured in a single batch to the same state or extent of oxidation, it is not necessary that the mediator be completely oxidized to the higher-valent state. Additionally, it is desirable that the air oxidation of the dissolved redox mediator should not be so fast that air-oxidation during the assay can interfere with or introduce error into the measurements.

[0223] Suitable mediators which are both air-oxidizable (i.e., O_2-oxidizable) and have electron transfer capabilities have been described hereinabove. One particular family of useful mediators are osmium complexes which are bound to electron-rich nitrogen-containing heterocycles or a combination of electron-rich nitrogen-containing heterocycles and halides. Electron-rich nitrogen-containing heterocycles include, but are not limited to, imidazole derivatives and pyridine or phenanthroline derivatives that contain electron-donating substituents such as alkyl, alkoxy, amino, alkylamino, amido and mercapto groups. Preferably, the osmium complexes have no more than one halide coordinated to the metal, so that the mediators are overall positively charged and thus are water soluble. An example is osmium complexed with mono-, di-, and polyalkoxy-2,2'-bipyridine. Other examples include mono-, di-, and polyalkoxy-1,10-phenanthroline, where the alkoxy groups have a carbon to oxygen ratio sufficient to retain solubility in water, are air-oxidizable. These osmium complexes typically have two substituted bipyridine or substituted phenanthroline ligands, the two ligands not necessarily being identical. These osmium complexes are further complexed with a monomeric or polymeric ligand with one or more nitrogen-containing heterocycles, such as pyridine and imidazole. Preferred polymeric ligands include poly(4-vinyl pyridine) and, more preferably, poly(1-vinyl imidazole) or copolymers thereof. $[Os[4,4'\text{-dimethoxy-}2,2'\text{-bipyridine}]_2Cl]^{+/+2}$ complexed with a poly(1-vinyl imidazole) or poly(4-vinyl pyridine) has been shown to be partic-

Abbott Ex. 1002 - 306/1438

ularly useful as the Os^{+2} cation is oxidizable by O_2 to Os^{+3}. Similar results are expected for complexes of [Os (4,7-dimethoxy-1,10-phenanthroline)$_2$Cl]$^{+/+2}$,and other mono-, di-, and polyalkoxy bipyridines and phenanthrolines, with the same polymers. Other halogen groups such as bromine may be substituted for chlorine. Similar results are also expected for complexes comprising the following structures, as specified above:



[0224] A complication associated with air-oxidizable mediators arises if the air oxidation of the redox mediator is so fast that a substantial portion of the analyte-reduced redox mediator is oxidized by O_2 during an analyte assay. This will result in an inaccurate assay as the amount of analyte will be underestimated because the mediator will be oxidized by air rather than by its electrooxidation at the electrode. It is preferred that the reaction of the redox mediator with O_2 proceeds more slowly than the electrooxidation of the mediator, because if the air oxidation of the mediator were fast, then dissolved air and the in-diffusion of air might affect the outcome of the measurement.

[0225] Because typically the assay takes about 10 minutes or less, preferably 5 minutes or less, and most preferably about 1 minute or less, it is preferred that the mediator, though air oxidizable in storage, will not be oxidized by dissolved oxygen during the time of the assay. Thus, mediators that are not air oxidized in 1 minute, and preferably not even in 10 minutes when dissolved in plasma or in serum, are preferred. Typically, less than 5%, and preferably less than 1%, of the reduced mediator should be oxidized by air during an assay.

[0226] The reaction rate of the air oxidation of the mediator can be controlled through choice of an appropriate complexing polymer. For example, the oxidation reaction is much faster for [Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl]$^{+/+2}$ coordinatively coupled to poly(1-vinyl imidazole) than for the same Os complex coupled to poly(4-vinyl pyridine). The choice of an appropriate polymer will depend on the expected analyte concentration and the potential applied between the electrodes, both of which determine the rate of the electrochemical reaction.

[0227] Thus, in one embodiment of the invention, the preferred redox mediator has the following characteristics: 1) the mediator does not react with any molecules in the sample or in the sensor other than the analyte (optionally, via a second electron transfer agent); 2) nearly all of the redox mediator is oxidized by an oxidizer such as O_2 prior to introduction of the sample in the sensor; and 3) the oxidation of the redox mediator by the oxidizer is slow compared to the electrooxidation of the mediator by the electrode.

[0228] Alternatively, if the redox mediator is to be oxidized in the presence of the analyte and electroreduced at the electrode, a reducer rather than an oxidizer would be required. The same considerations for the appropriate choice of reducer and mediator apply as described hereinabove for the oxidizer.

[0229] The use of stable air-oxidizable redox mediators in the electrochemical sensors of the invention provides an additional advantage during storage and packaging. Sensors of the invention which include air-oxidizable redox mediators can be packaged in an atmosphere containing molecular oxygen and stored for long periods of time, e.g., greater than one month, while maintaining at least 80% and preferably at least 90% of the redox species in the oxidized state.

Use of the Air-Oxidizable Mediators in Optical Sensors

[0230] The air-oxidizable redox species of the present invention can be used in other types of sensors. The osmium complexes described hereinabove are suitable for use in optical sensors, due to the difference in the absorption spectra, luminescence and/or fluorescence characteristics of the complexed Os^{+2} and Os^{+3} species. Absorption, transmission, reflection, luminescence and/or fluorescence measurements of the redox species will correlate with the amount of analyte in the sample (after reaction between an analyte and the redox species, either directly, or via a second electron transfer agent such as an enzyme). In this configuration, the molar amount of redox mediator should be greater, on a stoichiometric basis, than the molar amount of analyte reasonably expected to fill the measurement zone of the sensor.

[0231] Standard optical sensors, including light-guiding optical fiber sensors, and measurement techniques can be adapted for use with the air-oxidizable mediators. For example, the optical sensors of the invention may include a light-transmitting or light reflecting support on which the air-oxidizable redox species, and preferably an analyte-responsive enzyme, is coated to form a film. The-support film forms one boundary for the measurement zone in which the sample is placed. The other boundaries of the measurement zone are determined by the configuration of the cell. Upon filling the measurement zone with an analyte-containing sample, reduction of the air-oxidizable mediator by the analyte, preferably via reaction with the analyte-responsive enzyme, causes a shift in the mediator's oxidation state that is detected by a change in the light transmission, absorption, or reflection spectra or in the luminescence and/or fluores-

Abbott Ex. 1002 - 307/1438

cence of the mediator at one or more wavelengths of light.

Multiple Electrode Sensors and Calibration

[0232] Multiple electrode sensors may be used for a variety of reasons. For example, multiple electrode sensors may be used to test a variety of analytes using a single sample. One embodiment of a multiple electrode sensor, shown in Figure 5, has one or more sample chambers which in turn may contain one or more working electrodes 22 with each working electrode 22 defining a different measurement zone. If the redox mediator is non-leachable, one or more of the working electrodes have the appropriate chemical reagents, for example, an appropriate enzyme, to test a first analyte and one or more of the remaining working electrodes have appropriate chemical reagents to test a second analyte. The chemical reagents (e.g., redox mediator and/or second electron transfer agent) can be deposited as a sensing layer on the working electrode or, if diffusible reagents are used, they can be deposited on any surface of the sample chamber or placed in the sample. For example, a multiple electrode sensor might include 1) one or more working electrodes having glucose oxidase in the sensing layer to determine glucose concentration and 2) one or more working electrodes having lactate oxidase in the sensing layer to determine lactate concentration.

[0233] Multiple electrode sensors may also be used to improve the precision of the resulting readings. The measurements from each of the working electrodes (all or which are detecting the same analyte) can be averaged together to obtain a more precise reading. In some cases, measurements may be rejected if the difference between the value and the average exceeds a threshold limit. This threshold limit may be, for example, determined based on a statistical parameter, such as the standard deviation of the averaged measurements. The average may then be recalculated while omitting the rejected values. Furthermore, subsequent readings from an electrode that produced a rejected value may be ignored in later tests if it is assumed that the particular electrode is faulty. Alternatively, a particular electrode may be rejected only after having a predetermined number of readings rejected based on the readings from the other electrodes.

[0234] In addition to using multiple electrode sensors to increase precision, multiple measurements may be made at each electrode and averaged together to increase precision. This technique may also be used with a single electrode sensor to increase precision.

[0235] Errors in assays may occur when mass produced sensors are used because of variations in the volume of the measurement zone of the sensors. Two of the three dimensions of the measurement zone, the length and the width, are usually relatively large, between about 1-5 mm. Electrodes of such dimensions can be readily produced with a variance of 2% or less. The submicroliter measurement zone volume requires, however, that the third dimension be smaller than the length or width by one or two order of magnitude. As mentioned hereinabove, the thickness of the sample chamber is typically between about 50 and about 200 μm. Manufacturing variances in the thickness may be on the order of 20 to 50 μm. Therefore, it may be desirable that a method be provided to accommodate for this uncertainty in the volume of sample within the measurement zone.

[0236] In one embodiment of the invention, depicted in Figure 5, multiple working electrodes 42, 44, 46 are provided on a base material 48. These electrodes are covered by another base, not shown, which has counter electrodes, not shown, disposed upon it to provide multiple facing electrode pairs. The variance in the separation distance between the working electrode and the counter electrode among the electrode pairs on a given sensor is significantly reduced, because the working electrodes and counter electrodes are each provided on a single base with the same spacer 28 between each electrode pair (see Figure 3).

[0237] One example of a multiple electrode sensor that can be used to accurately determine the volume of the measurement zones of the electrode pairs and that is also useful in reducing noise is presented herein. In this example, one of the working electrodes 42 is prepared with a non-leachable redox mediator and a non-leachable second electron transfer agent (e.g., an enzyme). Sorbent material may be disposed between that working electrode 42 and its corresponding counter electrode. Another working electrode 44 includes non-leachable redox mediator, but no second electron transfer agent on the electrode. Again, this second electrode pair may have sorbent material between the working electrode 44 and the corresponding counter electrode. An optional third working electrode 46 has no redox mediator and no second electron transfer agent bound to the electrode, nor is there sorbent material between the working electrode 46 and its corresponding counter electrode. A similar configuration can be constructed using diffusible redox mediator and/or diffusible second electron transfer agent although diffusible components are not limited to being disposed on the working electrode. In some instances, the distance between electrode pairs is sufficient that redox mediator and/or enzyme do not substantially diffuse between electrode pairs within the measurement period and/or in the time period from introduction of the same sample into the sample chamber to the end of the measurement.

[0238] The sensor error caused by redox mediator in a non-uniform oxidation state prior to the introduction of the sample can be measured by concurrently electrolyzing the sample in the measurement zones that are proximate electrodes 42 and 44. At electrode 42, the analyte is electrolyzed to provide the sample signal. At electrode 44, the analyte is not electrolyzed because of the absence of the second electron transfer agent (assuming that a second electron

Abbott Ex. 1002 - 308/1438

transfer agent is necessary). However, a charge will pass (and a current will flow) due to the electrolysis of the redox mediator that was in a mixed oxidation state (i.e., some redox centers in the reduced state and some in the oxidized state) prior to the introduction of the sample and/or the shuttling of a diffusible redox mediator between the working electrode and the counter electrode. The small charge passed between the electrodes in this second electrode pair can be subtracted from the charge passed between the first electrode pair to substantially remove the error due to the oxidation state of the redox mediator and/or to remove the background current caused by a diffusible redox mediator. This procedure also reduces the error associated with other electrolyzed interferents, such as ascorbate, urate, and acetaminophen, as well as errors associated with capacitive charging and faradaic currents.

[0239] The thickness of the sample chamber can be determined by measuring the capacitance, preferably in the absence of any fluid, between electrode 46 (or any of the other electrodes 42, 44 in the absence of sorbent material) and its corresponding counter electrode. The capacitance of an electrode pair depends on the surface area of the electrodes, the interelectrode spacing, and the dielectric constant of the material between the plates. The dielectric constant of air is unity which typically means that the capacitance of this electrode configuration is a few picofarads (or about 100-1000 picofarads if there is fluid between the electrode and counter electrode given that the dielectric constant for most biological fluids is approximately 75). Thus, since the surface area of the electrodes are known, measurement of the capacitance of the electrode pair allows for the determination of the thickness of the measurement zone to within about 1-5%.

[0240] The amount of void volume in the sorbent material, can be determined by measuring the capacitance between electrode 44 (which has no second electron transfer agent) and its associated counter electrode, both before and after fluid is added. Upon adding fluid, the capacitance increases markedly since the fluid has a much larger dielectric constant. Measuring the capacitance both with and without fluid allows the determination of the spacing between the electrodes and the void volume in the sorbent, and thus the volume of the fluid in the reaction zone.

[0241] Other electrode configurations can also use these techniques (i.e., capacitance measurements and coulometric measurements in the absence of a critical component) to reduce background noise and error due to interferents and imprecise knowledge of the volume of the interrogated sample. Protocols involving one or more electrode pairs and one or more of the measurements described above can be developed and are within the scope of the invention. For example, only one electrode pair is needed for the capacitance measurements, however, additional electrode pairs may be used for convenience.

Fill Indicator

[0242] When using a sample chamber that is filled with 1 μL or less of fluid, it is often desirable to be able to determine when the sample chamber is filled. Figures 18A-18C illustrate one sensor having a fill indicator structure. Figure 18A illustrates a first substrate 500 upon which a working electrode 502 is printed. A spacer 504 (Figure 18B), such as, for example, a layer of adhesive or a double-sided tape, is formed over the first substrate 500 and working electrode 502 with a channel 506 formed in the layer to provide a sample chamber. A second substrate 508 is printed with two counter electrodes 510, 512, as shown in Figure 18C (inverted with respect to Figures 18A and 18B to show the electrode side up). In some instances, the counter electrode 510 nearest an entrance 514 of the channel 506 has a surface area within the sample chamber that is at least two times larger than the other counter electrode 512, and preferably at least five or ten times larger.

[0243] The sensor can be indicated as filled by observing a signal between the second counter electrode 512 and the working electrode 502 as the sensor fills with fluid. When fluid reaches the second counter electrode 512, the signal from that counter electrode should change. Suitable signals for observing include, for example, voltage, current, resistance, impedance, or capacitance between the second counter electrode 512 and the working electrode 502. Alternatively, the sensor may be observed after filling to determine if a value of the signal (e.g., voltage, current, resistance, impedance, or capacitance) has been reached indicating that the sample chamber is filled.

[0244] In alternative embodiments, the counter electrode and/or working electrode may be divided into two or more parts and the signals from the respective parts observed to determine whether the sensor has been filled. In one example, the working electrode is in a facing relationship with the counter electrode and the indicator electrode. In another example, the counter electrode, working electrode, and indicator electrode are not in a facing relationship, but may be, for example, side-by-side. In other cases, a second electrode pair may be used with signals from the second electrode pair being monitored for changes and/or for approaching a particular value to determine that the sensor has filled. Typically, the indicator electrode is further downstream from a sample inlet port than the working electrode and counter electrode.

[0245] For side-fill sensors, such as those illustrated in Figures 19A-19C and 20A-20C, two indicator electrodes may be disposed on either side of the primary counter electrode. This permits the user to fill the sample chamber from either the left or right side with an indicator electrode disposed further upstream. This three-electrode configuration is not necessary. Side-fill sensors can also have a single indicator electrode and, preferably, some indication as to which

Abbott Ex. 1002 - 309/1438

side should be placed in contact with the sample fluid.

[0246] In one embodiment, the use of three counter/reference electrodes and/or indicator electrodes, detects when the sample chamber begins to fill and when the sample chamber has been filled to prevent partial filling of the sample chamber. In this embodiment, the two indicator electrodes are held at a different potential than the largest counter/reference electrode. The start and completion of filling of the sample chamber is indicated by the flow of current between the indicator and counter/reference electrodes.

[0247] In other instances, the potential of each of the counter/reference electrodes may be the same. When the potential at all three counter/reference electrodes is the same for example, 0 volts, then as the measurement zone begins to fill, the fluid allows for electrical contact between a working electrode and the first counter/reference electrode, causing a current at the first counter/reference electrode due to the reaction of the analyte with the enzyme and the mediator. When the fluid reaches the third counter/reference electrode, another current may be measured similar to the first counter/reference electrode indicating that the measurement zone is full. When the measurement zone is full, the three counter/reference electrodes may be shorted together or their signals may be added or otherwise combined.

[0248] The indicator electrode may also be used to improve the precision of the analyte measurements according to the methods described above for multiple electrode sensors. The indicator electrode may operate as a working electrode or as a counter electrode or counter/reference electrode. In the embodiment of Figures 18A-18C, the indicator electrode 512 can act as a second counter or counter/reference electrode with respect to the working electrode 502. Measurements from the indicator electrode/working electrode pair can be combined (for example, added to and/or averaged) with those from the first counter or counter/reference electrode/working electrode pair to obtain more accurate measurements. In one embodiment, the indicator electrode may operate as a second working electrode with the counter electrode or counter/reference electrode. In another embodiment, the indicator electrode may operate as a second working electrode with a second counter electrode or counter/reference electrode. In still another embodiment, the indicator electrode may operate as a second counter electrode or counter/reference electrode with a second working electrode.

[0249] The sensor or a sensor reader may include a sign (e.g., a visual sign or auditory signal) that is activated in response to the indicator electrode to alert the user that the measurement zone has been filled. In some instances, the sensor or a sensor reader may be configured to initiate a reading when the indicator electrode indicates that the measurement zone has been filled with or without alerting the user. The reading can be initiated, for example, by applying a potential between the working electrode and the counter electrode and beginning to monitor the signals generated at the working electrode.

Heating of Sample

[0250] The sample may be heated to increase the rate of diffusion, oxidation, or reduction of the analyte. This heating may be accomplished by a variety of techniques including placing the sensor in a heated environment or applying a heating unit to the sensor.

[0251] Another technique includes providing a thermal heating element, such as, for example, a wire or an ink that is capable of converting electrical energy into heat energy, on the sensor. This wire or ink can be applied, for example, on the opposite side of a base material, such as a polymer film, from one or more of the working, counter, reference, or counter/reference electrodes, or applied around the periphery of the working, counter, reference, or counter/reference electrodes. In some instances, the sample may be heated up to 5 to 20°C above an initial temperature. In other instances, the temperature of the sample may not be known but a constant amount of power or current may be applied to the wire or ink.

EXAMPLES

[0252] The invention will be further characterized by the following examples. These examples are not meant to limit the scope of the invention which has been fully set forth in the foregoing description. Variations within the concepts of the invention are apparent to those skilled in the art. Examples 1 to 8 represent background art according to WO 98/35225.

Example 1

Preparation of a Small Volume *in vitro* Sensor for the Determination of Glucose Concentration

[0253] A sensor was constructed corresponding to the embodiment of the invention depicted in Figure 1. The working electrode was constructed on a Mylar™ film (DuPont), the Mylar™ film having a thickness of 0.175 mm and a diameter of about 2.5 cm. An approximately 12 micron thick carbon pad having a diameter of about 1 cm was screen printed on

Abbott Ex. 1002 - 310/1438

the Mylar™ film. The carbon electrode was overlaid with a water-insoluble dielectric insulator (Insulayer) having a thickness of 12 μm, and a 4 mm diameter opening in the center.

[0254] The center of the carbon electrode, which was not covered by the dielectric, was coated with a non-leachable redox mediator. The redox mediator was formed by complexing poly(1-vinyl imidazole) with Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$_2$ followed by cross-linking glucose oxidase with the osmium polymer using polyethylene glycol diglycidyl ether (PEGDGE) as described in Taylor et al., *J. Electroanal. Chem.*, 396:511 (1995). The ratio of osmium to imidazole functionalities in the redox mediator was approximately 1:15. The mediator was deposited on the working electrode in a layer having a thickness of 0.6 μm and a diameter of 4 mm. The coverage of the mediator on the electrode was about 60 μ g/cm^2 (dry weight). A spacer material was placed on the electrode surrounding the mediator-covered surface of the electrode. The spacer was made of polytetrafluoroethylene (PTFE) and had a thickness of about 0.040 mm.

[0255] A sorbent material was placed in contact with the mediator-covered surface of the working electrode. The sorbent was made of nylon (Tetko Nitex nylon 3-10/2). The sorbent had a diameter of 5 mm, a thickness of 0.045 mm, and a void volume of about 20%. The volume of sample in the measurement zone was calculated from the dimensions and characteristics of the sorbent and the electrode. The measurement zone had a diameter of 4 mm (the diameter of the mediator covered surface of the electrode) and a thickness of 0.045 mm (thickness of the nylon sorbent) to give a volume of 0.57 μL. Of this space, about 80% was filled with nylon and the other 20% was void space within the nylon sorbent. This resulting volume of sample within the measurement zone was about 0.11 μL.

[0256] A counter/reference electrode was placed in contact with the spacer and the side of the sorbent opposite to the working electrode so that the two electrodes were facing each other. The counter/reference electrode was constructed on a Mylar™ film having a thickness of 0.175 mm and a diameter of about 2.5 cm onto which a 12 micron thick layer of silver/silver chloride having a diameter of about 1 cm was screen printed.

[0257] The electrodes, sorbent, and spacer were pressed together using plates on either side of the electrode assembly. The plates were formed of polycarbonate plastic and were securely clamped to keep the sensor together. The electrodes were stored in air for 48 hours prior to use.

[0258] Tabs extended from both the working electrode and the counter/reference electrode and provided for an electrical contact with the analyzing equipment. A potentiostat was used to apply a potential difference of +200mV between the working and counter/reference electrodes, with the working electrode being the anode. There was no current flow between the electrodes in the absence of sample, which was expected, as no conductive path between the electrodes was present.

[0259] The sample was introduced via a small tab of nylon sorbent material formed as an extension from the nylon sorbent in the sample chamber. Liquid was wicked into the sorbent when contact was made between the sample and the sorbent tab. As the sample chamber filled and the sample made contact with the electrodes, current flowed between the electrodes. When glucose molecules in the sample came in contact with the glucose oxidase on the working electrode, the glucose molecules were electrooxidized to gluconolactone. The osmium redox centers in the redox mediator then reoxidized the glucose oxidase. The osmium centers were in turn reoxidized by reaction with the working electrode. This provided a current which was measured and simultaneously integrated by a coulometer (EG&G Princeton Applied Research Model #173).

[0260] The electrochemical reaction continued until the current reached a steady state value which indicated that greater than 95% of the glucose had been electroreduced. The current curve obtained by measurement of the current at specific intervals was integrated to determine the amount of charge passed during the electrochemical reaction. These charges were then plotted versus the known glucose concentration to produce a calibration curve.

[0261] The sensor was tested using 0.5 μL aliquots of solutions containing known concentrations of glucose in a buffer of artificial cerebrospinal fluid or in a control serum (Baxter-Dade, Monitrol Level 1, Miami, FL) in the range of 3 to 20 mM glucose. The artificial cerebrospinal fluid was prepared as a mixture of the following salts: 126 mM NaCl, 27.5 mM $NaHCO_3$, 2.4 mM KCl, 0.5 mM KH_2PO_4, 1.1 mM $CaCl_2 \cdot 2H_2O$, and 0.5 mM Na_2SO_4.

[0262] The results of the analyses are shown in Table 1 and in Figure 7. In Table 1, Q_{avg} is the average charge used to electrolyze the glucose in 3-6 identical test samples (Figure 7 graphs the charge for each of the test samples) and the 90% rise time corresponds to the amount of time required for 90% of the glucose to be electrolyzed. The data show a sensor precision of 10- 20%, indicating adequate sensitivity of the sensor for low glucose concentrations, as well as in the physiologically relevant range (30 μg/dL - 600 μg/dL).

Abbott Ex. 1002 - 311/1438

TABLE 1
Sensor Results Using Glucose Oxidase

	Number of Samples Tested	Q_{avg} (TC)	90% rise time (sec)
buffer only	4	9.9 ± 1.8	13 ± 6
3 mM glucose/buffer	5	17.8 ± 3.5	19 ± 5
6 mM glucose/buffer	4	49.4 ± 4.9	25 ± 3
10 mM glucose/buffer	6	96.1 ± 12.4	36 ± 17
15 mM glucose/buffer	5	205.2 ± 75.7	56 ± 23
20 mM glucose/buffer	4	255.7 ± 41.0	62 ± 17
4.2 mM glucose/serum	3	44.2 ± 4.3	44 ± 3
15.8 mM glucose/serum	3	218.2 ± 57.5	72 ± 21

[0263] The average measured values of glucose concentration were fit by one or more equations to provide a calibration curve. Figure 8 shows the calibration curves for the glucose/buffer data of Table 1. One of the 15.0 mM glucose measurements was omitted from these calculations because it was more than two standard deviations away from the average of the measurements. The higher glucose concentrations (10-20 mM) were fit by a linear equation. The lower glucose concentrations were fit by a second order polynomial.

[0264] Figure 9 shows the data of Table 1 plotted on an error grid developed by Clarke et al., *Diabetes Care*, 5, 622-27, 1987, for the determination of the outcome of errors based on inaccurate glucose concentration determination. The graph plots "true" glucose concentration vs. measured glucose concentration, where the measured glucose concentration is determined by calculating a glucose concentration using the calibration curves of figure 8 for each data point of figure 7. Points in zone A are accurate, those in zone B are clinically acceptable, and those in zones C, D, and E lead to increasingly inappropriate and finally dangerous treatments.

[0265] There were 34 data points. Of those data points 91 % fell in zone A, 6% in zone B, and 3 % in zone C. Only one reading was determined to be in zone C. This reading was off-scale and is not shown in figure 9. Thus, 97% of the readings fell in the clinically acceptable zones A and B.

[0266] The total number of Os atoms was determined by reducing all of the Os and then electrooxidizing it with a glucose-free buffer in the sample chamber. This resulted in a charge of 59.6 ± 5.4 μC. Comparison of this result with the glucose-free buffer result in Table 1 indicated that less than 20% of the Os is in the reduced form prior to introduction of the sample. The variability in the quantity of osmium in the reduced state is less than 5% of the total quantity of osmium present.

Example 2

Response of the Glucose Sensor to Interferents

[0267] A sensor constructed in the same manner as described above for Example 1 was used to determine the sensor's response to interferents. The primary electrochemical interferents for blood glucose measurements are ascorbate, acetaminophen, and urate. The normal physiological or therapeutic (in the case of acetaminophen) concentration ranges of these common interferents are:

ascorbate: 0.034 - 0.114 mM
acetaminophen: 0.066 - 0.200 mM
urate (adult male): 0.27 - 0.47 mM

Abbott Ex. 1002 - 312/1438

Tietz, in: *Textbook of Clinical Chemistry*, C.A. Burtis and E.R. Ashwood, eds., W.B. Saunders Co., Philadelphia 1994, pp. 2210-12.

[0268] Buffered glucose-free interferent solutions were tested with concentrations of the interferents at the high end of the physiological or therapeutic ranges listed above. The injected sample volume in each case was 0.5 μL. A potential of +100 mV or +200 mV was applied between the electrodes. The average charge (Q_{avg}) was calculated by subtracting an average background current obtained from a buffer-only (i.e., interferent-free) solution from an average signal recorded with interferents present. The resulting average charge was compared with the signals from Table 1 for 4 mM and 10 mM glucose concentrations to determine the percent error that would result from the interferent.

TABLE 2
Interferent Response of Glucose Sensors

Solution	E (mV)	n	Q_{avg} (TC)	Error @ 4 mM glucose	Error @ 10 mM glucose
0.114 mM ascorbate	100	4	0.4	2%	<1%
0.114 mM ascorbate	200	4	-0.5	2%	<1%
0.2 mM acetaminophen	100	4	0.1	<1%	<1%
0.2 mM acetaminophen	200	4	1.0	5%	1%
0.47 mM urate	100	4	6.0	30%	7%
0.47 mM urate	200	4	18.0	90%	21%

[0269] These results indicated that ascorbate and acetaminophen were not significant interferents for the glucose sensor configuration, especially for low potential measurements. However, urate provided significant interference. This interference can be minimized by calibrating the sensor response to a urate concentration of 0.37 mM, e.g., by subtracting an appropriate amount of charge as determined by extrapolation from these results from all glucose measurements of the sensor. The resulting error due to a 0.10 mM variation in urate concentration (the range of urate concentration is 0.27 - 0.47 in an adult male) would be about 6% at 4 mM glucose and 100mV.

Example 3

Sensor with Glucose Dehydrogenase

[0270] A sensor similar to that described for Example 1 was prepared and used for this example, except that glucose oxidase was replaced by pyrroloquinoline quinone glucose dehydrogenase and a potential of only +100 mV was applied as opposed to the +200 mV potential in Example 1. The results are presented in Table 3 below and graphed in Fig. 10.

Abbott Ex. 1002 - 313/1438

TABLE 3
Sensor Results Using Glucose Dehydrogenase

	n	Q_{avg} (TC)	90% rise time (s)
buffer	4	21.7 ± 5.2	14 ± 3
3 mM glucose/buffer	4	96.9 ± 15.0	24 ± 6
6 mM glucose/buffer	4	190.6 ± 18.4	26 ± 6
10 mM glucose/buffer	4	327.8 ± 69.3	42 ± 9

[0271] The results indicated that the charge obtained from the glucose dehydrogenase sensor was much larger than for the comparable glucose oxidase sensor, especially for low concentrations of glucose. For 4 mM glucose concentrations the measurements obtained by the two sensors differed by a factor of five. In addition, the glucose dehydrogenase sensor operated at a lower potential, thereby reducing the effects of interferent reactions.

[0272] In addition, the results from Table 3 were all fit by a linear calibration curve as opposed to the results in Example 1, as shown in Fig. 10. A single linear calibration curve is greatly preferred to simplify sensor construction and operation.

[0273] Also, assuming that the interferent results from Table 2 are applicable for this sensor, all of the interferents would introduce an error of less than 7% for a 3 mM glucose solution at a potential of 100 mV.

Example 4

Determination of Lactate Concentration in a Fluid Stream

[0274] The sensor of this Example was constructed using a flow cell (BioAnalytical Systems, Inc. # MF-1025) with a glassy carbon electrode. A redox mediator was coated on the electrode of the flow cell to provide a working electrode. In this case, the redox mediator was a polymer formed by complexing poly(1-vinyl imidazole) with Os(4,4'-dimethyl-2,2'-bipyridine)$_2$Cl$_2$ with a ratio of 1 osmium for every 15 imidazole functionalities. Lactate oxidase was cross-linked with the polymer via polyethylene glycol diglycidyl ether. The mediator was coated onto the electrode with a coverage of 500 μg/cm^2 and a thickness of 5 Tm. The mediator was covered by a polycarbonate track-etched membrane (Osmonics-Poretics #10550) to improve adherence in the flow stream. The membrane was then overlaid by a single 50 Tm thick spacer gasket (BioAnalytical Systems, Inc. #MF-1062) containing a void which defined the sample chamber and corresponding measurement zone. Assembly of the sensor was completed by attachment of a cell block (BioAnalytical Systems, Inc. #MF-1005) containing the reference and auxiliary electrodes of the flow cell.

[0275] The sample chamber in this case corresponded to a 50 Tm thick cylinder (the thickness of the spacer gasket) in contact with a mediator-coated electrode having a surface area of 0.031 cm^2. The calculated volume of sample in the measurement zone of this sensor was approximately 0.16 TL.

[0276] The flow rate of the fluid stream was 5 TL/min. A standard three electrode potentiostat was attached to the cell leads and a potential of +200 mV was applied between the redox mediator-coated glassy carbon electrode and the reference electrode. This potential was sufficient to drive the enzyme-mediated oxidation of lactate.

[0277] As the fluid stream flowed through the sensor, a steady-state current proportional to the lactate concentration was measured. At periodic intervals the fluid flow was stopped and current was allowed to flow between the electrodes until approximately all of the lactate in the measurement zone was electrooxidized, as indicated by the achievement of a stabilized, steady-state current. The total charge, Q, required for lactate electrooxidation was found by integration of the differential current registered from the flow stoppage until the current reached a steady-state. The concentration was then calculated by the following equation:

$$[\text{lactate}] = Q/2FV \quad (4)$$

where V is the volume of sample within the measurement zone and F is Faraday's constant.

[0278] This assay was performed using lactate solutions having nominal lactate concentrations of 1.0, 5.0, and 10.0

Abbott Ex. 1002 - 314/1438

mM. The measured concentrations for the assay were 1.9, 5.4, and 8.9 mM respectively.

Example 5

Determination of the Oxidation State of Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$^{+/+2}$ Complexed with poly(1-vinyl imidazole)

[0279] A sensor having a three electrode design was commercially obtained from Ecossensors Ltd., Long Hanborough, England, under the model name "large area disposable electrode". The sensor contained parallel and coplanar working, reference and counter electrodes. The working surface area (0.2 cm^2) and counter electrodes were formed of printed carbon and the reference electrode was formed of printed Ag/AgCl. A redox mediator was coated on the carbon working electrode. The redox mediator was formed by complexation of poly(1-vinyl imidazole) with Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$_2$ in a ratio of 15 imidazole groups per Os cation followed by cross linking the osmium polymer with glucose oxidase using polyethylene glycol diglycidyl ether.

[0280] The electrode was cured at room temperature for 24 hours. The coplanar electrode array was then immersed in a buffered electrolyte solution, and a potential of +200 mV (sufficient for conversion of Os(II) to Os(III),) was applied between the working electrode and the reference electrode.

[0281] Upon application of the potential, an undetectable charge of less than 1 μC was passed. Subsequent reduction and reoxidation of the redox mediator yielded a charge for conversion of all Os from Os(II) to Os(III) of 65 TC. Therefore, more than 98% of the Os cations in the redox mediator were in the desired oxidized Os(III) state.

Example 6

Determination of the Oxidation State of the Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$^{+/+2}$ Complexed with poly (4-vinyl pyridine)

[0282] A similar experiment to that of Example 5 was conducted with the same working/counter/reference electrode configuration except that the redox mediator on the working electrode was changed to a complex of Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$_2$ with poly(4-vinyl pyridine), with 12 pyridine groups per Os cation, cross linked with glucose oxidase via polyethylene glycol diglycidyl ether.

[0283] Two sensors were constructed. The electrodes of the two sensors were cured at room temperature for 24 hours. The electrodes were then immersed in a buffered electrolyte solution and a potential of +200 mV was applied between the working and reference electrodes.

[0284] Upon application of the potential to the electrodes, a charge of 2.5 TC and 3.8 TC was passed in the two sensors, respectively. Subsequent reduction and reoxidation of the redox mediators yielded oxidation charges of 27.9 TC and 28.0 T C, respectively. Therefore, the sensors originally contained 91% and 86% of the Os cations in the desirable oxidized Os(III) state.

Example 7

Optical Sensor

[0285] An optical sensor is constructed by applying a film of redox polymer with crosslinked enzyme onto a light-transparent support such as a glass slide. The quantity of redox mediator is equal to or greater than (in a stoichiometric sense) the maximum quantity of analyte expected to fill the measurement zone. The spacer material, sorbent and facing support are securely clamped. The sample chamber is adapted to transmit light through the assembled sensor to an optical density detector or to a luminescence and/or fluorescence detector. As sample fills the sample chamber and the redox mediator is oxidized, changes in the absorption, transmission, reflection or luminescence and/or fluorescence of the redox mediator in the chamber are correlated to the amount of glucose in the sample.

Example 8

Blood Volumes from Upper Arm Lancet Sticks

[0286] The forearm of a single individual was pierced with a lancet multiple times in order to determine the reproducibility of blood volumes obtained by this method. Despite more than thirty lancet sticks in the anterior portion of each forearm and the dorsal region of the left forearm, the individual identified each stick as virtually painless.

[0287] The forearm was pierced with a Payless Color Lancet. The blood from each stick was collected using a 1 μL

Abbott Ex. 1002 - 315/1438

capillary tube, and the volume was determined by measuring the length of the blood column. The volumes obtained from each stick are shown below in Table 4.

Table 4

Volume of Lancet Sticks

	Left Anterior Forearm, (nL)	Right Anterior Forearm, (nL)	Left Dorsal Forearm, (nL)
1	180	190	180
2	250	180	300
3	170	120	310
4	150	100	300
5	100	210	60
6	50	140	380
7	90	120	220
8	130	140	200
9	120	100	380
10		100	320
11			260
12			250
13			280
14			260
Avg.	138 ± 58 nL	140 ± 40 nL	264 ± 83 nL

Example 9

A Sensor with Diffusible Redox Mediator

[0288] A sensor was formed by printing graphite ink (Graphite #G4491, Ercon, Wareham, MA) on a polyester substrate. A mixture of 5.5 $\mu g/cm^2$ [Os(dimethyoxybipyridine)$_2$(vinylimidazole)Cl]Cl, 23.7 $\mu g/cm^2$ PQQ-glucose dehydrogenase, and 18.2 $\mu g/cm^2$ Zonyl FSO® surfactant (E. I. duPont de Nemours & Co., Inc., Wilmington, DE) were deposited on a portion of the working electrode. A 150 μm thick pressure sensitive adhesive tape was then applied to the working electrode leaving only a portion of the working electrode exposed to form a sample chamber. A second polyester film with a counter electrode disposed on the film was provided over the pressure sensitive adhesive tape. The counter electrode was formed by disposing Ag/AgCl ink (Silver/Silver Chloride #R414, Ercon, Wareham, MA) over the second polyester film. The Ag/AgCl counter electrode was coated with approximately 100 $\mu g/cm^2$ of methylated poly(vinylimidazole) crosslinked using PEGDGE.

Example 10

Measuring Glucose using Sensor with Diffusible Redox Mediator at a Potential of 0 V.

[0289] Sensors were formed as described in Example 9 and used to measure glucose/buffer solutions at 0, 90, 180, 270, and 360 mg/dL glucose concentration. The charge measured over time for each of these solutions is graphed in Figure 15. In the absence of glucose, the sensor indicates about 3 mg/dL glucose concentration. Figure 16 illustrates the measured charge versus glucose concentration for three sensors at each glucose concentration. The measured charge varies linearly with glucose concentration similar to what is observed for sensors using non-leachable redox mediator.

Abbott Ex. 1002 - 316/1438

Example 11

Other Sensors Formed Using Diffusible Redox Mediator

[0290] Sensors A and B were formed by printing graphite ink (Graphite #G4491, Ercon, Wareham, MA) on a polyester substrate. For Sensor A, a mixture of 8.0 μg/cm^2 [Os(dimethyoxybipyridine)$_2$(vinyl imidazole)Cl]Cl, 34.7 μg/cm^2 PQQ-glucose dehydrogenase, and 26.6 μg/cm^2 Zonyl FSO® surfactant (E.I. duPont de Nemours & Co., Inc., Wilmington, DE) were deposited on a portion of the working electrode. For Sensor B, a mixture of 24 μg/cm^2 [Os(dimethyoxybipyridine)$_2$(vinyl imidazole)Cl]Cl, 104 μg/cm^2 PQQ-glucose dehydrogenase, and 80 μg/cm^2 Zonyl FSO® surfactant (E.I. duPont de Nemours & Co., Inc., Wilmington, DE) were deposited on a portion of the working electrode. A 200 μm pressure sensitive adhesive tape was then formed over the working electrode of each sensor leaving only a portion of the working electrode exposed to form a sample chamber. A second polyester film with a counter electrode disposed on the film was provided over the pressure sensitive adhesive tape. The counter electrode of each sensor was formed by disposing Ag/AgCl ink (Silver/Silver Chloride #R414, Ercon, Wareham, MA) over the second polyester film. The Ag/AgCl counter electrode was coated with approximately 100 μg/cm^2 of methylated poly(vinylimidazole) crosslinked using PEGDGE.

Example 12

Varying the Amount of Diffusible Redox Mediator in the Sensor

[0291] Sensors A and B were each tested to determine the amount of time required for electrolysis of the analyte. Figure 17 illustrates the results. Increasing the amount of diffusible redox mediator in the sample decreases the response time of the sensor.

Example 13

Clinical Accuracy of the Small Volume Sensor

[0292] The sensor of this Example was constructed corresponding to the embodiment of the invention depicted in Figures 24A, 24B, and 24C. The carbon working electrode was printed on a Melinex™ polyester film (DuPont, Wilmington, Delaware), as described in Example 11. The carbon electrode was coated with 18 μ g/cm^2 Os[(MeO)$_2$bpy]$_2$(1-vinyl imidazole)Cl$_3$, 162 μg/cm^2 GDH (Toyobo, Japan), 1.35 μg/cm^2 PQQ (Fluka, Mila, Wisconsin), and 60 μg/cm^2 Zonyl FSO (DuPont, Wilmington, Delaware). The coatings were applied to the working electrode at 18°C and in 50% relative humidity. An adhesive (50 μm thickness) was placed on the carbon electrode surrounding the coated surface and forming a channel having a width of about 0.04 inches.

[0293] Two Ag/AgCl counter/reference electrodes were printed on a second Melinex™ polymer film, as described in Example 11. The film was then brought into contact with the adhesive and the working electrode film so that the working electrode and two counter electrodes were facing each other. The counter/reference electrodes were coated with 142 μg/cm^2 methylated polyvinyl imidazole, 18 μg/cm^2 PEGDGE (Polysciences, Warington, Pennsylvania), and 7 μg/cm^2 Zonyl FSO (DuPont, Wilmington, Delaware). One of the counter electrodes, upstream of the other counter electrode, was used as an indicator electrode to determine when the sample chamber was full. The sensors were laminated by three passes with a hand roller and aged for three days at room temperature over $CaSO_4$.

[0294] The sensors were constructed so that when sufficient current flowed between indicator and counter/reference electrodes, an external circuit emitted a visual signal indicating that the channel overlying the working electrode was full of blood.

[0295] A few days prior to using the sensors, dry capacitance measurements were taken to determine the uniformity of the sample chamber volume. The variation in capacitance reflected misalignment of electrodes and/or variation in adhesive thickness. The mean capacitance measured was 7.49 pF with a standard deviation of 0.28 pF or 3.8%. The maximum capacitance measured was 8.15 pF and the minimum capacitance measured was 6.66 pF.

[0296] The sensors were used to determine the glucose concentration in blood samples obtained from 23 people. In the study, the people ranged from 26 to 76 years of age, fourteen were men, and nine were women. Six of the people were diagnosed with Type 1 diabetes, sixteen were diagnosed with Type 2 diabetes, and one person was unknown regarding diabetic status. The people studied had an average hematocrit of 40.7% with a standard deviation of 3.9%. The maximum hematocrit was 49% and the minimum hematocrit was 33.2%.

[0297] One blood sample for each person was collected by pricking the finger of the subject. A small volume sensor was filled with this residual blood.

[0298] Three blood samples for each person were then collected in small volume sensors by using a 2mm Carelet™

Abbott Ex. 1002 - 317/1438

to lance the arm. If an adequate sample was not obtained in 10 seconds, the area around the puncture wound was kneaded, and then the sensor was filled. Sixteen of the sixty-nine samples required that the wound be kneaded.

[0299] Three blood samples per person were collected by venipuncture. YSI blood glucose measurements and hematocrit measurements were taken on at least one sample. Forty-six small volume sensors were also filled with blood from these samples.

[0300] Measurements from the sensor were performed at an applied potential of 0 mV. BAS potentiostats (CV50W, West Lafayette, Indiana) were "on" before any sample was applied, so that as the strips filled, electrolysis was immediate. Current collection was for 150 seconds (this charge is termed "complete" electrolysis), although most assays were essentially complete well before 150 seconds. No results were discarded. Three successive sensor blood glucose measurements were taken.

[0301] Measurements for the control samples were performed using YSI blood glucose measurement (Yellow Springs Instruments, Model 2300 Chemical Glucose Analyzer).

[0302] The data was plotted against YSI venous results and a linear function was determined from the data. All data was collected from "complete" (150 second) electrolysis of glucose in the sensor.

[0303] Figure 28 shows the data for 69 small volume sensors tested on blood obtained from the arm. R^2 was 0.947, the average CV (coefficient of variation) was 4.8%, and the RMS (root mean square) CV was 5.7%.

[0304] Figure 29 shows the data for 23 small volume sensors tested on blood obtained from the finger. R^2 was 0.986.

[0305] Figure 30 shows the data for 46 small volume sensors tested on venous blood. R^2 was 0.986. The average CV was 3.8%. The RMS CV was 4.6%.

[0306] The invention has been described with reference to various specific and preferred embodiments and techniques.

[0307] All publications and patent applications in this specification are indicative of the level of ordinary skill in the art to which this invention pertains.

Claims

1. A sensor (20) for determining the concentration of an analyte in a sample fluid, the sensor comprising:

   an electrode pair comprising a working electrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) and a counter electrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), wherein at least a portion of the working electrode is within an effective distance of no more than 200 μm of a portion of the counter electrode and, optionally, the counter electrode is a counter/reference electrode;
   an optional reference electrode (512, 532, 552, 572, 585, 612, 652);
   a sample chamber (26, 526, 546, 566, 582, 606, 646) for holding the sample fluid in electrolytic contact with the working electrode, the counter electrode, and the reference electrode, if present, the sample chamber comprising a measurement zone positioned adjacent to the working electrode, the counter electrode, and the reference electrode, if present, wherein the measurement zone is sized to contain a volume of no more than about 1 μL of sample fluid and, optionally, the sample chamber is sized to contain no more than about 1 μL of sample fluid; and
   an analyte-responsive enzyme and a diffusible redox mediator disposed in the measurement zone;
   the sensor having been configured and arranged so that a background signal generated by the diffusible redox mediator is no more than either:

      (a) five times a signal generated by oxidation or reduction of an average normal physiological amount of analyte; or
      (b) five times a signal generated by oxidation or reduction of an amount of the analyte corresponding to an average deviation from an average normal physiological amount of analyte.

2. A sensor (20) for determining the concentration of: the analyte glucose in a sample fluid, the sensor comprising:

   an electrode pair comprising a working electrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) and a counter electrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), wherein the working electrode and counter electrode are separated by an effective distance in a range of 25 to 1000 μm;
   a sample chamber (26, 526, 546, 566, 582, 606, 646) for holding the sample fluid, the sample chamber comprising a measurement zone positioned adjacent to the working electrode and the counter electrode, wherein the measurement zone is sized to contain a volume of no more than about 1μL of the sample; and
   an analyte-responsive enzyme and a diffusible redox mediator disposed in the measurement zone;

Abbott Ex. 1002 - 318/1438

the sensor having been configured and arranged so that a background signal generated by the diffusible redox mediator is no more than five times a signal generated by oxidation or reduction of 5 mM of glucose.

3. A sensor according to any of claims 1 and 2, wherein the sensor is configured and arranged so that a background signal generated by the diffusible redox mediator is the same or less than the signal generated by oxidation or reduction of the average normal physiological amount of analyte.

4. A sensor according to any of.claims 1 and 2, wherein the sensor is configured and arranged so that a background signal generated by the diffusible redox mediator is no more than 25% of the signal generated by oxidation or reduction of the analyte and, preferably, no more than 5% of the signal generated by oxidation or reduction of the analyte.

5. A sensor according to any of claims 1 to 4, wherein the sensor comprises:

(a) a first substrate (500, 520, 540, 560, 579, 600, 640) having a proximal end and a distal end, the first substrate defining a first side edge (656) and a second side edge (658) of the electrochemical sensor extending from the proximal end to the distal end of the first substrate, the distal end being configured and arranged for insertion into a sensor reader;
(b) a second substrate (508, 528, 548, 568, 583, 608, 648) disposed over the first substrate, the working electrode being disposed on one of the first and second substrates and the counter electrode being disposed on one of the first and second substrates;
(c) a spacer (28, 504, 524, 544, 564, 581, 604, 644) disposed between the first and second substrates and defining a first aperture along the first side edge of the sensor and a second aperture along the second side edge of the sensor, the sample chamber extending from the first aperture to the second aperture; and
(d) at least one indicator electrode disposed on at least one of the first and second substrates and positioned relative to either the.measurement zone or the sample chamber to determine when the measurement zone or sample chamber contains sample.

6. A sensor according to any of claims 1 to 4, wherein the sensor comprises:

(a) a first substrate having a proximal end and a distal end, the distal end being configured and arranged for insertion into a sensor reader, the first substrate defining a first side edge and a second side edge of the electrochemical sensor extending from the proximal end to the distal end of the first substrate;
(b) a second substrate disposed over the first substrate, the working electrode being disposed on one of the first and second substrates and the counter electrode being disposed on one of the first and second substrates;
(c) a spacer disposed between the first and second substrates and defining a first aperture along the proximal end of the sensor and a second aperture along the first side edge of the sensor, the sample chamber extending from the first aperture to the second aperture; and
(d) at least one indicator electrode disposed on at least one of the first and second substrates and positioned relative to either the measurement zone or the sample chamber to determine when the measurement zone or the sample chamber contains sample.

7. A sensor according to any of claims 1 to 4, wherein the sensor comprises an indicator electrode disposed in the sensor to indicate when either the measurement zone contains a sample or when the sample chamber contains a sample.

8. A sensor according to any of claims 5 to 7, wherein the indicator electrode is also a working electrode or a counter electrode.

9. A sensor according to any of claims 5 to 8, further comprising a visual or auditory sign, coupled to the indicator electrode, that activates when the indicator electrode indicates that the measurement zone or sample chamber contains sample.

10. A sensor according to any of claims 5 to 9, wherein the indicator electrode is disposed in facing relationship to one of the working electrode and the counter electrode.

11. A sensor according to any of claims 5 to 10, wherein the sensor comprises at least two indicator electrodes disposed in the sensor, wherein a first indicator electrode indicates when the measurement zone or sample chamber is

Abbott Ex. 1002 - 319/1438

beginning to fill with sample, and a second indicator electrode indicates when the measurement zone or sample chamber is substantially filled with sample.

12. A sensor according to any of claims 5 to 10, wherein the sensor comprises at least two indicator electrodes disposed in the sensor, wherein two of the indicator electrodes comprise a first counter/indicator electrode and a second counter/indicator electrode with the counter electrode disposed between the first and second counter/indicator electrodes.

13. A sensor according to any of claims 1 to 12, wherein the measurement zone and the sample chamber have a same volume.

14. A sensor according to any of claims 1 to 13, wherein the analyte is glucose and the analyte-responsive enzyme is a glucose-responsive enzyme.

15. A sensor according to any of claims 1 to 13, wherein the analyte is a drug.

16. A sensor according to any of claims 1 to 15, wherein the measurement zone is bounded on at least two sides by the working electrode and the counter electrode and, optionally, the working electrode and counter electrode form a facing electrode pair with the measurement zone positioned between the working electrode and the counter electrode.

17. A sensor according to any of claims 1 to 16, wherein the sensor is configured and arranged so that the mediator oxidizes the analyte and the half-wave potential of the redox mediator, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, is no more than about +100 millivolts relative to the potential of the counter/reference electrode.

18. A sensor according to any of claims 1 to 17, wherein the sensor is configured and arranged so that the mediator oxidizes the analyte and the half-wave potential of the redox mediator, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, is about the same as the potential of the counter/reference electrode.

19. A sensor according to any of claims 1 to 18, wherein the sensor is configured and arranged so that the mediator oxidizes the analyte and the half-wave potential of the redox mediator, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, is no more than about -150 millivolts relative to the potential of the counter/reference electrode.

20. A sensor according to any of claims i to 19, wherein, within the sensor, the effective diffusion coefficient of the redox mediator through the sample fluid is less than the effective diffusion coefficient of the analyte through the sample fluid and, preferably, at least ten times less than the effective diffusion coefficient of the analyte through the sample fluid.

21. A sensor according to any of claims 1 to 20, wherein the diffusible mediator has a molecular weight of at least 5,000 daltons.

22. A sensor according to any of claims 1 to 21, wherein the sensor is configured and arranged so that the redox mediator is more readily electrolyzed on the working electrode than the counter electrode.

23. A sensor according to any of claims 1 to 22, wherein the sensor comprises a molar amount of the redox mediator that is, on a stoichiometric basis, no more than an average normal physiological amount of the analyte and, preferably, the sensor comprises a molar amount of the redox mediator that is, on a stoichiometric basis, no more than 20% of an average normal physiological amount of the analyte.

24. A sensor according to any of claims 1 to 23, wherein the working electrode has a surface area of no more than about 0.01 cm^2 exposed in the measurement zone.

25. A sensor according to any of claims 1 to 24, wherein the activity of the enzyme is no more than 1 unit/cm^3

26. A sensor according to any of claims 1 to 25, wherein the sensor is configured and arranged so that the diffusible redox mediator precipitates when reacted at the counter electrode.

27. A sensor according to any of claims 1 to 26, wherein the sensor is configured and arranged so that a mathematical

Abbott Ex. 1002 - 320/1438

product of the effective diffusion coefficient of the redox mediator and the concentration of the redox mediator is no more than 1 x 10^{-12} moles cm^{-1} sec^{-1} when sample fluid fills the measurement zone.

28. A sensor according to any of claims 1 to 27, wherein the diffusible redox mediator is disposed on the working electrode.

29. A sensor according to any of claims 1 to 28, wherein the analyte-responsive enzyme is disposed on the working electrode.

30. A method for determining a concentration of an analyte in a sample, comprising the steps of:

contacting a sample with any of the electrochemical sensors of claims 1 to 29;
generating a sensor signal at the working electrode, and
determining the concentration of the analyte using the sensor signal.

31. A method according to claim 30, wherein the background signal that is generated by the diffusible redox mediator is no more than either:

(a) five times a signal generated by oxidation or reduction of an average normal physiological amount of analyte; or
(b) five times a signal generated by oxidation or reduction of an amount of the analyte corresponding to an average deviation from an average normal physiological amount of analyte; or
(c) five times a signal generated by oxidation or reduction of 5 mM of glucose.

32. A method according to any of claims 30 to 31, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by coulometry using the sensor signal.

33. A method according to any of claims 30 to 31, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by amperometry using the sensor signal.

34. A method according to any of claims 30 to 31, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by potentiometry using the sensor signal.

35. A method according to any of claims 30 to 31, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by chronoamperometry using the sensor signal.

36. A method according to any of claims 30 to 31, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by chronopotentiometry using the sensor signal.

37. A method according to any of claims 30 to 31, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by a Cotrell measurement technique using the sensor signal.

38. A method according to any of claims 30 to 37, further comprising:

providing calibration data on a batch of the electrochemical sensors to a measurement instrument, said calibration data comprising information related to a magnitude of a background charge for the batch of the electrochemical sensors;

wherein the step of determining the concentration of the analyte comprises determining the concentration of the analyte using the sensor signal and the calibration data.

39. A method for determining a concentration of an analyte in a sample, the method comprising the steps of:

contacting a sample with any of the electrochemical sensors of claims 1 to 29;
observing a signal from the indicator electrode to signify that the measurement zone contains sample;
applying a potential between the working electrode and the counter electrode to electrolyze the analyte in the sample;
generating an analyte-responsive signal from the sensor in response to electrolysis of the analyte in the sam-

Abbott Ex. 1002 - 321/1438

ple; and
determining the concentration of the analyte using the analyte-responsive signal.

40. A method of manufacturing any of the electrochemical sensors of claims 1 to 29, the method comprising:

(a) forming a plurality of working electrodes on a first substrate;
(b) forming a plurality of counter electrodes on a second substrate;
(c) disposing a spacer layer on one of the first and second substrates;
(d) removing a portion of the spacer layer to define sample chamber regions;
(e) laminating the first and second substrates together; and
(f) separating a plurality of electrochemical sensors from the laminated substrates, each electrochemical sensor comprising at least one of the working electrodes, at least one of the counter electrodes, and at least one of the sample chamber regions.

41. A method according to claim 40, wherein the first substrate is a first region of a substrate and the second substrate is a second region of the substrate, and further comprising:

folding the substrate to overlay the first and second regions of the substrate.

42. A method according to any of claims 40 and 41, wherein separating the plurality of electrochemical sensors comprises cutting the first and second substrates to separate the electrochemical sensors and to define at least one end of the sample chamber of the electrochemical sensors.

43. A method according to any of claims 40 to 42, further comprising forming a plurality of indicator electrodes on one of the first and second substrates.

44. A method according to any of claims 40 to 43, wherein the portion of the spacer layer is removed to define the sample chamber regions after the spacer layer is disposed on one of the first and second substrates.

Patentansprüche

1. Sensor (20) zur Bestimmung der Konzentration eines Analyten in einem Probenfluid, wobei der Sensor umfaßt:

ein Elektrodenpaar, das eine Arbeitselektrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) und eine Gegenelektrode (24, 510, 530, 550, 570, 584, 610, 650, 1020) umfaßt, wobei wenigstens ein Abschnitt der Arbeitselektrode innerhalb eines wirksamen Abstands von nicht mehr als 200 μm von einem Abschnitt der Gegenelektrode liegt und die Gegenelektrode gegebenenfalls eine Gegen/Bezugs-Elektrode ist;
eine fakultative Bezugselektrode (512, 532, 552, 572, 585, 612, 652) ;
eine Probenkammer (26, 526, 546, 566, 582, 606, 646), die das Probenfluid in elektrolytischem Kontakt mit der Arbeitselektrode, der Gegenelektrode und, soweit vorhanden, der Bezugselektrode halten kann, wobei die Probenkammer eine Meßzone umfaßt, die angrenzend an die Arbeitselektrode, die Gegenelektrode und, soweit vorhanden, die Bezugselektrode angeordnet ist, wobei die Meßzone so dimensioniert ist, dass sie ein Volumen von nicht mehr als etwa 1μL Probenfluid enthält und die Probenkammer gegebenenfalls so dimensioniert ist, dass sie nicht mehr als etwa 1 μL des Probenfluids enthält; und
ein auf den Analyten ansprechendes Enzym und einen diffundierbaren Redox-Mediator, die in der Meßzone angeordnet sind;

wobei der Sensor so konfiguriert und angeordnet ist, dass ein Hintergrundsignal, das durch den diffundierbaren RedoxMediator erzeugt wird, nicht größer ist als entweder

(a) das Fünffache eines Signals, das durch Oxidation oder Reduktion einer mittleren normalen physiologischen Menge des Analyten erzeugt wird; oder
(b) das Fünffache eines Signals, das durch Oxidation oder Reduktion einer solchen Menge des Analyten erzeugt wird, die einer mittleren Abweichung von einer mittleren normalen physiologischen Menge des Analyten entspricht.

2. Sensor (20) zur Bestimmung der Konzentration des Analyten Glucose in einem Probenfluid, wobei der Sensor

Abbott Ex. 1002 - 322/1438

umfaßt:

ein Elektrodenpaar, das eine Arbeitselektrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) und eine Gegenelektrode (24, 510, 530, 550, 570, 584, 610, 650, 1020) umfaßt, wobei die Arbeitselektrode und die Gegenelektrode durch einen wirksamen Abstand in einem Bereich von 25 bis 1000 μm voneinander getrennt sind; eine Probenkammer (26, 526, 546, 566, 582, 606, 646), die das Probenfluid hält, wobei die Probenkammer eine Meßzone umfaßt, die angrenzend an die Arbeitselektrode und die Gegenelektrode angeordnet ist, wobei die Meßkammer so dimensioniert ist, dass sie ein Volumen von nicht mehr als etwa 1 μL der Probe enthält; und ein auf den Analyten ansprechendes Enzym und einen diffundierbaren Redox-Mediator, die in der Meßzone angeordnet sind;

wobei der Sensor so konfiguriert und angeordnet ist, dass ein Hintergrundsignal, das von dem diffundierbaren Redox-Mediator erzeugt wird, nicht mehr als das Fünffache eines Signals beträgt, das durch Oxidation oder Reduktion von 5 mM Glucose erzeugt wird.

3. Sensor nach irgendeinem der Ansprüche 1 und 2, wobei der Sensor so konfiguriert und angeordnet ist, dass ein Hintergrundsignal, das durch den diffundierbaren Redox-Mediator erzeugt wird, gleich ist wie oder kleiner ist als das Signal, das durch Oxidation oder Reduktion der mittleren normalen physiologischen Menge des Analyten erzeugt wird.

4. Sensor nach irgendeinem der Ansprüche 1 und 2, wobei der Sensor so konfiguriert und angeordnet ist, dass sein Hintergrundsignal, das durch den diffundierbaren Redox-Mediator erzeugt wird, nicht mehr als 25% des Signals beträgt, das durch Oxidation oder Reduktion des Analyten erzeugt wird und vorzugsweise nicht mehr als 5% des Signals beträgt, das durch Oxidation oder Reduktion des Analyten erzeugt wird.

5. Sensor nach irgendeinem der Ansprüche 1 bis 4, wobei der Sensor umfaßt:

(a) ein erstes Substrat (500, 520, 540, 560, 579, 600, 640) mit einem proximalen Ende und einem distalen Ende, wobei das erste Substrat eine erste Seitenkante (656) und eine zweite Seitenkante (658) des elektrochemischen Sensors definiert, die sich von dem proximalen Ende bis zum distalen Ende des ersten Substrats erstrecken, wobei das distale Ende so konfiguriert und angeordnet ist, dass es in ein Sensor-Lesegerät einschiebbar ist;
(b) ein zweites Substrat (508, 528, 548, 568, 583, 608, 648), das über dem ersten Substrat angeordnet ist, wobei die Arbeitselektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist und die Gegenelektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist;
(c) einen Abstandhalter (28, 504, 524, 544, 564, 581, 604, 644), der zwischen dem ersten und dem zweiten Substrat angeordnet ist und eine erste Öffnung längs der ersten Seitenkante des Sensors definiert und eine zweite Öffnung entlang der zweiten Seitenkante des Sensors, wobei die Probenkammer sich von der ersten Öffnung zu der zweiten Öffnung erstreckt; und
(d) wenigstens eine Anzeigeelektrode, die auf wenigstens einem von dem ersten und dem zweiten Substrat angeordnet ist und im Hinblick auf die Meßzone oder die Probenkammer relativ so angeordnet ist, dass festgestellt wird, wenn die Meßzone oder Probenkammer Probe enthält.

6. Sensor nach irgendeinem der Ansprüche 1 bis 4, wobei der Sensor umfaßt:

(a) ein erstes Substrat mit einem proximalen Ende und einem distalen Ende, wobei das distale Ende für einen Einschub in ein Sensor-Lesegerät konfiguriert und angeordnet ist, wobei das erste Substrat eine erste Seitenkante und eine zweite Seitenkante des elektrochemischen Sensors definiert, die sich von dem proximalen Ende zu dem distalen Ende des ersten Substrats erstrecken;
(b) ein zweites Substrat, das über dem ersten Substrat angeordnet ist, wobei die Arbeitselektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist und die Gegenelektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist;
(c) einen Abstandshalter, der zwischen dem ersten und dem zweiten Substrat angeordnet ist und eine erste Öffnung längs des proximalen Endes des Sensors und eine zweite Öffnung längs der ersten Seitenkante des Sensors definiert, wobei sich die Probenkammer von der ersten Öffnung bis zu der zweiten Öffnung erstreckt; und
(d) wenigstens eine Anzeigeelektrode, die auf wenigstens einem von dem ersten und dem zweiten Substrat angeordnet ist und so gegenüber der Meßzone oder der Probenkammer angeordnet ist, dass festgestellt wird,

Abbott Ex. 1002 - 323/1438

wenn die Meßzone oder die Probenkammer Probe enthält.

7. Sensor nach irgendeinem der Ansprüche 1 bis 4, wobei der Sensor eine Anzeigeelektrode umfaßt, die in dem Sensor angeordnet ist und anzeigt, wenn entweder die Meßzone eine Probe enthält oder wenn die Probenkammer eine Probe enthält.

8. Sensor nach irgendeinem der Ansprüche 5 bis 7, wobei die Anzeigeelektrode auch eine Arbeitselektrode oder eine Gegenelektrode ist.

9. Sensor nach irgendeinem der Ansprüche 5 bis 8, der außerdem ein visuelles oder hörbares Zeichen umfaßt, das mit der Anzeigelektrode gekoppelt ist und aktiviert wird, wenn die Anzeigeelektrode anzeigt, dass die Meßzone oder die Probenkammer Probe enthält.

10. Sensor nach irgendeinem der Ansprüche 5 bis 9, wobei die Anzeigelektrode gegenüber einer von der Arbeitselektrode und der Gegenelektrode angeordnet ist.

11. Sensor nach irgendeinem der Ansprüche 5 bis 10, wobei der Sensor wenigstens zwei Anzeigeelektroden umfaßt, die in dem Sensor angeordnet sind, wobei eine erste Anzeigeelektrode anzeigt, wenn sich die Meßzone oder die Probenkammer mit Probe zu füllen beginnt, und eine zweite Anzeigenelektrode anzeigt, wenn die Meßzone oder die Probenkammer im wesentlichen mit Probe gefüllt ist.

12. Sensor nach irgendeinem der Ansprüche 5 bis 10, wobei der Sensor wenigstens zwei Anzeigeelektroden umfaßt, die in dem Sensor angeordnet sind, wobei zwei der Anzeigeelektroden eine erste Gegen/Anzeigeelektrode und eine zweite Gegen/Anzeigeelektrode umfassen, wobei die Gegenelektrode zwischen der ersten und der zweiten Gegen/Anzeigeelektrode angeordnet ist.

13. Sensor nach irgendeinem der Ansprüche 1 bis 12, wobei die Meßzone und die Probenkammer das gleiche Volumen aufweisen.

14. Sensor nach irgendeinem der Ansprüche 1 bis 13, wobei der Analyt Glucose ist, und das auf den Analyten entsprechende Enzym ein auf Glucose ansprechendes Enzym ist.

15. Sensor nach irgendeinem der Ansprüche 1 bis 13, wobei der Analyt eine Droge ist.

16. Sensor nach irgendeinem der Ansprüche 1 bis 15, wobei die Meßzone an wenigstens zwei Seiten durch die Arbeitselektrode und die Gegenelektrode begrenzt ist und die Arbeitselektrode und die Gegenelektrode ggf. ein sich gegenüberliegendes Elektronenpaar bilden, wobei die Meßzone zwischen der Arbeitselektrode und der Gegenelektrode angeordnet ist.

17. Sensor nach irgendeinem der Ansprüche 1 bis 16, wobei der Sensor so konfiguriert und angeordnet ist, dass der Mediator den Analyten oxidiert und das Halbwellenpotential des Redox-Mediators, gemessen durch zyklische Voltametrie in 0,1 M NaCl bei pH 7, nicht mehr als etwa +100 Millivolt beträgt, bezogen auf das Potential der Gegen/Bezugs-Elektrode.

18. Sensor nach irgendeinem der Ansprüche 1 bis 17, wobei der Sensor so konfiguriert und angeordnet ist, dass der Mediator den Analyten oxidiert und das Halbwellenpotential des Redox-Mediators, gemessen durch zyklische Voltametrie in 0,1 M NaCl bei pH 7, etwa das gleiche ist, wie das Potential der Gegen/Bezugs-Elektrode.

19. Sensor nach irgendeinem der Ansprüche 1 bis 18, wobei der Sensor so konfiguriert und angeordnet ist, dass der Mediator den Analyten oxidiert und das Halbwellenpotential des Redox-Mediators, gemessen durch zyklische Voltametrie in 0,1 M NaCl bei pH 7, nicht mehr als etwa -150 Millivolt, bezogen auf das Potential der Gegen/Referenz-Elektrode, beträgt.

20. Sensor nach irgendeinem der Ansprüche 1 bis 19, wobei innerhalb des Sensors der wirksame Diffusionskoeffizient des Redox-Mediators durch das Probenfluid geringer ist als der effektive Diffusionskoeffizient des Analyten durch das Probenfluid und vorzugsweise wenigstens 10-fach geringer ist als der effektive Diffusionskoeffizient des Analyten durch das Probenfluid.

Abbott Ex. 1002 - 324/1438

21. Sensor nach irgendeinem der Ansprüche 1 bis 20, wobei der diffundierbare Mediator ein Molekulargewicht von wenigstens 5.000 Dalton aufweist.

22. Sensor nach irgendeinem der Ansprüche 1 bis 21, wobei der Sensor so konfiguriert und angeordnet ist, dass der Redox-Mediator leichter an der Arbeitselektrode elektrolysiert wird als der Gegenelektrode.

23. Sensor nach irgendeinem der Ansprüche 1 bis 22, wobei der Sensor eine molare Menge des Redox-Mediators enthält, die auf einer stöchiometrischen Basis nicht mehr als eine mittlere normale physiologische Menge des Analyten beträgt und der Sensor vorzugsweise eine molare Menge des Redox-Mediators umfaßt, die auf einer stöchiometrischen Basis nicht mehr als 20% einer mittleren normalen physiologischen Menge des Analyten beträgt.

24. Sensor nach irgendeinem der Ansprüche 1 bis 23, wobei die Arbeitselektrode eine Oberfläche von nicht mehr als etwa 0,01 cm^2, die in der Meßzone freiliegt, aufweist.

25. Sensor nach irgendeinem der Ansprüche 1 bis 24, wobei die Aktivität des Enzyms nicht mehr als 1 Einheit/cm^3 beträgt.

26. Sensor nach irgendeinem der Ansprüche 1 bis 25, wobei der Sensor so konfiguriert und angeordnet ist, dass der diffundierbare Redox-Mediator ausgefällt wird, wenn er an der Gegenelektrode reagiert.

27. Sensor nach irgendeinem der Ansprüche 1 bis 26, wobei der Sensor so konfiguriert und angeordnet ist, dass ein mathematisches Produkt des wirksamen Diffusionskoeffizienten des Redox-Mediators und der Konzentration des Redox-Mediators nicht mehr als 1 x 10^{-12} Mol cm^{-1} s^{-1} beträgt, wenn das Probenfluid die Meßzone füllt.

28. Sensor nach irgendeinem der Ansprüche 1 bis 27, wobei der diffundierbare Redox-Mediator auf der Arbeitselektrode angeordnet ist.

29. Sensor nach irgendeinem der Ansprüche 1 bis 28, wobei das auf den Analyten ansprechende Enzym auf der Arbeitselektrode angeordnet ist.

30. Verfahren zur Bestimmung einer Konzentration eines Analyten in einer Probe, das die Schritte umfaßt:

    Inkontaktbringen einer Probe mit irgendeinem der elektrochemischen Sensoren der Ansprüche 1 bis 29;
    Erzeugen eines Sensorsignals an der Arbeitselektrode, und
    Bestimmung der Konzentration des Analyten unter Verwendung des Sensorsignals.

31. Verfahren nach Anspruch 30, wobei das Hintergrundsignal, das durch den diffundierbaren Redox-Mediator erzeugt wird, nicht mehr ist als entweder:

    (a) das Fünffache eines Signals, das durch Oxidation oder Reduktion einer mittleren normalen physiologischen Menge des Analyten erzeugt wird; oder
    (b) das Fünffache eines Signals, das durch Oxidation oder Reduktion einer Menge des Analyten erzeugt wird, die einer mittleren Abweichung von einer mittleren normalen physiologischen Menge des Analyten entspricht; oder
    (c) das Fünffache eines Signals, das durch Oxidation oder Reduktion von 5 mM Glucose erzeugt wird.

32. Verfahren nach irgendeinem der Ansprüche 30 bis 31, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Coulometrie unter Verwendung des Sensorsignals umfaßt.

33. Verfahren nach irgendeinem der Ansprüche 30 bis 31, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Amperometrie unter Verwendung des Sensorsignals umfaßt.

34. Verfahren nach irgendeinem der Ansprüche 30 bis 31, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Potentiometrie unter Verwendung des Sensorsignals umfaßt.

35. Verfahren nach irgendeinem der Ansprüche 30 bis 31, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Chronoamperometrie unter Verwendung des Sensorsignals

Abbott Ex. 1002 - 325/1438

umfaßt.

36. Verfahren nach irgendeinem der Ansprüche 30 bis 31, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Chronopotentiometrie unter Verwendung des Sensorsignals umfaßt.

37. Verfahren nach irgendeinem der Ansprüche 30 bis 31, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch eine Cottrell-Meßtechnik unter Verwendung des Sensorsignals umfaßt.

38. Verfahren nach irgendeinem der Ansprüche 30 bis 37, das außerdem umfaßt:

Bereitstellung von Eichdaten für eine Liefermenge von elektrochemischen Sensoren in einem Meßinstrument, wobei die Eichdaten eine Information umfassen, die einen Bezug zu einer Größe für eine Hintergrundladung für die Liefermenge der elektrochemischen Sensoren aufweist;

wobei die Stufe der Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten unter Verwendung des Sensorsignals und der Eichdaten umfaßt.

39. Verfahren zur Bestimmung einer Konzentration eines Analyten in einer Probe, wobei das Verfahren die Schritte umfaßt:

Inkontaktbringen einer Probe mit irgendeinem der elektrochemischen Sensoren der Ansprüche 1 bis 29;
Beachten eines Signals von der Anzeigeelektrode, das anzeigt, dass die Meßzone Probe enthält;
Anlegen eines Potentials zwischen der Arbeitselektrode und der Gegenelektrode, um den Analyten in der Probe zu elektrolysieren;
Erzeugung eines auf den Analyten ansprechenden Signals durch den Sensor in Reaktion auf die Elektrolyse des Analyten in der Probe; und
Bestimmen der Konzentration des Analyten unter Verwendung des auf den Analyten ansprechenden Signals.

40. Verfahren zur Herstellung irgendeines der elektrochemischen Sensoren der Ansprüche 1 bis 29, wobei das Verfahren umfaßt:

(a) Ausbilden einer Vielzahl von Arbeitselektroden auf einem ersten Substrat;
(b) Ausbilden einer Vielzahl von Gegenelektroden auf einem zweiten Substrat;
(c) Anordnen einer Abstandshalterschicht auf einem von dem ersten oder dem zweiten Substrat;
(d) Entfernen eines Teils der Abstandshalterschicht, um die Bereiche der Probenkammer zu definieren;
(e) Bildung eines Laminats aus dem ersten und dem zweiten Substrat; und
(f) Abtrennen einer Vielzahl von elektrochemischen Sensoren von den laminierten Substraten, wobei jeder elektrochemische Sensor wenigstens eine von den Arbeitselektroden, wenigstens eine von den Gegenelektroden und wenigstens einen von den Probenkammerbereichen umfaßt.

41. Verfahren nach Anspruch 40, wobei das erste Substrat ein erster Bereich eines Substrats ist und das zweite Substrat ein zweiter Bereich des Substrats ist, und das außerdem umfaßt:

Falten des Substrats, so dass sich die ersten und zweiten Bereiche des Substrats überlagern.

42. Verfahren nach irgendeinem der Ansprüche 40 und 41, wobei das Abtrennen der Vielzahl von elektrochemischen Sensoren das Schneiden des ersten und zweiten Substrats umfaßt, um die elektrochemischen Sensoren herauszutrennen und wenigstens ein Ende der Probenkammer der elektrochemischen Sensoren zu definieren.

43. Verfahren nach irgendeinem der Ansprüche 40 bis 42, das außerdem das Bilden einer Vielzahl von Anzeigeelektroden auf einem von dem ersten und zweiten Substrat umfaßt.

44. Verfahren nach irgendeinem der Ansprüche 40 bis 43, wobei der Bereich der Abstandshalterschicht entfernt wird, um die Probenkammerbereiche zu definieren, nachdem die Abstandshalterschicht auf dem ersten und zweiten Substrat angeordnet ist.

Abbott Ex. 1002 - 326/1438

Revendications

1. Détecteur (20) pour déterminer la concentration d'une substance à analyser dans un échantillon de fluide, le détecteur comprenant :

   une paire d'électrodes comprenant une électrode à étudier (22, 502, 522, 542, 562, 580, 602, 642, 1010) et une contre-électrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), dans lequel au moins une partie de l'électrode à étudier se trouve à une distance efficace inférieure à 200 μm d'une partie de la contre-électrode, et dans lequel, optionnellement, la contre-électrode est une contre-électrode/une électrode de référence ;
   une électrode de référence optionnelle (512, 532, 552, 572, 585, 612, 652) ;
   une chambre d'échantillonnage (26, 526, 546, 566, 582, 606, 646) pour maintenir l'échantillon de fluide en contact électrolytique avec l'électrode à étudier, la contre-électrode, et l'électrode de référence, si elle est présente, la chambre d'échantillonnage comprenant une zone de mesure adjacente à l'électrode à étudier, à la contre-électrode, et à l'électrode de référence, si elle est présente, dans lequel la zone de mesure est formée pour contenir un volume inférieur à environ 1 μL d'échantillon de fluide et dans lequel, optionnellement, la chambre d'échantillonnage est formée pour contenir moins de 1 μL environ de fluide d'échantillonnage ; et
   une enzyme réactive à la substance à analyser et un médiateur de redox diffusable disposé dans la zone de mesure ;
   le détecteur ayant été configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable soit inférieur à :

      (a) cinq fois un signal généré par l'oxydation ou la réduction d'une quantité physiologique moyenne normale d'une substance à analyser ; ou
      (b) cinq fois un signal généré par l'oxydation ou la réduction d'une quantité de substance à analyse correspondant à une déviation moyenne par rapport à une quantité physiologique moyenne normale de substance à analyser.

2. Détecteur (20) pour déterminer la concentration du glucose de la substance à analyser dans un échantillon de fluide, le détecteur comprenant :

   une paire d'électrodes comprenant une électrode à étudier (22, 502, 522, 542, 562, 580, 602, 642, 1010) et une contre-électrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), dans lequel l'électrode à étudier et la contre-électrode sont séparées par une distance efficace de l'ordre de 25 à 1000 μm ;
   une chambre d'échantillonnage (26, 526, 546, 566, 582, 606, 646) pour contenir l'échantillon de fluide, la chambre d'échantillonnage comprenant une zone de mesure adjacente à l'électrode à étudier et à la contre-électrode, dans laquelle la zone de mesure est formée pour contenir un volume inférieur à environ 1 μL d'échantillon ; et
   une enzyme réactive à la substance à analyser et un médiateur de redox diffusable disposés dans la zone de mesure ;
   le détecteur ayant été configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable soit inférieur à cinq fois un signal généré par l'oxydation ou la réduction de 5 mM de glucose.

3. Détecteur selon l'une quelconque des revendications 1 et 2, dans lequel le détecteur est configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable soit identique ou inférieur au signal généré par l'oxydation ou la réduction de la quantité physiologique moyenne normale de substance à analyser.

4. Détecteur selon l'une quelconque des revendications 1 et 2, dans lequel le détecteur est configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable soit inférieur à 25% du signal généré par l'oxydation ou la réduction de la substance à analyser et , de préférence, inférieur à 5% du signal généré par l'oxydation ou la réduction de la substance à analyser.

5. Détecteur selon l'une quelconque des revendications 1 à 4, dans lequel le détecteur comprend :

   (a) un premier substrat (500, 520, 560, 579, 600, 640) possédant une extrémité proximale et une extrémité distale, le premier substrat définissant un premier bord latéral (656) et un deuxième bord latéral (658) du détecteur électrochimique s'étendant de l'extrémité proximale jusqu'à l'extrémité distale du premier substrat, l'extrémité distale étant configurée et agencée pour être insérée dans un lecteur de détecteur ;
   (b) un deuxième substrat (508, 528, 548, 568, 583, 608, 648) disposé sur le premier substrat, l'électrode à

Abbott Ex. 1002 - 327/1438

étudier étant disposée sur l'un des premier et deuxième substrats et la contre-électrode étant disposée sur l'un des premier et deuxième substrats ;
(c) une entretoise (28, 504, 524, 544, 564, 581, 604, 644) disposée entre le premier et le deuxième substrats et définissant une première ouverture le long du premier bord latéral du détecteur et une deuxième ouverture le long du deuxième bord latéral du détecteur, la chambre d'échantillonnage s'étendant de la première ouverture jusqu'à la deuxième ouverture ; et
(d) au moins une électrode indicatrice disposée au moins sur l'un des premier et deuxième substrats et positionnée par rapport à la zone de mesure ou à la chambre d'échantillonnage afin de déterminer le moment auquel la zone de mesure ou la chambre d'échantillonnage contient l'échantillon.

6. Détecteur selon l'une quelconque des revendications 1 à 4, dans lequel le détecteur comprend :

(a) un premier substrat possédant une extrémité proximale et une extrémité distale, l'extrémité distale étant configurée et agencée pour être insérée dans un lecteur de détecteur, le premier substrat définissant un premier bord latéral et un deuxième bord latéral du détecteur électrochimique s'étendant de l'extrémité proximale jusqu'à l'extrémité distale du premier substrat ;
(b) un deuxième substrat disposé sur le premier substrat, l'électrode à étudier étant disposée sur l'un des premier et deuxième substrats et la contre-électrode étant disposée sur l'un des premier et deuxième substrats ;
(c) une entretoise disposée entre le premier et le deuxième substrats et définissant une première ouverture le long de l'extrémité proximale du détecteur et une deuxième ouverture le long du premier bord latéral du détecteur, la chambre d'échantillonnage s'étendant de la première ouverture jusqu'à la deuxième ouverture ; et
(d) au moins une électrode indicatrice disposée au moins sur l'un des premier et deuxième substrats et positionnée par rapport à la zone de mesure ou à la chambre d'échantillonnage afin de déterminer le moment auquel la zone de mesure ou la chambre d'échantillonnage contient l'échantillon.

7. Détecteur selon l'une quelconque des revendications 1 à 4, dans lequel le détecteur comprend une électrode indicatrice disposée dans le détecteur afin d'indiquer le moment auquel la zone de mesure contient un échantillon, ou le moment auquel la chambre d'échantillonnage contient un échantillon.

8. Détecteur selon l'une quelconque des revendications 5 à 7, dans lequel l'électrode indicatrice est également une électrode à étudier ou une contre-électrode.

9. Détecteur selon l'une quelconque des revendications 5 à 8, comprenant en outre un signe visuel ou sonore, couplé à l'électrode indicatrice, qui s'active lorsque l'électrode indicatrice indique que la zone de mesure ou la chambre d'échantillonnage contient l'échantillon.

10. Détecteur selon l'une quelconque des revendications 5 à 9, dans lequel l'électrode indicatrice est disposée face à l'une de l'électrode à étudier et de la contre-électrode.

11. Détecteur selon l'une quelconque des revendications 5 à 10, dans lequel le détecteur comprend au moins deux électrodes indicatrices disposées dans le détecteur, dans lequel une première électrode indicatrice indique le moment auquel la zone de mesure ou la chambre d'échantillonnage commence à se remplir d'échantillon, et dans lequel une deuxième électrode indicatrice indique le moment auquel la zone de mesure ou la chambre d'échantillonnage est sensiblement remplie d'échantillon.

12. Détecteur selon l'une quelconque des revendications 5 à 10, dans lequel le détecteur comprend au moins deux électrodes indicatrices disposées dans le détecteur, dans lequel deux des électrodes indicatrices comprennent une première contre-électrode/électrode indicatrice et une deuxième contre-électrode/électrode indicatrice avec la contre-électrode disposée entre les première et deuxième contre-électrodes/électrodes indicatrices.

13. Détecteur selon l'une quelconque des revendications 1 à 12, dans lequel la zone de mesure et la chambre d'échantillonnage possèdent un volume identique.

14. Détecteur selon l'une quelconque des revendications 1 à 13, dans laquelle la substance à analyser est du glucose et l'enzyme réactive à la substance à analyser est une enzyme réactive au glucose.

15. Détecteur selon l'une quelconque des revendications 1 à 13, dans lequel la substance à analyser est un médica-

Abbott Ex. 1002 - 328/1438

ment.

16. Détecteur selon l'une quelconque des revendications 1 à 15, dans lequel la zone de mesure est reliée sur au moins deux côtés par l'électrode à étudier et la contre-électrode, et dans lequel, optionnellement, l'électrode à étudier et la contre-électrode forment une paire d'électrodes se faisant face avec la zone de mesure positionnée entre l'électrode à étudier et la contre-électrode.

17. Détecteur selon l'une quelconque des revendications 1 à 16, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur oxyde la substance à analyser et que le potentiel e demi-onde du médiateur de redox, mesuré par voltamétrie dans 0,1 M de NaCl à un pH de 7, soit inférieur à environ ±100 millivolts par rapport au potentiel de la contre-électrode/de l'électrode de référence.

18. Détecteur selon l'une quelconque des revendications 1 à 17, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur oxyde la-substance à analyser et que le potentiel de demi-onde du médiateur de redox, mesuré par voltamétrie dans 0,1 M de NaCl à un pH de 7, soit à peu près. identique au potentiel de la contre-électrode/de l'électrode de référence.

19. Détecteur selon l'une quelconque des revendications 1 à 18, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur oxyde la substance à analyser et que le potentiel de demi-onde du médiateur de redox, mesuré par voltamétrie dans 0,1 M de NaCl à un pH de 7, soit à peu près inférieur à environ -150 millivolts par rapport au potentiel de la contre-électrode/de l'électrode de référence.

20. Détecteur selon l'une quelconque des revendications 1 à 19, dans lequel, dans le détecteur, le coefficient effectif de diffusion du médiateur de redox dans l'échantillon de fluide est inférieur au coefficient effectif de diffusion de la substance à analyser dans l'échantillon de fluide et, de préférence, au moins dix fois inférieur au coefficient effectif de diffusion de la substance à analyser dans l'échantillon de fluide.

21. Détecteur selon l'une quelconque des revendications 1 à 20, dans lequel le médiateur diffusable possède un poids moléculaire d'au moins 5000 daltons.

22. Détecteur selon l'une quelconque des revendications 1 à 21, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur de redox soit plus facilement électrolysé sur l'électrode à étudier que sur la contre-électrode.

23. Détecteur selon l'une quelconque des revendications 1 à 22, dans lequel le détecteur comprend une quantité molaire de médiateur de redox qui est, sur une base stoechiométrique, inférieure à une quantité physiologique normale moyenne de substance à analyser et dans lequel, de préférence, le détecteur comprend une quantité molaire de médiateur de redox qui est, sur une base stoechiométrique, inférieure à 20% d'une quantité physiologique normale moyenne de substance à analyser.

24. Détecteur selon l'une quelconque des revendications 1 à 23, dans lequel l'électrode à étudier possède une surface inférieure à environ 0,01 cm exposée dans la zone de mesure.

25. Détecteur selon l'une quelconque des revendications 1 à 24, dans lequel l'activité de l'enzyme est inférieure à 1 unité/cm^3.

26. Détecteur selon l'une quelconque des revendications 1 à 25, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur de redox diffusable se précipite lorsqu'il est réagi sur la contre-électrode.

27. Détecteur selon l'une quelconque des revendications 1 à 26, dans lequel le détecteur est configuré et agencé de telle sorte qu'un produit mathématique du coefficient effectif de diffusion du médiateur de redox et que la concentration en médiateur de redox soient inférieurs à 1×10^{-12} moles cm^{-1} sec^{-1} lorsque l'échantillon de fluide remplit la zone de mesure.

28. Détecteur selon l'une quelconque des revendications 1 à 27, dans lequel le médiateur de redox diffusable est disposé sur l'électrode à étudier.

29. Détecteur selon l'une quelconque des revendications 1 à 28, dans lequel l'enzyme réactive à la substance à ana-

Abbott Ex. 1002 - 329/1438

lyser est disposée sur l'électrode à étudier.

30. Procédé pour déterminer une concentration d'une substance à analyser dans un échantillon, comprenant les étapes consistant à :

mettre en contact un échantillon avec n'importe lequel des détecteurs électrochimiques des revendications 1 à 29 ;
générer un signal de détecteur au niveau de l'électrode à étudier, et
à déterminer la concentration de la substance à analyser en utilisant le signal du détecteur.

31. Procédé selon la revendication 30, dans lequel le signal de réaction qui est généré par le médiateur de redox diffusable est inférieur à :

(a) cinq fois un signal généré par l'oxydation ou la réduction d'une quantité physiologique moyenne normale d'une substance à analyser ; ou
(b) cinq fois un signal généré par l'oxydation ou la réduction d'une quantité de substance à analyse correspondant à une déviation moyenne par rapport à une quantité physiologique moyenne normale de substance à analyser ; ou
(c) cinq fois un signal généré par l'oxydation ou la réduction de 5 mM de glucose.

32. Procédé selon l'une quelconque des revendications 30 à 31, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par coulométrie en utilisant le signal du détecteur.

33. Procédé selon l'une quelconque des revendications 30 à 32, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par ampérométrie en utilisant le signal du détecteur.

34. Procédé selon l'une quelconque des revendications 30 à 31, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par potentiométrie en utilisant le signal du détecteur.

35. Procédé selon l'une quelconque des revendications 30 à 31, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par chronoampèremétrie en utilisant le signal du détecteur.

36. Procédé selon l'une quelconque des revendications 30 à 31, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par chronopotentiométrie en utilisant le signal du détecteur.

37. Procédé selon l'une quelconque des revendications 30 à 31, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par une technique de mesure de Cotrell en utilisant le signal du détecteur.

38. Procédé selon l'une quelconque des revendications 30 à 37, comprenant en outre :

la fourniture de données d'étalonnage concernant un lot de détecteurs électrochimiques à un instrument de mesure, lesdites données d'étalonnage comprenant des informations liées à l'ampleur d'une charge de réaction relative au lot de détecteurs électrochimiques ;

dans lequel l'étape de détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser en utilisant le signal du détecteur et les données d'étalonnage.

39. Procédé de détermination d'une concentration d'une substance à analyser dans un échantillon, le procédé comprenant les étapes consistant à :

mettre en contact un échantillon avec n'importe lequel des détecteurs électrochimiques des revendications 1 à 29 ;

Abbott Ex. 1002 - 330/1438

observer un signal de l'électrode indicatrice signifiant que la zone de mesure contient l'échantillon ;
appliquer un potentiel entre l'électrode à étudier et la contre-électrode afin d'électrolyser la substance à analyser dans l'échantillon ;
générer un signal réactif à la substance à analyser provenant du détecteur en réponse à l'électrolyse de la substance à analyser dans l'échantillon ; et
à déterminer la concentration de la substance à analyser en utilisant le signal réactif à la substance à analyser.

40. Procédé de fabrication de n'importe lequel des détecteurs électrochimiques des revendications 1 à 29, le procédé comprenant :

(a) la formation d'une pluralité d'électrodes à étudier sur un premier substrat ;
(b) la formation d'une pluralité de contre-électrodes sur un deuxième substrat ;
(c) l'agencement d'une couche d'espacement sur l'un des premier et deuxième substrats ;
(d) le retrait d'une partie de la couche d'espacement afin de définir des régions de chambre d'échantillonnage ;
(e) la stratification des premier et deuxième substrats ensemble ; et
(f) la séparation d'une pluralité de détecteurs électrochimiques des substrats stratifiés, chaque détecteur électrochimique comprenant au moins l'une des électrodes à étudier, au moins l'une des contre-électrodes, et au moins l'une des régions de chambre d'échantillonnage.

41. Procédé selon la revendication 40, dans lequel le premier substrat est une première région d'un substrat et le deuxième substrat est une deuxième région du substrat, et comprenant en outre :

le pliage du substrat afin de chevaucher les première et deuxième régions du substrat.

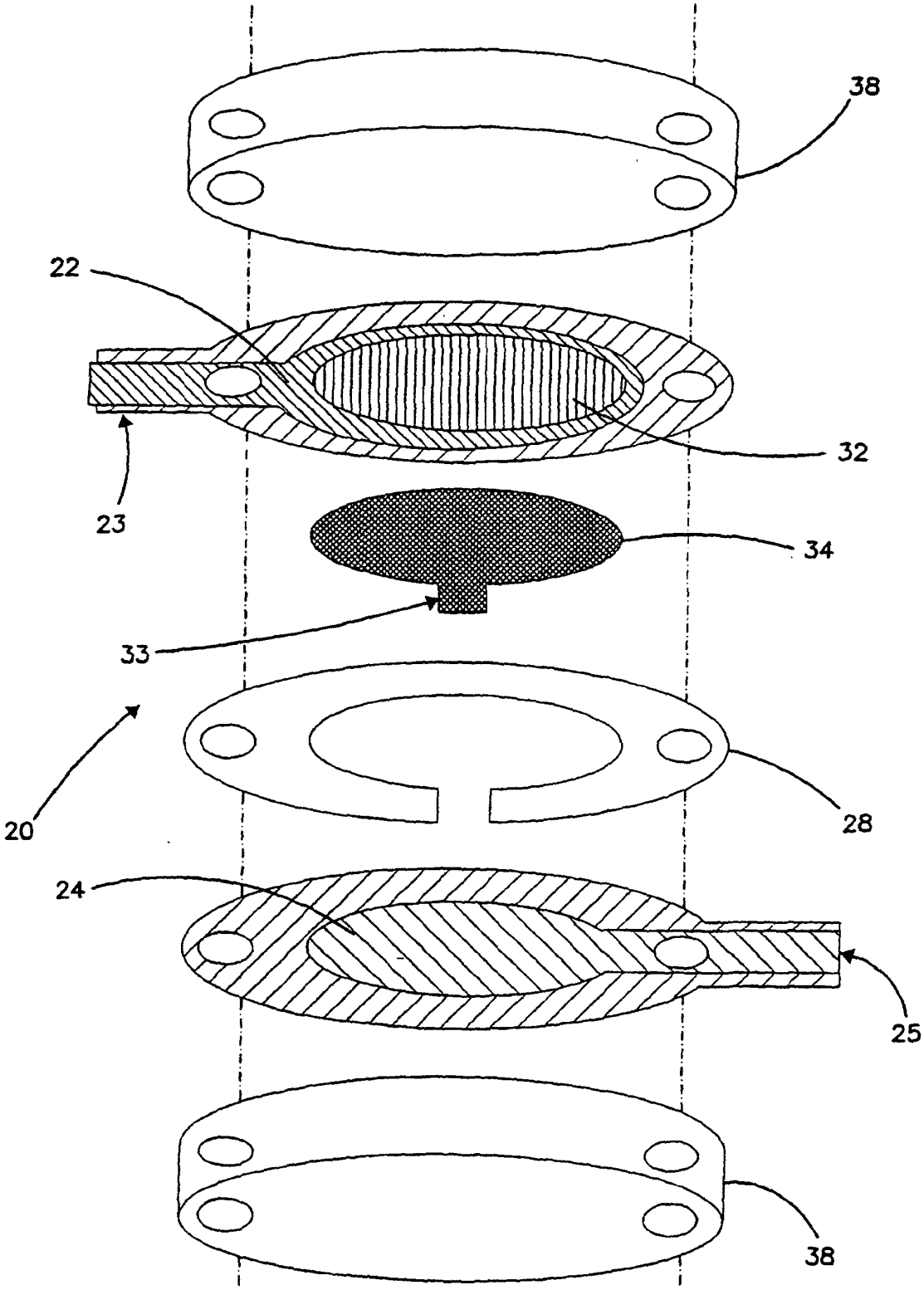
42. Procédé selon l'une quelconque des revendications 40 et 41, dans lequel la séparation de la pluralité de détecteurs électrochimiques comprend le découpage des premier et deuxième substrats afin de séparer les détecteurs électrochimiques et de définir au moins une extrémité de la chambre d'échantillonnage des détecteurs électrochimiques.

43. Procédé selon l'une quelconque des revendications 40 à 42, comprenant en outre la formation d'une pluralité d'électrodes indicatrices sur l'un des premier et deuxième substrats.

44. Procédé selon l'une quelconque des revendications 40 à 43, dans lequel la partie de la couche d'espacement est retirée afin de définir les régions de la chambre d'échantillonnage après que la couche d'espacement ait été disposée sur l'un des premier et deuxième substrats.

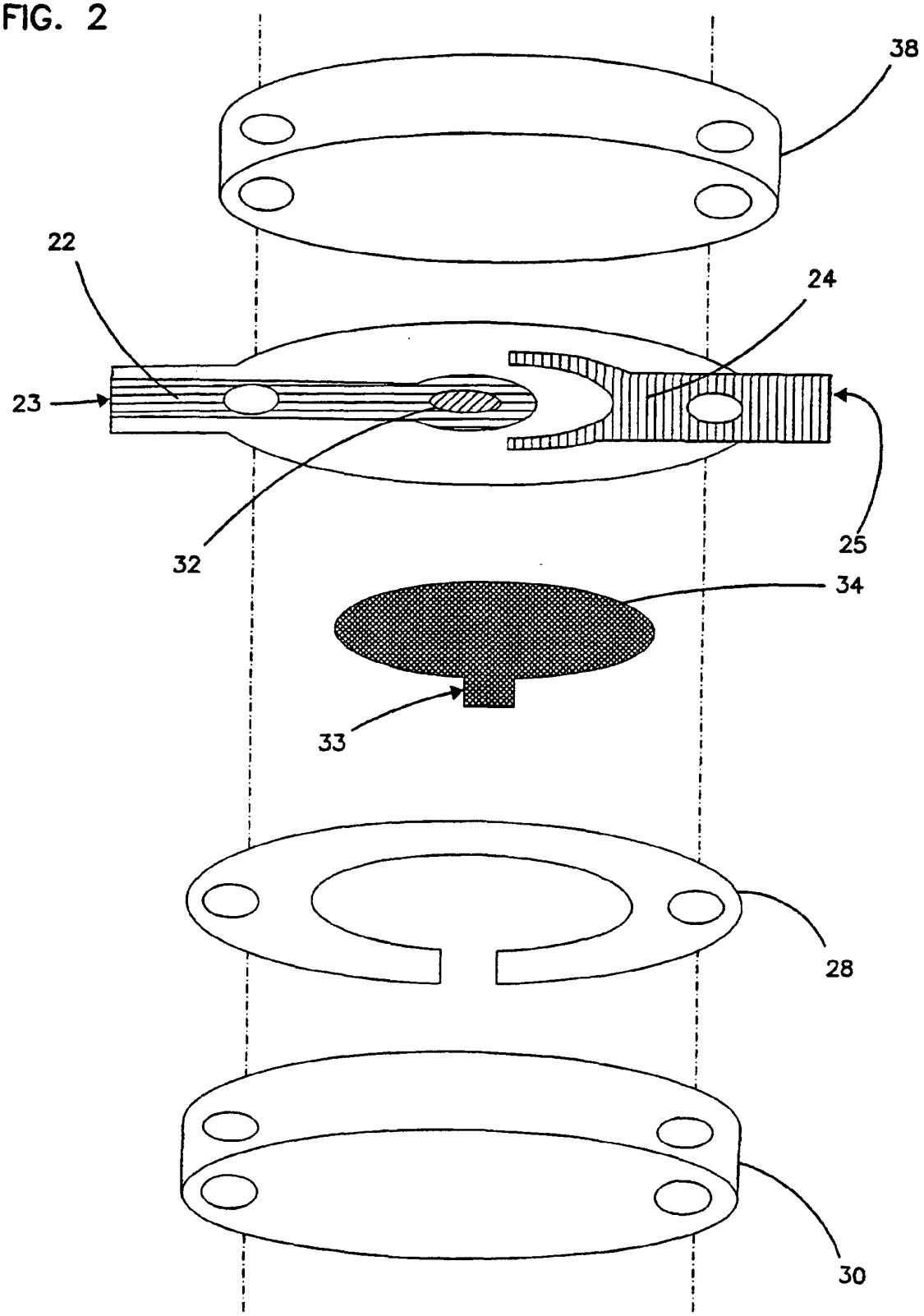
Abbott Ex. 1002 - 331/1438

FIG. 1



Abbott Ex. 1002 - 332/1438

FIG. 2



Abbott Ex. 1002 - 333/1438

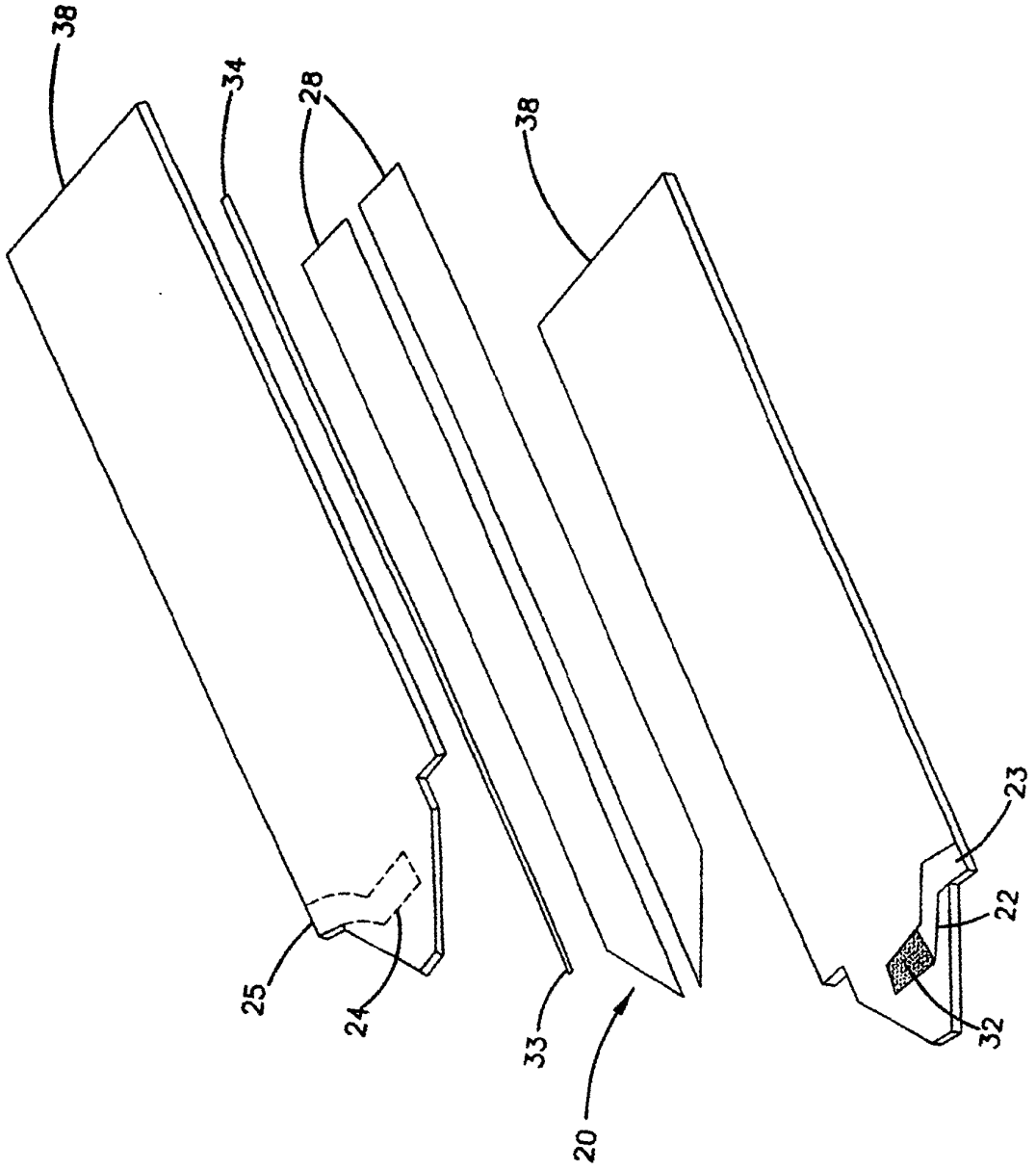


FIG. 3

Abbott Ex. 1002 - 334/1438

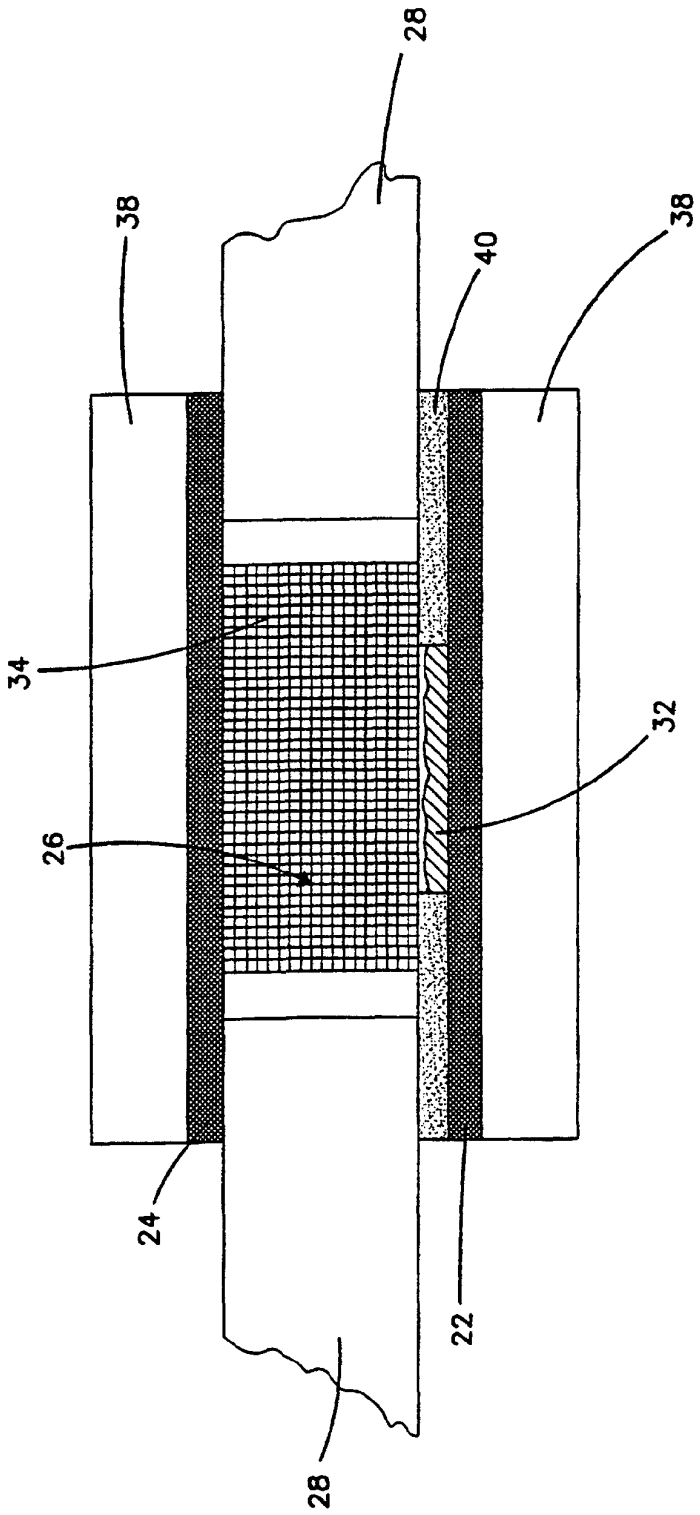
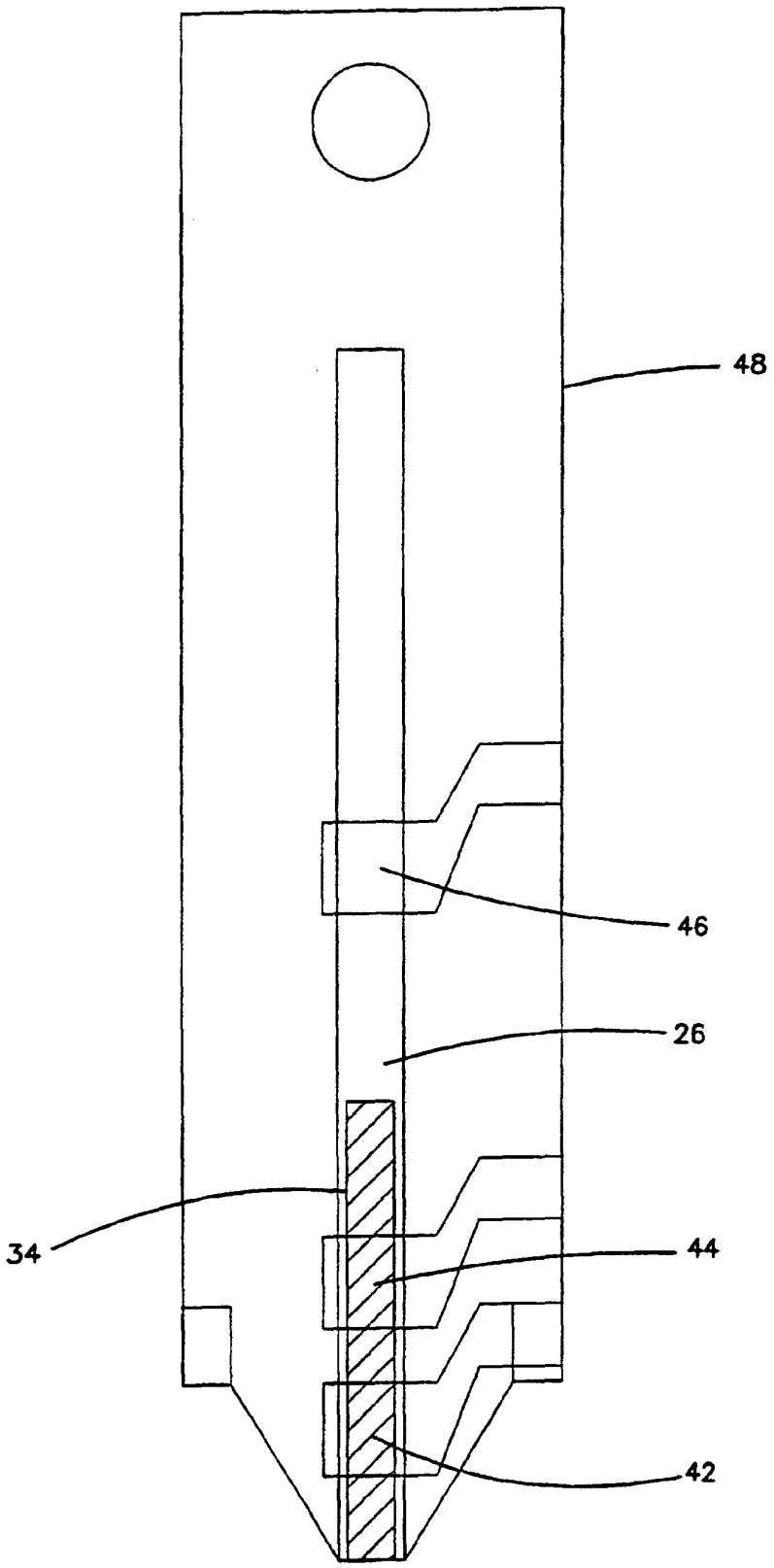


FIG. 4

Abbott Ex. 1002 - 335/1438

FIG. 5



Abbott Ex. 1002 - 336/1438

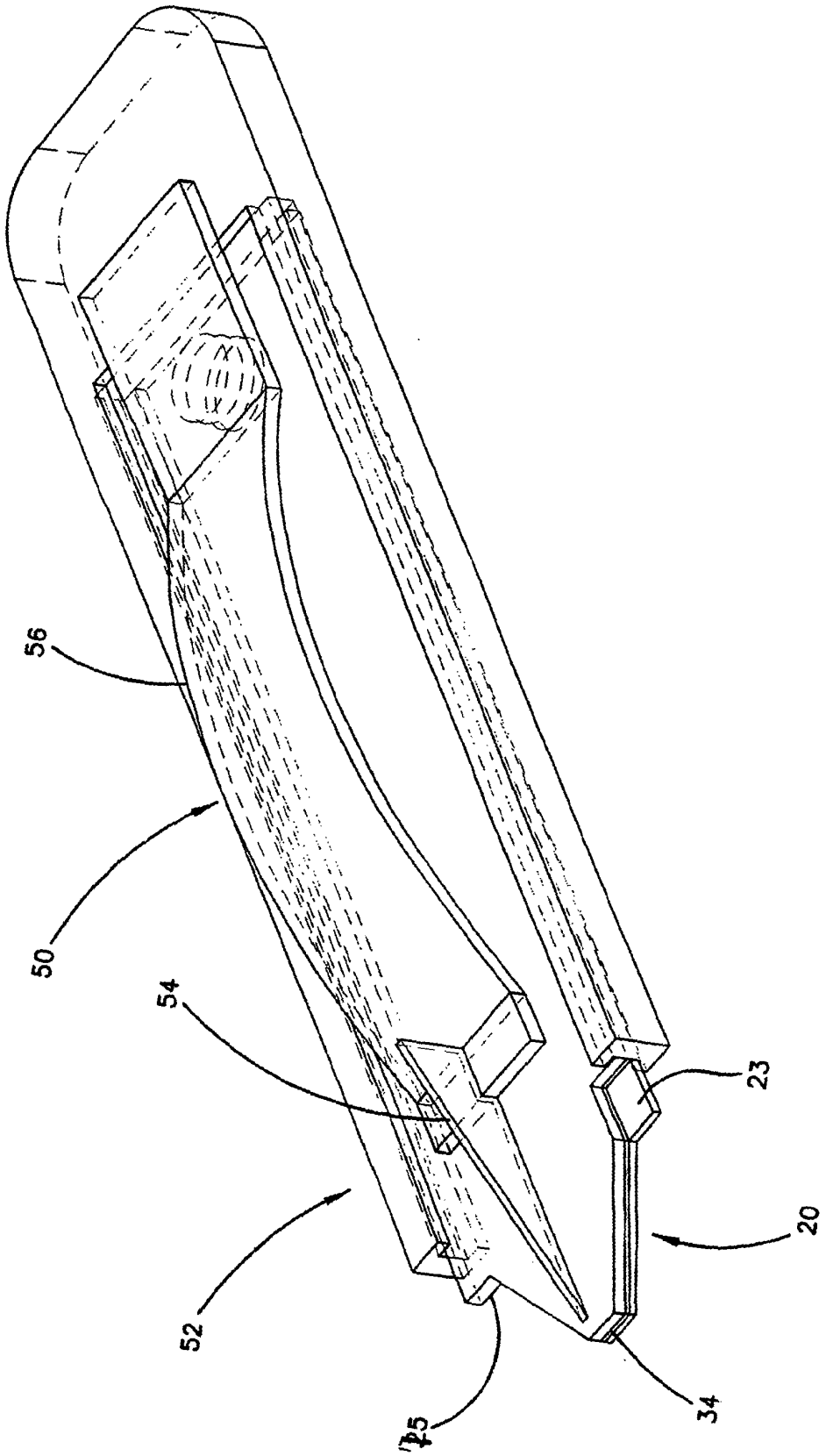
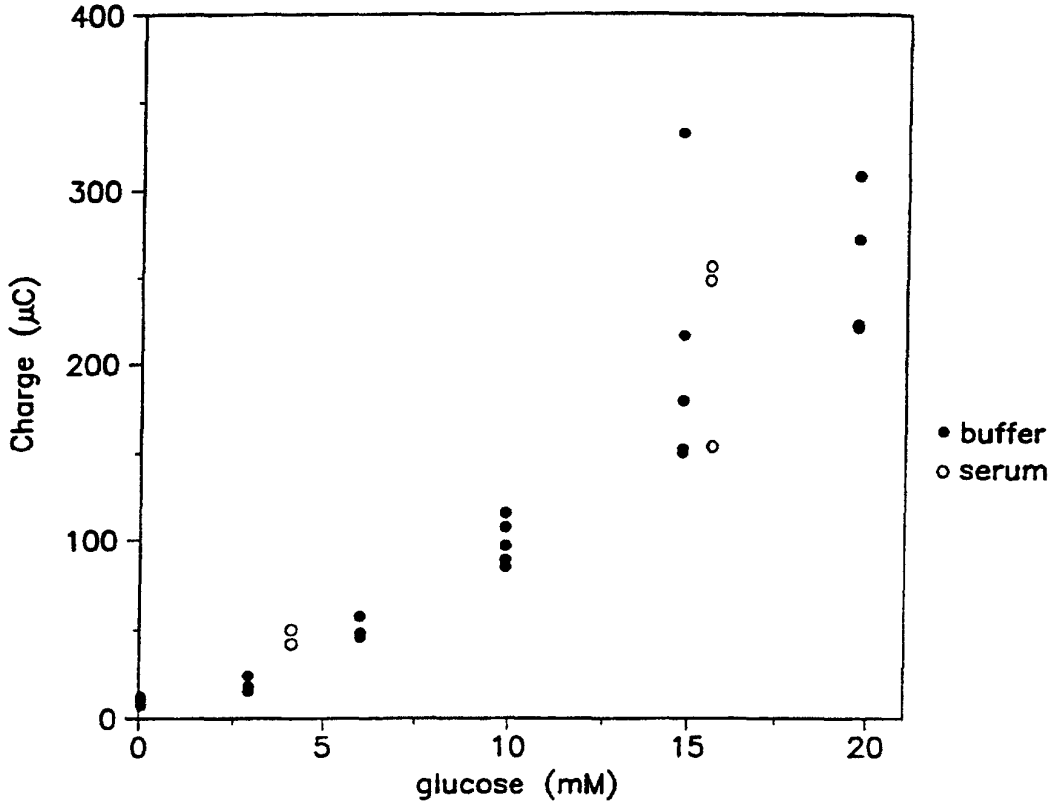


FIG. 6

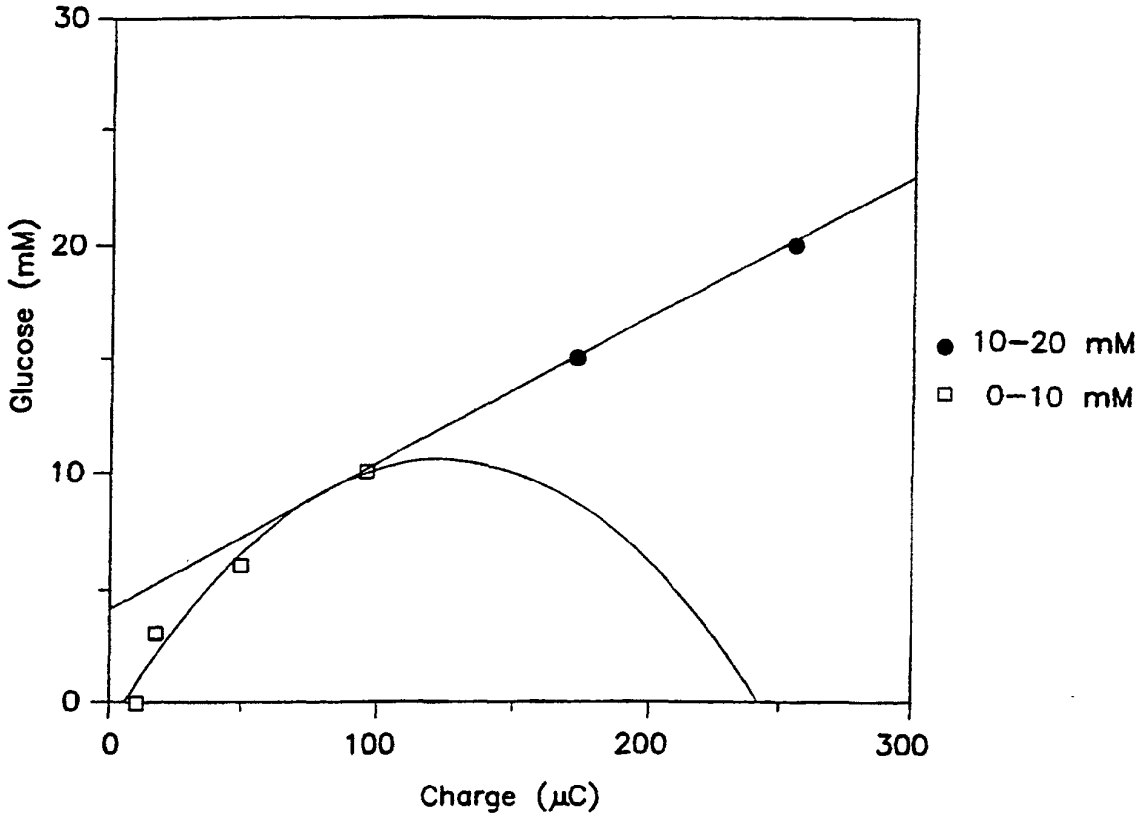
Abbott Ex. 1002 - 337/1438

FIG. 7



Abbott Ex. 1002 - 338/1438

FIG. 8



Abbott Ex. 1002 - 339/1438

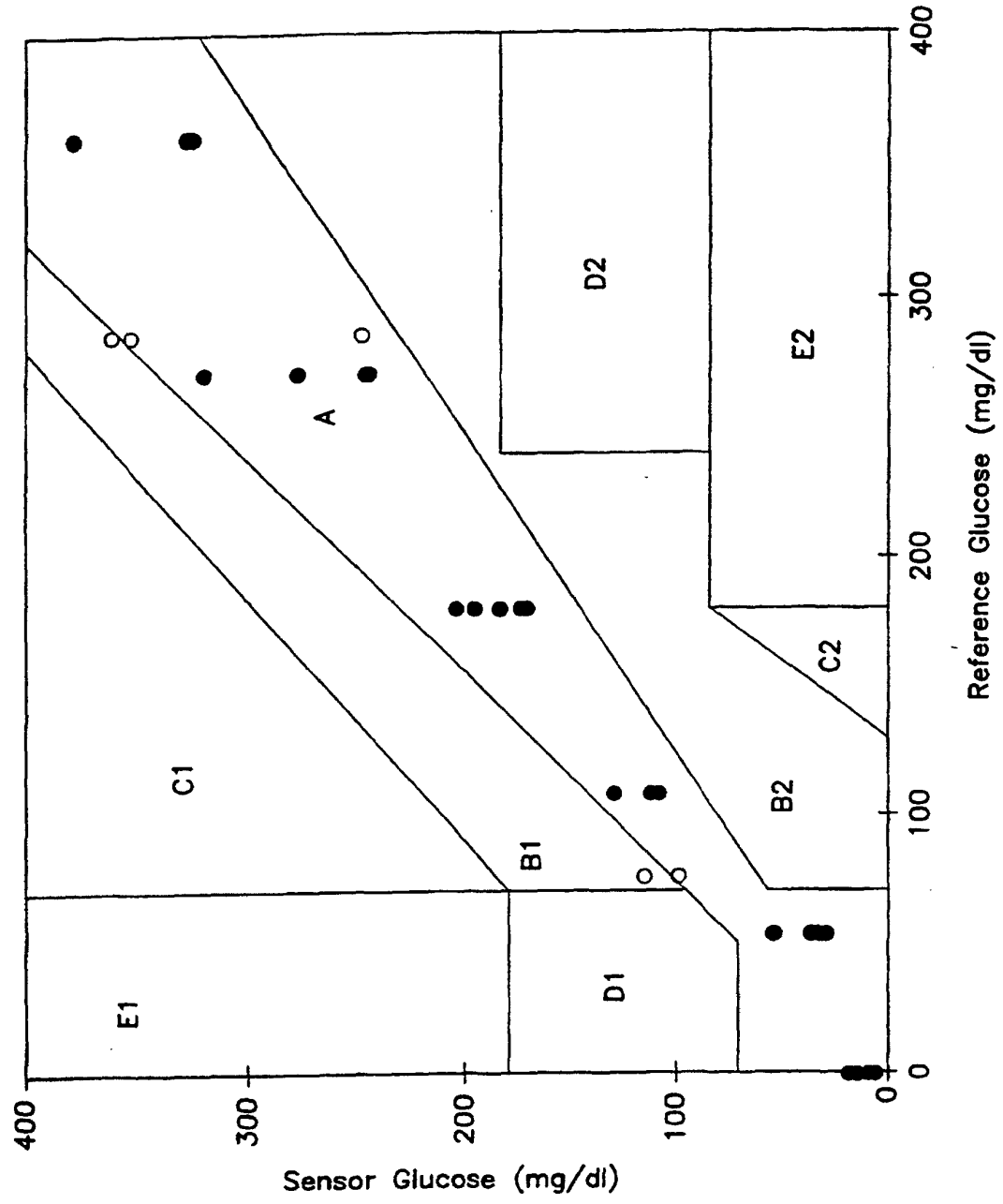
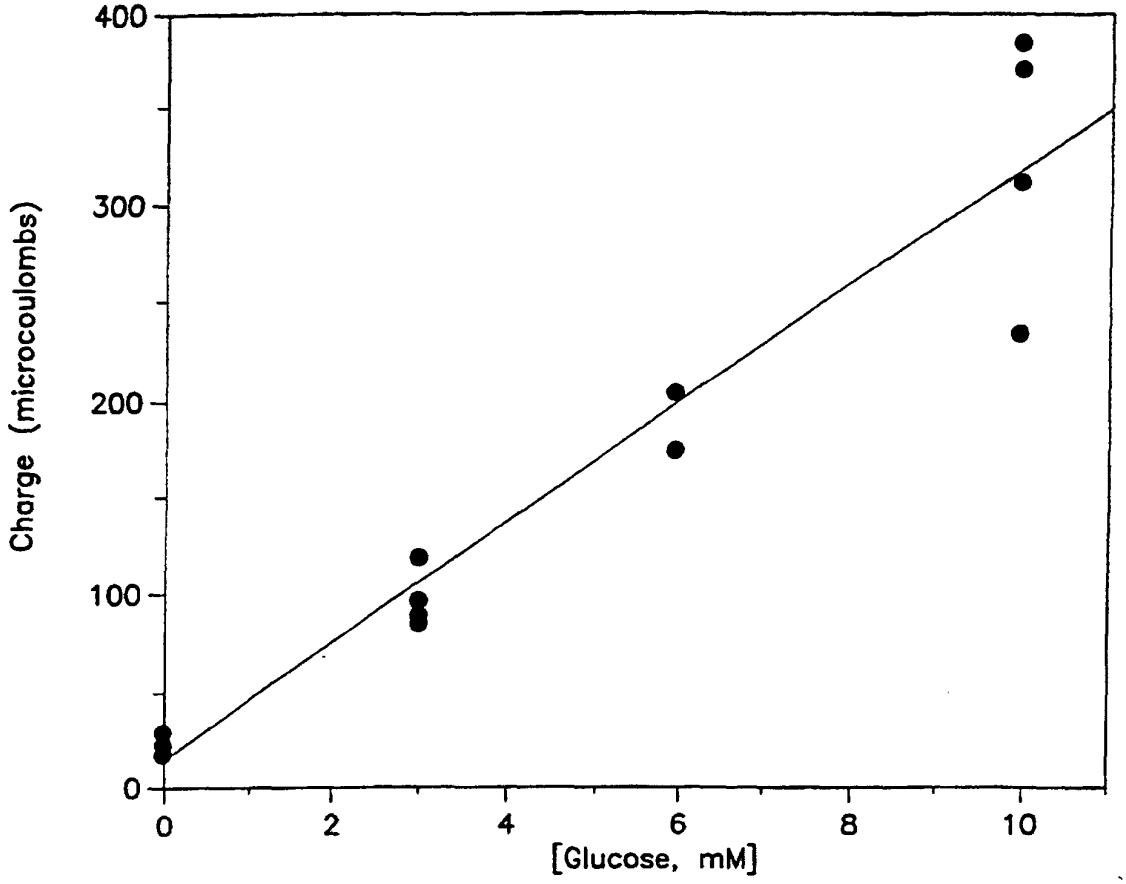


FIG. 9

Abbott Ex. 1002 - 340/1438

FIG. 10



Abbott Ex. 1002 - 341/1438

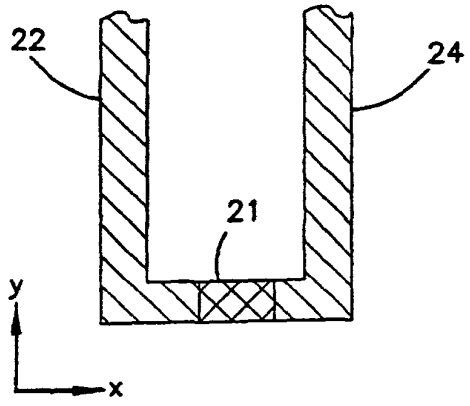


FIG. 11A

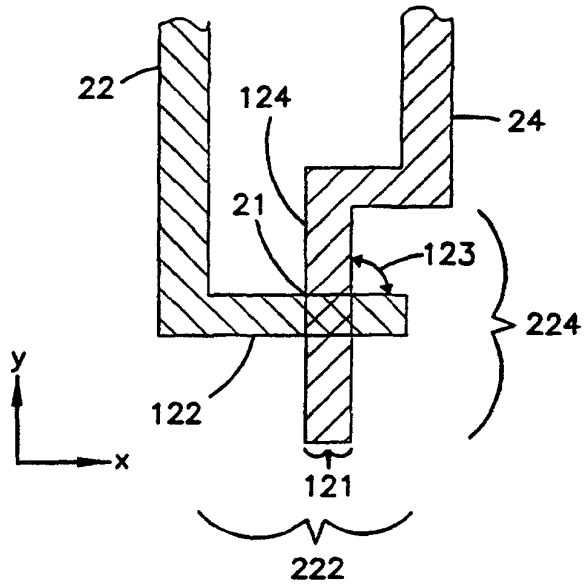


FIG. 11B

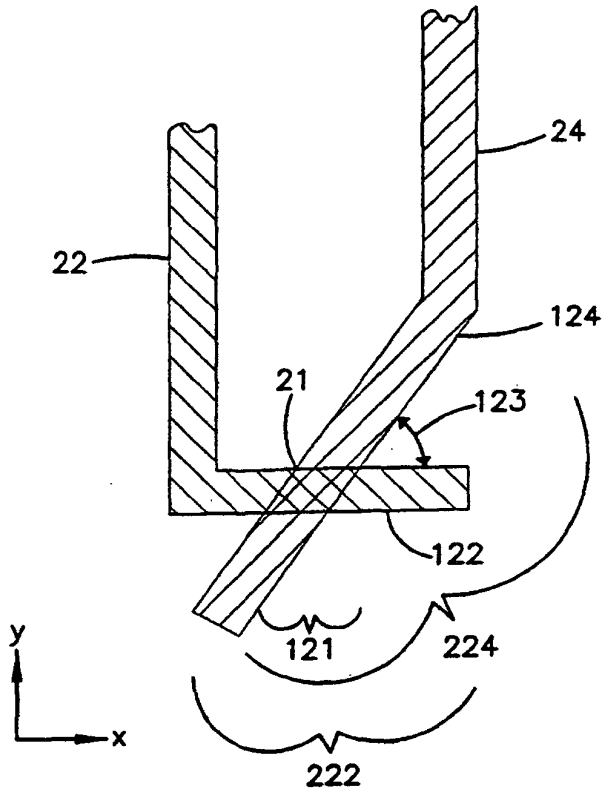


FIG. 11C

Abbott Ex. 1002 - 342/1438

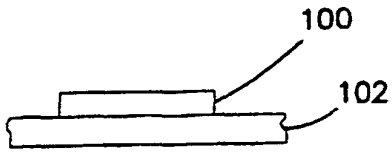


FIG. 12A

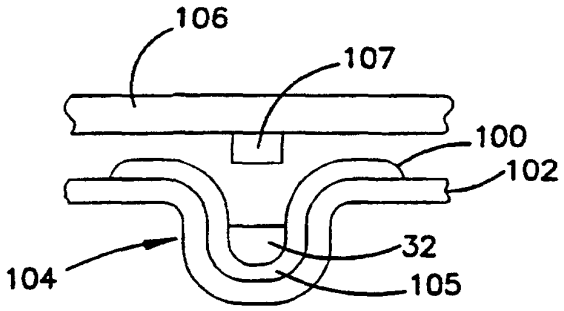


FIG. 12B

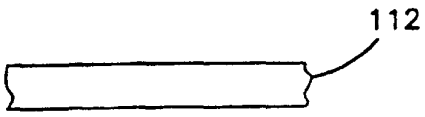


FIG. 13A

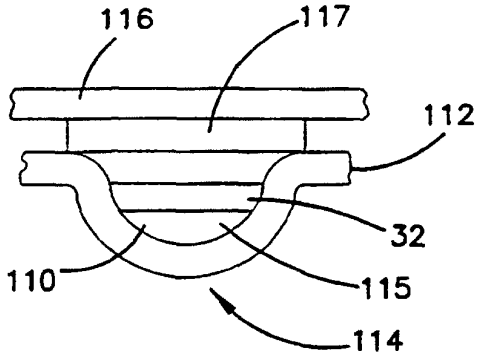


FIG. 13B

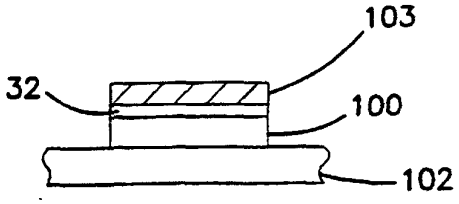


FIG. 14A

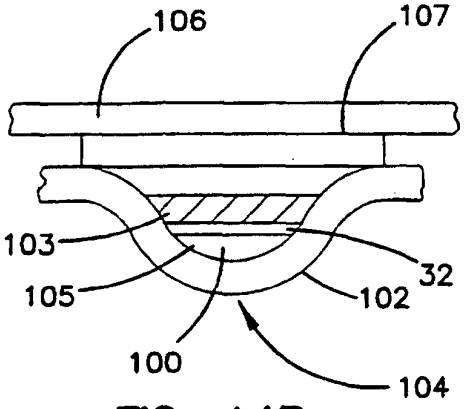
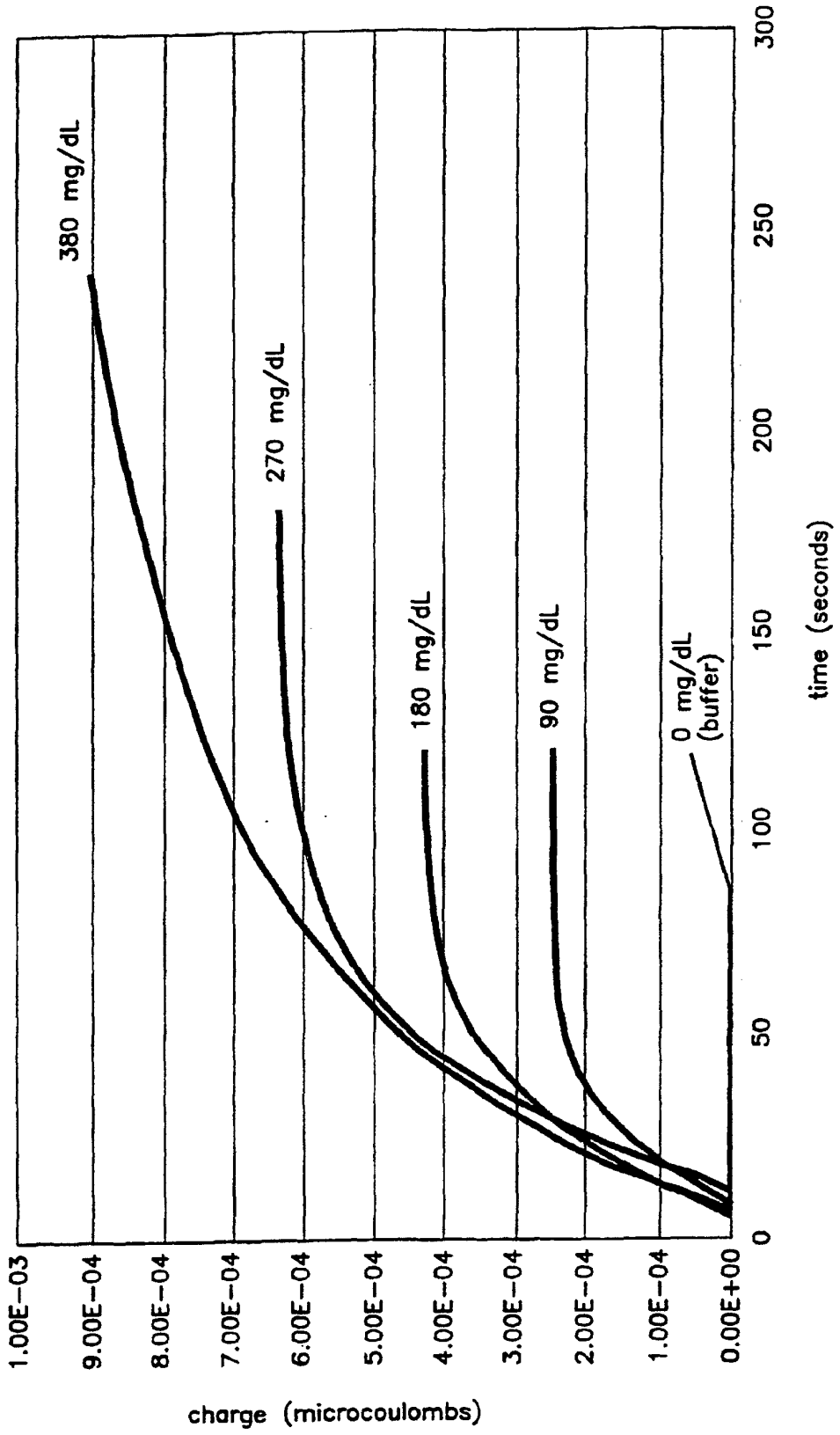


FIG. 14B

Abbott Ex. 1002 - 343/1438

FIG. 15



Abbott Ex. 1002 - 344/1438

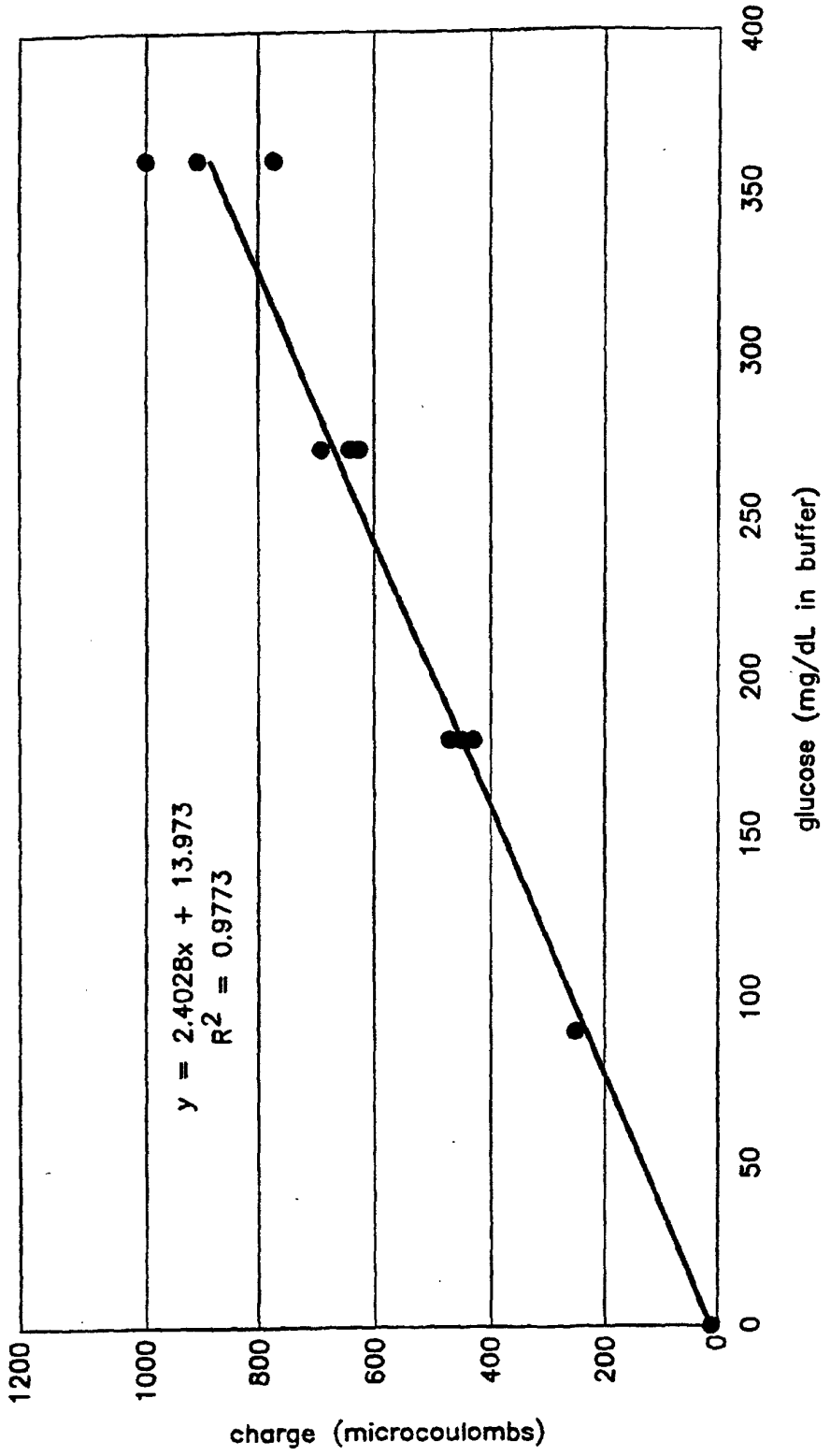
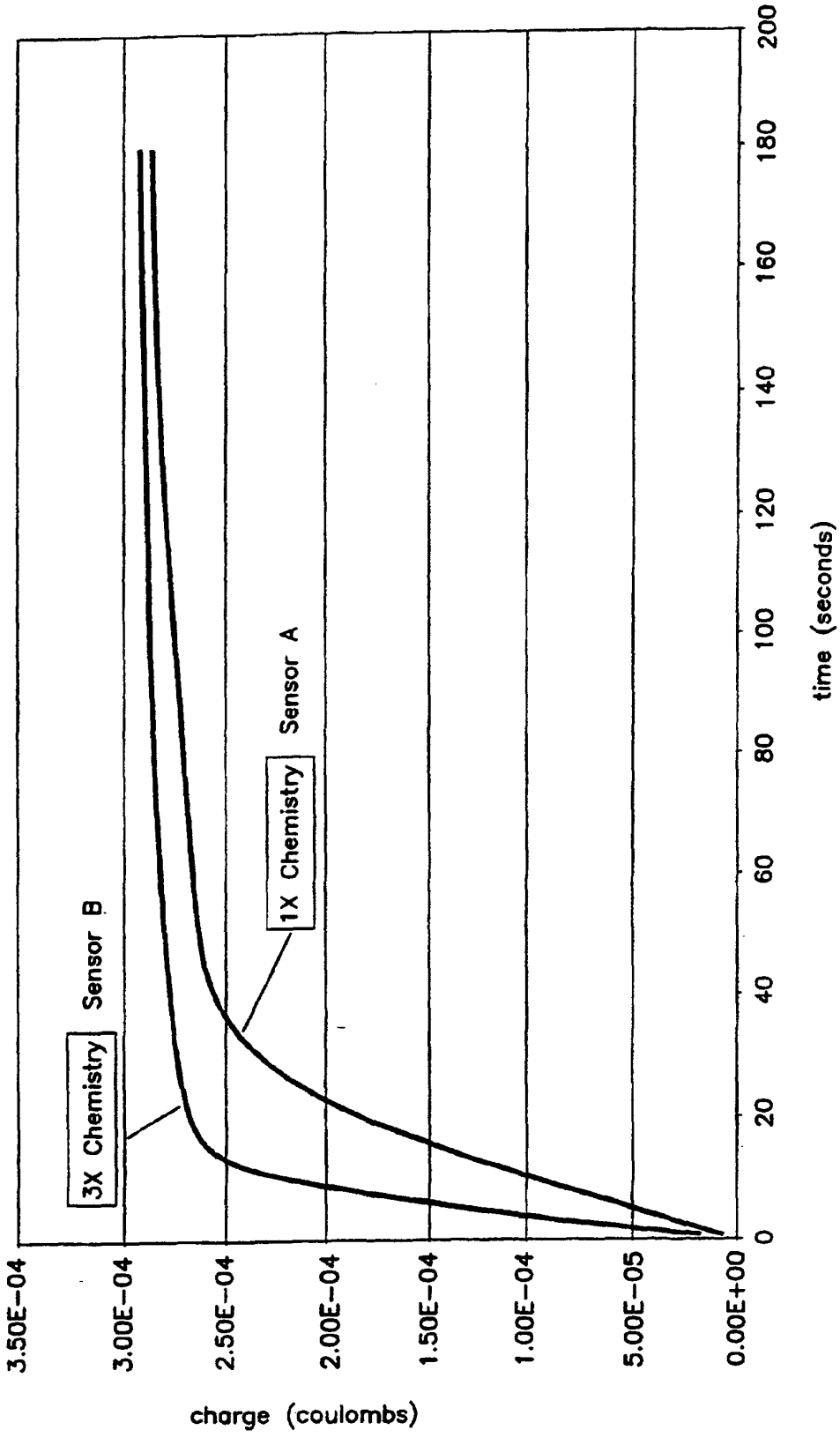


FIG. 16

Abbott Ex. 1002 - 345/1438

FIG. 17



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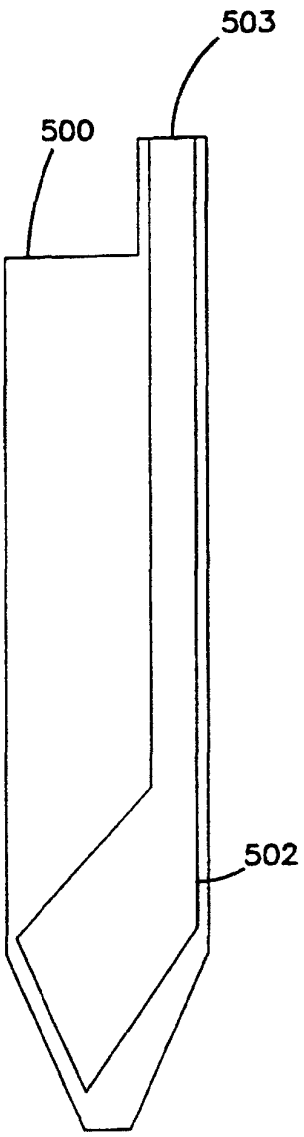


FIG. 18A

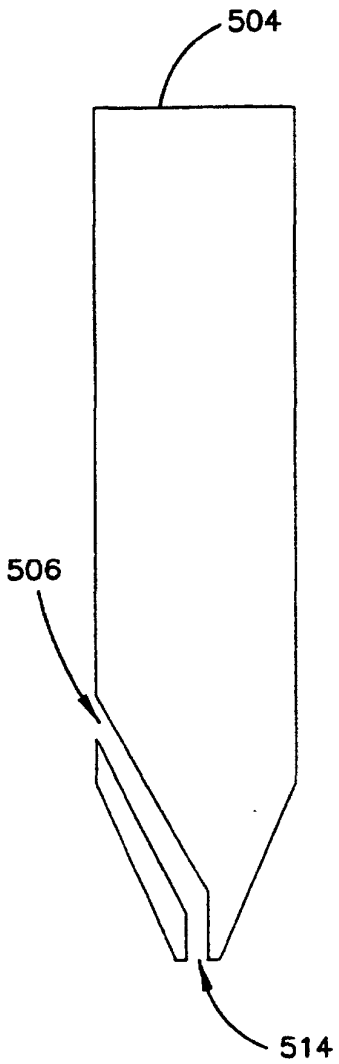


FIG. 18B

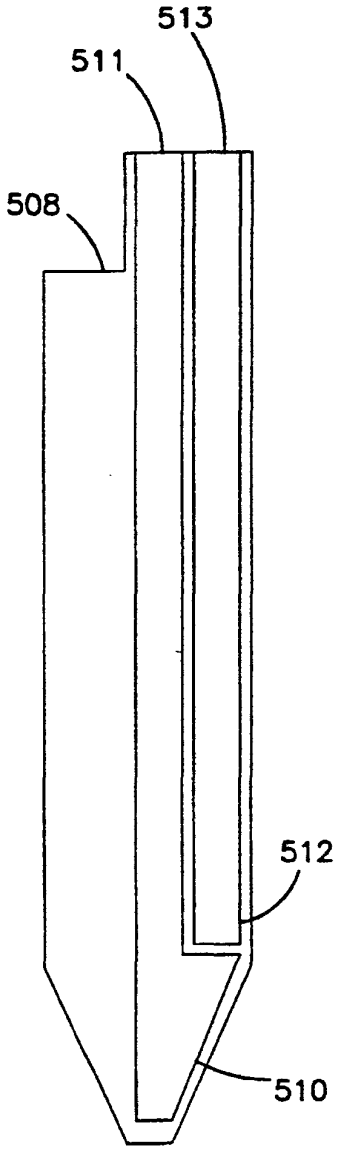


FIG. 18C

Abbott Ex. 1002 - 347/1438

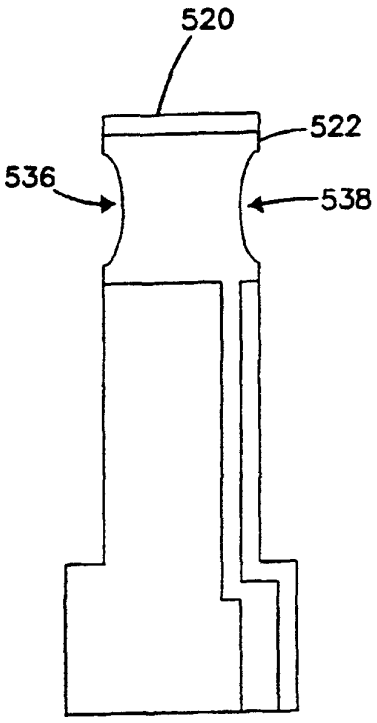


FIG. 19A

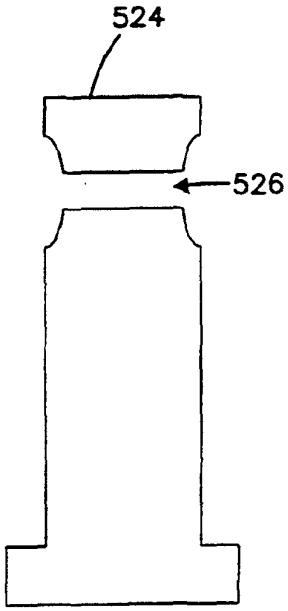


FIG. 19B

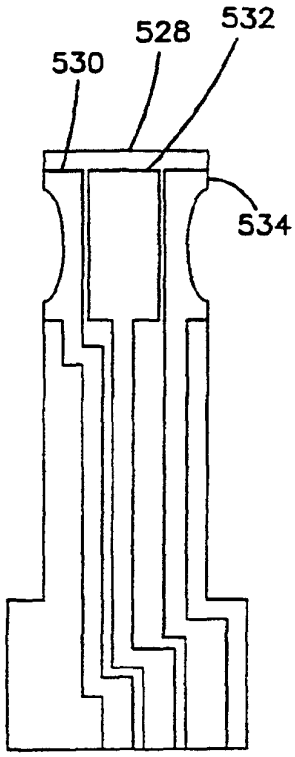


FIG. 19C

Abbott Ex. 1002 - 348/1438

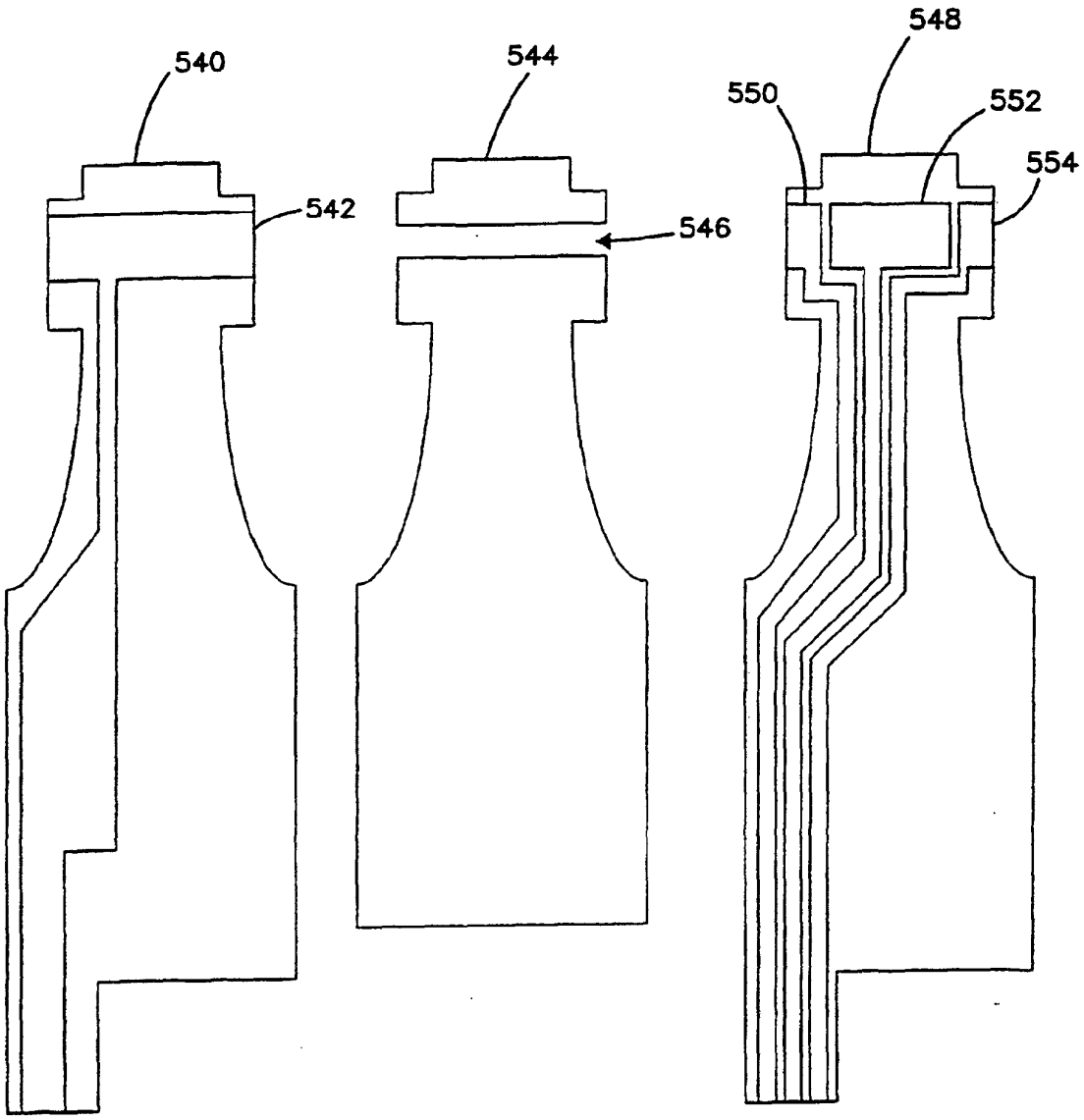


FIG. 20A FIG. 20B FIG. 20C

Abbott Ex. 1002 - 349/1438

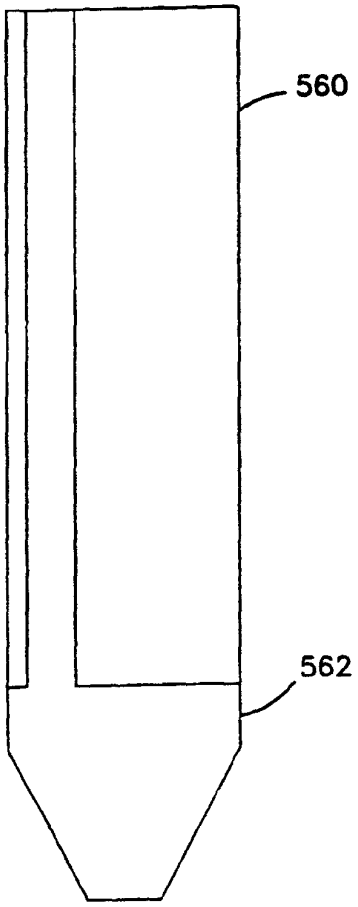


FIG. 21A

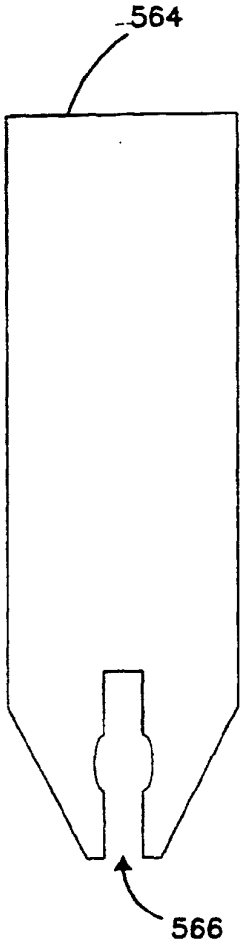


FIG. 21B

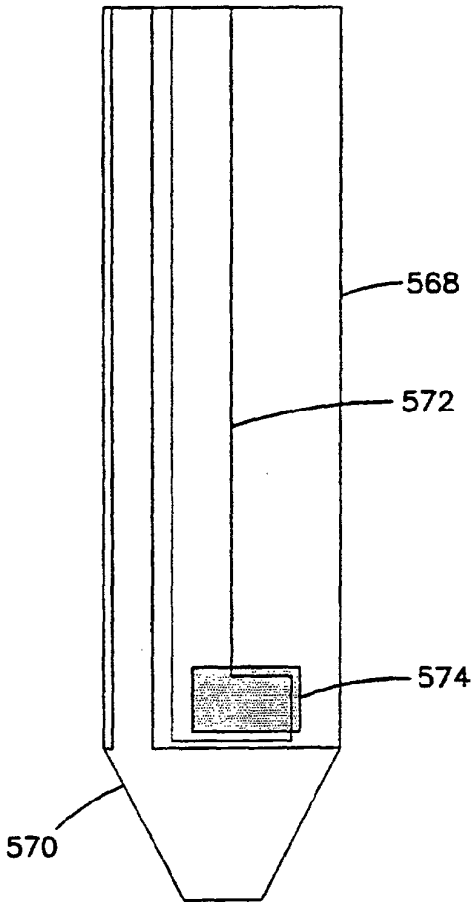


FIG. 21C

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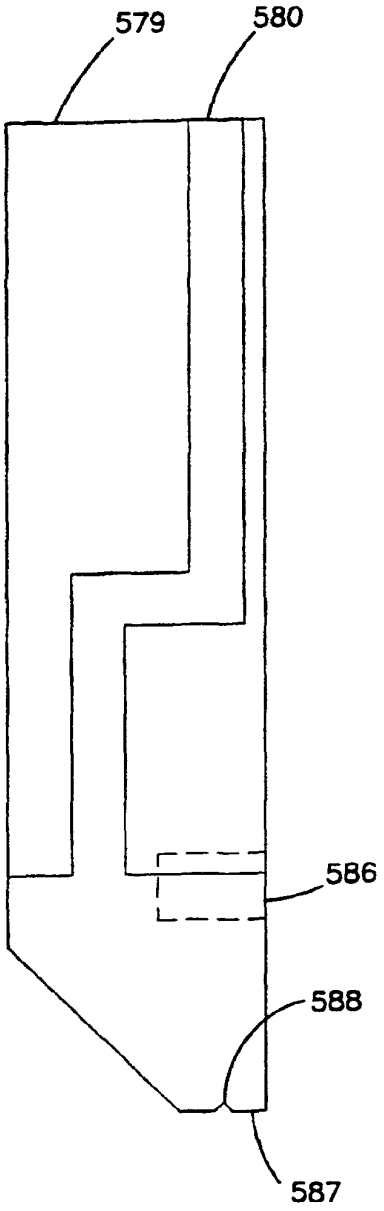


FIG. 22A

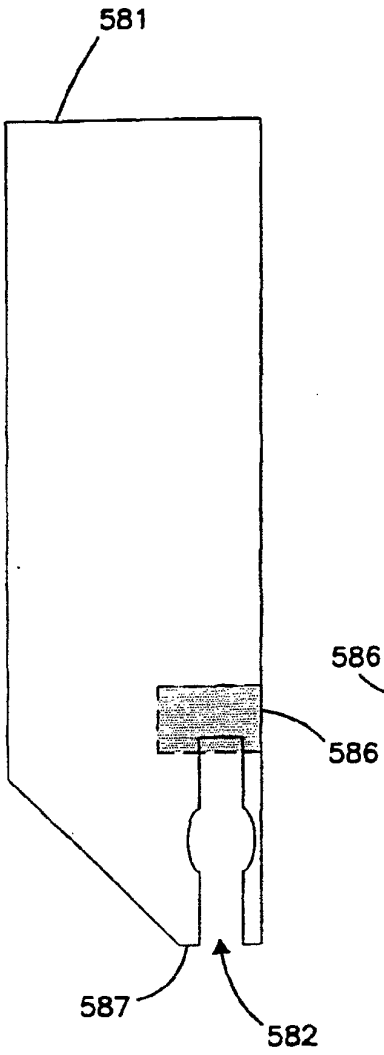


FIG. 22B

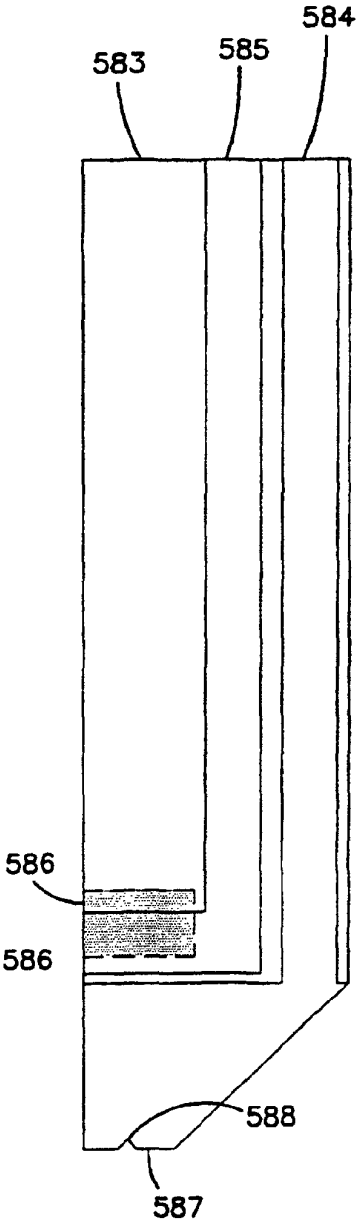


FIG. 22C

Abbott Ex. 1002 - 351/1438

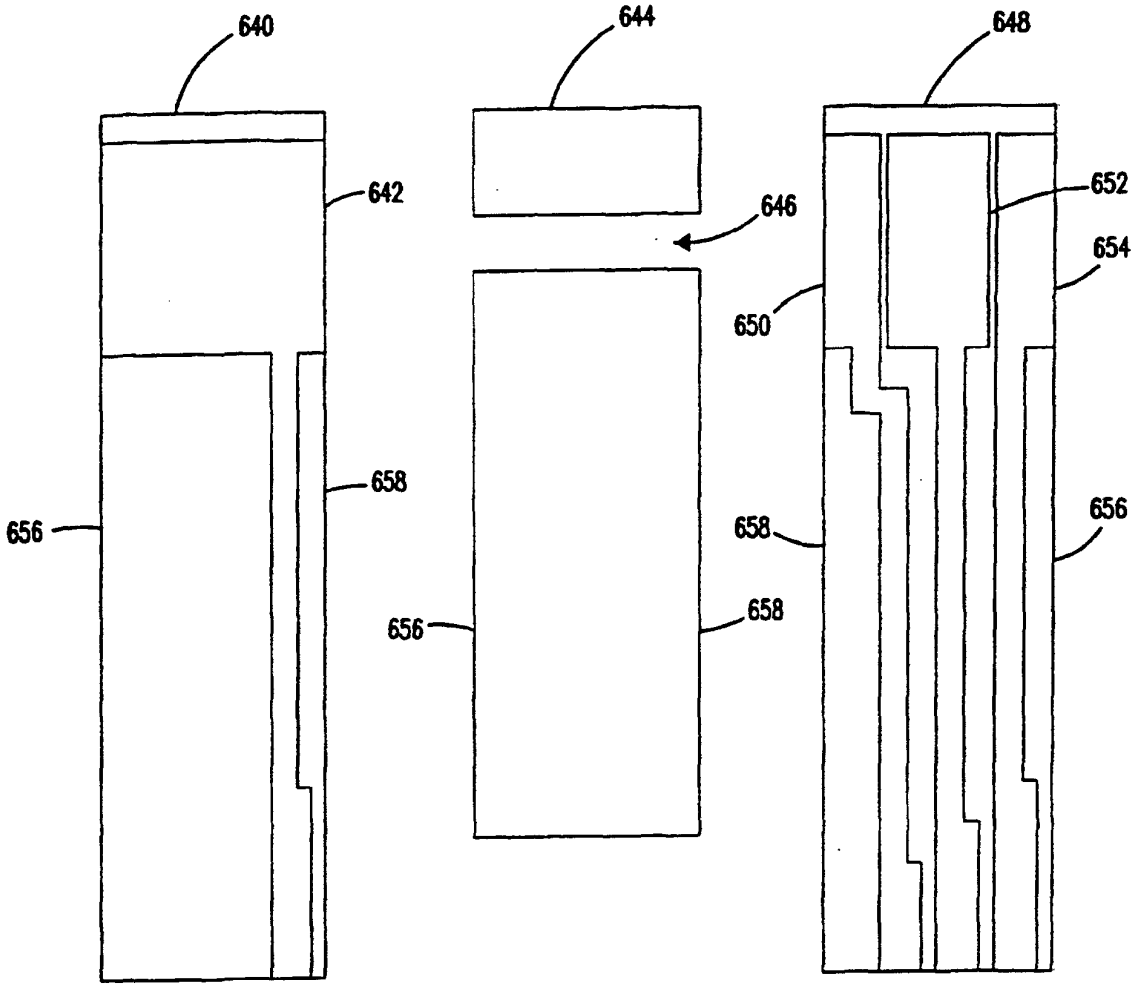


FIG. 23A FIG. 23B FIG. 23C

Abbott Ex. 1002 - 352/1438

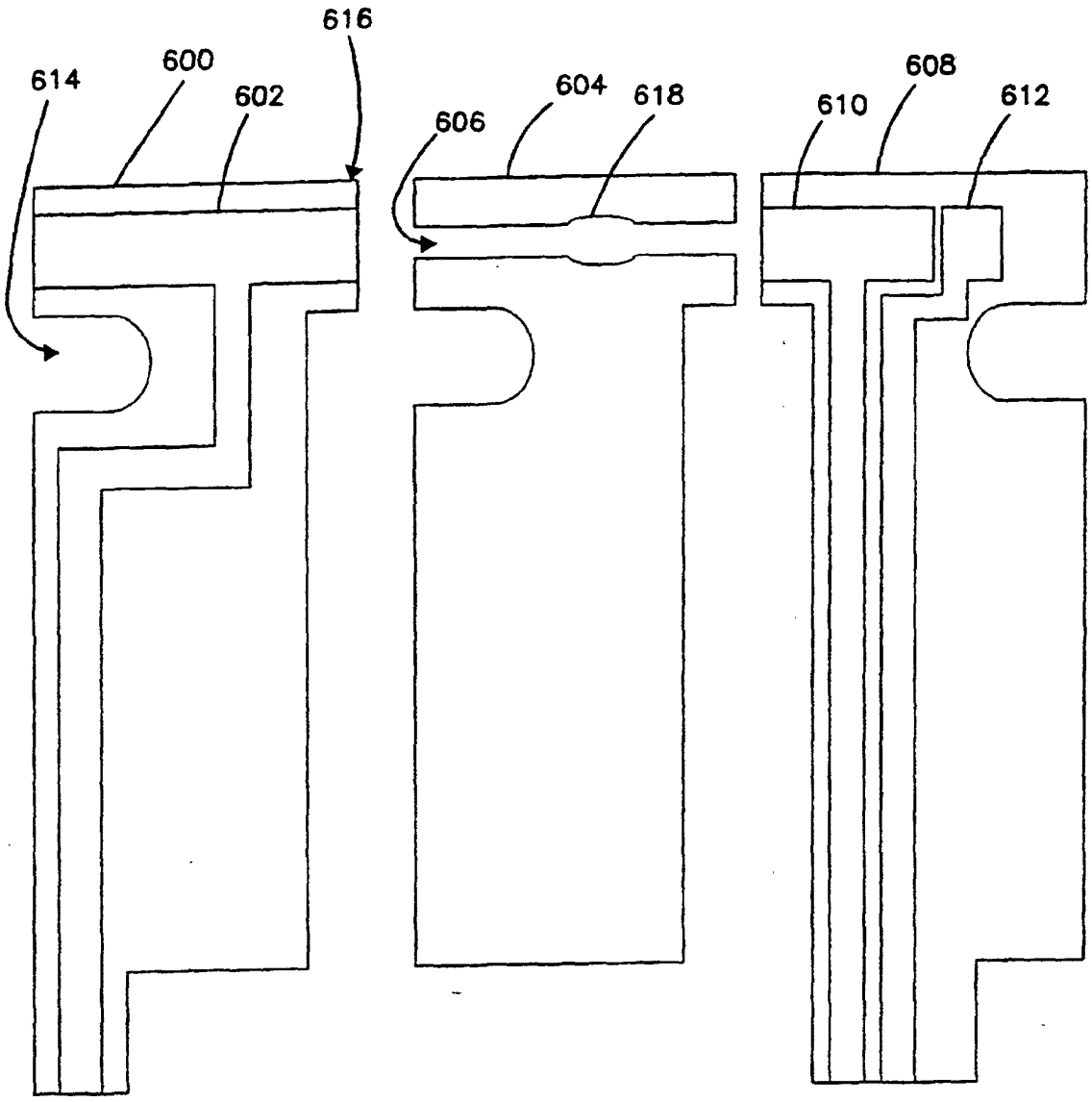


FIG. 24A FIG. 24B FIG. 24C

Abbott Ex. 1002 - 353/1438

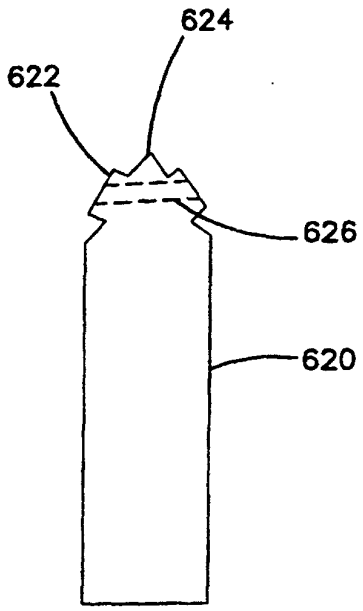


FIG. 25

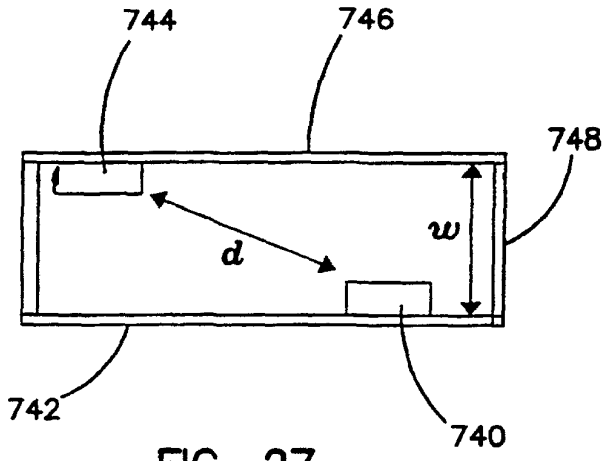


FIG. 27

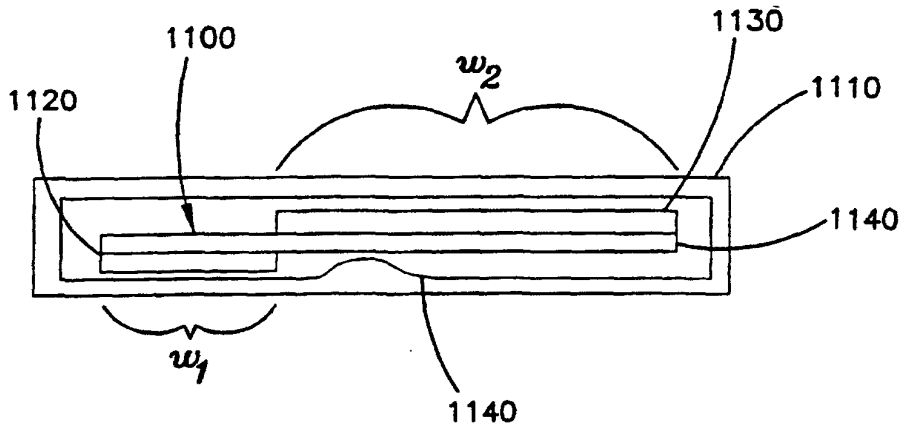


FIG. 32

Abbott Ex. 1002 - 354/1438

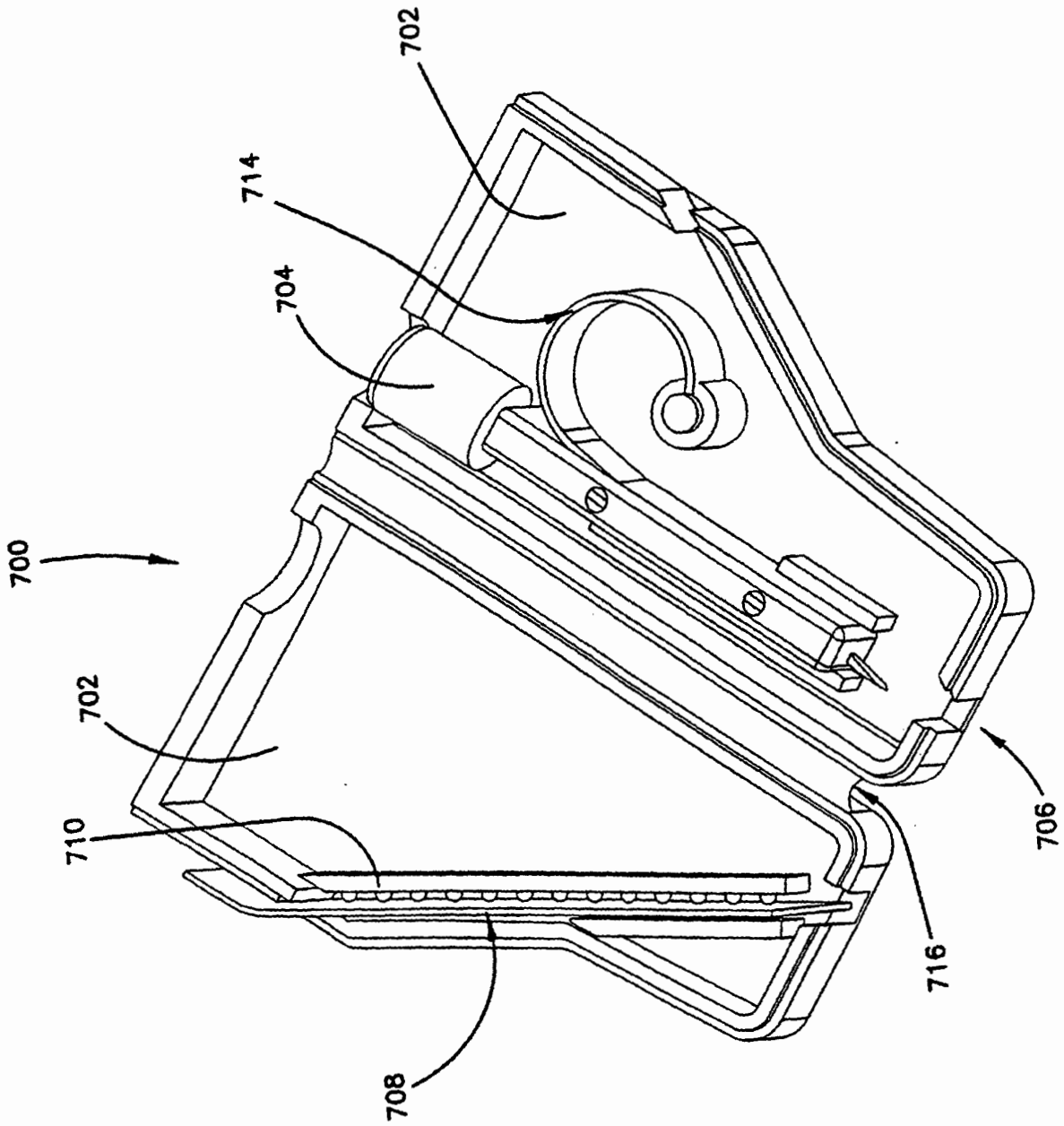
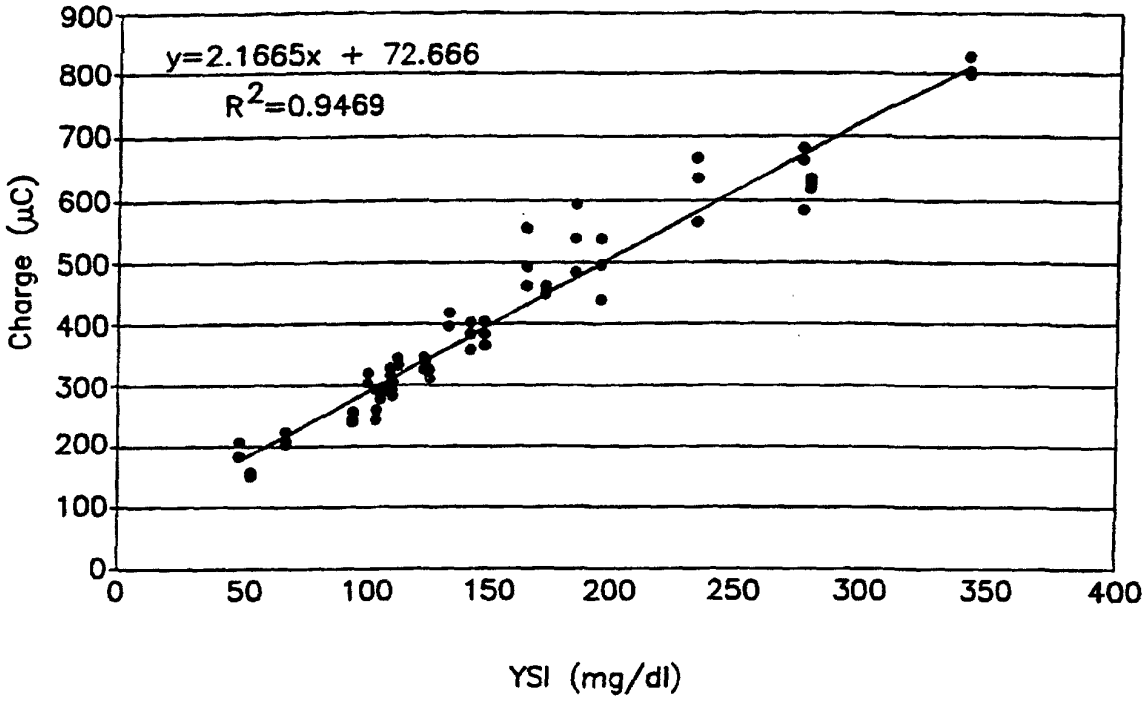


FIG. 26

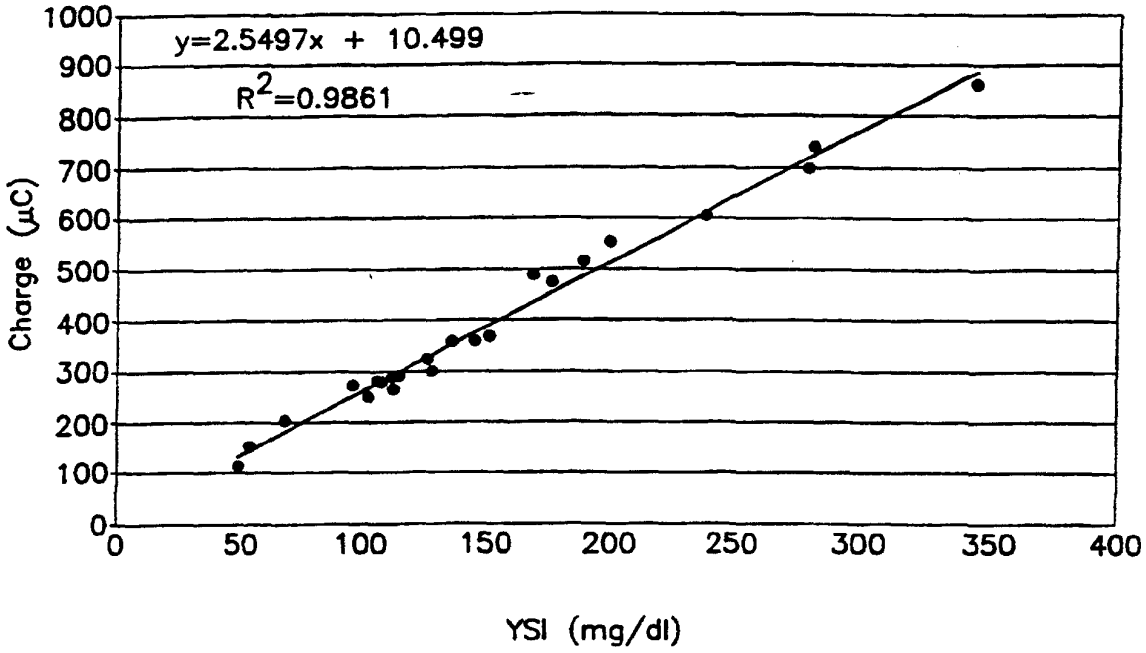
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FIG. 28



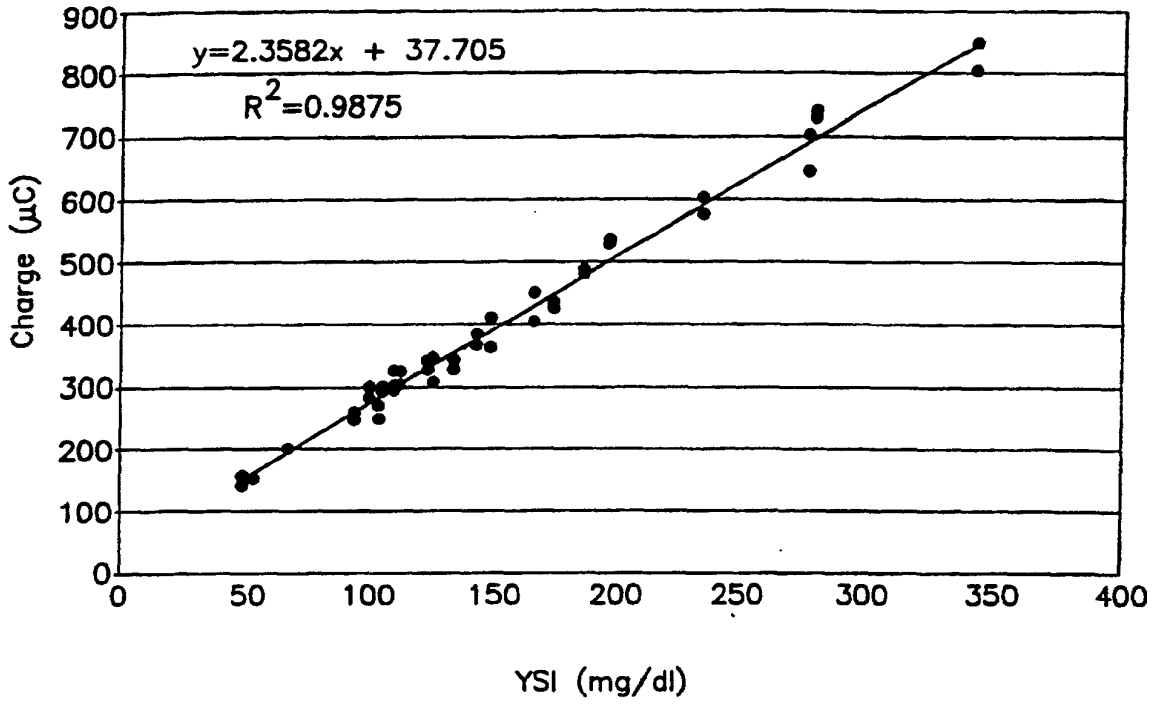
Abbott Ex. 1002 - 356/1438

FIG. 29



Abbott Ex. 1002 - 357/1438

FIG. 30



Abbott Ex. 1002 - 358/1438

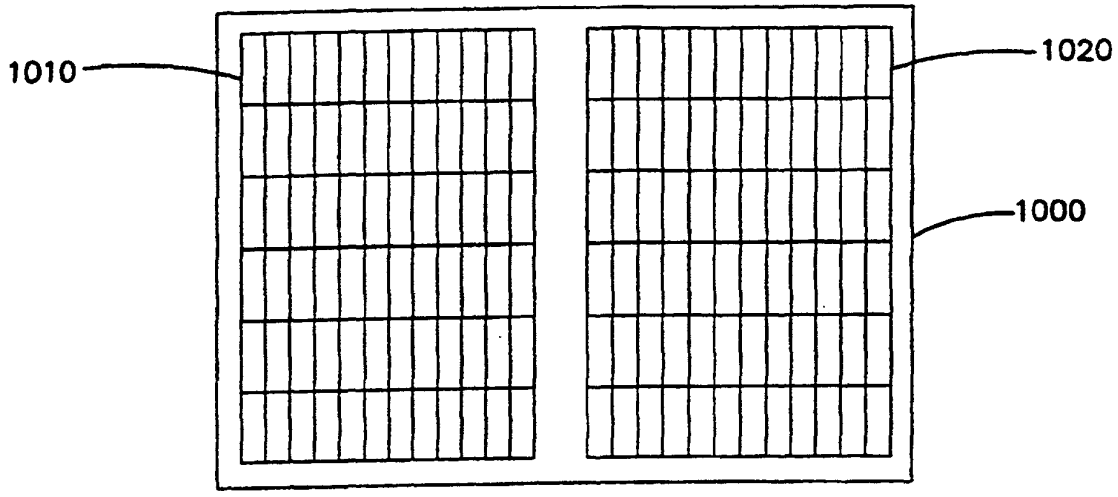


FIG. 31A

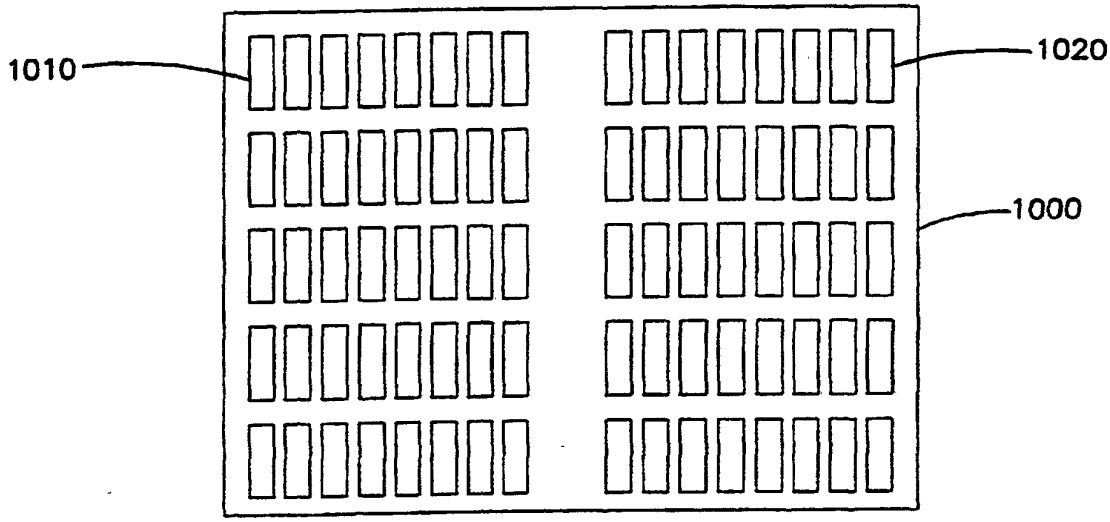


FIG. 31B

Abbott Ex. 1002 - 359/1438

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(87) International publication number:
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(54) **SMALL VOLUME IN VITRO ANALYTE SENSOR WITH DIFFUSIBLE OR NON-LEACHABLE REDOX MEDIATOR**

KLEINVOLUMIGER IN VITRO SENSOR MIT DIFFUSIONSFÄHIGEM ODER NICHTAUSWASCHBAREM REDOXVERMITTLER

DETECTEUR D'ANALYTES IN VITRO DANS DES PETITS VOLUMES UTILISANT UN MEDIATEUR DIFFUSIBLE OU NON LIXIVIABLE

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

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21.04.1999 US 295962

(43) Date of publication of application:
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(56) References cited:
WO-A-91/09139 **WO-A-97/00441**
WO-A-98/35225 **US-A- 5 695 947**

- **VIDAL J C ET AL: "A chronoamperometric sensor for hydrogen peroxide based on electron transfer between immobilized horseradish peroxidase on a glassy carbon electrode and a diffusing ferrocene mediator" SENSORS AND ACTUATORS B,CH,ELSEVIER SEQUOIA S.A., LAUSANNE, vol. 21, no. 2, 1 August 1994 (1994-08-01), pages 135-141, XP004012315 ISSN: 0925-4005**

EP 1 119 637 B2

Description

[0001] This invention relates to analytical sensors for the detection of bioanalytes in a small volume sample.

Background of the Invention

[0002] Analytical sensors are useful in chemistry and medicine to determine the presence and concentration of a biological analyte. Such sensors are needed, for example, to monitor glucose in diabetic patients and lactate during critical care events.

[0003] Currently available technology measures bioanalytes in relatively large sample volumes, e.g., generally requiring 3 microliters or more of blood or other biological fluid. These fluid samples are obtained from a patient, for example, using a needle and syringe, or by lancing a portion of the skin such as the fingertip and "milking" the area to obtain a useful sample volume. These procedures are inconvenient for the patient, and often painful, particularly when frequent samples are required. Less painful methods for obtaining a sample are known such as lancing the arm or thigh, which have a lower nerve ending density. However, lancing the body in the preferred regions typically produces submicroliter samples of blood, because these regions are not heavily supplied with near-surface capillary vessels.

[0004] It would therefore be desirable and very useful to develop a relatively painless, easy to use blood analyte sensor, capable of performing an accurate and sensitive analysis of the concentration of analytes in a small volume of sample. Sensors capable of electrochemically measuring an analyte in a sample are known in the art. Some sensors known in the art use at least two electrodes and may contain a redox mediator to aid in the electrochemical reaction. However, the use of an electrochemical sensor for measuring analyte in a small volume introduces error into the measurements. One type of inaccuracy arises from the use of a diffusible redox mediator. Because the electrodes are so close together in a small volume sensor, diffusible redox mediator may shuttle between the working and counter electrode and add to the signal measured for analyte. Another source of inaccuracy in a small volume sensor is the difficulty in determining the volume of the small sample or in determining whether the sample chamber is filled. It would therefore be desirable to develop a small volume electrochemical sensor capable of decreasing the errors that arise from the size of the sensor and the sample.

[0005] WO 98/35225 discloses a sensor having a working electrode, a counter electrode, and a sample chamber for receiving a sample having the analyte to be measured. The sample chamber includes a measurement zone having a volume of less than about 1 μl. A non-leachable redox mediator, which acts as an electron transfer agent between the analyte and the working electrode, is present on a portion of the working electrode.

Summary of the Invention

[0006] The sensors of the present invention provide a method for the detection and quantification of an analyte in submicroliter samples. In general, the invention includes a method and sensor for analysis of an analyte in a small volume of sample by, for example, coulometry, amperometry and/or potentiometry. A sensor of the invention utilizes a non-leachable or diffusible redox mediator. The sensor also includes a sample chamber to hold the sample in electrolytic contact with the working electrode. In many instances, the sensor also contains a non-leachable or diffusible second electron transfer agent.

[0007] In a preferred embodiment, the working electrode faces a counter electrode, forming a measurement zone within the sample chamber, between the two electrodes, that is sized to contain no more than about 1 μL of sample, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL of sample. A sorbent material is optionally positioned in the sample chamber and measurement zone to reduce the volume of sample needed to fill the sample chamber and measurement zone.

[0008] In one embodiment of the invention, a biosensor is provided which combines coulometric electrochemical sensing with a non-leachable or diffusible redox mediator to accurately and efficiently measure a bioanalyte in a submicroliter volume of sample. The preferred sensor includes an electrode, a non-leachable or diffusible redox mediator on the electrode, a sample chamber for holding the sample in electrical contact with the electrode and, preferably, sorbent material disposed within the sample chamber to reduce the volume of the chamber. The sample chamber, together with any sorbent material, is sized to provide for analysis of a sample volume that is typically no more than about 1 μL, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL. In some instances, the sensor also contains a non-leachable or diffusible second electron transfer agent.

[0009] One embodiment of the invention includes a method for determining the concentration of an analyte in a sample by, first, contacting the sample with an electrochemical sensor and then determining the concentration of the analyte. The electrochemical sensor includes a facing electrode pair with a working electrode and a counter electrode and a sample chamber, including a measurement zone, positioned between the two electrodes. The measurement zone is sized to contain no more than about 1 μL of sample.

Abbott Ex. 1002 - 361/1438

[0010] The invention also includes an electrochemical sensor with two or more facing electrode pairs. Each electrode pair has a working electrode, a counter electrode, and a measurement zone between the two electrodes, the measurement zone being sized to hold no more than about 1 μL of sample. In addition, the sensor also includes a non-leachable redox mediator on the working electrode of at least one of the electrode pairs or a diffusible redox mediator on a surface in the sample chamber or in the sample.

[0011] One aspect of the invention is a method of determining the concentration of an analyte in a sample by contacting the sample with an electrochemical sensor and determining the concentration of the analyte by coulometry. The electrochemical sensor includes an electrode pair with a working electrode and a counter electrode. The sensor also includes a sample chamber for holding a sample in electrolytic contact with the working electrode. Within the sample chamber is sorbent material to reduce the volume sample needed to fill the sample chamber so that the sample chamber is sized to contain no more than about 1 μL of sample. The sample chamber also contains a non-leachable or diffusible redox mediator and optionally contains a non-leachable or diffusible second electron transfer agent.

[0012] The sensors may also include a fill indicator, such as an indicator electrode or a second electrode pair, that can be used to determine when the measurement zone or sample chamber has been filled. An indicator electrode or a second electrode pair may also be used to increase accuracy of the measurement of analyte concentration. The sensors may also include a heating element to heat the measurement zone or sample chamber to increase the rate of oxidation or reduction of the analyte.

[0013] Sensors can be configured for side-filling or tip-filling. In addition, in some embodiments, the sensor may be part of an integrated sample acquisition and analyte measurement device. The integrated sample acquisition and analyte measurement device may include the sensor and a skin piercing member, so that the device can be used to pierce the skin of a user to cause flow of a fluid sample, such as blood, that can then be collected by the sensor. In at least some embodiments, the fluid sample can be collected without moving the integrated sample acquisition and analyte measurement device.

[0014] One method of forming a sensor, as described above, includes forming at least one working electrode on a first substrate and forming at least one counter or counter/reference electrode on a second substrate. A spacer layer is disposed on either the first or second substrates. The spacer layer defines a channel into which a sample can be drawn and held when the sensor is completed. A redox mediator and/or second electron transfer agent are disposed on the first or second substrate in a region that will be exposed within the channel when the sensor is completed. The first and second substrates are then brought together and spaced apart by the spacer layer with the channel providing access to the at least one working electrode and the at least one counter or counter/reference electrode. In some embodiments, the first and second substrates are portions of a single sheet or continuous web of material.

[0015] These and various other features which characterize the invention are pointed out with particularity in the attached claims. For a better understanding of the invention, its advantages, and objectives obtained by its use, reference should be made to the drawings and to the accompanying description, in which there is illustrated and described preferred embodiments of the invention.

Brief Description of the Drawings

[0016] Referring now to the drawings, wherein like reference numerals and letters indicate corresponding structure throughout the several views:

Figure 1 is a schematic view of a first embodiment of an electrochemical sensor in accordance with the principles of the present invention having a working electrode and a counter electrode facing each other;

Figure 2 is a schematic view of a second embodiment of an electrochemical sensor in accordance with the principles of the present invention having a working electrode and a counter electrode in a coplanar configuration;

Figure 3 is a schematic view of a third embodiment of an electrochemical sensor in accordance with the principles of the present invention having a working electrode and a counter electrode facing each other and having an extended sample chamber;

Figure 4 is a not-to-scale side-sectional drawing of a portion of the sensor of Figures 1 or 3 showing the relative positions of the redox mediator, the sample chamber, and the electrodes;

Figure 5 is a top view of a fourth embodiment of an electrochemical sensor in accordance with the principles of the present invention, this sensor includes multiple working electrodes;

Figure 6 is a perspective view of an embodiment of an analyte measurement device, in accordance with the principles of the present invention, having a sample acquisition means and the sensor of Figure 4;

Figure 7 is a graph of the charge required to electrooxidize a known quantity of glucose in an electrolyte buffered solution (filled circles) or serum solution (open circles) using the sensor of Figure 1 with glucose oxidase as the second electron transfer agent;

Figure 8 is a graph of the average glucose concentrations for the data of Figure 7 (buffered solutions only) with

Abbott Ex. 1002 - 362/1438

calibration curves calculated to fit the averages; a linear calibration curve was calculated for the 10-20 mM concentrations and a second order polynomial calibration curve was calculated for the 0-10 mM concentrations;
Figure 9 is a Clarke-type clinical grid analyzing the clinical relevance of the glucose measurements of Figure 7;
Figure 10 is a graph of the charge required to electrooxidize a known quantity of glucose in an electrolyte buffered solution using the sensor of Figure 1 with glucose dehydrogenase as the second electron transfer agent;
Figures 11A, 11B, and 11C are top views of three configurations for overlapping working and counter electrodes according to the present invention;
Figures 12A and 12B are cross-sectional views of one embodiment of an electrode pair formed using a recess of a base material, according to the invention;
Figures 13A and 13B are cross-sectional views of yet another embodiment of an electrode pair of the present invention formed in a recess of a base material;
Figures 14A and 14B are cross-sectional views of a further embodiment of an electrode pair of the present invention formed using a recess of a base material and a sorbent material;
Figure 15 is a graph of charge delivered by a sensor having a diffusible redox mediator over time for several concentrations of glucose;
Figure 16 is a graph of charge delivered by a sensor having a diffusible redox mediator for several glucose concentrations;
Figure 17 is a graph of charge delivered by sensors with different amounts of diffusible redox mediator over time.
Figure 18A illustrates a top view of a first film with a working electrode for use in a fifth embodiment of a sensor according to the invention;
Figure 18B illustrates a top view of a spacer for placement on the first film of Figure 18A;
Figure 18C illustrates a bottom view of a second film (inverted with respect to Figures 18A and 18B) with counter electrodes placement over the spacer of Figure 18B and first film of Figure 18A;
Figure 19A illustrates a top view of a first film with a working electrode for use in a sixth embodiment of a sensor according to the invention;
Figure 19B illustrates a top view of a spacer for placement on the first film of Figure 19A;
Figure 19C illustrates a bottom view of a second film (inverted with respect to Figures 19A and 19B) with counter electrodes placement over the spacer of Figure 19B and first film of Figure 19A;
Figure 20A illustrates a top view of a first film with a working electrode for use in a seventh embodiment of a sensor according to the invention;
Figure 20B illustrates a top view of a spacer for placement on the first film of Figure 20A;
Figure 20C illustrates a bottom view of a second film (inverted with respect to Figures 20A and 20B) with counter electrodes placement over the spacer of Figure 20B and first film of Figure 20A;
Figure 21A illustrates a top view of a first film with a working electrode for use in a eighth embodiment of a sensor according to the invention;
Figure 21B illustrates a top view of a spacer for placement on the first film of Figure 21A;
Figure 21C illustrates a bottom view of a second film (inverted with respect to Figures 21A and 21B) with counter electrodes placement over the spacer of Figure 21B and first film of Figure 21A;
Figure 22A illustrates a top view of a first film with a working electrode for use in a ninth embodiment of a sensor according to the invention;
Figure 22B illustrates a top view of a spacer for placement on the first film of Figure 22A;
Figure 22C illustrates a bottom view of a second film (inverted with respect to Figures 22A and 22B) with counter electrodes placement over the spacer of Figure 22B and first film of Figure 22A;
Figure 23A illustrates a top view of a first film with a working electrode for use in a tenth embodiment of a sensor according to the invention;
Figure 23B illustrates a top view of a spacer for placement on the first film of Figure 23A;
Figure 23C illustrates a bottom view of a second film (inverted with respect to Figures 23A and 23B) with counter electrodes placement over the spacer of Figure 23B and first film of Figure 23A;
Figure 24A illustrates a top view of a first film with a working electrode for use in a eleventh embodiment of a sensor according to the invention;
Figure 24B illustrates a top view of a spacer for placement on the first film of Figure 24A;
Figure 24C illustrates a bottom view of a second film (inverted with respect to Figures 24A and 24B) with counter electrodes placement over the spacer of Figure 24B and first film of Figure 24A;
Figure 25 illustrates a top view of a twelfth embodiment of an electrochemical sensor, according to the invention;
Figure 26 illustrates a perspective view of one embodiment of an integrated analyte acquisition and sensor device;
Figure 27 illustrates a cross-sectional view of a thirteenth embodiment of a sensor, according to the invention;
Figure 28 illustrates a graph comparing measurements of analyte concentration in blood samples collected from a subject's arm made by a sensor of the invention with those determined by a standard blood test;

Abbott Ex. 1002 - 363/1438

Figure 29 illustrates a graph comparing measurements of analyte concentration in blood samples collected from a subject's finger made by a sensor of the invention with those determined by a standard blood test;

Figure 30 illustrates a graph comparing measurements of analyte concentration in venous samples made by a sensor of the invention with those determined by a standard blood test;

Figure 31A illustrates a top view of one embodiment of a sheet of sensor components, according to the invention;

Figure 31B illustrates a top view of another embodiment of a sheet of sensor components, according to the invention; and

Figure 32 illustrates a cross-sectional view looking from inside the meter to a sensor of the invention disposed in a meter.

Detailed Description of the Preferred Embodiment

[0017] When used herein, the following definitions define the stated term:

[0018] An "air-oxidizable mediator" is a redox mediator that is oxidized by air, preferably so that at least 90% of the mediator is in an oxidized state upon storage in air either as a solid or as a liquid during a period of time, for example, one month or less, and, preferably, one week or less, and, more preferably, one day or less.

[0019] "Amperometry" includes steady-state amperometry, chronoamperometry, and Cottrell-type measurements.

[0020] A "biological fluid" is any body fluid in which the analyte can be measured, for example, blood, interstitial fluid, dermal fluid, sweat, and tears.

[0021] The term "blood" in the context of the invention includes whole blood and its cell-free components, such as, plasma and serum.

[0022] "Coulometry" is the determination of charge passed or projected to pass during complete or nearly complete electrolysis of the analyte, either directly on the electrode or through one or more electron transfer agents. The charge is determined by measurement of charge passed during partial or nearly complete electrolysis of the analyte or, more often, by multiple measurements during the electrolysis of a decaying current and elapsed time. The decaying current results from the decline in the concentration of the electrolyzed species caused by the electrolysis.

[0023] A "counter electrode" refers to one or more electrodes paired with the working electrode, through which passes an electrochemical current equal in magnitude and opposite in sign to the current passed through the working electrode. The term "counter electrode" is meant to include counter electrodes which also function as reference electrodes (i.e. a counter/reference electrode) unless the description provides that a "counter electrode" excludes a reference or counter/reference electrode.

[0024] An "effective diffusion coefficient" is the diffusion coefficient characterizing transport of a substance, for example, an analyte, an enzyme, or a redox mediator, in the volume between the electrodes of the electrochemical cell. In at least some instances, the cell volume may be occupied by more than one medium (e.g., the sample fluid and a polymer film). Diffusion of a substance through each medium may occur at a different rate. The effective diffusion coefficient corresponds to a diffusion rate through this multiple-media volume and is typically different than the diffusion coefficient for the substance in a cell filled solely with sample fluid.

[0025] An "electrochemical sensor" is a device configured to detect the presence of and/or measure the concentration of an analyte via electrochemical oxidation and reduction reactions. These reactions are transduced to an electrical signal that can be correlated to an amount or concentration of analyte.

[0026] "Electrolysis" is the electrooxidation or electroreduction of a compound either directly at an electrode or via one or more electron transfer agents (e.g., redox mediators and/or enzymes).

[0027] The term "facing electrodes" refers to a configuration of the working and counter electrodes in which the working surface of the working electrode is disposed in approximate opposition to a surface of the counter electrode. In at least some instances, the distance between the working and counter electrodes is less than the width of the working surface of the working electrode.

[0028] A compound is "immobilized" on a surface when it is entrapped on or chemically bound to the surface.

[0029] An "indicator electrode" includes one or more electrodes that detect partial or complete filling of a sample chamber and/or measurement zone.

[0030] A "layer" includes one or more layers.

[0031] The "measurement zone" is defined herein as a region of the sample chamber sized to contain only that portion of the sample that is to be interrogated during an analyte assay.

[0032] A "non-diffusible," "non-leachable," or "non-releasable" compound is a compound which does not substantially diffuse away from the working surface of the working electrode for the duration of the analyte assay.

[0033] The "potential of the counter/reference electrode" is the half cell potential of the reference electrode or counter/reference electrode of the cell when the solution in the cell is 0.1 M NaCl solution at pH7.

[0034] "Potentiometry" and "chronopotentiometry" refer to taking a potentiometric measurement at one or more points in time.

Abbott Ex. 1002 - 364/1438

[0035] A "redox mediator" is an electron transfer agent for carrying electrons between the analyte and the working electrode, either directly, or via a second electron transfer agent.

[0036] A "reference electrode" includes a reference electrode that also functions as a counter electrode (i.e., a counter/reference electrode) unless the description provides that a "reference electrode" excludes a counter/reference electrode.

[0037] A "second electron transfer agent" is a molecule that carries electrons between a redox mediator and the analyte.

[0038] "Sorbent material" is material that wicks, retains, and/or is wetted by a fluid sample and which typically does not substantially prevent diffusion of the analyte to the electrode.

[0039] A "surface in the sample chamber" includes a surface of a working electrode, counter electrode, counter/reference electrode, reference electrode, indicator electrode, a spacer, or any other surface bounding the sample chamber.

[0040] A "working electrode" is an electrode at which analyte is electrooxidized or electroreduced with or without the agency of a redox mediator.

[0041] A "working surface" is the portion of a working electrode that is covered with non-leachable redox mediator and exposed to the sample, or, if the redox mediator is diffusible, a "working surface" is the portion of the working electrode that is exposed to the sample.

[0042] The small volume, *in vitro* analyte sensors of the present invention are designed to measure the concentration of an analyte in a portion of a sample having a volume no more than about 1 μL, preferably no more than about 0.5 μL, more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL. The analyte of interest is typically provided in a solution or biological fluid, such as blood or serum. Referring to the Drawings in general and Figures 1- 4 in particular, a small volume, *in vitro* electrochemical sensor 20 of the invention generally includes a working electrode 22, a counter (or counter/reference) electrode 24, and a sample chamber 26 (see Figure 4). The sample chamber 26 is configured so that when a sample is provided in the chamber the sample is in electrolytic contact with both the working electrode 22 and the counter electrode 24. This allows electrical current to flow between the electrodes to effect the electrolysis (electrooxidation or electroreduction) of the analyte.

Working Electrode

[0043] The working electrode 22 may be formed from a molded carbon fiber composite or it may consist of an inert non-conducting base material, such as polyester, upon which a suitable conducting layer is deposited. The conducting layer typically has relatively low electrical resistance and is typically electrochemically inert over the potential range of the sensor during operation. Suitable conducting layers include gold, carbon, platinum, ruthenium dioxide, palladium, and conductive epoxies, such as, for example, ECCOCOAT CT5079-3 Carbon-Filled Conductive Epoxy Coating (available from W.R. Grace Company, Woburn, Massachusetts), as well as other non-corroding materials known to those skilled in the art. The electrode (e.g., the conducting layer) is deposited on the surface of the inert material by methods such as vapor deposition or printing.

[0044] A tab 23 may be provided on the end of the working electrode 22 for easy connection of the electrode to external electronics (not shown) such as a voltage source or current measuring equipment. Other known methods or structures (such as contact pads) may be used to connect the working electrode 22 to the external electronics.

[0045] To prevent electrochemical reactions from occurring on portions of the working electrode not coated by the mediator, when a non-leachable mediator is used, a dielectric 40 may be deposited on the electrode over, under, or surrounding the region with the redox mediator, as shown in Figure 4. Suitable dielectric materials include waxes and non-conducting organic polymers such as polyethylene. Dielectric 40 may also cover a portion of the redox mediator on the electrode. The covered portion of the redox mediator will not contact the sample, and, therefore, will not be a part of the electrode's working surface.

Sensing Chemistry

[0046] In addition to the working electrode 22, sensing chemistry materials are provided in the sample chamber 26 for the analysis of the analyte. This sensing chemistry preferably includes a redox mediator and a second electron transfer mediator, although in some instances, one or the other may be used alone. The redox mediator and second electron transfer agent can be independently diffusible or non-leachable (i.e., non-diffusible) such that either or both may be diffusible or non-leachable. Placement of sensor chemistry components may depend on whether they are diffusible or non-leachable. For example, non-leachable and/or diffusible component(s) typically form a sensing layer on the working electrode.

Alternatively, one or more diffusible components may be disposed on any surface in the sample chamber prior to the introduction of the sample. As another example, one or more diffusible component(s) may be placed in the sample prior to introduction of the sample into the sensor.

[0047] If the redox mediator is non-leachable, then the non-leachable redox mediator is typically disposed on the

Abbott Ex. 1002 - 365/1438

working electrode 22 as a sensing layer 32. In an embodiment having a redox mediator and a second electron transfer agent, if the redox mediator and second electron transfer agent are both non-leachable, then both of the non-leachable components are disposed on the working electrode 22 as a sensing layer 32.

[0048] If, for example, the second electron transfer agent is diffusible and the redox mediator is non-leachable, then at least the redox mediator is disposed on the working electrode 22 as a sensing layer 32. The diffusible second electron transfer agent need not be disposed on a sensing layer of the working electrode, but may be disposed on any surface of the sample chamber, including within the redox mediator sensing layer, or may be placed in the sample. If the redox mediator is diffusible, then the redox mediator may be disposed on any surface of the sample chamber or may be placed in the sample.

[0049] If both the redox mediator and second electron transfer agent are diffusible, then the diffusible components may be independently or jointly disposed on any surface of the sample chamber and/or placed in the sample (i.e., each diffusible component need not be disposed on the same surface of the sample chamber or placed in the sample).

[0050] The redox mediator, whether it is diffusible or non-leachable, mediates a current between the working electrode 22 and the analyte and enables the electrochemical analysis of molecules which may not be suited for direct electrochemical reaction on an electrode. The mediator functions as an electron transfer agent between the electrode and the analyte.

[0051] In one embodiment, the redox mediator and second electron transfer agent are diffusible and disposed on the same surface of the sample chamber, such as, for example, on the working electrode. In this same vein, both can be disposed on, for example, the counter electrode, counter/reference electrode, reference electrode, or indicator electrode. In other instances, the redox mediator and second electron transfer agent are both diffusible and independently placed on a surface of the sample chamber and/or in the sample. For example, the redox mediator may be placed on the working electrode while the second electron transfer agent is placed on any surface, except for the working electrode, or is placed in the sample. Similarly, the reverse situation in which the second electron transfer agent is disposed on the working electrode and the redox mediator is disposed on any surface, except for the working electrode, or is placed in the sample is also a suitable embodiment. As another example, the redox mediator may be disposed on the counter electrode and the second electron transfer agent is placed on any surface except for the counter electrode or is placed in the sample. The reverse situation is also suitable.

[0052] The diffusible redox mediator and/or second electron transfer agent may diffuse rapidly into the sample or diffusion may occur over a period of time. Similarly, the diffusible redox mediator and/or second electron transfer agent may first dissolve from the surface on which it was placed as a solid and then the diffusible redox mediator and/or second electron transfer agent may diffuse into the sample, either rapidly or over a period of time. If the redox mediator and/or second electron transfer agent diffuse over a period of time, a user may be directed to wait a period of time before measuring the analyte concentration to allow for diffusion of the redox mediator and/or second electron transfer agent.

Background Signal

[0053] In at least some instances, a diffusible redox mediator may shuttle back and forth from the working electrode to the counter electrode even in the absence of analyte. This typically creates a background signal. For coulometric measurements, this background signal is referred to herein as "Q_{Back}." The background signal corresponds to the charge passed in an electrochemical assay in the absence of the analyte. The background signal typically has both a transient component and a steady-state component. At least a portion of the transient component may result, for example, from the establishment of a concentration gradient of the mediator in a particular oxidation state. At least a portion of the steady-state component may result, for example, from the redox mediator shuttling between the working electrode and counter or counter/reference electrode. Shuttling refers to the redox mediator being electrooxidized (or electroreduced) at the working electrode and then being electroreduced (or electrooxidized) at the counter or counter/reference electrode, thereby making the redox mediator available to be electrooxidized (or electroreduced) again at the working electrode so that the redox mediator is cycling between electrooxidation and electroreduction.

[0054] The amount of shuttling of the redox mediator, and therefore, the steady-state component of the background signal varies with, for example, the effective diffusion coefficient of the redox mediator, the viscosity of the sample, the temperature of the sample, the dimensions of the electrochemical cell, the distance between the working electrode and the counter or counter/reference electrode, and the angle between the working electrode and the counter or counter/reference electrode.

[0055] In some instances, the steady-state component of the background signal may contain noise associated with (a) variability in, for example, the temperature of the sample, the sample viscosity, or any other parameter on which the background signal depends during the duration of the assay, or (b) imperfections in the electrochemical cell, such as, for example, non-uniform separation between the working electrode and the counter or counter/reference electrode, variations in electrode geometry, or protrusions from the working electrode, the counter electrode, and/or the counter/reference electrode.

Abbott Ex. 1002 - 366/1438

[0056] Although the steady-state component of the background signal may be reproducible, any noise inherently is not reproducible. As a result, the noise adversely affects accuracy. In some cases, the background signal and noise are related. As a result, the noise, and the error it introduces, can be reduced by reducing the background signal. For example, reducing the shuttling of the mediator between the working electrode and counter electrode or counter/reference electrode will likely reduce the noise associated with changes in sample temperature and viscosity which affect diffusion of the redox mediator.

[0057] Thus, to increase the accuracy of the measurements or to decrease error in the measurements in those instances when reducing a background signal also reduces noise, a moderate to near-zero level of background signal is desirable. The invention provides a sensor and method according to the claims. In the case of amperometry, this comparison may be made by determining the ratio of the current from the shuttling of the redox mediator to the current generated by the electrolysis of the analyte. In the case of potentiometry, this comparison may be made by determining the potential measurement from the shuttling of the redox mediator and the potential measurement generated by electrolysis of the analyte. In the case of coulometry, this comparison may be made by determining the charge transferred at the working electrode by the shuttling of the redox mediator and the charge transferred at the working electrode by the electrolysis of the analyte.

[0058] The size of the background signal may be compared to a predetermined amount of analyte. The predetermined amount of analyte in a sample may be, for example, an expected or average molar amount of analyte. The expected or average molar amount of analyte may be determined as, for example, the average value for users or individuals; an average value for a population; a maximum, minimum, or average of a normal physiological range; a maximum or minimum physiological value for a population; a maximum or minimum physiological value for users or individuals; an average, maximum, or minimum deviation outside a normal physiological range value for users, individuals, or a population; a deviation above or below an average value for a population; or an average, maximum, or minimum deviation above or below an average normal physiological value for users or individuals. A population may be defined by, for example, health, sex, or age, such as, for example, a normal adult, child, or newborn population. If a population is defined by health, the population may include people lacking a particular condition or alternatively, having a particular condition, such as, for example, diabetes. Reference intervals pertaining to average or expected values, such as, for example, those provided in Tietz Textbook of Clinical Chemistry, Appendix (pp. 2175-2217) (2nd Ed., Carl A. Burtis and Edward R. Ashwood, eds., W.D. Saunders Co., Philadelphia 1994) may be used as guidelines, but a physical examination or blood chemistry determination by a skilled physician may also be used to determine an average or expected value for an individual. For example, an adult may have glucose in a concentration of 65 to 95 mg/dL in whole blood or L-lactate in a concentration of 8.1 to 15.3 mg/dL in venous whole blood after fasting, according to Tietz Textbook of Clinical Chemistry. An average normal physiological concentration for an adult, for example, may then correspond to 80 mg/dL for glucose or 12.7 mg/dL for lactate. Other examples include a person having juvenile onset diabetes, yet good glycemic control, and a glucose concentration between about 50 mg/dL and 400 mg/dL, thereby having an average molar amount of 225 mg/dL. In another instance, a non-diabetic adult may have a glucose concentration between about 80 mg/dL (after fasting) and 140 mg/dL (after consuming food), thereby having an average molar amount of 110 mg/dL.

[0059] Additional analytes that may be determined include, for example, acetyl choline, amylase, bilirubin, cholesterol, chorionic gonadotropin, creatine kinase (e.g., CK-MB), creatine, DNA, fructosamine, glucose, glutamine, growth hormones, hormones, ketones, lactate, peroxide, prostate-specific antigen, prothrombin, RNA, thyroid stimulating hormone, and troponin. The concentration of drugs, such as, for example, antibiotics (e.g., gentamicin, vancomycin, and the like), digitoxin, digoxin, drugs of abuse, theophylline, and warfarin, may also be determined.

[0060] To construct a sensor having a particular ratio of background signal to analyte signal from electrolysis, several parameters relating to current and/or charge from the redox mediator shuttling background signal and/or from the signal generated by electrolysis of the analyte may be considered and chosen to obtain a desired ratio. Typically, the signal determined for a coulometric assay is the charge; whereas the signal determined for an amperometric assay is the current at the time when the measurement is taken. Because the current and charge depend on several parameters, the desired ratio for background signal generated by shuttling of the redox mediator to signal generated by electrolysis of the analyte may be accomplished by a variety of sensor configurations and methods for operating a sensor.

Controlling Background Signal

[0061] One method of controlling background signal includes using a redox mediator that a) oxidizes the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no more than about +100 mV relative to the potential of a reference or counter/reference electrode or b) reduces the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no less than about -100 mV relative to the potential of a reference or counter/reference electrode. A suitable reference or counter/reference electrode (e.g., a silver/silver chloride electrode) may be chosen. Preferably, the redox mediator a) oxidizes the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no more than about +50 mV, +25 mV, 0 mV, - 25 mV, -50 mV, -100 mV,

Abbott Ex. 1002 - 367/1438

or -150 mV relative to the potential of the reference or counter/reference electrode or b) reduces the analyte at a half wave potential, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, of no less than about -50 mV, -25 mV, 0 mV, +25 mV, +50 mV, +100 mV, +150 mV, or +200 mV relative to the potential of the reference or counter/reference electrode. Alternatively, in the case of reduction of the redox mediator by the counter electrode, the sensor is operated at an applied potential of no more than about +100 mV, +50 mV, +25 mV, 0 mV, -25 mV, -50 mV, -100 mV, or -150 mV between the working electrode and the counter or counter/reference electrode. In the case of oxidation of the redox mediator at the counter electrode, the sensor is operated at an applied potential of no less than about -100 mV, -50 mV, -25 mV, 0 mV, +25 mV, +50 mV, +100 mV, +150 mV, or +200 mV between the working electrode and the counter or counter/reference electrode.

[0062] Another method includes controlling the applied potential such that for an electrooxidative assay the redox mediator is not readily reduced at the counter or counter/reference electrode or for an electroreductive assay the redox mediator is not readily oxidized at the counter or counter/reference electrode. This can be accomplished, for example, in an electrooxidative assay by using a sensor having a diffusible redox mediator with a potential, relative to a reference or counter/reference electrode, that is negative with respect to the potential of the counter electrode (relative to a reference electrode) or the counter/reference electrode. The potential (relative to a reference or counter/reference electrode) of the working electrode is chosen to be positive with respect to the redox mediator and may be negative with respect to the counter or counter/reference electrode, so that the redox mediator is oxidized at the working electrode. For example, when the electrooxidation of an analyte is mediated by a diffusible redox mediator with a potential of -200 mV versus the reference or counter/reference electrode, and the potential at which the working electrode is poised is -150 mV relative to the reference or counter/reference electrode, then the redox mediator is substantially oxidized at the working electrode and will oxidize the analyte. Further, if some of the oxidized redox mediator reaches the counter or counter/reference electrode, the redox mediator will not be readily reduced at the counter or counter/reference electrode because the counter or counter/reference electrode is poised well positive (i.e., 150 mV) of the potential of the redox mediator.

[0063] In an electroreductive assay, a sensor is provided having a diffusible redox mediator with a formal potential, relative to a reference or counter/reference electrode, that is positive with respect to the potential of the counter or counter/reference electrode. The potential, relative to the reference or counter/reference electrode, of the working electrode is chosen to be negative with respect to the redox mediator and may be poised positive with respect to the counter or counter/reference electrode, so that the redox mediator is reduced at the working electrode.

[0064] Still another method of limiting background current includes having the redox mediator become immobilized when reacted on the counter electrode or counter/reference electrode by, for example, precipitation or polymerization. For example, the mediator may be cationic in the oxidized state, but neutral and much less soluble in the reduced state. Reduction at the counter/reference electrode leads to precipitation of the reduced, neutral mediator on the counter/reference electrode.

[0065] Another sensor configuration suitable for controlling background signal includes a sensor having a molar amount of redox mediator that is stoichiometrically the same as or less than an expected or average molar amount of analyte. The expected or average molar amount of analyte may be determined as already explained above. The expected or average molar amount of analyte may be determined as, for example, the average value for users or individuals; an average value for a population; a maximum, minimum, or average of a normal physiological range; a maximum or minimum physiological value for a population; a maximum or minimum physiological value for users or individuals; an average, maximum, or minimum deviation outside a normal physiological range value for users, individuals, or a population; a deviation above or below an average value for a population; or an average, maximum, or minimum deviation above or below an average normal physiological value for users or individuals. A population may be defined by, for example, health, sex, or age, such as, for example, a normal adult, child, or newborn population. If a population is defined by health, the population may include people lacking a particular condition or alternatively, having a particular condition, such as, for example, diabetes. Reference intervals pertaining to average or expected values, such as, for example, those provided in Tietz Textbook of Clinical Chemistry, *supra*, may be used as guidelines, but a physical examination or blood chemistry determination may also determine an average or expected value. For example, the physiological average molar amount of analyte may depend on the health or age of the person from whom the sample is obtained. This determination is within the knowledge of a skilled physician.

[0066] By reducing the concentration of the redox mediator relative to the concentration of the analyte, the signal attributable to the analyte relative to the signal attributable to the shuttling of the redox mediator is increased. In implementation of this method, the molar amount of redox mediator may be no more than 50%, 20%, 10%, or 5%, on a stoichiometric basis, of the expected or average molar amount of analyte.

[0067] The amount of redox mediator used in such a sensor configuration should fall within a range. The upper limit of the range may be determined based on, for example, the acceptable maximum signal due to shuttling of the redox mediator; the design of the electrochemical cell, including, for example, the dimensions of the cell and the position of the electrodes; the effective diffusion coefficient of the redox mediator; and the length of time needed for the assay. Moreover, the acceptable maximum signal due to redox mediator shuttling may vary from assay to assay as a result of

Abbott Ex. 1002 - 368/1438

one or more assay parameters, such as, for example, whether the assay is intended to be qualitative, semi-quantitative, or quantitative; whether small differences in analyte concentration serve as a basis to modify therapy; and the expected concentration of the analyte.

[0068] Although it is advantageous to minimize the amount of redox mediator used, the range for the acceptable amount of redox mediator does typically have a lower limit. The minimum amount of redox mediator that may be used is the concentration of redox mediator that is necessary to accomplish the assay within a desirable measurement time period, for example, no more than about 5 minutes or no more than about 1 minute. The time required to accomplish an assay depends on, for example, the distance between the working electrode and the counter or counter/reference electrode, the effective diffusion coefficient of the redox mediator, and the concentration of the analyte. In some instances, for example, when no kinetic limitations are present, i.e., shuttling of the redox mediator depends only on diffusion, the minimum concentration of redox mediator may be determined by the following formula:

$$C_m = (d^2 C_A) / D_m t$$

where C_m is the minimum concentration of mediator required; d is the distance between a working electrode and a counter or counter/reference electrode in a facing arrangement; C_A is the average analyte concentration in the sample; D_m is the effective diffusion coefficient of the mediator in the sample; and t is the desired measurement time.

[0069] For example, when the distance between the facing electrode pair is 50 μm, the analyte being measured is 5mM glucose, the redox mediator effective diffusion coefficient is 10^{-6} cm^2/sec and the desirable response time is no more than about 1 minute, then the minimum redox mediator concentration is 2.08mM. Under these conditions the background signal will be less than the signal from the electrooxidation of the analyte.

[0070] Yet another sensor configuration for limiting the background current generated by a diffusible redox mediator includes having a barrier to the flow of the diffusible mediator to the counter electrode. The barrier can be, for example, a film through which the redox mediator can not diffuse or through which the redox mediator diffuses slowly. Examples of suitable films include polycarbonate, polyvinyl alcohol, and regenerated cellulose or cellulose ester membranes. Alternatively, the barrier can include charged or polar particles, compounds, or functional groups to prevent or reduce the flow of a charged redox mediator relative to the flow of a charge neutral or less charged analyte. If the redox mediator is positively charged, as are many of the osmium redox mediators described below, the barrier can be a positively charged or polar film, such as a methylated poly(1-vinyl imidazole). If the redox mediator is negatively charged, the barrier can be a negatively charged or polar film, such as Nafion®. Examples of suitable polar matrices include a bipolar membrane, a membrane having a cationic polymer cross-linked with an anionic polymer, and the like. In some instances, the barrier reduces the oxidation or reduction of the diffusible redox mediator at the counter electrode by at least 25%, 50%, or 90%.

[0071] Still another sensor configuration for limiting the background current includes a sensor having a redox mediator that is more readily oxidized or reduced on the working electrode than reduced or oxidized on the counter electrode. The rate of reaction of the redox mediator at an electrode can be a function of the material of the electrode. For example, some redox mediators may react faster at a carbon electrode than at a Ag/AgCl electrode. Appropriate selection of the electrodes may provide a reaction rate at one electrode that is significantly slower than the rate at the other electrode. In some instances, the rate of oxidation or reduction of the diffusible redox mediator at the counter electrode is reduced by at least 25%, 50%, or 90%, as compared to the working electrode. In some instances the rate of reaction for the redox mediator at the counter or counter/reference electrode is controlled by, for example, choosing a material for the counter or counter/reference electrode that would require an overpotential or a potential higher than the applied potential to increase the reaction rate at the counter or counter/reference electrode.

[0072] Another sensor configuration for limiting background current includes elements suitable for reducing the diffusion of the redox mediator. Diffusion can be reduced by, for example, using a redox mediator with a relatively low diffusion coefficient or increasing the viscosity of the sample in the measurement zone. In another embodiment, the diffusion of the redox mediator may be decreased by choosing a redox mediator with high molecular weight, such as, for example, greater than 5,000 daltons, preferably greater than 25,000 daltons, and more preferably greater than 100,000 daltons.

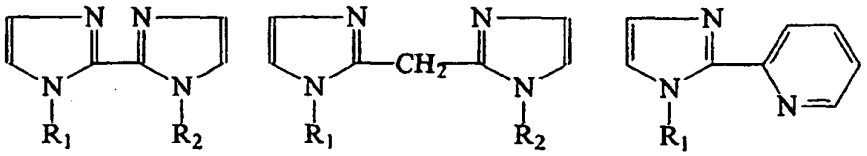
Redox Mediators

[0073] Although any organic or organometallic redox species can be used as a redox mediator, one type of suitable redox mediator is a transition metal compound or complex. Examples of suitable transition metal compounds or complexes include osmium, ruthenium, iron, and cobalt compounds or complexes. In these complexes, the transition metal is coordinatively bound to one or more ligands. The ligands are typically mono-, di-, tri-, or tetradentate. The most preferred ligands are heterocyclic nitrogen compounds, such as, for example, pyridine and/or imidazole derivatives. Multidentate

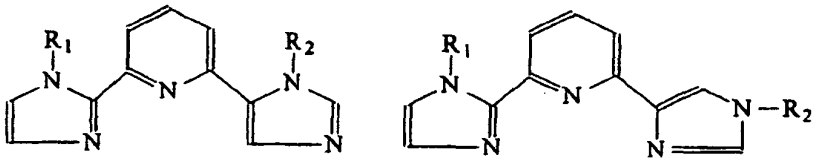
Abbott Ex. 1002 - 369/1438

ligands may include multiple pyridine and/or imidazole rings. Alternatively, metallocene derivatives, such as, for example, ferrocene, can be used.

[0074] Suitable redox mediators include osmium or ruthenium transition metal complexes with one or more ligands, each ligand having one or more nitrogen-containing heterocycles. Examples of such ligands include pyridine and imidazole rings and ligands having two or more pyridine and/or imidazole rings such as, for example, 2,2'-bipyridine; 2,2': 6',2"-terpyridine; 1,10-phenanthroline; and ligands having the following structures:



(I) (II) (III)



(IV) (V)

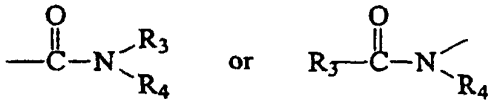
and derivatives thereof, wherein R_1 and R_2 are each independently hydrogen, hydroxy, alkyl, alkoxy, alkenyl, vinyl, allyl, amido, amino, vinylketone, keto, or sulfur-containing groups.

[0075] The term "alkyl" includes a straight or branched saturated aliphatic hydrocarbon chain having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl isopropyl (1-methylethyl), butyl, *tert*-butyl (1,1-dimethylethyl), and the like. Preferably the hydrocarbon chain has from 1 to 3 carbon atoms.

[0076] The term "alkoxy" includes an alkyl as defined above joined to the remainder of the structure by an oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy (1-methylethoxy), butoxy, *tert*-butoxy, and the like.

[0077] The term "alkenyl" includes an unsaturated aliphatic hydrocarbon chain having from 2 to 6 carbon atoms, such as, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-methy-1-propenyl, and the like. Preferably the hydrocarbon chain has from 2 to 3 carbon atoms.

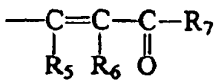
[0078] The term "amido" includes groups having a nitrogen atom bonded to the carbon atom of a carbonyl group and includes groups having the following formulas:



wherein R_3 and R_4 are each independently hydrogen, alkyl, alkoxy, or alkenyl.

[0079] The term "amino" as used herein includes alkylamino, such as methylamino, diethylamino, N,N-methylethylamino and the like; alkoxyalkylamino, such as N-(ethoxyethyl)amino, N,N-di(methoxyethyl)amino, N,N-(methoxyethyl)(ethoxyethyl)amino, and the like; and nitrogen-containing rings, such as piperidino, piperazino, morpholino, and the like.

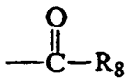
[0080] The term "vinylketone" includes a group having the formula:



Abbott Ex. 1002 - 370/1438

wherein R_5, R_6, and R_7 are each independently hydrogen, alkyl, alkoxy, or alkenyl.

[0081] The term "keto" includes a group having the formula:

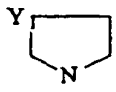


wherein R_8 is hydrogen, alkyl, alkoxy, or alkenyl.

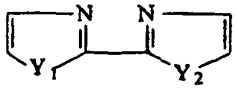
[0082] The term "sulfur-containing group" includes mercapto, alkylmercapto (such as methylmercapto, ethylmercapto, and the like), alkoxyalkylmercapto (such as methoxyethylmercapto and the like), alkylsulfoxide (such as methylsulfoxide and propylsulfoxide and the like), alkoxyalkylsulfoxide (such as ethoxyethylsulfoxide and the like), alkylsulfone (such as methylsulfone and propylsulfone and the like), and alkoxyalkylsulfone (such as methoxyethylsulfone and the like). Preferably, the sulfur-containing group is a mercapto group.

[0083] Other suitable redox mediators include osmium or ruthenium transition metal complexes with one or more ligands, each ligand having one or more nitrogen-containing heterocycles and each nitrogen-containing heterocycle having a second heteroatom selected from the group consisting of nitrogen, oxygen, sulfur, and selenium.

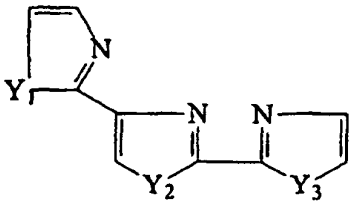
[0084] Examples of ligands having one or more nitrogen-containing heterocycles and in which each heterocycle has a second heteroatom include ligands having the following structures:



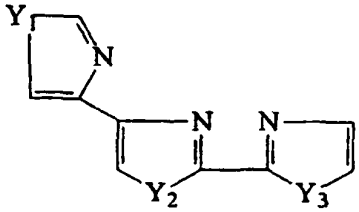
(VI)



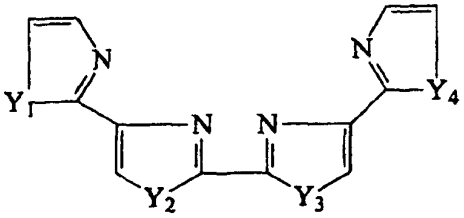
(VII)



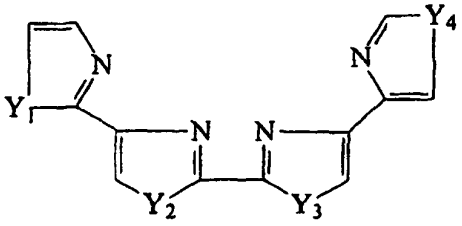
(VIII)



(IX)

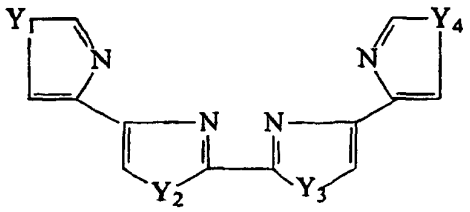


(X)



(XI)

Abbott Ex. 1002 - 371/1438



(XII)

wherein Y_1, Y_2, Y_3, and Y_4 are each independently an oxygen atom, a sulfur atom, a selenium atom, or a substituted nitrogen atom having the formula NR_9 wherein R_9 is hydrogen, hydroxy, alkyl, alkoxy, alkenyl, amido, amino, vinylketone, keto, or sulfur-containing group. The terms "alkyl," "alkoxy," "alkenyl," "amido," "amino," "vinylketone," "keto," and "sulfur-containing group" are as defined above.

[0085] Suitable derivatives of these ligands include, for example, the addition of alkyl, alkoxy, alkenyl, vinylester, and amido functional groups to any of the available sites on the heterocyclic ring, including, for example, on the 4-position (i.e., para to nitrogen) of the pyridine rings or on one of the nitrogen atoms of the imidazole ring.

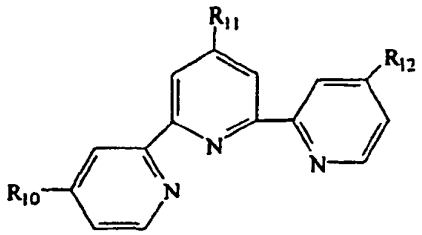
[0086] Suitable derivatives of 2,2'-bipyridine for complexation with the osmium cation include, for example, mono-, di-, and polyalkyl-2,2'-bipyridines, such as 4,4'-dimethyl-2,2'-bipyridine; mono-, di-, and polyalkoxy-2,2'-bipyridines, such as 4,4'-dimethoxy-2,2'-bipyridine and 2,6'-dimethoxy-2,2'-bipyridine; mono-, di-, and polyacetamido-2,2'-bipyridines, such as 4,4'-di(acetamido)-2,2'-bipyridine; mono-, di-, and polyalkylaminoalkoxy-2,2'-bipyridines, such as 4,4'-di(N,N-dimethylaminoethoxy)-2,2'-bipyridine; and substituted mono-, di-, and polypyrazolyl-2,2'-bipyridines, such as 4,4'-dimethoxy-6-(N-pyrazolyl)-2,2'-bipyridine and 4,4'-dimethoxy-6-(N-pyrazolylmethyl)-2,2'-bipyridine.

[0087] Suitable derivatives of 1,10-phenanthroline for complexation with the osmium cation include, for example, mono-, di-, and polyalkyl-1,10-phenanthrolines, such as 4,7-dimethyl-1,10-phenanthroline, and mono, di-, and polyalkoxy-1,10-phenanthrolines, such as 4,7-dimethoxy-1,10-phenanthroline and 5-methoxy-1,10-phenanthroline.

[0088] Suitable derivatives for 2,2':6',2"-terpyridine include, for example, mono-, di-, tri-, and polyalkyl-2,2':6',2"-terpyridines, such as 4,4',4"-trimethyl-2,2':6',2"-terpyridine, 4,4',4"-triethyl-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyalkoxy-2,2':6',2"-terpyridines, such as 4,4',4"-trimethoxy-2,2':6',2"-terpyridine and 4'-methoxy-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyamino-2,2':6',2"-terpyridine, such as 4'-amino-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyalkylamino-2,2':6',2"-terpyridine, such as 4'-dimethylamino-2,2':6',2"-terpyridine, and mono-, di-, tri-, and polyalkylthio-2,2':6',2"-terpyridine such as 4'-methylthio-2,2':6',2"-terpyridine and 4-methylthio-4'-ethylthio-2,2':6',2"-terpyridine.

[0089] Suitable derivatives for pyridine include, for example, mono-, di-, tri-, and polysubstituted pyridines, such as 2,6-bis(N-pyrazolyl)pyridine, 2,6-bis(3-methyl-N-pyrazolyl)pyridine, 2,6-bis(2-imidazolyl)pyridine, 2,6-bis(1-methyl-2-imidazolyl)pyridine, and 2,6-bis(1-vinyl-2-imidazolyl)pyridine, and mono-, di-, tri-, and polyaminopyridines, such as 4-aminopyridine, 4,4'-diaminobipyridine, 4,4'-di(dimethylamino)bipyridine, and 4,4',4"-triamino terpyridine.

[0090] Other suitable derivatives include compounds comprising three heterocyclic rings. For example, one suitable derivative includes a compound of the formula:



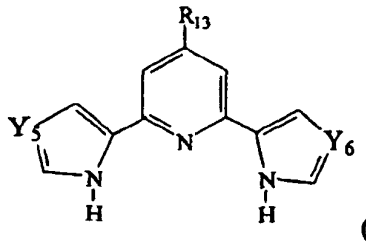
(XIII)

wherein R_{10}, R_{11}, and R_{12} are each independently hydrogen, hydroxy, alkyl, alkoxy, alkenyl, vinyl, allyl, amido, amino, vinylketone, keto, or sulfur-containing group.

[0091] The terms "alkyl," "alkoxy," "alkenyl," "amido," "amino," "vinylketone," "keto," and "sulfur-containing group" are as defined above.

[0092] Other suitable redox mediator derivatives include compounds of the formula:

Abbott Ex. 1002 - 372/1438

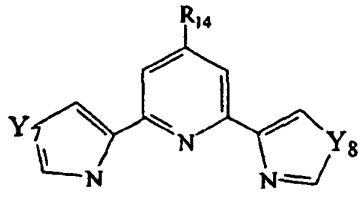


(XIV)

wherein R_{13} is hydrogen, hydroxy, alkyl, alkoxy, alkenyl, vinyl, allyl, vinylketone, keto, amido, amino, or sulfur-containing group; and Y_5 and Y_6 are each independently a nitrogen or carbon atom.

[0093] The terms "alkyl," "alkoxy," "alkenyl," "amido," "amino," "vinylketone," "keto," and "sulfur-containing group" are as defined above.

[0094] Still other suitable derivatives include compounds of the formula:



(XV)

wherein R_{14} is as defined above and Y_7 and Y_8 are each independently a sulfur or oxygen atom.

[0095] Examples of suitable redox mediators also include, for example, osmium cations complexed with (a) two bidentate ligands, such as 2,2'-bipyridine, 1,10-phenanthroline, or derivatives thereof (the two ligands not necessarily being the same), (b) one tridentate ligand, such as 2,2',2"-terpyridine and 2,6-di(imidazol-2-yl)-pyridine, or (c) one bidentate ligand and one tridentate ligand. Suitable osmium transition metal complexes include, for example, $[(bpy)_2OsLX]^{+/2+}$, $[(dimet)_2OsLX]^{+/2+}$, $[(dmo)_2OsLX]^{+/2+}$, $[terOsLX_2]^{0/+}$, $[trimetOsLX_2]^{0/+}$, and $[(ter)(bpy)LOs]^{2+/3+}$ where bpy is 2,2'-bipyridine, dimet is 4,4'-dimethyl-2,2'-bipyridine, dmo is 4,4'-dimethoxy-2,2'-bipyridine, ter is 2,2':6',2"-terpyridine, trimet is 4,4',4"-trimethyl-2,2':6',2"-terpyridine, L is a nitrogen-containing heterocyclic ligand, and X is a halogen, such as fluorine, chlorine, or bromine.

[0096] The redox mediators often exchange electrons rapidly with each other and with the electrode so that the complex can be rapidly oxidized and/or reduced. In general, iron complexes are more oxidizing than ruthenium complexes, which, in turn, are more oxidizing than osmium complexes. In addition, the redox potential generally increases with the number of coordinating heterocyclic rings; six-membered heterocyclic rings increase the potential more than five membered rings, except when the nitrogen coordinating the metal is formally an anion. This is the case only if the nitrogen in the ring is bound to both of its neighboring carbon atoms by single bonds. If the nitrogen is formally an anion then the redox potential generally increases more upon coordination of the metal ion.

[0097] At least some diffusible redox mediators include one or more pyridine or imidazole functional groups. The imidazole functional group can also include other substituents and can be, for example, vinyl imidazole, e.g., 1-vinyl imidazole, or methylimidazole, e.g., 1-methylimidazole. Examples of suitable diffusible mediators may include $[Os(dmo)_2(1\text{-vinyl imidazole})X]X$, $[Os(dmo)_2(1\text{-vinyl imidazole})X]X_2$, $[Os(dmo)_2(imidazole)X]X$, $[Os(dmo)_2(imidazole)X]X_2$, $[Os(dmo)_2(1\text{-methylimidazole})X]X_2$, and $[Os(dmo)_2(methylimidazole)X]X_2$, where dmo is 4,4'-dimethoxy-2,2'-bipyridine, and X is halogen as described above.

[0098] Other osmium-containing redox mediators include $[Os((methoxy)_2phenanthroline)_2(N\text{-methylimidazole})X]^{+/2+}$; $[Os((acetamido)_2bipyridine)_2(L)X]^{+/2+}$, where L is a monodentate nitrogen-containing compound (including, but not limited to, an imidazole derivative) chosen to refine the potential; and $Os(terpyridine)(L)_2Cl$, where L is an aminopyridine, such as a dialkylaminopyridine; an N-substituted imidazole, such as N-methyl imidazole; an oxazole; a thiazole; or an alkoxypyridine, such as methoxypyridine. X is halogen as described above.

[0099] Osmium-free diffusible redox mediators include, for example, phenoxazines, such as, 7-dimethylamino-1,2-benzophenoxazine (Meldola Blue), 1,2-benzophenoxazine, and Nile Blue; 3-β-naphthoyl (Brilliant Cresyl Blue); tetramethylphenylenediamine (TMPD); dichlorophenolindophenol (DCIP); N-methyl phenazonium salts, for example, phenazine methosulfate (PMS), N-methylphenazine methosulfate and methoxyphenazine methosulfate; tetrazolium salts, for

Abbott Ex. 1002 - 373/1438

example, tetrazolium blue or nitrotetrazolium blue; and phenothiazines, for example, toluidine blue O.

[0100] Examples of other redox species include stable quinones and species that in their oxidized state have quinoid structures, such as Nile Blue and indophenol. Examples of suitable quinones include, for example, derivatives of naphthoquinone, phenoquinone, benzoquinone, naphthenequinone, and the like. Examples of naphthoquinone derivatives include juglone (i.e., 5-hydroxy-1,4-naphthoquinone) and derivatives thereof, such as, for example, 2,3-dichloro-5,8-dihydroxy-1,4-naphthoquinone, 2,3-dimethyl-5,8-dihydroxy-1,4-naphthoquinone, 2-chloro-5,8-dihydroxy-1,4-naphthoquinone, 2,3-methoxy-5-hydroxy-1,4-naphthoquinone, and the like. Other examples include aminonaphthoquinones, such as, for example, morpholino-naphthoquinones, such as 2-chloro-3-morpholino-1,4-naphthoquinone; piperidino-naphthoquinones, such as 2-methyl-3-peperidino-1,4-naphthoquinone; piperazino-naphthoquinones, such as 2-ethoxy-3-piperazino-1,4-naphthoquinone; and the like.

[0101] Suitable phenoquinone derivatives include, for example, coerulignone (i.e., 3,3',5,5'-tetramethoxydiphenoquinone) and derivatives thereof, such as, for example, 3,3',5,5'-tetramethyldiphenoquinone, 3,3',5,5'-tetrahydroxydiphenoquinone, and the like.

[0102] Suitable benzoquinone derivatives include, for example, coenzyme Q_0 (i.e., 2,3-dimethoxy-5-methyl-1,4-benzoquinone) and derivatives thereof, such as, for example, 2,3,5-trimethyl-1,4-benzoquinone, 2,3-dimethyl-5-methoxy-1,4-benzoquinone, 2,3-dimethyl-5-hydroxy-1,4-benzoquinone, and the like.

[0103] Other suitable quinone derivatives include, for example, acenaphthenequinone and ubiquinones, such as, for example, coenzyme Q, including Q_1, Q_2, Q_6, Q_7, Q_9, and Q_{10}.

[0104] Still other suitable osmium-free diffusible redox mediators include, for example, Taylor's blue (i.e., 1,9-dimethylmethylene blue), N,N'-diethylthiacyanine iodide, and thionine.

[0105] In another method, a sensing layer 32 contains a non-leachable (i.e., non-releasable) redox mediator and is disposed on a portion of the working electrode 22. The non-leachable redox mediator can be, for example, a redox polymer (i.e., a polymer having one or more redox species). Preferably, there is little or no leaching of the non-leachable redox mediator away from the working electrode 22 into the sample during the measurement period, which is typically less than about 5 minutes. The redox mediators of this embodiment can be bound or otherwise immobilized on the working electrode 22 to prevent leaching of the mediator into the sample. The redox mediator can be bound or otherwise immobilized on the working electrode by known methods, for example, formation of multiple ion bridges with a counter-charged polyelectrolyte, covalent attachment of the redox mediator to a polymer on the working electrode, entrapment of the redox mediator in a matrix that has a high affinity for the redox mediator, or bioconjugation of the redox mediator with a compound bound to the working electrode. In one embodiment, a cationic exchange membrane may be used to entrap an anionic redox compound. Similarly, in another embodiment, an anionic exchange membrane may be used to entrap a cationic redox compound. In still another embodiment involving bioconjugation, a biotin-bound redox mediator can conjugate with avidin or straptavidin in a matrix near or immobilized on the working electrode. Still another embodiment includes having a digoxin or digoxigenin redox mediator react with antidigoxin in a matrix near or immobilized on a working electrode.

[0106] Preferred non-leachable redox mediators are redox polymers, such as polymeric transition metal compounds or complexes. Typically, the polymers used to form a redox polymer have nitrogen-containing heterocycles, such as pyridine, imidazole, or derivatives thereof for binding as ligands to the redox species. Suitable polymers for complexation with redox species, such as the transition metal complexes, described above, include, for example, polymers and copolymers of poly(1-vinyl imidazole) (referred to as "PVI") and poly(4-vinyl pyridine) (referred to as "PVP"), as well as polymers and copolymers ofpoly(acrylic acid) or polyacrylamide that have been modified by the addition of pendant nitrogen-containing heterocycles, such as pyridine and imidazole. Modification of poly(acrylic acid) may be performed by reaction of at least a portion of the carboxylic acid functionalities with an aminoalkylpyridine or aminoalkylimidazole, such as 4-ethylaminopyridine, to form amides. Suitable copolymer substituents of PVI, PVP, and poly(acrylic acid) include acrylonitrile, acrylamide, acrylhydrazide, and substituted or quatemized 1-vinyl imidazole. The copolymers can be random or block copolymers.

[0107] The transition metal complexes of non-leachable redox polymers are typically covalently or coordinatively bound with the nitrogen-containing heterocycles (e.g., imidazole and/or pyridine rings) of the polymer. The transition metal complexes may have vinyl functional groups through which the complexes can be co-polymerized. Suitable vinyl functional groups include, for example, vinylic heterocycles, amides, nitriles, carboxylic acids, sulfonic acids, or other polar vinylic compounds. An example of a redox polymer of this type is poly(vinyl ferrocene) or a derivative of poly(vinyl ferrocene) functionalized to increase swelling of the redox polymer in water.

[0108] Another type of redox polymer contains an ionically-bound redox species, by forming multiple ion-bridges. Typically, this type of mediator includes a charged polymer coupled to an oppositely charged redox species. Examples of this type of redox polymer include a negatively charged polymer such as Nafion® (DuPont) coupled to multiple positively charged redox species such as an osmium or ruthenium polypyridyl cation. Another example of an ionically-bound mediator is a positively charged polymer such as quaternized poly(4-vinyl pyridine) or poly(1-vinyl imidazole) coupled to a negatively charged redox species such as ferricyanide or ferrocyanide. The preferred ionically-bound redox

Abbott Ex. 1002 - 374/1438

species is a multiply charged, often polyanionic, redox species bound within an oppositely charged polymer.

[0109] Another suitable redox polymer includes a redox species coordinatively bound to a polymer. For example, the mediator may be formed by coordination of an osmium, ruthenium, or cobalt 2, 2'-bipyridyl complex to poly(1-vinyl imidazole) or poly(4-vinyl pyridine) or by co-polymerization of, for example, a 4-vinyl-2,2'-bipyridyl osmium, ruthenium, or cobalt complex with 1-vinyl imidazole or 4-vinyl pyridine.

[0110] Typically, the ratio of osmium or ruthenium transition metal complexes to imidazole and/or pyridine groups of the non-leachable redox polymers ranges from 1:20 to 1:1, preferably from 1:15 to 1:2, and more preferably from 1:10 to 1:4. Generally, the redox potentials depend, at least in part, on the polymer with the order of redox potentials being poly(acrylic acid) < PVI < PVP.

[0111] A variety of methods may be used to immobilize a redox polymer on an electrode surface. One method is adsorptive immobilization. This method is particularly useful for redox polymers with relatively high molecular weights. The molecular weight of a polymer may be increased, for example, by cross-linking. The polymer of the redox polymer may contain functional groups, such as, for example, hydrazide, amine, alcohol, heterocyclic nitrogen, vinyl, allyl, and carboxylic acid groups, that can be crosslinked using a crosslinking agent. These functional groups may be provided on the polymer or one or more of the copolymers. Alternatively or additionally, the functional groups may be added by a reaction, such as, for example, quaternization. One example is the quaternization of PVP with bromoethylamine groups.

[0112] Suitable cross-linking agents include, for example, molecules having two or more epoxide (e.g., poly(ethylene glycol) diglycidyl ether (PEGDGE)), aldehyde, aziridine, alkyl halide, and azide functional groups or combinations thereof. When a polymer has multiple acrylate functions, it can be crosslinked with a di- or polythiol; when it has multiple thiol functions it can be crosslinked with a di- or polyacrylate. Other examples of cross-linking agents include compounds that activate carboxylic acid or other acid functional groups for condensation with amines or other nitrogen compounds. These cross-linking agents include carbodiimides or compounds with active N-hydroxysuccinimide or imidate functional groups. Yet other examples of cross-linking agents are quinones (e.g., tetrachlorobenzoquinone and tetracyanoquinodimethane) and cyanuric chloride. Other cross-linking agents may also be used. In some embodiments, an additional cross-linking agent is not required. Further discussion and examples of cross-linking and cross-linking agents are found in U.S. Patents Nos. 5,262,035; 5,262,305; 5,320,725; 5,264,104; 5,264,105; 5,356,786; and 5,593,852.

[0113] In another embodiment, the redox polymer is immobilized by the functionalization of the electrode surface and then the chemical bonding, often covalently, of the redox polymer to the functional groups on the electrode surface. One example of this type of immobilization begins with a poly(4-vinyl pyridine). The polymer's pyridine rings are, in part, complexed with a reducible/oxidizable species, such as $[Os(bpy)_2Cl]^{+/2+}$ where bpy is 2,2'-bipyridine. Part of the pyridine rings are quatemized by reaction with 2-bromoethylamine. The polymer is then crosslinked, for example, using a diepoxide, such as poly(ethylene glycol) diglycidyl ether.

[0114] Carbon surfaces can be modified for attachment of a redox polymer, for example, by electroreduction of a diazonium salt. As an illustration, reduction of a diazonium salt formed upon diazotization of p-aminobenzoic acid modifies a carbon surface with phenylcarboxylic acid functional groups. These functional groups can be activated by a carbodiimide, such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC). The activated functional groups are bound with an amine-functionalized redox couple, such as, for example, the quatemized osmium-containing redox polymer described above or 2-aminoethylferrocene, to form the redox couple.

[0115] Similarly, gold and other metal surfaces can be functionalized by, for example, an amine, such as cystamine, or by a carboxylic acid, such as thioctic acid. A redox couple, such as, for example, $[Os(bpy)_2(\text{pyridine-4-carboxylate})Cl]^{0/+}$, is activated by 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) to form a reactive O-acylisourea which reacts with the gold-bound amine to form an amide. The carboxylic acid functional group of thioctic acid can be activated with EDC to bind a polymer or protein amine to form an amide.

[0116] When the enzyme used is PQQ glucose dehydrogenase or glucose oxidase, the preferred non-leachable redox mediators have a redox potential between about -300 mV to about +400 mV versus the standard calomel electrode (SCE). The most preferred non-leachable redox mediators have osmium redox centers and a redox potential more negative than +100 mV versus SCE, more preferably the redox potential is more negative than 0 mV versus SCE, and most preferably is near -150 mV versus SCE.

[0117] In at least some instances, the redox mediators of the sensors are air-oxidizable. This means that the redox mediator is oxidized by air, preferably, so that at least 90% of the mediator is in an oxidized state prior to introduction of sample into the sensor. Air-oxidizable redox mediators include osmium cations complexed with two mono-, di-, or polyalkoxy-2,2'-bipyridine or mono-, di-, or polyalkoxy-1,10-phenanthroline ligands, the two ligands not necessarily being the same, and further complexed with polymers or other ligands having pyridine and imidazole functional groups. In particular, $Os[4,4'\text{-dimethoxy-2,2'-bipyridine}]_2Cl^{+/+2}$ complexed with poly(4-vinyl pyridine) or poly(1-vinyl imidazole) attains approximately 90% or more oxidation in air. The air oxidation of the redox mediator may take place while the redox mediator is a solid, such as, for example, when it is coated on the sensor in a dry state and stored. Alternatively, the air oxidation of the redox mediator may take place while the redox mediator is in solution, such as, for example, prior to the solution being applied onto the sensor and dried. In the case in which the redox mediator is air oxidized in solution, the

Abbott Ex. 1002 - 375/1438

solution containing the redox mediator may be kept in storage for a period of time sufficient to air oxidize the mediator prior to use of the solution in the manufacturing process.

Second Electron Transfer Agent

[0118] In a preferred embodiment of the invention, the sensor includes a redox mediator and a second electron transfer agent which is capable of transferring electrons to or from the redox mediator and the analyte. The second electron transfer agent may be diffusible or may be non-leachable (e.g., entrapped in or coordinatively, covalently, or ionically bound to the redox polymer). One example of a suitable second electron transfer agent is an enzyme which catalyzes a reaction of the analyte. For example, a glucose oxidase or glucose dehydrogenase, such as pyrroloquinoline quinone glucose dehydrogenase (PQQ), is used when the analyte is glucose. A lactate oxidase fills this role when the analyte is lactate. Other enzymes can be used for other analytes. These enzymes catalyze the electrolysis of an analyte by transferring electrons between the analyte and the electrode via the redox mediator. In some embodiments, the second electron transfer agent is non-leachable, and more preferably immobilized on the working electrode, to prevent unwanted leaching of the agent into the sample. This is accomplished, for example, by cross-linking the non-leachable second electron transfer agent with the non-leachable redox mediator, thereby providing a sensing layer with non-leachable components on the working electrode. In other embodiments, the second electron transfer agent is diffusible (and may be disposed on any surface of the sample chamber or placed in the sample).

Counter Electrode

[0119] Counter electrode 24, as illustrated in Figures 1-4, may be constructed in a manner similar to working electrode 22. Counter electrode 24 may also be a counter/reference electrode. Alternatively, a separate reference electrode may be provided in contact with the sample chamber. Suitable materials for the counter/reference or reference electrode include Ag/AgCl or Ag/AgBr printed on a non-conducting base material or silver chloride on a silver metal base. The same materials and methods may be used to make the counter electrode as are available for constructing the working electrode 22, although different materials and methods may also be used. A tab 25 may be provided on the electrode for convenient connection to the external electronics (not shown), such as a coulometer, potentiostat, or other measuring device.

Electrode Configuration

[0120] In one embodiment of the invention, working electrode 22 and counter electrode 24 are disposed opposite to and facing each other to form a facing electrode pair as depicted in Figures 1 and 3. In this preferred configuration, the sample chamber 26 is typically disposed between the two electrodes. For this facing electrode configuration, it is preferred that the electrodes are separated by a distance of no more than about 0.2 mm (i.e., at least one portion of the working electrode is separated from one portion of the counter electrode by no more than 200 μm), preferably no more than 100 μm, and most preferably no more than 50 μm.

[0121] The electrodes need not be directly opposing each other; they may be slightly offset. Furthermore, the two electrodes need not be the same size. Preferably, the counter electrode 24 is at least as large as the working surface of the working electrode 22. The counter electrode 22 can also be formed with tines in a comb shape. Other configurations of both the counter electrode and working electrode are within the scope of the invention. However, for this particular embodiment, the separation distance between at least one portion of the working electrode and some portion of the counter electrode preferably does not exceed the limits specified hereinabove.

[0122] Figures 11A, 11B, and 11C illustrate different embodiments of pairs of facing electrodes 22, 24, as described above. A region 21 of overlap between the two electrodes 22, 24 typically corresponds to the measurement zone in which the sample will be interrogated. Each of the electrodes 22, 24 is a conducting surface and acts as a plate of a capacitor. The measurement zone between the electrodes 22, 24 acts as a dielectric layer between the plates. Thus, there is a capacitance between the two electrodes 22, 24. This capacitance is a function of the size of the overlapping electrodes 22, 24, the separation between the electrodes 22, 24, and the dielectric constant of the material between the electrodes 22, 24. Thus, if the size of the region 21 of the overlapping electrodes 22, 24 and the dielectric constant of the material between the electrodes (e.g., air or a sorbent material) are known, then the separation between the electrodes can be calculated to determine the volume of the measurement zone.

[0123] Figure 11A illustrates one embodiment of the invention in which the electrodes 22, 24 are positioned in a facing arrangement. For the capacitance to be uniform among similarly constructed analyte sensors having this particular sensor configuration, the registration (i.e., the positioning of the two electrodes relative to one another) should be uniform. If the position of either of the electrodes is shifted in the x-y plane from the position shown in Figure 11A, the size of the overlap, and therefore, of the capacitance, will change. The same principle holds for the volume of the measurement zone.

Abbott Ex. 1002 - 376/1438

[0124] Figures 11B and 11C illustrate other embodiments of the invention with electrodes 22, 24 in a facing arrangement. In these particular arrangements, the position of either of the electrodes may be shifted, by at least some minimum distance, in the x-y plane relative to the other electrode without a change in the capacitance or the volume of the measurement zone. In these electrode arrangements, each electrode 22, 24 includes an arm 122, 124, respectively, which overlaps with the corresponding arm of the other electrode. The two arms 122, 124 are not parallel to each other (such as illustrated in Figure 11A); rather, the arms 122, 124 are disposed at an angle 123, which is greater than zero, relative to each other. In addition, the two arms 122, 124 extend beyond the region 21 of overlap (i.e., each arm has extra length corresponding to the difference between the length of the arm 222, 224, respectively, and the width 121 of the overlap 21). With these electrode arrangements, there can be a certain amount of allowed imprecision in the registration of the electrodes 22, 24 which does not change the capacitance of the electrode arrangement. A desired amount of allowed imprecision in the registration can be designed into the electrode arrangement by varying the angle 123 at which the arms 122, 124 overlap and the size of the extra length of each arm 122, 124 relative to the width 121 of the region 21 of overlap. Typically, the closer that the arms 122, 124 are to being perpendicular (i.e., angle 123 is 90°), the greater the allowed imprecision. Also, the greater the extra length of each arm 122, 124 (which may both be the same length or different lengths) relative to the width 121 of the region 21 of overlap, the greater the allowed imprecision. Conversely, the greater the amount of allowed imprecision, the larger the size of the electrodes (for a given electrode width, thickness, and angle 123 of intersection with the other electrode). Thus, the minimum distance that one electrode can be shifted relative to the other is balanced against the amount of material needed for the electrodes. Typically, the angle 123 of intersection ranges from 5 to 90 degrees, preferably, 30 to 90 degrees, and more preferably 60 to 90 degrees. Typically, the ratio of the extra length of an arm 122, 124 (corresponding to the difference between the arm length 222, 224 and the width 121 of the region 21 of overlap) versus the width 121 of the region 21 of overlap ranges from 0.1:1 to 50:1, preferably 1:1 to 15:1, and more preferably 4:1 to 10:1.

[0125] In another embodiment of the invention, the two electrodes 22, 24 are coplanar as shown in Figure 2. In this case, the sample chamber 26 is in contact with both electrodes and is bounded on the side opposite the electrodes by a non-conducting inert base 30. Suitable materials for the inert base include non-conducting materials such as polyester.

[0126] Other configurations of the inventive sensors are also possible. For example, the two electrodes may be formed on surfaces that make an angle to each other. One such configuration would have the electrodes on surfaces that form a right angle. Another possible configuration has the electrodes on a curved surface such as the interior of a tube. The working and counter electrodes may be arranged so that they face each other from opposite sides of the tube. This is another example of a facing electrode pair. Alternatively, the electrodes may be placed near each other on the tube wall (e.g., one on top of the other or side-by-side).

[0127] In any configuration, the two electrodes must be configured so that they do not make direct electrical contact with each other, to prevent shorting of the electrochemical sensor. This may be difficult to avoid when the facing electrodes are separated, over the average, by no more than about 100μm.

[0128] A spacer 28 can be used to keep the electrodes apart when the electrodes face each other as depicted in Figures 1 and 3. The spacer is typically constructed from an inert non-conducting material such as pressure-sensitive adhesive, polyester, Mylar™, Kevlar™ or any other strong, thin polymer film, or, alternatively, a thin polymer film such as a Teflon™ film, chosen for its chemical inertness. In addition to preventing contact between the electrodes, the spacer 28 often functions as a portion of the boundary for the sample chamber 26 as shown in Figures 1- 4. Other spacers include layers of adhesive and double-sided adhesive tape (e.g., a carrier film with adhesive on opposing sides of the film).

Sample Chamber

[0129] The sample chamber 26 is typically defined by a combination of the electrodes 22, 24, an inert base 30, and a spacer 28 as shown in Figures 1-4. A measurement zone is contained within this sample chamber and is the region of the sample chamber that contains only that portion of the sample that is interrogated during the analyte assay. In the embodiment of the invention illustrated in Figures 1 and 2, sample chamber 26 is the space between the two electrodes 22, 24 and/or the inert base 30. In this embodiment, the sample chamber has a volume that is preferably no more than about 1 μL, more preferably no more than about 0.5 μL, and most preferably no more than about 0.25 μL. In the embodiment of the invention depicted in Figures 1 and 2, the measurement zone has a volume that is approximately equal to the volume of the sample chamber. In a preferred embodiment the measurement zone includes 80% of the sample chamber, 90% in a more preferred embodiment, and about 100% in a most preferred embodiment.

[0130] In another embodiment of the invention, shown in Figure 3, sample chamber 26 includes much more space than the region proximate electrodes 22, 24. This configuration makes it possible to provide multiple electrodes in contact with one or more sample chambers, as shown in Figure 5. In this embodiment, sample chamber 26 is preferably sized to contain a volume of no more than about 1 μL, more preferably no more than about 0.5 μL, and most preferably no more than about 0.25 μL. The measurement zone (i.e., the region containing the volume of sample to be interrogated) is generally sized to contain a volume of sample of no more than about 1 μL, preferably no more than about 0.5 μL,

Abbott Ex. 1002 - 377/1438

more preferably no more than about 0.25 μL, and most preferably no more than about 0.1 μL. One particularly useful configuration of this embodiment positions working electrode 22 and counter electrode 24 facing each other, as shown in Figure 3. In this embodiment, the measurement zone, corresponding to the region containing the portion of the sample which will be interrogated, is the portion of sample chamber 26 bounded by the working surface of the working electrode and disposed between the two facing electrodes.

[0131] In both of the embodiments discussed above, the thickness of the sample chamber and of the measurement zone correspond typically to the thickness of spacer 28 (e.g., the distance between the electrodes in Figures 1 and 3, or the distance between the electrodes and the inert base in Figure 2). The spacer may be, for example, an adhesive or double-sided adhesive tape or film. Preferably, this thickness is small to promote rapid electrolysis of the analyte, as more of the sample will be in contact with the electrode surface for a given sample volume. In addition, a thin sample chamber helps to reduce errors from diffusion of analyte into the measurement zone from other portions of the sample chamber during the analyte assay, because diffusion time is long relative to the measurement time. Typically, the thickness of the sample chamber is no more than about 0.2 mm. Preferably, the thickness of the sample chamber is no more than about 0.1 mm and, more preferably, the thickness of the sample chamber is about 0.05 mm or less.

[0132] The sample chamber may be formed by other methods. Exemplary methods include embossing, indenting, or otherwise forming a recess in a substrate within which either the working electrode 22 or counter electrode 24 is formed. Figures 12A and 12B illustrate one embodiment of this structure. First, a conducting layer 100 is formed on an inert non-conducting base material 102. As described above, the conducting layer 100 can include gold, carbon, platinum, ruthenium dioxide, palladium, or other non-corroding materials. The inert non-conducting base material 102 can be made using a polyester, other polymers, or other non-conducting, deformable materials. A recess 104 is then formed in a region of the non-conducting base material 102 so that at least a portion of the conducting layer 100 is included in the recess 104. The recess 104 may be formed using a variety of techniques including indenting, deforming, or otherwise pushing in the base material 102. One additional exemplary method for forming the recess includes embossing the base material 102. For example, the base material 102 may be brought into contact with an embossing roll or stamp having raised portions, such as punch members or channels, to form the recess 104. In some embodiments, the base material 102 may be heated to soften the material.

[0133] The recess 104 may be circular, oval, rectangular, or any other regular or irregular shape. Alternatively, the recess 104 may be formed as a channel which extends along a portion of the base material 102. The conducting layer 100 may extend along the entire channel or only a portion of the channel. The measurement zone may be restricted to a particular region within the channel by, for example, depositing the sensing layer 32 on only that portion of the conducting layer 100 within the particular region of the channel. Alternatively, the measurement zone may be defined by placing a second electrode 107 over only the desired region of the first electrode 105.

[0134] At least a portion, and in some cases, all, of the conducting layer 100 is situated in the recess 104. This portion of the conducting layer 100 may act as a first electrode 105 (a counter electrode or a working electrode). If the conducting layer 100 forms the working electrode, then a sensing layer 32 may be formed over a portion of the conducting layer 100 by depositing a non-leachable redox mediator and/or second electron transfer agent in the recess 104, as shown in Figure 12B. If a diffusible redox mediator or second electron transfer agent is used, then the diffusible material may be disposed on any surface in the sample chamber or in the sample.

[0135] A second electrode 107 is then formed by depositing a second conducting layer on a second base material 106. This second electrode 107 is then positioned over the first electrode 105 in a facing arrangement. Although not illustrated, if the redox mediator is non-leachable it will be understood that if the first electrode 105 were to function as a counter electrode, then the sensing layer 32 would be deposited on the second electrode 107 which would then function as the working electrode. If the redox mediator is diffusible, however, the redox mediator may be disposed on any surface of the sample chamber or may be placed in the sample.

[0136] In one embodiment, the second base material 106 rests on a portion of the first base material 102 and/or the-conducting layer 100 which is not depressed, so that the second electrode 107 extends into the recess. In another embodiment, there is a spacer (not shown) between the first and second base materials 102, 106. In this embodiment, the second electrode 107 may or may not extend into the recess. In any case, the first and second electrodes 105, 107 do not make contact, otherwise the two electrodes would be shorted.

[0137] The depth of the recess 104 and the volume of the conductive layer 100, sensing layer 32, and the portion, if any, of the second electrode 107 in the recess 104 determines the volume of the measurement zone. Thus, the predictability of the volume of the measurement zone relies on the extent to which the formation of the recess 104 is uniform.

[0138] In addition to the conducting layer 100, a sorbent layer 103, described in detail below, may be deposited on the base material 102 prior to forming the recess 104, as shown in Figure 14A. The sorbent material 103 may be indented, embossed, or otherwise deformed with the conducting layer 100 and base material 102, as shown in Figure 14B. Alternatively, the sorbent material 103 may be deposited after the conducting layer 100 and base material 102 are indented, embossed, or otherwise deformed to make the recess 104.

[0139] In another exemplary method for forming the analyte sensor, a recess 114 is formed in a first base material

Abbott Ex. 1002 - 378/1438

112, as shown in Figures 13A and 13B. The recess may be formed by indenting, embossing, etching (e.g., using photolithographic methods or laser removal of a portion of the base material), or otherwise deforming or removing a portion of the base material 112. Then a first conducting layer 110 is formed in the recess 114. Any of the conductive materials discussed above may be used. A preferred material is a conductive ink, such as a conductive carbon ink available, for example, from Ercon, Inc. (Wareham, MA). The conductive ink typically contains metal or carbon dissolved or dispersed in a solvent or dispersant. When the solvent or dispersant is removed, the metal or carbon forms a conductive layer 110 that can then be used as a first electrode 115. A second electrode 117 can be formed on a second base material 116 and positioned over the recess 114, as described above. In embodiments having a non-leachable redox mediator, a sensing layer 32 is formed on the first electrode 115 to form a working electrode, as shown in Figure 13B. In other embodiments having a non-leachable redox mediator, the sensing layer 32 may be formed on the second electrode 117 to form a working electrode. Alternatively, if a diffusible redox mediator is used, then the working electrode need not include the sensing layer disposed thereon. In fact, no sensing layer is required because the redox mediator may be placed in the sample and likewise for a diffusible second electron transfer agent, if one is present. Any diffusible components may be independently disposed on any surface of the sample chamber or placed in the sample. Furthermore, a sorbent material (not shown) may be formed within the recess, for example, on the first electrode 115.

[0140] A binder, such as a polyurethane resin, cellulose derivative, elastomer (e.g., silicones, polymeric dienes, or acrylonitrile-butadiene-styrene (ABS) resins), highly fluorinated polymer, or the like, may also be included in the conductive ink. Curing the binder may increase the conductivity of the conductive layer 110, however, curing is not necessary. The method of curing the binder may depend on the nature of the particular binder that is used. Some binders are cured by heat and/or ultraviolet light.

[0141] These structures allow for the formation of electrochemical sensors in which the volume of the measurement zone depends, at least in part, on the accuracy and reproducibility of the recess 104. Embossing, laser etching, photolithographic etching and other methods can be used to make reproducible recesses 104, even on the scale of 200 μm or less.

Sorbent Material

[0142] The sample chamber may be empty before the sample is placed in the chamber. Alternatively, the sample chamber may include a sorbent material 34 to sorb and hold a fluid sample during the measurement process. Suitable sorbent materials include polyester, nylon, cellulose, and cellulose derivatives such as nitrocellulose. The sorbent material facilitates the uptake of small volume samples by a wicking action which may complement or, preferably, replace any capillary action of the sample chamber. In addition or alternatively, a portion or the entirety of the wall of the sample chamber may be covered by a surfactant, such as, for example, Zonyl FSO.

[0143] In some embodiments, the sorbent material is deposited using a liquid or slurry in which the sorbent material is dissolved or dispersed. The solvent or dispersant in the liquid or slurry may then be driven off by heating or evaporation processes. Suitable sorbent materials include, for example, cellulose or nylon powders dissolved or dispersed in a suitable solvent or dispersant, such as water. The particular solvent or dispersant should also be compatible with the material of the working electrode 22 (e.g., the solvent or dispersant should not dissolve the electrode).

[0144] One of the most important functions of the sorbent material is to reduce the volume of fluid needed to fill the sample chamber and corresponding measurement zone of the sensor. The actual volume of sample within the measurement zone is partially determined by the amount of void space within the sorbent material. Typically, suitable sorbents consist of about 5% to about 50% void space. Preferably, the sorbent material consists of about 10% to about 25% void space.

[0145] The displacement of fluid by the sorbent material is advantageous. By addition of a sorbent, less sample is needed to fill sample chamber 26. This reduces the volume of sample that is required to obtain a measurement and also reduces the time required to electrolyze the sample.

[0146] The sorbent material 34 may include a tab 33 which is made of the same material as the sorbent and which extends from the sensor, or from an opening in the sensor, so that a sample may be brought into contact with tab 33, sorbed by the tab, and conveyed into the sample chamber 26 by the wicking action of the sorbent material 34. This provides a preferred method for directing the sample into the sample chamber 26. For example, the sensor may be brought into contact with a region of an animal (including human) that has been pierced with a lancet to draw blood. The blood is brought in contact with tab 33 and drawn into sample chamber 26 by the wicking action of the sorbent 34. The direct transfer of the sample to the sensor is especially important when the sample is very small, such as when the lancet is used to pierce a portion of the animal that is not heavily supplied with near-surface capillary vessels and furnishes a blood sample volume of 1 μL or less.

[0147] Methods other than the wicking action of a sorbent may be used to transport the sample into the sample chamber or measurement zone. Examples of such methods for transport include the application of pressure on a sample to push it into the sample chamber, the creation of a vacuum by a pump or other vacuum-producing method in the

Abbott Ex. 1002 - 379/1438

sample chamber to pull the sample into the chamber, capillary action due to interfacial tension of the sample with the walls of a thin sample chamber, as well as the wicking action of a sorbent material.

[0148] The sensor can also be used in conjunction with a flowing sample stream. In this configuration, the sample stream is made to flow through a sample chamber. The flow is stopped periodically and the concentration of the analyte is determined by an electrochemical method, such as coulometry. After the measurement, the flow is resumed, thereby removing the sample from the sensor. Alternatively, sample may flow through the chamber at a very slow rate, such that all of the analyte is electrolyzed in transit, yielding a current dependent only upon analyte concentration and flow rate.

[0149] Other filler materials may be used to fill the measurement zone and reduce the sample volume. For example, glass beads can be deposited in the measurement zone to occupy space. Preferably, these filler materials are hydrophilic so that the body fluid can easily flow into the measurement zone. In some cases, such as glass beads with a high surface area, these filler materials may also wick the body fluid into the measurement zone due to their high surface area and hydrophilicity.

[0150] The entire sensor assembly is held firmly together to ensure that the sample remains in contact with the electrodes and that the sample chamber and measurement zone maintain the same volume. This is an important consideration in the coulometric analysis of a sample, where measurement of a defined sample volume is needed. One method of holding the sensor together is depicted in Figures 1 and 2. Two plates 38 are provided at opposite ends of the sensor. These plates are typically constructed of non-conducting materials such as plastics. The plates are designed so that they can be held together with the sensor between the two plates. Suitable holding devices include adhesives, clamps, nuts and bolts, screws, and the like.

Alternative Sensor Designs

[0151] Figures 18A to 18C illustrate one alternative sensor design for formation of thin film sensors. The sensor includes a first substrate 500 upon which a working electrode 502 is formed. The working electrode 502 includes a contact region 503 for connection with external electronics. A spacer 504 (Figure 18B), such as, for example, a layer of adhesive or a double-sided tape defines a channel 506 to produce a sample chamber for the sensor. Two counter (or counter/reference) electrodes 510, 512 are formed on a second substrate 508, as shown in Figure 18C (inverted with respect to Figures 18A and 18B to show the electrode side up). This multiple counter electrode arrangement may provide a fill indicator function, as described below. Each counter electrode 510, 512 has a contact region 511, 513 for connection with external electronics. The second substrate 508 is inverted and placed over the first substrate 500, with the spacer 504 between, so that the working electrode 502 and the two counter electrodes 510, 512 are facing in the region of the channel 506.

[0152] In some instances, the counter electrode 510 nearest an entrance 514 of the channel 506 has a surface area within the sample chamber that is at least two times larger than the other counter electrode 512, and may be at least five or ten times larger. The non-leachable or diffusible redox mediator and/or second electron transfer agent can be provided on either the first or second substrates 500, 508 in a region corresponding to the channel 506, as described above.

[0153] The working electrode and counter electrodes can be formed to cover the entire channel region (except for a small space between the two counter electrodes). In this embodiment, the sample chamber and measurement zone are effectively the same and have the same volume. In other embodiments, the measurement zone has, for example, 80% or 90% of the volume of the sample chamber. It will be understood that similar sensors could be made using one counter electrode or three or more counter electrodes. It will also be understood that multiple working electrodes may also be provided on the sensor.

[0154] One example of a method for making the thin film sensors is described with respect to the sensor arrangement displayed in Figures 18A to 18C and can be used to make a variety of other sensor arrangements, including those described before. A substrate, such as a plastic substrate, is provided. The substrate can be an individual sheet or a continuous roll on a web. This substrate can be used to make a single sensor or to make multiple sensors. The multiple sensors can be formed on a substrate 1000 as working electrodes 1010 and counter electrode(s) 1020. In some embodiments, the substrate can be scored and folded to bring the working electrodes 1010 and counter electrodes 1020 together to form the sensor. In some embodiments, as illustrated in Figure 31A, the individual working electrodes 1010 (and, in a separate section, the counter electrode(s) 1020) can be formed next to each other on the substrate 1000, to reduce waste material, as illustrated in Figure 31A. In other embodiments, the individual working electrodes 1010 (and, in a separate section, the counter electrode(s) 1020) can be spaced apart, as illustrated in Figure 31B. The remainder of the process is described for the manufacture of multiple sensors, but can be readily modified to form individual sensors.

[0155] Carbon or other electrode material (e.g., metal, such as gold or platinum) is formed on the substrate to provide a working electrode for each sensor. The carbon or other electrode material can be deposited by a variety of methods including printing a carbon or metal ink, vapor deposition, and other methods.

[0156] Optionally, a non-conductive material, such as a non-conductive ink, can be formed adjacent the working

Abbott Ex. 1002 - 380/1438

electrode to provide a planar surface along the path of travel of the sample fluid. The non-conductive material is suitable for creating a smooth surface to facilitate filling by capillary action and/or for reducing the likelihood that air bubbles will become entrapped near the working electrode. This non-conductive material can be colored or colorless and may be formed on the substrate by printing or other techniques. The non-conductive material may be deposited prior to or subsequent to the formation of the working electrode.

[0157] The counter electrode or counter electrodes are formed on the substrate. The counter electrode(s) are formed by depositing carbon or other electrode material onto the substrate. In one embodiment, the material of the counter electrode(s) is a Ag/AgCl ink. The material of the counter electrode(s) may be deposited by a variety of methods including printing or vapor deposition. In some embodiments, the counter electrodes are formed using different materials and/or one electrode is a counter or counter/reference electrode and the other electrode is a reference or counter/reference electrode. In one embodiment, the working electrodes are formed on a first half of a polymer sheet or web and the counter electrodes are formed on a second half of the polymer sheet or web so that the sheet or web can be folded to superimpose the working and counter electrodes in a facing arrangement.

[0158] A second non-conductive material may be deposited adjacent and/or between the counter electrode(s) to provide a planar surface along the path of travel of the sample fluid. This may be particularly desirable in the region between the counter electrodes that will be part of the sample chamber to planarize the surface of the sample chamber. The non-conductive material is suitable for creating a smooth surface to faciliate filling by capillary action and/or for reducing the likelihood that air bubbles will become entrapped between or near the counter electrode(s). This non-conductive material can be colored or colorless and may be formed on the by printing or other techniques. The non-conductive material may be deposited prior to or subsequent to the formation of the counter electrode(s).

[0159] An adhesive spacer is formed over at least one of the substrate/working electrode and substrate/counter electrode(s). The adhesive spacer may be a single layer of adhesive or a double-sided adhesive tape (e.g., a polymer carrier film with adhesive disposed on opposing surfaces). To form the channel, the spacer, optionally provided with one or more release liners, may be cut (e.g., die-cut) to remove the portion of the adhesive corresponding to the channel prior to disposing the spacer on the substrate. Alternatively, the adhesive may be printed or otherwise disposed on the substrate according to a pattern which defines the channel region. The thickness of the spacer typically determines the spacing between the working and counter electrodes. When the uniformity of this spacing among sensors is necessary (e.g., for coulometric measurements), uniformity in the thickness of the spacer is important. Preferably, the thickness does not vary more than $\pm$ 5% over the individual sensor and/or among individual sensors in a batch.

[0160] The non-leachable or diffusible redox mediator and/or second electron transfer agent are disposed onto the substrate in at least the sample chamber region. If either or both of these components is non-leachable, that component or components must be disposed on the working electrode. If either or both of these components is diffusible, that component or components can be disposed on any surface of the substrate in the channel region. The redox mediator and/or second electrode transfer agent can be disposed independently or together on the substrate prior to or after disposition of the spacer. The redox mediator and/or second electrode transfer agent may be disposed by a variety of methods including, for example, screen printing, ink jet printing, spraying, painting, striping along a row or column of aligned and/or adjacent electrodes, and the like. Other components may be deposited separately or with the redox mediator and/or second electrode transfer agent including, for example, surfactants, polymers, polymer films, preservatives, binders, buffers, and cross-linkers.

[0161] After disposing the spacer, redox mediator, and second electron transfer agent, the substrate can be folded to form the sensor. The faces of the substrate are joined by the adhesive of the spacer. After bringing the faces together, the sensor can be cut out using a variety of methods including, for example, die cutting, slitting, or otherwise cutting away the excess substrate material and separating the individual sensors. In some embodiments, a combination of methods may be used. For example, some features may be die cut, while the remainder of the sensor is cut by slitting. As another alternative, the sensor components (e.g., the components illustrated in Figures 18A and 18C) may first be cut out of the substrates and then brought together to form the sensor by adhesively joining the two components using the spacer adhesive.

[0162] The embodiment of a sensor illustrated in Figures 18A to 18C is an example of a tip-fill sensor. An alternative sensor construction is illustrated in Figures 19A to 19C. This is a side-fill sensor. Figure 19A illustrates a first substrate 520 with a working electrode 522. Figure 19B illustrates a spacer 524 defining a channel 526. Figure 19C (inverted with respect to Figures 19A and 19B to illustrate the electrodes) illustrates a second substrate 528 with three counter (or counter/reference) electrodes 530, 532, 534.

[0163] This sensor can be manufactured as described above. The symmetric disposition of the counter electrodes allow the sensor to be filled from either the left or right side for convenience of left-handed and right-handed people. It will be understood, however, that similar sensor arrangements can be formed using one, two, or four or more counter electrode(s) and/or two or more working electrodes. The scalloped regions 536, 538 may be formed, for example, by die cutting and may, at least in some instances, be precisely controlled to provide a reproducible channel length. As an alternative arrangement, the sides of the sensor may be straight to allow the sensor to be cut out from the remainder of

Abbott Ex. 1002 - 381/1438

the substrate and/or from other sensors by slitting the substrate in parallel directions using, for example, a gang arbor blade system. As illustrated in Figures 19A, 19B, and 19C, the edges of the sensor can define edges of the sample chamber and/or measurement zone. By accurately controlling the distance between cuts, variability in sample chamber volume can often be reduced. In some instances, these cuts are preferably parallel to each other, as parallel cuts may be the easiest to make reproducibly.

[0164] Figures 20A, 20B, and 20C illustrate another example of a side-filling sensor arrangement. Figure 20A illustrates a first substrate 540 with a working electrode 542. Figure 20B illustrates a spacer 544 defining a channel 546. Figure 20C (inverted with respect to Figures 20A and 20B) illustrates a second substrate 548 with three counter (or counter/reference) electrodes 550, 552, 554.

[0165] Figures 21A, 21B, and 21C illustrate another example of a tip-filling sensor arrangement. Figure 21A illustrates a first substrate 560 with a working electrode 562. Figure 21B illustrates a spacer 564 defining a channel 566. Figure 21C (inverted with respect to Figures 21A and 21B) illustrates a second thin film substrate 568 with two counter (or counter/reference) electrodes 570, 572. A vent hole 574 (indicated as a shaded region in Figure 21C) is provided through the second substrate. In the illustrated embodiment, this vent hole 574 is made through only the substrate 568 that carries the counter electrode(s) and, optionally, the spacer 564. In this embodiment, the vent hole may be formed by, for example, die cutting a portion of the substrate. This die cut may remove a portion of at least one counter electrode, but a sufficient amount of the counter electrode should remain for contact with the sample in the channel and for electrical connection to a contact at the other end of the sensor. In another embodiment, the vent hole 574 may be made through all of the layers or through the first substrate and not the second substrate.

[0166] Another embodiment is illustrated in Figures 22A, 22B, and 22C, with a different shape. This sensor includes a first substrate 579 with at least one working electrode 580, as illustrated in Figure 22A. The sensor also includes a spacer 581 with a channel 582 formed in the spacer 581, as shown in Figure 22B. The sensor further includes a second substrate 583 with two counter electrodes 584, 585, as shown in Figure 22C (inverted with respect to Figures 22A and 22B). A venting aperture 586 is cut typically through all of the layers and extends from a side of the sensor. In some embodiments, the venting aperture and the front portion 587 of the sensor are simultaneously cut with a reproducible distance between the venting aperture and the front portion 587 of the sensor to provide a reproducible length for the channel 582 and the working electrode 580. Figures 22A, 22B, and 22C also illustrate another feature that can be used with any sensor arrangement. An indentation 588 may be formed at the filling opening of the channel 582 to facilitate the drawing of fluid into the sensor. In this configuration, the fluid is not provided with a flat face, but rather an indented face that may aid in wicking or capillary filling of the channel (i.e., sample chamber). This configuration may also reduce the likelihood that the user of the sensor will block the channel during collection of the sample. A flat faced sensor might be blocked by pressing the tip of the sensor edgewise against the skin.

[0167] Figures 23A, 23B, and 23C illustrate another example of a side-filling sensor arrangement. Figure 23A illustrates a first substrate 640 with a working electrode 642. Figure 23B illustrates a spacer 644 defining a channel 646. Figure 23C (inverted with respect to Figures 23A and 23B) illustrates a second substrate 648 with three counter (or counter/reference) electrodes 650, 652, 654. This sensor can be formed by making straight cuts of the substrates. The sensors can be made adjacent to one another, as illustrated in Figure 31A, which may produce less waste material. The length of the channel 646 is typically defined by the two parallel cuts along the sides 656, 658 of the sensors. Another optional processing advantage, particularly if the sensor are formed adjacent to each other, is that the redox mediator and/or second electron transfer agent can be disposed in the channel by striping a continuous stream of these components along a row or column of adjacent sensors. This may result in better efficiency and less waste of the redox mediator and/or second electron transfer agent, as compared to other techniques, such as individually placing these components within the individual channels.

[0168] Figures 24A, 24B, and 24C illustrate another sensor configuration. This sensor includes a first substrate 600 with at least one working electrode 602, as illustrated in Figure 24A. The sensor also includes a spacer 604 with a channel 606 formed in the spacer 604, as shown in Figure 24B. The sensor further includes a second substrate 608 with two counter electrodes 610, 612, as shown in Figure 24C (inverted with respect to Figures 24A and 24B). The sensor may also include, for example, an indicator, such as a slot 614 or an extension 616 from the body of the sensor that indicates to the user which side should be placed adjacent to the sample. This may be particularly important where the sensor reading is only correct when sample enters from a particular side.

[0169] Figure 24B also illustrates another optional feature that may be used in any of the sensor configurations. In this illustration, the sample chamber 606 is not formed using straight lines, but there is an expanded region 618 within the sample chamber. This permits larger sample chambers without forming larger openings. This expanded region can be formed as any shape including circular, square, rectangular, and other regular and irregular shapes.

[0170] Figure 25 is an example of an assembled sensor illustrating another alternative sensor arrangement for a side-fill sensor 620. This sensor includes extensions 622 from the sensor body 624 to indicate to a user where the openings for the sample chamber 626 are provided.

[0171] One optional feature is illustrated in Figure 32 which is an edge-on view of the sensor from the inside of the

Abbott Ex. 1002 - 382/1438

meter. Figure 32 illustrates a first substrate 1120 and a second substrate 1130 that extend into the meter from the remainder of the sensor 1100 (i.e., portion 1140 is recessed with respect to substrates 1120 and 1130 in Figure 32). Examples of this configuration are illustrated in Figures 18A-18C and 24A-24C. Typically, the sensor 1100 is coupled to a meter 1110 that includes contact pads (not shown) that contact the contact regions (e.g., regions 503, 511, and 513 in Figures 18A and 18C) of the electrodes of the sensor 1100. The end of the sensor 1100 which contains the contact regions can be slid into the meter 1110. It is typically important that the contact pads of the meter 1110 make contact with the correct contact regions of the sensor so that the working electrode and counter electrode(s) are correctly coupled to the meter. In some instances, the sensor is configured so that the contact region for the working electrode on the first substrate 1120 has a different width, w1, than width, w2, for the contact region of the second substrate 1130 carrying the counter electrode(s). Examples of electrode configurations with this structure are provided in Figures 18A-18C and 24A-24C. To ensure proper insertion of the sensor 1100 into the meter 1110, the meter 1110 may include a raised area 1140 that prevents or hinders the insertion of the sensor in an improper direction. For example, the width, w2, of the contact region of the second substrate 1130 may be wider than the width, w1, of the contact region of the first substrate 1120, as illustrated in Figure 32. In this instance, the raised area 1140 is positioned to allow sensor 1100 to be slid into the meter so that the first substrate 1120 is next to the surface 1150 from which the raised area 1140 protrudes, but would prevent or hinder having the second substrate 1130 next to the surface 1150 from which the raised area 1140 protrudes. Objects other than a raised area can also be used to guide the user in correct introduction of the sensor into the meter.

Integrated Sample Acquisition and Analyte Measurement Device

[0172] Many approaches are known in the art for acquiring and/or transporting a small sample from the body to a sensor. These include, for example, U.S. Patent Numbers 5,746,217; 5,820,570; 5857983; and 5879311. Any of these sample acquisition and/or transporting methods may be employed with the sensor of the current invention.

[0173] In a preferred embodiment of the invention, an analyte measurement device 52 constructed according to the principles of the present invention includes a sensor 20, as described hereinabove, combined with a sample acquisition apparatus 50 to provide an integrated sampling and measurement device. The sample acquisition apparatus 50 illustrated in Figure 6, includes, for example, a skin piercing member 54, such as a lancet, attached to a resilient deflectable strip 56 (or other similar device, such as a spring) which may be pushed to inject the lancet into a patient's skin to cause blood flow.

[0174] The resilient strip 56 is then released and the skin piercing member 54 retracts. Blood flowing from the area of skin pierced by member 54 can then be transported, for example, by the wicking action of sorbent material 34, into sensor 20 for analysis of the analyte. The analyte measurement device 52 may then be placed in a reader, not shown, which connects a coulometer or other electrochemical analysis equipment to the electrode tabs 23, 25 to determine the concentration of the analyte by electroanalytical means. Preferably, the analyte measurement device is enclosed within the reader when connected to the coulometer or other electrochemical analysis equipment.

[0175] In a preferred embodiment, the integrated sample acquisition and analyte measurement device comprises a lancing instrument that holds a lancet and measurement strip. The lancing instrument preferably requires active cocking. By requiring the user to cock the device prior to use, the risk of inadvertently triggering the lancet is minimized.

[0176] Preferably, the lancing instrument is automatically triggered when the lancing instrument is pressed firmly against the skin with an adequate amount of pressure. As is already known in the art, a larger sample of body fluid such as blood or interstitial fluid is expressed when pressure is applied around a site where a hole has been created the skin. For example, see the above-mentioned U.S. patents to Integ and Amira as well as the tip design of the lancing instruments sold by Becton Dickenson. All of these lancing devices have a protruding ring that surrounds the lancing site to create pressure that forces sample out of the wound. However, all of these devices require the user to apply adequate pressure to the wound site to express the sample, and all of the lancing instruments are triggered by a button push by the user. Design of an appropriate pressure trigger is well-known to one skilled in the art.

[0177] Preferably, the lancing instrument will also permit the user to adjust the depth of penetration of the lancet into the skin. Such devices are already commercially available from companies such as Boehringer Mannheim and Palco. This feature allows users to adjust the lancing device for differences in skin thickness, skin durability, and pain sensitivity across different sites on the body and across different users.

[0178] In a more preferred embodiment, the lancing instrument and the test reader are integrated into a single device. To operate the device the user need only insert a disposable cartridge containing a measurement strip and lancing device into the integrated device, cock the lancing instrument, press it against the skin to activate it, and read the result of the measurement. Such an integrated lancing instrument and test reader simplifies the testing procedure for the user and minimizes the handling of body fluids.

[0179] Figure 26 illustrates another example of an integrated sample acquisition and sensor device 700. The integrated sample acquisition and sensor device 700 includes a housing 702, a skin piercing member (e.g., a lancet) 704, a piercing/

Abbott Ex. 1002 - 383/1438

collecting aperture 706, an optionally removable sensor 708, a sensor guide 710, and a retraction mechanism 714 for the skin piercing member. This device 700 can be designed for reuse (e.g., by making the skin piercing member 704 and sensor 708 removable) or for single use.

[0180] The housing 702 may be formed of a variety of materials including metal and plastic. The housing 702 may include a hinge 716 or other configuration (e.g., adhesive or interlocking parts) for holding portions of the housing together.

[0181] The piercing/collecting aperture 706 is provided in the housing 702 to allow the skin piercing member 704 to extend through the aperture 706 and pierce the skin of a user, thereby causing blood (or other body fluid) flow. The sensor 708 also extends to the edge or out of the aperture 706 to collect the blood (or other body fluid) through an opening (not shown) in the tip of the sensor. This may allow the user to pierce the skin and collect the fluid sample without moving the device 700. Alternatively, separate apertures may be provided for the skin piercing member 704 and sensor 708. The sensor guide may be formed in the housing 702 or added to the housing to guide the sensor 708 into place if the sensor is inserted into and through the housing and/or to support the sensor within the housing and during sample collection.

[0182] The skin piercing member 704 may include an actuator (not shown) that includes a mechanism that allows for cocking and releasing the skin piercing member 704 or the skin piercing member may be actuated externally. For example, a sensor reader (not shown) or other device may be coupled to the sample acquisition and sensor device, the sensor reader or other device including a mechanism that cocks and/or releases the skin piercing member 704.

[0183] The retraction mechanism 714 of the device 700 may be, for example, a spring or resilient metal strip that retracts the skin piercing member 704 back into the housing after piercing the skin of the user. This may allow for unobstructed collection of the sample and/or prevent further piercing of the skin of the user or others to reduce or prevent contamination or infection caused by transfer of body fluids or other harmful agents. Alternatively, retraction of the skin piercing member may be accomplished using an external device or apparatus.

[0184] One example of operation includes cocking the skin piercing member 704 and then releasing the skin piercing member 704 so that it extends out of the housing 702 through the piercing/collecting aperture 706 and pierces the skin of the user. The skin piercing element 704 optionally pushes the sensor out of the way while extending out of the housing. The skin piercing element 704 is retracted back within the housing 702 using the retraction mechanism 714. Upon retraction of the skin piercing element, the sensor collects a sample fluid from the pierced skin through an opening in the sensor 708.

[0185] If a sensor reader is used, the sensor reader may also be configured to couple with a contact end of the sensor. The sensor reader may include a potentiostat or other component to provide a potential and/or current for the electrodes of the sensor. The sensor reader may also include a processor (e.g., a microprocessor or hardware) for determining analyte concentration from the sensor signals. The sensor reader may include a display or a port for coupling a display to the sensor. The display may display the sensor signals and/or results determined from the sensor signals including, for example, analyte concentration, rate of change of analyte concentration, and/or the exceeding of a threshold analyte concentration (indicating, for example, hypo- or hyperglycemia). This sensor reader may be used in conjunction with the integrated sample acquisition and sensor device or the sensor reader may be used with the sensor alone, the contacts of the sensor making connection with contacts in the sensor reader.

Operation of the Sensor

[0186] An electrochemical sensor of the invention may be operated with or without applying a potential. In one embodiment, the electrochemical reaction occurs spontaneously and a potential need not be applied between the working and counter electrodes.

[0187] In another embodiment, a potential is applied between the working and counter electrodes. Yet the potential does not need to remain constant. The magnitude of the required potential is dependent on the redox mediator. The potential at which the electrode poises itself, or where it is poised by applying an external bias, and where the analyte is electrolyzed is typically such that the electrochemical reaction is driven to or near completion, but it is, preferably, not oxidizing enough to result in significant electrochemical reaction of interferents, such as urate, ascorbate, and acetaminophen, that may affect the signal measured. For non-leachable redox mediators, the potential is typically between about -350 mV and about +400 mV versus the standard calomel electrode (SCE). Preferably, the potential of the redox mediator is more negative than +100 mV, more preferably the potential is more negative than 0 mV, and most preferably the potential is about -150 mV versus SCE.

[0188] When an external potential is applied, it may be applied either before or after the sample has been placed in the sample chamber. If the measurement zone comprises only a portion of the sample chamber then the potential is preferably applied after the sample has come to rest in the sample chamber to prevent electrolysis of sample passing through the measurement zone as the sample chamber is filling. Alternatively, in the case where the measurement zone comprises most or all of the sample chamber, the potential, optionally, may be applied before or during the filling of the sample chamber without affecting the accuracy of the assay. When the potential is applied and the sample is in the

Abbott Ex. 1002 - 384/1438

measurement zone, an electrical current will flow between the working electrode and the counter electrode. The current is a result, at least in part, of the electrolysis of the analyte in the sample. This electrochemical reaction occurs via the redox mediator and the optional second electron transfer agent. For many biomolecules, B, the process is described by the following reaction equations:

$$nA(ox) + B \xrightarrow{\text{enzyme}} nA(red) + C \qquad (1)$$

$$nA(red) \rightarrow nA(ox) + ne^- \qquad (2)$$

Biochemical B is oxidized to C by redox mediator species A in the presence of an appropriate enzyme. Then the redox mediator A is oxidized at the electrode. Electrons are collected by the electrode and the resulting current is measured. The measured current may also include a background current resulting in a measured background charge, due, at least in part, to the shuttling of a diffusible redox mediator between the working electrode and the counter electrode. This background current can be minimized or accounted for, as described above.

[0189] As an example, one sensor of the present invention is based on the reaction of a glucose molecule with two $[Os(dmo\text{-}phen)_2(NMI)Cl]^{2+}$ cations, where dmo-phen is 4,8-dimethoxy phenanthroline and NMI is N-methyl-imidazole, in the presence of glucose oxidase to produce two $[Os(dmo\text{-}phen)_2(NMI)Cl]^{+}$ cations, two protons, and an oxidation product of glucose, for example, gluconolactone or another ketone. The amount of glucose present is assayed by electrooxidizing the $[Os(dmo\text{-}phen)_2(NMI)Cl]^{+}$ cations to $[Os(dmo\text{-}phen)_2(NMI)Cl]^{2+}$ cations and measuring the total charge passed.

[0190] Those skilled in the art will recognize that there are many different reactions that will provide the same result; namely the electrolysis of an analyte through a reaction pathway incorporating a redox mediator. Equations (1) and (2) are a non-limiting example of such a reaction.

Coulometry

[0191] In a preferred embodiment of the invention, coulometry is used to determine the concentration of the analyte. This measurement technique utilizes current measurements obtained at intervals over the course of the assay, to determine analyte concentration. These current measurements are integrated over time to obtain the amount of charge, Q, passed to or from the electrode. Q is then used to calculate the concentration of the analyte (C_A) by the following equation (when the redox mediator is non-leachable):

$$C_A = Q/nFV \qquad (3a)$$

where n is the number of electron equivalents required to electrolyze the analyte, F is Faraday's constant (approximately 96,500 coulombs per equivalent), and V is the volume of sample in the measurement zone. When using a diffusible mediator, the concentration of the analyte can be obtained from the following equation:

$$C_A = (Q_{tot} - Q_{back})/nFV \qquad (3b)$$

where Q_{tot} is the total charge transferred during the measurement and Q_{back} is the amount of charge transferred that was not due to the analyte, e.g., charge transferred by the shuttling of the diffusible mediator between the working electrode and the counter electrode. In at least some instances, the sensor is constructed so that the background charge is at most 5 times the size of the charge generated by electrolysis of an amount of analyte. Preferably, the background signal is at most 200%, 100%, 50%, 25%, 10%, or 5% of the charge generated by electrolysis of the analyte.

[0192] One example of a method for determining the ratio of background signal to signal generated by electrolysis of the analyte is described as follows for the facing electrode pairs. If the shuttling of the redox mediator is not disabled by the applied potential, the charge that results from the shuttling of the redox mediator may be represented by the following formula:

Abbott Ex. 1002 - 385/1438

$$Q_{back} = (A\ F\ D_M\ C_M / d)\ (t\ n_M)$$

where A is the area of the working electrode; F is Faraday's constant (96,500 coulombs/equivalent); D_M is the effective diffusion coefficient of the redox mediator; C_M is the concentration of the redox mediator in the measurement zone; d is the distance separating facing electrodes; t is the amount of time for the measurement; and n_M is the number of electrons gained or lost by the redox mediator.

[0193] Additionally, the charge of the analyte, for example, glucose, when the analyte is electrooxidized to about 90% completion in the measurement period may be represented by the following formula:

$$Q_G = A\ d(0.90)\ C_G\ n_G\ F$$

where A is the area of the working electrode; d is the distance separating facing electrodes; C_G is the concentration of glucose; n is the number of electrons needed to electrolyze the analyte (e.g., 2 electrons per glucose molecule); and F is Faraday's constant. When C_G is 5 mM (or 5 x 10^{-6} moles/cm^3), t is 60 seconds, n_G is 2, and n_M is 1, the ratio of charge from the redox mediator to the charge from electrooxidation of the analyte may be represented by the following formula:

$$Q_{Back}/Q_G = (D_M C_M/d^2)(t\ n_M/(0.9\ n_G\ C_G)) = (D_M\ C_M\ /\ d^2)\ x\ (6.7\ x\ 10^6)$$

For example, if the ratio of Q_{Back}/Q_G is 5, then $(D_M\ C_M)/\ d^2$ is 7.5 x 10^{-7} moles/(cm^3 sec). Also for example, if the ratio of Q_{Back}/Q_G is 1, then $(D_M\ C_M)/\ d^2$ is 1:5 x 10^{-7} moles/(cm^3 sec). Still another example, if the ratio is 0.1, then $(D_M\ C_M)\ /\ d^2$ is 1.5 x 10^{-8} moles/(cm^3 sec). Thus, depending on the ratio desired, a sensor may be configured to have the desired ratio by choosing D_M, C_M, and d accordingly. For example, the concentration of the redox mediator may be reduced (i.e., C_M may be reduced). Alternatively, or additionally, the diffusion of the redox mediator may be reduced by, for example, having a barrier to the flow of the diffusible mediator to the counter electrode (i.e., reduce the effective diffusion coefficient of the redox mediator—D_M). Other sensor configurations are also suitable for controlling the ratio of background signal to signal generated by the analyte and will be described below.

[0194] The background charge, Q_{back}, can be accounted for in a variety of ways. Q_{back} can be made small, for example, by using only limited amounts of diffusible redox mediator; by providing a membrane over the counter electrode that limits diffusion of the redox mediator to the counter electrode; or by having a relatively small potential difference between the working electrode and the counter electrode. Other examples of sensor configurations and methods suitable for reducing Q_{back} include those already described such as sensors having a redox mediator reaction rate at the working electrode that is significantly faster than that at the counter electrode; immobilizing the redox mediator on the working electrode; having the redox mediator become immobilized on the counter or counter/reference electrode upon its reaction at the counter or counter/reference electrode; or slowing the diffusion of the redox mediator.

[0195] Alternatively, the sensor may be calibrated individually or by batch to determine a calibration curve or a value for Q_{back}. Another option is to include a second electrode pair that is missing an item necessary for electrolysis of the analyte, such as, for example, the second electron transfer agent, so that the entire signal from this second electrode pair corresponds to Q_{back}.

[0196] For coulometric measurements, at least 20% of the analyte is electrolyzed. Preferably at least 50%, more preferably at least 80%, and even more preferably at least 90% of the analyte is electrolyzed. In one embodiment of the invention, the analyte is completely or nearly completely electrolyzed. The charge can then be calculated from current measurements made during the electrochemical reaction, and the concentration of the analyte is determined using equation (3a) or (3b). The completion of the electrochemical reaction is typically signaled when the current reaches a steady-state value. This indicates that all or nearly all of the analyte has been electrolyzed. For this type of measurement, at least 90% of the analyte is typically electrolyzed, preferably, at least 95% of the analyte is electrolyzed and, more preferably, at least 99% of the analyte is electrolyzed.

[0197] For coulometry, it is typically desirable that the analyte be electrolyzed quickly. The speed of the electrochemical reaction depends on several factors, including the potential that is applied between the electrodes and the kinetics of reactions (1) and (2). (Other significant factors include the size of the measurement zone and the presence of sorbent in the measurement zone.) In general, the larger the potential, the larger the current through the cell (up to a transport limited maximum) and therefore, the faster the reaction will typically occur. However, if the potential is too large, other electrochemical reactions may introduce significant error in the measurement. Typically, the potential between the

Abbott Ex. 1002 - 386/1438

electrodes as well as the specific redox mediator and optional second electron transfer agent are chosen so that the analyte will be almost completely electrolyzed in less than 5 minutes, based on the expected concentration of the analyte in the sample. Preferably, the analyte will be almost completely electrolyzed within about 2 minutes and, more preferably, within about 1 minute.

[0198] In another embodiment of the invention, the analyte is only partially electrolyzed. The current is measured during the partial reaction and then extrapolated using mathematical techniques known to those skilled in the art to determine the current curve for the complete or nearly complete electrolysis of the analyte. Integration of this curve yields the amount of charge that would be passed if the analyte were completely or nearly completely electrolyzed and, using equation (3a) or (3b), the concentration of the analyte is calculated.

[0199] Although coulometry has the disadvantage of requiring the volume of the measured sample be known, coulometry is a preferred technique for the analysis of the small sample because it has the advantages of, for example, no temperature dependence for the measurement, no enzyme activity dependence for the measurement, no redox-mediator activity dependence for the measurement, and no error in the measurement from depletion of analyte in the sample. As already described above, coulometry is a method for determining the amount of charge passed or projected to pass during complete or nearly complete electrolysis of the analyte. One coulometric technique involves electrolyzing the analyte on a working electrode and measuring the resulting current between the working electrode and a counter electrode at two or more times during the electrolysis. The electrolysis is complete when the current reaches a steady state. The charge used to electrolyze the sample is then calculated by integrating the measured currents over time and accounting for any background signal. Because the charge is directly related to the amount of analyte in the sample there is no temperature dependence of the measurement. In addition, the activity of the enzyme does not affect the value of the measurement, but only the time required to obtain the measurement (i.e., less active enzyme requires a longer time to achieve complete electrolysis of the sample) so that decay of the enzyme over time will not render the analyte concentration determination inaccurate. And finally, the depletion of the analyte in the sample by electrolysis is not a source of error, but rather the objective of the technique. (However, the analyte need not be completely electrolyzed if the electrolysis curve is extrapolated from the partial electrolysis curve based on well-known electrochemical principles.)

Non-Coulometric Assays

[0200] Although coulometric assays are useful, those skilled in the art will recognize that a sensor of the invention may also utilize potentiometric, amperometric, voltammetric, and other electrochemical techniques to determine the concentration of an analyte in a sample. The measurements obtained by these non-coulometric methods may not be temperature independent as are coulometric measurements.

[0201] In addition, the measurements obtained by these non-coulometric electrochemical techniques may be sensitive to the amount of active enzyme provided in the sensor. If the enzyme deactivates or decays over time, the resulting measurements may be affected. This may limit the shelf life of such sensors unless the enzyme is very stable.

[0202] Finally, the measurements obtained by non-coulometric electrochemical techniques, such as steady-state amperometry, may be negatively affected if a substantial portion of the analyte and/or redox mediator is electrolyzed during the measurement period. An accurate steady-state measurement may not be obtainable unless there is sufficient analyte and/or redox mediator so that only a relatively small portion of the analyte and/or redox mediator is electrolyzed during the measurement process. This may be challenging in a sample size of no more than 1 μl.

[0203] It may be desirable in some instances to utilize non-coulometric assays, such as amperometric or potentiometric measurement techniques. For example, coulometry requires that the volume of the measured sample be known. And, the volume of the sample in the measurement zone of a small volume sensor (i.e., no more than one microliter) may be difficult to accurately reproduce if the manufacturing tolerances of one or more dimensions of the measurement zone have significant variances.

[0204] As described for coulometric measurements, the background signal resulting from the shuttling of the redox mediator between the electrodes can be a source of measurement error in amperometric or potentiometric assays of samples of no more than 1 μL in thin layer electrochemical cells. In general, it is desirable that the mediator does not shuttle between a pair of electrodes more than ten times in the period of the measurement, preferably not more than once, and more preferably not more than 0.1 times, on average. To decrease error arising from background signal, methods and sensor configurations similar to, and in some cases identical to, those used for coulometric measurements may be used. Examples include all of the methods and structures described above, such as performing the electrochemical assay at relatively low applied potential, electrooxidizing the analyte at negative applied potentials or electroreducing the analyte at positive applied potentials, using a counter electrode at which the redox mediator reacts relatively slowly (particularly as compared to the reaction of the redox mediator at the working electrode), and/or using a redox mediator that undergoes an irreversible reaction at the counter electrode. Other examples are discussed below.

[0205] As described for coulometric measurements, it is preferred that the sensor be designed and operated so that the background signal is at most five times the size of the signal generated by electrolysis of the analyte. Preferably,

Abbott Ex. 1002 - 387/1438

the background signal is at most 200%, 100%, 50%, 25%, 10%, or 5% of the signal generated by electrolysis of an amount of analyte. The amount of analyte against which the background signal is compared is described above in the section entitled "Background Signal." In the case of amperometry, the signal generated by electrolysis of an amount of analyte is the current at the time or times at which the measurement is taken. In the case of potentiometry, the signal generated by electrolysis of an amount of analyte is the potential at the time or times at which the measurement is taken.

[0206] Under a given set of operating conditions, for example, temperature, cell geometry, and electrode size, the magnitude of the background current, I_{back}, is given by the following expression:

$$i_{back} = KC_M D_M / d$$

where: K is a proportionality constant; C_M is the concentration of the mediator in the measurement zone; D_m is the effective diffusion coefficient of the mediator in the measurement zone under normal operating conditions; and d is the distance between the electrodes.

[0207] It is desirable to reduce background current for non-coulometric assays. The sensor configurations and methods described above are generally useful and include, for example, using low concentrations of the redox mediator and/or the second electron transfer agent (e.g., enzyme) relative to the concentration of the analyte and/or using a large redox mediator having a relatively low effective diffusion constant. Other useful methods described above include methods for reducing the diffusion of the redox mediator by, for example, having a barrier (e.g., a charged or polar barrier) to the flow of the diffusible mediator or using a redox mediator having a relatively low effective diffusion constant.

[0208] In some instances, the effective diffusion coefficient is no more than about 1×10^{-6} cm^2/sec, no more than about 1×10^{-7} cm^2/sec, or no more than about 1×10^{-8} cm^2/sec. Moreover, in some cases, the product of $C_M D_M$ (the concentration of redox mediator times the effective diffusion coefficient) is no more than about 1×10^{-12} moles/cm·sec, no more than about 1×10^{-13} moles/cm·sec, or no more than about 1×10^{-14} moles/cm·sec.

[0209] The following provides a specific example for the case of an amperometric measurement of glucose carried out for 60 seconds during which time 10% of the glucose is electrolyzed in a 1 microliter cell with facing electrodes separated by a distance of d = 0.01 cm. If the measurement was carried out under the following conditions: a glucose concentration of, C_G = 5 mM (or 5×10^{-6} moles/cm^3), an area of A = 0.1 cm^2, a number of electrons from the redox mediator of n_M = 1, and a number of electrons from glucose n_G = 2, then the background current generated by the redox mediator and by the glucose is determined as follows.

$$i_{back} = A\,F\,n_M\,D_M\,C_M/d$$

$$= (0.1)\,(96{,}500)\,(1)\,D_M\,C_M/(0.01)$$

$$= 9.65 \times 10^5\,C_M\,D_M$$

$$i_G = n_G\,A\,d(0.1)\,F\,C_G/t$$

$$= (2)\,(0.01)\,(0.1)\,(96{,}500)\,(5 \times 10^{-6})/60 = 1.61\ \mu amps$$

[0210] Thus if $i_{back}/i_G = 5$, the value of $C_M D_M$ equal 8.34×10^{-12} moles/cm^2 sec. As another example, if $i_{back}/i_G = 0.5$, the value of $C_M D_M$ equal 8.34×10^{-13} moles/cm^2 sec. Additionally if $i_{back}/i_G = 0.05$, the value of $C_M D_M$ equal 8.34×10^{-14} moles/cm^2 sec.

[0211] In some amperometric or potentiometric embodiments, the redox mediator circulation is decreased by separating the working electrode from the counter or counter/reference electrode such that the distance through which the redox mediator would diffuse during the measurement period is no greater than, for example, the distance between the electrodes. A redox mediator can diffuse a distance equal to $(D_m t)^{1/2}$, where D_m is the effective diffusion coefficient for the medium between the electrodes and t is time. For a measurement time period of 30 seconds and a redox mediator with effective diffusion coefficient between 10^{-5} and 10^{-6} cm^2/second, the electrodes should be separated by at least 100μm, preferably at least 200μm, and even more preferably at least 400μm.

[0212] One method of separating the working and counter electrodes is to use a thicker spacer between the electrodes. One alternative method is illustrated in Figure 27. In this embodiment, the working electrode 740 is disposed on a first

Abbott Ex. 1002 - 388/1438

substrate 742 and the counter electrode 744 is disposed on a second substrate 746 (alternatively, the electrodes may be disposed on the same substrate). The working electrode 742 and the counter electrode 744 are offset so that the effective distance, d, between the two electrodes is greater than the thickness, w, of the spacer layer 748. In one embodiment, the distance between the electrodes, d, is selected to be in the range of 25 to 1000 μm, 50 to 500 μm, or 100 to 250 μm.

[0213] Additionally or alternatively, in the case of steady-state amperometry and potentiometry, background signal may be controlled by limiting the rate of electrolysis such that the rate is slow enough to prevent the analyte concentration from decreasing by more than about 20%, 10%, or 5% or less, during a measurement period, e.g., 30 second, 1 minute, 5 minutes, or 10 minutes. In some instances, to control the rate of electrolysis the concentration or activity of the second electron transfer agent may be reduced and/or the working electrode area may be reduced.

[0214] For example, the second electron transfer agent can be an enzyme and the enzyme activity can be a limiting factor for the electrolysis rate. If, for example, the analyte concentration is 5mM glucose (i.e., 5 x 10^{-9} moles of glucose in 1 μl) and no more than 10% of the glucose (5 x 10^{-10} moles) is to be electrooxidized during a 30-second measurement period, the current should not exceed 3.3 x 10^{-6} amperes for 1μL. One unit of an enzyme is that amount of the enzyme which catalyzes electrolysis of 1 μmole of its substrate in 60 seconds at pH of 7.4 at 37° C in HEPES buffer. Accordingly, for glucose, a current of up to 3.3 x 10^{-3} amperes in 1 cm^3 (i.e., 1 mL) can be generated. Therefore, the maximum amount of enzyme used in a sensor that limits the amount of electrolysis by controlling the amount of enzyme should be 1 unit/cm^3 or less.

[0215] The rate of electrolysis may also be limited by using a relatively small working electrode area. When the working electrode area is sufficiently small (e.g., no more than about 0.01 cm^2, no more than about 0.0025 cm^2, or no more than about 0.001 cm^2), then radial diffusion of analyte to the electrode may result in a steady-state current, at a constant applied potential, that is representative of the analyte concentration. For circular electrodes, the appropriate surface area may be achieved using an electrode with a radius of no more than 60μm, no more than 30μ m, or no more than 20μm. Radial diffusion of the analyte includes transport of analyte from all directions and not just from the direction normal to the electrode surface and can, therefore, reduce or prevent depletion of analyte near the electrode surface. A small electrode on a planar surface permits radial diffusion. In a sensor having a larger surface area electrodes, the transport of analyte to the electrode may be modeled as semi-infinite linear diffusion instead of radial diffusion. Thus, the transport of the analyte to the electrode is dominated by diffusion from the direction normal to the electrode surface. As a result, the reduced transport rate is typically unable to overcome the depletion of analyte near the electrode surface, and at constant applied potential the current decreases with time, t, according to $t^{-1/2}$.

[0216] For a potentiometric assay of the type proposed by Yarnitzky and Heller, J. Phys. Chem., 102:10057-61 (1998), in which the potential varies linearly with the analyte concentration, the concentration of the analyte and/or redox mediator in a particular oxidation state should vary no more than about 20% during the assay. If the concentration varies by more than 20%, then the diffusion of the analyte or redox mediator should be controlled by, for example, controlling temperature and/or volume of the sample chamber and/or measurement zone.

[0217] While this description has described electrolysis of an analyte, one skilled in the art would recognize that the same devices and techniques would also be suitable for measurements of the average oxidation state of the mediator, such as, for example, in Cottrell types of reactions.

Air-oxidizable Redox Mediators

[0218] In a sensor having a redox mediator, a potential source of measurement error is the presence of redox mediator in an unknown mixed oxidation state (i.e., mediator not reproducibly in a known oxidation state). The charge passed when the redox mediator is electrooxidized or electroreduced at the working electrode is affected by its initial oxidation state. Referring to equations (1) and (2) discussed above under the section entitled "Operation of the Sensor," the current not attributable to the oxidation of biochemical B will flow because of electrooxidation of that portion of the redox mediator, A, that is in its reduced form prior to the addition of the sample. Thus, it may be important to know the oxidation state of the analyte prior to introduction of the sample into the sensor. Furthermore, it is desirable that all or nearly all of the redox mediator have the same state or extent of oxidation prior to the introduction of the sample into the sensor.

[0219] Each redox mediator has a reduced form or state and an oxidized form or state. It is preferred that the amount of redox mediator in the reduced form prior to the introduction of sample be significantly smaller than the expected amount of analyte in a sample in order to avoid a significant background contribution to the measured current. In this embodiment of the invention, the molar amount of redox mediator in the reduced form prior to the introduction of the analyte is preferably no more than, on a stoichiometric basis, about 10%, and more preferably no more than about 5%, and most preferably no more than 1%, of the molar amount of analyte for expected analyte concentrations. (The relative molar amounts of analyte and redox mediator are compared based on the stoichiometry of the applicable redox reaction. If, for example, two moles of redox mediator are needed to electrolyze one mole of analyte, then the molar amount of redox mediator in the reduced form prior to introduction of the analyte is preferably no more than 20% and more preferably

Abbott Ex. 1002 - 389/1438

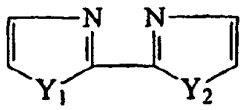
no more than about 10% and most preferably no more than about 2% of the molar amount of analyte for expected analyte concentrations.) Methods for controlling the amount of reduced mediator are discussed below.

[0220] In another aspect of the invention, it is preferred that the ratio of the amounts of oxidized redox mediator to reduced redox mediator, prior to introduction of the sample in the sensor, be relatively constant between similarly constructed sensors. Any deviation from holding the ratio relatively constant may increase the scatter of the results obtained for the same sample with multiple similarly made sensors. For this aspect of the invention, the percentage of the redox mediator in the reduced form prior to introduction of the sample in the sensor varies by no more than about 20% and preferably no more than about 10% between similarly constructed sensors.

[0221] One method of controlling the amount of reduced redox mediator prior to the introduction of the sample in the sensor is to provide an oxidizer to oxidize the reduced form of the mediator. One of the most convenient oxidizers is O_2. Oxygen is usually readily available to perform this oxidizing function. Oxygen can be supplied by exposing the sensor to air. In addition, most polymers and fluids absorb O_2 from the air unless special precautions are taken. Typically, at least 90% of an air-oxidizable (i.e., O_2 oxidizable) mediator in the solid state is in the oxidized state upon storage or exposure to air for a useful period of time, e.g., one month or less, and preferably, one week or less, and, more preferably, one day or less. The air oxidation may take place in either the solid state or as a solution stored for a time period sufficient to air oxidize the mediator before deposition on the sensor. In the case of air oxidizable redox mediators in solution, it is desirable that the time required to achieve at least 80%, preferably at least 90%, oxidation of the redox mediator is at least 10 times the expected duration of the assay and is also less than the pot life of the solution. Preferably, at least 80%, more preferably at least 90%, of the redox mediator is air oxidized in less than 1 week, preferably, in less than 1 day, more preferably, in less than 8 hours, and even more preferably, in less than 1 hour.

[0222] While it is desirable to bring the mediators of the sensors manufactured in a single batch to the same state or extent of oxidation, it is not necessary that the mediator be completely oxidized to the higher-valent state. Additionally, it is desirable that the air oxidation of the dissolved redox mediator should not be so fast that air-oxidation during the assay can interfere with or introduce error into the measurements.

[0223] Suitable mediators which are both air-oxidizable (i.e., O_2-oxidizable) and have electron transfer capabilities have been described hereinabove. One particular family of useful mediators are osmium complexes which are bound to electron-rich nitrogen-containing heterocycles or a combination of electron-rich nitrogen-containing heterocycles and halides. Electron-rich nitrogen-containing heterocycles include, but are not limited to, imidazole derivatives and pyridine or phenanthroline derivatives that contain electron-donating substituents such as alkyl, alkoxy, amino, alkylamino, amido and mercapto groups. Preferably, the osmium complexes have no more than one halide coordinated to the metal, so that the mediators are overall positively charged and thus are water soluble. An example is osmium complexed with mono-, di-, and polyalkoxy-2,2'-bipyridine. Other examples include mono-, di-, and polyalkoxy-1,10-phenanthroline, where the alkoxy groups have a carbon to oxygen ratio sufficient to retain solubility in water, are air-oxidizable. These osmium complexes typically have two substituted bipyridine or substituted phenanthroline ligands, the two ligands not necessarily being identical. These osmium complexes are further complexed with a monomeric or polymeric ligand with one or more nitrogen-containing heterocycles, such as pyridine and imidazole. Preferred polymeric ligands include poly (4-vinyl pyridine) and, more preferably, poly(1-vinyl imidazole) or copolymers thereof. $[Os[4,4'\text{-dimethoxy-}2,2'\text{-bipyridine}]_2Cl]^{+/+2}$ complexed with a poly(1-vinyl imidazole) or poly(4-vinyl pyridine) has been shown to be particularly useful as the Os^{+2} cation is oxidizable by O_2 to Os^{+3}. Similar results are expected for complexes of $[Os(4,7\text{-dimethoxy-}1,10\text{-phenanthroline})_2Cl]^{+/+2}$,and other mono-, di-, and polyalkoxy bipyridines and phenanthrolines, with the same polymers. Other halogen groups such as bromine may be substituted for chlorine. Similar results are also expected for complexes comprising the following structures, as specified above:



[0224] A complication associated with air-oxidizable mediators arises if the air oxidation of the redox mediator is so fast that a substantial portion of the analyte-reduced redox mediator is oxidized by O_2 during an analyte assay. This will result in an inaccurate assay as the amount of analyte will be underestimated because the mediator will be oxidized by air rather than by its electrooxidation at the electrode. It is preferred that the reaction of the redox mediator with O_2 proceeds more slowly than the electrooxidation of the mediator, because if the air oxidation of the mediator were fast, then dissolved air and the in-diffusion of air might affect the outcome of the measurement.

[0225] Because typically the assay takes about 10 minutes or less, preferably 5 minutes or less, and most preferably about 1 minute or less, it is preferred that the mediator, though air oxidizable in storage, will not be oxidized by dissolved oxygen during the time of the assay. Thus, mediators that are not air oxidized in 1 minute, and preferably not even in

Abbott Ex. 1002 - 390/1438

10 minutes when dissolved in plasma or in serum, are preferred. Typically, less than 5%, and preferably less than 1%, of the reduced mediator should be oxidized by air during an assay.

[0226] The reaction rate of the air oxidation of the mediator can be controlled through choice of an appropriate complexing polymer. For example, the oxidation reaction is much faster for $[Os(4,4'\text{-dimethoxy-}2,2'\text{-bipyridine})_2Cl]^{+/+2}$ coordinatively coupled to poly(1-vinyl imidazole) than for the same Os complex coupled to poly(4-vinyl pyridine). The choice of an appropriate polymer will depend on the expected analyte concentration and the potential applied between the electrodes, both of which determine the rate of the electrochemical reaction.

[0227] Thus, in one embodiment of the invention, the preferred redox mediator has the following characteristics: 1) the mediator does not react with any molecules in the sample or in the sensor other than the analyte (optionally, via a second electron transfer agent); 2) nearly all of the redox mediator is oxidized by an oxidizer such as O_2 prior to introduction of the sample in the sensor; and 3) the oxidation of the redox mediator by the oxidizer is slow compared to the electrooxidation of the mediator by the electrode.

[0228] Alternatively, if the redox mediator is to be oxidized in the presence of the analyte and electroreduced at the electrode, a reducer rather than an oxidizer would be required. The same considerations for the appropriate choice of reducer and mediator apply as described hereinabove for the oxidizer.

[0229] The use of stable air-oxidizable redox mediators in the electrochemical sensors of the invention provides an additional advantage during storage and packaging. Sensors of the invention which include air-oxidizable redox mediators can be packaged in an atmosphere containing molecular oxygen and stored for long periods of time, e.g., greater than one month, while maintaining at least 80% and preferably at least 90% of the redox species in the oxidized state.

Use of the Air-Oxidizable Mediators in Optical Sensors

[0230] The air-oxidizable redox species of the present invention can be used in other types of sensors. The osmium complexes described hereinabove are suitable for use in optical sensors, due to the difference in the absorption spectra, luminescence and/or fluorescence characteristics of the complexed Os^{+2} and Os^{+3} species. Absorption, transmission, reflection, luminescence and/or fluorescence measurements of the redox species will correlate with the amount of analyte in the sample (after reaction between an analyte and the redox species, either directly, or via a second electron transfer agent such as an enzyme). In this configuration, the molar amount of redox mediator should be greater, on a stoichiometric basis, than the molar amount of analyte reasonably expected to fill the measurement zone of the sensor.

[0231] Standard optical sensors, including light-guiding optical fiber sensors, and measurement techniques can be adapted for use with the air-oxidizable mediators. For example, the optical sensors of the invention may include a light-transmitting or light reflecting support on which the air-oxidizable redox species, and preferably an analyte-responsive enzyme, is coated to form a film. The-support film forms one boundary for the measurement zone in which the sample is placed. The other boundaries of the measurement zone are determined by the configuration of the cell. Upon filling the measurement zone with an analyte-containing sample, reduction of the air-oxidizable mediator by the analyte, preferably via reaction with the analyte-responsive enzyme, causes a shift in the mediator's oxidation state that is detected by a change in the light transmission, absorption, or reflection spectra or in the luminescence and/or fluorescence of the mediator at one or more wavelengths of light.

Multiple Electrode Sensors and Calibration

[0232] Multiple electrode sensors may be used for a variety of reasons. For example, multiple electrode sensors may be used to test a variety of analytes using a single sample. One embodiment of a multiple electrode sensor, shown in Figure 5, has one or more sample chambers which in turn may contain one or more working electrodes 22 with each working electrode 22 defining a different measurement zone. If the redox mediator is non-leachable, one or more of the working electrodes have the appropriate chemical reagents, for example, an appropriate enzyme, to test a first analyte and one or more of the remaining working electrodes have appropriate chemical reagents to test a second analyte. The chemical reagents (e.g., redox mediator and/or second electron transfer agent) can be deposited as a sensing layer on the working electrode or, if diffusible reagents are used, they can be deposited on any surface of the sample chamber or placed in the sample. For example, a multiple electrode sensor might include 1) one or more working electrodes having glucose oxidase in the sensing layer to determine glucose concentration and 2) one or more working electrodes having lactate oxidase in the sensing layer to determine lactate concentration.

[0233] Multiple electrode sensors may also be used to improve the precision of the resulting readings. The measurements from each of the working electrodes (all or which are detecting the same analyte) can be averaged together to obtain a more precise reading. In some cases, measurements may be rejected if the difference between the value and the average exceeds a threshold limit. This threshold limit may be, for example, determined based on a statistical parameter, such as the standard deviation of the averaged measurements. The average may then be recalculated while omitting the rejected values. Furthermore, subsequent readings from an electrode that produced a rejected value may

Abbott Ex. 1002 - 391/1438

be ignored in later tests if it is assumed that the particular electrode is faulty. Alternatively, a particular electrode may be rejected only after having a predetermined number of readings rejected based on the readings from the other electrodes.

[0234] In addition to using multiple electrode sensors to increase precision, multiple measurements may be made at each electrode and averaged together to increase precision. This technique may also be used with a single electrode sensor to increase precision.

[0235] Errors in assays may occur when mass produced sensors are used because of variations in the volume of the measurement zone of the sensors. Two of the three dimensions of the measurement zone, the length and the width, are usually relatively large, between about 1-5 mm. Electrodes of such dimensions can be readily produced with a variance of 2% or less. The submicroliter measurement zone volume requires, however, that the third dimension be smaller than the length or width by one or two order of magnitude. As mentioned hereinabove, the thickness of the sample chamber is typically between about 50 and about 200 μm. Manufacturing variances in the thickness may be on the order of 20 to 50 μm. Therefore, it may be desirable that a method be provided to accommodate for this uncertainty in the volume of sample within the measurement zone.

[0236] In one embodiment of the invention, depicted in Figure 5, multiple working electrodes 42, 44, 46 are provided on a base material 48. These electrodes are covered by another base, not shown, which has counter electrodes, not shown, disposed upon it to provide multiple facing electrode pairs. The variance in the separation distance between the working electrode and the counter electrode among the electrode pairs on a given sensor is significantly reduced, because the working electrodes and counter electrodes are each provided on a single base with the same spacer 28 between each electrode pair (see Figure 3).

[0237] One example of a multiple electrode sensor that can be used to accurately determine the volume of the measurement zones of the electrode pairs and that is also useful in reducing noise is presented herein. In this example, one of the working electrodes 42 is prepared with a non-leachable redox mediator and a non-leachable second electron transfer agent (e.g., an enzyme). Sorbent material may be disposed between that working electrode 42 and its corresponding counter electrode. Another working electrode 44 includes non-leachable redox mediator, but no second electron transfer agent on the electrode. Again, this second electrode pair may have sorbent material between the working electrode 44 and the corresponding counter electrode. An optional third working electrode 46 has no redox mediator and no second electron transfer agent bound to the electrode, nor is there sorbent material between the working electrode 46 and its corresponding counter electrode. A similar configuration can be constructed using diffusible redox mediator and/or diffusible second electron transfer agent although diffusible components are not limited to being disposed on the working electrode. In some instances, the distance between electrode pairs is sufficient that redox mediator and/or enzyme do not substantially diffuse between electrode pairs within the measurement period and/or in the time period from introduction of the same sample into the sample chamber to the end of the measurement.

[0238] The sensor error caused by redox mediator in a non-uniform oxidation state prior to the introduction of the sample can be measured by concurrently electrolyzing the sample in the measurement zones that are proximate electrodes 42 and 44. At electrode 42, the analyte is electrolyzed to provide the sample signal. At electrode 44, the analyte is not electrolyzed because of the absence of the second electron transfer agent (assuming that a second electron transfer agent is necessary). However, a charge will pass (and a current will flow) due to the electrolysis of the redox mediator that was in a mixed oxidation state (i.e., some redox centers in the reduced state and some in the oxidized state) prior to the introduction of the sample and/or the shuttling of a diffusible redox mediator between the working electrode and the counter electrode. The small charge passed between the electrodes in this second electrode pair can be subtracted from the charge passed between the first electrode pair to substantially remove the error due to the oxidation state of the redox mediator and/or to remove the background current caused by a diffusible redox mediator. This procedure also reduces the error associated with other electrolyzed interferents, such as ascorbate, urate, and acetaminophen, as well as errors associated with capacitive charging and faradaic currents.

[0239] The thickness of the sample chamber can be determined by measuring the capacitance, preferably in the absence of any fluid, between electrode 46 (or any of the other electrodes 42, 44 in the absence of sorbent material) and its corresponding counter electrode. The capacitance of an electrode pair depends on the surface area of the electrodes, the interelectrode spacing, and the dielectric constant of the material between the plates. The dielectric constant of air is unity which typically means that the capacitance of this electrode configuration is a few picofarads (or about 100-1000 picofarads if there is fluid between the electrode and counter electrode given that the dielectric constant for most biological fluids is approximately 75). Thus, since the surface area of the electrodes are known, measurement of the capacitance of the electrode pair allows for the determination of the thickness of the measurement zone to within about 1-5%.

[0240] The amount of void volume in the sorbent material, can be determined by measuring the capacitance between electrode 44 (which has no second electron transfer agent) and its associated counter electrode, both before and after fluid is added. Upon adding fluid, the capacitance increases markedly since the fluid has a much larger dielectric constant. Measuring the capacitance both with and without fluid allows the determination of the spacing between the electrodes

Abbott Ex. 1002 - 392/1438

and the void volume in the sorbent, and thus the volume of the fluid in the reaction zone.

[0241] Other electrode configurations can also use these techniques (i.e., capacitance measurements and coulometric measurements in the absence of a critical component) to reduce background noise and error due to interferents and imprecise knowledge of the volume of the interrogated sample. Protocols involving one or more electrode pairs and one or more of the measurements described above can be developed and are within the scope of the invention. For example, only one electrode pair is needed for the capacitance measurements, however, additional electrode pairs may be used for convenience.

Fill Indicator

[0242] When using a sample chamber that is filled with 1 μL or less of fluid, it is often desirable to be able to determine when the sample chamber is filled. Figures 18A-18C illustrate one sensor having a fill indicator structure. Figure 18A illustrates a first substrate 500 upon which a working electrode 502 is printed. A spacer 504 (Figure 18B), such as, for example, a layer of adhesive or a double-sided tape, is formed over the first substrate 500 and working electrode 502 with a channel 506 formed in the layer to provide a sample chamber. A second substrate 508 is printed with two counter electrodes 510, 512, as shown in Figure 18C (inverted with respect to Figures 18A and 18B to show the electrode side up). In some instances, the counter electrode 510 nearest an entrance 514 of the channel 506 has a surface area within the sample chamber that is at least two times larger than the other counter electrode 512, and preferably at least five or ten times larger.

[0243] The sensor can be indicated as filled by observing a signal between the second counter electrode 512 and the working electrode 502 as the sensor fills with fluid. When fluid reaches the second counter electrode 512, the signal from that counter electrode should change. Suitable signals for observing include, for example, voltage, current, resistance, impedance, or capacitance between the second counter electrode 512 and the working electrode 502. Alternatively, the sensor may be observed after filling to determine if a value of the signal (e.g., voltage, current, resistance, impedance, or capacitance) has been reached indicating that the sample chamber is filled.

[0244] In alternative embodiments, the counter electrode and/or working electrode may be divided into two or more parts and the signals from the respective parts observed to determine whether the sensor has been filled. In one example, the working electrode is in a facing relationship with the counter electrode and the indicator electrode. In another example, the counter electrode, working electrode, and indicator electrode are not in a facing relationship, but may be, for example, side-by-side. In other cases, a second electrode pair may be used with signals from the second electrode pair being monitored for changes and/or for approaching a particular value to determine that the sensor has filled. Typically, the indicator electrode is further downstream from a sample inlet port than the working electrode and counter electrode.

[0245] For side-fill sensors, such as those illustrated in Figures 19A-19C and 20A-20C, two indicator electrodes may be disposed on either side of the primary counter electrode. This permits the user to fill the sample chamber from either the left or right side with an indicator electrode disposed further upstream. This three-electrode configuration is not necessary. Side-fill sensors can also have a single indicator electrode and, preferably, some indication as to which side should be placed in contact with the sample fluid.

[0246] In one embodiment, the use of three counter/reference electrodes and/or indicator electrodes, detects when the sample chamber begins to fill and when the sample chamber has been filled to prevent partial filling of the sample chamber. In this embodiment, the two indicator electrodes are held at a different potential than the largest counter/reference electrode. The start and completion of filling of the sample chamber is indicated by the flow of current between the indicator and counter/reference electrodes.

[0247] In other instances, the potential of each of the counter/reference electrodes may be the same. When the potential at all three counter/reference electrodes is the same for example, 0 volts, then as the measurement zone begins to fill, the fluid allows for electrical contact between a working electrode and the first counter/reference electrode, causing a current at the first counter/reference electrode due to the reaction of the analyte with the enzyme and the mediator. When the fluid reaches the third counter/reference electrode, another current may be measured similar to the first counter/reference electrode indicating that the measurement zone is full. When the measurement zone is full, the three counter/reference electrodes may be shorted together or their signals may be added or otherwise combined.

[0248] The indicator electrode may also be used to improve the precision of the analyte measurements according to the methods described above for multiple electrode sensors. The indicator electrode may operate as a working electrode or as a counter electrode or counter/reference electrode. In the embodiment of Figures 18A-18C, the indicator electrode 512 can act as a second counter or counter/reference electrode with respect to the working electrode 502. Measurements from the indicator electrode/working electrode pair can be combined (for example, added to and/or averaged) with those from the first counter or counter/reference electrode/working electrode pair to obtain more accurate measurements. In one embodiment, the indicator electrode may operate as a second working electrode with the counter electrode or counter/reference electrode. In another embodiment, the indicator electrode may operate as a second working electrode with a second counter electrode or counter/reference electrode. In still another embodiment, the indicator electrode may

Abbott Ex. 1002 - 393/1438

operate as a second counter electrode or counter/reference electrode with a second working electrode.

[0249] The sensor or a sensor reader may include a sign (e.g., a visual sign or auditory signal) that is activated in response to the indicator electrode to alert the user that the measurement zone has been filled. In some instances, the sensor or a sensor reader may be configured to initiate a reading when the indicator electrode indicates that the measurement zone has been filled with or without alerting the user. The reading can be initiated, for example, by applying a potential between the working electrode and the counter electrode and beginning to monitor the signals generated at the working electrode.

Heating of Sample

[0250] The sample may be heated to increase the rate of diffusion, oxidation, or reduction of the analyte. This heating may be accomplished by a variety of techniques including placing the sensor in a heated environment or applying a heating unit to the sensor.

[0251] Another technique includes providing a thermal heating element, such as, for example, a wire or an ink that is capable of converting electrical energy into heat energy, on the sensor. This wire or ink can be applied, for example, on the opposite side of a base material, such as a polymer film, from one or more of the working, counter, reference, or counter/reference electrodes, or applied around the periphery of the working, counter, reference, or counter/reference electrodes. In some instances, the sample may be heated up to 5 to 20°C above an initial temperature. In other instances, the temperature of the sample may not be known but a constant amount of power or current may be applied to the wire or ink.

EXAMPLES

[0252] The invention will be further characterized by the following examples. These examples are not meant to limit the scope of the invention which has been fully set forth in the foregoing description. Variations within the concepts of the invention are apparent to those skilled in the art. Examples 1 to 8 represent background art according to WO 98/35225.

Example 1

Preparation of a Small Volume *in vitro* Sensor for the Determination of Glucose Concentration

[0253] A sensor was constructed corresponding to the embodiment of the invention depicted in Figure 1. The working electrode was constructed on a Mylar™ film (DuPont), the Mylar™ film having a thickness of 0.175 mm and a diameter of about 2.5 cm. An approximately 12 micron thick carbon pad having a diameter of about 1 cm was screen printed on the Mylar™ film. The carbon electrode was overlaid with a water-insoluble dielectric insulator (Insulayer) having a thickness of 12 μm, and a 4 mm diameter opening in the center.

[0254] The center of the carbon electrode, which was not covered by the dielectric, was coated with a non-leachable redox mediator. The redox mediator was formed by complexing poly(1-vinyl imidazole) with Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$_2$ followed by cross-linking glucose oxidase with the osmium polymer using polyethylene glycol diglycidyl ether (PEGDGE) as described in Taylor et al., *J. Electroanal. Chem.*, 396:511 (1995). The ratio of osmium to imidazole functionalities in the redox mediator was approximately 1:15. The mediator was deposited on the working electrode in a layer having a thickness of 0.6 μm and a diameter of 4 mm. The coverage of the mediator on the electrode was about 60 μ g/cm^2 (dry weight). A spacer material was placed on the electrode surrounding the mediator-covered surface of the electrode. The spacer was made of polytetrafluoroethylene (PTFE) and had a thickness of about 0.040 mm.

[0255] A sorbent material was placed in contact with the mediator-covered surface of the working electrode. The sorbent was made of nylon (Tetko Nitex nylon 3-10/2). The sorbent had a diameter of 5 mm, a thickness of 0.045 mm, and a void volume of about 20%. The volume of sample in the measurement zone was calculated from the dimensions and characteristics of the sorbent and the electrode. The measurement zone had a diameter of 4 mm (the diameter of the mediator covered surface of the electrode) and a thickness of 0.045 mm (thickness of the nylon sorbent) to give a volume of 0.57 μL. Of this space, about 80% was filled with nylon and the other 20% was void space within the nylon sorbent. This resulting volume of sample within the measurement zone was about 0.11 μL.

[0256] A counter/reference electrode was placed in contact with the spacer and the side of the sorbent opposite to the working electrode so that the two electrodes were facing each other. The counter/reference electrode was constructed on a Mylar™ film having a thickness of 0.175 mm and a diameter of about 2.5 cm onto which a 12 micron thick layer of silver/silver chloride having a diameter of about 1 cm was screen printed.

[0257] The electrodes, sorbent, and spacer were pressed together using plates on either side of the electrode assembly. The plates were formed of polycarbonate plastic and were securely clamped to keep the sensor together. The electrodes were stored in air for 48 hours prior to use.

Abbott Ex. 1002 - 394/1438

[0258] Tabs extended from both the working electrode and the counter/reference electrode and provided for an electrical contact with the analyzing equipment. A potentiostat was used to apply a potential difference of +200mV between the working and counter/reference electrodes, with the working electrode being the anode. There was no current flow between the electrodes in the absence of sample, which was expected, as no conductive path between the electrodes was present.

[0259] The sample was introduced via a small tab of nylon sorbent material formed as an extension from the nylon sorbent in the sample chamber. Liquid was wicked into the sorbent when contact was made between the sample and the sorbent tab. As the sample chamber filled and the sample made contact with the electrodes, current flowed between the electrodes. When glucose molecules in the sample came in contact with the glucose oxidase on the working electrode, the glucose molecules were electrooxidized to gluconolactone. The osmium redox centers in the redox mediator then reoxidized the glucose oxidase. The osmium centers were in turn reoxidized by reaction with the working electrode. This provided a current which was measured and simultaneously integrated by a coulometer (EG&G Princeton Applied Research Model #173).

[0260] The electrochemical reaction continued until the current reached a steady state value which indicated that greater than 95% of the glucose had been electroreduced. The current curve obtained by measurement of the current at specific intervals was integrated to determine the amount of charge passed during the electrochemical reaction. These charges were then plotted versus the known glucose concentration to produce a calibration curve.

[0261] The sensor was tested using 0.5 μL aliquots of solutions containing known concentrations of glucose in a buffer of artificial cerebrospinal fluid or in a control serum (Baxter-Dade, Monitrol Level 1, Miami, FL) in the range of 3 to 20 mM glucose. The artificial cerebrospinal fluid was prepared as a mixture of the following salts: 126 mM NaCl, 27.5 mM $NaHCO_3$, 2.4 mM KCl, 0.5 mM KH_2PO_4, 1.1 mM $CaCl_2 \cdot 2H_2O$, and 0.5 mM Na_2SO_4.

[0262] The results of the analyses are shown in Table 1 and in Figure 7. In Table 1, Q_{avg} is the average charge used to electrolyze the glucose in 3-6 identical test samples (Figure 7 graphs the charge for each of the test samples) and the 90% rise time corresponds to the amount of time required for 90% of the glucose to be electrolyzed. The data show a sensor precision of 10- 20%, indicating adequate sensitivity of the sensor for low glucose concentrations, as well as in the physiologically relevant range (30 μg/dL - 600 μg/dL).

TABLE 1

Sensor Results Using Glucose Oxidase			
	Number of Samples Tested	Q_{avg}(TC)	90% rise time (sec)
buffer only	4	9.9 ± 1.8	13 ± 6
3 mM glucose/buffer	5	17.8 ± 3.5	19 ± 5
6 mM glucose/buffer	4	49.4 ± 4.9	25 ± 3
10 mM glucose/buffer	6	96.1 ± 12.4	36 ± 17
15 mM glucose/buffer	5	205.2 ± 75.7	56 ± 23
20 mM glucose/buffer	4	255.7 ± 41.0	62 ± 17
4.2 mM glucose/buffer	3	44.2 ± 4.3	44 ± 3
15.8 mM glucose/buffer	3	218.2 ± 57.5	72 ± 21

[0263] The average measured values of glucose concentration were fit by one or more equations to provide a calibration curve. Figure 8 shows the calibration curves for the glucose/buffer data of Table 1. One of the 15.0 mM glucose measurements was omitted from these calculations because it was more than two standard deviations away from the average of the measurements. The higher glucose concentrations (10-20 mM) were fit by a linear equation. The lower glucose concentrations were fit by a second order polynomial.

[0264] Figure 9 shows the data of Table 1 plotted on an error grid developed by Clarke et al., *Diabetes Care*, 5, 622-27, 1987, for the determination of the outcome of errors based on inaccurate glucose concentration determination. The graph plots "true" glucose concentration vs. measured glucose concentration, where the measured glucose concentration is determined by calculating a glucose concentration using the calibration curves of figure 8 for each data point of figure 7. Points in zone A are accurate, those in zone B are clinically acceptable, and those in zones C, D, and E lead to increasingly inappropriate and finally dangerous treatments.

[0265] There were 34 data points. Of those data points 91 % fell in zone A, 6% in zone B, and 3 % in zone C. Only

Abbott Ex. 1002 - 395/1438

one reading was determined to be in zone C. This reading was off-scale and is not shown in figure 9. Thus, 97% of the readings fell in the clinically acceptable zones A and B.

[0266] The total number of Os atoms was determined by reducing all of the Os and then electrooxidizing it with a glucose-free buffer in the sample chamber. This resulted in a charge of 59.6 ± 5.4 μC. Comparison of this result with the glucose-free buffer result in Table 1 indicated that less than 20% of the Os is in the reduced form prior to introduction of the sample. The variability in the quantity of osmium in the reduced state is less than 5% of the total quantity of osmium present.

Example 2

Response of the Glucose Sensor to Interferents

[0267] A sensor constructed in the same manner as described above for Example 1 was used to determine the sensor's response to interferents. The primary electrochemical interferents for blood glucose measurements are ascorbate, acetaminophen, and urate. The normal physiological or therapeutic (in the case of acetaminophen) concentration ranges of these common interferents are:

ascorbate: 0.034 - 0.114 mM
acetaminophen: 0.066 - 0.200 mM
urate (adult male): 0.27 - 0.47 mM

Tietz, in: *Textbook of Clinical Chemistry*, C.A. Burtis and E.R. Ashwood, eds., W.B. Saunders Co., Philadelphia 1994, pp. 2210-12.

[0268] Buffered glucose-free interferent solutions were tested with concentrations of the interferents at the high end of the physiological or therapeutic ranges listed above. The injected sample volume in each case was 0.5 μL. A potential of +100 mV or +200 mV was applied between the electrodes. The average charge (Q_{avg}) was calculated by subtracting an average background current obtained from a buffer-only (i.e., interferent-free) solution from an average signal recorded with interferents present. The resulting average charge was compared with the signals from Table 1 for 4 mM and 10 mM glucose concentrations to determine the percent error that would result from the interferent.

TABLE 2

Interferent Response of Glucose Sensors					
Solution	E(mV)	n	Q_{avg}(TC)	Error @ 4 mM glucose	Error @ 10 mM glucose
0.114 mM ascorbate	100	4	0.4	2%	<1%
0.114 mM ascorbate	200	4	-0.5	2%	<1%
0.2 mM acetaminophen	100	4	0.1	<1%	<1%
0.2 mM acetaminophen	200	4	1.0	5%	1%
0.47 mM urate	100	4	6.0	30%	7%
0.47 mM urate	200	4	18.0	90%	21%

[0269] These results indicated that ascorbate and acetaminophen were not significant interferents for the glucose sensor configuration, especially for low potential measurements. However, urate provided significant interference. This interference can be minimized by calibrating the sensor response to a urate concentration of 0.37 mM, e.g., by subtracting an appropriate amount of charge as determined by extrapolation from these results from all glucose measurements of the sensor. The resulting error due to a 0.10 mM variation in urate concentration (the range of urate concentration is 0.27 - 0.47 in an adult male) would be about 6% at 4 mM glucose and 100mV.

Abbott Ex. 1002 - 396/1438

Example 3

Sensor with Glucose Dehydrogenase

[0270] A sensor similar to that described for Example 1 was prepared and used for this example, except that glucose oxidase was replaced by pyrroloquinoline quinone glucose dehydrogenase and a potential of only +100 mV was applied as opposed to the +200 mV potential in Example 1. The results are presented in Table 3 below and graphed in Fig. 10.

TABLE 3

Sensor Results Using Glucose Dehydrogenase			
	n	Q_{avg}(TC)	90% rise time (s)
buffer	4	21.7 ± 5.2	14 ± 3
3 mM glusose/buffer	4	96.9 ± 15.0	24 ± 6
6 mM glusose/buffer	4	190.6 ± 18.4	26 ± 6
10 mM glusose/buffer	4	327.8 ± 69.3	42 ± 9

[0271] The results indicated that the charge obtained from the glucose dehydrogenase sensor was much larger than for the comparable glucose oxidase sensor, especially for low concentrations of glucose. For 4 mM glucose concentrations the measurements obtained by the two sensors differed by a factor of five. In addition, the glucose dehydrogenase sensor operated at a lower potential, thereby reducing the effects of interferent reactions.

[0272] In addition, the results from Table 3 were all fit by a linear calibration curve as opposed to the results in Example 1, as shown in Fig. 10. A single linear calibration curve is greatly preferred to simplify sensor construction and operation.

[0273] Also, assuming that the interferent results from Table 2 are applicable for this sensor, all of the interferents would introduce an error of less than 7% for a 3 mM glucose solution at a potential of 100 mV.

Example 4

Determination of Lactate Concentration in a Fluid Stream

[0274] The sensor of this Example was constructed using a flow cell (BioAnalytical Systems, Inc. # MF-1025) with a glassy carbon electrode. A redox mediator was coated on the electrode of the flow cell to provide a working electrode. In this case, the redox mediator was a polymer formed by complexing poly(1-vinyl imidazole) with Os(4,4'-dimethyl-2,2'-bipyridine)$_2$Cl$_2$ with a ratio of 1 osmium for every 15 imidazole functionalities. Lactate oxidase was cross-linked with the polymer via polyethylene glycol diglycidyl ether. The mediator was coated onto the electrode with a coverage of 500 $\mu g/cm^2$ and a thickness of 5 Tm. The mediator was covered by a polycarbonate track-etched membrane (Osmonics-Poretics #10550) to improve adherence in the flow stream. The membrane was then overlaid by a single 50 Tm thick spacer gasket (BioAnalytical Systems, Inc. #MF-1062) containing a void which defined the sample chamber and corresponding measurement zone. Assembly of the sensor was completed by attachment of a cell block (BioAnalytical Systems, Inc. #MF-1005) containing the reference and auxiliary electrodes of the flow cell.

[0275] The sample chamber in this case corresponded to a 50 Tm thick cylinder (the thickness of the spacer gasket) in contact with a mediator-coated electrode having a surface area of 0.031 cm^2. The calculated volume of sample in the measurement zone of this sensor was approximately 0.16 TL.

[0276] The flow rate of the fluid stream was 5 TL/min. A standard three electrode potentiostat was attached to the cell leads and a potential of +200 mV was applied between the redox mediator-coated glassy carbon electrode and the reference electrode. This potential was sufficient to drive the enzyme-mediated oxidation of lactate.

[0277] As the fluid stream flowed through the sensor, a steady-state current proportional to the lactate concentration was measured. At periodic intervals the fluid flow was stopped and current was allowed to flow between the electrodes until approximately all of the lactate in the measurement zone was electrooxidized, as indicated by the achievement of a stabilized, steady-state current. The total charge, Q, required for lactate electrooxidation was found by integration of the differential current registered from the flow stoppage until the current reached a steady-state. The concentration was then calculated by the following equation:

$$[\text{lactate}] = Q/2FV \qquad (4)$$

Abbott Ex. 1002 - 397/1438

where V is the volume of sample within the measurement zone and F is Faraday's constant.

[0278] This assay was performed using lactate solutions having nominal lactate concentrations of 1.0, 5.0, and 10.0 mM. The measured concentrations for the assay were 1.9, 5.4, and 8.9 mM respectively.

Example 5

Determination of the Oxidation State of Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$^{+/+2}$ Complexed with poly(1-vinyl imidazole)

[0279] A sensor having a three electrode design was commercially obtained from Ecossensors Ltd., Long Hanborough, England, under the model name "large area disposable electrode". The sensor contained parallel and coplanar working, reference and counter electrodes. The working surface area (0.2 cm^2) and counter electrodes were formed of printed carbon and the reference electrode was formed of printed Ag/AgCl. A redox mediator was coated on the carbon working electrode. The redox mediator was formed by complexation of poly(1-vinyl imidazole) with Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$_2$ in a ratio of 15 imidazole groups per Os cation followed by cross linking the osmium polymer with glucose oxidase using polyethylene glycol diglycidyl ether.

[0280] The electrode was cured at room temperature for 24 hours. The coplanar electrode array was then immersed in a buffered electrolyte solution, and a potential of +200 mV (sufficient for conversion of Os(II) to Os(III),) was applied between the working electrode and the reference electrode.

[0281] Upon application of the potential, an undetectable charge of less than 1 μC was passed. Subsequent reduction and reoxidation of the redox mediator yielded a charge for conversion of all Os from Os(II) to Os(III) of 65 TC. Therefore, more than 98% of the Os cations in the redox mediator were in the desired oxidized Os(III) state.

Example 6

Determination of the Oxidation State of the Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$^{+/+2}$ Complexed with poly(4-vinyl pyridine)

[0282] A similar experiment to that of Example 5 was conducted with the same working/counter/reference electrode configuration except that the redox mediator on the working electrode was changed to a complex of Os(4,4'-dimethoxy-2,2'-bipyridine)$_2$Cl$_2$ with poly(4-vinyl pyridine), with 12 pyridine groups per Os cation, cross linked with glucose oxidase via polyethylene glycol diglycidyl ether.

[0283] Two sensors were constructed. The electrodes of the two sensors were cured at room temperature for 24 hours. The electrodes were then immersed in a buffered electrolyte solution and a potential of +200 mV was applied between the working and reference electrodes.

[0284] Upon application of the potential to the electrodes, a charge of 2.5 TC and 3.8 TC was passed in the two sensors, respectively. Subsequent reduction and reoxidation of the redox mediators yielded oxidation charges of 27.9 TC and 28.0 T C, respectively. Therefore, the sensors originally contained 91% and 86% of the Os cations in the desirable oxidized Os(III) state.

Example 7

Optical Sensor

[0285] An optical sensor is constructed by applying a film of redox polymer with crosslinked enzyme onto a light-transparent support such as a glass slide. The quantity of redox mediator is equal to or greater than (in a stoichiometric sense) the maximum quantity of analyte expected to fill the measurement zone. The spacer material, sorbent and facing support are securely clamped. The sample chamber is adapted to transmit light through the assembled sensor to an optical density detector or to a luminescence and/or fluorescence detector. As sample fills the sample chamber and the redox mediator is oxidized, changes in the absorption, transmission, reflection or luminescence and/or fluorescence of the redox mediator in the chamber are correlated to the amount of glucose in the sample.

Example 8

Blood Volumes from Upper Arm Lancet Sticks

[0286] The forearm of a single individual was pierced with a lancet multiple times in order to determine the reproducibility of blood volumes obtained by this method. Despite more than thirty lancet sticks in the anterior portion of each forearm

Abbott Ex. 1002 - 398/1438

and the dorsal region of the left forearm, the individual identified each stick as virtually painless.

[0287] The forearm was pierced with a Payless Color Lancet. The blood from each stick was collected using a 1 μL capillary tube, and the volume was determined by measuring the length of the blood column. The volumes obtained from each stick are shown below in Table 4.

Table 4

Volume of Lancet Sticks

	Left Anterior Forearm, (nL)	Right Anterior Forearm, (nL)	Left Dorsal Forearm, (nL)
1	180	190	180
2	250	180	300
3	170	120	310
4	150	100	300
5	100	210	60
6	50	140	380
7	90	120	220
8	130	140	200
9	120	100	380
10		100	320
11			260
12			250
13			280
14			260
Avg.	138 ± 58 nL	140 ± 40 nL	264 ± 83 nL

Example 9

A Sensor with Diffusible Redox Mediator

[0288] A sensor was formed by printing graphite ink (Graphite #G4491, Ercon, Wareham, MA) on a polyester substrate. A mixture of 5.5 μg/cm^2 [Os(dimethyoxybipyridine)$_2$(vinylimidazole)Cl]Cl, 23.7 μg/cm^2 PQQ-glucose dehydrogenase, and 18.2 μg/cm^2 Zonyl FSO® surfactant (E. I. duPont de Nemours & Co., Inc., Wilmington, DE) were deposited on a portion of the working electrode. A 150 μm thick pressure sensitive adhesive tape was then applied to the working electrode leaving only a portion of the working electrode exposed to form a sample chamber. A second polyester film with a counter electrode disposed on the film was provided over the pressure sensitive adhesive tape. The counter electrode was formed by disposing Ag/AgCl ink (Silver/Silver Chloride #R414, Ercon, Wareham, MA) over the second polyester film. The Ag/AgCl counter electrode was coated with approximately 100 μg/cm^2 of methylated poly(vinylimidazole) crosslinked using PEGDGE.

Example 10

Measuring Glucose using Sensor with Diffusible Redox Mediator at a Potential of 0 V.

[0289] Sensors were formed as described in Example 9 and used to measure glucose/buffer solutions at 0, 90, 180, 270, and 360 mg/dL glucose concentration. The charge measured over time for each of these solutions is graphed in Figure 15. In the absence of glucose, the sensor indicates about 3 mg/dL glucose concentration. Figure 16 illustrates the measured charge versus glucose concentration for three sensors at each glucose concentration. The measured charge varies linearly with glucose concentration similar to what is observed for sensors using non-leachable redox mediator.

Abbott Ex. 1002 - 399/1438

Example 11

Other Sensors Formed Using Diffusible Redox Mediator

[0290] Sensors A and B were formed by printing graphite ink (Graphite #G4491, Ercon, Wareham, MA) on a polyester substrate. For Sensor A, a mixture of 8.0 μg/cm^2 [Os(dimethyoxybipyridine)$_2$(vinyl imidazole)Cl]Cl, 34.7 μg/cm^2 PQQ-glucose dehydrogenase, and 26.6 μg/cm^2 Zonyl FSO® surfactant (E.I. duPont de Nemours & Co., Inc., Wilmington, DE) were deposited on a portion of the working electrode. For Sensor B, a mixture of 24 μg/cm^2 [Os(dimethyoxybipyridine)$_2$(vinyl imidazole)Cl]Cl, 104 μg/cm^2 PQQ-glucose dehydrogenase, and 80 μg/cm^2 Zonyl FSO® surfactant (E.I. duPont de Nemours & Co., Inc., Wilmington, DE) were deposited on a portion of the working electrode. A 200 μm pressure sensitive adhesive tape was then formed over the working electrode of each sensor leaving only a portion of the working electrode exposed to form a sample chamber. A second polyester film with a counter electrode disposed on the film was provided over the pressure sensitive adhesive tape. The counter electrode of each sensor was formed by disposing Ag/AgCl ink (Silver/Silver Chloride #R414, Ercon, Wareham, MA) over the second polyester film. The Ag/AgCl counter electrode was coated with approximately 100 μg/cm^2 of methylated poly(vinylimidazole) crosslinked using PEGDGE.

Example 12

Varying the Amount of Diffusible Redox Mediator in the Sensor

[0291] Sensors A and B were each tested to determine the amount of time required for electrolysis of the analyte. Figure 17 illustrates the results. Increasing the amount of diffusible redox mediator in the sample decreases the response time of the sensor.

Example 13

Clinical Accuracy of the Small Volume Sensor

[0292] The sensor of this Example was constructed corresponding to the embodiment of the invention depicted in Figures 24A, 24B, and 24C. The carbon working electrode was printed on a Melinex™ polyester film (DuPont, Wilmington, Delaware), as described in Example 11. The carbon electrode was coated with 18 μ g/cm^2 Os[(MeO)$_2$bpy]$_2$(1-vinyl imidazole)Cl$_3$, 162 μg/cm^2 GDH (Toyobo, Japan), 1.35 μg/cm^2 PQQ (Fluka, Mila, Wisconsin), and 60 μg/cm^2 Zonyl FSO (DuPont, Wilmington, Delaware). The coatings were applied to the working electrode at 18°C and in 50% relative humidity. An adhesive (50 μm thickness) was placed on the carbon electrode surrounding the coated surface and forming a channel having a width of about 0.04 inches.

[0293] Two Ag/AgCl counter/reference electrodes were printed on a second Melinex™ polymer film, as described in Example 11. The film was then brought into contact with the adhesive and the working electrode film so that the working electrode and two counter electrodes were facing each other. The counter/reference electrodes were coated with 142 μg/cm^2 methylated polyvinyl imidazole, 18 μg/cm^2 PEGDGE (Polysciences, Warington, Pennsylvania), and 7 μg/cm^2 Zonyl FSO (DuPont, Wilmington, Delaware). One of the counter electrodes, upstream of the other counter electrode, was used as an indicator electrode to determine when the sample chamber was full. The sensors were laminated by three passes with a hand roller and aged for three days at room temperature over $CaSO_4$.

[0294] The sensors were constructed so that when sufficient current flowed between indicator and counter/reference electrodes, an external circuit emitted a visual signal indicating that the channel overlying the working electrode was full of blood.

[0295] A few days prior to using the sensors, dry capacitance measurements were taken to determine the uniformity of the sample chamber volume. The variation in capacitance reflected misalignment of electrodes and/or variation in adhesive thickness. The mean capacitance measured was 7.49 pF with a standard deviation of 0.28 pF or 3.8%. The maximum capacitance measured was 8.15 pF and the minimum capacitance measured was 6.66 pF.

[0296] The sensors were used to determine the glucose concentration in blood samples obtained from 23 people. In the study, the people ranged from 26 to 76 years of age, fourteen were men, and nine were women. Six of the people were diagnosed with Type 1 diabetes, sixteen were diagnosed with Type 2 diabetes, and one person was unknown regarding diabetic status. The people studied had an average hematocrit of 40.7% with a standard deviation of 3.9%. The maximum hematocrit was 49% and the minimum hematocrit was 33.2%.

[0297] One blood sample for each person was collected by pricking the finger of the subject. A small volume sensor was filled with this residual blood.

Abbott Ex. 1002 - 400/1438

Claims

1. A sensor (20) for determining the concentration of an analyte In a sample fluid, the sensor comprising:

an electrode pair comprising a working electrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) and a counter electrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), wherein at least a portion of the working electrode is within an effective distance of no more than 200 μm of a portion of the counter electrode and, optionally, the counter electrode is a counter/reference electrode;
an optional reference electrode (512, 532, 552, 572, 585, 612. 652);
a sample chamber (26, 526, 546. 566, 582, 606, 646) for holding the sample fluid in electrolytic contact with the working electrode, the counter electrode, and the reference electrode, if present, the sample chamber comprising a measurement zone positioned adjacent to the working electrode, the counter electrode, and the reference electrode, if present, wherein the measurement zone is sized to contain a volume of no more than about 1 μL of sample fluid and the sample chamber is sized to contain no more than about 1 μL of sample fluid; and
an analyte-responsive enzyme and a diffusible redox mediator disposed in the measurement zone;
the sensor having been configured and arranged so that a background signal generated by the diffusible redox mediator is no more than the signal generated by oxidation or reduction of the average normal physiological amount of analyte.

2. A sensor (20) for determining the concentration of: the analyte glucose in a sample fluid, the sensor comprising:

an electrode pair comprising a working electrode (22. 502. 522, 542. 562, 580. 602, 642, 1010) and a counter electrode (24, 510, 530. 550, 570, 584, 610, 650, 1020), wherein the working electrode and counter electrode are separated by an effective distance in a range of 25 to 1000 μm:
a sample chamber (26, 526; 546, 566, 582, 606, 646) for holding the sample fluid, the sample chamber comprising a measurement zone positioned adjacent to the working electrode and the counter electrode, wherein the measurement zone and the sample chamber are sized to contain a volume of no more than about 1 μL of the sample; and
an analyte-responsive enzyme and a diffusible redox mediator disposed in the measurement zone:
the sensor having been configured and arranged so that a background signal generated by the diffusible redox mediator is no more than five times a signal generated by oxidation or reduction of 5 mM of glucose and the signal generated by oxidation or reduction of the average normal physiological amount of analyte.

3. A sensor according to any of claims 1 and 2, wherein the sensor is configured and arranged so that a background signal generated by the diffusible redox mediator is no more than 25% of the signal generated by oxidation or reduction of the analyte and, preferably, no more than 5% of the signal generated by oxidation or reduction of the analyte.

4. A sensor according to any of claims 1 to 3, wherein the sensor comprises:

(a) a first substrate (500, 520, 540, 560, 579, 600, 640) having a proximal end and a distal end, the first substrate defining a first side edge (656) and a second side edge (658) of the electrochemical sensor extending from the proximal end to the distal end of the first substrate, the distal end being configured and arranged for insertion into a sensor reader,
(b) a second substrate (508, 528, 548, 568, 583, 608, 648) disposed over the first substrate, the working electrode being disposed on one of the first and second substrates and the counter electrode being disposed on one of the first and second substrates;
(c) a spacer (28, 504, 524, 544, 564, 581, 604, 644) disposed between the first and second substrates and defining a first aperture along the first side edge of the sensor and a second aperture along the second side edge of the sensor, the sample chamber extending from the first aperture to the second aperture: and
(d) at least one indicator electrode disposed on at least one of the first and second substrates and positioned relative to either the.measurement zone or the sample chamber to determine when the measurement zone or sample chamber contains sample.

5. A sensor according to any of claims 1 to 3, wherein the sensor comprises:

(a) a first substrate having a proximal end and a distal end, the distal end being configured and arranged for insertion into a sensor reader, the first substrate defining a first side edge and a second side edge of the

Abbott Ex. 1002 - 401/1438

electrochemical sensor extending from the proximal end to the distal end of the first substrate;
(b) a second substrate disposed over the first substrate, the working electrode being disposed on one of the first and second substrates and the counter electrode being disposed on one of the first and second substrates:
(c) a spacer disposed between the first and second substrates and defining a first aperture along the proximal end of the sensor and a second aperture along the first side edge of the sensor, the sample chamber extending from the first aperture to the second aperture; and
(d) at least one indicator electrode disposed on at least one of the first and second substrates and positioned relative to either the measurement zone or the sample chamber to determine when the measurement zone or the sample chamber contains sample.

6. A sensor according to any of claims 1 to 3, wherein the sensor comprises an Indicator electrode disposed in the sensor to indicate when either the measurement zone contains a sample or when the sample chamber contains a sample.

7. A sensor according to any of claims 4 to 6, wherein the indicator electrode is also a working electrode or a counter electrode.

8. A sensor according to any of claims 4 to 7, further comprising a visual or auditory sign, coupled to the indicator electrode, that activates when the indicator electrode indicates that the measurement zone or sample chamber contains sample.

9. A sensor according to any of claims 4 to 8, wherein the indicator electrode is disposed in facing relationship to one of the working electrode and the counter electrode.

10. A sensor according to any of claims 4 to 9, wherein the sensor comprises at least two indicator electrodes disposed in the sensor wherein a first indicator electrode indicates when the measurement zone or sample chamber is beginning to fill with sample, and a second indicator electrode indicates when the measurement zone or sample chamber is substantially filled with sample.

11. A sensor according to any of claims 4 to 9, wherein the sensor comprises at least two indicator electrodes disposed in the sensor, wherein two of the indicator electrodes comprise a first counter/indicator electrode and a second counter/indicator electrode with the counter electrode disposed between the first and second counter/indicator electrodes.

12. A sensor according to any of claims 1 to 11, wherein the measurement zone and the sample chamber have a same volume.

13. A sensor according to any of claims 1 to 12, wherein the analyte is glucose and the analyte-responsive enzyme is a glucose-responsive enzyme.

14. A sensor according to any of claims 1 to 12, wherein the analyte is a drug.

15. A sensor according to any of claims 1 to 14, wherein the measurement zone is bounded on at least two sides by the working electrode and the counter electrode and, optionally, the working electrode and counter electrode form a facing electrode pair with the measurement zone positioned between the working electrode and the counter electrode.

16. A sensor according to any of claims 1 to 15, wherein the sensor is configured and arranged so that the mediator oxidizes the analyte and the half-wave potential of the redox mediator, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, is no more than about +100 millivolts relative to the potential of the counter/reference electrode.

17. A sensor according to any of claims 1 to 16, wherein the sensor Is configured and arranged so that the mediator oxidizes the analyte and the half-wave potential of the redox mediator, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, is about the same as the potential of the counter/reference electrode.

18. A sensor according to any of claims 1 to 17, wherein the sensor is configured and arranged so that the mediator oxidizes the analyte, and the half-wave potential of the redox mediator, as measured by cyclic voltammetry in 0.1 M NaCl at pH 7, is no more than about -150 millivolts relative to the potential of the counter/reference electrode.

Abbott Ex. 1002 - 402/1438

19. A sensor according to any of claims 1 to 18, wherein, within the sensor, the effective diffusion coefficient of the redox mediator through the sample fluid is less than the effective diffusion coefficient of the analyte through the sample fluid and, preferably, at least ten times less than the effective diffusion coefficient of the analyte through the sample fluid.

20. A sensor according to any of claims 1 to 19, wherein the diffusible mediator has a molecular weight of at least 5,000 daltons.

21. A sensor according to any of claims 1 to 20, wherein the sensor is configured and arranged so that the redox mediator is more readily electrolyzed on the working electrode than the counter electrode.

22. A sensor according to any of claims 1 to 21, wherein the sensor comprises a molar amount of the redox mediator that is, on a stoichiometric basis, no more than an average normal physiological amount of the analyte and, preferably, the sensor comprises a molar amount of the redox mediator that is, on a stoichiometric basis, no more than 20% of an average norman physiological amount of the analyte.

23. A sensor according to any of claims 1 to 22, wherein the working electrode has a surface area of no more than about 0.01 cm^2 exposed in the measurement zone.

24. A sensor according to any of claims 1 to 23, wherein the activity of the enzyme is no more than 1 unit/cm^3

25. A sensor according to any of claims 1 to 24, wherein the sensor is configured and arranged so that the diffusible redox mediator precipitates when reacted at the counter electrode.

26. A sensor according to any of claims 1 to 25, wherein the sensor is configured and arranged so that a mathematical product of the effective diffusion coefficient of the redox mediator and the concentration of the redox mediator is no more than 1 x 10^{-12} moles cm^{-1} sec^{-1} when sample fluid fills the measurement zone.

27. A sensor according to any of claims 1 to 26, wherein the diffusible redox mediator Is disposed on the working electrode.

28. A sensor according to any of claims 1 to 27, wherein the analyte-responsive enzyme is disposed on the working electrode.

29. A method for determining a concentration of an analyte in a sample, comprising the steps of:

contacting a sample with any of the electrochemical sensors of claims 1 to 28;
generating a sensor signal at the working electrode, and
determining the concentration of the analyte using the sensor signal.

30. A method according to claim 29, wherein the background signal that is generated by the diffusible redox mediator is no more than the signal generated by oxidation or reduction of the average normal physiological amount of analyte.

31. A method according to any of claims 29 to 30, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by coulometry using the sensor signal.

32. A method according to any of ciaims 29 to 30, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by amperometry using the sensor signal.

33. A method according to any of claims 29 to 30, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by potentiometry using the sensor signal.

34. A method according to any of claims 29 to 30, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by chronoamperometry using the sensor signal.

35. A method according to any of claims 29 to 30, wherein determining the concentration of the analyte comprises determining the concentration of the analyte by chronopotentiometry using the sensor signal.

36. A method according to any of claims 29 to 30, wherein determining the concentration of the analyte comprises

Abbott Ex. 1002 - 403/1438

determining the concentration of the analyte by a Cotrell measurement technique using the sensor signal.

37. A method according to any of claims 29 to 36, further comprising:

providing calibration data on a batch of the electrochemical sensors to a measurement instrument, said calibration data comprising information related to a magnitude of a background charge for the batch of the electrochemical sensors;
wherein the step of determining the concentration of the analyte comprises determining the concentration of the analyte using the sensor signal and the calibration data.

38. A method for determining a concentration of an analyte in a sample, the method comprising the steps of:

contacting a sample with any of the electrochemical sensors of claims 1 to 28;
observing a signal from the indicator electrode to signify that the measurement zone contains sample;
applying a potential between the working electrode and the counter electrode to electrolyze the analyte in the sample;
generating an analyte-responsive signal from the sensor in response to electrolysis of the analyte in the sample; and
determining the concentration of the analyte using the analyte-responsive signal.

39. A method of manufacturing any of the electrochemical sensors of claims 1 to 28, the method comprising:

(a) forming a plurality of working electrodes on a first substrate;
(b) forming a plurality of counter electrodes on a second substrate;
(c) disposing a spacer layer on one of the first and second substrates;
(d) removing a portion of the spacer layer to define sample chamber regions;
(e) laminating the first and second substrates together; and
(f) separating a plurality of electrochemical sensors from the laminated substrates, each electrochemical sensor comprising at least one of the working electrodes at least one of the counter electrodes, and at least one of the sample chamber regions.

40. A method according to claim 39, wherein the first substrate is a first region of a substrate and the second substrate is a second region of the substrate, and further comprising:

folding the substrate to overlay the first and second regions of the substrate.

41. A method according to any of claims 39 and 40, wherein separating the plurality of electrochemical sensors comprises cutting the first and second substrates to separate the electrochemical sensors and to define at least one end of the sample chamber of the electrochemical sensors.

42. A method according to any of claims 39 to 41, further comprising forming a plurality of indicator electrodes on one of the first and second substrates

43. A method according to any of claims 39 to 42, wherein the portion of the spacer layer is removed to define the sample chamber regions after the spacer layer is disposed on one of the first and second substrates.

Patentansprüche

1. Sensor (20) zur Bestimmung der Konzentration eines Analyten in einem Probenfluid, wobei der Sensor umfasst:

ein Elektrodenpaar, das eine Arbeitselektrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) und eine Gegenelektrode (24, 510, 530, 550, 570, 584, 610, 650, 1020) umfasst, wobei wenigstens ein Abschnitt der Arbeitselektrode innerhalb eines wirksamen Abstands von nicht mehr als 200 µm von einem Abschnitt der Gegenelektrode liegt und die Gegenelektrode gegebenenfalls eine Gegen/Bezugs-Elektrode ist;
eine fakultative Bezugselektrode (512, 532, 552, 572, 585, 612, 652);
eine Probenkammer (26, 526, 546, 566, 582, 606, 646), die das Probenfluid in elektrolytischem Kontakt mit der Arbeitselektrode, der Gegenelektrode und, soweit vorhanden, der Bezugselektrode halten kann, wobei die

Abbott Ex. 1002 - 404/1438

Probenkammer eine Messzone umfasst, die angrenzend an die Arbeitselektrode, die Gegenelektrode und, soweit vorhanden, die Bezugselektrode angeordnet ist, wobei die Messzone so dimensioniert ist, dass sie ein Volumen von nicht mehr als etwa 1 μL Probenfluid enthält und die Probenkammer so dimensioniert ist, dass sie nicht mehr als etwa 1 μL des Probenfluids enthält; und

ein auf den Analyten ansprechendes Enzym und einen diffundierbaren Redox-Mediator, die in der Messzone angeordnet sind;

wobei der Sensor so konfiguriert und angeordnet worden ist, dass ein Hintergrundsignal, das durch den diffundierbaren Redox-Mediator erzeugt wird, nicht größer ist als das Signal, das durch Oxidation oder Reduktion der mittleren normalen physiologischen Menge des Analyten erzeugt wird.

2. Sensor (20) zur Bestimmung der Konzentration des Analyten Glucose in einem Probenfluid, wobei der Sensor umfasst:

ein Elektrodenpaar, das eine Arbeitselektrode (22, 502, 522, 542, 562, 580, 602, 642, 1010) und eine Gegenelektrode (24, 510, 530, 550, 570, 584, 610, 650, 1020) umfasst, wobei die Arbeitselektrode und die Gegenelektrode durch einen wirksamen Abstand in einem Bereich von 25 bis 1000 μm voneinander getrennt sind;

eine Probenkammer (26, 526, 546, 566, 582, 606, 646), die das Probenfluid aufnimmt, wobei die Probenkammer eine Messzone umfasst, die angrenzend an die Arbeitselektrode und die Gegenelektrode angeordnet ist, wobei die Messzone und die Probenkammer so dimensioniert sind, dass sie ein Volumen von nicht mehr als etwa 1 μL der Probe enthalten; und

ein auf den Analyten ansprechendes Enzym und einen diffundierbaren Redox-Mediator, die in der Messzone angeordnet sind;

wobei der Sensor so konfiguriert und angeordnet worden ist, dass ein Hintergrundsignal, das von dem diffundierbaren Redox-Mediator erzeugt wird, nicht mehr als das Fünffache eines Signals, das durch Oxidation oder Reduktion von 5 mM Glucose erzeugt wird, und als das Signal, das durch Oxidation oder Reduktion der mittleren normalen physiologischen Menge des Analyten erzeugt wird, beträgt.

3. Sensor nach irgendeinem der Ansprüche 1 und 2, wobei der Sensor so konfiguriert und angeordnet ist, dass ein Hintergrundsignal, das durch den diffundierbaren Redox-Mediator erzeugt wird, nicht mehr als 25% des Signals beträgt, das durch Oxidation oder Reduktion des Analyten erzeugt wird und vorzugsweise nicht mehr als 5% des Signals beträgt, das durch Oxidation oder Reduktion des Analyten erzeugt wird.

4. Sensor nach irgendeinem der Ansprüche 1 bis 3, wobei der Sensor umfasst:

(a) ein erstes Substrat (500, 520, 540, 560, 579, 600, 640) mit einem proximalen Ende und einem distalen Ende, wobei das erste Substrat eine erste Seitenkante (656) und eine zweite Seitenkante (658) des elektrochemischen Sensors definiert, die sich von dem proximalen Ende bis zum distalen Ende des ersten Substrats erstrecken, wobei das distale Ende so konfiguriert und angeordnet ist, dass es in ein Sensor-Lesegerät einschiebbar ist;

(b) ein zweites Substrat (508, 528, 548, 568, 583, 608, 648), das über dem ersten Substrat angeordnet ist, wobei die Arbeitselektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist und die Gegenelektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist;

(c) einen Abstandhalter (28, 504, 524, 544, 564, 581, 604, 644), der zwischen dem ersten und dem zweiten Substrat angeordnet ist und eine erste Öffnung längs der ersten Seitenkante des Sensors und eine zweite Öffnung entlang der zweiten Seitenkante des Sensors definiert, wobei die Probenkammer sich von der ersten Öffnung zu der zweiten Öffnung erstreckt; und

(d) wenigstens eine Anzeigeelektrode, die auf wenigstens einem von dem ersten und dem zweiten Substrat angeordnet ist und in Bezug auf entweder die Messzone oder die Probenkammer so angeordnet ist, dass festgestellt wird, wenn die Messzone oder Probenkammer Probe enthält.

5. Sensor nach irgendeinem der Ansprüche 1 bis 3, wobei der Sensor umfasst:

(a) ein erstes Substrat mit einem proximalen Ende und einem distalen Ende, wobei das distale Ende für ein Einschieben in ein Sensor-Lesegerät konfiguriert und angeordnet ist, wobei das erste Substrat eine erste Seitenkante und eine zweite Seitenkante des elektrochemischen Sensors definiert, die sich von dem proximalen Ende zu dem distalen Ende des ersten Substrats erstrecken;

(b) ein zweites Substrat, das über dem ersten Substrat angeordnet ist, wobei die Arbeitselektrode auf einem von dem ersten und dem zweiten Substrat angeordnet ist und die Gegenelektrode auf einem von dem ersten

Abbott Ex. 1002 - 405/1438

und dem zweiten Substrat angeordnet ist;
(c) einen Abstandshalter, der zwischen dem ersten und dem zweiten Substrat angeordnet ist und eine erste Öffnung längs des proximalen Endes des Sensors und eine zweite Öffnung längs der ersten Seitenkante des Sensors definiert, wobei sich die Probenkammer von der ersten Öffnung bis zu der zweiten Öffnung erstreckt; und
(d) wenigstens eine Anzeigeelektrode, die auf wenigstens einem von dem ersten und dem zweiten Substrat angeordnet ist und in Bezug auf entweder die Messzone oder die Probenkammer so angeordnet ist, dass festgestellt wird, wenn die Messzone oder die Probenkammer Probe enthält.

6. Sensor nach irgendeinem der Ansprüche 1 bis 3, wobei der Sensor eine Anzeigeelektrode umfasst, die in dem Sensor angeordnet ist, um anzuzeigen, wenn entweder die Messzone eine Probe enthält oder wenn die Probenkammer eine Probe enthält.

7. Sensor nach irgendeinem der Ansprüche 4 bis 6, wobei die Anzeigeelektrode auch eine Arbeitselektrode oder eine Gegenelektrode ist.

8. Sensor nach irgendeinem der Ansprüche 4 bis 7, der außerdem ein visuelles oder hörbares Zeichen umfasst, das mit der Anzeigeelektrode gekoppelt ist, das aktiviert wird, wenn die Anzeigeelektrode anzeigt, dass die Messzone oder die Probenkammer Probe enthält.

9. Sensor nach irgendeinem der Ansprüche 4 bis 8, wobei die Anzeigeelektrode gegenüber einer von der Arbeitselektrode und der Gegenelektrode angeordnet ist.

10. Sensor nach irgendeinem der Ansprüche 4 bis 9, wobei der Sensor wenigstens zwei Anzeigeelektroden umfasst, die in dem Sensor angeordnet sind, wobei eine erste Anzeigeelektrode anzeigt, wenn sich die Messzone oder die Probenkammer mit Probe zu füllen beginnt, und eine zweite Anzeigeelektrode anzeigt, wenn die Messzone oder die Probenkammer im Wesentlichen mit Probe gefüllt ist.

11. Sensor nach irgendeinem der Ansprüche 4 bis 9, wobei der Sensor wenigstens zwei Anzeigeelektroden umfasst, die in dem Sensor angeordnet sind, wobei zwei der Anzeigeelektroden eine erste Gegen/Anzeigeelektrode und eine zweite Gegen/Anzeigeelektrode umfassen, wobei die Gegenelektrode zwischen der ersten und der zweiten Gegen/Anzeigeelektrode angeordnet ist.

12. Sensor nach irgendeinem der Ansprüche 1 bis 11, wobei die Messzone und die Probenkammer das gleiche Volumen aufweisen.

13. Sensor nach irgendeinem der Ansprüche 1 bis 12, wobei der Analyt Glucose ist und das auf den Analyten entsprechende Enzym ein auf Glucose ansprechendes Enzym ist.

14. Sensor nach irgendeinem der Ansprüche 1 bis 12, wobei der Analyt ein Arzneimittel bzw. eine Droge ist.

15. Sensor nach irgendeinem der Ansprüche 1 bis 14, wobei die Messzone an wenigstens zwei Seiten durch die Arbeitselektrode und die Gegenelektrode begrenzt ist und die Arbeitselektrode und die Gegenelektrode gegebenenfalls ein sich gegenüberliegendes Elektrodenpaar bilden, wobei die Messzone zwischen der Arbeitselektrode und der Gegenelektrode angeordnet ist.

16. Sensor nach irgendeinem der Ansprüche 1 bis 15, wobei der Sensor so konfiguriert und angeordnet ist, dass der Mediator den Analyten oxidiert und das Halbwellenpotential des Redox-Mediators, gemessen durch zyklische Voltametrie in 0,1 M NaCl bei pH 7, nicht mehr als etwa +100 Millivolt bezogen auf das Potential der Gegen/Bezugs-Elektrode beträgt.

17. Sensor nach irgendeinem der Ansprüche 1 bis 16, wobei der Sensor so konfiguriert und angeordnet ist, dass der Mediator den Analyten oxidiert und das Halbwellenpotential des Redox-Mediators, gemessen durch zyklische Voltametrie in 0,1 M NaCl bei pH 7, etwa das gleiche ist wie das Potential der Gegen/Bezugs-Elektrode.

18. Sensor nach irgendeinem der Ansprüche 1 bis 17, wobei der Sensor so konfiguriert und angeordnet ist, dass der Mediator den Analyten oxidiert und das Halbwellenpotential des Redox-Mediators, gemessen durch zyklische Voltametrie in 0,1 M NaCl bei pH 7, nicht mehr als etwa -150 Millivolt bezogen auf das Potential der Gegen/Referenz-Elektrode beträgt.

Abbott Ex. 1002 - 406/1438

19. Sensor nach irgendeinem der Ansprüche 1 bis 18, wobei innerhalb des Sensors der effektive Diffusionskoeffizient des Redox-Mediators durch das Probenfluid geringer ist als der effektive Diffusionskoeffizient des Analyten durch das Probenfluid und vorzugsweise wenigstens 10-fach geringer ist als der effektive Diffusionskoeffizient des Analyten durch das Probenfluid.

20. Sensor nach irgendeinem der Ansprüche 1 bis 19, wobei der diffundierbare Mediator ein Molekulargewicht von wenigstens 5.000 Dalton aufweist.

21. Sensor nach irgendeinem der Ansprüche 1 bis 20, wobei der Sensor so konfiguriert und angeordnet ist, dass der Redox-Mediator leichter an der Arbeitselektrode elektrolysiert wird als an der Gegenelektrode.

22. Sensor nach irgendeinem der Ansprüche 1 bis 21, wobei der Sensor eine molare Menge des Redox-Mediators enthält, die auf einer stöchiometrischen Basis nicht mehr als eine mittlere normale physiologische Menge des Analyten beträgt, und der Sensor vorzugsweise eine molare Menge des Redox-Mediators umfasst, die auf einer stöchiometrischen Basis nicht mehr als 20% einer mittleren normalen physiologischen Menge des Analyten beträgt.

23. Sensor nach irgendeinem der Ansprüche 1 bis 22, wobei die Arbeitselektrode eine Oberfläche von nicht mehr als etwa 0,01 cm^2, die in der Messzone freiliegt, aufweist.

24. Sensor nach irgendeinem der Ansprüche 1 bis 23, wobei die Aktivität des Enzyms nicht mehr als 1 Einheit/cm^3 beträgt.

25. Sensor nach irgendeinem der Ansprüche 1 bis 24, wobei der Sensor so konfiguriert und angeordnet ist, dass der diffundierbare Redox-Mediator ausgefällt wird, wenn er an der Gegenelektrode reagiert hat.

26. Sensor nach irgendeinem der Ansprüche 1 bis 25, wobei der Sensor so konfiguriert und angeordnet ist, dass ein mathematisches Produkt des effektiven Diffusionskoeffizienten des Redox-Mediators und der Konzentration des Redox-Mediators nicht mehr als 1 x 10^{-12} Mol cm^{-1} s^{-1} beträgt, wenn Probenfluid die Messzone füllt.

27. Sensor nach irgendeinem der Ansprüche 1 bis 26, wobei der diffundierbare Redox-Mediator auf der Arbeitselektrode angeordnet ist.

28. Sensor nach irgendeinem der Ansprüche 1 bis 27, wobei das auf den Analyten ansprechende Enzym auf der Arbeitselektrode angeordnet ist.

29. Verfahren zur Bestimmung einer Konzentration eines Analyten in einer Probe, das die Schritte umfasst:

Inkontaktbringen einer Probe mit irgendeinem der elektrochemischen Sensoren der Ansprüche 1 bis 28;
Erzeugen eines Sensorsignals an der Arbeitselektrode und
Bestimmung der Konzentration des Analyten unter Verwendung des Sensorsignals.

30. Verfahren nach Anspruch 29, wobei das Hintergrundsignal, das durch den diffundierbaren Redox-Mediator erzeugt wird, nicht mehr ist als das Signal, das durch Oxidation oder Reduktion der mittleren normalen physiologischen Menge des Analyten erzeugt wird.

31. Verfahren nach irgendeinem der Ansprüche 29 bis 30, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Coulometrie unter Verwendung des Sensorsignals umfasst.

32. Verfahren nach irgendeinem der Ansprüche 29 bis 30, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Amperometrie unter Verwendung des Sensorsignals umfasst.

33. Verfahren nach irgendeinem der Ansprüche 29 bis 30, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Potentiometrie unter Verwendung des Sensorsignals umfasst.

34. Verfahren nach irgendeinem der Ansprüche 29 bis 30, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch Chronoamperometrie unter Verwendung des Sensorsignals umfasst.

35. Verfahren nach irgendeinem der Ansprüche 29 bis 30, wobei die Bestimmung der Konzentration des Analyten die

Abbott Ex. 1002 - 407/1438

Bestimmung der Konzentration des Analyten durch Chronopotentiometrie unter Verwendung des Sensorsignals umfasst.

36. Verfahren nach irgendeinem der Ansprüche 29 bis 30, wobei die Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten durch eine Cottrell-Messtechnik unter Verwendung des Sensorsignals umfasst.

37. Verfahren nach irgendeinem der Ansprüche 29 bis 36, das außerdem umfasst:

Bereitstellung von Eichdaten für eine Liefermenge von elektrochemischen Sensoren in einem Messinstrument, wobei die Eichdaten eine Information umfassen, die einen Bezug zu einer Größe für eine Hintergrundladung für die Liefermenge der elektrochemischen Sensoren aufweist;
wobei die Stufe der Bestimmung der Konzentration des Analyten die Bestimmung der Konzentration des Analyten unter Verwendung des Sensorsignals und der Eichdaten umfasst.

38. Verfahren zur Bestimmung einer Konzentration eines Analyten in einer Probe, wobei das Verfahren die Schritte umfasst:

Inkontaktbringen einer Probe mit irgendeinem der elektrochemischen Sensoren der Ansprüche 1 bis 28;
Beobachten eines Signals von der Anzeigeelektrode, das anzeigt, dass die Messzone Probe enthält;
Anlegen eines Potentials zwischen der Arbeitselektrode und der Gegenelektrode, um den Analyten in der Probe zu elektrolysieren;
Erzeugung eines auf den Analyten ansprechenden Signals durch den Sensor in Reaktion auf die Elektrolyse des Analyten in der Probe; und
Bestimmen der Konzentration des Analyten unter Verwendung des auf den Analyten ansprechenden Signals.

39. Verfahren zur Herstellung irgendeines der elektrochemischen Sensoren der Ansprüche 1 bis 28, wobei das Verfahren umfasst:

(a) Ausbilden einer Mehrzahl von Arbeitselektroden auf einem ersten Substrat;
(b) Ausbilden einer Mehrzahl von Gegenelektroden auf einem zweiten Substrat;
(c) Anordnen einer Abstandshalterschicht auf einem von dem ersten und dem zweiten Substrat;
(d) Entfernen eines Teils der Abstandshalterschicht, um Bereiche der Probenkammer zu definieren;
(e) Bildung eines Laminats aus dem ersten und dem zweiten Substrat; und
(f) Abtrennen einer Mehrzahl von elektrochemischen Sensoren von den laminierten Substraten, wobei jeder elektrochemische Sensor wenigstens eine von den Arbeitselektroden, wenigstens eine von den Gegenelektroden und wenigstens einen von den Probenkammerbereichen umfasst.

40. Verfahren nach Anspruch 39, wobei das erste Substrat ein erster Bereich eines Substrats ist und das zweite Substrat ein zweiter Bereich des Substrats ist, und das außerdem umfasst:

Falten des Substrats, so dass sich die ersten und zweiten Bereiche des Substrats überlagern.

41. Verfahren nach irgendeinem der Ansprüche 39 und 40, wobei das Abtrennen der Mehrzahl von elektrochemischen Sensoren das Schneiden des ersten und zweiten Substrats umfasst, um die elektrochemischen Sensoren herauszutrennen und wenigstens ein Ende der Probenkammer der elektrochemischen Sensoren zu definieren.

42. Verfahren nach irgendeinem der Ansprüche 39 bis 41, das außerdem das Bilden einer Mehrzahl von Anzeigeelektroden auf einem von dem ersten und zweiten Substrat umfasst.

43. Verfahren nach irgendeinem der Ansprüche 39 bis 42, wobei der Abschnitt der Abstandshalterschicht entfernt wird, um die Probenkammerbereiche zu definieren, nachdem die Abstandshalterschicht auf einem von dem ersten und zweiten Substrat angeordnet ist.

Revendications

1. Détecteur (20) pour déterminer la concentration d'une substance à analyser dans un échantillon de fluide, le détecteur

Abbott Ex. 1002 - 408/1438

comprenant :

une paire d'électrodes comprenant une électrode à étudier (22, 502, 522, 542, 562, 580, 602, 642, 1010) et une contre-électrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), dans lequel au moins une partie de l'électrode à étudier se trouve à une distance efficace inférieure à 200 μm d'une partie de la contre-électrode, et dans lequel, optionnellement, la contre-électrode est une contre-électrode/une électrode de référence ;
une électrode de référence optionnelle (512, 532, 552, 572, 585, 612, 652) ;
une chambre d'échantillonnage (26, 526, 546, 566, 582, 606, 646) pour maintenir l'échantillon de fluide en contact électrolytique avec l'électrode à étudier, la contre-électrode, et l'électrode de référence, si elle est présente, la chambre d'échantillonnage comprenant une zone de mesure adjacente à l'électrode à étudier, à la contre-électrode, et à l'électrode de référence, si elle est présente, dans lequel la zone de mesure est formée pour contenir un volume inférieur à environ 1 μL d'échantillon de fluide et dans lequel, optionnellement, la chambre d'échantillonnage est formée pour contenir moins de 1 μL environ de fluide d'échantillonnage ; et
une enzyme réactive à la substance à analyser et un médiateur de redox diffusable disposé dans la zone de mesure ;
le détecteur ayant été configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable ne soit pas supérieur au signal généré par oxydation ou réduction de la quantité physiologique normale moyenne d'analyte.

2. Détecteur (20) pour déterminer la concentration du glucose de la substance à analyser dans un échantillon de fluide, le détecteur comprenant :

une paire d'électrodes comprenant une électrode à étudier (22, 502, 522, 542, 562, 580, 602, 642, 1010) et une contre-électrode (24, 510, 530, 550, 570, 584, 610, 650, 1020), dans lequel l'électrode à étudier et la contre-électrode sont séparées par une distance efficace de l'ordre de 25 à 1000 μm ;
une chambre d'échantillonnage (26, 526, 546, 566, 582, 606, 646) pour contenir l'échantillon de fluide, la chambre d'échantillonnage comprenant une zone de mesure adjacente à l'électrode à étudier et à la contre-électrode, la zone de mesure et la chambre d'échantillonnage étant dimensionnées pour contenir un volume inférieur à environ 1 μL d'échantillon ; et
une enzyme réactive à la substance à analyser et un médiateur de redox diffusable disposés dans la zone de mesure ;
le détecteur ayant été configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable ne soit pas supérieur à cinq fois un signal généré par l'oxydation ou la réduction de 5 mM de glucose et au signal généré par oxydation ou réduction de la quantité physiologique normale moyenne d'analyte.

3. Détecteur selon l'une quelconque des revendications 1 et 2, dans lequel le détecteur est configuré et agencé de telle sorte qu'un signal de réaction généré par le médiateur de redox diffusable soit inférieur à 25% du signal généré par l'oxydation ou la réduction de la substance à analyser et , de préférence, inférieur à 5% du signal généré par l'oxydation ou la réduction de la substance à analyser.

4. Détecteur selon l'une quelconque des revendications 1 à 3, dans lequel le détecteur comprend :

(a) un premier substrat (500, 520, 560, 579, 600, 640) possédant une extrémité proximale et une extrémité distale, le premier substrat définissant un premier bord latéral (656) et un deuxième bord latéral (658) du détecteur électrochimique s'étendant de l'extrémité proximale jusqu'à l'extrémité distale du premier substrat, l'extrémité distale étant configurée et agencée pour être insérée dans un lecteur de détecteur ;
(b) un deuxième substrat (508, 528, 548, 568, 583, 608, 648) disposé sur le premier substrat, l'électrode à étudier étant disposée sur l'un des premier et deuxième substrats et la contre-électrode étant disposée sur l'un des premier et deuxième substrats ;
(c) une entretoise (28, 504, 524, 544, 564, 581, 604, 644) disposée entre le premier et le deuxième substrats et définissant une première ouverture le long du premier bord latéral du détecteur et une deuxième ouverture le long du deuxième bord latéral du détecteur, la chambre d'échantillonnage s'étendant de la première ouverture jusqu'à la deuxième ouverture ; et
(d) au moins une électrode indicatrice disposée au moins sur l'un des premier et deuxième substrats et positionnée par rapport à la zone de mesure ou à la chambre d'échantillonnage afin de déterminer le moment auquel la zone de mesure ou la chambre d'échantillonnage contient l'échantillon.

5. Détecteur selon l'une quelconque des revendications 1 à 3, dans lequel le détecteur comprend :

Abbott Ex. 1002 - 409/1438

(a) un premier substrat possédant une extrémité proximale et une extrémité distale, l'extrémité distale étant configurée et agencée pour être insérée dans un lecteur de détecteur, le premier substrat définissant un premier bord latéral et un deuxième bord latéral du détecteur électrochimique s'étendant de l'extrémité proximale jusqu'à l'extrémité distale du premier substrat ;

(b) un deuxième substrat disposé sur le premier substrat, l'électrode à étudier étant disposée sur l'un des premier et deuxième substrats et la contre-électrode étant disposée sur l'un des premier et deuxième substrats ;

(c) une entretoise disposée entre le premier et le deuxième substrats et définissant une première ouverture le long de l'extrémité proximale du détecteur et une deuxième ouverture le long du premier bord latéral du détecteur, la chambre d'échantillonnage s'étendant de la première ouverture jusqu'à la deuxième ouverture ; et

(d) au moins une électrode indicatrice disposée au moins sur l'un des premier et deuxième substrats et positionnée par rapport à la zone de mesure ou à la chambre d'échantillonnage afin de déterminer le moment auquel la zone de mesure ou la chambre d'échantillonnage contient l'échantillon.

6. Détecteur selon l'une quelconque des revendications 1 à 3, dans lequel le détecteur comprend une électrode indicatrice disposée dans le détecteur afin d'indiquer le moment auquel la zone de mesure contient un échantillon, ou le moment auquel la chambre d'échantillonnage contient un échantillon.

7. Détecteur selon l'une quelconque des revendications 4 à 6, dans lequel l'électrode indicatrice est également une électrode à étudier ou une contre-électrode.

8. Détecteur selon l'une quelconque des revendications 4 à 7, comprenant en outre un signe visuel ou sonore, couplé à l'électrode indicatrice, qui s'active lorsque l'électrode indicatrice indique que la zone de mesure ou la chambre d'échantillonnage contient l'échantillon.

9. Détecteur selon l'une quelconque des revendications 4 à 8, dans lequel l'électrode indicatrice est disposée face à l'une de l'électrode à étudier et de la contre-électrode.

10. Détecteur selon l'une quelconque des revendications 4 à 9, dans lequel le détecteur comprend au moins deux électrodes indicatrices disposées dans le détecteur, dans lequel une première électrode indicatrice indique le moment auquel la zone de mesure ou la chambre d'échantillonnage commence à se remplir d'échantillon, et dans lequel une deuxième électrode indicatrice indique le moment auquel la zone de mesure ou la chambre d'échantillonnage est sensiblement remplie d'échantillon.

11. Détecteur selon l'une quelconque des revendications 4 à 9, dans lequel le détecteur comprend au moins deux électrodes indicatrices disposées dans le détecteur, dans lequel deux des électrodes indicatrices comprennent une première contre-électrode/électrode indicatrice et une deuxième contre-électrode/électrode indicatrice avec la contre-électrode disposée entre les première et deuxième contre-électrodes/électrodes indicatrices.

12. Détecteur selon l'une quelconque des revendications 1 à 11, dans lequel la zone de mesure et la chambre d'échantillonnage possèdent un volume identique.

13. Détecteur selon l'une quelconque des revendications 1 à 12, dans laquelle la substance à analyser est du glucose et l'enzyme réactive à la substance à analyser est une enzyme réactive au glucose.

14. Détecteur selon l'une quelconque des revendications 1 à 12, dans lequel la substance à analyser est un médicament.

15. Détecteur selon l'une quelconque des revendications 1 à 14, dans lequel la zone de mesure est reliée sur au moins deux côtés par l'électrode à étudier et la contre-électrode, et dans lequel, optionnellement, l'électrode à étudier et la contre-électrode forment une paire d'électrodes se faisant face avec la zone de mesure positionnée entre l'électrode à étudier et la contre-électrode.

16. Détecteur selon l'une quelconque des revendications 1 à 15, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur oxyde la substance à analyser et que le potentiel e demi-onde du médiateur de redox, mesuré par voltamétrie dans 0,1 M de NaCl à un pH de 7, soit inférieur à environ $\pm$100 millivolts par rapport au potentiel de la contre-électrode/de l'électrode de référence.

17. Détecteur selon l'une quelconque des revendications 1 à 16, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur oxyde la substance à analyser et que le potentiel de demi-onde du médiateur de redox,

Abbott Ex. 1002 - 410/1438

mesuré par voltamétrie dans 0,1 M de NaCl à un pH de 7, soit à peu près identique au potentiel de la contre-électrode/de l'électrode de référence.

18. Détecteur selon l'une quelconque des revendications 1 à 17, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur oxyde la substance à analyser et que le potentiel de demi-onde du médiateur de redox, mesuré par voltamétrie dans 0,1 M de NaCl à un pH de 7, soit à peu près inférieur à environ -150 millivolts par rapport au potentiel de la contre-électrode/de l'électrode de référence.

19. Détecteur selon l'une quelconque des revendications 1 à 18, dans lequel, dans le détecteur, le coefficient effectif de diffusion du médiateur de redox dans l'échantillon de fluide est inférieur au coefficient effectif de diffusion de la substance à analyser dans l'échantillon de fluide et, de préférence, au moins dix fois inférieur au coefficient effectif de diffusion de la substance à analyser dans l'échantillon de fluide.

20. Détecteur selon l'une quelconque des revendications 1 à 19, dans lequel le médiateur diffusable possède un poids moléculaire d'au moins 5000 daltons.

21. Détecteur selon l'une quelconque des revendications 1 à 20, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur de redox soit plus facilement électrolysé sur l'électrode à étudier que sur la contre-électrode.

22. Détecteur selon l'une quelconque des revendications 1 à 21, dans lequel le détecteur comprend une quantité molaire de médiateur de redox qui est, sur une base stoechiométrique, inférieure à une quantité physiologique normale moyenne de substance à analyser et dans lequel, de préférence, le détecteur comprend une quantité molaire de médiateur de redox qui est, sur une base stoechiométrique, inférieure à 20% d'une quantité physiologique normale moyenne de substance à analyser.

23. Détecteur selon l'une quelconque des revendications 1 à 22, dans lequel l'électrode à étudier possède une surface inférieure à environ 0,01 cm^2 exposée dans la zone de mesure.

24. Détecteur selon l'une quelconque des revendications 1 à 23, dans lequel l'activité de l'enzyme est inférieure à 1 unité/cm^3.

25. Détecteur selon l'une quelconque des revendications 1 à 24, dans lequel le détecteur est configuré et agencé de telle sorte que le médiateur de redox diffusable se précipite lorsqu'il est réagi sur la contre-électrode.

26. Détecteur selon l'une quelconque des revendications 1 à 25, dans lequel le détecteur est configuré et agencé de telle sorte qu'un produit mathématique du coefficient effectif de diffusion du médiateur de redox et que la concentration en médiateur de redox soient inférieurs à 1 x 10^{-12} moles cm^{-1} sec^{-1} lorsque l'échantillon de fluide remplit la zone de mesure.

27. Détecteur selon l'une quelconque des revendications 1 à 26, dans lequel le médiateur de redox diffusable est disposé sur l'électrode à étudier.

28. Détecteur selon l'une quelconque des revendications 1 à 27, dans lequel l'enzyme réactive à la substance à analyser est disposée sur l'électrode à étudier.

29. Procédé pour déterminer une concentration d'une substance à analyser dans un échantillon, comprenant les étapes consistant à :

mettre en contact un échantillon avec n'importe lequel des détecteurs électrochimiques des revendications 1 à 28 ;
générer un signal de détecteur au niveau de l'électrode à étudier, et
à déterminer la concentration de la substance à analyser en utilisant le signal du détecteur.

30. Procédé selon la revendication 29, dans lequel le signal de réaction qui est généré par le médiateur de redox diffusable n'est pas supérieur au signal généré par oxydation ou réduction de la quantité physiologique normale d'analyte.

Abbott Ex. 1002 - 411/1438

31. Procédé selon l'une quelconque des revendications 29 à 30, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par coulométrie en utilisant le signal du détecteur.

32. Procédé selon l'une quelconque des revendications 29 à 30, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par ampérométrie en utilisant le signal du détecteur.

33. Procédé selon l'une quelconque des revendications 29 à 30, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par potentiométrie en utilisant le signal du détecteur.

34. Procédé selon l'une quelconque des revendications 29 à 30, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par chronoampèremétrie en utilisant le signal du détecteur.

35. Procédé selon l'une quelconque des revendications 29 à 30, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par chronopotentiométrie en utilisant le signal du détecteur.

36. Procédé selon l'une quelconque des revendications 29 à 30, dans lequel la détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser par une technique de mesure de Cotrell en utilisant le signal du détecteur.

37. Procédé selon l'une quelconque des revendications 29 à 36, comprenant en outre :

la fourniture de données d'étalonnage concernant un lot de détecteurs électrochimiques à un instrument de mesure, lesdites données d'étalonnage comprenant des informations liées à l'ampleur d'une charge de réaction relative au lot de détecteurs électrochimiques ;
dans lequel l'étape de détermination de la concentration de la substance à analyser comprend la détermination de la concentration de la substance à analyser en utilisant le signal du détecteur et les données d'étalonnage.

38. Procédé de détermination d'une concentration d'une substance à analyser dans un échantillon, le procédé comprenant les étapes consistant à :

mettre en contact un échantillon avec n'importe lequel des détecteurs électrochimiques des revendications 1 à 28;
observer un signal de l'électrode indicatrice signifiant que la zone de mesure contient l'échantillon ;
appliquer un potentiel entre l'électrode à étudier et la contre-électrode afin d'électrolyser la substance à analyser dans l'échantillon ;
générer un signal réactif à la substance à analyser provenant du détecteur en réponse à l'électrolyse de la substance à analyser dans l'échantillon ; et
à déterminer la concentration de la substance à analyser en utilisant le signal réactif à la substance à analyser.

39. Procédé de fabrication de n'importe lequel des détecteurs électrochimiques des revendications 1 à 28, le procédé comprenant :

(a) la formation d'une pluralité d'électrodes à étudier sur un premier substrat ;
(b) la formation d'une pluralité de contre-électrodes sur un deuxième substrat ;
(c) l'agencement d'une couche d'espacement sur l'un des premier et deuxième substrats ;
(d) le retrait d'une partie de la couche d'espacement afin de définir des régions de chambre d'échantillonnage ;
(e) la stratification des premier et deuxième substrats ensemble ; et
(f) la séparation d'une pluralité de détecteurs électrochimiques des substrats stratifiés, chaque détecteur électrochimique comprenant au moins l'une des électrodes à étudier, au moins l'une des contre-électrodes, et au moins l'une des régions de chambre d'échantillonnage.

40. Procédé selon la revendication 39, dans lequel le premier substrat est une première région d'un substrat et le deuxième substrat est une deuxième région du substrat, et comprenant en outre :

Abbott Ex. 1002 - 412/1438

le pliage du substrat afin de chevaucher les première et deuxième régions du substrat.

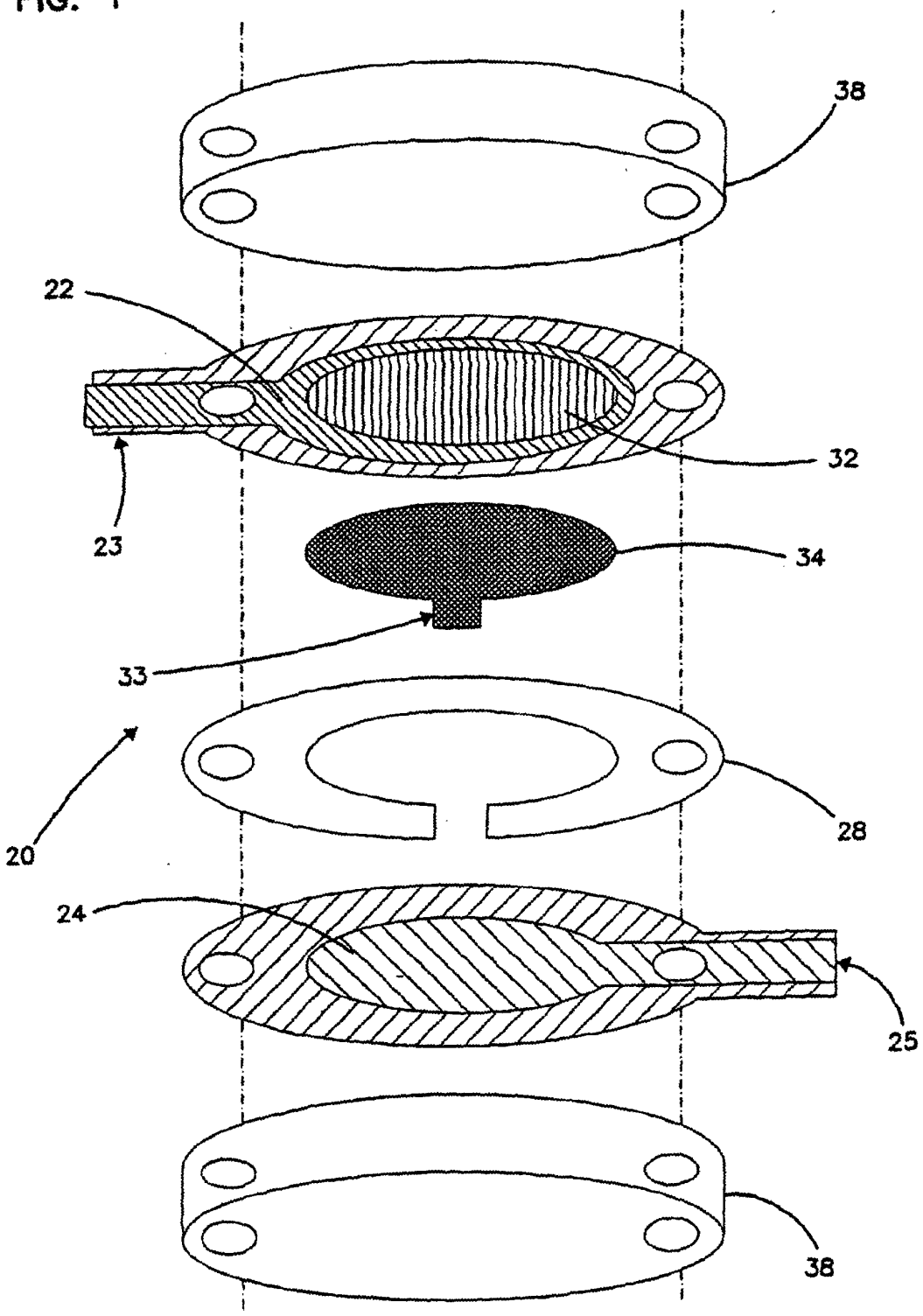
41. Procédé selon l'une quelconque des revendications 39 et 40, dans lequel la séparation de la pluralité de détecteurs électrochimiques comprend le découpage des premier et deuxième substrats afin de séparer les détecteurs électrochimiques et de définir au moins une extrémité de la chambre d'échantillonnage des détecteurs électrochimiques.

42. Procédé selon l'une quelconque des revendications 39 à 41, comprenant en outre la formation d'une pluralité d'électrodes indicatrices sur l'un des premier et deuxième substrats.

43. Procédé selon l'une quelconque des revendications 39 à 42, dans lequel la partie de la couche d'espacement est retirée afin de définir les régions de la chambre d'échantillonnage après que la couche d'espacement ait été disposée sur l'un des premier et deuxième substrats.

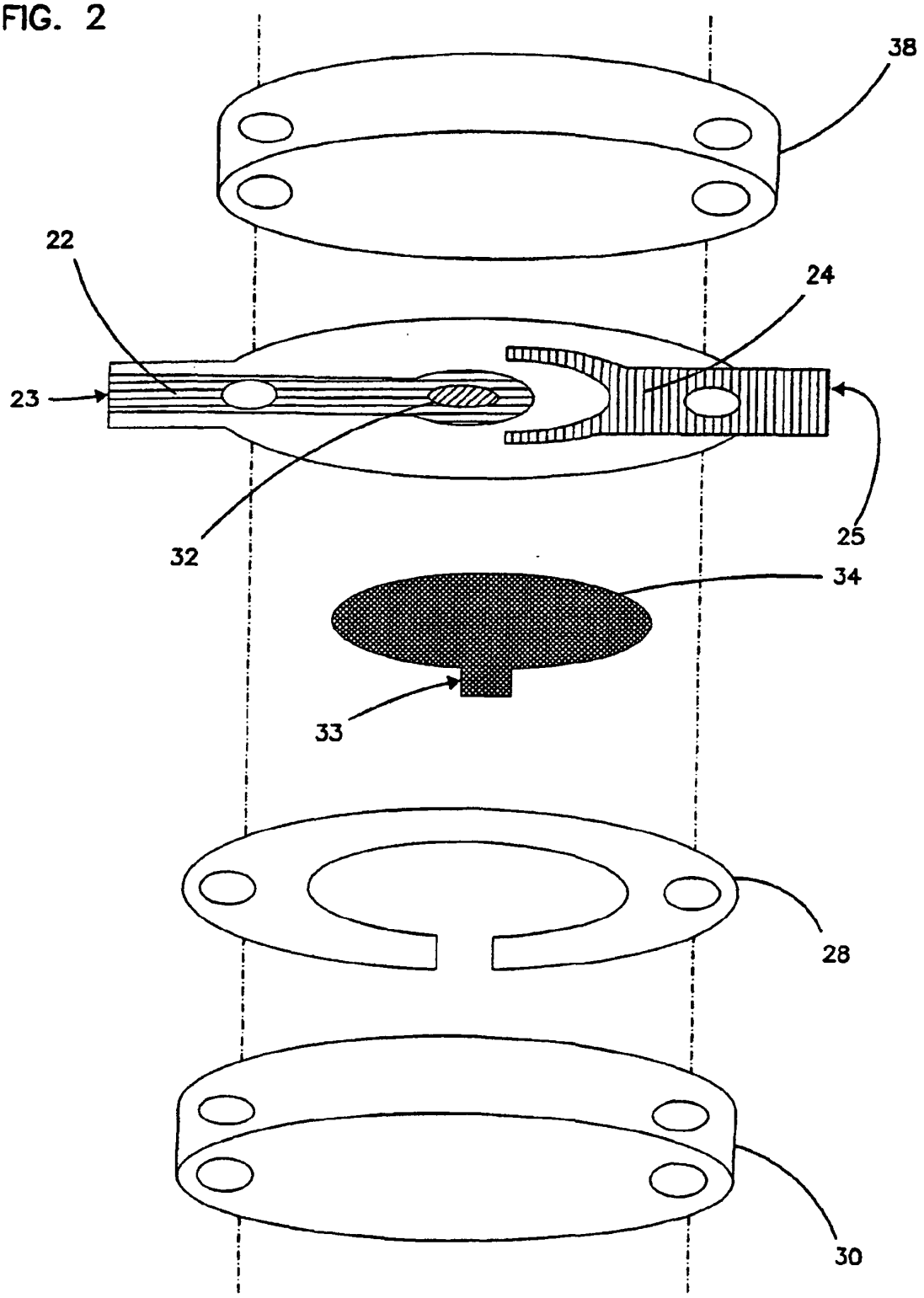
Abbott Ex. 1002 - 413/1438

FIG. 1



Abbott Ex. 1002 - 414/1438

FIG. 2



Abbott Ex. 1002 - 415/1438

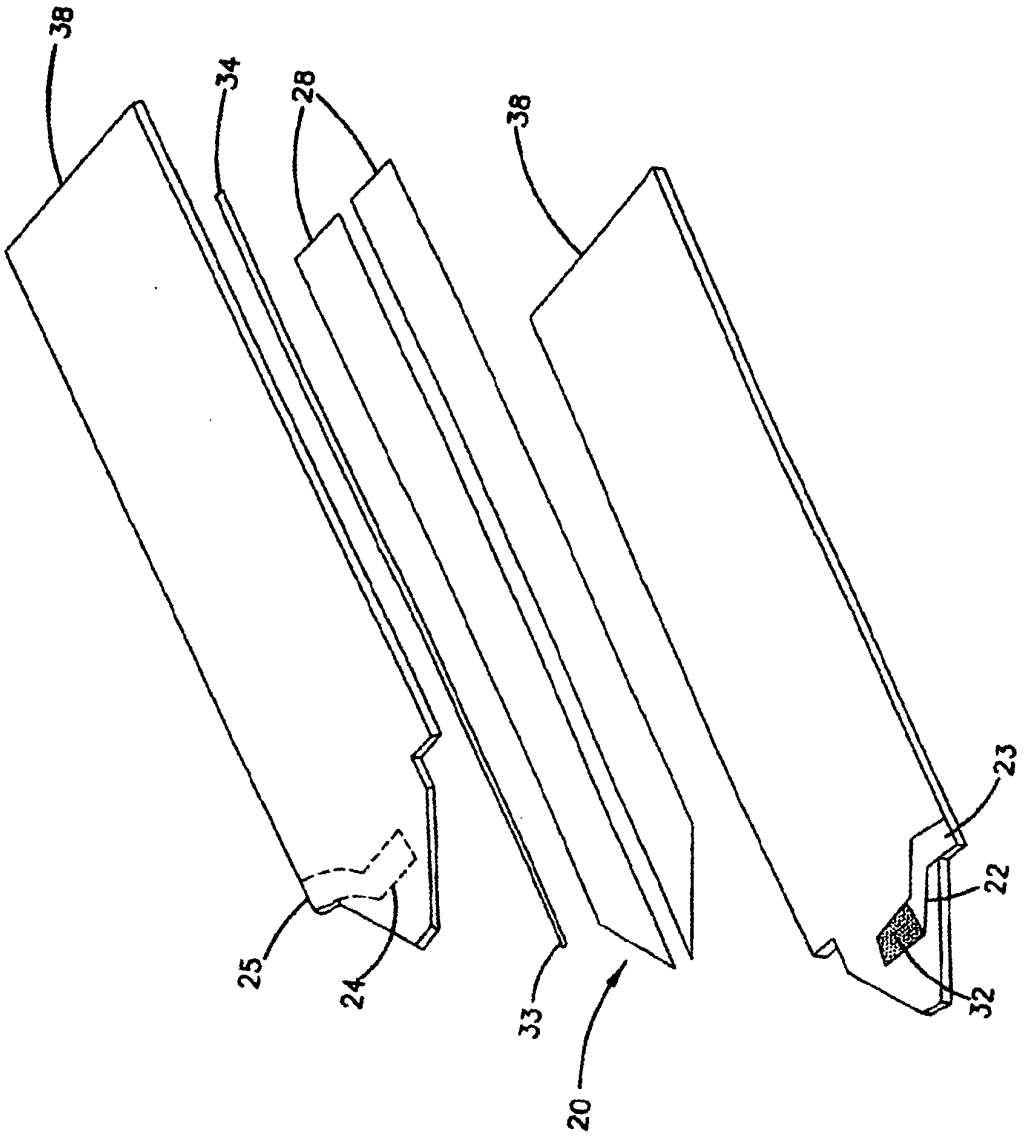


FIG. 3

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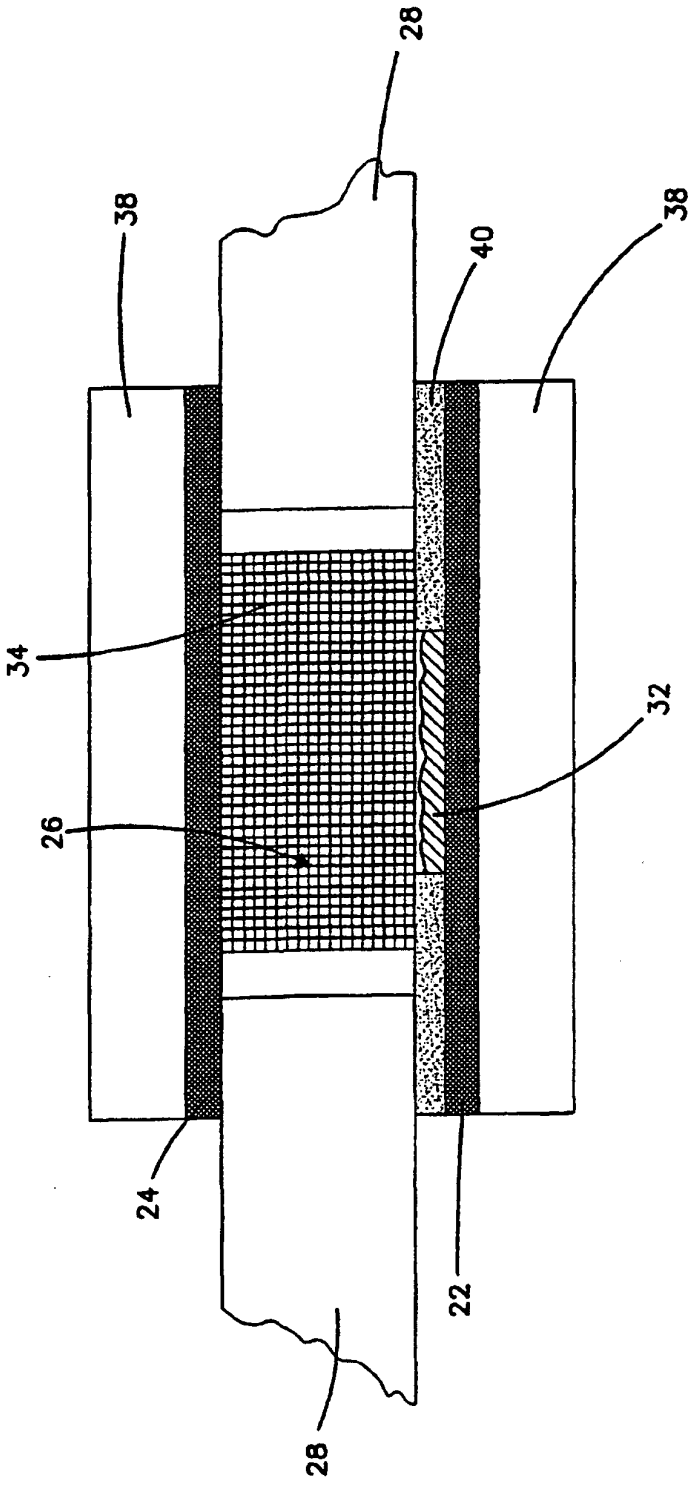
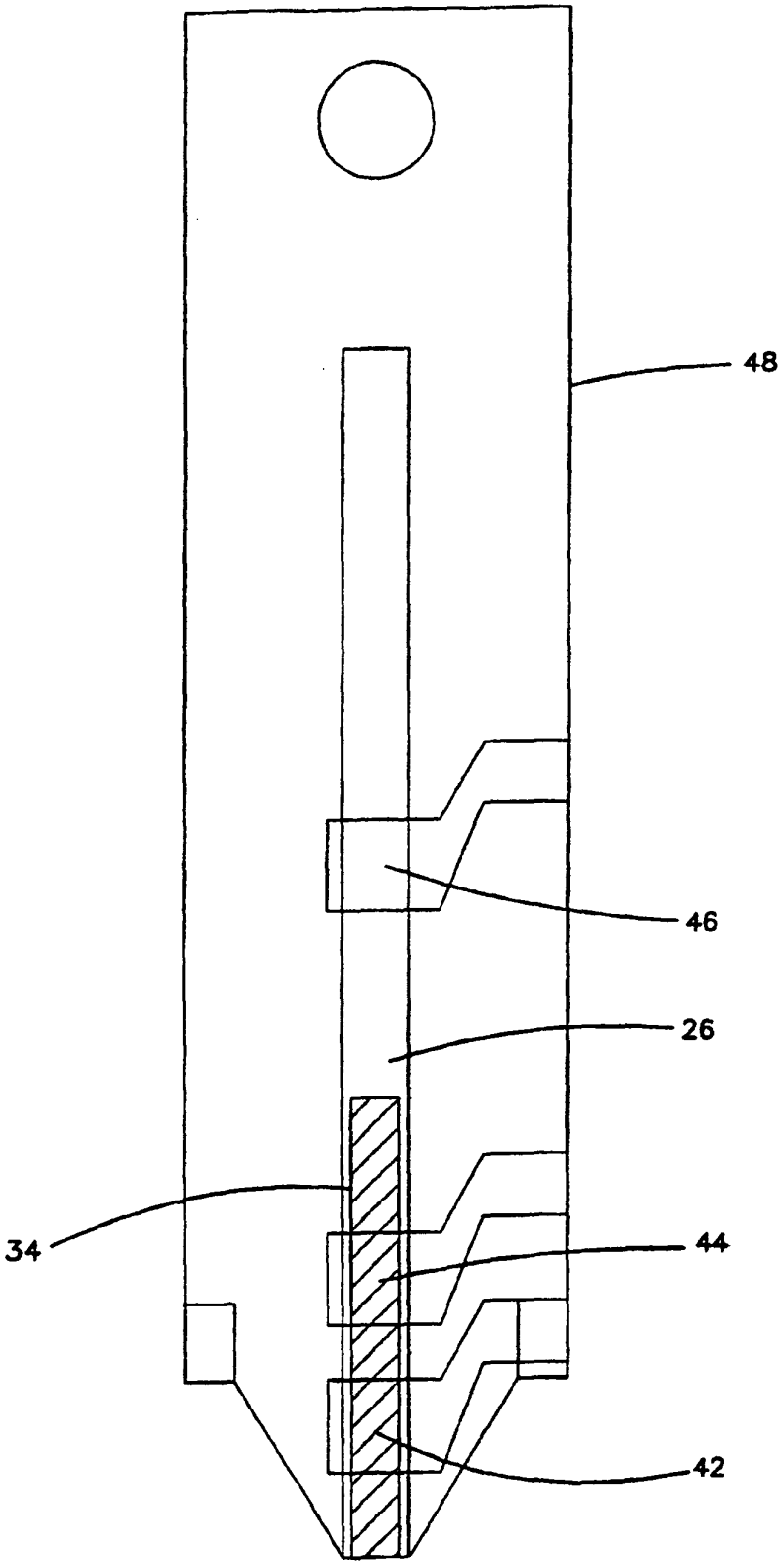


FIG. 4

Abbott Ex. 1002 - 417/1438

FIG. 5



Abbott Ex. 1002 - 418/1438

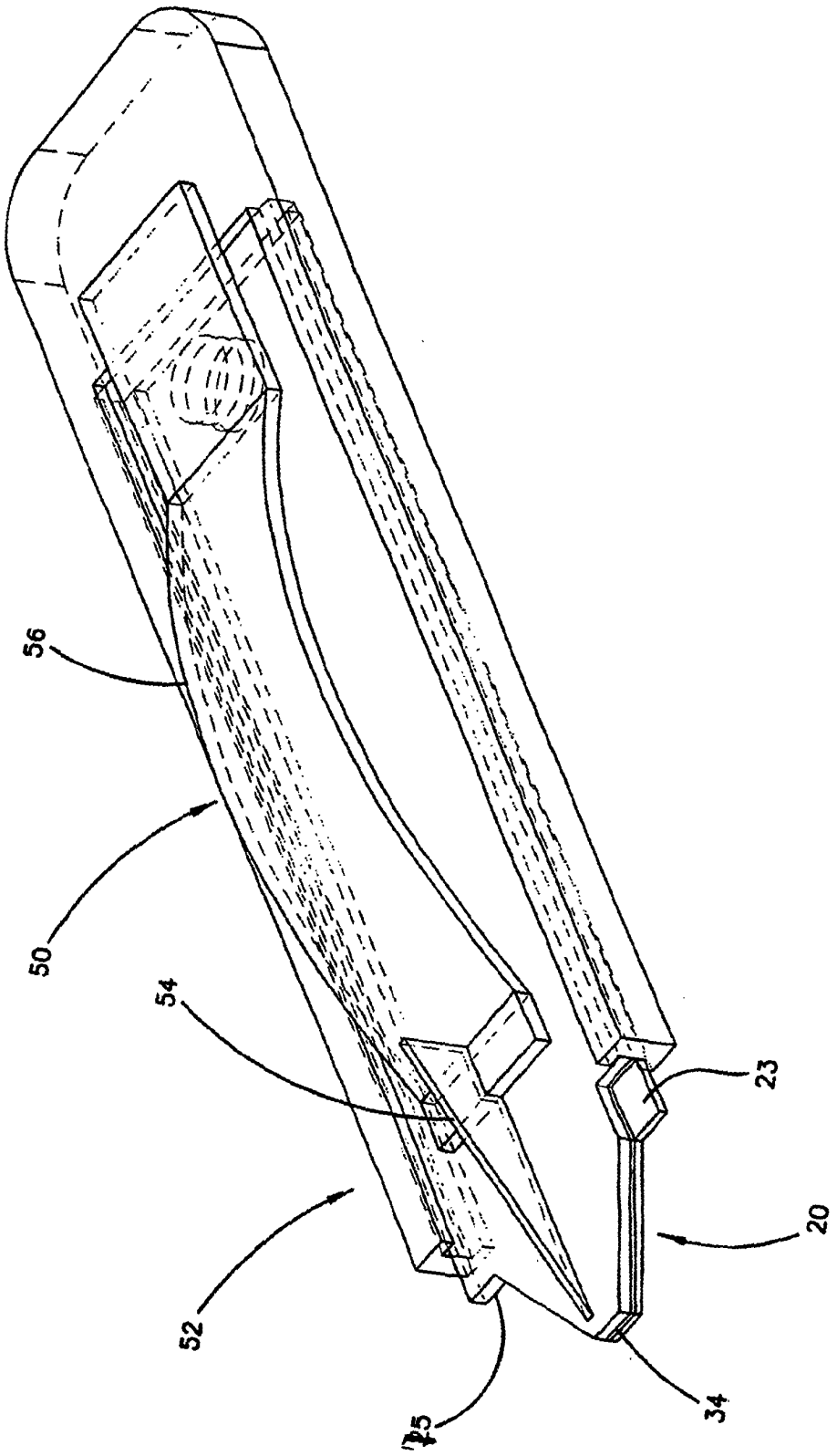
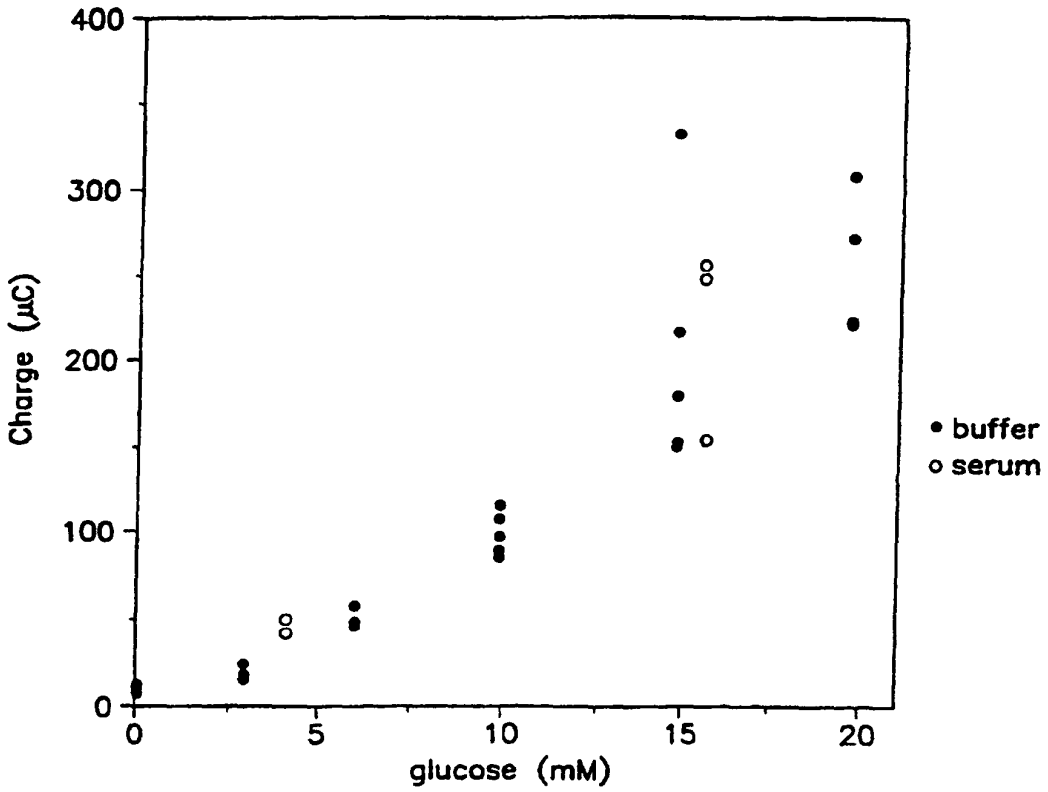


FIG. 6

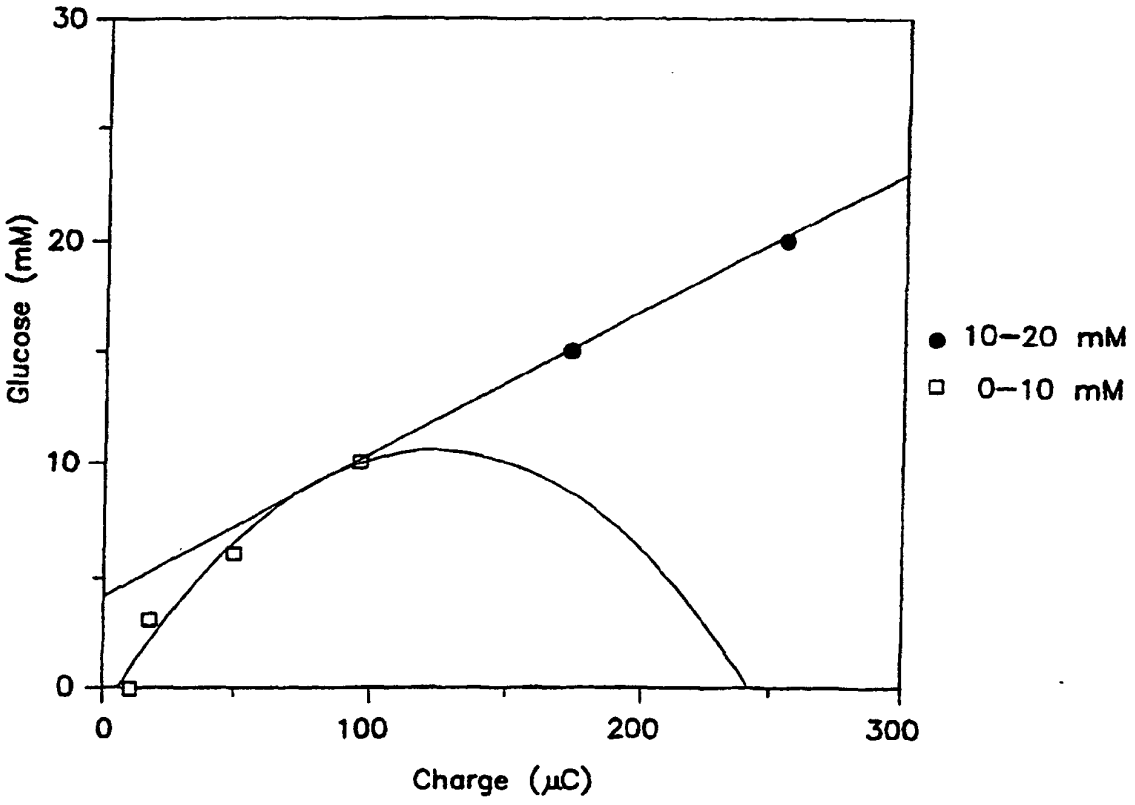
Abbott Ex. 1002 - 419/1438

FIG. 7



Abbott Ex. 1002 - 420/1438

FIG. 8



Abbott Ex. 1002 - 421/1438

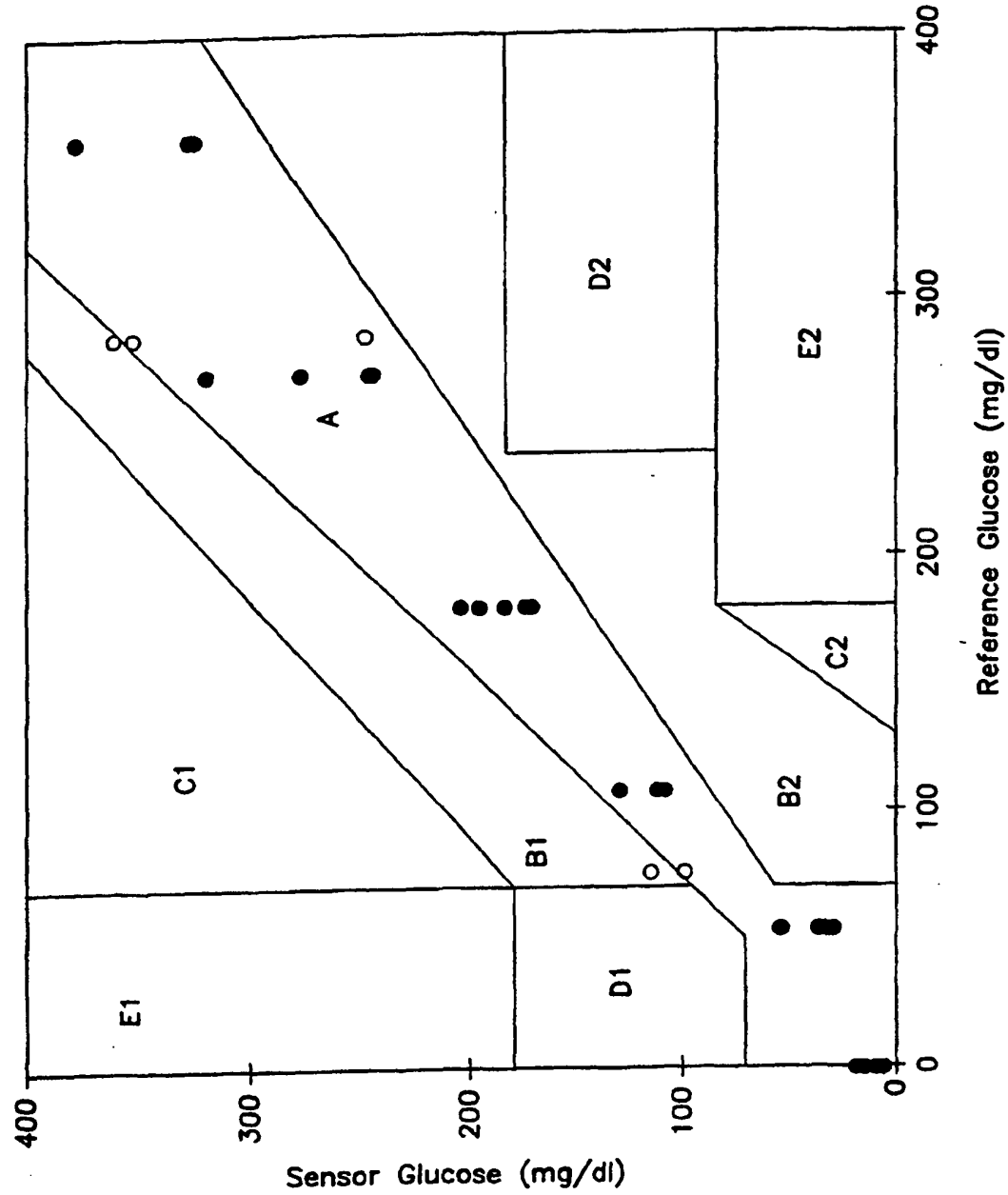
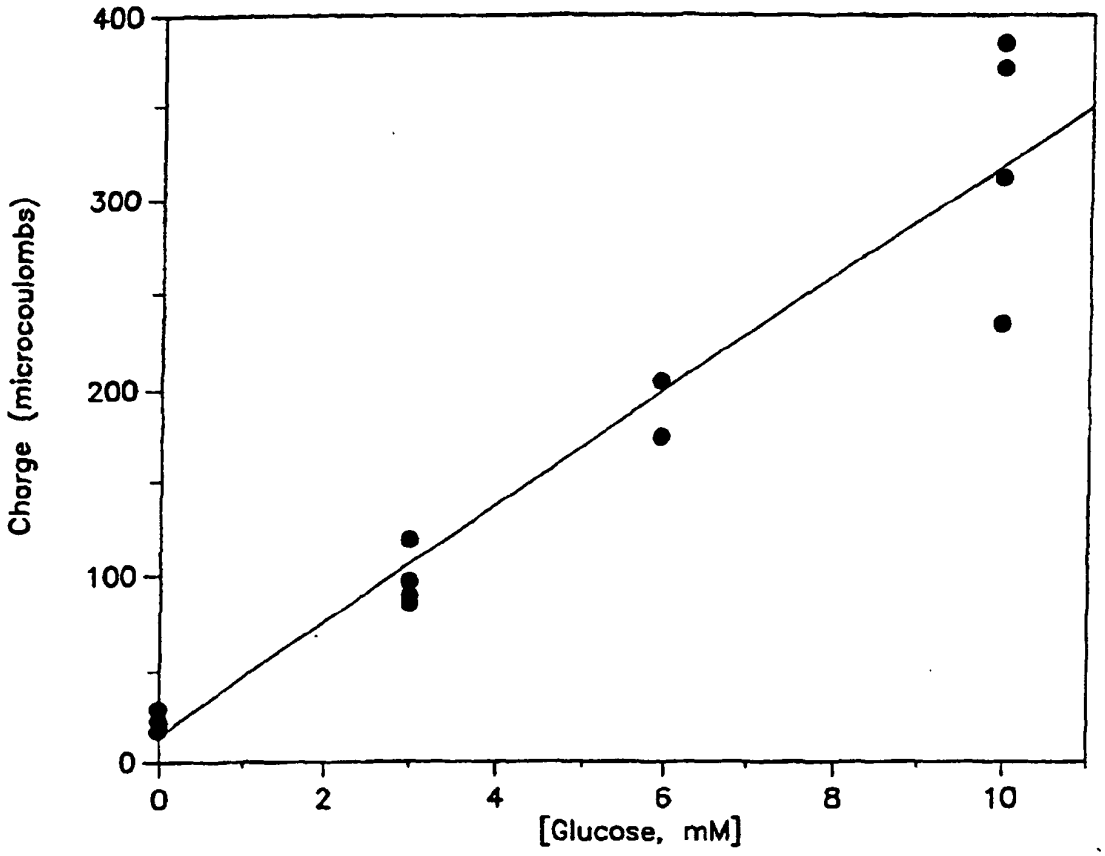


FIG. 9

Abbott Ex. 1002 - 422/1438

FIG. 10



Abbott Ex. 1002 - 423/1438

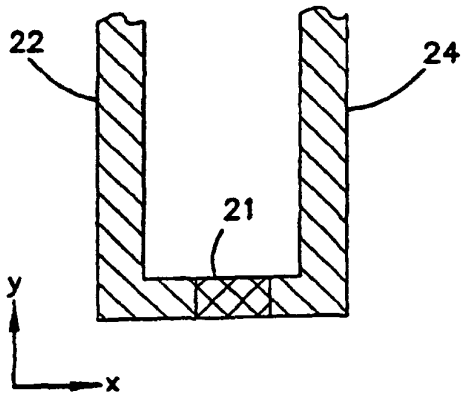


FIG. 11A

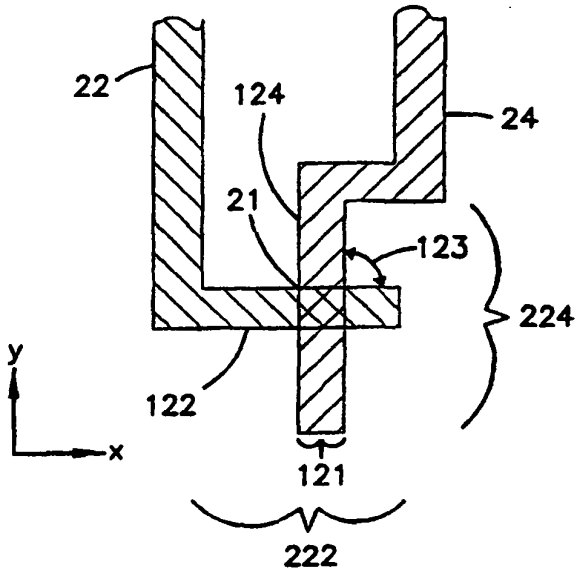


FIG. 11B

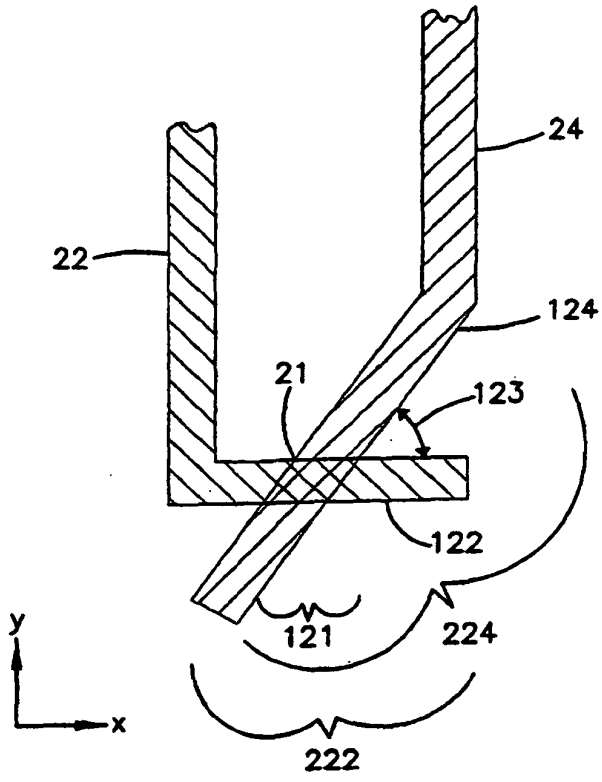


FIG. 11C

Abbott Ex. 1002 - 424/1438

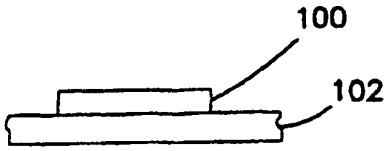


FIG. 12A

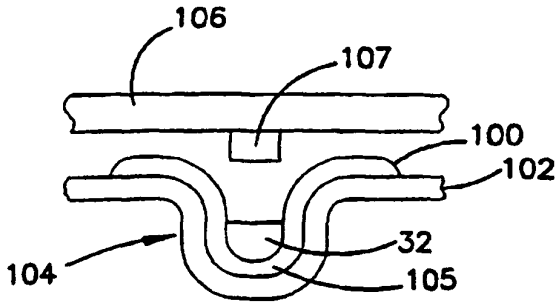


FIG. 12B

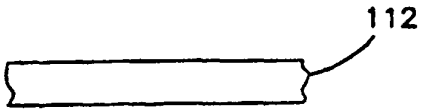


FIG. 13A

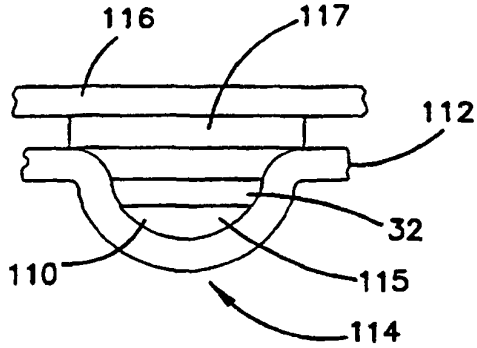


FIG. 13B

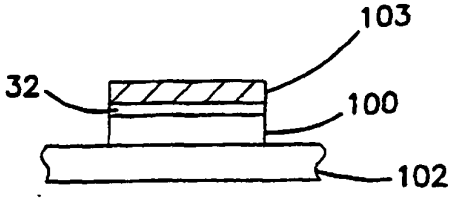


FIG. 14A

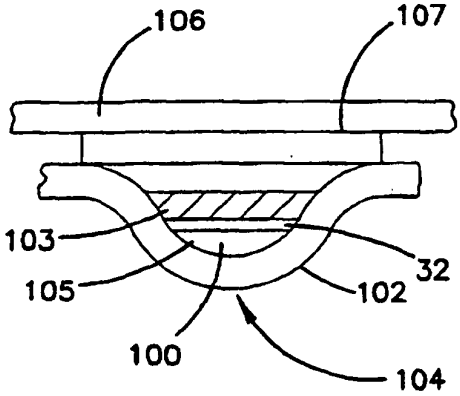
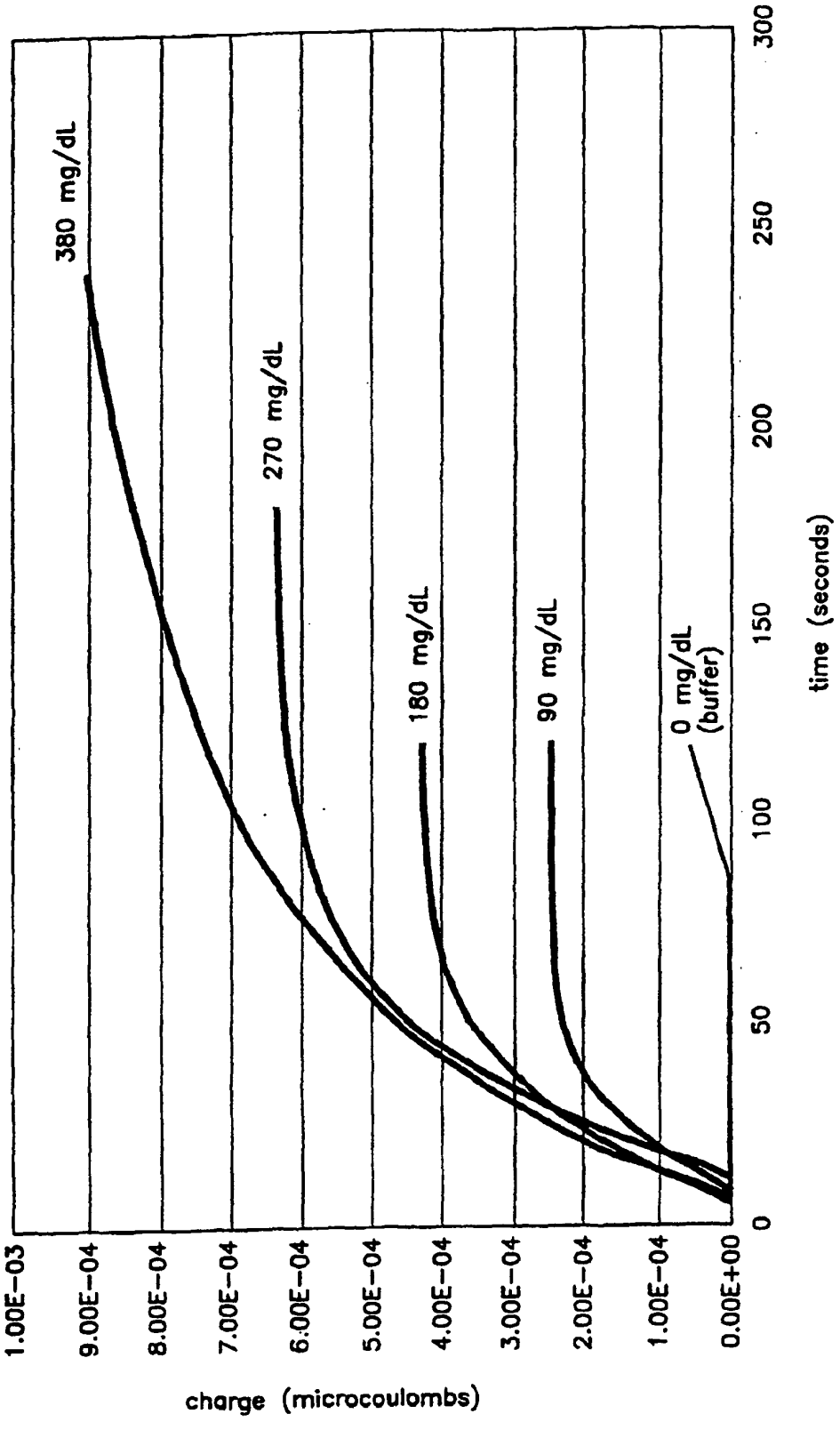


FIG. 14B

Abbott Ex. 1002 - 425/1438

FIG. 15



Abbott Ex. 1002 - 426/1438

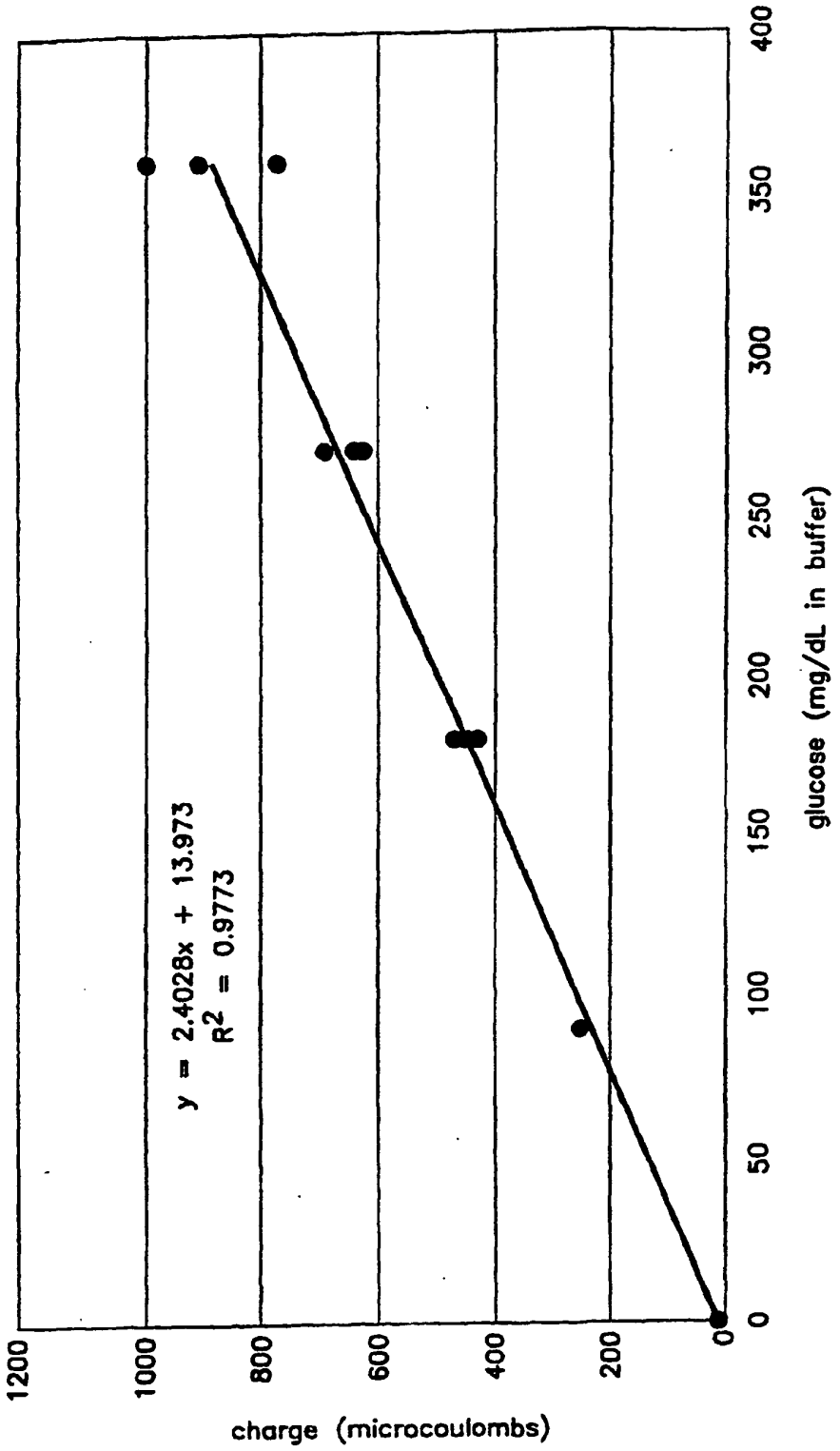
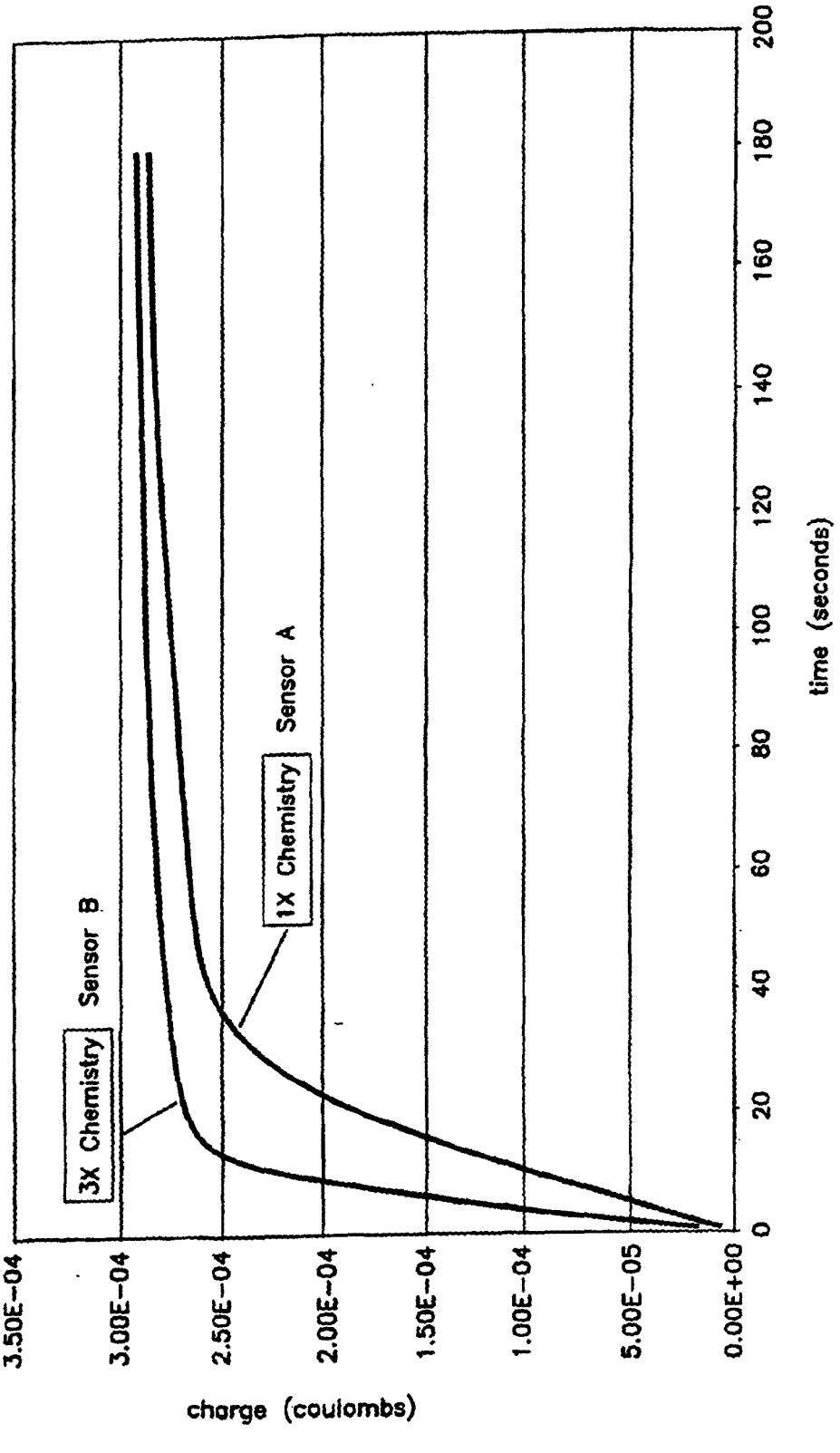


FIG. 16

Abbott Ex. 1002 - 427/1438

FIG. 17



Abbott Ex. 1002 - 428/1438

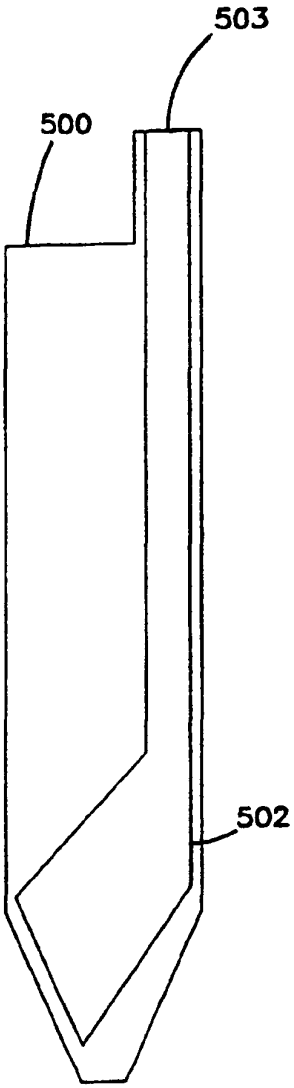


FIG. 18A

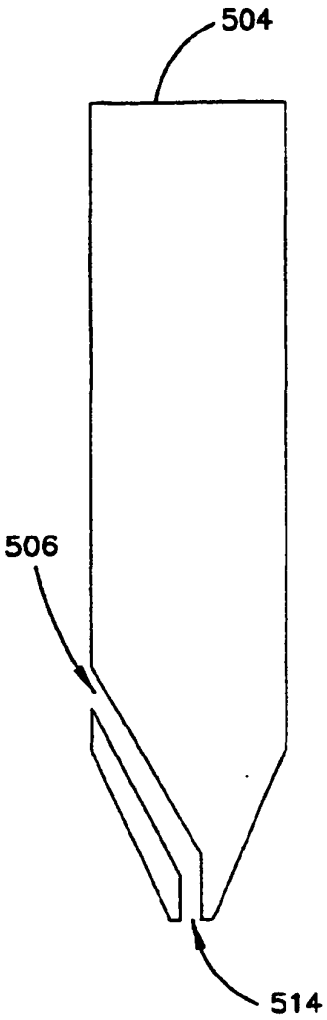


FIG. 18B

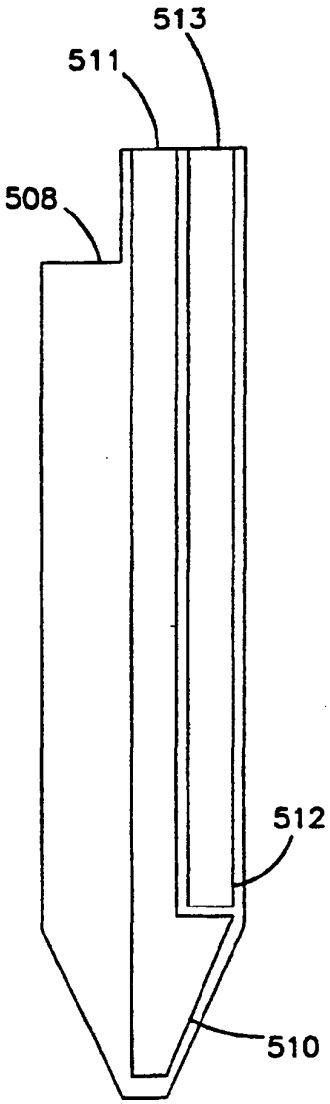


FIG. 18C

Abbott Ex. 1002 - 429/1438

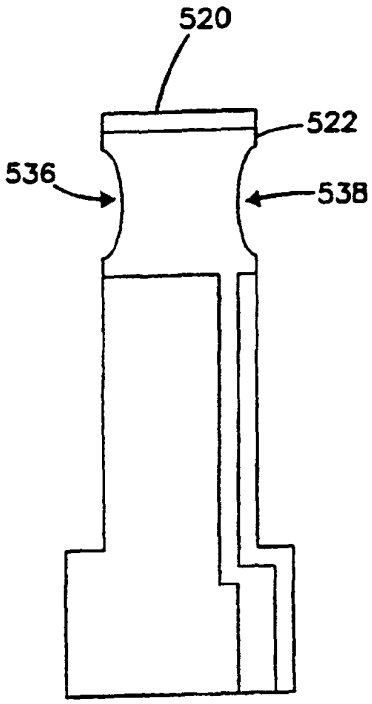


FIG. 19A

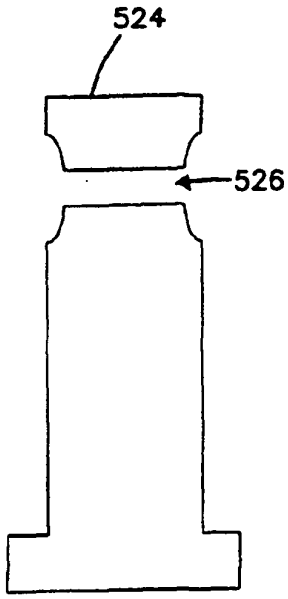


FIG. 19B

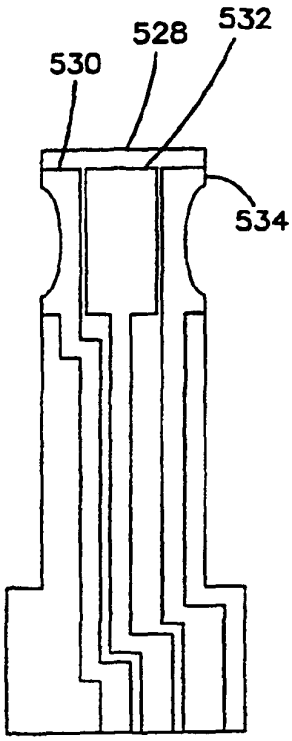


FIG. 19C

Abbott Ex. 1002 - 430/1438

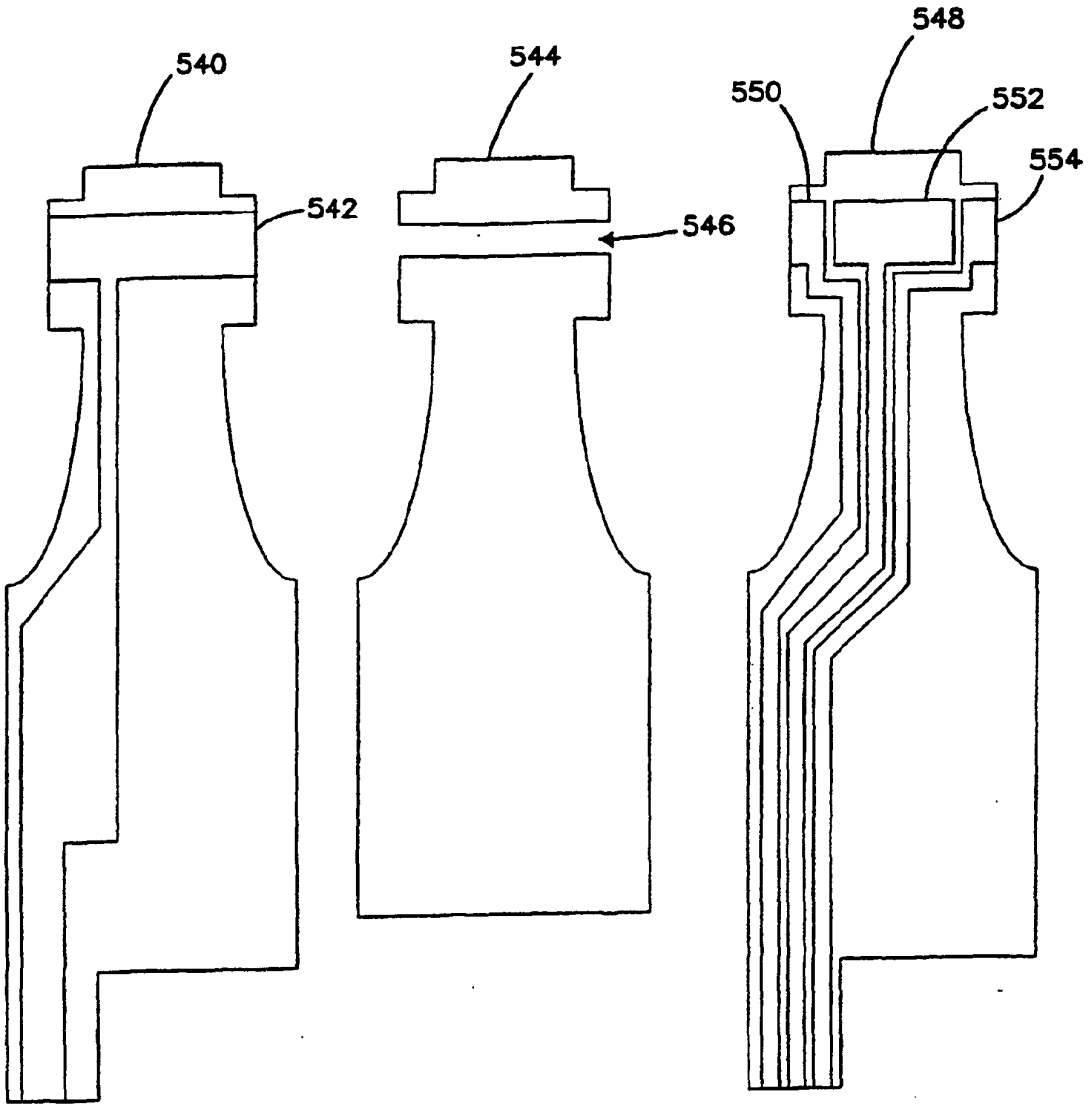


FIG. 20A FIG. 20B FIG. 20C

Abbott Ex. 1002 - 431/1438

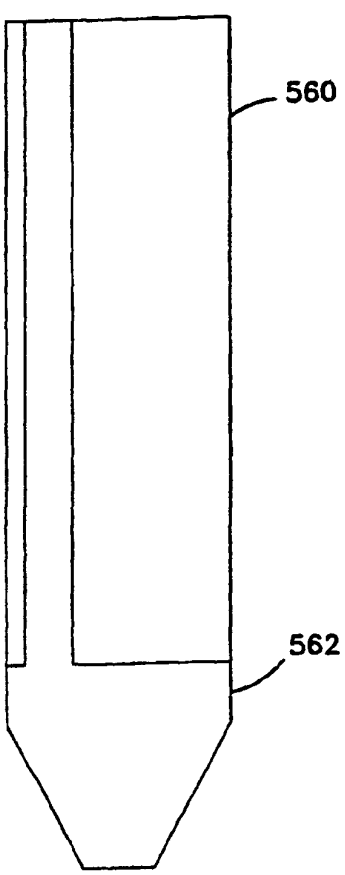


FIG. 21A

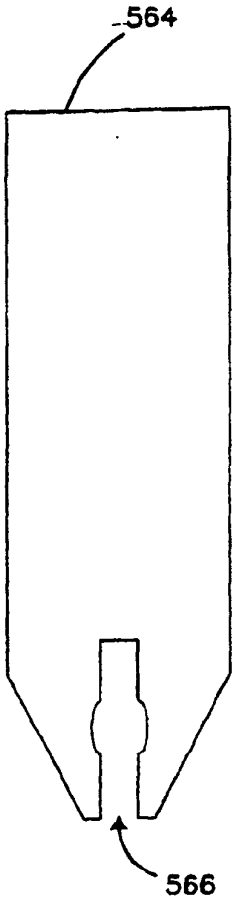


FIG. 21B

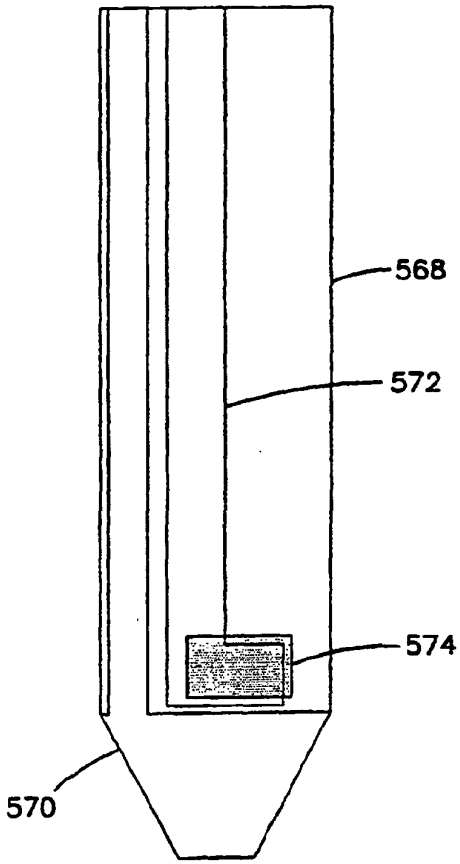


FIG. 21C

Abbott Ex. 1002 - 432/1438

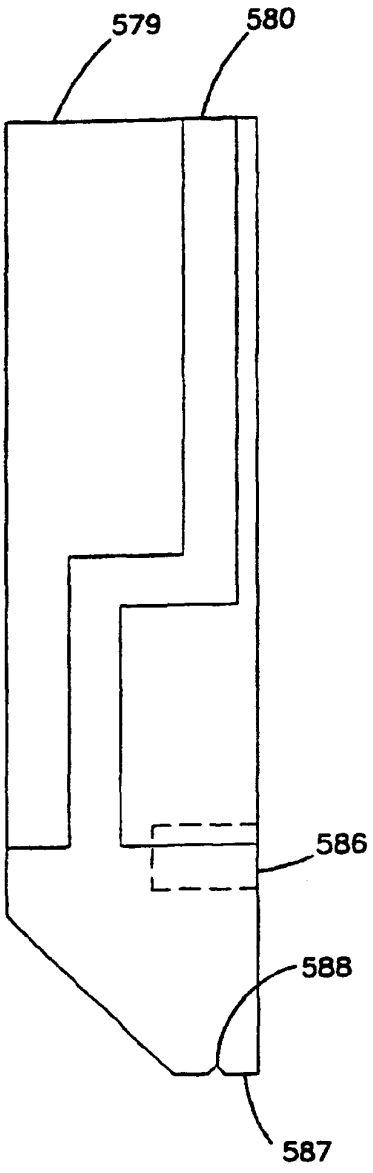


FIG. 22A

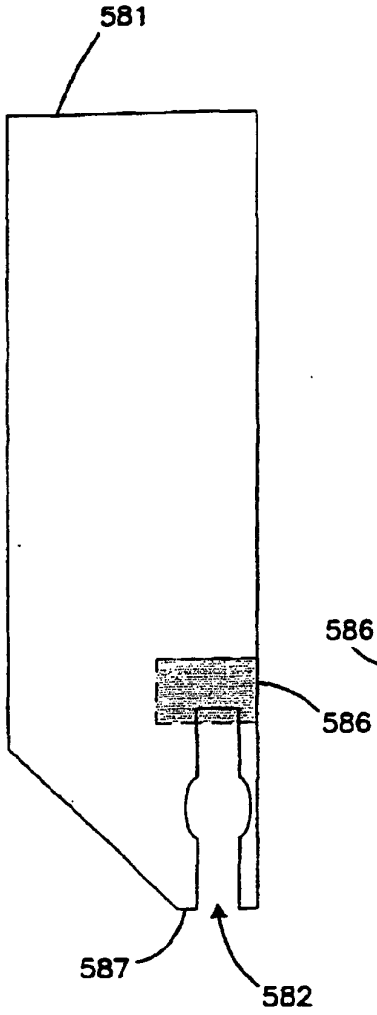


FIG. 22B

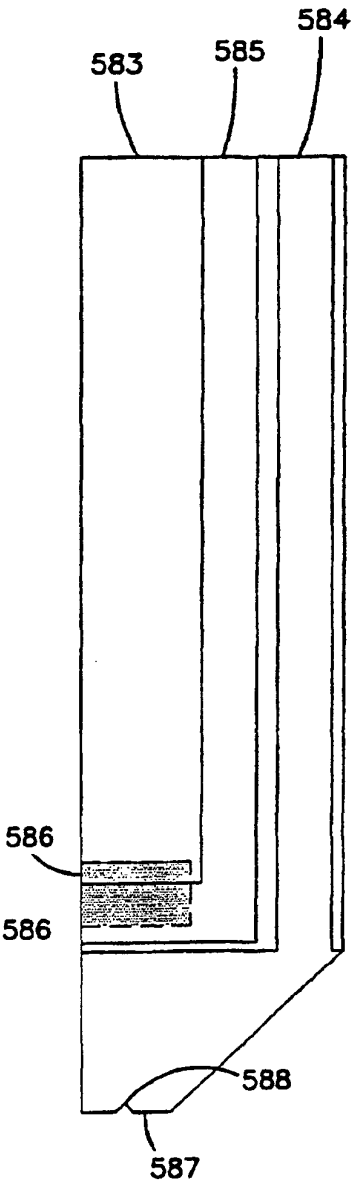


FIG. 22C

Abbott Ex. 1002 - 433/1438

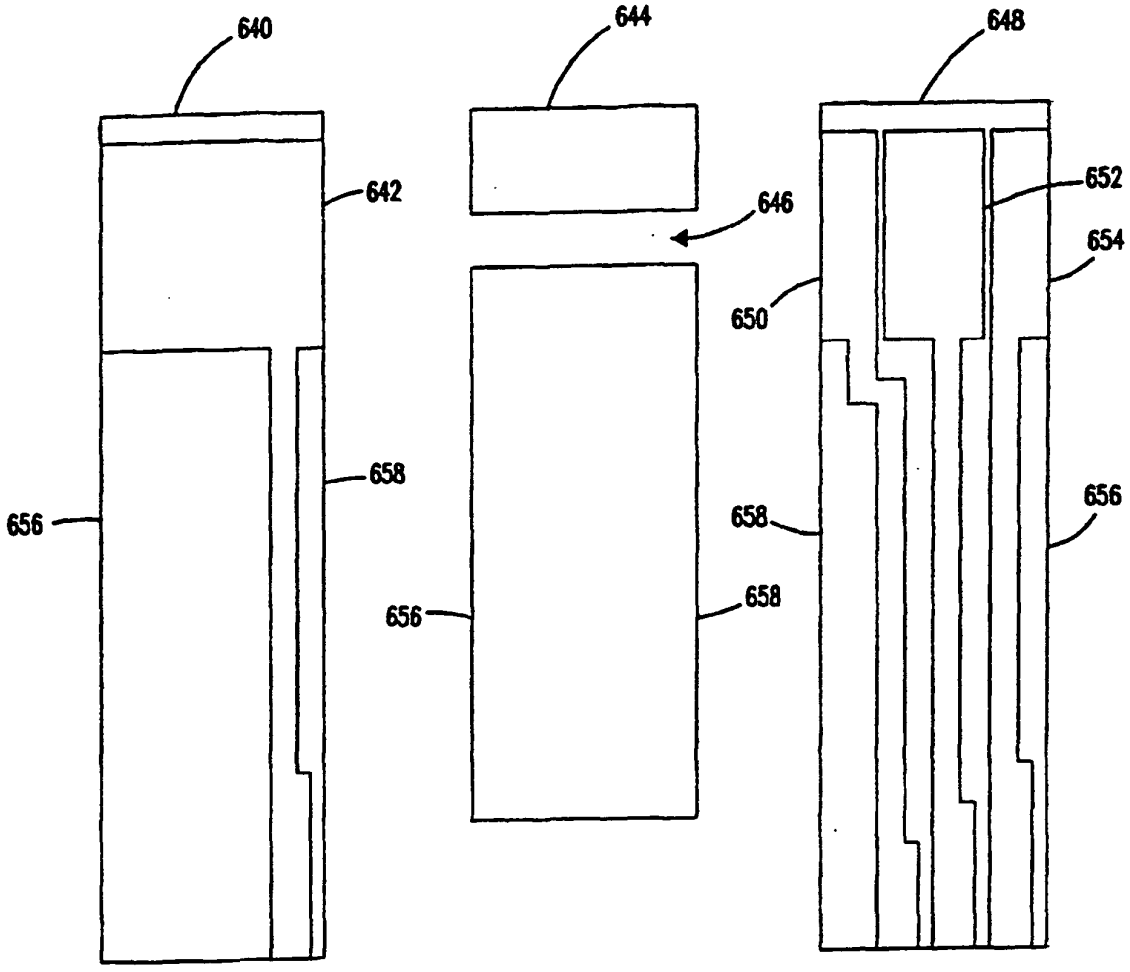


FIG. 23A FIG. 23B FIG. 23C

Abbott Ex. 1002 - 434/1438

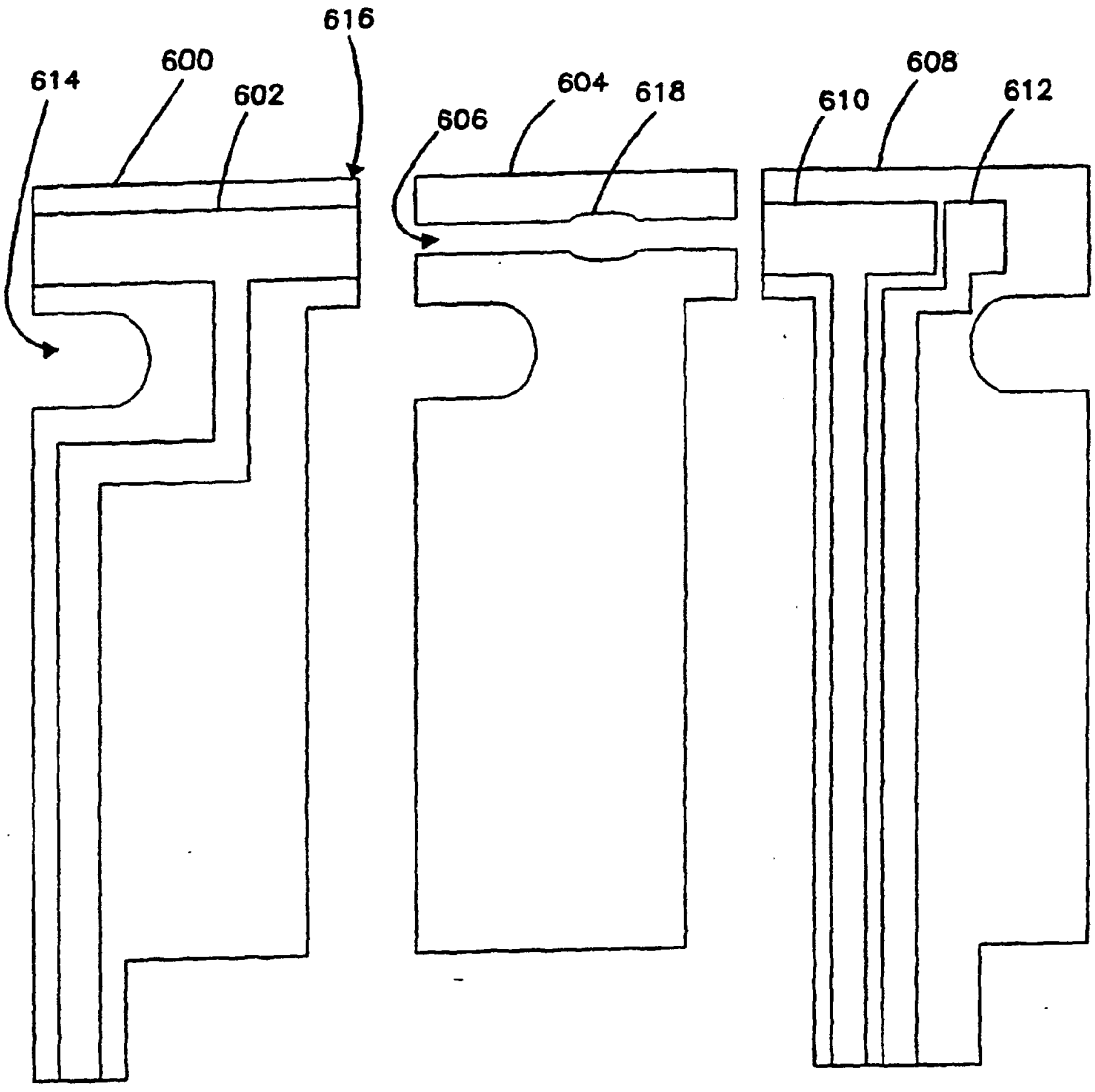


FIG. 24A FIG. 24B FIG. 24C

Abbott Ex. 1002 - 435/1438

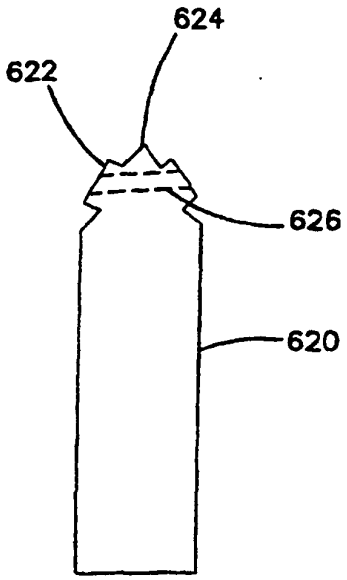


FIG. 25

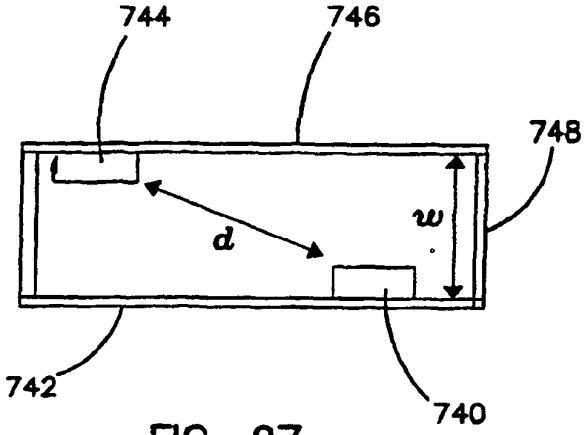


FIG. 27

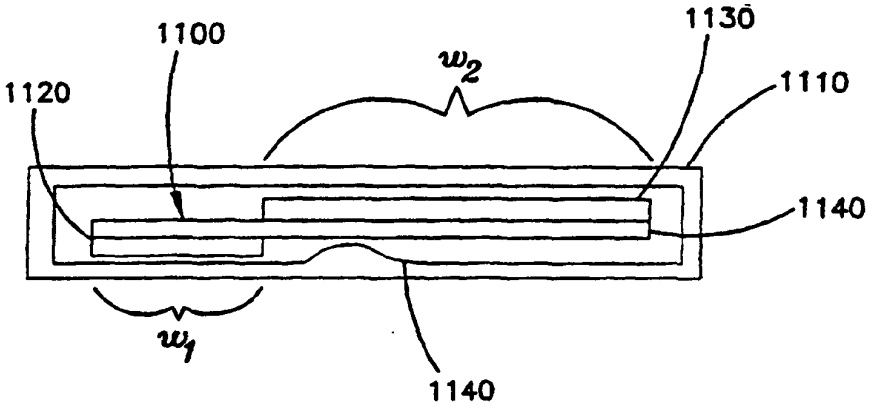


FIG. 32

Abbott Ex. 1002 - 436/1438

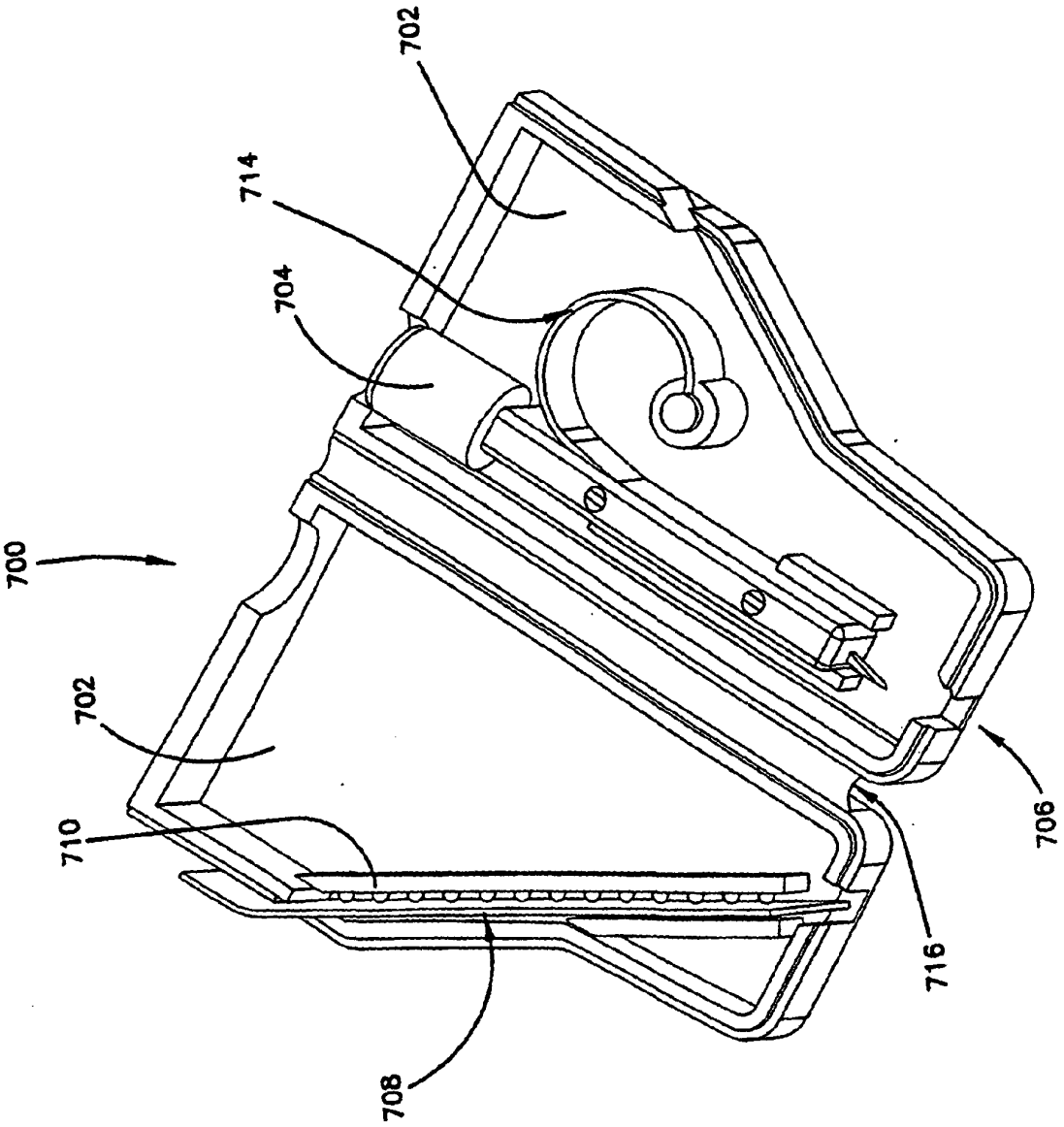
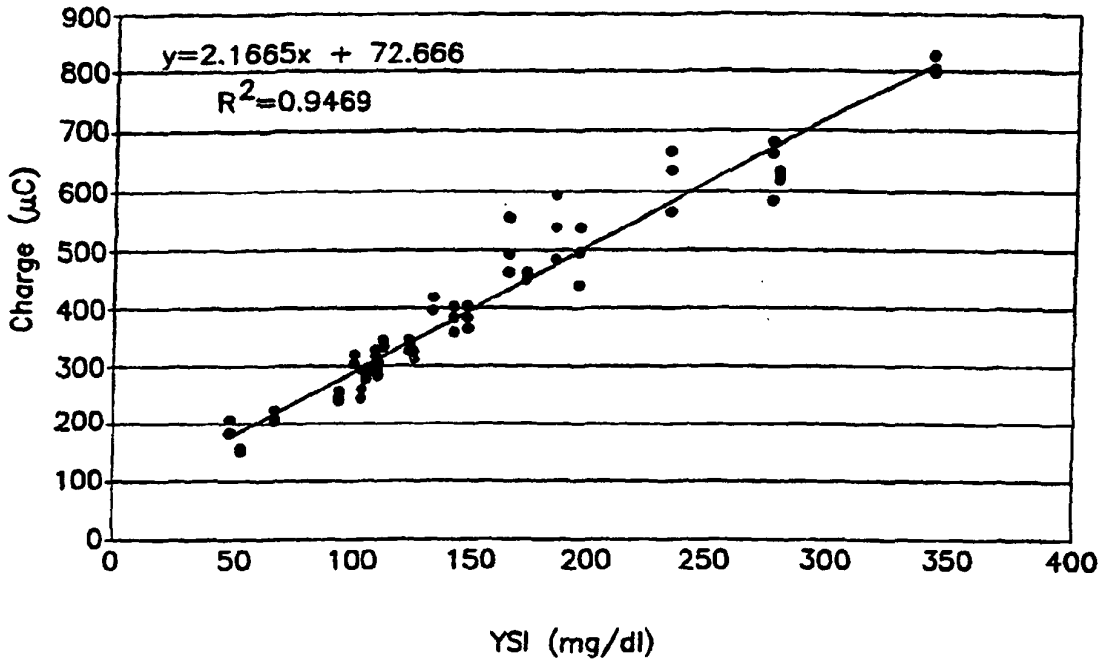


FIG. 26

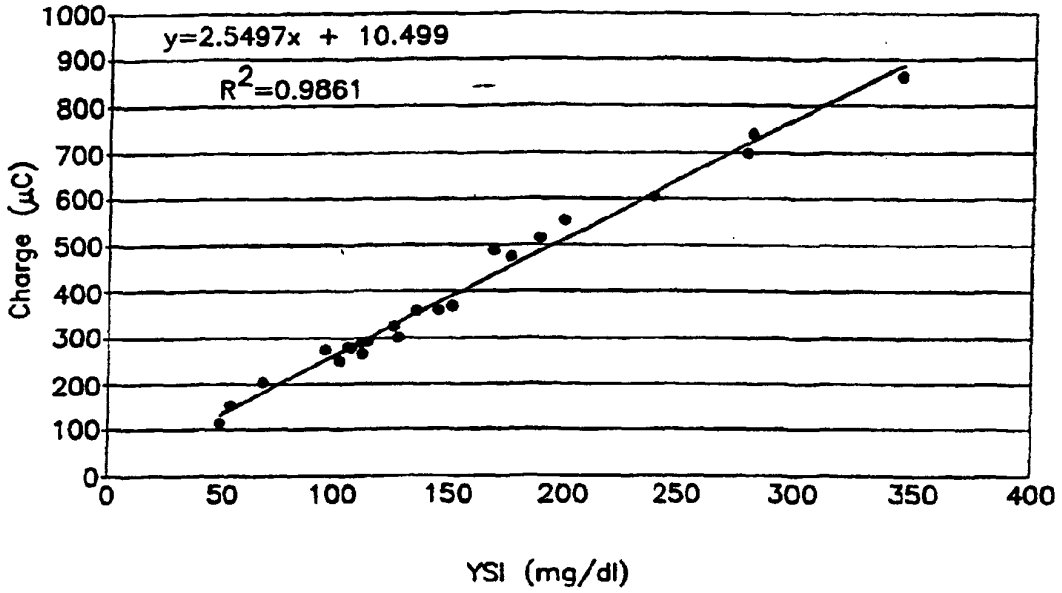
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FIG. 28



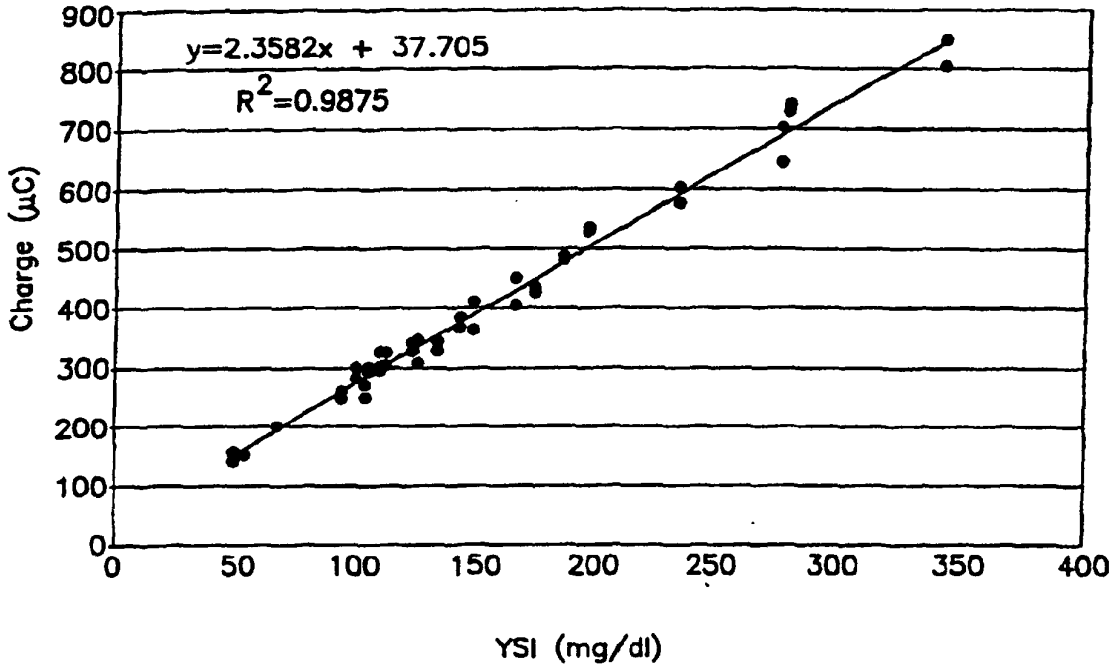
Abbott Ex. 1002 - 438/1438

FIG. 29



Abbott Ex. 1002 - 439/1438

FIG. 30



Abbott Ex. 1002 - 440/1438

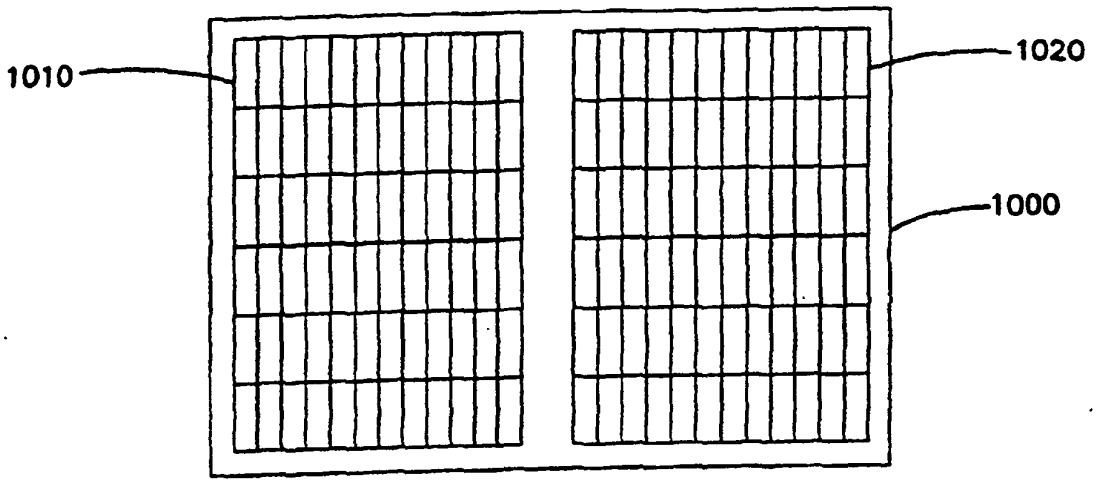


FIG. 31A

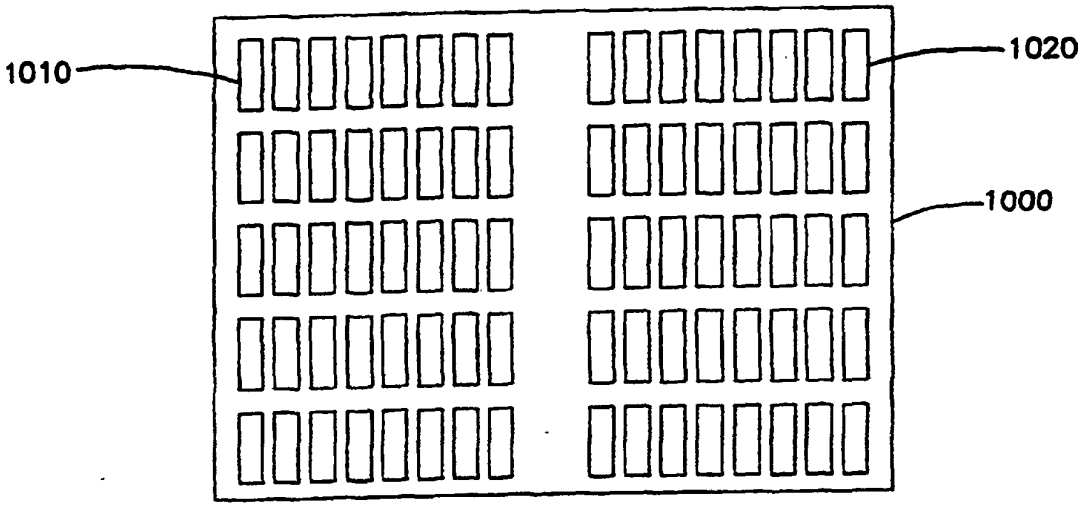


FIG. 31B

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REFERENCES CITED IN THE DESCRIPTION

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- US 5857983 A **[0172]**
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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 119 637 B8

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**
Note: Bibliography reflects the latest situation

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(21) Application number: **99951856.6**

(22) Date of filing: **08.10.1999**

(51) Int Cl.[7]: **C12Q 1/00**

(86) International application number:
PCT/US1999/023425

(87) International publication number:
WO 2000/020626 (13.04.2000 Gazette 2000/15)

(54) **SMALL VOLUME IN VITRO ANALYTE SENSOR WITH DIFFUSIBLE OR NON-LEACHABLE REDOX MEDIATOR**

KLEINVOLUMIGER IN VITRO SENSOR MIT DIFFUSIONSFÄHIGEM ODER NICHTAUSWASCHBAREM REDOXVERMITTLER

DETECTEUR D'ANALYTES IN VITRO DANS DES PETITS VOLUMES UTILISANT UN MEDIATEUR DIFFUSIBLE OU NON LIXIVIABLE

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **08.10.1998 US 103627 P**
08.10.1998 US 105773 P
21.04.1999 US 295962

(43) Date of publication of application:
01.08.2001 Bulletin 2001/31

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US-A- 5 695 947

- **VIDAL J C ET AL: "A chronoamperometric sensor for hydrogen peroxide based on electron transfer between immobilized horseradish peroxidase on a glassy carbon electrode and a diffusing ferrocene mediator" SENSORS AND ACTUATORS B,CH,ELSEVIER SEQUOIA S.A., LAUSANNE, vol. 21, no. 2, 1 August 1994 (1994-08-01), pages 135-141, XP004012315 ISSN: 0925-4005**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 119 637 B8

Abbott Ex. 1002 - 443/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 144 028 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
23.06.2004 Bulletin 2004/26

(21) Application number: **99957259.7**

(22) Date of filing: **30.11.1999**

(51) Int Cl.[7]: **A61M 5/00**, A61B 5/00, G06F 19/00, G11C 11/00

(86) International application number:
PCT/DK1999/000670

(87) International publication number:
WO 2000/032258 (08.06.2000 Gazette 2000/23)

(54) **A SYSTEM FOR ASSISTING A USER IN A MEDICAL SELF TREATMENT, SAID SELF TREATMENT COMPRISING A PLURALITY OF ACTIONS**

SYSTEM ZUR UNTERSTüTZUNG EINER MEDIZINISCHEN SELBSTBEHANDLUNG,WELCHE EINE MEHRZAHL VON SCHRITTEN UMFASST

SYSTEME PERMETTANT A UN UTILISATEUR DE S'ADMINISTRER SEUL SON TRAITEMENT MEDICAL, LEDIT TRAITEMENT MEDICAL COMPRENANT PLUSIEURS ACTES

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **30.11.1998 DK 981578**
09.12.1998 US 111721 P

(43) Date of publication of application:
17.10.2001 Bulletin 2001/42

(60) Divisional application:
04008423.8

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- **POULSEN, Jens, Ulrik**
  DK-2830 Virum (DK)
- **CHRISTENSEN, Lars, Hofmann**
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(74) Representative: **HOFFMANN - EITLE**
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81925 München (DE)

(56) References cited:
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US-A- 6 012 034

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EP 1 144 028 B1

Printed by Jouve, 75001 PARIS (FR)

Abbott Ex. 1002 - 444/1438

Description

[0001] The present invention relates to a computer system, a computer readable medium and an apparatus as defined in the preamble of claims 1, 18, 35, respectively.

[0002] They may be used for assisting a user in a medical self treatment, said self treatment comprising a plurality of actions.

[0003] In the following a user/patient will be a patient having diabetes.

[0004] For a number of years it has been possible to purchase various devices for the treatment of diabetes, e.g. for injecting insulin, for measuring blood sugar (such a device is referred to as BGM in the following), for withdrawing blood samples, and other accessories, the purpose of which is to enable the patient to nurse his disease discretely and with a high standard of safety.

[0005] Many diabetic patients are elderly people who can easily get insecure with respect to the medical equipment. It is very reassuring and therefore also very important that the user can have feedback from the system which confirms to the user that everything is OK right from the technical function of the system to the patient's physiological condition. This stretches out a psychological safety net under the patient, which contributes to improving the quality of life of patients having a disease such as diabetes.

[0006] Traditionally, diabetic people live under strict rules of "do's and don'ts". There is a historical need in order to comply with a therapeutic regimen. The purpose of this being a well controlled blood glucose level (BGL) and thereby a much lesser risk of later complications. This is a highly undesirably situation from a 'quality-of-life' point of view. It often results in bad mood - which is known to lead to a poor BGL regulation. Thus an evil circle is created which is hard for the diabetic to break.

[0007] Additionally, in certain cultures/societies there is a reluctance against using syringes/needles to administer medication and people therefore choose alternative ways to try to comply with a regimen. However, this often has the unfortunate result that people choose alternatives that do not fully or at all correspond to the optimal regimen and thereby choose wrong alternatives with adverse effects.

[0008] Further, the metabolism is a very complex and dynamic system. It is very hard to get and maintain an overview for the diabetic as many factors play a role. It is very likely that the diabetic looses an overview or relies on too simple rules of operation or eventually neglect the illness.

[0009] Various systems trying to ease the hazels of diabetes have been proposed over time. These systems have basically an accounting role and simply keep track of whatever input the user specifies. In these systems input of food and exercise are usually a task that the user needs to initiate. Systems that rely on the user to take action can be hard to make function well due to the user's reluctance to deal with it.

[0010] Patent specification WO 95/32480 discloses a medical information reporting system which has a patient sensor device controlled via a patient operated interface device by a micro-controller which writes data to a memory and a report writer. The specification further discloses a warning algorithm with zone boundary values which is specified by the user and consent to by a physician. This system simply keep track of whatever input the user specifies.

[0011] Patent specification WO 94/24929 discloses a patient support and monitoring system, which has a database located at a remote location for collection of information in a remote database from sensors and a medicine administration system. This system also keep track of whatever input the user specifies and may initiate a medical reaction on the basis of received parameters.

[0012] The object of the invention is to provide a computer system, a computer readable medium and an apparatus which provide a user with a freedom of operation with respect to a self-treatment. This object is achieved by a computer system of claim 1, a computer readable medium of claim 18, and an apparatus of claim 35. Further advantageous embodiments and impprovements of the invention are listed in the dependent claims.

[0013] One aspect of the invention is guiding the user with respect to a self treatment by presenting options/possibilities in such a way that compliance to a regimen may be obtained in numerous ways.

[0014] Another aspect of the invention relates to assisting a user in a medical self treatment, said self treatment comprising a plurality of actions, comprising the steps of

- collecting in one or more databases data representing values of parameters relevant for processing said one or more databases so as to provide for alternative choices between two or more actions and a corresponding value for each two or more actions.

[0015] Hereby, the user's self-treatments change from restrictions to possibilities thereby enhancing the overall 'quality-of-life' for the user and better ensuring that the user's self-treatment complies better or fully with a specified regimen by choosing proposed choices which complies with the regimen. This avoids that the user chooses actions and alternatives which do not fully or at all correspond to the optimal regimen due to a lack of a clear overview of the complex factors involved in the self-treatment.

Abbott Ex. 1002 - 445/1438

[0016] By providing the user with a number of options he maychoose the one(s) he likes best and still obtain the right and full treatment instead of choosing the easiest and most appealing course of action on his own, which may be wrong or insufficient and result in adverse effects.

[0017] Additionally, the possibility of choices fulfilling a prescribed regimen makes the patient feel more in control of the treatment and enhances the therapeutic value of the treatment and improves the patient's ability to adapt his treatment to his daily life.

[0018] Additionally, the user's feeling of being ill is reduced, since the user has options of choices instead of a dictation of actions.

[0019] One further aspect of the invention is to estimate one of more future values for one of said parameters, in order to obtain information of the user's condition in the near future, hereby enhancing the possibilities of presenting better/more relevant choices.

[0020] One way of estimating one or more future values may be done on the basis on a dynamic model representing the human metabolism.

[0021] An advantage of the invention is to provide effective monitoring of electronic data/information which are used by a patient for self-treatment of a disease, so that a greater level of safety, both functionally and emotionally, and an effective feedback to the patient are obtained.

[0022] The invention also relates to computer system having means for executing a program, where the program when executed is to make the computer execute a method according to claims 1 - 17.

[0023] One example of the computer system is a system comprising processing means and being programmable at one time or another in order to execute a set of instructions/commands like a system for the self-treatment of a patient e.g. comprising one or more of sensor, medication administering device, data collection, and displaying means or a general computer system as a PC, laptop, palmtop, or a system having at least one device comprising a micro controller adapted to execute a program (either in hard- and/or software), and so on.

[0024] The invention further relates to a computer readable medium having a program recorded thereon, where the program when executed is to make the computer execute the method according to claims 18-34.

[0025] The computer readable medium may e.g. be a CD-ROM, magnetic disk, ROM circuit, a network connection or generally any medium that may provide a computer system with information of how to execute instructions/commands.

[0026] The above mentioned system and method need as good as possible data collection in order to present relevant and useful choices/proposals to the user. In a preferred embodiment a system/method relating to individual apparatuses, which are provided with electronic communications equipment so that the apparatuses - when in a state of mutual communication - frequently exchange information between them, are provided. Hereby a greater functional safety can be achieved and the total data capacity of the system can be increased, so that the feedback possibilities, e.g. of the system checking that every apparatus is OK and set up properly and of the patient be given a number of possible and up to date choices to choose from in a given situation, are increased.

[0027] The individual devices may be arranged for various respective functions relevant to the treatment of e.g. diabetes, such as: a lancet device, a body fluid analyser, one or more drug administration apparatuses for administering a predetermined dose of medication to the patient. Further, there may be a number of other aids which the diabetic patient uses, e.g. test strips for the blood analyser, needles, napkins for wiping off blood, extra insulin cartridge, glucose tablets, waste containers, etc.

[0028] The apparatuses according to the example may communicate information such as: amount of medication, type of medication, the concentration of relevant substances in the body e.g. body fluid level/concentration, time stamp, amount of food (e.g. amount or units of carbohydrate), measurement of physical activity, notification (e.g. alert and warning) to the patient, body characteristics (e.g. weight, blood pressure etc.) and inventory logistics. This ensures that relevant information, for e.g. a drug administration system like a doser, i.e. number of units of insulin, insulin type and time and date for administering, can automatically be stored, displayed, received and transmitted to and from all the relevant apparatuses and more particularly in one or more database accessible by a system/method for processing in order to obtain the results described above and later. The doser could also receive information regarding a predetermined number of units of insulin to be administered and automatically set the amount of medication to be administered by electromechanical means. In this way elderly and handicapped people do not have to set the relevant amount of medication themselves but just activate the doser and a confirmation of the actual administered dose may be used as input .

[0029] Other types of drug administration systems like an inhaler adapted to administer a dose of medication in an air stream or a tablet dispenser may be included instead or in combination with the doser. The inhaler and/or tablet dispenser may also communicate with the other units for relevant information like the doser according to the invention.

[0030] It is especially useful to transmit the data from all apparatuses to the functional master module/apparatus containing the highest priority program for safe keeping, calibration and updating of data and possible transmission to e.g. an external unit like a PC or database for further data acquisition, storage and processing. In this way the patient,

Abbott Ex. 1002 - 446/1438

a physician or an expert care-team can obtain the behavior over time of the patient, and a check for compliance to a diet or treatment given to the patient by a physician or an expert care-team can be made. This enhances the possibility of choices according to the invention.

[0031] Additionally, it is also possible for the patient to manually input information about the treatment. This information may be historic information as well as information about a future scheme (behavioral pattern) e.g. planned physical exercise, administering of insulin, intake of food and other medications. This information may be collected and thus serve as an electronic diabetes diary or may be used to notify the patient through the receiving means as to whether the planned actions are dangerous or not. The patient can further receive recommended amounts of medication, exercise, food, etc. from a physician; from an expert-team or automatically. All this information may be used to estimate one or more future parameter values, e.g. BGL.

[0032] It is evident that since the apparatuses are to be carried by the patient, there is a potential lack of space for an advanced input device e.g. a keyboard. Therefore, information which cannot be input on a standardized form e.g. personal comments on the treatment may be typed into the apparatus by the patient using a simple input device once and can subsequently be chosen from a list, if needed again.

[0033] Preferably, all the apparatuses of the system exchange information so that every apparatus (or at least every apparatus within range) is updated with the combined information, but still one particular apparatus is the link to any outside systems, so that every bit of information is mirrored for better safety and backup. This demands a greater amount of total memory capacity for the system.

[0034] For a BGM according to an embodiment of the invention the relevant information could be the time and date for measurement, measured level/concentration of blood glucose which could be stored or transmitted to another apparatus.

[0035] For a doser according to an embodiment of the invention the relevant information could be the type of medication (e.g. long acting or short acting insulin), number of units of insulin to be administered and the time and date of the administering. This information could both be set manually by the patient or remotely by a physician, an expert care-team or automatically.

[0036] For an inhaler according to an embodiment of the invention the relevant information could be the type of medication, the number of units of medication to be administered and the time and date of the administering. This information could both be set manually by the patient or remotely by a physician, an expert care-team or automatically.

[0037] For a storage container according to an embodiment of the invention the relevant information could be used to keep track of the contents of the container so that every time an object (e.g. cartridge, needle, etc.) is used, the storage container will update the inventory list. This list could be transferred to a unit of highest priority immediately or later, which could in turn update the patient's total holdings of objects, so that the system could notify the patient when he should order a new stock of objects in order to keep all the different proposed actions available. The ordering could also be done automatically by the system if the inventory list is transferred to an external unit, which greatly. improves the confidence, comfort and safety of the patient.

[0038] For a tablet dispenser according to an embodiment of the invention the relevant information could be the number of dispensed tablets, the number of remaining tablets, the time of dispension and the type of dispensed tablets. The dispenser could store and/or communicate this information to an available unit of highest priority or other units within communication range.

[0039] In the following a preferred embodiment according to the invention is described in detail. This particular embodiment is meant as one example only of the invention and should not as such limit the scope of protection as claimed in the appended claims.

[0040] The term "Margin Maker" is used in the following for a method/system according to the invention.

[0041] The invention will now be explained in detail with reference to the figures 1 - 8, in which

Figure 1 shows a flowchart for an embodiment of the invention illustrating an exemplary implementation of a Margin Maker system;

Figure 2a, 2b and 2c show examples of user interfaces presenting and receiving choices to and from a user;

Figure 3 illustrates a schematic diagram of an exemplary expert system using a model;

Figure 4 shows a more detailed representation of a time dependent dynamic patient model according to the invention;

Figure 5 shows an example of a preferred system which may contain an embodiment according to the invention;

Figure 6 shows another embodiment according to the invention;

Abbott Ex. 1002 - 447/1438

Figure 7 illustrates the general concept according to an embodiment of the invention with respect to communication and exchange of information;

Figure 8 illustrates the communication between a system of apparatuses and a central system.

[0042] Figure 1 shows a flowchart for an embodiment of the invention illustrating an exemplary implementation of a Margin Maker system.

[0043] In step 101 input data is provided/updated. More specifically different types of input data are updated as represented by the steps 102 - 105.

[0044] In step 102 data from a care-team is provided/updated. This data describes individual user/patient characteristics which are true/valid in the time interval between consultations with the care-team. The data is typically derived as a result of tests performed by health care professionals (e.g. insulin sensitivity) and entered into the system by the care-team, e.g. wireless via a mobile telephone system as described in connection with Figure 8.

[0045] In step 103 treatment input data is provided from various devices, e.g. from a system of portable apparatus as described above and in connection with Figs. 5 - 7.

[0046] Input data specified manually by a user may also be input in step 103. Manually specified input data may e. g. be a value representing the body temperature of the user e.g. because he is feverish. Manually specified input may preferably if it differs from his normal value

[0047] This data describes the actual treatment received by the patient (e.g. insulin intake as a function of time) and the resulting effect on the user (e.g. blood glucose level as a function of time). The data is gathered by the various devices used by the patient in his home-treatment and communicated automatically to the Margin Maker.

[0048] In step 104 the previous choices, i.e. input from the user, are provided/updated.

[0049] This is a record of the previous activities which the user has chosen to perform and which are either not yet confirmed by other input means (e.g. insulin injection prior to synchronization between the insulin doser an the Margin Maker) or not confirmable by other input means (e.g. physical exercise or food intake).

[0050] In step 105 information of time is provided from a system clock in the form of a time stamp. Additionally the date may be specified as well.

[0051] It is necessary for the method to know the time because the alternative proposals available to the user change over time.

[0052] The information provided/updated in the steps 102 - 105 is collected in a database as a dataset at step 106.

[0053] Prior to processing the input data the system performs a test at step 107 to find out if the amount and/or quality of the input information is sufficient to produce valid and relevant proposals for user behaviour to present for the user of the Margin Maker system.

[0054] If the test fails, i.e. the input data is insufficient to produce a relevant output, the user is made aware of the fact that at the moment the Margin Maker is unable to offer guidance due to lack of input information and displays a request for more (comprehensive) data and issues a warning at step 108.

[0055] If the test is successful, the method continues in step 109, where the provided/inputted data is processed in an expert system e.g. using a model.

[0056] The expert system is in principle a model of a control loop for the blood glucose level in a human. Based on the input and the historical data accumulated in the Margin Maker the parameters of the model is adapted to mimic and predict the blood glucose control of the individual user of the Margin Maker system. Refer to Figs. 3 and 4 for a more detailed description of the expert system.

[0057] For each of the n possible user actions implemented in the Margin Maker system the model is fed with information of the present blood glucose level, the target blood glucose level, the current time, the n-1 user actions set to their present value (ceteris paribus), and 1 user action is treated as a variable parameter. After n recalculations of the control loop, one for each of the n possible user actions treated as the variable parameter, the expert system has derived n ways of bringing the present blood glucose level to its target value. Then an evaluation of the n alternative proposals is needed in order to exclude proposals that are not implementable (e.g. it is not possible to eat a negative amount of food), thereby providing the 'up to n' valid and implementable proposals of possible choices 110.

[0058] In general, the sooner proposals are chosen, i.e. a situation is acted upon, the more options/proposals is available to the user. Put in another way, as the time goes the proposals/options become fewer and fewer as well as more and more restrictive, since the user's situation gets more and more serious, i.e. drifts away from a normal BGL, if not paid attention to/acted upon.

[0059] Another criteria for exclusion of proposals may e.g. be in a system, as described above, comprising different portable/handheld devices that the specific device being used to implement the proposal is present and activated among a user selected group of the devices. In this way the user will only be presented with proposals that he actually has the possibility of executing.

[0060] Finally, the time is considered variable in the expert system - other things being equal - to test whether a

Abbott Ex. 1002 - 448/1438

potentially dangerous situation is expected to occur within a given time frame. If this is found to be the case, a warning flag is set in step 111.

[0061] In step 112 a test whether the warning flag has been set is executed. If the test is true/yes (i.e. the warning flag has been set) a warning signal is sent to the user in step 113, regardless of whether the user is accessing the system, e.g. by audio to attract the user's attention and/or by activation of the display containing appropriate information. After the signal is given the method continues in step 115 where the warning and proposals are presented as will be described later.

[0062] If the test in step 112 results in false/no, another test is executed in step 114 as to whether the system is accessed by the user. If this is not the case, the method continues from the beginning in step 101 and awaits new and/or updated input since the present situation does not specifically require the attention of the user (warning flag not set).

[0063] If the test in step 114 is true and the user is accessing/has activated the system, step 115 is executed.

[0064] In step 115 the valid and implementable proposals are presented to the user. Any warnings are also displayed to the user if the preceding step was step 113 in order to alert the user and obtain an immediate action from the user. Issued warnings could e.g. comprise information that the user should seek medical attendance or administer a given medication as quickly as possible, etc.

[0065] The proposals may e.g. be presented in the form shown in Figs. 2a, 2b and 2c or other suitable forms.

[0066] In step 116 the system awaits a user choice of one of the proposed actions or a time out from the system.

[0067] Each of the proposals presented to the user of the Margin Maker will bring his/her blood glucose level "back on track" but that does not in any way exclude the possibility that the user chooses only to partly follow a suggested proposal, e.g. administering half the dose of medication instead of the proposed dosage, or to combine several proposals fully or in part. Once the user has entered his/her choice the Margin Maker performs a rerun of the flowchart to update the relevant proposals, given the new situation. An example of proposals and selected choices is shown in Figure 2a.

[0068] If the user chooses to do nothing, the system will eventually issue a time out and perform a rerun of the flowchart to update the relevant proposals taking into account that time has elapsed since the last user action.

[0069] Hereby a user is presented with a number of choices each fulfilling a regimen where he may choose the one (s) he likes best and still obtain the right and full treatment instead of choosing the easiest and most appealing course of action on his own, which may be wrong or insufficient and result in adverse effects.

[0070] Additionally, the possibility of choices makes the patient feel more in control of the treatment and enhances the therapeutic value of the treatment and improves the patient's ability to adapt his treatment to his daily life.

[0071] Figures 2a, 2b and 2c show examples of user interfaces presenting and receiving choices to and from a user.

[0072] Figure 2a shows an example of a user interface where one column 201 comprises different graphical icons 205 - 210 each representing one choice of action according to a proposal. Shown in this example are icons 205 - 210 for administering fast acting insulin 205, administering slow acting insulin 206, administering tablets of a given type 207, exercise 208, intake of food 209, and intake of alcohol 210. Additionally, other icons like administering tablets of another kind, administering a dosage medication from an inhaler, etc. may be presented if these options are available to the user.

[0073] At column 202 the n proposals suggested by Margin Maker are shown (corresponds to step 115 in Figure 1), where each proposal of action, if executed, brings the current BGL to the target BGL. In this example the Margin Maker has proposed to the user/patient either to administer 10 units (IU) of fast acting insulin, administer 0 IU of slow acting insulin, administer two tablets of a given type, exercise for 60 minutes, intake 0 units of food, or drink 0 units of alcohol.

[0074] At column 203 the user input is shown. After he has input the choice and amount of action, the Margin Maker displays and derives updated proposals on the basis of the changed situation. Here the user has chosen to administer 5 IU of fast acting insulin, and the Margin Maker now presents the updated proposals at column 202', given the new situation and taking into account the user's choice.

[0075] The updated proposals at column 202' are now to administer additionally 5 IU of fast acting insulin, administer 0 IU of slow acting insulin, administer one tablet of a given type, exercise for 30 minutes, intake 0 units of food, or drink 0 units of alcohol.

[0076] The user now chooses to exercise 30 minutes, which is shown at column 203', and the model updates the proposals accordingly. The proposals shown at column 202" show that after the user has performed the specified choices/actions his BGL should be at the target level.

[0077] The columns 204 represent previous and later proposals and user input, so it is possible to scroll through the values for different points in time.

[0078] This specific form of user interface requires a display of a certain quality or with a certain resolution. Other more simple forms may be provided, e.g. as shown in Figure 2c, either instead or in combination in devices with a smaller display.

[0079] Alternatively, the display will only display one column of icons 201, proposals 202 and user input 203 at a time, e.g. with buttons to scroll through previous proposals and input.

Abbott Ex. 1002 - 449/1438

[0080] The user may input data in many different ways according to specific embodiments of the invention as generally known in the art, e.g. utilising a touch screen with a stylus, touch pad and a cursor on the display, etc.

[0081] It is evident that if the apparatuses are to be carried by the patient, there is a potential lack of space for an advanced input device e.g. a keyboard. Therefore, information which cannot be input on a standardized form e.g. personal comments on the treatment is typed into the apparatus by the patient using a simple input device once and can subsequently be chosen from a list, if needed again.

[0082] Preferably, a system comprising a plurality of portable devices with mutual data communication, as described above, is used in connection with the Margin Maker.

[0083] In this way e.g. a doser may communicate an administered dose to the device containing the Margin Maker automatically or by user request and the different devices may communicate measured values representing physiological parameters automatically or by user request, e.g. a BGM may communicate the measured BGL as input to the Margin Maker.

[0084] Additionally, information of which devices are present and activated may be transmitted to the device containing the Margin Maker which may hereby only present proposals with a corresponding present and/or activated device, so that e.g. if a doser containing slow acting insulin is not available to the user, then the icon 206 and the corresponding proposal will not be displayed at all.

[0085] In Figure 2b an example of a user interface is shown where input of information is given to the Margin Maker which is needed in order to derive the proposals of actions. Shown is a column 220 containing icons 224 representing a value obtained from the BGM and 225 representing a value for the temperature of the user. The corresponding values, specified at a given time, are listed in a column 221 and are in this example 10.5 mmol/l and 37.5° for the BGM and the temperature, respectively. The other columns 222 represents values specified at different points in time where in this example no values are specified. Alternatively, only columns having a specified value are shown in the user interface e.g. with a corresponding time stamp.

[0086] The columns 223 represent previous and later user input, so it is possible to scroll through the values for different points in time.

[0087] This information is used by the Margin Maker together with additional information to better estimate the target glucose level and obtain a measure of the present glucose level. The input temperature is used by the expert system to determine whether the user is feverish or not as this influences the required amount of insulin.

[0088] This information may either be input manually by the user, automatically or both, e.g. by a BGM device and/or a temperature sensor with communication means which may communicate with a Margin Maker device (may correspond to step 103 in Figure 1).

[0089] Figure 2c shows an example of a different user interface which may be more suited for a smaller display. Shown is an example of a graph 230 with a time axis 231 and three BGL bars 232 and 232' obtained at three different points in time of the day. Two previously obtained BGLs 232 and one BGL 232' obtained at the actual time. The BGL may be obtained from a BGM and may be received either automatically or manually by the Margin Maker as input for the expert system as described above.

[0090] Also shown are two bars 233 representing the dose of insulin, that the user chose to administer previously after obtaining the BGLs 232, respectively. The dosages 233 may have been fully or partly as proposed by the Margin Maker at the respective time. Alternatively, the user may have administered the dosages 233 completely on his own and just specified the dosage and type of medication. The actual dosages 233 administered may have been specified (together with the time and type of insulin) by user input or via communication from the administering doser to a device containing the Margin Maker.

[0091] The previously obtained BGLs 232 and administered dosages 233 together with the BGL 232', obtained at the actual time and other relevant input, as described in connection with Figure 1, and used to predict a future course of BGL for the user and derive one or more proposals to the user in order to account for the future course of BGL.

[0092] The Margin Maker has proposed in this example that the user should administer a dosage as indicated by the blinking bar 233'. Additionally, other proposals may be shown elsewhere. The proposed dosage and type of insulin may be transmitted automatically to a corresponding doser, so if the user wishes to follow this proposal fully he just has to activate a button on the doser to accurately receive the proposed dosage. Alternatively, the user may manually specify the proposed dosage on the doser.

[0093] Additionally, the user may choose to only administer a part of the proposed dosage (which may also be transmitted automatically after indication by the user) if he e.g. wants to exercise as well. After the Margin Maker has registered the user's choice of only administering a part of the proposed dosage of medication, the expert system is updated accordingly and new proposals are derived taking into account the new situation.

[0094] The user interfaces described in connection with Figs. 2a, 2b and 2c are just examples and other interfaces may be just as applicable. Alternatively, the user interface may be character based and using no graphics thereby reducing the complexity of the system with respect to implementation.

[0095] Figure 3 illustrates a schematic diagram of an exemplary expert system using a model.

Abbott Ex. 1002 - 450/1438

[0096] A number of models have been proposed in order to describe the metabolism of the insulin dependent diabetic patient. Furthermore, some effort has been put into constructing systems for controlling the blood glucose level using insulin.

[0097] In the following one expert system is described as an example but other expert systems known in the prior art may be used with similar results. The shown expert system comprises input variables 301 and 302, physiological parameters and model inputs 306, proposal generators 305, patient actions 304, and a patient model 303, all of which will be described in the following.

[0098] An input variable "Desired blood glucose level " 301 is specified in the expert system and is preferably (pre) determined by the care-team or other professionals.
The variable 301 may be similar to the blood glucose level of a healthy person, but may due to regimen, differ from this value, e.g. be higher in order to prevent hypoglycaemia.

[0099] Another input variable used by the expert system is the variable "Blood glucose measurement" 302 representing the BGL at a given time.

[0100] The patient may measure the BGL, giving the blood glucose measurement variable 302, with a certain frequency or use a continuous blood glucose sensor. Given the dynamics of the human metabolism, there is a certain lower limit of the sample frequency which will allow the expert system to work properly.

[0101] The patient model 303 is a dynamic model which describes the metabolism of the diabetic patient. The model 303 incorporates parameters 306 such as e.g. weight of the patient and insulin sensitivity, which vary from patient to patient and may be considered constant between consultations of the care-team. The model 303 may also incorporate model input 306 such as injections of long acting insulin, fast acting insulin, oral diabetic agents, exercise, food intake, alcohol intake and fever. Given a certain combination of model input 306, the model 303 describes the blood glucose level over time. The model 303 describes some key state variables of the human metabolism.

[0102] The proposal generators 305 are the analogy of regulators in a control system. The input to the proposal generators 305 is the difference between the desired blood glucose level 301 and the actual blood glucose level 302 and the state variables of the patient model. Given the input each proposal generator 305 proposes a patient action and a corresponding amount/dosage - eat a certain amount of food, exercise for a certain amount of time, inject a certain amount of fast acting insulin, etc. - as indicated in the proposal boxes 305. The proposals are calculated, presuming that only one of the proposals is followed.

[0103] The patient has the final decision as indicated by patient action 304 for each possible action in the expert system. He may or may not choose to follow the proposals. By choosing one of the proposals fully or partly, his action 304 is fed into the patient model, either by manual input or automatically by the diabetes specific devices - the dosers or the blood glucose monitor. The patient model 303 now generates a new input to the proposal generators 305 which represents the updated situation.

[0104] Figure 4 shows a more detailed representation of a time dependent dynamic patient model according to the invention. This model is used by the expert system to give a prediction/estimate of a future BGL.

[0105] In the literature many such models are described. Here a very simple one of applicant's origin is taken to explain the principles. This model can be developed to a high degree of detail, if needed.

[0106] The model 400 simulates the dynamics of the carbohydrate metabolism. Based on the input of one or more of the following parameters

- BGL,
- dosage of medication,
- type of medication,
- food intake,
- drinks intake,
- exercise,
- time stamp,
- insulin sensitivity
- weight of the user,
- blood pressure,
- temperature, and
- other.

[0107] The model is tuned in to mimic the user's carbohydrate metabolism closely. By the continuous tuning by input of updated data from the expert system a drift away from a close mimic of the true status is prevented. The structure of the model 400 matches the functionalities of the metabolism to a needed degree. Due to this correspondence the expert system/model 400 will be able to predict trends or even future BGL.

[0108] The expert system continuously gives suggestions about the user's freedom of operation. Based on all re-

Abbott Ex. 1002 - 451/1438

corded events a margin for exercise and food is suggested.

[0109] If suggestions are confirmed (e.g. tapping an indication on the touch screen of the handheld device), these are regarded as input to the algorithm and used for future suggestions.

[0110] Preferably, the dialogue is implemented via a graphic display showing the history, and input is given either via a touch screen or traditional buttons.

[0111] In order for the expert system to give recommendations and margins as described above it is needed to predict how things will evolve from any known state.

[0112] This can be done using a model 400 of the carbohydrate metabolism as an engine for the Margin Maker concept.

[0113] Shown in the figure is a model 400 with two pools: Body Blood Glucose 402 and Insulin 401. Each has a filling source 403, 403' and a drain 404, 404' (i.e. two rates), respectively. Body Blood Glucose 402 has the filling source POG (Production of Glucose) 403 and the drain UOG (Use of Glucose) 404, and Insulin 401 has the filling source POI (Production of Insulin) 403' and the drain UOI (Use of Insulin) where all the rates 403, 403' , 404 and 404' may vary with time dependent on the parameters controlling the rates.

[0114] The parameters controlling the rates, e.g. food, dosing, exercise, etc., are given in the table below.

[0115] The model 400 can also be expressed in terms of a set of differential equations for the states 402 and 401, each being controlled by their respective rates 403, 404 for the state Body Blood Glucose 402 and 403' and 404' for the state Insulin 401. In this form the model can be implemented in a microprocessor relatively easily and display the results of the latest input for any given time.

[0116] The differential equations for the model 400 may be expressed as:

$$BBG(t) = BBG(t - dt) + (POG - UOG) * dt$$

$$\text{INFLOWS:} \quad POG = f(F,t)$$

$$\text{OUTFLOWS:} \quad UOG = g(BM+KD+IIUOG+E,t)$$

$$I(t) = I(t - dt) + (POI - UOI) * dt$$

$$\text{INFLOWS:} \quad POI = h(MPI,t)$$

$$\text{OUTFLOWS:} \quad UOI = j(HL,t)$$

[0117] The factors are explained in the table below:

Factor	Explanation	Unit	Function
Input/Output			
D	Dosing	IU	Output to the user about possible insulin doses to take. Alternatively the user can give input about a wanted amount of insulin and the system can suggest appropriate food intake. Whenever an insulin dose is taken the system automatically loads the value into the model and the predictions are calculated accordingly.
E	Exercise	mol	Output to the user about possible exercise to take in the given situation. Alternatively the user can give input about a wanted amount exercise and the system can suggest appropriate food intake. The user accepting the suggestion will be an input to the system and calculation will be accordingly. Conversion to mol will be made by the system.

Abbott Ex. 1002 - 452/1438

(continued)

Factor	Explanation	Unit	Function
Input/Output			
F	Food intake	mol	Output to the user about possible food to take in the given situation. The user accepting the suggestion will work as an input to the system and calculation will be accordingly. Alternatively the user can give input about a wanted amount of food and the system can suggest either dosing of insulin or exercise. Conversion to mol will be made by the system.
Concentrations and levels			
BBG	Body Blood Glucose	mol	Simulated total amount of glucose in the blood. It is calculated as the integration over time of production and usage of glucose. Between measurements it is used to give an estimate of the user's current BGL. At measurements the BBG is updated according to the measured BGL.
BGL	Blood Glucose Level	mol/l	This calculated by dividing the BBG with the blood volume. The model has the ability to predict the BGL over time and the value is very important to the user and can be displayed at any time. Every time the user makes a measurement of the actual BGL this is automatically loaded into the model by the system and it overrules the calculated one and resets the model. Initial value: 5 mmol/l
I	Insulin	mol	Insulin level in the body. The model has the ability to predict the Insulin level over time. It is calculated as the integration over time of production and usage of insulin. The initial value is set by the physician according to measurements and can be calibrated by the physician when the user meets for consultations.
Rates			
POG	Production Of Glucose	mol/min	This rate is driven by the food intake entered and accepted by the user. It is also a function of time as different types of food have different dynamic impact on BGL.
POI	Production Of Insulin	mol/min	This rate is driven by the injected insulin through a conversion factor (MPI). It is also a function of time as different types of insulin have different dynamic impacts on BGL.
UOI	Use Of Insulin	mol/min	This rate is defined by the half life (IHL) of insulin by which the level decays exponentially.
UOG	Use Of Glucose	mol/min	This rate is driven by 4 factors: Basal Metabolism (BM), Kidney Diurese (KD), Insulin Induced Use Of Glucose (IIUOG), Exercise (E).

Abbott Ex. 1002 - 453/1438

(continued)

Factor	Explanation	Unit	Function
Constants & Transfer functions			
BM	Basal Metabolisme	mol/min	Constant for each Individual determined by the physician. Typical value: 0,56 mol/min
IHL	Insulin Half Life	min	The metabolism of insulin is usually expressed in terms of half life. Typical value: 10 min
IIUOG	Insulin Induced Use Of Glucose	mol/min	This factor describes the nonlinear relation between insulin in the body and the disappearance of glucose from the blood. This factor can be measured or derived from literature.
KD	Kidney Diurese	mol/min	This factor describes the nonlinear relation between diurese and BGL. At BGL levels below 10 mmol/l the KD is virtually zero. Above 10 mmol/l an increasing KD will occur
MPI	Mol Per IU	mol/IU	Conversion factor between International Units of insulin and mol

[0118] This model 400 is just one relatively simple example of a model that may be used to predict a future BGL.

[0119] Alternatively, the model and/expert system or parts hereof may be located in a stationary unit with greater computational power and receive input and transmit information regarding proposed choices.

[0120] Figure 5 shows an example of a system which may contain an embodiment according to the invention.

[0121] Shown is a doser 20 with a cap 10 where the cap 10, in an embodiment, functions as the functional master module. In the preferred embodiment the Margin Maker resides in the functional master module. The functional master module 10 has displaying means 11 and buttons 36 for operation and selection of proposed choices.

[0122] The doser 20 is a conventional doser with has transmitting and receiving means 12. This enables the doser 20 to transmit stored data, i.e. the time, date, amount and type of medication, to the functional master module 10 for storage and presentation there via the master modules receiving means 12. Additionally, the transmitted data may be input to the Margin Maker automatically, thereby updating the model and deriving and presenting new proposals/choices, reflecting the updated situation, to the user on the display 11.

[0123] The doser 20 can also receive information via the receiving means 12 from the master module 10. This information could for instance be a predetermined amount of medication as dictated by a proposal from the Margin Maker if the user chooses to administer the full amount given by the proposal. The received information is then used to automatically set the correct amount of medication to be administered so that the patient does not have to worry about that aspect. Alternatively, if the user only wishes to administer only a part of the proposed dosage, he may indicate this via the buttons 36 or directly on the doser 20, after which information of the administered dose is sent to the Margin Maker as input and used to update the model.

[0124] Also shown is a BGM 30 which has means 34 for inserting test strips 52 containing a sample of blood, for analysis by the BGM 30 by operating the buttons 36. The result of the analysis is stored and either shown in the display 32 or transmitted to the master module 10 via the transmitting means 12 for storage and input to the Margin Maker and presentation on the larger display 11 or both. The patient can at the same time be presented with the last couple of results over a time period.

[0125] A test strip container 50 is provided for the safe keeping/storing of test strips 52 in the space 55 and can be added/attached through locking means 31. With this addition, a test strip 52 will always be available.

[0126] Further shown is a lancet device 40 removably attached to the BGM 30 or the test strip container 50 by the locking means 31. This lancet device 40 is used by first loading the lancet device through the grip 44 and then pressing the button 42, which releases the lancet, piercing the skin, so that a blood sample can be obtained. With this inclusion, the lancet device 40 is always at hand. This has the advantage that a lancet device 40 is always available, for taking a blood sample and applying it to a test strip 52. The test strip 52 can then be inserted via the means 34 into the BGM 30, which will start analysing the blood sample and, after completion of the analysis, will show the result in the display 32. It is very useful to have the BGM 30 and the lancet device 40 attached together in one compact unit, since a BGM 30 would not normally be used without the lancet device 40.

[0127] In this way, information relevant to the Margin Maker and the individual devices 20, 30 may automatically be

Abbott Ex. 1002 - 454/1438

received and transmitted between the functional master module 10 and the various devices 20, 30, which ensure an automatical update of the system.

[0128] Alternatively, the Margin Maker may only present choices to the user where there is a present and activated device for performing these choices (where applicable), e.g. a proposal of administering a certain amount of long acting insulin is only presented if a doser containing long acting insulin is present, or a doser and a separate cartridge containing long acting insulin. The functional master module is responsible for keeping track of which individual devices that are present and activated.

[0129] If the device containing the master module and/or the Margin Maker, the system may designate a new master module and a new Margin Maker either by transmitting and/or activating the relevant information in the designated device(s).

[0130] Figure 6 shows another embodiment according to the invention. Two dosers 610 are shown. The dosers 610 may contain different types of insulin (fast and slow acting). Also shown is a device 600 with a display 602, buttons for operation 601. In this particular embodiment the device 600 is both the functional master module and the Margin Maker. The device 600 is also provided with the functionality of a BGM and a slot 603 for receiving test strips containing a blood sample.

[0131] The dosers 610 and the BGM functionality may, together with user specified input e.g. a the device 600, provide the Margin Maker with relevant input information to the model and/or expert system, so that the Margin Maker may present the resulting choices on the display 602.

[0132] Figure 7 illustrates the general concept according to an embodiment of the invention with respect to communication and exchange of information. Here the system consists of the portable units: a functional master module, a doser, a BGM, an inhaler, the remote units: Remote Receiver, Physician/Expert Care-team and Stationary Unit and a Communication Interface between them.

[0133] The functional master module controls the information and data flow between itself and the other apparatuses and collects relevant data and information from all the other portable units and uses this information to update the model accordingly. This data and information could e.g. be amount of medication, type of medication, body fluid concentration, time stamp (date and time) and inventory logistics. Additionally, the patient can manually input information and data related to amount of food, measurement of physical activity in the way described above.

[0134] This data and information can then be transmitted via a communication interface (which may be built into the master module) to external units like a database for data acquisition of the patient's data over time or a computer which the patient uses to be kept informed about his treatment. Alternatively, all the apparatuses could communicate to all the others.

[0135] The information in the database can be accessed by a physician or an expert care-team who could easily and quickly check for compliance to e.g. a diet or treatment course/progress. The physician or expert care-team could send a notification (e.g. alert, warning and/or change of regimen) to the patient if the data shows an inappropriate future treatment span. The patient could also be notified of a future appointment in this way or receive guidance.

[0136] The system gives the patient a number of choices to a given situation based on the model as described earlier. The patient could e.g. be informed that the blood glucose level/concentration is quite high and the patient could be presented with the choices of either exercising for given amount of time or administering a given amount of a given type of medication. The possibility of choices makes the patient feel more in control of the treatment and enhances the therapeutic value of the treatment.

[0137] Figure 8 illustrates two dosers and their communication paths. The dosers are identical for the typical patient, one doser containing fast acting insulin, the other doser containing slow acting insulin. The dosers comprise a micro controller and memory. The dosers are capable of holding information about the insulin type they contain. This information may either be obtained by the doser reading e.g. a bar code on the cartridge or the information may be input from the patient. Thus the features of the doser enable it to log information about the insulin treatment (insulin type size of the dose and time stamp)

[0138] One doser is equipped with a cap unit 73 which acts as a storage container for an extra insulin cartridge, needles etc. The storage container is capable of keeping track of the contents of the container which enables it to keep the inventory list updated, as described earlier in the present document.

[0139] The other doser is equipped with a cap unit 74 comprising a BGM, a micro controller and memory. This enables the cap unit 74 to log information about the blood glucose concentration (with time stamp).

[0140] All the dosers 71,72 and the cap units 73, 74 comprise an interface which enables them to exchange data. In the present example the functional master device comprises the Margin Maker and is the BGM cap unit 74, which, in addition to the local interface, comprises an interface that enables it to communicate with external units through standard communication links (RS-232, Wireless local area network, phone, cellular phone, pager, satellite link, etc.). Through these communication links, the patient's treatment data can be transferred to the patient's own computer 80 or via e.g. the telephone system 75 to the patient's electronic medical record on a central server 76. From here, the treatment data may be accessed by the patient e.g. from a web page, using a stationary computer 77, a laptop computer

Abbott Ex. 1002 - 455/1438

78, a handheld computer 79, etc. Apart from the patient, the care-team can access the patient's treatment data. The patient's master unit 74 can receive data from the central server 76, in addition to transmitting data.

[0141] This system has the advantage that the system can function on 3 levels:
If one of the patient's devices 71, 72, 73, 74 is isolated by means of communication, it will log data.

[0142] When the patient's devices 71, 72, 73, 74 are within communication distance, the treatment data are transferred to the master unit 74, enabling it to supply the patient with an overview of his treatment and present choices as well as warnings or alarms if data shows that a potential dangerous situation may occur.

[0143] When the master device 74 is connected to the central server 76 through standard communication links, the treatment data is transferred to the patient's electronic medical record. This enables an expert system on the central server to notify the care-team if needed. The care-team may send information back to the user or send help if needed.

[0144] Furthermore it is well known that due to the safety of the patient, the development of a medical device is a time consuming task. Using a local communication form between the patient's devices 71, 72, 73, 74 has the advantage that only the master device 74 need to be redesigned to keep up with the continuous change in the standard communication links.

Claims

1. A computer system having means for executing a program, where the program when executed is to make the computer execute **a method comprising the following steps:**

   - collecting, in a user individual database, data representing values of a group of parameters relating to the user's physiological condition,

   characterized by the following steps:

   - estimating one or more future values for a specific parameter from the group of the parameters on the basis of information in the user individual database, and

   - automatically calculating a plurality of options on the basis of the estimated one or more future values and the data in the user individual database, so as to provide for two or more options and at least one related value for each option, each option and related value bringing a value of the specific parameter within a range of acceptable values at a given future point in time.

2. System according to claim 1, **characterized in that** the step of collecting data comprises collecting on or more of the following :

   - individual characteristics and/or data for the the user specified by a care-team and/or a professional and/or a central system,

   - data from at least one portable apparatus,

   - manually specified input,

   - an option selected by the user and a corresponding value, and

   - the time and date.

3. System according to claims 1 - 2,
   characterized in that
   the step of collecting data comprises automatically collecting data from at least one portable apparatus and that said at least one portable apparatus is selected from the group of:

   - a body fluid analyzer,

   - a blood glucose monitor,

   - a drug administration device,

Abbott Ex. 1002 - 456/1438

- an insulin administration device,
- a tablet dispenser,
- an inhaler, and
- a continuous blood glucose monitor/sensor.

4. System according to claims 1 - 3,
characterized in that the method further
comprises the step of:

- presenting at least one apparatus dependent option of said calculated options where said apparatus dependent option involves a use of a portable apparatus, where only apparatus dependent options for present and active portable apparatuses is presented.

5. System according to claims 1 - 4,
characterized in that
the method further comprises the steps of:

- transmitting information to a drug administration device, the information comprising a predetermined number of units of a medication to be administered according to a given option of said calculated options, and
- automatically setting the number of units of the medication to be administered.

6. System according to claims 1 - 5,
characterized in that
the step of estimating is done on the basis of a dynamic model representing the human metabolism.

7. System according to claims 1 - 6,
characterized in that the step of calculating a plurality of options is done by comparing an estimated future value for the specific parameter with a predetermined target value and for each option calculating the related value for the given option by using the difference between the estimated value for the specific parameter and the target value and using a relationship between the given option and the specific parameter.

8. System according to claims 1 - 7,
characterized in that the method further comprises the step of notifying said user if at least one of said one or more future values are outside a predetermined range of acceptable values.

9. System according to claims 1 - 8,
characterized in that said method further comprises the step of notifying a care-team/professional/central system if at least one o said one or more future values are outside a predetermined range of acceptable values.

10. System according to claims 1 - 9
characterized in that said one or more future
values represents a predicted blood glucose level (BGL) at different future points in time.

11. System according to claims 1 - 10,
characterized in that said group of parameters comprises one or more of the following

- a blood glucose level (BGL),
- a body fluid concentration,
- an amount of administered medication,
- an amount of administered insulin,

Abbott Ex. 1002 - 457/1438

- a type of medication,
- a time stamp,
- an amount of intake of food,
- an amount of intake of drinks,
- a measurement of physical activity,
- a value representing the Insulin sensitivity for the user,
- a temperature of the user,
- a blood pressure of the user, and
- a weight of said user.

12. System according to claims 1 - 11,
characterized in that said options are selected from the group of

- administer a predetermined type and amount of medication,
- administer slow acting insulin,
- administer fast acting insulin,
- administer tablets,
- exercise for a given period of time,
- intake a given amount of food, and
- intake a given amount of drinks.

13. A system according to claim 1 - 12,
characterized in that said method relates to one or more of the following medications:

- insulin,
- growth hormones,
- OHA (Oral Hyperglychemical Agent), and
- HRT (Hormone Replacement Therapy).

14. A system according to claims 1 - 13,
characterized in that said method further comprises the step of controlling data information between a plurality of portable apparatuses for use by the user, the use including a first action and at. least a second action, said portable apparatuses comprising a first apparatus (15) for performing the first action, and at least a second apparatus for performing the second action, where

- each apparatus has means for one or more of the following: storing, transmitting, receiving, processing and displaying information,
- an attempted data communication between said apparatuses is initiated an request, said communication being controlled by a functional master module,

Abbott Ex. 1002 - 458/1438

- designating said functional master module among at least two of said apparatuses, and
- designating a processing apparatus comprising said one or more databases among at least two of said apparatuses.

15. A system according to claim 14,
characterized in that program information having the highest priority with respect to control and monitoring of mutual data communication between said apparatuses is stored/activated in said functional master module.

16. A system according to claims 14 - 15,
characterized in that said method further comprises designating a new functional master module if the current designated master module becomes unavailable.

17. A system according to claims 14 - 15,
characterized in that said method further comprises designating a new processing apparatus if the current designated processing apparatus becomes unavailable.

18. A computer readable medium having a program recorded thereon, where the program when executed is to make the computer execute **a method comprising the following steps:**

- collecting, in a user individual database, data representing values of a group of parameters relating to the user's physiological condition,

characterized by the following steps:

- estimating one or more future values for a specific parameter from the group of the parameters on the basis of information in the user individual database, and
- automatically calculating a plurality of options on the basis of the estimated one or more future values and the data in the user individual database, so as to provide for two or more options and at least one related value for each option, each option and related value bringing a value of the specific parameter within a range of acceptable values at a given point in time.

19. Medium according to claim 18,
characterized in that
the step of collecting data comprises collecting one or more of the following:

- individual characteristics and/or data for the user specified by a care-team and/or a professional and/or a central system,
- data from at least one portable apparatus,
- manually specified input,
- an option selected by the user and a corresponding value, and
- the time and date.

20. Medium according to claims 18-19,
characterized in that
the step of collecting data comprises automatically collecting data from at least one portable apparatus and that said at least one portable apparatus is selected from the group of:

- a body fluid analyzer,
- a blood glucose monitor,
- a drug administration device,

Abbott Ex. 1002 - 459/1438

- an insulin administration device,
- a tablet dispenser,
- an inhaler, and
- a continuous blood glucose monitor/sensor.

21. Medium according to claims 18-20
characterized in that the method further comprises the step of:

- presenting at least one apparatus dependent option of said calculated options where said apparatus dependent option involves a use of a portable apparatus, where only apparatus dependent options for present and active portable apparatuses is presented.

22. Medium according to claims 18-21,
characterized in that
the method further comprises the steps of:

- transmitting information to a drug administration device, the information comprising a predetermined number of units of a medication to be administered according to a given option of said calculated options, and
- automatically setting the number of units of the medication to be administered.

23. Medium according to claims 18-22,
characterized in that
the step of estimating is done on the basis of a dynamic model representing the human metabolism.

24. Medium according to claims 18-23,
characterized in that the step of calculating a plurality of options is done by comparing an estimated future value for the specific parameter with a predetermined target value and for each option calculating the related value for the given option by using the difference between the estimated value for the specific parameter and the target value and using a relationship between the given option and the specific parameter.

25. Medium according to claims 18-24
characterized in that the method further comprises the step of notifying said user if at least one of said one or more future values are outside a predetermined range of acceptable values.

26. Medium according to claims 18-25,
characterized in that said method further comprises the step of notifying a care-team/professional/central system if at least one o said one or more future values are outside a predetermined range of acceptable values.

27. Medium according to claims 18-26
characterized in that said one or more future
values represents a predicted blood glucose level (BGL) at different future points in time.

28. Medium according to claims 18-27,
characterized in that said group of parameters comprises one or more of the following

- a blood glucose level (BGL),
- a body fluid concentration,
- an amount of administered medication,
- an amount of administered insulin,
- a type of medication,

Abbott Ex. 1002 - 460/1438

- a time stamp,
- an amount of intake of food,
- an amount of intake of drinks,
- a measurement of physical activity,
- a value representing the Insulin sensitivity for the user,
- a temperature of the user,
- a blood pressure of the user, and
- a weight of said user.

29. Medium according to claims 18-28,
characterized in that said options are selected from the group of

- administer a predetermined type and amount of medication,
- administer slow acting insulin,
- administer fast acting insulin,
- administer tablets,
- exercise for a given period of time,
- intake a given amount of food, and
- intake a given amount of drinks.

30. A medium according to claim 18-29,
characterized in that said method relates to one or more of the following medications:

- insulin,
- growth hormones,
- OHA (Oral Hyperglychemical Agent), and
- HRT (Hormone Replacement Therapy).

31. A medium according to claims 18-30,
characterized in that said method further comprises the step of controlling data information between a plurality of portable apparatuses for use by the user, the use including a first action and at. least a second action, said portable apparatuses comprising a first apparatus (15) for performing the first action, and at least a second apparatus for performing the second action, where

- each apparatus has means for one or more of the following: storing, transmitting, receiving, processing and displaying information,
- an attempted data communication between said apparatuses is initiated an request, said communication being controlled by a functional master module,
- designating said functional master module among at least two of said apparatuses, and
- designating a processing apparatus comprising said one or more databases among at least two of said apparatuses.

32. A medium according to claim 31,
characterized in that program information having the highest priority with respect to control and monitoring of mutual data communication between said apparatuses is stored/activated in said functional master module.

Abbott Ex. 1002 - 461/1438

33. A medium according to claims 31-32, ***characterized in that*** said method further comprises designating a new functional master module if the current designated master module becomes unavailable.

34. A medium according to claims 31-32,
characterized in that said method further comprises designating a new processing apparatus if the current designated processing apparatus becomes unavailable.

35. An apparatus for calculating a plurality of options for bringing a user into and/or keeping a user substantially in compliance with a medical regime of a medical self treatment, the apparatus comprising:

- means programmed to collect data in a user individual database in memory means, the data representing values of a group of parameters relating to the user's physiological condition,

characterized by

- processing means programmed to estimate one or more future values for a specific parameter from the group of the parameters on the basis of information in the user individual database, and where the processing means is further programmed to automatically calculate a plurality of options on the basis of the estimated one or more future values and the data in the user individual database, so as to provide for two or more options and at least one related value for each option, each option and related value bringing a value of the specific parameter within a range of acceptable values at a given future point in time.

36. Apparatus according to claim 35,
characterized in that the means for collecting data is adapted to collect one or more of the following:

individual characteristics for the user specified by a care-team/professional/central system,

data from at least one portable apparatus,

manually specified input,

an option selected by the user and a corresponding value, and

the time and date.

37. Apparatus according to claims 35-36,
characterized in that the means for collecting data is adapted to automatically collect data from at least one portable apparatus and that said at least one portable apparatus is selected from the group of:

a body fluid analyzer,

a blood glucose monitor,

a drug administration device, an insulin administration device,

a tablet dispenser,

an inhaler, and

a continuous blood glucose monitor/sensor.

38. Apparatus according to claim 37,
characterized in that the apparatus further comprises means for:

- presenting at least one apparatus dependent option of said calculated options where said apparatus dependent option involves a use of a portable apparatus, where only apparatus dependent options for present and active portable apparatuses is presented.

Abbott Ex. 1002 - 462/1438

39. Apparatus according to claims 35-38,
characterized in that the apparatus is further adapted to:

- transmit information to a drug administration device, the information comprising a predetermined number of units of a medication to be administered according to a given option of said calculated options, and enable automatic setting of the, number of units of the medication to be administered in the drug administration device.

40. Apparatus according to claims 35-39,
characterized in that said estimation of one or more future values is done on the basis of a dynamic model representing the human metabolism.

41. Apparatus according to claims 35-40,
characterized in that the processing means is adapted to calculate the plurality of options by comparing an estimated future value for the specific parameter with a predetermined target value and for each option calculating the related value for the given option by using the difference between the estimated value for the specific parameter and the target value and using a relationship between the given option and the specific parameter.

42. Apparatus according to claims 35-41,
characterized in that said apparatus further comprises means for notifying said user if at least one of said one or more future values are outside a predetermined range of acceptable values.

43. Apparatus according to claims 35-42,
characterized in that said apparatus further comprises means for notifying .at least one of a care-team, a professional and a central system if at least one of said one or more future values are outside a predetermined range of acceptable values.

44. Apparatus according to claims 35-43,
characterized in that said self treatment is a self treatment for diabetes and said one or more future values represents a predicted blood glucose level (BGL) at different future points in time.

45. Apparatus according to claims 35-44,
characterized in that said group of parameters comprises one or more of the following

a blood glucose level (BGL),

a body fluid concentration,

an amount of administered medication,

an amount of administered insulin,

a type of medication,

a time stamp,

an amount of intake of food,

an amount of intake of drinks,

a measurement of physical activity,

a value representing the insulin sensitivity for the user,

a temperature of the user,

a blood pressure of the user, and

a weight of said user.

Abbott Ex. 1002 - 463/1438

46. Apparatus according to claims 35-45,
characterized in that said options are selected from the group of

- administer a predetermined type and amount of medication,
- administer slow acting insulin,
- administer fast acting insulin,
- administer tablets,
- exercise for a given period of time,
- intake a given amount of food, and
- intake a given amount of drinks.

47. Apparatus according to claims 35 - 46,
characterized in that said apparatus relates to one or more of the following medications:

- insulin,
- growth hormones,
- OHA (Oral Hyperglychemical Agent), and
- HRT (Hormone Replacement Therapy).

48. Apparatus according to claims 35-47,
characterized in that said apparatus further comprises means for controlling data information between a plurality of portable apparatuses for use by a patient for medical self treatment, the treatment including a first action and at least a second action, said portable apparatuses comprising a first apparatus for performing the first operation, and at least a second apparatus for performing the second action, where

- each apparatus belonging to the medical self treatment has means for one or more of the following: storing, transmitting, receiving, processing arid displaying information,
- an attempted data communication between said apparatuses is initiated an request, said communication being controlled by a functional master module,
- designating said functional master module among at least two of said apparatuses, and
- designating a processing apparatus comprising said memory means among at least two of said apparatuses.

49. Apparatus according to claim 48, ***characterized in that*** program information having the highest priority with respect to control arid monitoring of mutual data communication between said apparatuses is stored/activated in said functional master module.

50. Apparatus according to claims 48-49,
characterized in that said apparatus further comprises means for designating a new functional master module if the current designated master module becomes unavailable.

51. Apparatus according to claims 48-49,
characterized in that said apparatus further comprises means for designating a new processing apparatus if the current designated processing apparatus becomes unavailable.

Abbott Ex. 1002 - 464/1438

Patentansprüche

1. Computersystem mit Elementen zum Durchführen eines Programms, wobei das Programm beim Durchführen bewirkt, dass der Computer ein Verfahren durchführt, umfassend die folgenden Schritte:

   - Sammeln von Daten, die Werte einer Gruppe von mit dem physiologischen Zustand des Anwenders verbundenen Parametern darstellen, in einer Anwender-individuellen Datenbank,

   durch die folgenden Schritte gekennzeichnet:

   - Schätzen eines oder mehrerer zukünftiger Werte für einen spezifischen Parameter aus der Gruppe von Parametern auf der Basis von Information in der Anwender-individuellen Datenbank und
   - automatisches Berechnen einer Vielzahl von Optionen auf der Basis des einen geschätzten zukünftigen Werts oder der mehreren geschätzten zukünftigen Werte und der Daten in der Anwender-individuellen Datenbank, so dass zwei oder mehrere Optionen und mindestens ein damit verbundener Wert für jede Option bereitgestellt werden, wobei jede Option und jeder damit verbundene Wert einen Wert des spezifischen Parameters zu einem vorgegebenen zukünftigen Zeitpunkt innerhalb eines Bereichs von annehmbaren Werten bringt.

2. System nach Anspruch 1, **dadurch gekennzeichnet, dass** der Schritt des Sammelns von Daten das Sammeln eines oder mehrere von Folgendem umfasst:

   - individuelle Eigenschaften und/oder Daten für den Verwender, die von einem Behandlungsteam und/oder einem Experten und/oder einem zentralen System spezifiziert sind,
   - Daten von mindestens einer tragbaren Apparatur,
   - manuell spezifizierte Eingabe,
   - eine vom Anwender ausgewählten Option und ein entsprechender Wert und
   - die Zeit und das Datum.

3. System nach den Ansprüchen 1 - 2,
   dadurch gekennzeichnet, dass der Schritt des Sammelns von Daten, das automatische Sammeln von Daten aus mindestens einer tragbaren Apparatur umfasst, und dass die mindestens eine tragbare Apparatur ausgewählt ist aus

   - einem Körperflüssigkeitsanalysator,
   - einem Blutzuckerüberwachungsgerät,
   - einer Vorrichtung zur Verabreichung eines Arzneimittels,
   - einer Vorrichtung zur Verabreichung von Insulin,
   - einem Tablettenverteiler,
   - einem Inhalator und
   - einem kontinuierlichen Blutzuckerüberwachungsgerät/-messfühler.

4. System nach den Ansprüchen 1 - 3,
   dadurch gekennzeichnet, dass das Verfahren ferner die folgenden Schritte umfasst:

   - Bereitstellen mindestens einer Apparatur-abhängigen Option der berechneten Optionen, wobei die Apparatur-abhängige Option die Verwendung einer tragbaren Apparatur beinhalten, wobei nur Apparatur-abhängige Optionen für gegenwärtige und aktive, tragbare Apparaturen bereitgestellt werden.

5. System nach den Ansprüchen 1 - 4,
   dadurch gekennzeichnet, dass das Verfahren ferner den Schritt des

   - Übertragens von Information an eine Vorrichtung zur Arzneimittelverabreichung, wobei die Information eine vorbestimmte Anzahl an Einheiten für eine gemäß einer vorgegebenen Option der berechneten Optionen zu verabreichende Medikation umfasst, und
   - automatischen Einstellens der Anzahl an Einheiten der zu verabreichenden Medikation

   umfasst.

Abbott Ex. 1002 - 465/1438

6. System nach den Ansprüchen 1 - 5,
dadurch gekennzeichnet, dass der Schritt des Schätzens auf der Basis eines dynamischen Modells, das den menschlichen Stoffwechsel darstellt, durchgeführt wird.

7. System nach den Ansprüchen 1 - 6,
dadurch gekennzeichnet, dass der Schritt des Berechnens einer Vielzahl von Optionen durch Vergleichen eines geschätzten zukünftigen Werts für den spezifischen Parameter mit einem vorbestimmten Zielwert und Berechnen für jede Option des damit verbundenen Werts für eine vorgegebene Option unter Verwendung des Unterschieds zwischen dem geschätzten Wert für den spezifischen Parameter und dem Zielwert und unter Verwendung eines Verhältnisses zwischen der vorgegebenen Option und dem spezifischen Parameter durchgeführt wird.

8. System nach den Ansprüchen 1 - 7,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt des Benachrichtigens des Anwenders, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

9. System nach den Ansprüchen 1 - 8,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt des Benachrichtigendens Behandlungsteams/Experten/zentralen Systems, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

10. System nach den Ansprüchen 1 - 9
dadurch gekennzeichnet, dass der eine zukünftige Wert oder die mehreren zukünftigen Werte einen vorhergesagten Blutzuckergehalt (blood glucose level, BGL) zu verschiedenen zukünftigen Zeitpunkten darstellt.

11. System nach den Ansprüchen 1-10,
dadurch gekennzeichnet, dass die Gruppe von Parametern eines oder mehrere von Folgendem umfasst:

- den Blutzuckergehalt (BGL),
- die Körperflüssigkeitskonzentration,
- die Menge an verabreichter Medikation,
- die Menge an verabreichtem Insulin,
- die Medikationsart,
- einen Zeitstempel,
- die Nahrungsmittelaufnahmemenge,
- die Getränkeaufnahmemenge,
- die Messung der physikalischen Aktivität,
- den Wert, der die Insulinempfindlichkeit für den Anwender darstellt,
- die Temperatur des Anwenders,
- den Blutdruck des Anwenders und
- das Gewicht des Anwenders.

12. System nach den Ansprüchen 1-11,
dadurch gekennzeichnet, dass die Optionen ausgewählt sind aus

- Verabreichen einer vorbestimmten Medikationsart und -menge,
- Verabreichen von langsam wirkendem Insulin,
- Verabreichen von schnell wirkendem Insulin,
- Verabreichen von Tabletten,
- Durchführen für eine vorgegebene Zeitdauer,
- Aufnahme einer vorgegebenen Nahrungsmittelmenge und
- Aufnahme einer vorgegebenen Getränkemenge.

13. System nach den Ansprüchen 1-12,
dadurch gekennzeichnet, dass das Verfahren eine oder mehrere der folgenden Medikationen betrifft:

- Insulin,
- Wachstumshormone,

Abbott Ex. 1002 - 466/1438

- OHA (orales, hyperglykämisches Mittel) und
- HRT (Hormonersatztherapie).

14. System nach den Ansprüchen 1-13,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt der Steuerung von Dateninformation zwischen einer Vielzahl von tragbaren Apparaturen zur Verwendung durch den Anwender umfasst, wobei die Verwendung eine erste Handlung und mindestens eine zweite Handlung einschließt, wobei die tragbare Apparatur eine erste Apparatur (15) zur Durchführung der ersten Handlung und mindestens eine zweite Apparatur zur Durchführung der zweiten Handlung umfasst, wobei

- jede Apparatur Elemente für eines oder mehrere von Folgendem aufweist: Speicherung, Übertragung, Empfang, Verarbeitung und Anzeigen von Information,
- eine versuchte Datenkommunikation zwischen der Apparatur eine Aufforderung initiiert, wobei die Kommunikation durch ein funktionelles Hauptmodul gesteuert wird,
- Benennen des funktionellen Hauptmoduls unter mindestens zwei der Apparaturen und
- Benennen einer die eine oder mehreren Datenbanken umfassenden Verarbeitungsapparatur unter mindestens zwei der Apparaturen.

15. System nach Anspruch 14,
dadurch gekennzeichnet, dass eine Programminformation mit der höchsten Priorität im Hinblick auf die Steuerung und das Überwachen von wechselseitiger Datenkommunikation zwischen den Apparaturen im funktionellen Hauptmodul gespeichert/aktiviert wird.

16. System nach den Ansprüchen 14 - 15,
dadurch gekennzeichnet, dass das Verfahren ferner das Benennen eines neuen funktionellen Hauptmoduls umfasst, wenn das gegenwärtige benannte Hauptmodul unverfügbar wird.

17. System nach den Ansprüchen 14 - 15,
dadurch gekennzeichnet, dass das Verfahren ferner das Benennen einer neuen Verarbeitungsapparatur umfasst, wenn die gegenwärtige benannte Verarbeitungsapparatur unverfügbar wird.

18. Computer-lesbares Medium mit einem darauf aufgezeichneten Programm, wobei das Programm beim Durchführen bewirkt, dass der Computer ein Verfahren durchführt, umfassend die folgenden Schritte:

- Sammeln von Daten, die Werte einer Gruppe von mit dem physiologischen Zustand des Anwenders verbundenen Parametern darstellen, in einer Anwender-individuellen Datenbank,

durch die folgenden Schritte gekennzeichnet:

- Schätzen eines oder mehrerer zukünftiger Werte für einen spezifischen Parameter aus der Gruppe von Parametern auf der Basis von Information in der Anwender-individuellen Datenbank und
- automatisches Berechnen einer Vielzahl von Optionen auf der Basis des einen geschätzten zukünftigen Werts oder der mehreren geschätzten zukünftigen Werte und der Daten in der Anwender-individuellen Datenbank, so dass zwei oder mehrere Optionen und mindestens ein damit verbundener Wert für jede Option bereitgestellt werden, wobei jede Option und jeder damit verbundene Wert des spezifischen Parameters zu einem vorgegebenen Zeitpunkt innerhalb eines Bereichs von annehmbaren Werten liegt.

19. Medium nach Anspruch 18, **dadurch gekennzeichnet, dass** der Schritt des Sammelns von Daten das Sammeln eines oder mehrere von Folgendem umfasst:

- individuelle Eigenschaften und/oder Daten für den Verwender, die von einem Behandlungsteam und/oder einem Experten und/oder einem zentralen System spezifiziert sind,
- Daten von mindestens einer tragbaren Apparatur,
- manuell spezifizierte Eingabe,
- eine vom Anwender ausgewählten Option und ein entsprechender Wert und
- die Zeit und das Datum.

20. Medium nach den Ansprüchen 18 - 19,

Abbott Ex. 1002 - 467/1438

dadurch gekennzeichnet, dass der Schritt des Sammelns von Daten, das automatische Sammeln von Daten aus mindestens einer tragbaren Apparatur umfasst, und dass die mindestens eine tragbare Apparatur ausgewählt ist aus

- einem Körperflüssigkeitsanalysator,
- einem Blutzuckerüberwachungsgerät,
- einer Vorrichtung zur Verabreichung eines Arzneimittels,
- einer Vorrichtung zur Verabreichung von Insulin,
- einem Tablettenverteiler,
- einem Inhalator und
- einem kontinuierlichen Blutzuckerüberwachungsgerät/-messfühler.

21. Medium nach den Ansprüchen 18 - 20,
dadurch gekennzeichnet, dass das Verfahren ferner die folgenden Schritte umfasst:

- Bereitstellen mindestens einer Apparatur-abhängigen Option der berechneten Optionen, wobei die Apparatur-abhängige Option die Verwendung einer tragbaren Apparatur beinhalten, wobei nur Apparatur-abhängige Optionen für gegenwärtige und aktive, tragbare Apparaturen bereitgestellt werden.

22. Medium nach den Ansprüchen 18-21,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt des

- Übertragens von Information an eine Vorrichtung zur Arzneimittelverabreichung, wobei die Information eine vorbestimmte Anzahl an Einheiten für eine gemäß einer vorgegebenen Option der berechneten Optionen zu verabreichende Medikation umfasst, und
- automatischen Einstellens der Anzahl an Einheiten der zu verabreichenden Medikation

umfasst.

23. Medium nach den Ansprüchen 18 - 22,
dadurch gekennzeichnet, dass der Schritt des Schätzens auf der Basis eines dynamischen Modells, das den menschlichen Stoffwechsel darstellt, durchgeführt wird.

24. Medium nach den Ansprüchen 13 - 23,
dadurch gekennzeichnet, dass der Schritt des Berechnens einer Vielzahl von Optionen durch Vergleichen eines geschätzten zukünftigen Werts für den spezifischen Parameter mit einem vorbestimmten Zielwert und Berechnen für jede Option des damit verbundenen Werts für eine vorgegebene Option unter Verwendung des Unterschieds zwischen dem geschätzten Wert für den spezifischen Parameter und dem Zielwert und unter Verwendung eines Verhältnisses zwischen der vorgegebenen Option und dem spezifischen Parameter durchgeführt wird.

25. Medium nach den Ansprüchen 18 - 24,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt des Benachrichtigens des Anwenders, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

26. Medium nach den Ansprüchen 18 - 25,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt des Benachrichtigens Behandlungsteams/Experten/zentralen Systems, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

27. Medium nach den Ansprüchen 18 - 26,
dadurch gekennzeichnet, dass der eine zukünftige Wert oder die mehreren zukünftigen Werte einen vorhergesagten Blutzuckergehalt (blood glucose level, BGL) zu verschiedenen zukünftigen Zeitpunkten darstellt.

28. Medium nach den Ansprüchen 18-27,
dadurch gekennzeichnet, dass die Gruppe von Parametern eines oder mehrere von Folgendem umfasst:

- den Blutzuckergehalt (BGL),

Abbott Ex. 1002 - 468/1438

- die Körperflüssigkeitskonzentration,
- die Menge an verabreichter Medikation,
- die Menge an verabreichtem Insulin,
- die Medikationsart,
- einen Zeitstempel,
- die Nahrungsmittelaufnahmemenge,
- die Getränkeaufnahmemenge,
- die Messung der physikalischen Aktivität,
- den Wert, der die Insulinempfindlichkeit für den Anwender darstellt,
- die Temperatur des Anwenders,
- den Blutdruck des Anwenders und
- das Gewicht des Anwenders.

29. Medium nach den Ansprüchen 18 - 28,
dadurch gekennzeichnet, dass die Optionen ausgewählt sind aus

- Verabreichen einer vorbestimmten Medikationsart und -menge,
- Verabreichen von langsam wirkendem Insulin,
- Verabreichen von schnell wirkendem Insulin,
- Verabreichen von Tabletten,
- Durchführen für eine vorgegebene Zeitdauer,
- Aufnahme einer vorgegebenen Nahrungsmittelmenge und
- Aufnahme einer vorgegebenen Getränkemenge.

30. Medium nach den Ansprüchen 18 - 29,
dadurch gekennzeichnet, dass das Verfahren eine oder mehrere der folgenden Medikationen betrifft:

- Insulin,
- Wachstumshormone,
- OHA (orales, hyperglykämisches Mittel) und
- HRT (Hormonersatztherapie).

31. Medium nach den Ansprüchen 18 - 30,
dadurch gekennzeichnet, dass das Verfahren ferner den Schritt der Steuerung von Dateninformation zwischen einer Vielzahl von tragbaren Apparaturen zur Verwendung durch den Anwender umfasst, wobei die Verwendung eine erste Handlung und mindestens eine zweite Handlung einschließt, wobei die tragbare Apparatur eine erste Apparatur (15) zur Durchführung der ersten Handlung und mindestens eine zweite Apparatur zur Durchführung der zweiten Handlung umfasst, wobei

- jede Apparatur Elemente für eines oder mehrere von Folgendem aufweist: Speicherung, Übertragung, Empfang, Verarbeitung und Anzeigen von Information,
- eine versuchte Datenkommunikation zwischen der Apparatur eine Aufforderung initiiert, wobei die Kommunikation durch ein funktionelles Hauptmodul gesteuert wird,
- Benennen des funktionellen Hauptmoduls unter mindestens zwei der Apparaturen und
- Benennen einer die eine oder mehreren Datenbanken umfassenden Verarbeitungsapparatur unter mindestens zwei der Apparaturen.

32. Medium nach Anspruch 31,
dadurch gekennzeichnet, dass eine Programminformation mit der höchsten Priorität im Hinblick auf die Steuerung und das Überwachen von wechselseitiger Datenkommunikation zwischen den Apparaturen im funktionellen Hauptmodul gespeichert/aktiviert wird.

33. Medium nach den Ansprüchen 31 - 31,
dadurch gekennzeichnet, dass das Verfahren ferner das Benennen eines neuen funktionellen Hauptmoduls umfasst, wenn das gegenwärtige benannte Hauptmodul unverfügbar wird.

34. Medium nach den Ansprüchen 31 - 32,
dadurch gekennzeichnet, dass das Verfahren ferner das Benennen einer neuen Verarbeitungsapparatur um-

Abbott Ex. 1002 - 469/1438

fasst, wenn die gegenwärtige benannte Verarbeitungsapparatur unverfügbar wird.

35. Apparatur zum Berechnen einer Vielzahl von Optionen zum Bewirken oder Aufrechterhalten dessen, dass ein Anwender eine medizinische Verordnung einer medizinischen Selbstbehandlung im Wesentlichen einhält, wobei die Apparatur

- ein Element umfasst, das so programmiert ist, dass Daten in einer Anwender-individuellen Datenbank in Speicherelementen gesammelt werden, wobei die Daten Werte einer Gruppe von mit dem physiologischen Zustand des Anwenders verbundenen Parametern darstellen,

gekennzeichnet durch

- ein Verarbeitungselement, das so programmiert ist, dass ein oder mehrere zukünftige Werte für einen spezifischen Parameter aus der Gruppe von Parametern auf der Basis von Information in der Anwender-individuellen Datenbank geschätzt werden und wobei das Verarbeitungselement ferner so programmiert ist, dass eine Vielzahl von Optionen auf der Basis des einen geschätzten Werts oder der mehreren geschätzten zukünftigen Werte und der Daten in der Anwender-individuellen Datenbank berechnet werden, so dass zwei oder mehrere Optionen und mindestens ein damit verbundener Wert für jede Option bereitgestellt wird, wobei jede Option und jeder damit verbundene Wert einen Wert des spezifischen Parameters bei einem vorgegebenen zukünftigen Zeitpunkt innerhalb eines Bereichs von annehmbaren Werten bringt.

36. Apparatur nach Anspruch 35, **dadurch gekennzeichnet, dass** das Element zum Sammeln von Daten so angepasst ist, dass eines oder mehrere von Folgendem gesammelt wird:

- individuelle Eigenschaften und/oder Daten für den Verwender, die von einem Behandlungsteam und/oder einem Experten und/oder einem zentralen System spezifiziert sind,
- Daten von mindestens einer tragbaren Apparatur,
- manuell spezifizierte Eingabe,
- eine vom Anwender ausgewählten Option und ein entsprechender Wert und
- die Zeit und das Datum.

37. Apparatur nach den Ansprüchen 35 - 36,
dadurch gekennzeichnet, dass das Element zum Sammeln von Daten so angepasst ist, dass Daten aus mindestens einer tragbaren Apparatur gesammelt werden, und dass die mindestens eine tragbare Apparatur ausgewählt ist aus

- einem Körperflüssigkeitsanalysator,
- einem Blutzuckerüberwachungsgerät,
- einer Vorrichtung zur Verabreichung eines Arzneimittels,
- einer Vorrichtung zur Verabreichung von Insulin,
- einem Tablettenverteiler,
- einem Inhalator und
- einem kontinuierlichen Blutzuckerüberwachungsgerät/-messfühler.

38. Apparatur nach Anspruch 37,
dadurch gekennzeichnet, dass das Verfahren ferner ein Element zum

- Bereitstellen mindestens einer Apparatur-abhängigen Option der berechneten Optionen, wobei die Apparatur-abhängige Option die Verwendung einer tragbaren Apparatur beinhalten, wobei nur Apparatur-abhängige Optionen für gegenwärtige und aktive, tragbare Apparaturen bereitgestellt werden.

umfasst.

39. Apparatur nach den Ansprüchen 35 - 38,
dadurch gekennzeichnet, dass das Verfahren ferner so angepasst ist, dass

- Information an eine Vorrichtung zur Arzneimittelverabreichung übertragen wird, wobei die Information eine vorbestimmte Anzahl an Einheiten für eine gemäß einer vorgegebenen Option der berechneten Optionen zu

Abbott Ex. 1002 - 470/1438

verabreichende Medikation umfasst, und automatisches Einstellen der Anzahl an Einheiten des zu verabreichenden Arzneimittels in der Vorrichtung zur Verabreichung eines Arzneimittels ermöglicht wird.

40. Apparatur nach den Ansprüchen 35 - 39,
dadurch gekennzeichnet, die Schätzung des einen zukünftigen Werts oder der mehreren zukünftigen Werte auf der Basis eines dynamischen Modells, das den menschlichen Stoffwechsel darstellt, durchgeführt wird.

41. Apparatur nach den Ansprüchen 35 - 40,
dadurch gekennzeichnet, dass das Verarbeitungselement so angepasst ist, dass die Vielzahl von Optionen durch Vergleichen eines geschätzten zukünftigen Werts für den spezifischen Parameter mit einem vorbestimmten Zielwert und Berechnen für jede Option des damit verbundenen Werts für eine vorgegebene Option unter Verwendung des Unterschieds zwischen dem geschätzten Wert für den spezifischen Parameter und dem Zielwert und unter Verwendung eines Verhältnisses zwischen der vorgegebenen Option und dem spezifischen Parameter berechnet wird.

42. Apparatur nach den Ansprüchen 35-41,
dadurch gekennzeichnet, dass die Apparatur ferner ein Element zum Benachrichtigen des Anwenders, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

43. Apparatur nach den Ansprüchen 35-42,
dadurch gekennzeichnet, dass die Apparatur ferner ein Element zum Benachrichtigen des Behandlungsteams, eines Experten und eines zentralen Systems, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

44. Apparatur nach den Ansprüchen 35-43,
dadurch gekennzeichnet, dass die Selbstbehandlung eine Selbstbehandlung für Diabetes ist und der eine zukünftige Wert oder die mehreren zukünftigen Werte einen vorhergesagten Blutzuckergehalt (BGL) zu verschiedenen zukünftigen Zeitpunkten darstellt.

45. Apparatur nach den Ansprüchen 35-44,
dadurch gekennzeichnet, dass die Gruppe von Parametern eines oder mehrere von Folgendem umfasst:

- den Blutzuckergehalt (BGL),
- die Körperflüssigkeitskonzentration,
- die Menge an verabreichter Medikation,
- die Menge an verabreichtem Insulin,
- die Medikationsart,
- einen Zeitstempel
- die Nahrungsmittelaufnahmemenge,
- die Getränkeaufnahmemenge,
- die Messung der physikalischen Aktivität,
- den Wert, der die Insulinempfindlichkeit für den Anwender darstellt,
- die Temperatur des Anwenders,
- den Blutdruck des Anwenders und
- das Gewicht des Anwenders.

46. Apparatur nach den Ansprüchen 35-45,
dadurch gekennzeichnet, dass die Optionen ausgewählt sind aus

- Verabreichen einer vorbestimmten Medikationsart und -menge,
- Verabreichen von langsam wirkendem Insulin,
- Verabreichen von schnell wirkendem Insulin,
- Verabreichen von Tabletten,
- Durchführen für eine vorgegebene Zeitdauer,
- Aufnahme einer vorgegebenen Nahrungsmittelmenge und
- Aufnahme einer vorgegebenen Getränkemenge.

Abbott Ex. 1002 - 471/1438

47. Apparatur nach den Ansprüchen 35-46,
dadurch gekennzeichnet, dass das Verfahren eine oder mehrere der folgenden Medikationen betrifft:

- Insulin,
- Wachstumshormone,
- OHA (orales, hyperglykämisches Mittel) und
- HRT (Hormonersatztherapie).

48. Apparatur nach den Ansprüchen 35 - 47,
dadurch gekennzeichnet, dass das Verfahren ferner ein Element zur Steuerung von Dateninformation zwischen einer Vielzahl von tragbaren Apparaturen zur Verwendung durch den Anwender für medizinische Selbstbehandlung umfasst, wobei die Selbstbehandlung eine erste Handlung und mindestens eine zweite Handlung einschließt, wobei die tragbare Apparatur eine erste Apparatur (15) zur Durchführung der ersten Handlung und mindestens eine zweite Apparatur zur Durchführung der zweiten Handlung umfasst, wobei

- jede Apparatur Elemente für eines oder mehrere von Folgendem aufweist: Speicherung, Übertragung, Empfang, Verarbeitung und Anzeigen von Information,
- eine versuchte Datenkommunikation zwischen der Apparatur eine Aufforderung initiiert, wobei die Kommunikation durch ein funktionelles Hauptmodul gesteuert wird,
- Benennen des funktionellen Hauptmoduls unter mindestens zwei der Apparaturen und
- Benennen einer die eine oder mehreren Datenbanken umfassenden Verarbeitungsapparatur unter mindestens zwei der Apparaturen.

49. Apparatur nach Anspruch 48,
dadurch gekennzeichnet, dass eine Programminformation mit der höchsten Priorität im Hinblick auf die Steuerung und das Überwachen von wechselseitiger Datenkommunikation zwischen den Apparaturen im funktionellen Hauptmodul gespeichert/aktiviert wird.

50. Apparatur nach den Ansprüchen 48 - 49,
dadurch gekennzeichnet, dass die Apparatur ferner ein Element zum Benennen eines neuen funktionellen Hauptmoduls umfasst, wenn das gegenwärtige benannte Hauptmodul unverfügbar wird.

51. Apparatur nach den Ansprüchen 48 - 49,
dadurch gekennzeichnet, dass das Verfahren ferner ein Element zum Benennen einer neuen Verarbeitungsapparatur umfasst, wenn die gegenwärtige benannte Verarbeitungsapparatur unverfügbar wird.

Revendications

1. Système informatique ayant des moyens pour exécuter un programme, dans lequel le programme, lorsqu'il est exécuté, consiste à amener l'ordinateur à exécuter un procédé comportant les étapes suivantes consistant à :

- collecter, dans une base de données individuelle d'utilisateur, des données représentant des valeurs d'un groupe de paramètres concernant la condition physiologique d'un utilisateur,

caractérisé par les étapes suivantes consistant à :

- estimer une ou plusieurs valeurs futures pour un paramètre spécifique du groupe des paramètres sur la base d'informations de la base de données individuelle d'utilisateur, et
- calculer automatiquement une pluralité d'options sur la base des unes ou plusieurs valeurs futures estimées et des données de la base de données individuelle d'utilisateur, de manière à fournir deux ou plus de deux options et au moins une valeur associée pour chaque option, chaque option et valeur associée amenant une valeur du paramètre spécifique dans une plage de valeurs acceptables à un instant futur donné dans le temps.

2. Système selon la revendication 1, **caractérisé en ce que** l'étape de collecte de données comporte la collecte d'un ou plusieurs éléments parmi ceux qui suivent :

- des caractéristiques individuelles et/ou des données concernant l'utilisateur spécifiées par une équipe de

Abbott Ex. 1002 - 472/1438

soins et/ou un professionnel et/ou un système central,
- des données provenant d'au moins un dispositif portable,
- une entrée manuellement spécifiée,
- une option sélectionnée par l'utilisateur et une valeur correspondante, et
- l'heure et la date.

3. Système selon les revendications 1 et 2,
caractérisé en ce que
l'étape de collecte de données comporte la collecte automatique de données à partir d'au moins un dispositif portable et **en ce que** ledit au moins un dispositif portable est sélectionné parmi le groupe constitué de :

- un analyseur de fluide corporel,
- un dispositif de surveillance de glucose sanguin,
- un dispositif d'administration de médicament,
- un dispositif d'administration d'insuline,
- un distributeur de comprimés,
- un inhalateur, et
- un dispositif de surveillance/capteur de glucose sanguin continu.

4. Système selon les revendications 1 à 3,
caractérisé en ce que le procédé comporte de plus l'étape consistant à :

- présenter au moins une option dépendante d'un dispositif parmi lesdites options calculées lorsque ladite option dépendante d'un dispositif implique l'utilisation d'un dispositif portable, seules des options dépendantes d'un dispositif pour des dispositifs porta- bles présents et actifs étant présentées.

5. Système selon les revendications 1 à 4,
caractérisé en ce que
le procédé comporte de plus les étapes consistant à :

- transmettre des informations à un dispositif d'administration de médicament, les informations comportant un nombre prédéterminé d'unités d'une médication à administrer conformément à une option donnée parmi lesdites options calculées, et
- établir automatiquement le nombre d'unités de la médication à administrer.

6. Système selon les revendications 1 à 5,
caractérisé en ce que
l'étape d'estimation est effectuée sur la base d'un modèle dynamique représentant le métabolisme humain.

7. Système selon les revendications 1 à 6,
caractérisé en ce que l'étape de calcul d'une pluralité d'options est effectuée en comparant une valeur future estimée pour le paramètre spécifique à une valeur cible prédéterminée et, pour chaque option, en calculant la valeur associée pour l'option donnée en utilisant la différence entre la valeur estimée pour le paramètre spécifique et la valeur cible et en utilisant une relation entre l'option donnée et le paramètre spécifique.

8. Système selon les revendications 1 à 7,
caractérisé en ce que le procédé comporte de plus l'étape consistant à notifier audit utilisateur si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

9. Système selon les revendications 1 à 8,
caractérisé en ce que ledit procédé comporte de plus l'étape consistant à notifier à une équipe de soins/professionnel/système central si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

10. Système selon les revendications 1 à 9,
caractérisé en ce que lesdites une ou plusieurs valeurs futures représentent un niveau de glucose sanguin prévu (BGL) à différents instants futurs dans le temps.

Abbott Ex. 1002 - 473/1438

11. Système selon les revendications 1 à 10,
caractérisé en ce que ledit groupe de paramètres comporte un ou plusieurs des éléments suivants

- un niveau de glucose sanguin (BGL),
- une concentration de fluide corporel,
- une quantité de médication administrée,
- une quantité d'insuline administrée,
- un type de médication,
- une estampille,
- une quantité d'absorption d'aliments,
- une quantité d'absorption de boissons,
- une mesure d'activité physique,
- une valeur représentant la sensibilité à l'insuline de l'utilisateur,
- une température de l'utilisateur,
- une pression sanguine de l'utilisateur, et
- un poids dudit utilisateur.

12. Système selon les revendications 1 à 11,
caractérisé en ce que lesdites options sont sélectionnées parmi le groupe constitué de :

- l'administration d'un type et d'une quantité prédéterminés de médication,
- l'administration d'une insuline à action lente,
- l'administration d'une insuline à action rapide,
- l'administration de comprimés,
- un effort pendant une période donnée de temps,
- l'absorption d'une quantité donnée d'aliments, et
- l'absorption d'une quantité donnée de boissons.

13. Système selon les revendications 1 à 12,
caractérisé en ce que ledit procédé concerne une ou plusieurs des médications suivantes :

- insuline,
- hormones de croissance,
- OHA (Agent Hyperglycémique Oral), et
- HRT (Thérapie de Remplacement d'Hormones).

14. Système selon les revendications 1 à 13,
caractérisé en ce que ledit procédé comporte de plus l'étape consistant à commander des informations de données entre une pluralité de dispositifs portables pour une utilisation par l'utilisateur, l'utilisation incluant une première action et au moins une seconde action, lesdits dispositifs portables comportant un premier dispositif (15) destiné à effectuer la première action, et au moins un second dispositif destiné à effectuer la seconde action, dans lequel

- chaque dispositif a des moyens pour réaliser une ou plusieurs fonctions suivantes : la mémorisation, la transmission, la réception, le traitement et l'affichage d'informations,
- une communication de données tentée entre lesdits dispositifs est initialisée par une requête, ladite communication étant commandée par un module maître fonctionnel,
- la désignation dudit module maître fonctionnel parmi au moins deux desdits dispositifs, et
- la désignation d'un dispositif de traitement comportant lesdites une ou plusieurs bases de données parmi au moins deux desdits dispositifs.

15. Système selon la revendication 14,
caractérisé en ce que les informations de programme ayant la priorité la plus élevée par rapport à la commande et la surveillance d'une communication de données mutuelle entre lesdits dispositifs sont mémorisées/activées dans ledit module maître fonctionnel.

16. Système selon les revendications 14 et 15,
caractérisé en ce que ledit procédé comporte de plus la désignation d'un nouveau module maître fonctionnel

Abbott Ex. 1002 - 474/1438

si le module maître désigné actuel devient indisponible.

17. Système selon les revendications 14 et 15,
caractérisé en ce que ledit procédé comporte de plus la désignation d'un nouveau dispositif de traitement si le dispositif de traitement désigné courant devient indisponible.

18. Support lisible d'ordinateur ayant un programme enregistré dessus, dans lequel le programme, lorsqu'il est exécuté, consiste à amener l'ordinateur à exécuter un procédé comportant les étapes suivantes consistant à :

- collecter, dans une base de données individuelle d'utilisateur, des données représentant des valeurs d'un groupe de paramètres concernant la condition physiologique d'un utilisateur,

caractérisé par les étapes suivantes consistant à :

- estimer une ou plusieurs valeurs futures pour un paramètre spécifique du groupe des paramètres sur la base d'informations de la base de données individuelle d'utilisateur, et
- calculer automatiquement une pluralité d'options sur la base des unes ou plusieurs valeurs futures estimées et des données de la base de données individuelle d'utilisateur, de manière à fournir deux ou plus de deux options et au moins une valeur associée pour chaque option, chaque option et valeur associée amenant une valeur du paramètre spécifique dans une plage de valeurs acceptables à un instant futur donné dans le temps.

19. Support selon la revendication 18,
caractérisé en ce que
l'étape de collecte de données comporte la collecte d'un ou plusieurs éléments parmi ceux qui suivent :

- des caractéristiques individuelles et/ou des données concernant l'utilisateur spécifiées par une équipe de soins et/ou un professionnel et/ou un système central,
- des données provenant d'au moins un dispositif portable,
- une entrée manuellement spécifiée,
- une option sélectionnée par l'utilisateur et une valeur correspondante, et
- l'heure et la date.

20. Support selon les revendications 18 et 19,
caractérisé en ce que
l'étape de collecte de données comporte la collecte automatique de données à partir d'au moins un dispositif portable et **en ce que** ledit au moins un dispositif portable est sélectionné parmi le groupe constitué de :

- un analyseur de fluide corporel,
- un dispositif de surveillance de glucose sanguin,
- un dispositif d'administration de médicament,
- un dispositif d'administration d'insuline,
- un distributeur de comprimés,
- un inhalateur, et
- un dispositif de surveillance/capteur de glucose sanguin continu.

21. Support selon les revendications 18 à 20,
caractérisé en ce que le procédé comporte de plus l'étape consistant à :

- présenter au moins une option dépendante d'un dispositif parmi lesdites options calculées lorsque ladite option dépendante d'un dispositif implique l'utilisation d'un dispositif portable, seules des options dépendantes d'un dispositif pour des dispositifs portables présents et actifs étant présentées.

22. Support selon les revendications 18 à 21,
caractérisé en ce que
le procédé comporte de plus les étapes consistant à :

- transmettre des informations à un dispositif d'administration de médicament, les informations comportant un nombre prédéterminé d'unités d'une médication à administrer conformément à une option donnée parmi les-

Abbott Ex. 1002 - 475/1438

dites options calculées, et

- établir automatiquement le nombre d'unités de la médication à administrer.

23. Support selon les revendications 18 à 22,
caractérisé en ce que
l'étape d'estimation est effectuée sur la base d'un modèle dynamique représentant le métabolisme humain.

24. Support selon les revendications 18 à 23,
caractérisé en ce que l'étape de calcul d'une pluralité d'options est effectuée en comparant une valeur future estimée pour le paramètre spécifique à une valeur cible prédéterminée et, pour chaque option, en calculant la valeur associée pour l'option donnée en utilisant la différence entre la valeur estimée pour le paramètre spécifique et la valeur cible et en utilisant une relation entre l'option donnée et le paramètre spécifique.

25. Support selon les revendications 18 à 24,
caractérisé en ce que le procédé comporte de plus l'étape consistant à notifier audit utilisateur si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

26. Support selon les revendications 18 à 25,
caractérisé en ce que ledit procédé comporte de plus l'étape consistant à notifier à une équipe de soins/professionnel/système central si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

27. Support selon les revendications 18 à 26,
caractérisé en ce que lesdites une ou plusieurs valeurs futures représentent un niveau de glucose sanguin prévu (BGL) à différents instants futurs dans le temps.

28. Support selon les revendications 18 à 27,
caractérisé en ce que ledit groupe de paramètres comporte un ou plusieurs des éléments suivants

- un niveau de glucose sanguin (BGL),
- une concentration de fluide corporel,
- une quantité de médication administrée,
- une quantité d'insuline administrée,
- un type de médication,
- une estampille,
- une quantité d'absorption d'aliments,
- une quantité d'absorption de boissons,
- une mesure d'activité physique,
- une valeur représentant la sensibilité à l'insuline de l'utilisateur,
- une température de l'utilisateur,
- une pression sanguine de l'utilisateur, et
- un poids dudit utilisateur.

29. Support selon les revendications 18 à 28,
caractérisé en ce que lesdites options sont sélectionnées parmi le groupe constitué de :

- l'administration d'un type et d'une quantité prédéterminés de médication,
- l'administration d'une insuline à action lente,
- l'administration d'une insuline à action rapide,
- l'administration de comprimés,
- un effort pendant une période donnée de temps,
- l'absorption d'une quantité donnée d'aliments, et
- l'absorption d'une quantité donnée de boissons.

30. Support selon les revendications 18 à 29,
caractérisé en ce que ledit procédé concerne une ou plusieurs des médications suivantes :

Abbott Ex. 1002 - 476/1438

- insuline,
- hormones de croissance,
- OHA (Agent Hyperglycémique Oral), et
- HRT (Thérapie de Remplacement d'Hormones).

31. Support selon les revendications 18 à 30,
caractérisé en ce que ledit procédé comporte de plus l'étape consistant à commander des informations de données entre une pluralité de dispositifs portables pour une utilisation par l'utilisateur, l'utilisation incluant une première action et au moins une seconde action, lesdits dispositifs portables comportant un premier dispositif (15) destiné à effectuer la première action, et au moins un second dispositif destiné à effectuer la seconde action, dans lequel

- chaque dispositif a des moyens pour réaliser une ou plusieurs fonctions suivantes : la mémorisation, la transmission, la réception, le traitement et l'affichage d'informations,
- une communication de données tentée entre lesdits dispositifs est initialisée par une requête, ladite communication étant commandée par un module maître fonctionnel,
- la désignation dudit module maître fonctionnel parmi au moins deux desdits dispositifs, et
- la désignation d'un dispositif de traitement comportant lesdites une ou plusieurs bases de données parmi au moins deux desdits dispositifs.

32. Support selon la revendication 31,
caractérisé en ce que les informations de programme ayant la priorité la plus élevée par rapport à la commande et la surveillance d'une communication de données mutuelle entre lesdits dispositifs sont mémorisées/activées dans ledit module maître fonctionnel.

33. Support selon les revendications 31 et 32,
caractérisé en ce que ledit procédé comporte de plus la désignation d'un nouveau module maître fonctionnel si le module maître désigné actuel devient indisponible.

34. Support selon les revendications 31 et 32,
caractérisé en ce que ledit procédé comporte de plus la désignation d'un nouveau dispositif de traitement si le dispositif de traitement désigné courant devient indisponible.

35. Dispositif pour calculer une pluralité d'options afin d'amener un utilisateur et/ou maintenir un utilisateur essentiellement en conformité avec un régime médical d'une automédication médicale, le dispositif comportant :

- des moyens programmés pour collecter des données dans une base de données individuelle d'utilisateur dans des moyens de mémoire, les données représentant des valeurs d'un groupe de paramètres concernant la condition physiologique d'un utilisateur,

caractérisé par

- des moyens de traitement programmés pour estimer une ou plusieurs valeurs futures pour un paramètre spécifique parmi le groupe des paramètres sur la base d'informations de la base de données individuelle d'utilisateur, et dans lequel les moyens de traitement sont de plus programmés pour calculer automatiquement une pluralité d'options sur la base des une ou plusieurs valeurs futures estimées et des données de la base de données individuelle d'utilisateur, de manière à fournir deux ou plus de deux options et au moins une valeur associée pour chaque option, chaque option et valeur associée amenant une valeur du paramètre spécifique dans une plage de valeurs acceptables à un instant futur donné dans le temps.

36. Dispositif selon la revendication 35,
caractérisé en ce que les moyens de collecte de données sont adaptés pour collecter un ou plusieurs des éléments suivants :

des caractéristiques individuelles concernant l'utilisateur spécifiées par une équipe de soins/professionnel/système central,
des données provenant d'au moins un dispositif portable,
une entrée manuellement spécifiée,

Abbott Ex. 1002 - 477/1438

une option sélectionnée par l'utilisateur et une valeur correspondante, et
l'heure et la date.

37. Dispositif selon les revendications 35 et 36,
caractérisé en ce que les moyens de collecte de données sont adaptés pour collecter automatiquement des données depuis au moins un dispositif portable et **en ce que** ledit au moins un dispositif portable est sélectionné parmi le groupe constitué de :

un analyseur de fluide corporel,
un dispositif de surveillance de glucose sanguin, un dispositif d'administration de médicament, un dispositif d'administration d'insuline,
un distributeur de comprimés,
un inhalateur, et
un dispositif de surveillance/capteur de glucose sanguin continu.

38. Dispositif selon la revendication 37,
caractérisé en ce que le dispositif comporte de plus des moyens pour :

- présenter au moins une option dépendante d'un dispositif parmi lesdites options calculées lorsque ladite option dépendante d'un dispositif implique l'utilisation d'un dispositif portable, seules des options dépendantes d'un dispositif pour des dispositifs portables présents et actifs étant présentées.

39. Dispositif selon les revendications 35 à 38,
caractérisé en ce que le dispositif est de plus adapté pour :

- transmettre des informations à un dispositif d'administration de médicament, les informations comportant un nombre prédéterminé d'unités d'une médication à administrer conformément à une option donnée parmi lesdites options calculées, et permettre d'établir automatiquement le nombre d'unités de la médication à administrer dans le dispositif d'administration de médicament.

40. Dispositif selon les revendications 35 à 39,
caractérisé en ce que ladite estimation d'une ou plusieurs valeurs futures est effectuée sur la base d'un modèle dynamique représentant le métabolisme humain.

41. Dispositif selon les revendications. 35 à 40,
caractérisé en ce que les moyens de traitement sont adaptés pour calculer la pluralité d'options en comparant une valeur future estimée pour le paramètre spécifique à une valeur cible prédéterminée et, pour chaque option, calculer la valeur associée pour l'option donnée en utilisant la différence entre la valeur estimée pour le paramètre spécifique et la valeur cible et en utilisant une relation entre l'option donnée et le paramètre spécifique.

42. Dispositif selon les revendications 35 à 41,
caractérisé en ce que ledit dispositif comporte de plus des moyens pour notifier audit utilisateur si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

43. Dispositif selon les revendications 35 à 42,
caractérisé en ce que ledit dispositif comporte de plus des moyens pour notifier à au moins une équipe de soins, un professionnel ou un système central si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

44. Dispositif selon les revendications 35 à 43,
caractérisé en ce que ladite automédication est une automédication pour le diabète et lesdites une ou plusieurs valeurs futures représentent un niveau de glucose sanguin prévu (BGL) à différents instants futurs dans le temps.

45. Dispositif selon les revendications 35 à 44,
caractérisé en ce que ledit groupe de paramètres comporte un ou plusieurs des éléments suivants
un niveau de glucose sanguin (BGL),

Abbott Ex. 1002 - 478/1438

une concentration de fluide corporel,
une quantité de médication administrée,
une quantité d'insuline administrée,
un type de médication,
une estampille,
une quantité d'absorption d'aliments,
une quantité d'absorption de boissons,
une mesure d'activité physique,
une valeur représentant la sensibilité à l'insuline de l'utilisateur,
une température de l'utilisateur,
une pression sanguine de l'utilisateur, et
un poids dudit utilisateur.

46. Dispositif selon les revendications 35 à 45,
caractérisé en ce que lesdites options sont sélectionnées parmi le groupe constitué de :

- l'administration d'un type et d'une quantité prédéterminés de médication,
- l'administration d'une insuline à action lente,
- l'administration d'une insuline à action rapide,
- l'administration de comprimés,
- un effort pendant une période donnée de temps,
- l'absorption d'une quantité donnée d'aliments, et
- l'absorption d'une quantité donnée de boissons.

47. Dispositif selon les revendications 35 à 46,
caractérisé en ce que ledit dispositif concerne une ou plusieurs des médications suivantes :

- insuline,
- hormones de croissance,
- OHA (Agent Hyperglycémique Oral), et
- HRT (Thérapie de Remplacement d'Hormones).

48. Dispositif selon les revendications 35 à 47,
caractérisé en ce que ledit dispositif comporte de plus des moyens pour commander des informations de données entre une pluralité de dispositifs portables pour une utilisation par un patient pour une automédication médicale, le traitement comportant une première action et au moins une seconde action, lesdits dispositifs portables comportant un premier dispositif pour effectuer la première action, et au moins un second dispositif pour effectuer la seconde action, dans lequel

- chaque dispositif appartenant à l'automédication médicale a des moyens pour réaliser une ou plusieurs fonctions suivantes :

  la mémorisation, la transmission, la réception,
  le traitement et l'affichage d'informations,

- une communication de données tentée entre lesdits dispositifs est initialisée par une requête, ladite communication étant commandée par un module maître fonctionnel,
- la désignation dudit module maître fonctionnel parmi au moins deux desdits dispositifs, et
- la désignation d'un dispositif de traitement comportant lesdits moyens de mémoire parmi au moins deux desdits dispositifs.

49. Dispositif selon la revendication 48,
caractérisé en ce que les informations de programme ayant la priorité la plus élevée par rapport à la commande et la surveillance d'une communication de données mutuelle entre lesdits dispositifs sont mémorisées/activées dans ledit module maître fonctionnel.

50. Dispositif selon les revendications 48 et 49,
caractérisé en ce que ledit dispositif comporte de plus des moyens pour désigner un nouveau module

Abbott Ex. 1002 - 479/1438

maître fonctionnel si le module maître désigné courant devient indisponible.

51. Dispositif selon les revendications 48 et 49,
caractérisé en ce que ledit dispositif comporte de plus des moyens pour désigner un nouveau dispositif de traitement si le dispositif de traitement désigné courant devient indisponible.

Abbott Ex. 1002 - 480/1438

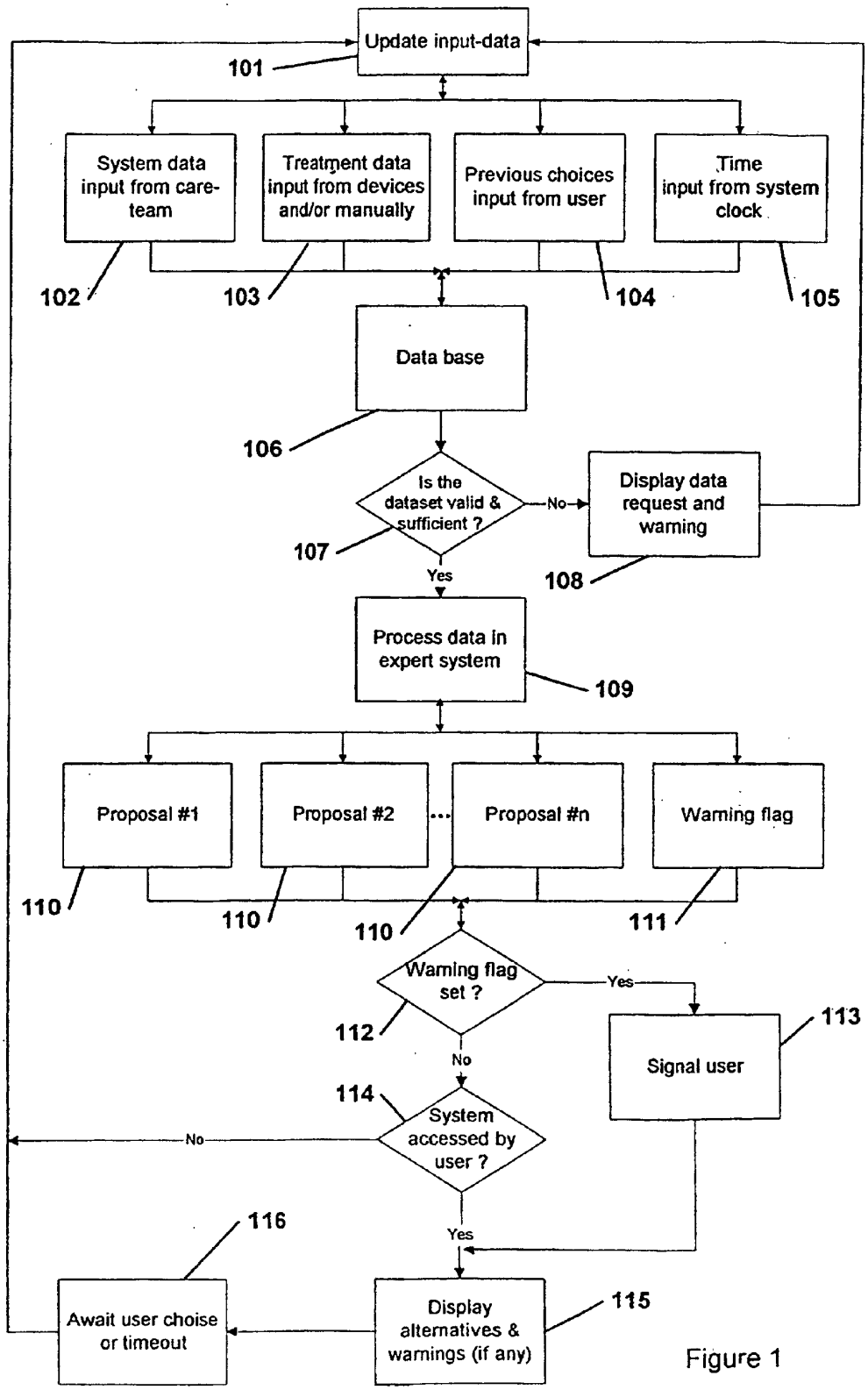


Figure 1

Abbott Ex. 1002 - 481/1438

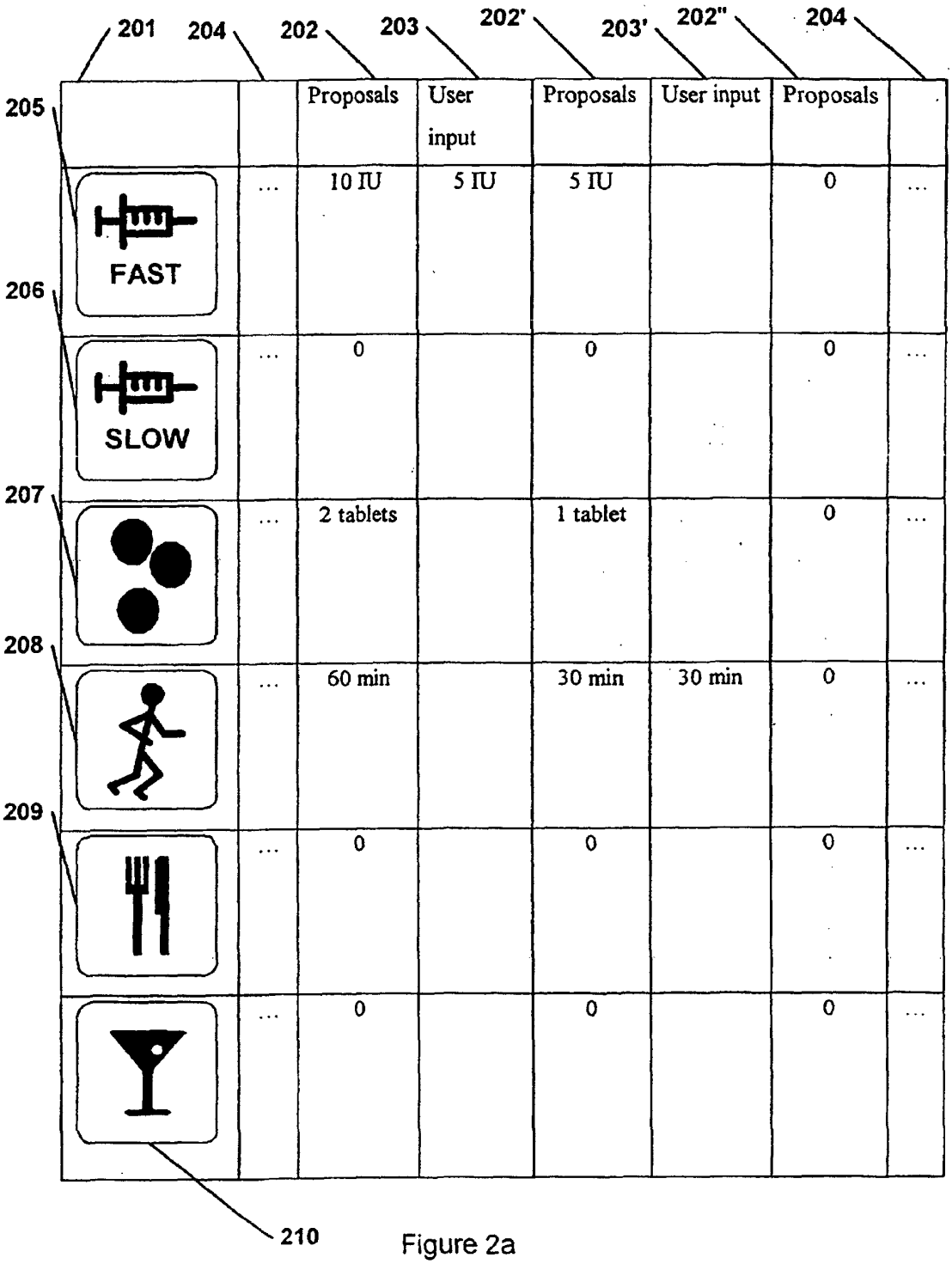


Figure 2a

Abbott Ex. 1002 - 482/1438

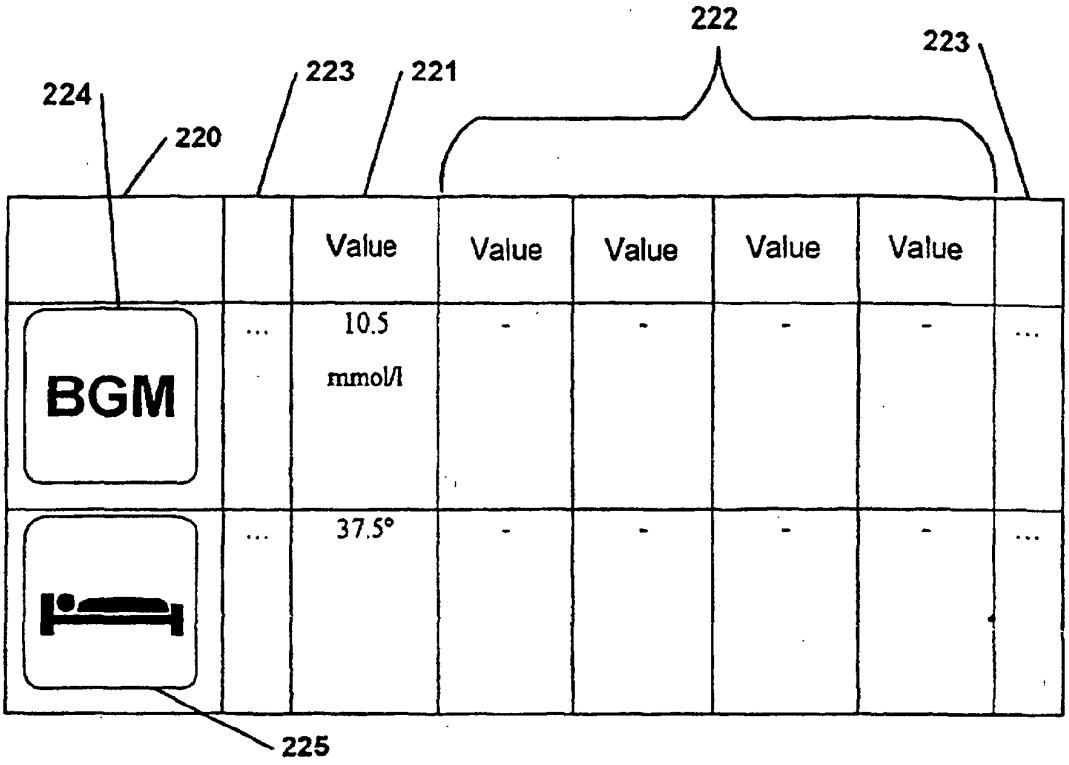


Figure 2b

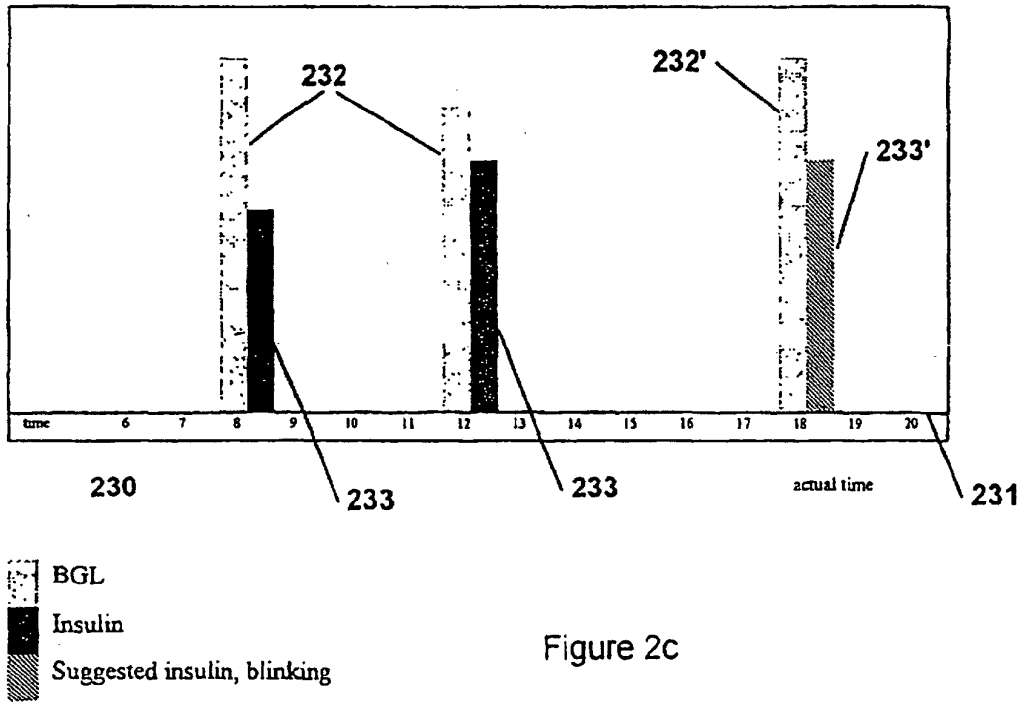


Figure 2c

Abbott Ex. 1002 - 483/1438

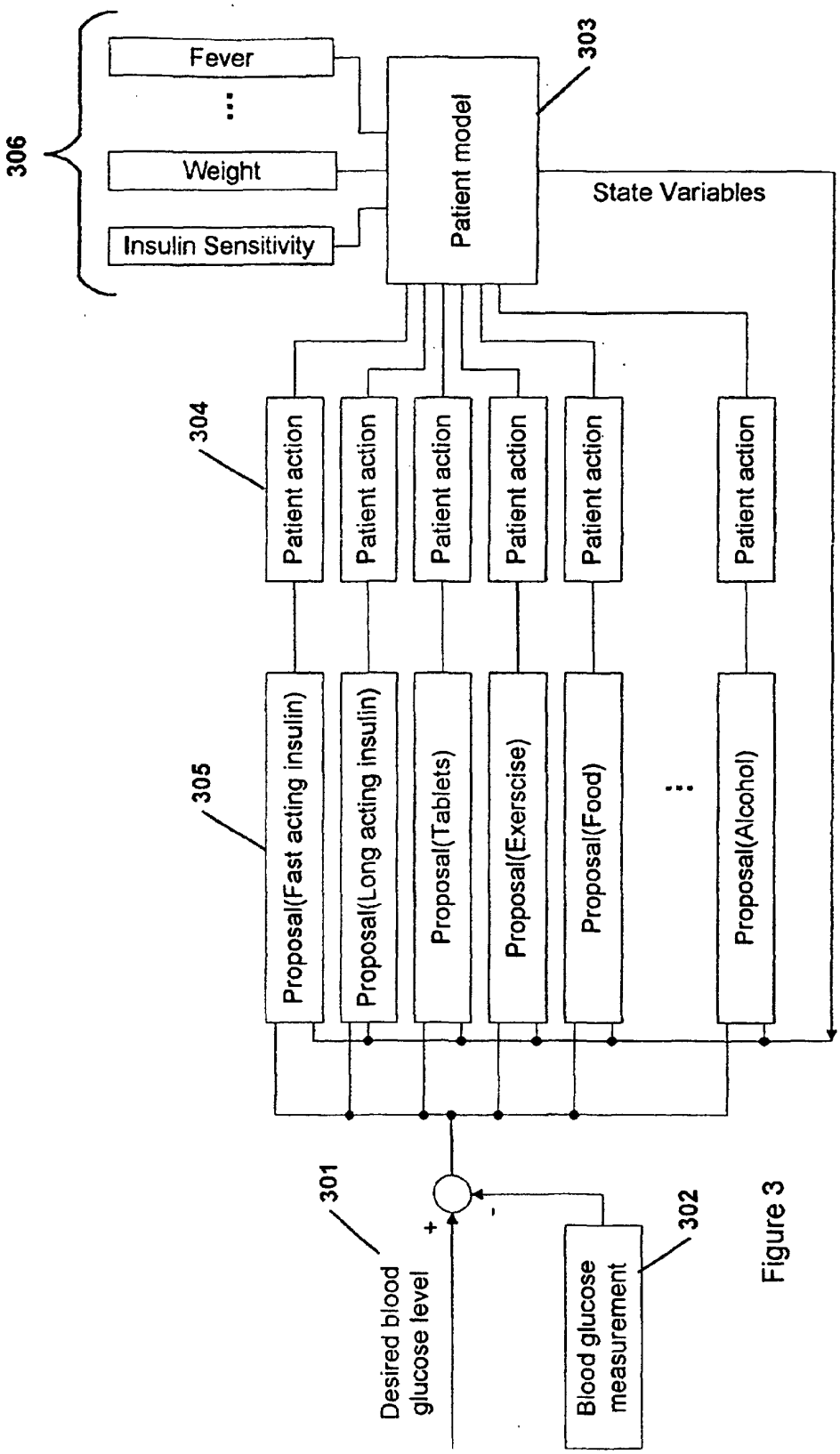


Figure 3

Abbott Ex. 1002 - 484/1438

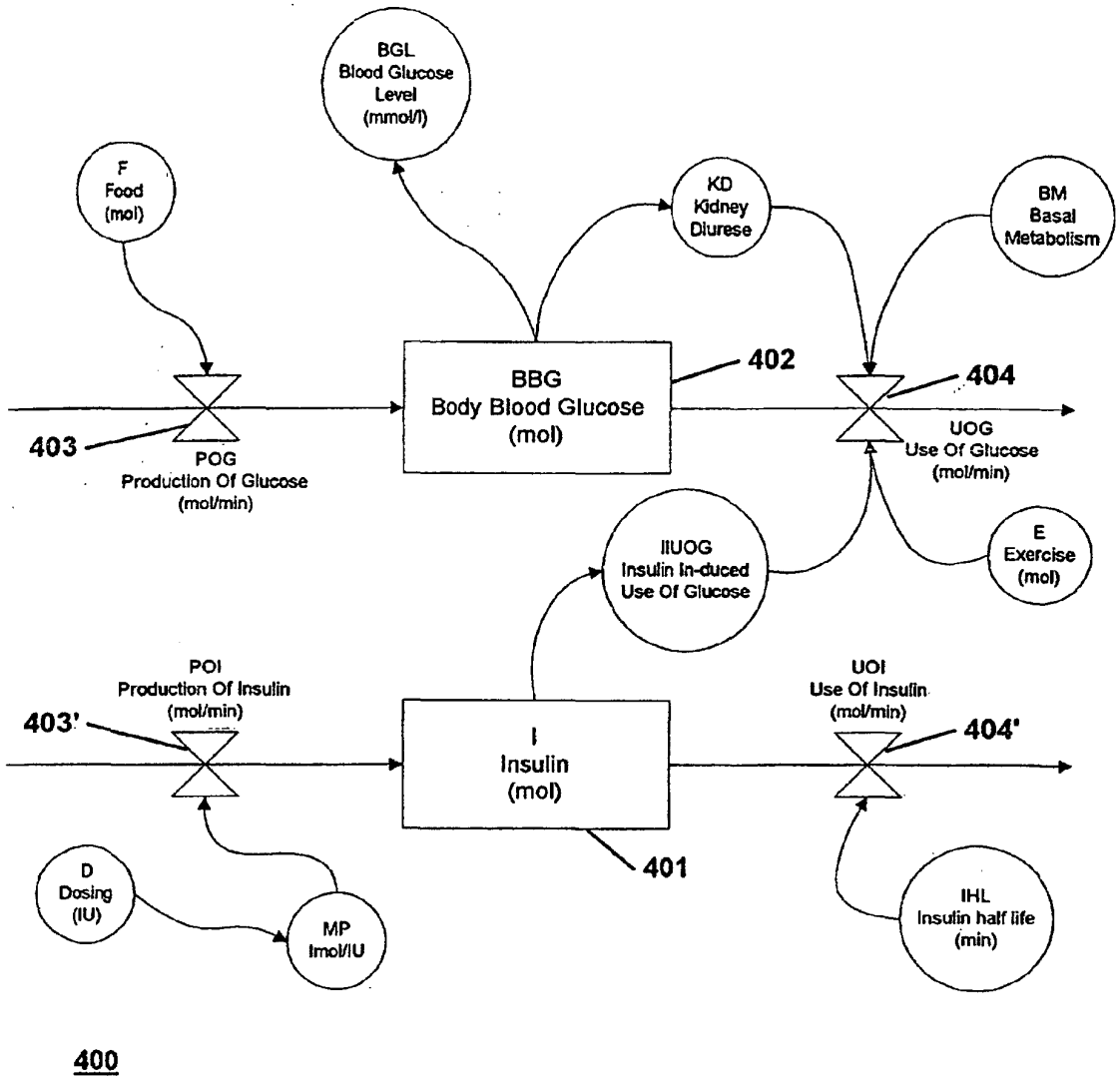


Figure 4

Abbott Ex. 1002 - 485/1438

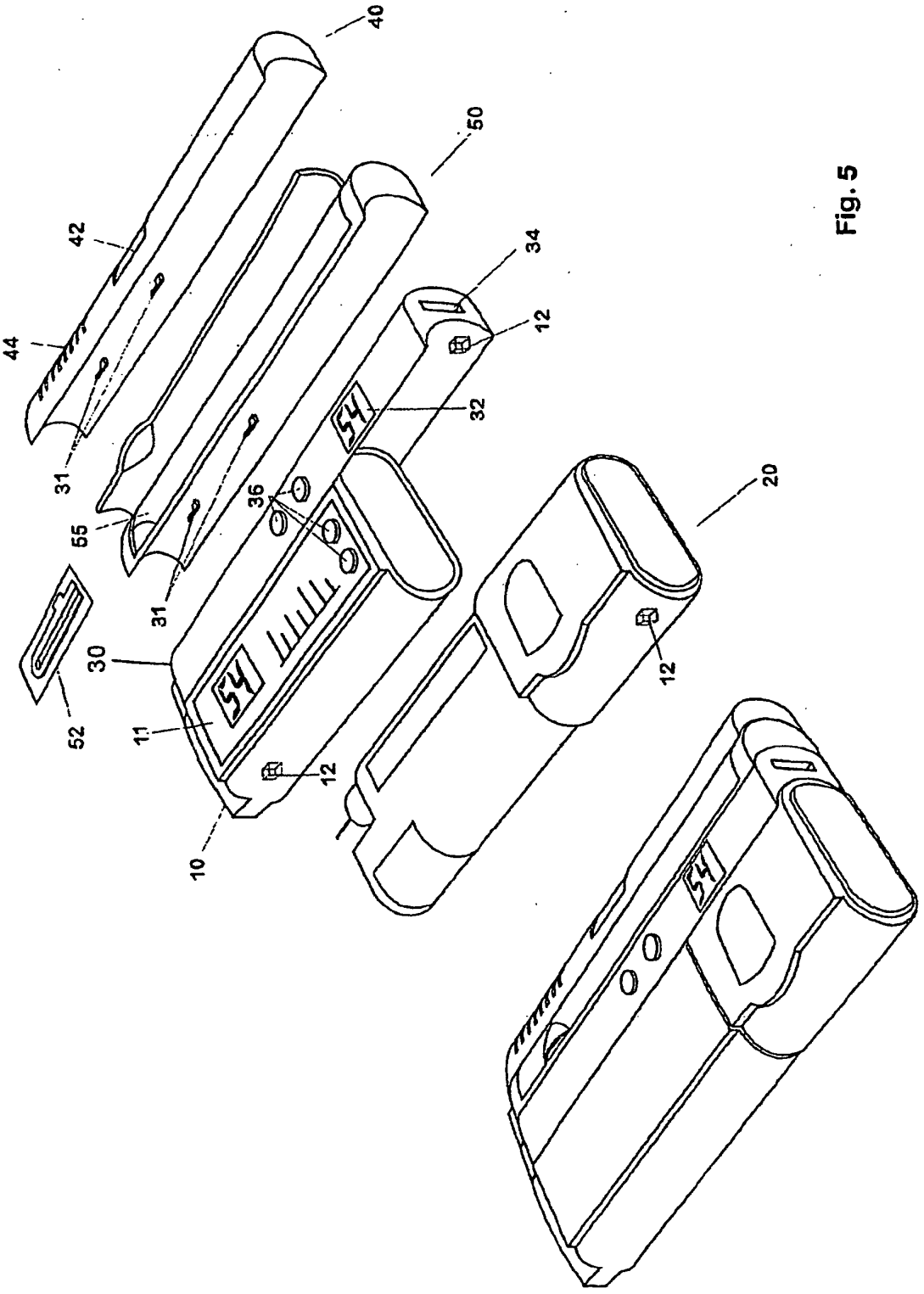


Fig. 5

Abbott Ex. 1002 - 486/1438

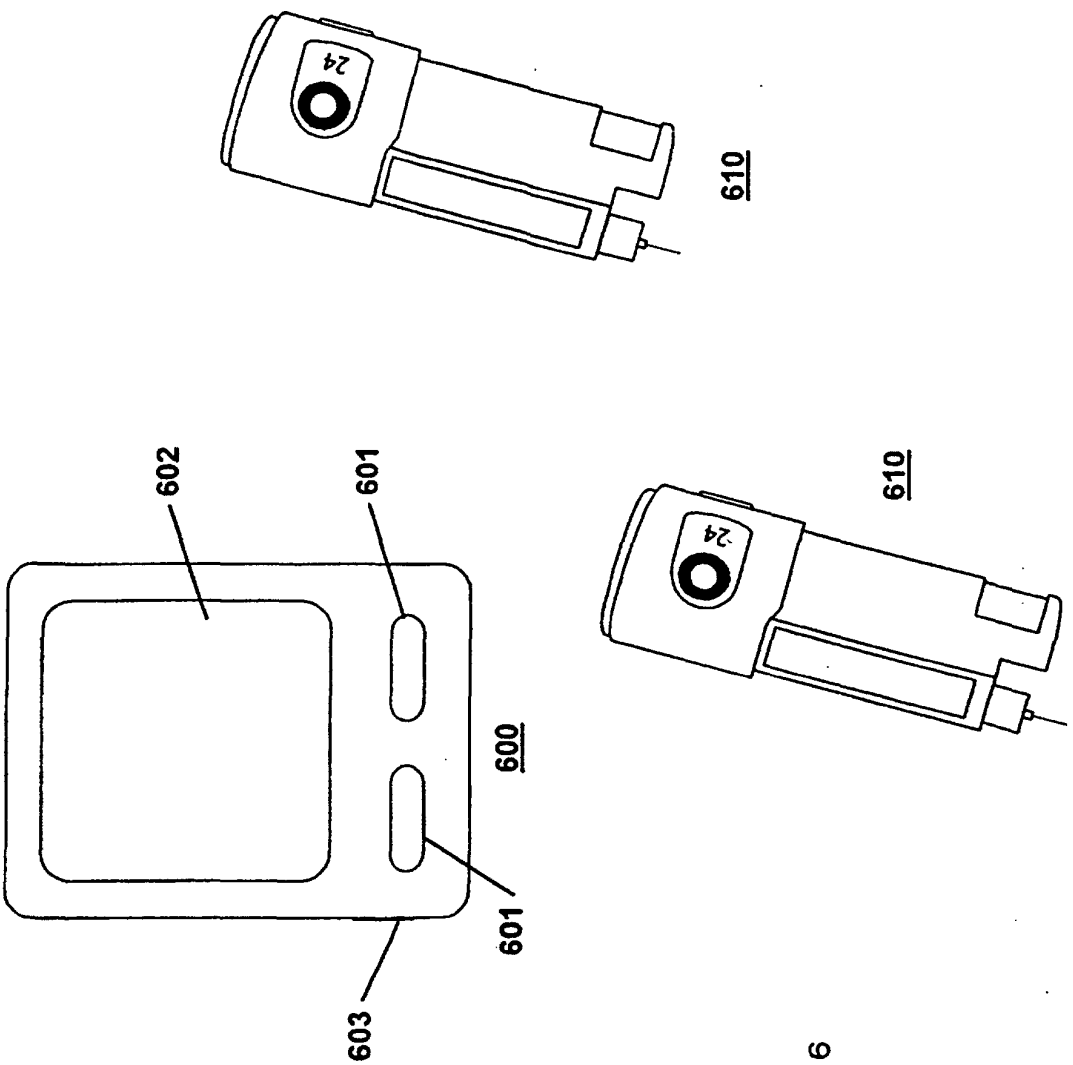


Figure 6

Abbott Ex. 1002 - 487/1438

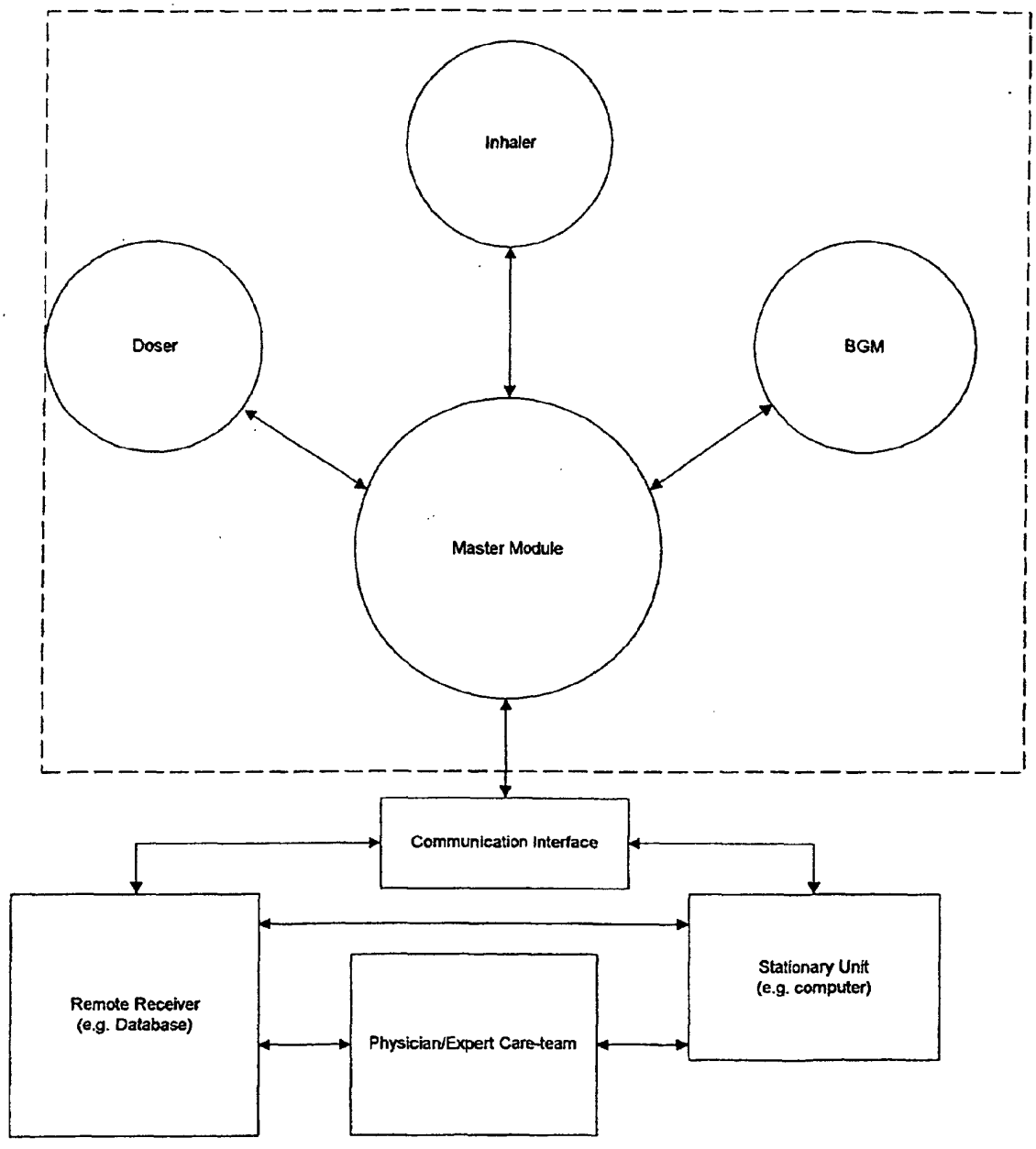


Figure 7

Abbott Ex. 1002 - 488/1438

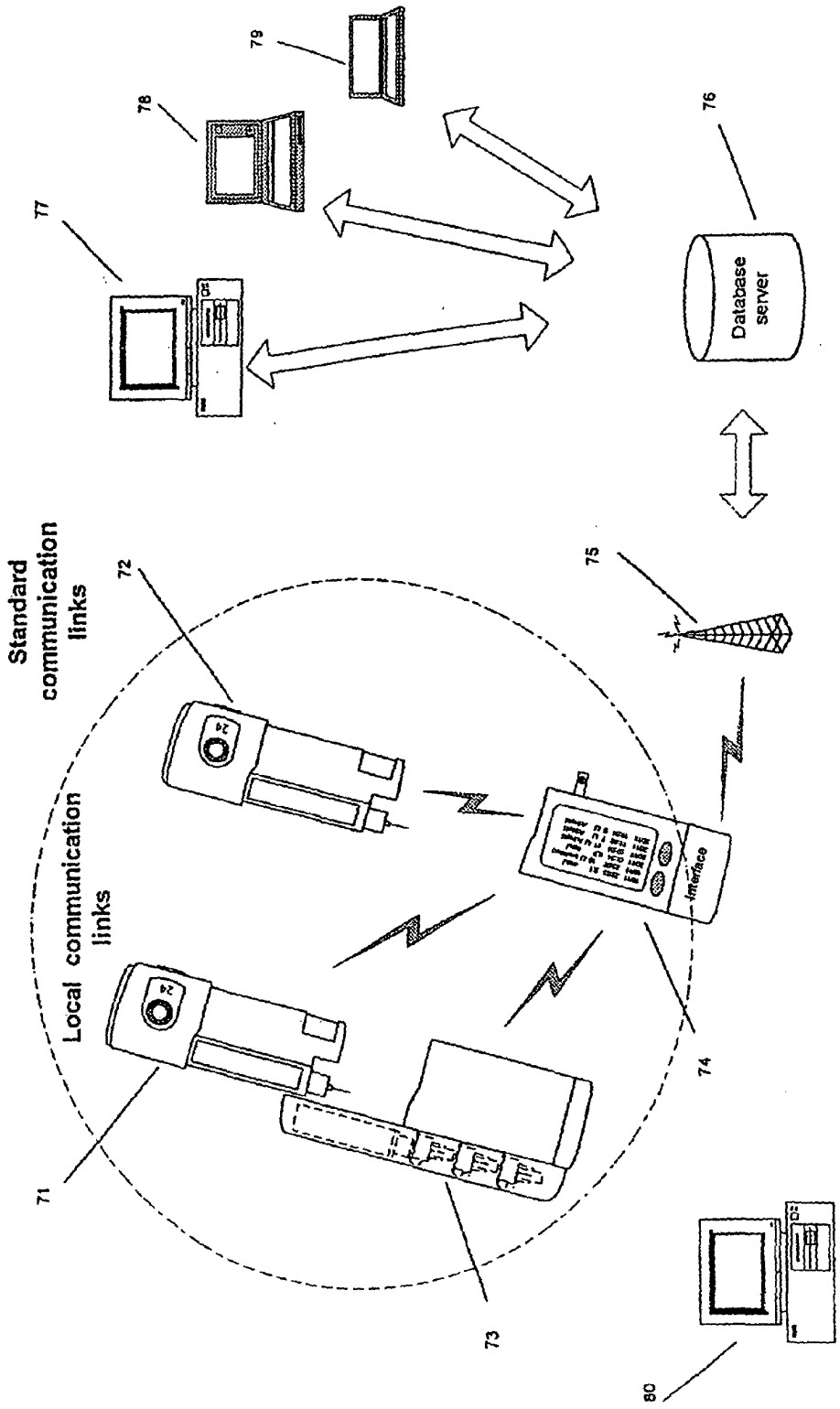


Figure 8

Abbott Ex. 1002 - 489/1438

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(54) **A method for assisting a user in a medical self treatment**

Verfahren zur Unterstützung einer medizinischen Selbstbehandlung

Procédé permettant à un utilisateur de s'administrer seul son traitement médical

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(56) References cited:
DE-U- 29 718 990
US-A- 5 673 691
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Description

[0001] The present invention relates to a method of assisting a user in a medical self treatment, said self treatment comprising a plurality of actions. The closest prior art is US-A-5 822 715, which defines the preamble of claim 1.

[0002] In the following a user/patient will be a patient having diabetes.

[0003] For a number of years it has been possible to purchase various devices for the treatment of diabetes, e.g. for injecting insulin, for measuring blood sugar (such a device is referred to as BGM in the following), for withdrawing blood samples, and other accessories, the purpose of which is to enable the patient to nurse his disease discretely and with a high standard of safety.

[0004] Many diabetic patients are elderly people who can easily get insecure with respect to the medical equipment. It is very reassuring and therefore also very important that the user can have feedback from the system which confirms to the user that everything is OK right from the technical function of the system to the patient's physiological condition. This stretches out a psychological safety net under the patient, which contributes to improving the quality of life of patients having a disease such as diabetes.

[0005] Traditionally, diabetic people live under strict rules of "do's and don'ts". There is a historical need in order to comply with a therapeutic regimen. The purpose of this being a well controlled blood glucose level (BGL) and thereby a much lesser risk of later complications. This is a highly undesirably situation from a 'quality-of-life' point of view. It often results in bad mood - which is known to lead to a poor BGL regulation. Thus an evil circle is created which is hard for the diabetic to break.

[0006] Additionally, in certain cultures/societies there is a reluctance against using syringes/needles to administer medication and people therefore choose alternative ways to try to comply with a regimen. However, this often has the unfortunate result that people choose alternatives that do not fully or at all correspond to the optimal regimen and thereby choose wrong alternatives with adverse effects.

[0007] Further, the metabolism is a very complex and dynamic system. It is very hard to get and maintain an overview for the diabetic as many factors play a role. It is very likely that the diabetic looses an overview or relies on too simple rules of operation or eventually neglect the illness.

[0008] Various systems trying to ease the hazels of diabetes have been proposed over time. These systems have basically an accounting role and simply keep track of whatever input the user specifies. In these systems input of food and exercise are usually a task that the user needs to initiate. Systems that rely on the user to take action can be hard to make function well due to the user's reluctance to deal with it.

[0009] Patent specification WO 95/32480 discloses a medical information reporting system which has a patient sensor device controlled via a patient operated interface device by a micro-controller which writes data to a memory and a report writer. The specification further discloses a warning algorithm with zone boundary values which is specified by the user and consent to by a physician. This system simply keep track of whatever input the user specifies.

[0010] Patent specification WO 94/24929 discloses a patient support and monitoring system, which has a database located at a remote location for collection of information in a remote database from sensors and a medicine administration system. This system also keep track of whatever input the user specifies and may initiate a medical reaction on the basis of received parameters.

[0011] The object of the invention is to provide a method which provides a user with a freedom of operation with respect to a self-treatment.

[0012] This is achieved by the method according to claim 1, which guides the user with respect to a self treatment by presenting options/possibilities in such a way that compliance to a regimen may be obtained in numerous ways.

[0013] Hereby, the user's self-treatments change from restrictions to possibilities thereby enhancing the overall 'quality-of-life' for the user and better ensuring that the user's self-treatment complies better or fully with a specified regimen by choosing proposed choices which complies with the regimen. This avoids that the user chooses actions and alternatives which do not fully or at all correspond to the optimal regimen due to a lack of a clear overview of the complex factors involved in the self-treatment.

[0014] By providing the user with a number of options he may choose the one(s) he likes best and still obtain the right and full treatment instead of choosing the easiest and most appealing course of action on his own, which may be wrong or insufficient and result in adverse effects.

[0015] Additionally, the possibility of choices fulfilling a prescribed regimen makes the patient feel more in control of the treatment and enhances the therapeutic value of the treatment and improves the patient's ability to adapt his treatment to his daily life.

[0016] Additionally, the user's feeling of being ill is reduced, since the user has options of choices instead of a dictation of actions.

[0017] An additional object of the invention is to estimate one or more future values for one of said parameters, in order to obtain information of the user's condition in the near future, hereby enhancing the possibilities of presenting better/more relevant choices.

Abbott Ex. 1002 - 491/1438

[0018] An additional object of the invention is to provide effective monitoring of electronic data/information which are used by a patient for self-treatment of a disease, so that a greater level of safety, both functionally and emotionally, and an effective feedback to the patient are obtained.

[0019] The invention refers to computer system.

[0020] By computer system is meant a system comprising processing means and being programmable at one time or another in order to execute a set of instructions/commands like a system for the self-treatment of a patient e.g. comprising one or more of sensor, medication administering device, data collection, and displaying means or a general computer system as a PC, laptop, palmtop, or a system having at least one device comprising a micro controller adapted to execute a program (either in hard- and/or software), and so on.

[0021] The above mentioned method needs as good as possible data collection in order to present relevant and useful choices/proposals to the user. A method relating to individual apparatuses, which are provided with electronic communications equipment so that the apparatuses - when in a state of mutual communication - frequently exchange information between them, is provided. Hereby a greater functional safety can be achieved and the total data capacity of the system can be increased, so that the feedback possibilities, e.g. of the system checking that every apparatus is OK and set up properly and of the patient be given a number of possible and up to date choices to choose from in a given situation, are increased.

[0022] The individual devices may be arranged for various respective functions relevant to the treatment of e.g. diabetes, such as: a lancet device, a body fluid analyser, one or more drug administration apparatuses for administering a predetermined dose of medication to the patient. Further, there may be a number of other aids which the diabetic patient uses, e.g. test strips for the blood analyser, needles, napkins for wiping off blood, extra insulin cartridge, glucose tablets, waste containers, etc.

[0023] The apparatuses according to the example may communicate information such as: amount of medication, type of medication, the concentration of relevant substances in the body e.g. body fluid level/concentration, time stamp, amount of food (e.g. amount or units of carbohydrate), measurement of physical activity, notification (e.g. alert and warning) to the patient, body characteristics (e.g. weight, blood pressure etc.) and inventory logistics. This ensures that relevant information, for e.g. a drug administration system like a doser, i.e. number of units of insulin, insulin type and time and date for administering, can automatically be stored, displayed, received and transmitted to and from all the relevant apparatuses and more particularly in one or more database accessible by a system/method for processing in order to obtain the results described above and later. The doser could also receive information regarding a predetermined number of units of insulin to be administered and automatically set the amount of medication to be administered by electromechanical means. In this way elderly and handicapped people do not have to set the relevant amount of medication themselves but just activate the doser and a confirmation of the actual administered dose may be used as input .

[0024] Other types of drug administration systems like an inhaler adapted to administer a dose of medication in an air stream or a tablet dispenser may be included instead or in combination with the doser. The inhaler and/or tablet dispenser may also communicate with the other units for relevant information like the doser according to the invention.

[0025] It is especially useful to transmit the data from all apparatuses to the functional master module/apparatus containing the highest priority program for safe keeping, calibration and updating of data and possible transmission to e.g. an external unit like a PC or database for further data acquisition, storage and processing. In this way the patient, a physician or an expert care-team can obtain the behavior over time of the patient, and a check for compliance to a diet or treatment given to the patient by a physician or an expert care-team can be made. This enhances the possibility of choices according to the invention.

[0026] Additionally, it is also possible for the patient to manually input information about the treatment. This information may be historic information as well as information about a future scheme (behavioral pattern) e.g. planned physical exercise, administering of insulin, intake of food and other medications. This information may be collected and thus serve as an electronic diabetes diary or may be used to notify the patient through the receiving means as to whether the planned actions are dangerous or not. The patient can further receive recommended amounts of medication, exercise, food, etc. from a physician, from an expert-team or automatically. All this information may be used to estimate one or more future parameter values, e.g. BGL.

[0027] It is evident that since the apparatuses are to be carried by the patient, there is a potential lack of space for an advanced input device e.g. a keyboard. Therefore, information which cannot be input on a standardized form e.g. personal comments on the treatment may be typed into the apparatus by the patient using a simple input device once and can subsequently be chosen from a list, if needed again.

[0028] Preferably, all the apparatuses of the system exchange information so that every apparatus (or at least every apparatus within range) is updated with the combined information, but still one particular apparatus is the link to any outside systems, so that every bit of information is mirrored for better safety and backup. This demands a greater amount of total memory capacity for the system.

[0029] For a BGM, the relevant information could be the time and date for measurement, measured level/concentration of blood glucose which could be stored or transmitted to another apparatus.

Abbott Ex. 1002 - 492/1438

[0030] For a doser, the relevant information could be the type of medication (e.g. long acting or short acting insulin), number of units of insulin to be administered and the time and date of the administering. This information could both be set manually by the patient or remotely by a physician, an expert care-team or automatically.

[0031] For an inhaler, the relevant information could be the type of medication, the number of units of medication to be administered and the time and date of the administering. This information could both be set manually by the patient or remotely by a physician, an expert care-team or automatically.

[0032] For a storage container, the relevant information could be used to keep track of the contents of the container so that every time an object (e.g. cartridge, needle, etc.) is used, the storage container will update the inventory list. This list could be transferred to a unit of highest priority immediately or later, which could in turn update the patient's total holdings of objects, so that the system could notify the patient when he should order a new stock of objects in order to keep all the different proposed actions available. The ordering could also be done automatically by the system if the inventory list is transferred to an external unit, which greatly improves the confidence, comfort and safety of the patient.

[0033] For a tablet dispenser, the relevant information could be the number of dispensed tablets, the number of remaining tablets, the time of dispension and the type of dispensed tablets. The dispenser could store and/or communicate this information to an available unit of highest priority or other units within communication range.

[0034] In the following a preferred embodiment according to the invention is described in detail. This particular embodiment is meant as one example only of the invention and should not as such limit the scope of protection as claimed in the appended claims.

[0035] The term "Margin Maker" is used in the following for a method according to the invention.

[0036] The invention will now be explained in detail with reference to the figures 1 - 8, in which

Figure 1 shows a flowchart for an embodiment of the invention illustrating an exemplary implementation of a Margin Maker system;

Figure 2a, 2b and 2c show examples of user interfaces presenting and receiving choices to and from a user;

Figure 3 illustrates a schematic diagram of an exemplary expert system using a model;

Figure 4 shows a more detailed representation of a time dependent dynamic patient model according to the invention;

Figure 5 shows an example of a preferred system which may contain an embodiment according to the invention;

Figure 6 shows another embodiment according to the invention;

Figure 7 illustrates the general concept according to an embodiment of the invention with respect to communication and exchange of information;

[0037] Figure 8 illustrates the communication between a system of apparatuses and a central system.

[0038] Figure 1 shows a flowchart for an embodiment of the invention illustrating an exemplary implementation of a Margin Maker method.

[0039] In step 101 input data is provided/updated. More specifically different types of input data are updated as represented by the steps 102 - 105.

[0040] In step 102 data from a care-team is provided/updated. This data describes individual user/patient characteristics which are true/valid in the time interval between consultations with the care-team. The data is typically derived as a result of tests performed by health care professionals (e.g. insulin sensitivity) and entered into the system by the care-team, e.g. wireless via a mobile telephone system as described in connection with Figure 8.

[0041] In step 103 treatment input data is provided from various devices, e.g. from a system of portable apparatus as described above and in connection with Figs. 5 - 7.

[0042] Input data specified manually by a user may also be input in step 103. Manually specified input data may e.g. be a value representing the body temperature of the user e.g. because he is feverish. Manually specified input may preferably if it differs from his normal value

[0043] This data describes the actual treatment received by the patient (e.g. insulin intake as a function of time) and the resulting effect on the user (e.g. blood glucose level as a function of time). The data is gathered by the various devices used by the patient in his home-treatment and communicated automatically to the Margin Maker.

[0044] In step 104 the previous choices, i.e. input from the user, are provided/updated.

[0045] This is a record of the previous activities which the user has chosen to perform and which are either not yet confirmed by other input means (e.g. insulin injection prior to synchronization between the insulin doser an the Margin Maker) or not confirmable by other input means (e.g. physical exercise or food intake).

Abbott Ex. 1002 - 493/1438

[0046] In step 105 information of time is provided from a system clock in the form of a time stamp. Additionally the date may be specified as well.

[0047] It is necessary for the method to know the time because the alternative proposals available to the user change over time.

[0048] The information provided/updated in the steps 102 - 105 is collected in a database as a dataset at step 106.

[0049] Prior to processing the input data the system performs a test at step 107 to find out if the amount and/or quality of the input information is sufficient to produce valid and relevant proposals for user behaviour to present for the user of the Margin Maker method.

[0050] If the test fails, i.e. the input data is insufficient to produce a relevant output, the user is made aware of the fact that at the moment the Margin Maker is unable to offer guidance due to lack of input information and displays a request for more (comprehensive) data and issues a warning at step 108.

[0051] If the test is successful, the method continues in step 109, where the provided/inputted data is processed in an expert system e.g. using a model.

[0052] The expert system is in principle a model of a control loop for the blood glucose level in a human. Based on the input and the historical data accumulated in the Margin Maker the parameters of the model is adapted to mimic and predict the blood glucose control of the individual user of the Margin Maker method. Refer to Figs. 3 and 4 for a more detailed description of the expert system.

[0053] For each of the n possible user actions implemented in the Margin Maker method the model is fed with information of the present blood glucose level, the target blood glucose level, the current time, the n-1 user actions set to their present value (ceteris paribus), and 1 user action is treated as a variable parameter. After n recalculations of the control loop, one for each of the n possible user actions treated as the variable parameter, the expert system has derived n ways of bringing the present blood glucose level to its target value. Then an evaluation of the n alternative proposals is needed in order to exclude proposals that are not implementable (e.g. it is not possible to eat a negative amount of food), thereby providing the 'up to n' valid and implementable proposals of possible choices 110.

[0054] In general, the sooner proposals are chosen, i.e. a situation is acted upon, the more options/proposals is available to the user. Put in another way, as the time goes the proposals/options become fewer and fewer as well as more and more restrictive, since the user's situation gets more and more serious, i.e. drifts away from a normal BGL, if not paid attention to/acted upon.

[0055] Another criteria for exclusion of proposals may e.g. be in a system, as described above, comprising different portable/handheld devices that the specific device being used to implement the proposal is present and activated among a user selected group of the devices. In this way the user will only be presented with proposals that he actually has the possibility of executing.

[0056] Finally, the time is considered variable in the expert system - other things being equal - to test whether a potentially dangerous situation is expected to occur within a given time frame. If this is found to be the case, a warning flag is set in step 111.

[0057] In step 112 a test whether the warning flag has been set is executed. If the test is true/yes (i.e. the warning flag has been set) a warning signal is sent to the user in step 113, regardless of whether the user is accessing the system, e.g. by audio to attract the user's attention and/or by activation of the display containing appropriate information. After the signal is given the method continues in step 115 where the warning and proposals are presented as will be described later.

[0058] If the test in step 112 results in false/no, another test is executed in step 114 as to whether the system is accessed by the user. If this is not the case, the method continues from the beginning in step 101 and awaits new and/or updated input since the present situation does not specifically require the attention of the user (warning flag not set).

[0059] If the test in step 114 is true and the user is accessing/has activated the system, step 115 is executed.

[0060] In step 115 the valid and implementable proposals are presented to the user. Any warnings are also displayed to the user if the preceding step was step 113 in order to alert the user and obtain an immediate action from the user. Issued warnings could e.g. comprise information that the user should seek medical attendance or administer a given medication as quickly as possible, etc.

[0061] The proposals may e.g. be presented in the form shown in Figs. 2a, 2b and 2c or other suitable forms.

[0062] In step 116 the system awaits a user choice of one of the proposed actions or a time out from the system.

[0063] Each of the proposals presented to the user of the Margin Maker will bring his/her blood glucose level "back on track" but that does not in any way exclude the possibility that the user chooses only to partly follow a suggested proposal, e.g. administering half the dose of medication instead of the proposed dosage, or to combine several proposals fully or in part. Once the user has entered his/her choice the Margin Maker performs a rerun of the flowchart to update the relevant proposals, given the new situation. An example of proposals and selected choices is shown in Figure 2a.

[0064] If the user chooses to do nothing, the system will eventually issue a time out and perform a rerun of the flowchart to update the relevant proposals taking into account that time has elapsed since the last user action.

[0065] Hereby a user is presented with a number of choices each fulfilling a regimen where he may choose the one

Abbott Ex. 1002 - 494/1438

(s) he likes best and still obtain the right and full treatment instead of choosing the easiest and most appealing course of action on his own, which may be wrong or insufficient and result in adverse effects.

[0066] Additionally, the possibility of choices makes the patient feel more in control of the treatment and enhances the therapeutic value of the treatment and improves the patient's ability to adapt his treatment to his daily life.

[0067] Figures 2a, 2b and 2c show examples of user interfaces presenting and receiving choices to and from a user.

[0068] Figure 2a shows an example of a user interface where one column 201 comprises different graphical icons 205 - 210 each representing one choice of action according to a proposal. Shown in this example are icons 205 - 210 for administering fast acting insulin 205, administering slow acting insulin 206, administering tablets of a given type 207, exercise 208, intake of food 209, and intake of alcohol 210. Additionally, other icons like administering tablets of another kind, administering a dosage medication from an inhaler, etc. may be presented if these options are available to the user.

[0069] At column 202 the n proposals suggested by Margin Maker are shown (corresponds to step 115 in Figure 1), where each proposal of action, if executed, brings the current BGL to the target BGL. In this example the Margin Maker has proposed to the user/patient either to administer 10 units (IU) of fast acting insulin, administer 0 IU of slow acting insulin, administer two tablets of a given type, exercise for 60 minutes, intake 0 units of food, or drink 0 units of alcohol.

[0070] At column 203 the user input is shown. After he has input the choice and amount of action, the Margin Maker displays and derives updated proposals on the basis of the changed situation. Here the user has chosen to administer 5 IU of fast acting insulin, and the Margin Maker now presents the updated proposals at column 202', given the new situation and taking into account the user's choice.

[0071] The updated proposals at column 202' are now to administer additionally 5 IU of fast acting insulin, administer 0 IU of slow acting insulin, administer one tablet of a given type, exercise for 30 minutes, intake 0 units of food, or drink 0 units of alcohol.

[0072] The user now chooses to exercise 30 minutes, which is shown at column 203', and the model updates the proposals accordingly. The proposals shown at column 202'' show that after the user has performed the specified choices/actions his BGL should be at the target level.

[0073] The columns 204 represent previous and later proposals and user input, so it is possible to scroll through the values for different points in time.

[0074] This specific form of user interface requires a display of a certain quality or with a certain resolution. Other more simple forms may be provided, e.g. as shown in Figure 2c, either instead or in combination in devices with a smaller display.

[0075] Alternatively, the display will only display one column of icons 201, proposals 202 and user input 203 at a time, e.g. with buttons to scroll through previous proposals and input.

[0076] The user may input data in many different ways according to specific embodiments of the invention as generally known in the art, e.g. utilising a touch screen with a stylus, touch pad and a cursor on the display, etc.

[0077] It is evident that if the apparatuses are to be carried by the patient, there is a potential lack of space for an advanced input device e.g. a keyboard. Therefore, information which cannot be input on a standardized form e.g. personal comments on the treatment is typed into the apparatus by the patient using a simple input device once and can subsequently be chosen from a list, if needed again.

[0078] Preferably, a system comprising a plurality of portable devices with mutual data communication, as described above, is used in connection with the Margin Maker.

[0079] In this way e.g. a doser may communicate an administered dose to the device containing the Margin Maker automatically or by user request and the different devices may communicate measured values representing physiological parameters automatically or by user request, e.g. a BGM may communicate the measured BGL as input to the Margin Maker.

[0080] Additionally, information of which devices are present and activated may be transmitted to the device containing the Margin Maker which may hereby only present proposals with a corresponding present and/or activated device, so that e.g. if a doser containing slow acting insulin is not available to the user, then the icon 206 and the corresponding proposal will not be displayed at all.

[0081] In Figure 2b an example of a user interface is shown where input of information is given to the Margin Maker which is needed in order to derive the proposals of actions. Shown is a column 220 containing icons 224 representing a value obtained from the BGM and 225 representing a value for the temperature of the user. The corresponding values, specified at a given time, are listed in a column 221 and are in this example 10.5 mmol/l and 37.5° for the BGM and the temperature, respectively. The other columns 222 represents values specified at different points in time where in this example no values are specified. Alternatively, only columns having a specified value are shown in the user interface e.g. with a corresponding time stamp.

[0082] The columns 223 represent previous and later user input, so it is possible to scroll through the values for different points in time.

[0083] This information is used by the Margin Maker together with additional information to better estimate the target glucose level and obtain a measure of the present glucose level. The input temperature is used by the expert system

Abbott Ex. 1002 - 495/1438

to determine whether the user is feverish or not as this influences the required amount of insulin.

[0084] This information may either. be input manually by the user, automatically or both, e.g. by a BGM device and/or a temperature sensor with communication means which may communicate with a Margin Maker device (may correspond to step 103 in Figure 1).

[0085] Figure 2c shows an example of a different user interface which may be more suited for a smaller display. Shown is an example of a graph 230 with a time axis 231 and three BGL bars 232 and 232' obtained at three different points in time of the day. Two previously obtained BGLs 232 and one BGL 232' obtained at the actual time. The BGL may be obtained from a BGM and may be received either automatically or manually by the Margin Maker as input for the expert system as described above.

[0086] Also shown are two bars 233 representing the dose of insulin, that the user chose to administer previously after obtaining the BGLs 232, respectively. The dosages 233 may have been fully or partly as proposed by the Margin Maker at the respective time. Alternatively, the user may have administered the dosages 233 completely on his own and just specified the dosage and type of medication. The actual dosages 233 administered may have been specified (together with the time and type of insulin) by user input or via communication from the administering doser to a device containing the Margin Maker.

[0087] The previously obtained BGLs 232 and administered dosages 233 together with the BGL 232', obtained at the actual time and other relevant input, as described in connection with Figure 1, and used to predict a future course of BGL for the user and derive one or more proposals to the user in order to account for the future course of BGL.

[0088] The Margin Maker has proposed in this example that the user should administer a dosage as indicated by the blinking bar 233'. Additionally, other proposals may be shown elsewhere. The proposed dosage and type of insulin may be transmitted automatically to a corresponding doser, so if the user wishes to follow this proposal fully he just has to activate a button on the doser to accurately receive the proposed dosage. Alternatively, the user may manually specify the proposed dosage on the doser.

[0089] Additionally, the user may choose to only administer a part of the proposed dosage (which may also be transmitted automatically after indication by the user) if he e.g. wants to exercise as well. After the Margin Maker has registered the user's choice of only administering a part of the proposed dosage of medication, the expert system is updated accordingly and new proposals are derived taking into account the new situation.

[0090] The user interfaces described in connection with Figs. 2a, 2b and 2c are just examples and other interfaces may be just as applicable. Alternatively, the user interface may be character based and using no graphics thereby reducing the complexity of the system with respect to implementation.

[0091] Figure 3 illustrates a schematic diagram of an exemplary expert system using a model.

[0092] A number of models have been proposed in order to describe the metabolism of the insulin dependent diabetic patient. Furthermore, some effort has been put into constructing systems for controlling the blood glucose level using insulin.

[0093] In the following one expert system is described as an example but other expert systems known in the prior art may be used with similar results. The shown expert system comprises input variables 301 and 302, physiological parameters and model inputs 306, proposal generators 305, patient actions 304, and a patient model 303, all of which will be described in the following.

[0094] An input variable "Desired blood glucose level" 301 is specified in the expert system and is preferably (pre) determined by the care-team or other professionals. The variable 301 may be similar to the blood glucose level of a healthy person, but may due to regimen differ from this value, e.g. be higher in order to prevent hypoglycaemia.

[0095] Another input variable used by the expert system is the variable "Blood glucose measurement" 302 representing the BGL at a given time.

[0096] The patient may measure the BGL, giving the blood glucose measurement variable 302, with a certain frequency or use a continuous blood glucose sensor. Given the dynamics of the human metabolism, there is a certain lower limit of the sample frequency which will allow the expert system to work properly.

[0097] The patient model 303 is a dynamic model which describes the metabolism of the diabetic patient. The model 303 incorporates parameters 306 such as e.g. weight of the patient and insulin sensitivity, which vary from patient to patient and may be considered constant between consultations of the care-team. The model 303 may also incorporate model input 306 such as injections of long acting insulin, fast acting insulin, oral diabetic agents, exercise, food intake, alcohol intake and fever. Given a certain combination of model input 306, the model 303 describes the blood glucose level over time. The model 303 describes some key state variables of the human metabolism.

[0098] The proposal generators 305 are the analogy of regulators in a control system. The input to the proposal generators 305 is the difference between the desired blood glucose level 301 and the actual blood glucose level 302 and the state variables of the patient model. Given the input each proposal generator 305 proposes a patient action and a corresponding amount/dosage - eat a certain amount of food, exercise for a certain amount of time, inject a certain amount of fast acting insulin, etc. - as indicated in the proposal boxes 305. The proposals are calculated, presuming that only one of the proposals is followed.

Abbott Ex. 1002 - 496/1438

[0099] The patient has the final decision as indicated by patient action 304 for each possible action in the expert system. He may or may not choose to follow the proposals. By choosing one of the proposals fully or partly, his action 304 is fed into the patient model, either by manual input or automatically by the diabetes specific devices - the dosers or the blood glucose monitor. The patient model 303 now generates a new input to the proposal generators 305 which represents the updated situation.

[0100] Figure 4 shows a more detailed representation of a time dependent dynamic patient model according to the invention. This model is used by the expert system to give a prediction/estimate of a future BGL.

[0101] In the literature many such models are described. Here a very simple one of applicant's origin is taken to explain the principles. This model can be developed to a high degree of detail, if needed.

[0102] The model 400 simulates the dynamics of the carbohydrate metabolism. Based on the input of one or more of the following parameters

- BGL,
- dosage of medication,
- type of medication,
- food intake,
- drinks intake,
- exercise,
- time stamp,
- insulin sensitivity
- weight of the user,
- blood pressure,
- temperature, and
- other.

[0103] The model is tuned in to mimic the user's carbohydrate metabolism closely. By the continuous tuning by input of updated data from the expert system a drift away from a close mimic of the true status is prevented. The structure of the model 400 matches the functionalities of the metabolism to a needed degree. Due to this correspondence the expert system/model 400 will be able to predict trends or even future BGL.

[0104] The expert system continuously gives suggestions about the user's freedom of operation. Based on all recorded events a margin for exercise and food is suggested.

[0105] If suggestions are confirmed (e.g. tapping an indication on the touch screen of the handheld device), these are regarded as input to the algorithm and used for future suggestions.

[0106] Preferably, the dialogue is implemented via a graphic display showing the history, and input is given either via a touch screen or traditional buttons.

[0107] In order for the expert system to give recommendations and margins as described above it is needed to predict how things will evolve from any known state.

[0108] This can be done using a model 400 of the carbohydrate metabolism as an engine for the Margin Maker concept.

[0109] Shown in the figure is a model 400 with two pools: Body Blood Glucose 402 and Insulin 401. Each has a filling source 403, 403' and a drain 404, 404' (i.e. two rates), respectively. Body Blood Glucose 402 has the filling source POG (Production of Glucose) 403 and the drain UOG (Use of Glucose) 404, and Insulin 401 has the filling source POI (Production of Insulin) 403' and the drain UOI (Use of Insulin) where all the rates 403, 403', 404 and 404' may vary with time dependent on the parameters controlling the rates.

[0110] The parameters controlling the rates, e.g. food, dosing, exercise, etc., are given in the table below.

[0111] The model 400 can also be expressed in terms of a set of differential equations for the states 402 and 401, each being controlled by their respective rates 403, 404 for the state Body Blood Glucose 402 and 403' and 404' for the state Insulin 401. In this form the model can be implemented in a microprocessor relatively easily and display the results of the latest input for any given time.

[0112] The differential equations for the model 400 may be expressed

Abbott Ex. 1002 - 497/1438

$$BBG(t) = BBG(t - dt) + (POG - UOG) * dt$$

INFLOWS: $POG = f(F,t)$

OUTFLOWS: $UOG = g(BM+KD+IIUOG+E,t)$

$$I(t) = I(t - dt) + (POI - UOI) * dt$$

INFLOWS: $POI = h(MPI,t)$

OUTFLOWS: $UOI = j(HL,t)$

as:

[0113] The factors are explained in the table below:

Factor	Explanation	Unit	Function
Input/Output			
D	Dosing	IU	Output to the user about possible insulin doses to take. Alternatively the user can give input about a wanted amount of insulin and the system can suggest appropriate food intake. Whenever an insulin dose is taken the system automatically loads the value into the model and the predictions are calculated accordingly.
E	Exercise	mol	Output to the user about possible exercise to take in the given situation. Alternatively the user can give input about a wanted amount exercise and the system can suggest appropriate food intake. The user accepting the suggestion will be an input to the system and calculation will be accordingly. Conversion to mol will be made by the system.
F	Food intake	mol	Output to the user about possible food to take in the given situation. The user accepting the suggestion will work as an input to the system and calculation will be accordingly. Alternatively the user can give input about a wanted amount of food and the system can suggest either dosing of insulin or exercise. Conversion to mol will be made by the system.
Concentrations and levels			
BBG	Body Blood Glucose	mol	Simulated total amount of glucose in the blood. It is calculated as the integration over time of production and usage of glucose. Between measurements it is used to give an estimate of the user's current BGL. At measurements the BBG is updated according to the measured BGL.
BGL	Blood Glucose Level	mol/l	This calculated by dividing the BBG with the blood volume. The model has the ability to predict the BGL over time and the value is very important to the user and can be displayed at any time. Every time the user makes a measurement of the actual BGL this is automatically loaded into the model by the system and it overrules the calculated one and resets the model. Initial value: 5 mmol/l

Abbott Ex. 1002 - 498/1438

(continued)

Concentrations and levels			
I	Insulin	mol	Insulin level in the body. The model has the ability to predict the Insulin level over time. It is calculated as the integration over time of production and usage of insulin. The initial value is set by the physician according to measurements and can be calibrated by the physician when the user meets for consultations.
Rates			
POG	Production Of Glucose	mol/min	This rate is driven by the food intake entered and accepted by the user. It is also a function of time as different types of food have different dynamic impact on BGL.
POI	Production Of Insulin	mol/min	This rate is driven by the injected insulin through a conversion factor (MPI). It is also a function of time as different types of insulin have different dynamic impacts on BGL.
UOI	Use Of Insulin	mol/min	This rate is defined by the half life (IHL) of insulin by which the level decays exponentially.
UOG	Use Of Glucose	mol/min	This rate is driven by 4 factors: Basal Metabolism (BM), Kidney Diurese (KD), Insulin Induced Use Of Glucose (IIUOG), Exercise (E).
Constants & Transfer functions			
BM	Basal Metabolisme	mol/min	Constant for each Individual determined by the physician. Typical value: 0,56 mol/min
IHL	Insulin Half Life	min	The metabolism of insulin is usually expressed in terms of half life. Typical value: 10 min
IIUOG	Insulin Induced Use Of Glucose	mol/min	This factor describes the nonlinear relation between insulin in the body and the disappearance of glucose from the blood. This factor can be measured or derived from literature.
KD	Kidney Diurese	mol/min	This factor describes the nonlinear relation between diurese and BGL. At BGL levels below 10 mmol/l the KD is virtually zero. Above 10 mmol/l an increasing KD will occur
MPI	Mol Per IU	mol/IU	Conversion factor between International Units of insulin and mol

[0114] This model 400 is just one relatively simple example of a model that may be used to predict a future BGL.

[0115] Alternatively, the model and/expert system or parts hereof may be located in a stationary unit with greater computational power and receive input and transmit information regarding proposed choices.

[0116] Figure 5 shows an example of a system which may contain an embodiment according to the invention.

[0117] Shown is a doser 20 with a cap 10 where the cap 10, in an embodiment, functions as the functional master module. In the preferred embodiment the Margin Maker resides in the functional master module. The functional master module 10 has displaying means 11 and buttons 36 for operation and selection of proposed choices.

[0118] The doser 20 is a conventional doser with has transmitting and receiving means 12. This enables the doser 20 to transmit stored data, i.e. the time, date, amount and type of medication, to the functional master module 10 for storage and presentation there via the master modules receiving means 12. Additionally, the transmitted data may be input to the Margin Maker automatically, thereby updating the model and deriving and presenting new proposals/choices, reflecting the updated situation, to the user on the display 11.

[0119] The doser 20 can also receive information via the receiving means 12 from the master module 10. This information could for instance be a predetermined amount of medication as dictated by a proposal from the Margin Maker if

Abbott Ex. 1002 - 499/1438

the user chooses to administer the full amount given by the proposal. The received information is then used to automatically set the correct amount of medication to be administered so that the patient does not have to worry about that aspect. Alternatively, if the user only wishes to administer only a part of the proposed dosage, he may indicate this via the buttons 36 or directly on the doser 20, after which information of the administered dose is sent to the Margin Maker as input and used to update the model.

[0120] Also shown is a BGM 3 0 which has means 34 for inserting test strips 52 containing a sample of blood, for analysis by the BGM 30 by operating the buttons 36. The result of the analysis is stored and either shown in the display 32 or transmitted to the master module 10 via the transmitting means 12 for storage and input to the Margin Maker and presentation on the larger display 11 or both. The patient can at the same time be presented with the last couple of results over a time period.

[0121] A test strip container 50 is provided for the safe keeping/storing of test strips 52 in the space 55 and can be added/attached through locking means 31. With this addition, a test strip 52 will always be available.

[0122] Further shown is a lancet device 40 removably attached to the BGM 30 or the test strip container 50 by the locking means 31. This lancet device 40 is used by first loading the lancet device through the grip 44 and then pressing the button 42, which releases the lancet, piercing the skin, so that a blood sample can be obtained. With this inclusion, the lancet device 40 is always at hand. This has the advantage that a lancet device 40 is always available, for taking a blood sample and applying it to a test strip 52. The test strip 52 can then be inserted via the means 34 into the BGM 30, which will start analysing the blood sample and, after completion of the analysis, will show the result in the display 32. It is very useful to have the BGM 30 and the lancet device 40 attached together in one compact unit, since a BGM 30 would not normally be used without the lancet device 40.

[0123] In this way, information relevant to the Margin Maker and the individual devices 20, 30 may automatically be received and transmitted between the functional master module 10 and the various devices 20, 30, which ensure an automatical update of the system.

[0124] Alternatively, the Margin Maker may only present choices to the user where there is a present and activated device for performing these choices (where applicable), e.g. a proposal of administering a certain amount of long acting insulin is only presented if a doser containing long acting insulin is present, or a doser and a separate cartridge containing long acting insulin. The functional master module is responsible for keeping track of which individual devices that are present and activated.

[0125] If the device containing the master module and/or the Margin Maker, the system may designate a new master module and a new Margin Maker either by transmitting and/or activating the relevant information in the designated device (s).

[0126] Figure 6 shows another embodiment according to the invention. Two dosers 610 are shown. The dosers 610 may contain different types of insulin (fast and slow acting). Also shown is a device 600 with a display 602, buttons for operation 601. In this particular embodiment the device 600 is both the functional master module and the Margin Maker. The device 600 is also provided with the functionality of a BGM and a slot 603 for receiving test strips containing a blood sample.

[0127] The dosers 610 and the BGM functionality may, together with user specified input e.g. a the device 600, provide the Margin Maker with relevant input information to the model and/or expert system, so that the Margin Maker may present the resulting choices on the display 602.

[0128] Figure 7 illustrates the general concept according to an embodiment of the invention with respect to communication and exchange of information. Here the system consists of the portable units: a functional master module, a doser, a BGM, an inhaler, the remote units: Remote Receiver, Physician/Expert Care-team and Stationary Unit and a Communication Interface between them.

[0129] The functional master module controls the information and data flow between itself and the other apparatuses and collects relevant data and information from all the other portable units and uses this information to update the model accordingly. This data and information could e.g. be amount of medication, type of medication, body fluid concentration, time stamp (date and time) and inventory logistics. Additionally, the patient can manually input information and data related to amount of food, measurement of physical activity in the way described above.

[0130] This data and information can then be transmitted via a communication interface (which may be built into the master module) to external units like a database for data acquisition of the patient's data over time or a computer which the patient uses to be kept informed about his treatment. Alternatively, all the apparatuses could communicate to all the others.

[0131] The information in the database can be accessed by a physician or an expert care-team who could easily and quickly check for compliance to e.g. a diet or treatment course/progress. The physician or expert care-team could send a notification (e.g. alert, warning and/or change of regimen) to the patient if the data shows an inappropriate future treatment span. The patient could also be notified of a future appointment in this way or receive guidance.

[0132] The system gives the patient a number of choices to a given situation based on the model as described earlier. The patient could e.g. be informed that the blood glucose level/concentration is quite high and the patient could be

Abbott Ex. 1002 - 500/1438

presented with the choices of either exercising for given amount of time or administering a given amount of a given type of medication. The possibility of choices makes the patient feel more in control of the treatment and enhances the therapeutic value of the treatment.

[0133] Figure 8 illustrates two dosers and their communication paths. The dosers are identical for the typical patient, one doser containing fast acting insulin, the other doser containing slow acting insulin. The dosers comprise a micro controller and memory. The dosers are capable of holding information about the insulin type they contain. This information may either be obtained by the doser reading e.g. a bar code on the cartridge or the information may be input from the patient. Thus the features of the doser enable it to log information about the insulin treatment (insulin type size of the dose and time stamp)

[0134] One doser is equipped with a cap unit 73 which acts as a storage container for an extra insulin cartridge, needles etc. The storage container is capable of keeping track of the contents of the container which enables it to keep the inventory list updated, as described earlier in the present document.

[0135] The other doser is equipped with a cap unit 74 comprising a BGM, a micro controller and memory . This enables the cap unit 74 to log information about the blood glucose concentration (with time stamp).

[0136] All the dosers 71,72 and the cap units 73, 74 comprise an interface which enables them to exchange data. In the present example the functional master device comprises the Margin Maker and is the BGM cap unit 74, which, in addition to the local interface, comprises an interface that enables it to communicate with external units through standard communication links (RS-232, Wireless local area network, phone, cellular phone, pager, satellite link, etc.). Through these communication links, the patient's treatment data can be transferred to the patient's own computer 80 or via e.g. the telephone system 75 to the patient's electronic medical record on a central server 76. From here, the treatment data may be accessed by the patient e.g. from a web page, using a stationary computer 77, a laptop computer 78, a handheld computer 79, etc. Apart from the patient, the care-team can access the patient's treatment data. The patient's master unit 74 can receive data from the central server 76, in addition to transmitting data.

[0137] This system has the advantage that the system can function on 3 levels:
If one of the patient's devices 71, 72, 73, 74 is isolated by means of communication, it will log data.

[0138] When the patient's devices 71, 72, 73, 74 are within communication distance, the treatment data are transferred to the master unit 74, enabling it to supply the patient with an overview of his treatment and present choices as well as warnings or alarms if data shows that a potential dangerous situation may occur.

[0139] When the master device 74 is connected to the central server 76 through standard communication links, the treatment data is transferred to the patient's electronic medical record. This enables an expert system on the central server to notify the care-team if needed. The care-team may send information back to the user or send help if needed.

[0140] Furthermore it is well known that due to the safety of the patient, the development of a medical device is a time consuming task. Using a local communication form between the patient's devices 71, 72, 73, 74 has the advantage that only the master device 74 need to be redesigned to keep up with the continuous change in the standard communication links.

Claims

1. Method of calculating in a computer system a plurality of options for bringing a user into and/or keeping a user substantially in compliance with a medical regime of a medical self treatment, the method comprising the steps of:

   a) collecting by a processing means programmed to do so, in a user individual database, data representing values of a group of parameters relating to the user's physiological condition, and
   b) estimating by a processing means programmed to do so using a dynamic model (303) describing the human metabolism, one or more future values for a specific parameter from the group of the parameters on the basis of information in the user individual database,
   characterised by the following step:
   c) automatically calculating by a processing means programmed to do so using an expert system using the model (303) describing the human metabolism, a plurality of options on the basis of the estimated one or more future values and the data in the user individual database, so as to provide for two or more options and at least one related value for each option, each option and related value bringing a value of the specific parameter within a range of acceptable values at a given future point in time.

2. Method according to claim 1,
   characterized in that
   the step of collecting data comprises collecting one or more of the following:

Abbott Ex. 1002 - 501/1438

- individual characteristics and/or data for the user specified by a care-team and/or a professional and/or a central system,
- data from at least one portable apparatus,
- manually specified input,
- an option selected by the user and a corresponding value, and
- the time and date.

3. Method according to claims 1 - 2,
characterized in that
the step of collecting data comprises automatically collecting data by a processing means programmed to do so from at least one portable apparatus and that said at least one portable apparatus is selected from the group of:

- a body fluid analyzer,
- a blood glucose monitor,
- a drug administration device,
- an insulin administration device,
- a tablet dispenser,
- an inhaler, and
- a continuous blood glucose monitor/sensor.

4. Method according to claims 1 - 3,
characterized in that the method further
comprises the step of:

- presenting at least one apparatus dependent option of said calculated options where said apparatus dependent option involves a use of a portable apparatus, where only apparatus dependent options for present and active portable apparatuses is presented.

5. Method according to claims 1-4,
characterized in that
the method further comprises the steps of:

- transmitting information to a drug administration device, the information comprising a predetermined number of units of a medication to be administered according to a given option of said calculated options, and
- automatically setting the number of units of the medication to be administered.

6. Method according to claims 1 - 5,
characterized in that the step of calculating a plurality of options is done by comparing an estimated future value for the specific parameter with a predetermined target value and for each option calculating the related value for the given option by using the difference between the estimated value for the specific parameter and the target value and using a relationship between the given option and the specific parameter.

7. Method according to claims 1-6,
characterized in that the method further comprises the step of notifying said user if at least one of said one or more future values are outside a predetermined range of acceptable values.

8. Method according to claims 1 - 7,
characterized in that said method further comprises the step of notifying a care-team/professional/central system if at least one of said one or more future values are outside a predetermined range of acceptable values.

9. Method according to claims 1 - 8
characterized in that said one or more future
values represents a predicted blood glucose level (BGL) at different future points in time.

10. Method according to claims 1 - 9,
characterized in that said group of parameters comprises one or more of the following

- a blood glucose level (BGL),

Abbott Ex. 1002 - 502/1438

- a body fluid concentration,
- an amount of administered medication,
- an amount of administered insulin,
- a type of medication,
- a time stamp,
- an amount of intake of food,
- an amount of intake of drinks,
- a measurement of physical activity,
- a value representing the Insulin sensitivity for the user,
- a temperature of the user,
- a blood pressure of the user, and
- a weight of said user.

11. Method according to claims 1 - 10,
characterized in that said options are selected from the group of

- administer a predetermined type and amount of medication,
- administer slow acting insulin,
- administer fast acting insulin,
- administer tablets,
- exercise for a given period of time,
- intake a given amount of food, and
- intake a given amount of drinks.

12. A method according to claim 1-11,
characterized in that said method relates to one or more of the following medications:

- insulin,
- growth hormones,
- OHA (Oral Hyperglychemical Agent), and
- HRT (Hormone Replacement Therapy).

13. A method according to claims 1-12,
characterized in that said method further comprises the step of controlling data information between a plurality of portable apparatuses for use by the user, the use including a first action and at least a second action, said portable apparatuses comprising a first apparatus (15) for performing the first action, and at least a second apparatus for performing the second action, where

- each apparatus has means for one or more of the following: storing, transmitting, receiving, processing and displaying information,
- an attempted data communication between said apparatuses is initiated on request, said communication being controlled by a functional master module,
- designating said functional master module among at least two of said apparatuses, and
- designating a processing apparatus comprising said one or more databases among at least two of said apparatuses.

14. A method according to claim 13,
characterized in that program information having the highest priority with respect to control and monitoring of mutual data communication between said apparatuses is stored/activated in said functional master module.

15. A method according to claims 13 - 14,
characterized in that said method further comprises designating a new functional master module if the current designated master module becomes unavailable.

16. A method according to claims 13 - 14,
characterized in that said method further comprises designating a new processing apparatus if the current designated processing apparatus becomes unavailable.

Abbott Ex. 1002 - 503/1438

17. Method according to claim 9,
characterized in that said self treatment is a self treatment for diabetes.

18. A method according to claim 1, further comprising the step of automatically communicating by a processing means programmed to do so, said options and related value to the user via a communication means.

19. A method of claim 18, **characterized in that** said communication means is a display means (Fig. 1a, 2b, 2c).

Patentansprüche

1. Verfahren eines Berechnens in einem Computersystem einer Vielzahl von Optionen zum Bringen eines Benutzers und/oder Haltens eines Benutzers im Wesentlichen in Übereinstimmung mit einem medizinischen System einer medizinischen Selbstbehandlung, wobei das Verfahren die Schritte umfasst:

a) Sammeln von Daten, die Werte einer Gruppe von mit dem physiologischen Zustand des Anwenders verbundenen Parametern darstellen, in einer Anwender-individuellen Datenbank, durch eine verarbeitende Vorrichtung, die dazu programmiert ist, und
b) Schätzen eines oder mehrerer zukünftiger Werte für einen spezifischen Parameter aus der Gruppe von Parametern auf der Basis von Information in der Anwender-individuellen Datenbank unter Verwendung eines dynamischen Models (303), das den menschlichen Stoffwechsel beschreibt, durch eine verarbeitende Vorrichtung, die dazu programmiert ist,
gekennzeichnet durch den folgenden Schritt:
c) automatisches Berechnen einer Vielzahl von Optionen auf der Basis des einen geschätzten zukünftigen Werts oder der mehreren geschätzten zukünftigen Werte und der Daten in der Anwender-individuellen Datenbank unter Verwendung eines Expertensystems, das das Model (303) verwendet, dass den menschlichen Stoffwechsel beschreibt, **durch** eine verarbeitende Vorrichtung, die dazu programmiert ist, so dass zwei oder mehrere Optionen und mindestens ein damit verbundener Wert für jede Option bereitgestellt werden, wobei jede Option und jeder damit verbundene Wert einen Wert des spezifischen Parameters zu einem vorgegebenen zukünftigen Zeitpunkt innerhalb eines Bereichs von annehmbaren Werten bringt.

2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** der Schritt des Sammelns von Daten das Sammeln eines oder mehrere von Folgendem umfasst:

individuelle Eigenschaften und/oder Daten für den Verwender, die von einem Behandlungsteam und/oder einem Experten und/oder einem zentralen System spezifiziert sind,
Daten von mindestens einer tragbaren Apparatur,
manuell spezifizierte Eingabe,
eine vom Anwender ausgewählten Option und ein entsprechender Wert und
die Zeit und das Datum.

3. Verfahren nach den Ansprüchen 1 - 2,
dadurch gekennzeichnet, dass der Schritt des Sammelns von Daten, ein automatisches Sammeln von Daten aus mindestens einer tragbaren Apparatur umfasst, und dass die mindestens eine tragbare Apparatur ausgewählt ist aus
einem Körperflüssigkeitsanalysator,
einem Blutzuckerüberwachungsgerät,
einer Vorrichtung zur Verabreichung eines Arzneimittels,
einer Vorrichtung zur Verabreichung von Insulin,
einem Tablettenverteiler,
einem Inhalator und
einem kontinuierlichen Blutzuckerüberwachungsgerät/-messfühler.

4. Verfahren nach den Ansprüchen 1 - 3, **dadurch gekennzeichnet, dass** das Verfahren ferner die folgenden Schritte umfasst:

Bereitstellen mindestens einer Apparatur-abhängigen Option der berechneten Optionen, wobei die Apparatur-abhängige Option die Verwendung einer tragbaren Apparatur umfasst, wobei nur Apparatur-abhängige Optio-

Abbott Ex. 1002 - 504/1438

nen für gegenwärtige und aktive; tragbare Apparaturen bereitgestellt werden.

5. Verfahren nach den Ansprüchen 1 - 4, **dadurch gekennzeichnet, dass** das Verfahren ferner den Schritt des Übertragens von Information an eine Vorrichtung zur Arzneimittelverabreichung, wobei die Information eine vorbestimmte Anzahl an Einheiten für eine gemäß einer vorgegebenen Option der berechneten Optionen zu verabreichende Medikation umfasst, und
automatischen Einstellens der Anzahl an Einheiten der zu verabreichenden Medikation
umfasst.

6. Verfahren nach den Ansprüchen 1 - 5,
dadurch gekennzeichnet, dass der Schritt des Berechnens einer Vielzahl von Optionen durch Vergleichen eines geschätzten zukünftigen Werts für den spezifischen Parameter mit einem vorbestimmten Zielwert und Berechnen für jede Option des damit verbundenen Werts für eine vorgegebene Option unter Verwendung des Unterschieds zwischen dem geschätzten Wert für den spezifischen Parameter und dem Zielwert und unter Verwendung eines Verhältnisses zwischen der vorgegebenen Option und dem spezifischen Parameter durchgeführt wird.

7. Verfahren nach den Ansprüchen 1 - 6, **dadurch gekennzeichnet, dass** das Verfahren ferner den Schritt des Benachrichtigens des Anwenders, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

8. Verfahren nach den Ansprüchen 1 - 7, **dadurch gekennzeichnet, dass** das Verfahren ferner den Schritt des Benachrichtigen des Behandlungsteams/Experten/zentralen Systems, ob der eine zukünftige Wert oder die mehreren zukünftigen Werte außerhalb eines vorbestimmten Bereichs von annehmbaren Werten liegt, umfasst.

9. Verfahren nach den Ansprüchen 1 - 8, **dadurch gekennzeichnet, dass** der eine zukünftige Wert oder die mehreren zukünftigen Werte einen vorhergesagten Blutzuckergehalt (blood glucose level, BGL) zu verschiedenen zukünftigen Zeitpunkten darstellt.

10. Verfahren nach den Ansprüchen 1 - 9, **dadurch gekennzeichnet, dass** die Gruppe von Parametern eines oder mehrere von Folgendem umfasst:

    den Blutzuckergehalt (BGL),
    die Körperflüssigkeitskonzentration,
    die Menge an verabreichter Medikation,
    die Menge an verabreichtem Insulin,
    die Medikationsart,
    einen Zeitstempel,
    die Nahrungsmittelaufnahmemenge,
    die Getränkeaufnahmemenge,
    die Messung der physikalischen Aktivität,
    den Wert, der die Insulinempfindlichkeit für den Anwender darstellt,
    die Temperatur des Anwenders,
    den Blutdruck des Anwenders und
    das Gewicht des Anwenders.

11. Verfahren nach den Ansprüchen 1 - 10, **dadurch gekennzeichnet, dass** die Optionen ausgewählt sind aus
Verabreichen einer vorbestimmten Medikationsart und -menge,
Verabreichen von langsam wirkendem Insulin,
Verabreichen von schnell wirkendem Insulin,
Verabreichen von Tabletten,
Durchführen für eine vorgegebene Zeitdauer,
Aufnahme einer vorgegebenen Nahrungsmittelmenge und
Aufnahme einer vorgegebenen Getränkemenge.

12. Verfahren nach den Ansprüchen 1 - 11, **dadurch gekennzeichnet, dass** das Verfahren eine oder mehrere der folgenden Medikationen betrifft:
Insulin,
Wachstumshormone,

Abbott Ex. 1002 - 505/1438

OHA (orales, hyperglykämisches Mittel) und
HRT (Hormonersatztherapie).

13. Verfahren nach den Ansprüchen 1 - 12, **dadurch gekennzeichnet, dass** das Verfahren ferner den Schritt der Steuerung von Dateninformation zwischen einer Vielzahl von tragbaren Apparaturen zur Verwendung durch den Anwender umfasst, wobei die Verwendung eine erste Handlung und mindestens eine zweite Handlung einschließt, wobei die tragbare Apparatur eine erste Apparatur (15) zur Durchführung der ersten Handlung und mindestens eine zweite Apparatur zur Durchführung der zweiten Handlung umfasst, wobei
jede Apparatur Elemente für eines oder mehrere von Folgendem aufweist: Speicherung, Übertragung, Empfang, Verarbeitung und Anzeigen von Information, eine versuchte Datenkommunikation zwischen der Apparatur eine Aufforderung initiiert, wobei die Kommunikation durch ein funktionelles Hauptmodul gesteuert wird,
Benennen des funktionellen Hauptmoduls unter mindestens zwei der Apparaturen und
Benennen einer die eine oder mehreren Datenbanken umfassenden Verarbeitungsapparatur unter mindestens zwei der Apparaturen.

14. Verfahren nach Anspruch 13, **dadurch gekennzeichnet, dass** eine Programminformation mit der höchsten Priorität im Hinblick auf die Steuerung und das Überwachen von wechselseitiger Datenkommunikation zwischen den Apparaturen im funktionellen Hauptmodul gespeichert/aktiviert wird.

15. Verfahren nach den Ansprüchen 13 - 14, **dadurch gekennzeichnet, dass** das Verfahren ferner das Benennen eines neuen funktionellen Hauptmoduls umfasst, wenn das gegenwärtige benannte Hauptmodul unverfügbar wird.

16. Verfahren nach den Ansprüchen 13 - 14, **dadurch gekennzeichnet, dass** das Verfahren ferner das Benennen einer neuen Verarbeitungsapparatur umfasst, wenn die gegenwärtige benannte Verarbeitungsapparatur unverfügbar wird.

17. Verfahren nach Anspruch 9, **dadurch gekennzeichnet, dass** die Selbstbehandlung eine Behandlung für Diabetes ist.

18. Verfahren nach Anspruch 1, weiter mit dem Schritt eines automatischen Kommunizierens der Optionen und verwandten Werte an den Benutzer über eine Kommunikationsvorrichtung durch eine verarbeitende Vorrichtung, die dazu programmiert ist.

19. Verfahren nach Anspruch 18, **dadurch gekennzeichnet, dass** die Kommunikationsvorrichtung eine Anzeigevorrichtung ist (Fig. 1a, 2b, 2c).

Revendications

1. Procédé de calcul dans un système informatique d'une pluralité d'options pour amener un utilisateur à et/ou maintenir un utilisateur sensiblement dans l'observation d'un régime médical d'un auto-traitement médical, le procédé comportant les étapes consistant à :

   a) collecter par un moyen de traitement programmé pour le faire, dans une base de données individuelle d'utilisateur, des données représentant des valeurs d'un groupe de paramètres concernant la condition physiologique de l'utilisateur, et
   b) estimer par un moyen de traitement programmé pour le faire en utilisant un modèle dynamique (303) décrivant le métabolisme humain, une ou plusieurs valeurs futures, pour un paramètre spécifique du groupe des paramètres sur la base d'information de la base de données individuelle d'utilisateur,
   caractérisé par l'étape suivante :
   c) calculer automatiquement par un moyen de traitement programmé pour le faire en utilisant un système expert utilisant le modèle (303) décrivant le métabolisme humain, une pluralité d'options sur la base des unes ou plusieurs valeurs futures estimées et des données de la base de données individuelle d'utilisateur, de manière à fournir deux ou plus de deux options et au moins une valeur associée pour chaque option, chaque option et valeur associée amenant une valeur du paramètre spécifique dans une plage de valeurs acceptables à un instant futur donné dans le temps.

2. Système selon la revendication 1, **caractérisé en ce que** l'étape de collecte de données comporte la collecte d'un

Abbott Ex. 1002 - 506/1438

ou plusieurs éléments parmi ceux qui suivent

- des caractéristiques individuelles et/cu des données concernant l'utilisateur spécifiées par une équipe de soins et/ou un professionnel et/ou un système central,
- des données provenant d'au moins un dispositif portable,
- une entrée manuellement spécifiée,
- une option sélectionnée par l'utilisateur st une valeur correspondante, et
- l'heure et la date,

3. Système selon les revendications 1 et 2,
caractérisé en ce que
l'étape de collecte de données comporte la collecte automatique de données par un moyen de traitement programmé pour le faire à partir d'au moins un dispositif portable et **en ce que** ledit au moins un dispositif portable est sélectionné parmi le groupe constitué de

- un analyseur de fluide corporel,
- un dispositif de surveillance de glucose sanguin,
- un dispositif d'administration de médicament,
- un dispositif d'administration d'insuline,
- un distributeur de comprimés,
- un inhalateur, et
- un dispositif de surveillance/capteur de glucose sanguin continu.

4. Système selon les revendications 1 à 3, **caractérisé en ce que** le procédé comporte de plus l'étape consistant à :

- présenter au moins une option dépendante d'un dispositif parmi lesdites options calculées lorsque ladite option dépendante d'un dispositif implique l'utilisation d'un dispositif portable, seules des options dépendantes d'un dispositif pour des dispositifs portables présents et actifs étant présentées.

5. Système selon les revendications 1 à 4,
caractérisé en ce que
le procédé comporte de plus les étapes consistant à :

- transmettre des informations à un dispositif d'administration de médicament, les informations comportant un nombre prédéterminé d'unités d'une médiation à administrer conformément à une option donnée parmi lesdites options calculées, et

établir automatiquement le nombre d'unités de la médication à administrer.

6. système selon les revendications 1 à 5,
caractérisé en ce que l'étape de calcul d'une pluralité d'options est effectuée en comparant une valeur future estimée pour le paramètre spécifique à une valeur cible prédéterminée et, pour chaque option, en calculant la valeur associée pour l'option donnée en utilisant la différence entre la valeur estimée pour le paramètre spécifique et la valeur cible et en utilisant une relation entre l'option donnée et le paramètre spécifique.

7. Système selon les revendications 1 à 6,
caractérisé en ce que le procédé comporte de plus l'étape consistant à notifier audit utilisateur si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

8. système selon les revendications 1 à 7,
caractérisé en ce que ledit procédé comporte de plus l'étape consistant à notifier à une équipe de soins/professionnel/ayatème central si au moins une valeur parmi lesdites une ou plusieurs valeurs futures se trouve à l'extérieur d'une plage prédéterminée de valeurs acceptables.

9. Système selon les revendications 1 à 8,
caractérisé en ce que lesdits une ou plusieurs valeurs futures représentent un niveau de glucose sanguin prévu (BGL) à différents instants futurs dans le temps .

Abbott Ex. 1002 - 507/1438

10. Système selon les revendications 1 à 9,
caractérisé en ce que ledit groupe de paramètres comporte un ou plusieurs des éléments suivants

- un niveau de glucose sanguin (BGL),
- une concentration de fluide corporel,
- une quantité de médication administrée,
- une quantité d'insuline administrée,
- un type de médication,
- une estampille,
- une quantité d'absorption d'aliments,
- une quantité d'absorption de boissons,
- une mesure d'activité physique,
- une valeur représentant la sensibilité à l'insuline de l'utilisateur,
- une température de l'utilisateur,
- une pression sanguine de l'utilisateur, et
- un poids dudit utilisateur.

11. Système selon les revendications 1 à 10,
caractérisé en ce que lesdites options sont sélectionnées parmi le groupe constitué de :

- l'administration d'un type et d'une quantité prédéterminés de médication,
- l'administration d'une insuline à action lente,
- l'administration d'une insuline à action rapide,
- l'administration de comprimés,
- un effort pendant une période donnée de temps,
- l'absorption d'une quantité donnée d'aliments, et
- l'absorption d'une quantité donnée de boissons.

12. Système selon les revendications 1 à 11,
caractérisé en ce que ledit procédé concerne une ou plusieurs des médications suivantes :

- insuline,
- hormones de croissance,
- OHA (Agent Hyperglycémique Oral), et
- HRT (Thérapie de Remplacement d'Hormones).

13. Système selon les revendications 1 à 12,
caractérisé en ce que ledit procédé comporte de plus l'étape consistant à commander des informations de données entre une pluralité de dispositifs portables pour une utilisation par l'utilisateur, l'utilisation incluant une première action et au moins une seconde action, lesdits dispositifs portables comportant un premier dispositif (15) destiné à effectuer la première action, et au moins un second dispositif destiné à effectuer la seconde action, dans lequel

- chaque dispositif a des moyens pour réaliser une ou plusieurs fonctions suivantes : la mémorisation, la transmission, la réception, le traitement et l'affichage d'informations,
- une communication de données tentée entre lesdits dispositifs est initialisée par une requête, ladite communication étant commandée par un module maître fonctionnel,
- la désignation dudit module maître fonctionnel parmi au moins deux desdits dispositifs, et
- la désignation d'un dispositif de traitement comportant lesdites une ou plusieurs bases de données parmi au moins deux desdits dispositifs.

14. Système selon la revendication 13,
caractérisé en ce que les informations de programme ayant la priorité la plus élevée par rapport à la commande et la surveillance d'une communication de données mutuelle entre lesdits dispositifs sont mémorisées/activées dans ledit module maître fonctionnel.

15. Système selon les revendications 13 et 14,
caractérisé en ce que ledit procédé comporte de plus la désignation d'un nouveau module maître fonctionnel si le module maître désigné actuel devient indisponible.

Abbott Ex. 1002 - 508/1438

16. Système selon les revendications 13 et 14,
caractérisé en ce que ledit procédé comporte de plus la désignation d'un nouveau dispositif de traitement si le dispositif de traitement désigné actuel devient indisponible.

17. Système selon la revendication 9,
caractérisé en ce que ledit auto-traitement est un auto-traitement pour le diabète.

18. système selon la revendication 1, comportant de plus l'étape consistant à communiquer automatiquement par un moyen de traitement programmé pour le faire, lesdites options et la valeur associée à l'utilisateur via un moyen de communication.

19. Système selon la revendication 18 , **caractérisé en ce que** ledit moyen de communication est un moyen d'affichage (Fig. 1a, 2b, 2c).

Abbott Ex. 1002 - 509/1438

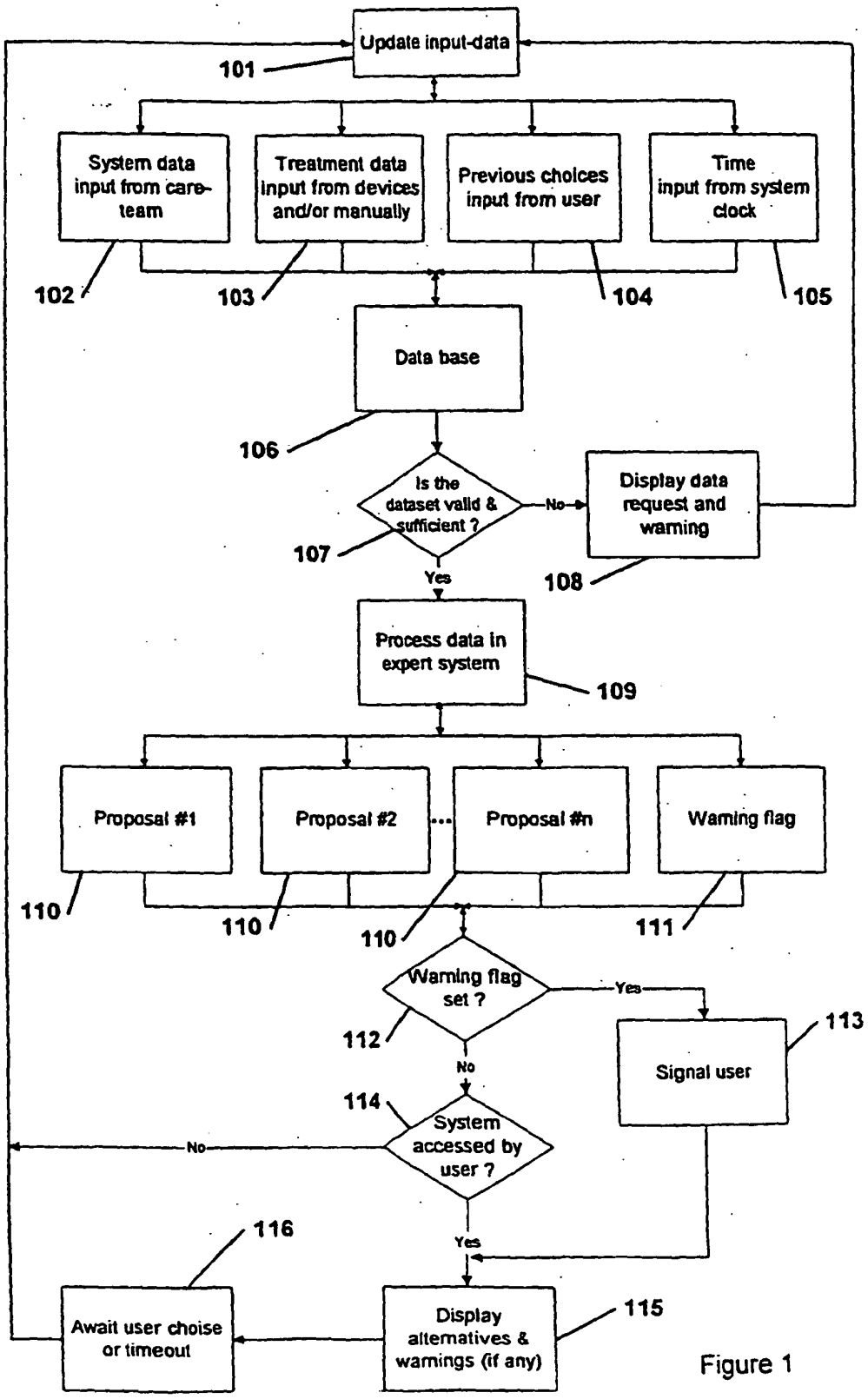


Figure 1

Abbott Ex. 1002 - 510/1438

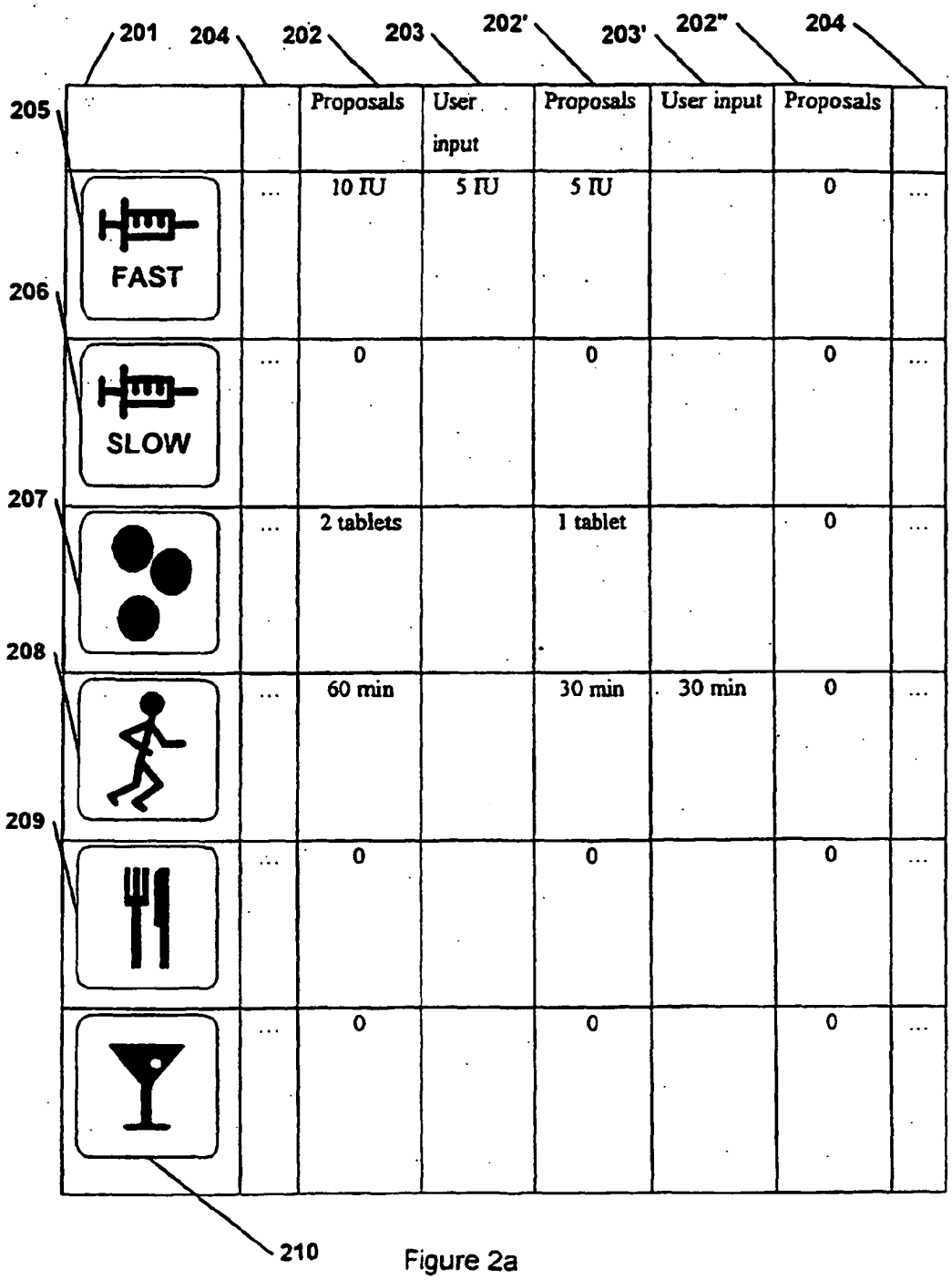


Figure 2a

Abbott Ex. 1002 - 511/1438

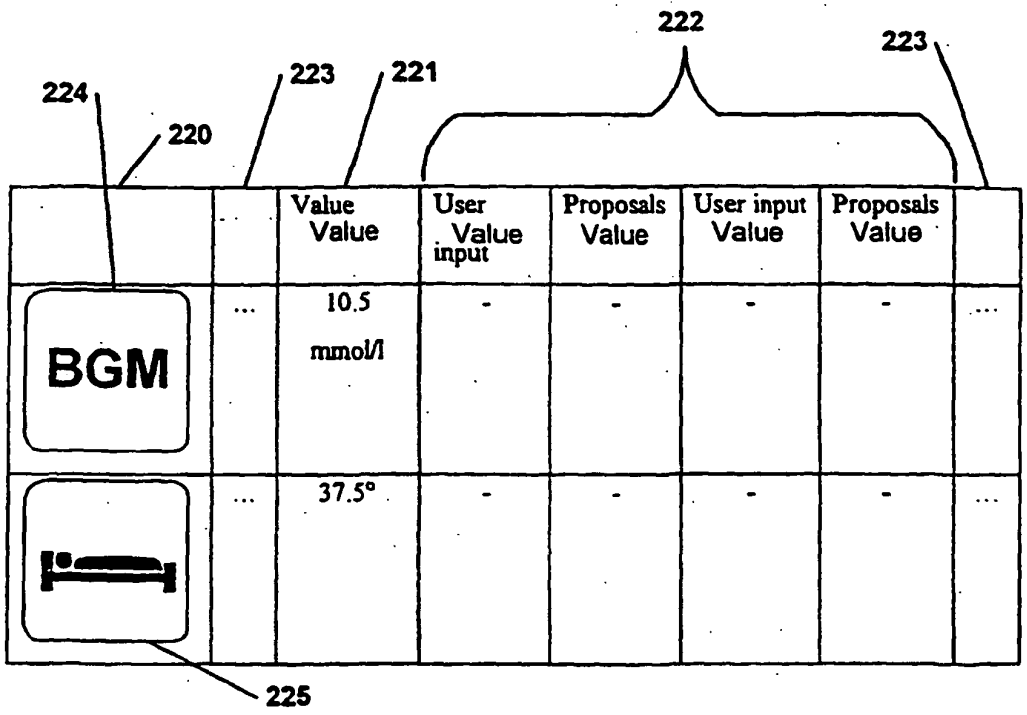


Figure 2b

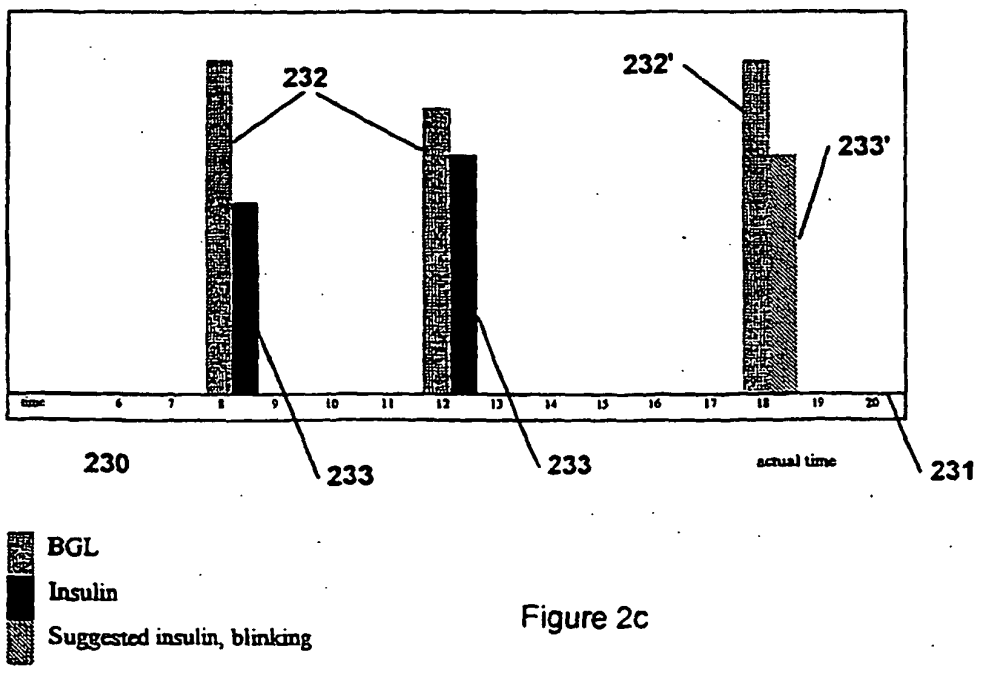


Figure 2c

Abbott Ex. 1002 - 512/1438

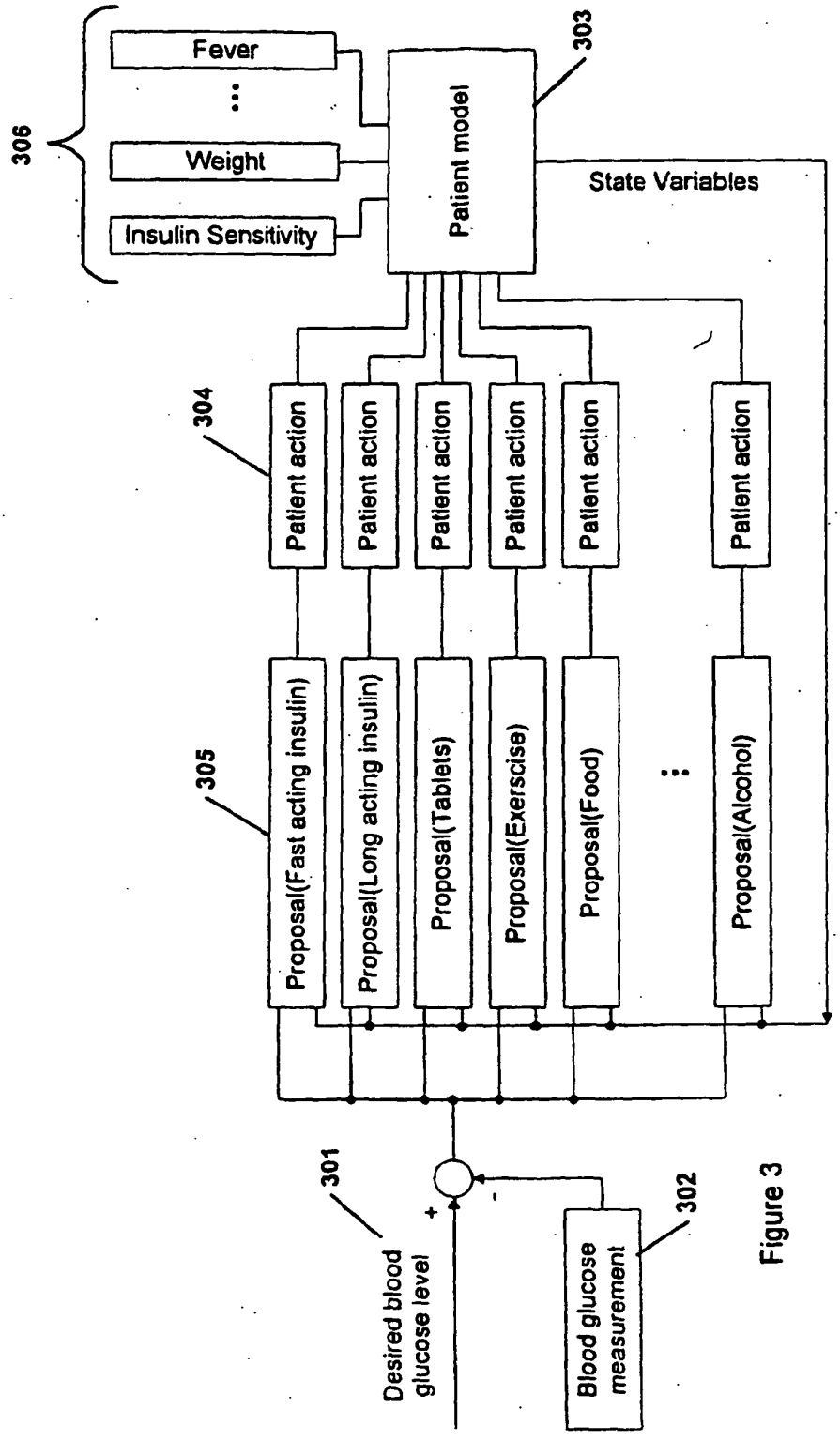


Figure 3

Abbott Ex. 1002 - 513/1438

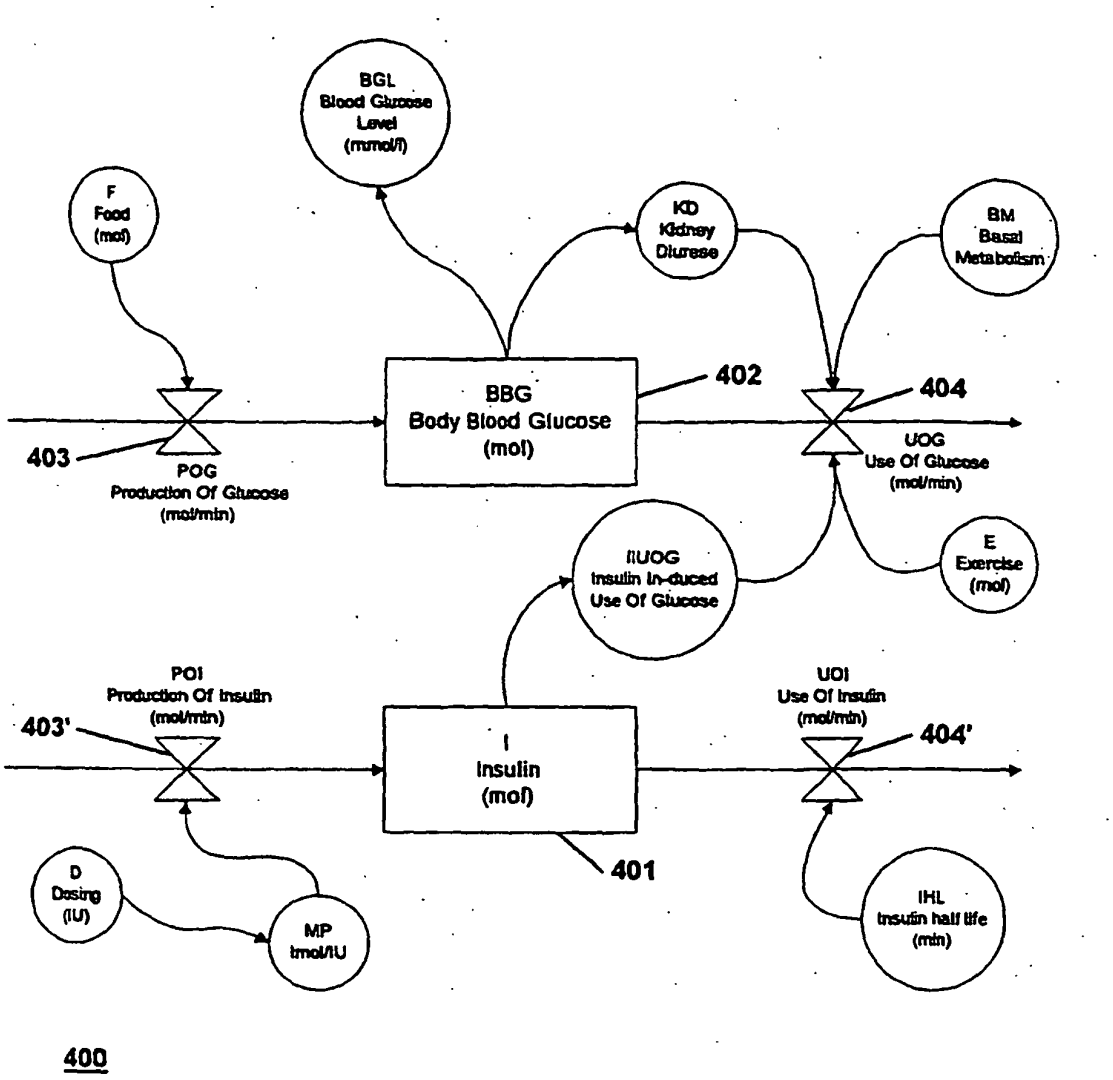


Figure 4

Abbott Ex. 1002 - 514/1438

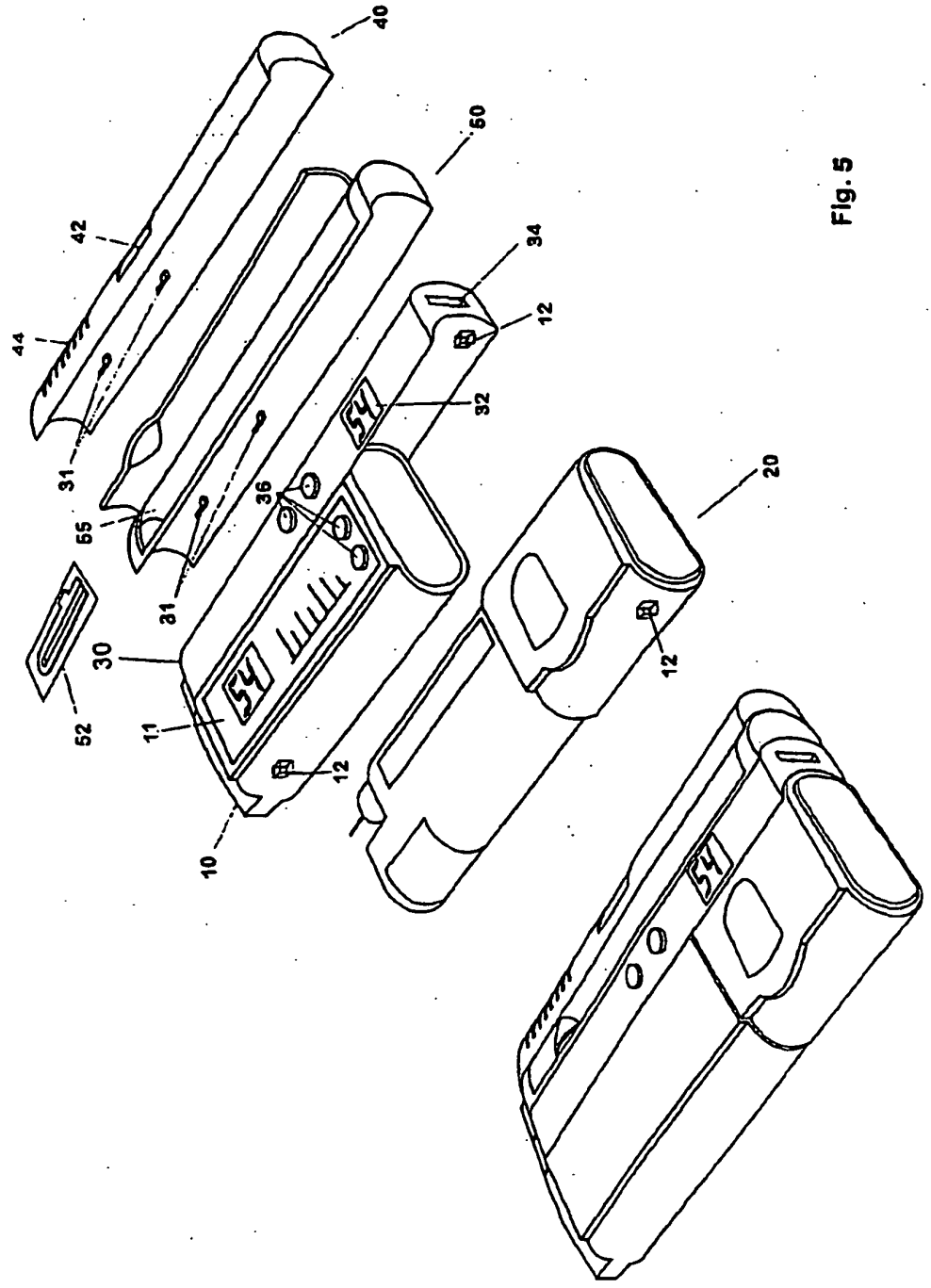


Fig. 5

Abbott Ex. 1002 - 515/1438

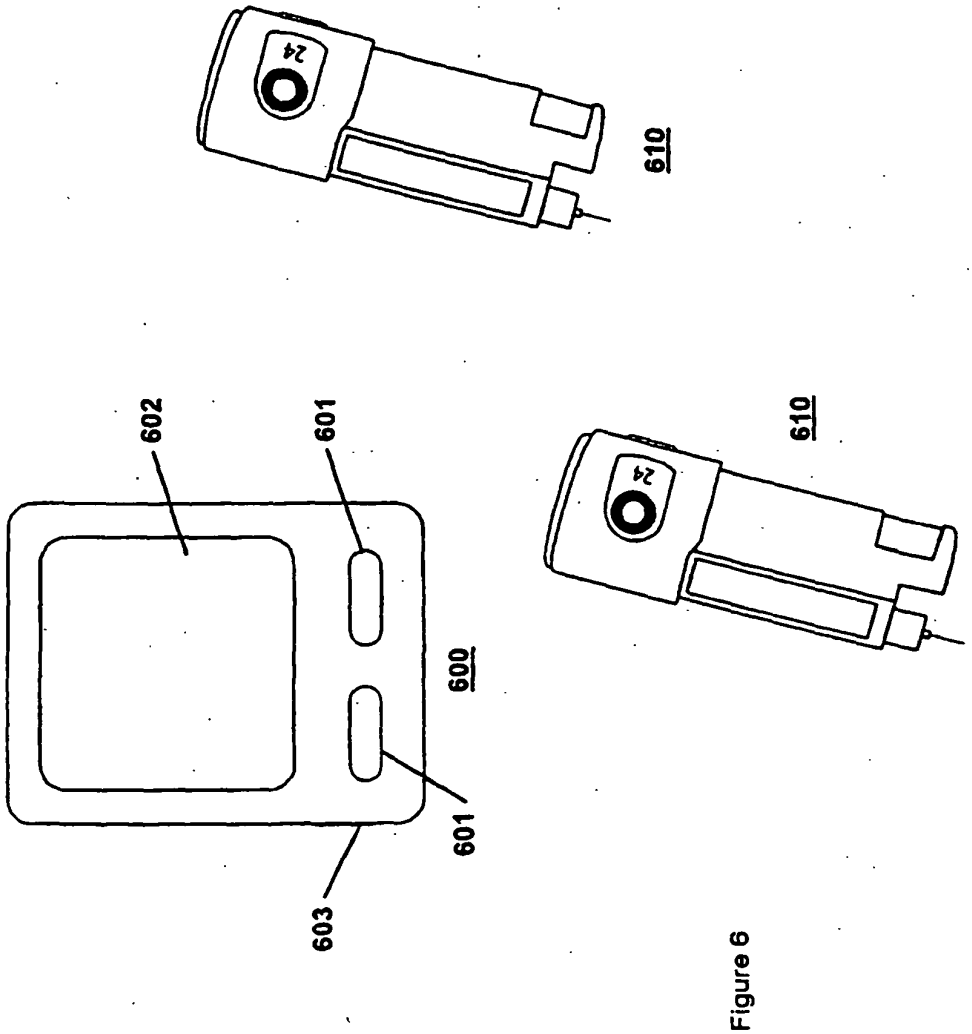


Figure 6

Abbott Ex. 1002 - 516/1438

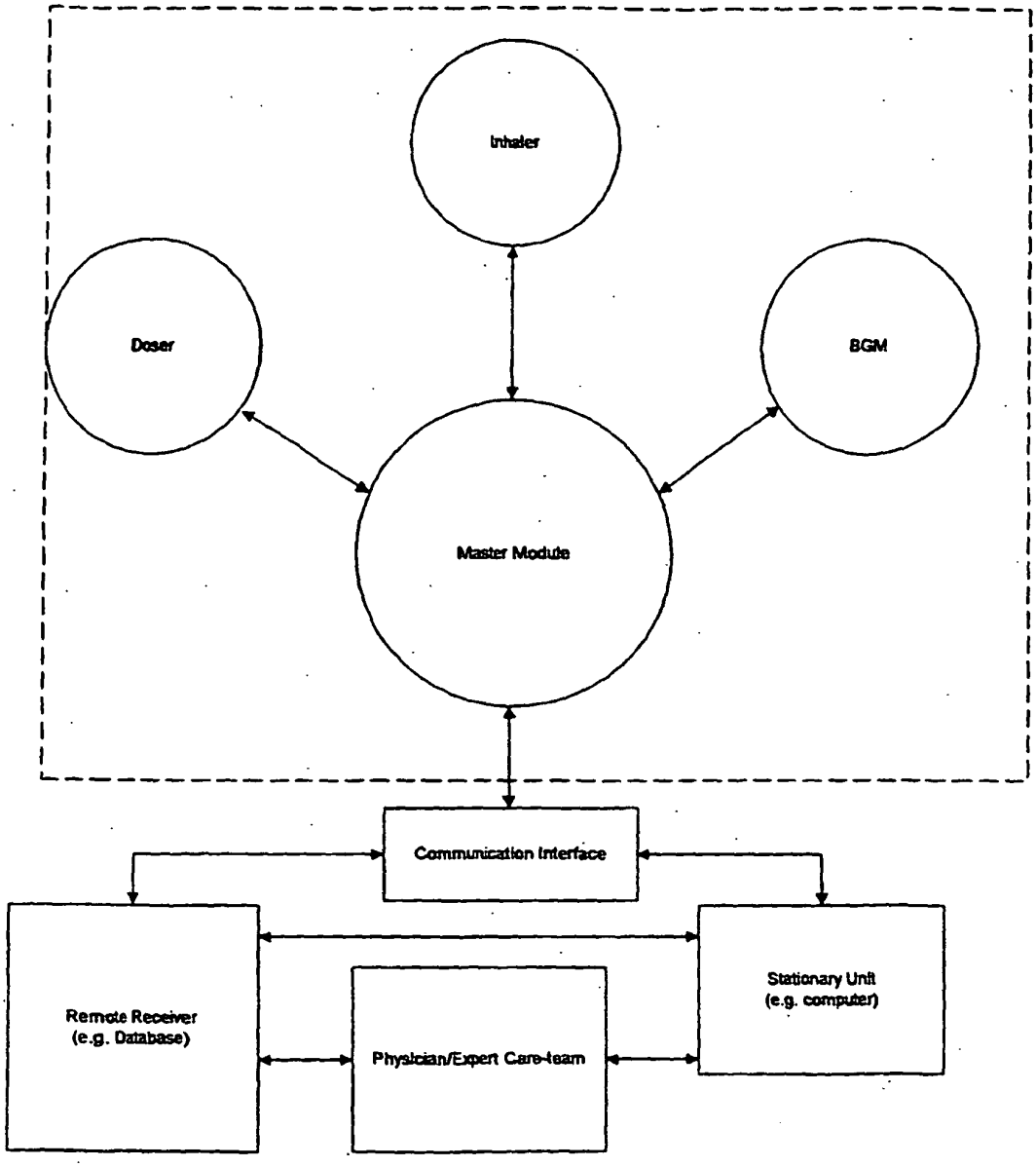


Figure 7

Abbott Ex. 1002 - 517/1438

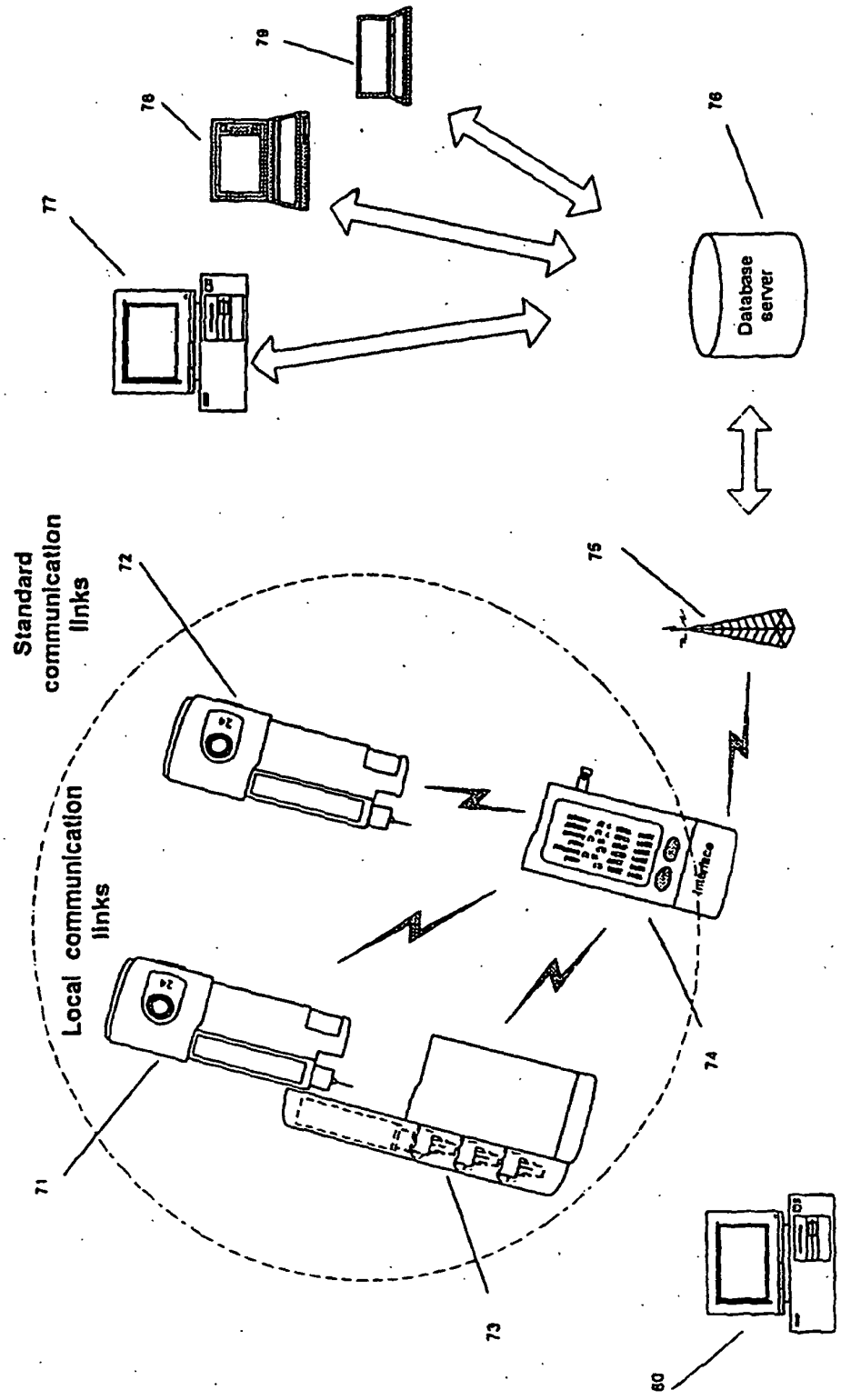


Figure 8

Abbott Ex. 1002 - 518/1438

REFERENCES CITED IN THE DESCRIPTION

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Abbott Ex. 1002 - 519/1438

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(54) External infusion device with remote programming, bolus estimator and/or vibration alarm capabilities

Infusionsvorrichtung mit Fernprogrammierung, Bolusplaner und/oder Alarmfähigkeiten in Form von Vibrationen

Dispositif externe pour perfusion à téléprogrammation, estimation de bolus et/ou alarme vibratoire

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EP 1 473 050 B1

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Description

FIELD OF THE INVENTION

[0001] This invention relates to external infusion devices and, in particular embodiments, to a medication infusion device that includes the capability to be remotely controlled, a bolus estimator to determine the dosage to be administered by the infusion device, and a vibration alarm.

BACKGROUND OF THE INVENTION

[0002] Insulin must be provided to people with Type I and many with Type II diabetes. Traditionally, since it cannot be taken orally, insulin has been injected with a syringe. More recently, use of external infusion pump therapy has been increasing, especially for delivering insulin for diabetics using devices worn on a belt, in a pocket, or the like, with the insulin delivered via a catheter with a percutaneous needle or cannula placed in the subcutaneous tissue. For example, as of 1995, less than 5% of Type I diabetics in the United States were using pump therapy. There are now about 7% of the currently over 900,000 Type I diabetics in the U.S. using insulin pump therapy, and the percentage is now growing at an absolute rate of over 2% each year. Moreover, the number of Type I diabetics is growing at 3% or more per year. In addition, growing numbers of insulin using Type II diabetics are also using external insulin infusion pumps. Physicians have recognized that continuous infusion provides greater control of a diabetic's condition, and are also increasingly prescribing it for patients. In addition, medication pump therapy is becoming more important for the treatment and control of other medical conditions, such as pulmonary hypertension, HIV and cancer. Although offering control, pump therapy can suffer from several complications that make use of a pump less desirable for the user.

[0003] Document US 5,582,593, on which the pre-characterizing part of claim 1 is based, shows an ambulatory medication delivery system including a ambulatory pump unit with a programmed delivery schedule that may be altered through communication with a remote monitoring location via a telephone data access line or via radio frequency communication. The device has both audio and vibration alarms. The audio alarm indicates there is malfunction concerning the dispensing and the vibration alarm indicates that the battery requires recharging or replacement.

[0004] Whether an audio or vibration alarm is appropriate however depends very much on the environment in which the pump is to be used. This is not considered in US 5,582,593.

[0005] Another drawback to using an infusion pump, is the step of priming the external infusion pump to remote gas bubbles in the reservoir and/or tubing. The user must first manually shake the reservoir to move any bubbles to the distal end of the reservoir. Then the user must carefully expel the bubbles through the tubing. However, unless all bubbles are moved to the distal end of the reservoir, the user will have to expel a larger amount of medication, which can be wasteful, and very costly for special types of medications, such as those used in HIV and cancer treatment. Improved methods of priming the external infusion pump are needed.

SUMMERY OF THE DISCLOSURE

[0006] It is an object of an embodiment of the present invention to provide an improved external infusion device, which obviates for practical purposes, some of the above mentioned limitations. The invention is as defined in claim 1 below.

[0007] In an embodiment, an external infusion device for infusion of a liquid into a body includes a housing containing a reservoir, a processor and a vibration device. The processor is coupled to the housing. The vibration device is used in conjunction with the processor to provide an alarm, and to generate sufficient vibration to assist in removing gas bubbles from the fluid in the reservoir during priming of the external infusion device. In further embodiments, the vibration device is used to agitate the fluid in the reservoir in between periodic deliveries of the fluid by the external infusion device and/or during delivery of the fluid by the external infusion device.

[0008] In other embodiments, an external infusion device for infusion of a liquid into a body includes a housing containing a reservoir, a processor, an audible alarm and a vibration device. The processor is coupled to the housing, and the audible alarm. The vibration device is used in conjunction with the processor and the audible alarm to provide an alarm. In further embodiments, the vibration device is also used to agitate the fluid in the reservoir in between periodic deliveries of the fluid by the external infusion device and/or during delivery of the fluid by the external infusion device. The processor selects to activate one of the audible alarm and vibration alarm independently of the unselected alarm.

[0009] Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings which illustrate, by way of example, various features of embodiments of the invention.

Abbott Ex. 1002 - 521/1438

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] A detailed description of embodiments of the invention will be made with reference to the accompanying drawings, wherein like numerals designate corresponding parts in the several figures.

Fig. 1 is a simplified block diagram of an external infusion device and system in accordance with an embodiment of the present invention.

Fig. 2 is a perspective view of an external infusion device and system in accordance with an embodiment of the present invention.

Fig. 3 is a top perspective view of an RF programmer in accordance with an embodiment of the present invention.

Fig. 4 is a top perspective view of a remote commander in accordance with another embodiment of the present invention.

Fig. 5 is a front plan view of an LCD display for use in an embodiment of the present invention.

Fig. 6 is a table of Setup II options used on external infusion devices in accordance with embodiments of the present invention.

Fig. 7 is a flow diagram illustrating the steps used to set a bolus with and without the carbohydrate estimator in accordance with embodiments of the present invention.

Figs. 8(a) and 8(b) are flow diagrams illustrating the steps used to access the features of the setup II menu options shown in Fig. 6.

Fig. 9 is a table of the main menu options used on external infusion devices in accordance with embodiments of the present invention.

Fig. 10 is a table of Setup I menu options used on external infusion devices in accordance with embodiments of the present invention.

Fig. 11 is a flow diagram illustrating the steps used to access the main menu options shown in Fig. 9.

Fig. 12 is a flow diagram illustrating the steps used to access the features of the setup I menu options shown in Fig. 10.

Fig. 13 is a graph showing units delivered versus expected days of operation on a set of batteries.

Fig. 14 is a chart illustrating factory default setting used by embodiments of the present invention.

Fig. 15 is a simplified diagram of an external infusion device and system in accordance with another embodiment of the present invention.

Fig. 16 is a simplified block diagram of an external infusion device and system in accordance with still another embodiment of the present invention.

Fig. 17 is a simplified block diagram of an external infusion device and system in accordance with yet another embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0011] As shown in the drawings for purposes of illustration, the invention is embodied in an external infusion device for infusion of a liquid, such as medication, chemicals, enzymes, antigens, hormones, vitamins or the like, into a body of a user. In preferred embodiments of the present invention, the external infusion device is an external infusion pump, which includes an RF programming capability, a carbohydrate (or bolus) estimation capability and/or vibration alarm capability. Particular embodiments are directed towards use in humans; however, in alternative embodiments, the external infusion devices may be used in animals.

[0012] As illustrated in Fig. 1, preferred embodiments of the external infusion device 10 include a remote RF programmer 12, a carbohydrate (or bolus) estimator 14 and/or a vibration alarm 16. The RF programmer 12 and carbohydrate estimator 14 communicate with a processor 18 contained in a housing 20 of the external infusion device 10. The processor 18 is used to run programs and control the external infusion device 10, and is connected to an internal memory device 22 that stores programs, historical data, user defined information and parameters. In preferred embodiments, the memory device is a Flash memory and SRAM; however, in alternative embodiments, the memory device 22 may include other memory storage devices such as ROM, DRAM, RAM, EPROM, dynamic storage such as other flash memory, energy efficient hard-drive, or the like. In preferred embodiments, the external infusion device 10 is an external infusion pump that is programmed through a keypad 24 on the housing 20 or by commands received from the RF programmer 12 through a transmitter/receiver 26. Feedback from the external infusion device 10 on status or programming changes are displayed on an LCD 28 and/or audibly through a speaker 30. In alternative embodiments, the keypad 24 may be omitted and the LCD 28 may be used as a touch screen input device or the keypad 24 may utilize more keys or different key arrangements then those illustrated in the figures. The processor 18 is also coupled to a drive mechanism 32 that is connected to a fluid reservoir 34 containing fluid that is expelled through an outlet 36 in the reservoir 34 and housing 20, and then into a body of a user through tubing and a set 38. In further alternative embodiments, the keypad 24, LCD 20, speaker 24 may be omitted from the external infusion device, and all programming and data transfer is handled

Abbott Ex. 1002 - 522/1438

through the RF programmer 12.

[0013] Generally, as shown in Fig. 2, preferred embodiments of the external infusion device 10 are an external insulin pump having the capability to deliver 0 to 35 Units/hour in basal rates and up to 25.0 Units per meal bolus of U-100 Insulin. In alternative embodiments, the external pump delivers other concentrations of insulin, or other liquids, and may use other limits on the delivery rate.

[0014] The external infusion device 10 will also give the user the choice of an audible alarm and/or vibration alarm 16 such as of a warning that is indicative of a low reservoir situation or low battery or some malfunction of the system, such as an occlusion of the outlet that restricts the delivery of the fluid. Alarms may start out at a low level and escalate until acknowledged by the user. In further embodiments, both an audible alarm and a vibration alarm may be given at the same time.

[0015] As shown in Fig. 5, embodiments of the external infusion device 10 will utilize a segmented screen LCD 28 that offers multiple-language capability in approximately 6 languages. However, alternative embodiments may include larger or smaller language capabilities. Further alternative embodiments, may utilize an LCD that uses a dot matrix, active matrix, or the like. A scratch resistant window may be utilized to provide improved durability, better viewing and less glare.

[0016] Several programming options will be available in the external infusion device 10, and will include at least two customized basal profiles, a carbohydrate (or bolus) estimator 14 and an alarm clock, as well as remote and on-device programming. Additionally, a physician/educator will be able to configure the external infusion device 10 through a Communications Station (Communication-Station - shown in Fig. 15) to provide or restrict access to certain programming options. Particular embodiments of the external infusion device 10 will also download stored information through the Communication-Station. Further description of a Communication Station of this general type is be found in U.S. Patent. No. 5,376,070 to Purvis et al., entitled DATA TRANSFER SYSTEM FOR AN INFUSION PUMP, which is herein incorporated by reference. This information can be used alone or combined with information from a Glucose Meter and/or a Glucose Sensor (not shown) to assist the user and/or the health care professional in making intelligent therapy decisions. Moreover, the information, programs and data may be downloaded to a remote or local PC, laptop, Communication-Station, or the like, for analysis and review by a MiniMed or a trained health care professional through the transmitter/receiver 26. The data may also be downloaded through a Communication-Station 8 to a remotely located computer 6 such as a PC, laptop, or the like, over communication lines 7, by modem or wireless connection, as shown in Fig. 15.

[0017] The external infusion device 10 will also have additional memory capacity to allow configuring of the display during manufacturing to display information in several different foreign languages, and allow for future upgrades and revisions without the requirement of a hardware change. For example, a PC program will enable manufacturing to select the language for the pump. Languages are contingent upon available space, but will include English, French, Spanish, Italian, Dutch, Swedish and German. In alternative embodiments, other languages will be determined based upon space availability.

RF Programmer

[0018] The remote RF programmer 12 (or remote commander) will enable the user to perform basic external infusion device 10 programming steps without accessing the keyboard 24 on the external infusion device 10 or looking at the LCD (Liquid Crystal Display) 28 screen. This will benefit visually impaired users of the external infusion device 10, since the remote RF programmer 12 will give them ready access to the most commonly used operations of the external infusion device 10, and will obviate the need for visual feedback. Of particular importance to the sight impaired will be the auditory feedback (and/or vibration feedback as discussed below) that the external infusion device 10 will provide. The instructions from the RF programmer 12 will be confirmed by a series of audible beeps (or if requested by programming, vibration) from the external infusion device 10. In alternative embodiments, the RF programmer 12 may include a receiver and provide an audio (or vibration) indication that the commands have been received and acknowledged by the external infusion device 10. In further embodiments, the keypad 102 on the remote RF programmer 12 will have the letters defining the capability of the key encoded in Braille, and the ridges that orient the user to the keypad 102 will be quite pronounced to assist in guiding the user to the proper function key. Other embodiments may utilize keys that have different sizes or shapes to further enhance the ability for users to identify the correct buttons to activate the various features and functions.

[0019] A remote RF programmer 12 will provide convenience and discretion for the user of the external infusion device 10 by allowing concealment of the external infusion device 10 under clothes, in pouches, or the like. Preferably, the RF programmer 12 is an optional accessory item on the external infusion device 10, and the external infusion device 10 will be fully functional without the use of the RF programmer 12. However, in alternative embodiments, the keypad 24 in the external infusion device 10 may be omitted and all programming would be handled by a local or remote PC, laptop, Communication-Station, RF programmer or the like. In preferred embodiments, the RF programmer 12 will also provide the user with the ability to perform the following functions: deliver a bolus, suspend/restart the external infusion device,

Abbott Ex. 1002 - 523/1438

and set and cancel a temporary basal rate. However, in alternative embodiments, the RF programmer may include still additional capabilities such as data transfer (e.g., external infusion device history data or data from other medical devices), updates to software and programming, or the like. In preferred embodiments, the data transfer capabilities between the RF programmer 12 and the transmitter/receiver 26 of the external infusion device 10 are two-way. In alternative embodiments, the data transfer from the RF programmer 12 to the external infusion device 10 is one-way, such that the RF programmer 12 does not receive transmissions from the external infusion device 10. In further embodiments, the RF programmer acts as a relay, or shuttle, for data transmission between the external infusion device 10 and a PC, laptop, Communication-station, or the like.

[0020] In addition, as shown in Fig. 16, a relay or repeater 4 may be used with an external infusion device 10 and an RF programmer 12 to increase the distance from which the RF programmer 12 can be used with the external infusion device 10. For example, the relay could be used to provide information to parents of children using the external infusion device 10 and allow them to program the external infusion device 10 from a distance with the RF programmer 12. The information could be used when children are in another room during sleep or doing activities in a location remote from the parents. In further embodiments, the relay 4 can include the capability to sound an alarm. In addition, the relay 4 may be capable of providing external infusion device 10 information to a remotely located individual via a modem connected to the relay 4 for display on a monitor, pager or the like. In a still further embodiment of the present invention, the external infusion device 10 is capable of being programmed by multiple RF programmers 12, as shown in Fig. 17. For instance, each RF programmer 12 would learn (or be programmed with) the unique code (discussed below) of the external infusion device 10. This would be useful for users that desired to have multiple RF programmers 12, such as at home, office and/or school or needed a replacement for an RF programmer that was lost.

[0021] In preferred embodiments, the RF programmer 12 is similar in appearance to the type of remote that is used to lock and unlock car doors. It will have four (4) keys on a keypad 102 on a housing 104, which will be laid out in a square grid pattern, similar in appearance and layout to the keypad 24 on the external infusion device 10, as shown in Figs. 2 and 3. In alternative embodiments, fewer keys may be used to simplify the RF programmer 12 (see Fig. 15), reduce manufacturing costs and/or to reduce the number of program capabilities available (such as Suspend (S), bolus (B), or the like). Preferably, the RF programmer 12 should include a ring 106 that fits on a key ring to lessen the likelihood that it might be lost. It should also have a "quick release" feature to allow the user to disconnect it from the key ring. Preferably, the RF programmer 12 is less than 1 cubic inch in volume; although larger or smaller volumes may be used. Preferred embodiments utilize RF frequencies; however, alternative embodiments, may use optical, infrared (IR), ultrasonic frequencies, magnetic effects, or the like, to communicate with the external infusion device 10.

[0022] Alternative embodiments of the RF programmer (controller or commander) 12', as shown in Fig. 4, may have more complex keypad arrangements 152, and may include a display device 150, such as an LCD, LED, plasma screen, or the like, to assist in programming the external infusion device 10. Further alternatives may include a microphone (not shown) and related circuitry to allow voice activated control of the external infusion device. In further alternative embodiments, the RF programmer 12' may be formed in larger sizes, comparable to a TV controller or a pocket calculator, and may include a display to facilitate more complicated or easier programming. Still further embodiments, may include the ability to receive data and information from the external infusion device 10 and/or a glucose monitoring device, and the ability to relay the information to another medical device, external infusion device 10, glucose monitor device, PC, laptop, Communication-Station, or the like. Data transmission may be to other devices or include the capability to receive data or instructions. An RF activation capability may be included in addition to the programming capability.

[0023] Each RF programmer 12 will include the capability to "learn" the unique code of the external infusion device 10 for which it is intended to be used. In one embodiment, the user will perform the following steps to learn the unique code: 1) remove the battery from the RF programmer 12; 2) wait a few seconds and then replace the battery in the battery compartment; 3) press and hold the ACT key 110 on the remote keypad 102 (preferably, the remote will confirm that it has been activated with a long audible beep); and then the remote is held within approximately 12" to 18" (alternatively larger or smaller distances may be used) of the external infusion device 10 to receive the unique code from the transmitter/receiver 26 of the external infusion device 10. The RF programmer 12 will confirm successful learning of the unique code with audible beeps and/or vibration from the external infusion device 10 and/or RF programmer 12. In alternative embodiments, the user may manually enter or scan in the unique code identifying the RF programmer. In further alternative embodiments, the RF programmer 12 may also transmit a unique identification code that uniquely identifies the RF programmer 12 to the external infusion device 10 so that the external infusion device 10 will only accept commands from a particular RF programmer 12. In other embodiments, the unique code includes the serial number of the device to prevent confusion with other devices. In particular embodiments, the RF programmer 12 transmits commands to the infusion device 10, but does not include a receiver to receive back data from the infusion device 10. In this embodiment, the infusion device 10 includes the ability to store 3 unique codes to permit the infusion device 10 to be programmed by up to 3 different RF programmers 12. In other embodiments, the infusion device 10 may include more or less storage locations to permit programming of the infusion device 10 with a corresponding more or less number of RF programmers 12.

Abbott Ex. 1002 - 524/1438

[0024] In preferred embodiments, the external infusion device 10 includes a receiver to receive the commands from the RF programmer 12. Normally, the receiver is in a standby mode (e.g., not receiving) and becomes active for short periods every 2.5 seconds (approximately) to see if there is any RF activity from the RF programmer 12. In alternative embodiments, the receiver of the external infusion device 10 may be on continuously or may become active more often or less often, with the selection being dependent on power capacity, expected frequency of use of the RF programmer 12, or the like. Generally, the receiver of the external infusion device 10 requires that the RF programmer send an activating message for a period lasting about 5 seconds for the RF programmer to be recognized by the receiver. In alternative embodiments, longer or shorter periods of time for sending the activating message may be used.

[0025] Once the receiver recognizes that there is a valid RF programmer 12 sending a message to the external infusion device 10 (i.e., with this device 10's unique code), the receiver will remain in an active mode until a complete sequence of commands has been received, or until the receiver times out due to a lack of RF communications from the RF programmer 12. Preferably, upon recognition of a valid RF programmer 12 trying to communicate with the receiver, the external infusion device 10 will activate its audio beeper (or its vibrator or the like) to let the user know that the external infusion device 10 has been activated by the RF programmer 12. Typically, the receiver of the infusion device 10 expects to receive a message with a valid preamble and message type, a recognized unique code, a valid function code (e.g., activate, bolus, suspend, or the like), an appropriate message count used by the receiver for reduction of RF interference problems, and a valid CRC on the transmitted message to ensure message integrity. Alternative embodiments, may include different message contents or components.

[0026] In operation, as discussed above, the RF programmer 12 may be used to program several capabilities, such as an audio (or vibration) bolus, a suspension of external infusion device operation, a temporary basal rate, an extended bolus (such as square wave, ramp, triangular or the like) or dual wave bolus. In addition, the user may program a profiled bolus that uniquely matches the needs of the individual user (for instance it may contain square, ramp, pulse or curved portions that make up the profile to be delivered over a period of time). It should be noted that the capabilities may also be directly programmed on the external infusion device 10 using the same sequence on the keypad of the external infusion device 10. The following are examples of how the various capabilities can be programmed using the keypad 102 on the RF programmer 12 (or similarly with the keypad 24 on the external infusion device 10).

Example I - RF programmed Audio bolus

[0027] To deliver an audio bolus with the RF programmer 12, the user will press the "B" or Up arrow key (▲) 108 in the upper right hand comer of the RF programmer 12 keypad 102. Each time the Up arrow key (▲) 108 is pushed the amount of the audio bolus will increment in either .5 units or 1.0 units (depending on what the user programmed as the incremental step on the "audio" screen of the Set-up 1 menu - alternative embodiments may use other increments). In these examples, units are an increment of insulin. However, alternative embodiments, may define units to be any fluid volume, such as micro-liters, ccs, or the like, with the volume being dependent on the type of fluid to be infused. If the user exceeds the desired setting he can wait for an error signal, such as a "raspberry" type sound, buzzing, vibration, or the like, and then press the Up arrow key (▲) 108 on the RF programmer 12 to begin the process again.

[0028] When the desired audio bolus amount is programmed, the user presses the "activate" or ACT key 110 in the lower left comer of the keypad 102 on the RF programmer 12. The external infusion device 10 will then confirm the audio bolus amount with a series of audible beeps. In alternative embodiments, vibration may be used instead of or in addition to audible beeps. To deliver the audio bolus, the user will then press the ACT key 110 again to start delivery of the bolus. Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 150 and will provide a visual confirmation with or without an audio confirmation.

[0029] Counting the bolus increments will be facilitated by varying the audio tones for beeps that accompany the Up arrow key (▲) 108 presses. Four notes belonging to a musical chord will be used in repeating sequence as the Up arrow key (▲) 108 is repeatedly pressed to select a desired bolus amount. In alternative embodiments, more or fewer notes (and/or vibration) may be used. For example, if 0.5U (U-100) is the bolus increment, the first key press of the Up arrow key (▲) 108 will set the external infusion device 10 and LCD 28 to 0.5 U, and it will be accompanied by the first note in a chord. The second key press of the Up arrow key (▲) 108 will increment the external infusion device and the LCD 28 to 1.0 U, and it will be accompanied by the second note in the chord. The third key press of the Up arrow key (▲) 108 will increment the external infusion device 10 and LCD 28 to 1.5 U, and it will be accompanied by the third note in the chord. The fourth key press of the Up arrow key (▲) 108 will increment the external infusion device 10 and the LCD 28 to 2.0 U, and it will also be accompanied by the fourth note in the chord. On the fifth key press of the Up arrow key (▲) 108, the displayed bolus amount will be incremented again and the audio sequence will repeat in the same manner as just described.

[0030] When the desired bolus amount is displayed and/or sounded, the user continues by pressing the ACT key 110. The external infusion device 10 will play back the beep sequence generated during the bolus amount selection. The

Abbott Ex. 1002 - 525/1438

bolus delivery will commence after the user confirms the bolus amount selection by pressing the ACT key 110 once again. To cancel this bolus before it starts, the user may either allow the external infusion device 10 to time out and return to the time display or press the Down arrow key (▼) 112. Either of these will be accompanied by a "raspberry" type beep (and/or vibration) indicating the bolus has been cleared. Preferably, a standard time-out delay of 15 seconds applies to all keypresses involved during the bolus amount selection, but other time periods may be used.

[0031] Preferably, a BOLUS element, the word DELIVERY, and the updated amount delivered will be displayed on the LCD 28 while delivery is in progress. The external infusion device 10 will beep once at the end of the dose. In alternative embodiments, audible indications may be provided, such as beeps, chords, speech, or the like, and/or vibration.

Example II - RF programmed suspension of External Infusion Device Operation

[0032] To temporarily suspend the operation of the external infusion device 10, the user will press the "select" or SEL key 114 in the upper left hand corner of the keypad 102 of the remote RF programmer 12, and then press the ACT key 110. The external infusion device 10 will confirm that it is in suspend mode with three (3) audible beeps (although different numbers of beeps and/or vibration may be used). In preferred embodiments, when the external infusion device 10 is in suspend mode, the LCD 28 will show "-S-", the word "STOPPED", and the time that the external infusion device 10 was placed in the suspend mode. When in the suspend mode, there is no drug delivery (either basal rate, or meal boluses). Preferably, the external infusion device 10 will beep an alert tone (and/or vibrate) every half hour to indicate that delivery has stopped. In alternative embodiments, other time periods may be used, or the alert tone may be omitted.

[0033] To restart the external infusion device 10, the user will again press the SEL key 114 and then presses the ACT key 110. The external infusion device 10 will beep once (and/or vibrate) to confirm the restart and then resume normal basal delivery and infusion device 10 operation. Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 150 and will provide a visual confirmation of the status of the external infusion device 10, with or without an audio confirmation.

Example III - RF programmed Temporary Basal Rate

[0034] A temporary basal rate, or basal override rate, is a rate that is delivered in lieu of a programmed, user defined profile segment rate that is generally delivered during this time period. The temporary basal rate is programmed with a rate and a duration.

[0035] To set a temporary basal rate, the user will press the "T" or Down arrow key (▼) 112 in the lower right hand comer of the keypad 102 on the RF programmer 12. Each press of the Down arrow key (▼) 112 will increment the duration of the temporary basal rate by 30 minutes. Counting the temporary basal rate duration increments will be facilitated by varying the audio tones for beeps that accompany the Down arrow key (▼) 112 presses. Four notes belonging to a musical chord will be used in repeating sequence as Down arrow key (▼) 112 is repeatedly pressed to select a desired duration of the basal rate. In alternative embodiments, more or fewer notes (and/or vibration) may be used. The temporary basal duration may be programmed from 30 minutes to 24 hours in half-hour increments. In alternative embodiments, other time periods may be used. In preferred embodiments, the tone of the beeps for a temporary basal rate may be distinctly different from a tone for incrementing a bolus. In alternative embodiments, different vibration may be used instead or in addition to the different audible beeps. If the user exceeds the desired setting, they can wait for an error signal, such as a "raspberry", buzzing, vibration, or the like, and then press the Down arrow (▼) 112 to begin the process again.

[0036] When the desired temporary basal rate duration has been set, the user will press the ACT key 110. The external infusion device 10 will confirm the duration of the temporary bolus rate with a series of audible beeps (and/or vibration). The user will then press the ACT key 110 again to confirm and accept the duration of the temporary basal rate. If the ACT key 110 is not pushed to confirm the amount, the external infusion device 10 will emit an audible error signal such as a "raspberry", buzzing, vibration, or the like. Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 150 and will provide visual confirmation of the temporary basal rate duration, with or without an audio confirmation.

[0037] To set the amount of the temporary basal rate, the user will press the Down arrow key (▼) 112 again. Each press of the Down arrow key (▼) 112 will increment the amount of the temporary basal by 0.1 units. Counting the amount temporary basal rate increments will be facilitated by varying the audio tones for beeps that accompany the Down arrow key (▼) 112 presses. Four notes belonging to a musical chord will be used in repeating sequence as Down arrow key (▼) 112 is repeatedly pressed to select a desired amount of the temporary basal rate. In alternative embodiments, more or fewer notes (and/or vibration) may be used. In these examples, units are an increment of insulin. However, alternative embodiments may define units to be any fluid volume, such as micro-liters, ccs, or the like, with the volume being dependent on the type of fluid to be infused. The rate may be set to a value from 0.0 U to the maximum programmable

Abbott Ex. 1002 - 526/1438

value of the basal rate. In alternative embodiments, different increments may be used. Preferably, the tone of these beeps (and/or vibration) will be distinctly different than the tone (and/or vibration) for setting the duration of the temporary basal rate. Once the desired amount has been set, the user will press the ACT key 110. The external infusion device 10 will confirm the amount of the temporary basal rate with a series of audible beeps (and/or vibration). The user will then press the ACT key 110 again to confirm and accept the amount of the temporary basal rate. If the ACT key 110 is not pushed to confirm the amount, the external infusion device 10 will emit an audible error signal, such as "raspberry", buzzing, vibration, or the like. Three short beeps (an/or vibration) every 30 minutes will confirm that the temporary basal rate is active. Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 150 and will provide visual confirmation of the temporary basal rate, with or without an audio confirmation.

[0038] To cancel a programmed temporary basal rate at any time during its intended operation, and resume the normal programmed basal rate, the user presses the Down arrow key (▼) 112 and then presses the SEL key 114 on the keypad 102 of the RF programmer 12. If a temporary basal rate had time remaining, the user will hear a long beep (and/or vibrate) to confirm that the temporary basal has been canceled. Otherwise, if no time was remaining, the user hears an error signal such as a "raspberry", buzzing, vibration, or the like, indicating that there was no time remaining on the temporary basal rate. Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 150 and will provide visual confirmation of the temporary basal rate, with or without an audio confirmation.

Example IV - RF programmed Extended Bolus

[0039] An extended bolus (such as a square wave bolus, ramp bolus, triangular bolus, profiled bolus or the like) is a bolus that is delivered over an extended period of time; rather, than all being delivered at once. To program an extended bolus with the RF programmer 12, the user will need access to the display LCD 28 of the external infusion device or perform the programming in two separate steps. Alternatively, an RF programmer 12' having a built in display 150 may be used.

[0040] To set an extended bolus, the user will set the duration of the extended bolus in the same manner that they set the duration for a Temporary Basal Rate. This involves using the Down arrow key (▼) 112 in the lower right comer of the keypad of the RF programmer 12, in the same manner as described above. The user will also select the type of extended bolus such as a square wave bolus, ramp bolus, triangular bolus, profiled bolus, or the like, to be delivered by previous selection of the type of extended bolus in the setup mode or by using an RF programmer in conjunction with a display. The remainder of the example demonstrates setting a square wave bolus.

[0041] When the ACT key 110 is pressed while a desired bolus amount is displayed, the bolus duration will be displayed on the LCD 28. The default bolus duration can be 30, 60 or 90 minutes, depending on the largest basal value of current setting and the desired bolus amount. The duration may be scrolled by using the Up arrow key (▲) 108 and the Down arrow key (▼) 112 on the keypad 102 of the RF programmer 12. Pressing the Up arrow key (▲) 108 will cause the duration to scroll in increments of 30 minutes up to 8 hours (the preferred maximum duration - although other durations or increments may be used), at which point it will wrap around to minimum duration. Pressing the Down arrow key (▼) 112 will cause the duration to wrap around to 8 hours, then scroll down in increments of 30 minutes. In further embodiments, the use of the Down arrow (▼) 112 will always stop at zero to avoid a wrap-around or require one or more additional depressions (possibly accompanied by a beep and/or vibration) to warn a user that they are now at the maximum value. Alternatively, the RF programmer 12' may include different additional keys (such as 152 in Fig. 4) that can be used to implement the square wave bolus, or a selectable menu on the RF programmer 12'.

[0042] Next, to set the amount of the square wave bolus, the user will press the Up arrow key (▲) 108 in the upper right hand comer of the keypad 102 of the RF programmer 12. Each depression will enable incrementing the amount of the square wave bolus in 0.1 unit increments; although other increments may be used. The external infusion device 10 will give a distinct auditory (and/or vibrating) confirmation of the selected bolus amount. The square wave will not be implemented until the user presses the ACT key 110 to accept the selected amount. Preferably, the external infusion device 10 provides confirmation by an audible beep (and/or vibration). Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 152 and will provide visual confirmation of the square wave bolus, with or without an audio confirmation.

[0043] To enhance flexibility, preferred embodiments of the external infusion device 10 will enable the user to deliver a normal bolus during a programmed Square Wave. Once the normal bolus has been delivered, the square wave will resume operation until completed.

Example V - RF Programmed Dual Wave Bolus

[0044] A dual wave bolus is a combination of a normal (or immediately given) bolus with a square wave bolus. To

Abbott Ex. 1002 - 527/1438

program a dual wave bolus with the RF programmer 12, the user will need access to the display LCD 28 of the external infusion device or perform the programming in two separate steps. Alternatively, an RF programmer 12' having a built in display 150 may be used.

[0045] To set a dual wave bolus, the user will press the ACT key 110 on the bolus history screen. The word "NORMAL" will start to blink on the LCD 28 and/or provide an audible (and/or vibration) indication. The user can press the Up arrow key (▲) 108 or Down arrow key (▼) 112 to choose the type of bolus desired. By pressing the ACT key 110, while the LCD 28 of the external infusion device 10 blinks the word "DUAL" (and/or provides an audible indication), a dual bolus is chosen. The LCD 28 of the external infusion device 10 will show the word "NOW" and/or the dashes for the normal bolus portion amount will blink on the LCD 28 (and/or an audible and/or vibration indication is provided). The user can then select a bolus amount for the "normal" bolus portion using the Up arrow key (▲) 108 or Down arrow key (▼) 112, and then press the ACT key 110. The LCD 28 of the external infusion device 10 will show the word "SQUARE" and/or the dashes for the bolus amount will now blink (and/or an audible and/or vibration indication is provided). The user can press the Up arrow key (▲) 108 or the Down arrow key (▼) 112 to choose the desired square wave bolus portion amount. When the ACT key 110 is pressed, while a desired square wave bolus portion amount is displayed on the LCD 28, the square wave bolus portion duration will be then displayed (and/or an audible and/or vibration indication is provided). The user can then select the desired square wave bolus portion duration from 30 minutes to 8 hours (although other increments or duration's may be used). After the ACT key 110 is pressed for the desired square wave bolus portion duration, the external infusion device 10 will start delivering the normal bolus portion first. The square wave bolus portion will then start right after the end of the normal bolus portion. The word "BOLUS" and the amount of the bolus that has been delivered so far will be displayed on the LCD 28 (and/or an audible and/or vibration indication will be provided). When the dual bolus is finished, the external infusion device 10 will beep (and/or vibrate) and display the amount of the bolus delivered for 5 seconds, then return to the normal time display. Alternatively, the external infusion device 10 may provide an audible indication by speech. In further alternative embodiments, the RF programmer 12' will have a display 150 and will provide visual confirmation of the square wave bolus, with or without an audio confirmation.

[0046] Other programming, commands, or data transfer may be accomplished by the RF programmer 12 (or remote commander), and the RF programmer 12 (or remote commander) should not be limited to the above-described Examples I-V. For instance, the RF programmer 12', since it includes a display 150 may use the same programming protocol and key sequences as those used to program the external infusion device 10 using the keypad 24 and LCD 28 on the external infusion device 10. Alternatively, the RF programmer 12' may use more sophisticated programming techniques, such as single key programming, if the display 150 includes the capability to use touch screen techniques, or may use additional keys in the keypad 152 that are specifically identified with particular programming features on the external infusion device 10.

Bolus Estimator

[0047] The Bolus estimator 14 (or carbohydrate estimator that estimates a bolus based on carbohydrate consumption (CHO)) assists the user with carbohydrate counting and in determining precise dosing adjustments to account for meals. Carbohydrates are the primary, but not the only, factor affecting blood glucose levels. Generally, it is sufficient to account just for the carbohydrates. It also encourages the user to enter current blood glucose values before using this feature, which will also be viewed quite favorably by the health care professional, since it increases compliance with the medical regimen and improves control. In alternative embodiments, the bolus estimator 14 in the external infusion device 10 can be connected or coupled to a glucose monitor by way of the RF programmer 12 (or other data transfer) to provide direct input to the bolus estimator 14.

[0048] In preferred embodiments, as shown in Figs. 1, 6, 7 and 8(b), the bolus estimator 14 is used to assist the external infusion device 10 user with the estimations that are done to determine the proper bolus amount that is needed to cover the anticipated carbohydrate intake at meals. The bolus estimator 14 does this by suggesting a bolus based on a pre-programmed carbohydrate ratio that is stored in the memory 22 of the external infusion device 10. The bolus estimator 14 will also take into account the user's insulin sensitivity and the differential between the user's pre-programmed target blood glucose (BG) level and the user's current BG level at the time the carbohydrate estimator 14 is activated. The recommendation, or result of the bolus estimator 14, is sometimes referred to as a "correction bolus".

[0049] The bolus estimator 14 is generally activated by the user, or preferably the health care professional, in the Set-up II menu of the external infusion device 10 (see Figs. 6 and 8(b)), before it is operational, and preferably after the user has demonstrated a sufficient understanding of estimating carbohydrate intake. In preferred embodiments, the bolus estimator 14 is activated and programmed by using the keypad 24 on the external infusion device 10. However, in alternative embodiments, the bolus estimator 14 may be programmed and activated with an RF programmer 12 or 12'. In further alternative embodiments, the current glucose readings for the user my be provided by receipt of the glucose level measurement from a glucose monitor or via the RF programmer 12 to facilitate a correction for changing blood glucose (BG) levels. Further description of correcting infusion rates based on blood glucose readings may be found in

Abbott Ex. 1002 - 528/1438

U.S. Patent. No. 5,569,186 to Lord et al., entitled "CLOSED LOOP INFUSION PUMP SYSTEM WITH REMOVABLE GLUCOSE SENSOR," and U.S. Patent No. 5,665,065 to Colman et al., entitled "MEDICATION INFUSION DEVICE WITH BLOOD GLUCOSE DATA INPUT", which are herein incorporated by reference. In alternative embodiments, the user may be able to use other combinations of the values to suggest different bolus types and amounts. In alternative embodiments, the carbohydrate estimator 14 can be used in a closed-loop system to augment the readings or check the closed-loop system's capability based on carbohydrate estimated meals. In still further embodiments, the bolus estimator 14 may be used to calculate correction boluses based on other parameters, with the type of bolus corrections being determined by the fluid being infused, body characteristics, or the like. Preferably, the bolus estimator 14 uses stored values or parameters related to the individual with current values, parameters or measurements and an algorithm to provide a recommended bolus that can be accepted, modified or rejected by the user. For instance in pregnancy, tocolysis may be infused and the measurement of the contraction rate may be used to suggest additional boluses of tocolysis medication. In HIV cases, a bolus amount of medication being infused may be adjusted based on a relationship to the current viral loads in the patient. In stroke or cardiac cases, the coagulation rate may be used to determine the bolus amount of heparin to be administered. Other calculations may be made and should not be limited to the above-described examples.

[0050] After the bolus estimator 14 has been enabled, the user will be prompted to store the following three (3) values in the memory 22 of the external infusion device 10. In alternative embodiments, more or fewer values may be needed or used. These values are used by the bolus estimator 14 and the processor 18 of the external infusion device 10 to perform the necessary calculations in suggesting a bolus amount. In preferred embodiments, access to programming and changing these values may be restricted to the health care professional. In alternative embodiments, these values can be restricted to entry through an RF programmer 12 or a connection of the external infusion device 10 with a programming device, such as a PC, laptop or the like. The inputted values needed to be stored for the bolus estimator 14 are:

[0051] Target Blood Glucose (Target), which is the target blood glucose (BG) that the user would like to achieve and maintain. Generally, the programmable blood glucose (BG) values for this range are between 60 to 200 in five unit increments. Preferably, the carbohydrate calculator has the capability to accept values that range between 20 to 600 in 1 unit increments to cover a large number of possible scenarios. However, in alternative embodiments, different ranges and increments may be used.

[0052] Insulin Sensitivity (Set Sens), which is a value that reflects how far the user's blood glucose drops in milligrams per deciliter (mg/dl) when one unit of insulin is taken. Preferably, the programmable values for this range are between 5 to 180 in one unit increments. However, in alternative embodiments, different ranges and increments may be used. In preferred embodiments, insulin sensitivity is programmable for up to four different time periods, the use of which will require four separate profiles to be stored in the memory 22. Setting the Insulin Sensitivity profiles is similar to setting the basal profiles. In alternative embodiments, more or fewer time periods (and corresponding profiles) may be used.

[0053] Carbohydrate Ratio (Set Carbs), which is a value that reflects the amount of carbohydrates that are covered by one unit of insulin. Generally, the values are in the range of 1 to 300 in increments of 1 unit (or, alternatively, in ranges of 0.1 to 5.0 in increments of 0.1 for carbohydrate exchanges). Preferably, the programmable values for this range are between 5 to 30 in one unit increments. However, in alternative embodiments, different ranges and increments may be used.

[0054] As a safety precaution, the user or healthcare professional may also set a Lockout Period, which takes into account the pharmacokinetic effect of insulin when suggesting a bolus. The purpose is to prevent a successive use of a correction bolus when the pharmacokinetic effects of the previous bolus have not yet been accounted for. The programmable values for this range are between 30 minutes to 240 minutes, programmable in 15 or 30 minute increments. However, in alternative embodiments, different ranges and increments may be used. In further alternative embodiments, the lock out period may be automatically calculated based on boluses recently delivered and/or canceled based on new blood glucose (BG) readings. In other embodiments, the carbohydrate calculator 14 may include a programmable reminder to check the post-prandial blood glucose value to determine if additional boluses and or corrections should be made at a later time after the meal. The programmable reminder values are between 30 minutes to 240 minutes, programmable in 15 or 30 minute increments. However, in alternative embodiments, different values and increments may be used.

[0055] After the above values are set in the memory 22 of the external infusion device 10, the bolus estimator 14 will suggest a bolus based on the entry of the estimated carbohydrate intake and current and target blood glucose (BG) levels. The calculation will only be performed if the three values are programmed and stored in the memory 22. Preferred embodiments use the following equation:

Abbott Ex. 1002 - 529/1438

$$Bolus = \frac{(CurrentBG - Target BG)}{InsulinSensitivity} + \frac{CarbohydratesToBeConsumed}{CarbohydrateRatio}$$

[0056] If the user wishes the external infusion device 10 to suggest a bolus for the estimated carbohydrate intake only, then the only value they need to program is for the Carbohydrate Ratio, and the BG portion of the equation will be ignored. In alternative embodiments, variations or different equations may be used.

[0057] In operation, once the bolus estimator 14 has been enabled and the above listed values have been programmed into the memory 22 of the external infusion device 10, the bolus estimator 14 can be used to suggest a correction or meal bolus. The user may then accept or change the bolus amount suggested by the bolus estimator 14. In one embodiment, processor 18 stores in memory 22 a record of whether the suggested bolus amount from the bolus estimator 14 was accepted or changed by the user, and records the suggested and changed bolus amounts. The stored data can be used for later analysis by downloading the data to a computer by RF or IR transmissions, for example by IR transmissions from the external infusion device 10 through the communication station 8 to the computer 6, as shown in Fig. 15, or the like. The following examples illustrate hypothetical carbohydrate calculation scenarios. The examples show use of the bolus estimator 14 by the keypad 24 on the external infusion device 10. However, it should be understood that the bolus estimator 14 could be activated and programmed by the RF programmer 12 or the like. Alternatively, the keypad 24 (or RF programmer 12) may include an additional key.

[0058] Preferred embodiments use a normal bolus. In alternative embodiments, the user may be given the choice of a normal, dual, square wave bolus, extended bolus, profiled bolus, or the like, by enabling these capabilities on the variable bolus menu in the Setup II menu (see Figs. 6 and 8) on the external infusion device 10. If the variable bolus capability is not enabled, then every bolus would be a normal bolus. As discussed, preferred embodiments of the present invention use normal one time boluses. However, alternative embodiments may utilize different bolus types to spread out the correction or meal bolus determined by the carbohydrate estimator 14.

[0059] The same set of pre-programmed values as described above and shown below in Table 1 will be used for each of the following examples VI-IX:

Table 1 - Pre-programmed Values for the Examples

Pre-programmed Values	
Target BG	100
Insulin Sensitivity	30
Carbohydrate Ratio	15
Lockout Period	60

Example VI - Bolus Estimator - Square Wave

[0060] The user presses the SEL key 114 and then the ACT key 110 on the external infusion device 10 to choose a "Normal" bolus, and uses the ACT key 110 to select the carbohydrate estimator 14. To operate the bolus estimator 14, and assuming that the user measures his/her blood sugar level to be 160 mg/dl, and assuming the user estimates that a meal of 75 grams of carbohydrates is to be consumed, the following "dialog" occurs between the user and the external infusion device 10:

External infusion device 10 Prompt: "Enter BG" (preferably, there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "160" by scrolling the Up arrow key 10 and pressing the ACT key 110. 160 is displayed and then entered.

External infusion device 10 Prompt: "# gm CHO" meaning the number of grams of carbohydrate to be consumed (there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "75" by scrolling the Up arrow key (▲) 108 and pressing the ACT key 110. 75 is displayed and then entered.

External infusion device 10 Prompt: Suggests a "7.0" unit bolus (2 units of correction and 5 units to account for the

Abbott Ex. 1002 - 530/1438

carbohydrates to be consumed).

User: Can accept the suggested bolus by pushing the ACT key 110 or use the Up arrow key (▲) 108 or the Down arrow key (▼) 112 to select a different bolus amount, and then presses the ACT key 110 to start the bolus.

Example VII - Bolus Estimator - Dual Wave

[0061] The user presses the SEL key 114 and chooses a "Dual" wave bolus, and then the ACT key 110. To operate the bolus estimator 14, and assuming that the user measures his/her blood sugar level to be 160 mg/dl, and assuming the user estimates that a meal of 75 grams of carbohydrates is to be consumed, the following "dialog" occurs between the user and the external infusion device 10. The following "dialog" will then take place between the user and the external infusion device 10:

External infusion device 10 Prompt: "Enter BG" (there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "160" by scrolling the Up arrow key (▲) 108 and pressing the ACT key 110. 160 is displayed and then entered.

External infusion device 10 Prompt: " # gm Carbs" which means the number of grams of carbohydrate to be consumed (there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "75" by scrolling the Up arrow key (▲) 108 and presses the ACT key 110. 75 is displayed and then entered.

External infusion device 10 Prompt: Suggests a "7.0" unit bolus.

User: Can accept the suggested bolus by pressing the ACT key 110 or use the Up arrow key (▲) 108 or the Down arrow key (▼) 112 to select a different bolus amount.

External infusion device 10 Prompt: "Now" with the accepted value of "7.0" units blinking. Typically the user will scroll down using the Down arrow key (▼) 112 to select only part of the bolus now. Lets say the user selects "2.0" and presses the ACT Key 110.

External infusion device 10 Prompt: "Square" will appear on the screen with the remainder of the bolus (i.e., "5.0") blinking. The user can again select this amount or scroll to a different amount. The duration will be set by activating the SEL key 114 and incrementing the time.

Example VIII - Bolus Estimator - Square Wave - Lower BG

[0062] The user presses the SEL key 114 and then the ACT key 110 on the external infusion device 10 to choose a "Normal" bolus, and uses the ACT key 110 to select the bolus estimator 14. To operate the bolus estimator 14, and assuming that the user measures his/her blood sugar level to be 70 mg/dl, and assuming the user estimates that a meal of 75 grams of carbohydrates is to be consumed, the following "dialog" occurs between the user and the external infusion device 10:

External infusion device 10 Prompt: "Enter BG" (there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "70" by scrolling the Up arrow key (▲) 108 and pressing the ACT key 110. 70 is displayed and then entered.

External infusion device 10 Prompt: " # gm Carbs" which means the number of grams of carbohydrate to be consumed (there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "75" by scrolling the Up arrow key (▲) 108 and presses the ACT key 110. 75 is displayed and then entered.

Abbott Ex. 1002 - 531/1438

External infusion device 10 Prompt: Suggests a "4.0" unit bolus (-1 unit correction and 5 units to account for the carbohydrates to be consumed).

User: Can accept the suggested bolus by pressing the ACT key 110 or use the Up arrow key (▲) 108 or the Down arrow key (▼) 112 to select a different bolus amount.

[0063] Preferred embodiments of the bolus estimator 14 utilize general rules to minimize the potential for inaccurate results from the bolus estimator 14 or administering a bolus at an inappropriate time. For instance, if a correction bolus has been previously given such that the BG Now > BG Target, then the Lockout period is activated and the bolus estimator 14 will not calculate a correction bolus. In alternative embodiments, the bolus estimator 14 may determine a bolus based on carbohydrates to be consumed and omit the portion of the calculation that utilizes the blood glucose level to determine the correction portion of the bolus. Thus, the external infusion device 10 will not prompt the user with "Enter BG" during the Lockout period, and will effectively operate only as a carbohydrate estimator. Once the Lockout period has expired, the external infusion device 10 will prompt the user for a current BG value, and then suggest a correction bolus if the user enters a current BG value. Also, if the bolus estimator 14 estimates a bolus to be a negative value (BG is below target and carbohydrate intake amount is minimal) then the external infusion device 10 will display "No Bolus!" as a warning. Also, if the user enters a current blood glucose (BG) level that is lower than a certain value, such as 50 (although other values may be used), the external infusion device will display "Low BG".

Example IX - Bolus Estimator - Insulin Duration Factor

[0064] A further embodiment of the bolus estimator 14 may include the ability to account for the effects of recently taken insulin that is still, at least partially, still active in the body of the user. The concern would be that the remaining insulin could have the effect of lowering the blood glucose level too quickly, or too far, if the remaining insulin was not accounted for. Thus, this embodiment utilizes an Insulin Duration Factor to account for the effects of the insulin still remaining in the body.

[0065] The Insulin Duration Factor would also be a programmable parameter that is in the Setup II section of the pump along with the other parameters, as described above. The user would program the approximate duration time that insulin is active in their system. For instance, users of fast acting insulin analogs would program 1 to 4 hours in 15 or 30 minute intervals, and users of Regular insulin would program 2 to 8 hours in 15 or 30 minute intervals. However, in alternative embodiments, different values and increments may be used. Preferably, the insulin duration factor should be selected and adjusted by the health care professional or the user upon recommendation and/or consultation with the health care professional. Preferred embodiments use the following equation (note if a negative value is returned (i.e., the insulin from a previous bolus is used up) the equation will return a value of 0 for no insulin remaining to avoid over correcting):

$$Insulin\,\mathrm{Re}maining = \frac{(InsulinDurantionFactor - TimeSinceLastBolus)}{InsulinDurationFactor}\ If \geq 0$$

$$Otherwise$$

$$Insulin\,\mathrm{Re}maining = 0$$

[0066] In this example, it is assumed that the user programs a 3 unit correction bolus at 11:00am to correct for a 190 BG value. The user then decides to use the bolus estimator 14 at 12 Noon to estimate a bolus for meal containing 75 grams of carbohydrate. The Insulin Duration Factor is set to 3 hours.

[0067] The user presses the SEL key 114 and then the ACT key 110 on the external infusion device 10 to choose a "Normal" bolus, and uses the ACT key 110 to select the bolus estimator 14. To operate the bolus estimator 14, and assuming that the user measures his/her blood sugar level to be 160 mg/dl, and assuming the user estimates that a meal of 75 grams of carbohydrates is to be consumed, the following "dialog" occurs between the user and the external infusion device 10:

External infusion device 10 Prompt: "Enter BG" (preferably, there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "160" by scrolling the Up arrow key 10 and pressing the ACT key 110. 160 is displayed and

Abbott Ex. 1002 - 532/1438

then entered.

External infusion device 10 Prompt: "# gm CHO" meaning the number of grams of carbohydrate to be consumed (there will be three dashes in the upper right comer of the display - although other displays or indications may be used).

User: Enters the value "75" by scrolling the Up arrow key (▲) 108 and pressing the ACT key 110. 75 is displayed and then entered.

Insulin Remaining: 3.0 (Insulin Taken) x 2/3 (Insulin Duration Remaining) = (2.0) units

External infusion device 10 Prompt: Suggests a "5.0" unit bolus (2 units of correction and 5 units to account for the carbohydrates to be consumed and a subtraction to account for the remaining insulin in the user).

User: Can accept the suggested bolus by pushing the ACT key 110 or use the Up arrow key (▲) 108 or the Down arrow key (▼) 112 to select a different bolus amount, and then presses the ACT key 110 to start the bolus.

[0068] Since the external infusion device 10 stores the time of each bolus delivery, the above simple algorithm can be designed to take into account the amount of insulin that might still be remaining in the user's body from a previous bolus. The longer the programmed time for the "Insulin Duration Factor" then the more conservative the estimate becomes. In further embodiments, the external infusion device 10 could adjust for several boluses that were delivered within the insulin duration window. Although it is difficult to predict how long insulin will actually remain active in the body, the above described algorithm does at least consider the effects on the amount of insulin actually needed. This provides an additional level of conservative estimation in the external infusion device 10 by accounting for insulin delivered within a programmable window. Without such an algorithm, in the example above the pump would have suggested a "7.0" unit bolus because the remaining insulin would not have been accounted for in the suggested bolus.

[0069] The bolus estimator 14 has the advantage of prompting the user to enter his/her blood glucose (BG) value, and thus serves as a useful reminder to check BG levels regularly. This makes testing more advantageous then ever, since the results directly assist the user in maintaining control of his/her condition. Also, the bolus estimator 14 enables the external infusion device 10 to capture information on carbohydrate intake which is valuable for helping the user to refine carbohydrate counting skills. This data may also be downloaded to a PC, laptop, Communication-Station, RF programmer, or the like.

[0070] In further embodiments, an external infusion device 10 and user can utilize the bolus estimator 14 information to "learn" insulin sensitivity values, carbohydrate counting, the effects of high fat meals and other variables that can lead to better control, and use this to adjust the results of the bolus estimator 14. In alternative embodiments, the user can omit entering specific carbohydrate amounts each time calculations are made by the user. For instance, the external infusion device 10 may store the carbohydrate amounts for several meals that are regularly eaten by the user in the memory 22, and then allow the user to recall the stored meals. In other alternative embodiments, a list of general foods may be provided with a carbohydrate equivalent. In still further embodiments, the external infusion device 10 may utilize a more complicated keypad and/or RF programmer 12, and a code is assigned for each food. Then the code for each food to be consumed is entered into the external infusion device 10.

Vibration Alarm

[0071] Further embodiments of the present invention include a vibration alarm 16 that provides a noticeable vibration in addition to or in lieu of an audible alarm. The resulting tactile sensation of the vibration make the alarms more noticeable during sleep, when not thinking clearly due to various conditions, or the like, to improve the likelihood that the user will respond to an alarm. Thus, a vibration alarm 16 can improve safety and control. In addition, the vibration alarm 16 may be less publicly noticeable, and thus more useable in quiet settings, such as libraries, lectures, shows, or the like, or in loud settings where the alarm might go unnoticed, such as parties, concerts, or the like. In further embodiments, the RF programmer 12 may include a vibration alarm (not shown) that can deliver a vibration alarm to the user in addition to, or instead of, the vibration alarm 16 from the external infusion device 10. Alternatively, the RF programmer 12 may provide a vibration alarm and the external infusion device 10 may provide an audible alarm or vice versa.

[0072] The vibration alarm 16 also provides an additional capability used during priming or operation of the external infusion device 10. It has been found that activating the vibration alarm 16, before or during priming, will assist in removing

Abbott Ex. 1002 - 533/1438

air bubbles in the reservoir or tubing. This procedure minimizes the amount of medication that must be expelled to clear the air bubbles, by allowing bubbles to move towards the outlet and the tubing based on the agitation of the reservoir. Use of the vibration alarm 16 during priming can result in substantial savings when using expensive or concentrated medications with the external infusion device 10. This also simplifies and somewhat automates the priming of the external infusion device 10. In addition, the vibration alarm 16 may be used to agitate the medication (such as suspensions of a drug) during administration so as to minimize sedimentation or separation of the medication, or, if power requirements are an issue, between infusion increments of the fluid by the external infusion device 10, if such agitation is desired.

Other Capabilities

[0073] Particular embodiments will include a "Low Reservoir Alert". The alert will sound when the plunger of the external infusion device 10 reaches the point where approximately 0.200 ml of fluid remains in the reservoir. However, in alternative embodiments, larger or smaller activation thresholds may be used. An icon indicating "Low Volume" will appear on the main LCD 28 screen until the condition is corrected. If correction of the low volume has not happened at an approximate level of .100 ml, the external infusion device 10 will beep again. However, in alternative embodiments, larger or smaller activation thresholds may be used. Preferably, the external infusion device 10 will keep track of the reservoir volume in the software and request the user to update the reservoir volume manually whenever the prime function is activated.

[0074] Other embodiments may utilize a "Take a Break Bolus". This is particularly well adapted for short acting medications or fluids. The purpose of this capability is to deliver an extra bolus before disconnecting from the external infusion device 10, to make certain that the clinically needed amount of medication or fluid is delivered before interrupting the administration. This will help the user remain above the minimum therapeutic level during an interruption of medication or fluid delivery. Preferably, four durations of an interruption of the medication or fluid infusion will be possible: 30 minutes; 1 hour; 1 hour and 30 minutes; and 2 hours. However, additional, or longer or shorter intervals may be used. Generally, this capability is activated in the Setup II menu by the health care specialist, who will program the dose for each of the 4 possible times of delivery interruptions. The dose is set based on the medication or fluid and the condition of the user. If the health care specialist programs only certain durations (for example 30 minutes and 1 hour only), the user will only be able to take a break for those durations. In preferred embodiments, in the "Take a Break Bolus" screen, the user will program the duration of the planned interruption. The external infusion device 10 will then beep after the delivery of the previously set dose. The user will then disconnect from the external infusion device 10 and will be reminded by the external infusion device 10 to reconnect when the time is up. Preferably, the reminder alarm will continue to sound (or vibrate) until the user reactivates the external infusion device 10.

[0075] Particular embodiments include a "Lockout function". Preferred embodiments will have multiple lockout levels, with the selection be dependent on the anticipated usage, the external infusion device model, the sophistication of the user, or the like. For instance, the following lockout levels may be used (a lockout levels means that some of the features of the external infusion device will not be accessible to the patient (or user), but will be accessible to the Health Care Professional or the parent of a child using the external infusion device 10):

"None" (0) will let the user program and access all features of the external infusion device 10;
"Setup" (1) will lock the user out of changing both Setup I and Setup II parameters. The user will only have access to activated features of the external infusion device 10, but can not change the pre-set parameters. The user will be able to review the settings, and only change the lockout level with an authorized key sequence. The only Setup feature that will still be available is Selftest.
"All except Suspend" (2) will only allow the user to suspend the external infusion device and to perform a Selftest. All other features will be locked out. The user will be able to review the settings, and only change the lockout level with an authorized key sequence.

[0076] The "Lockout function" will be in Setup II. A special key sequence (or code) will be required to change the lockout level. This will minimize the possibility of an unauthorized change of the lockout levels. In preferred embodiments, an icon (lock) will be displayed on the LCD 28 when the external infusion device 10 is in Lockout mode 1 or in Lockout mode 2.

[0077] Preferred embodiments of the external infusion device 10 will include a configurable menu that is accessible by password through the use of a PC, laptop, RF programmer or the like. This ability allows the physician, or sophisticated user, to select only the external infusion device 10 capabilities that are required for an individual user. A "lock out" capability will enable the physician to exclude certain options from the user. This may be useful with new users or children using the external infusion device 10.

[0078] Further embodiments may include a "Suspend/Storage Mode". In addition to the regular Suspend Mode (discussed above), the external infusion device 10 can be put in a "Storage Mode" in which no recurring alert (beeping and/or vibrating) will remind the user of the external infusion device 10 being in the "Storage Mode". Thus, for example,

Abbott Ex. 1002 - 534/1438

in "Suspend Mode", the external infusion device 10 will display the time of day, STOPPED and -S- on the LCD 28. In addition, the external infusion device 10 will beep (and/or vibrate) 6 times every 30 minutes as a reminder. In suspend "Storage Mode", the external infusion device 10 LCD 28 will display the -S- only and will not repeatedly beep (and/or vibrate).

[0079] In preferred embodiments, software options will appear as choices for the user if they are first selected from the Main Menu, the Setup I and Setup II screen, as shown in Figs. 6-12. The physician will also be able to control what range of choices are available for the user, either in the office or remotely through a PC connected to a Communication-Station. In preferred embodiments, the external infusion device 10 will have the ability to transmit all the stored memory content to a Computer 6 or external FAX/Modem connected to a Communication-Station 8, as shown in Fig. 15. Further description of a Communication Station of this general type is be found in U.S. Patent. No. 5,376,070 to Purvis et al., entitled DATA TRANSFER SYSTEM FOR AN INFUSION PUMP, which is herein incorporated by reference.

[0080] Preferred embodiments, use scrollable menus to set various capabilities. In alternative embodiments, different menu structures or ways of moving through the menus may be used. In preferred embodiments, the user presses the SEL key 114 to scroll the external infusion device 10 through a series of informative displays or Select States (e.g., main menu, setup I and setup II - see Figs. 6-12). The displays differ depending upon the current status (state of software execution) of the external infusion device 10.

[0081] Preferably, the programming capabilities that are accessed infrequently are kept in the Setup menus. The external infusion device 10 has two layers of setup menus, Setup I and Setup II. Setup I contains capabilities that are used more often than those in Setup II. Both Setup I and Setup II menus will be accessible through the main menu by pressing the SEL key 114 at the links between the Setup I and Setup II (see Figs. 6-12). The Setup I menu (see Figs. 10 and 12) will be entered by pressing the ACT key 110, while the Setup I screen is being displayed. While in the Setup I menu, the screens that are displayed are Time Adjustment, Automatic Off Duration, Beep Volume, User Self Test, Setup II and Setup Exit. The Setup II menu (see Figs. 9 and 11) can be entered by pressing the ACT key 110 while the Setup II screen is being displayed. While in the Setup II menu, the screens that are displayed are Audio Enhanced Bolus Mode On/Off & Increment, Variable Boluses Mode On/Off, Bolus Estimator (carbohydrate calculator), Maximum Bolus, Maximum Basal rate, Time Mode (12/24 hour display), Insulin Concentration, Alarm Review, Alarm Mode, Child-lock (lock-out), Set RF Device, Personal Delivery Patterns, Setup I and Setup Exit.

[0082] Generally, none of the values can be changed directly from the Select States. To alter a value on an informative display, the user must first press the ACT key 110. This is referred to as entering a Set State. The word "SET" will appear on the display (and/or an audible and/or vibration indication is provided), and the value that can be changed will be blinking. Pressing the Up arrow key (▲) 108 or the Down arrow key (▼) 112 will change the blinking value. After scrolling to the desired value, the ACT key 110 must be pressed again. This will activate the new value and return the external infusion device 10 to the normal operating (time) display. If more than one value can be changed on a single display, pressing the ACT key 110 will cause the other value to be selected and the Up arrow key (▲) 108 and the Down arrow key (▼) 112 will affect this next value. Two general exceptions to the preferred rule governing the parameter selection described above are the normal operating (time) display and the Total History state. Both are Select States. When the normal operating (time) display is in effect, pressing the ACT key 110 will show the user the amount of battery power left, or, alternatively, or in addition to, the amount of medication remaining in the reservoir (thus time cannot be changed from it, since time setting is handled in the SetUp I menu). The Total History state is for information only. Historical total values may be viewed directly from the select state with the arrow keys.

[0083] In preferred embodiments, if the external infusion device 10 is left idle while in a Set State, the software will return to the time display state after approximately 15 seconds, no changed values will be activated. If the external infusion device 10 is left idle in a Select State, it will return to the time display state in approximately 7 seconds. In alternative embodiments, longer or shorter time periods for the various states may be used.

[0084] The external infusion device 10 will preferably include the following Select States in the main menu (see Figs. 9 and 11): time display, bolus history, suspend, basal rate, temporary basal rate, total history, prime bolus, Setup I menu and Setup II menu. The Setup I menu (see Figs. 10 and 12) will feature the additional select states: time and date adjustment, automatic off duration, beep volume, user self test, Setup II, and Setup exit. The Setup II menu (see Figs. 6 and 8) will feature the following options: audio enhanced bolus mode enable/disable & increment, variable bolus mode enable/disable, maximum bolus, maximum basal rate, bolus estimator setting, personal delivery pattern selection, alarm clock setting, insulin concentration, alarm review, lock-out, RF programmer set up, Setup I, and Setup exit. After a capability is activated in any Set State in the normal operating menu, the normal operating display (time display) will be displayed. In alternative embodiments, other values may be displayed.

[0085] Preferably, after a capability is activated in one of the Setup menus, the next Setup Select State will be displayed. Once in one of the Setup Menus, the user may use the SEL key 114 to view all of the Setup Select States until the keyboard is allowed to time out (in approximately 15 seconds) or the user presses the ACT key 110 on the Exit Setup state.

[0086] Preferably, the SEL key 114 is used to select an option. For safety, using this key will never change any value. If there is more than one option in a single programming sequence (Set State), such as hours, minutes, and date on the

Abbott Ex. 1002 - 535/1438

time setting display, the options are selected with the ACT key 110. The ACT key 110 is used to allow changing of values by entering set states, and to activate changed values. The Up arrow key (▲) 108 and the Down arrow key (▼) 112 are available as valid keys when numbers or dashes are blinking. However, in preferred embodiments, there are two exceptions: while normal operating (time) screen is displayed, 1) pressing the Up arrow key (▲) 108 invokes the audio enhanced bolus function if enabled in setup II; and 2) pressing the Down arrow key (▼) 112 turns on the LCD backlighting. The backlight will remain on for about fifteen seconds after the last key press. Any key press before the expiration of fifteen seconds will restart the fifteen second time-out.

[0087] The external infusion device 10 can be programmed to deliver up to forty-eight basal rates daily. The user does not need to program all forty-eight rates. The multiple basal rates are called profile segments. Profile segments are preferably programmed with a start time and a basal rate. A profile segment rate will become active at the profile segment start time. This allows for several different delivery schedules to occur without requiring the user to reprogram the external infusion device 10. The first profile segment always begins at midnight. The other profile segments always start on even hour or half-hour boundaries. The delivery pattern will repeat daily. In alternative embodiments, the external infusion device 10 may contain more, or less, than forty eight profiles, with amount being dependent on memory, time increment for each profile, and the like.

[0088] A Setup option will allow the user access to three "personal patterns" in order to accommodate individual lifestyle requirements. The first personal pattern is the current basal profile pattern. The second personal pattern will follow the first personal pattern and a "2" icon will be displayed by the external infusion device at all times, on the main screen and the basal screen. The third pattern will follow the second pattern and display a "3" icon at all times. The patterns will be presented to the user in a circular manner until the user selects dashes as the time for the next basal rate. The user will choose their personal pattern by selecting a 1, 2, or 3 in the setup II menu. The user will know which pattern is current by looking for either a blank (i.e., pattern 1 is on), a "2" icon (i.e., pattern 2 is on), or a "3" icon (i.e., pattern 3 is on).

[0089] Preferably, the user, or healthcare professional, may program two separate limits into the external infusion device 10. A maximum meal bolus can be set to limit the size of meal boluses. When setting a meal bolus the software will not allow the scrolling to exceed the maximum. There is also a maximum basal rate that limits the rate of profile segments and the temporary basal rate. When setting profile segment rates or a temporary basal rate, the software will not allow any values greater than the maximum basal rate.

[0090] The meal bolus history function will allow the user to view the last twelve meal boluses in reverse-chronological order. The Up arrow key (▲) 108 and the Down arrow key (▼) 112 are valid from the Select State. The most recently delivered bolus will be displayed as bolus history 1. Older boluses will be histories 2 through 24. The display of the most recent bolus will show the word "LAST." The display of the older boluses will show the day of the week that they were delivered. for safety reasons, the historical meal boluses may not be changed.

[0091] The external infusion device 10 will maintain a history of the daily totals for the last 90 days. The user can only display the last 7 days through the pump's display, (generally 90 days are accessible by downloading only - although other numbers of days may be used). This display is accessed as a Select State. The day for the total may be scrolled to view total history directly from the display state. The total delivered Select State will have the day (displayed as "TODAY" for today's date or DayMonthYear [01SEP97] for any other day) blinking. When the day is scrolled, the display shows the corresponding day's total.

[0092] The user will be able to review the last 200 events that occurred to the pump. Generally, these may be reviewed on the LCD 28 of the external infusion device 10. Alternatively, the events are only available by downloading the data through the transmitter/receiver 26 (for example using IR serial communication) of the external infusion device 10. Typical types of events that can be received or downloaded are: time adjustment; auto-off duration; maximum bolus; maximum basal rate; insulin concentration; suspend on; suspend off; basal rate profile; temp. basal rate; battery removal and battery replacement, and carbohydrate estimator stored set values and history. The external infusion device 10 may be capable of communicating via its bi-directional telemetry. It will be capable of sending data and receiving and executing commands according to a well-defined protocol.

[0093] The LCD 28 of the external infusion device 10 introduces the capability to use icons for easier identification and use. For example, the following icons are available: a clock alarm icon, a low battery alarm icon, a low insulin alarm icon, and one or more personal pattern icons. In alternative embodiments, more or fewer icons may be used. The use of icons makes an understanding of the display and alarm conditions easier, thus increasing safety and efficient use of the external infusion device 10.

[0094] Alarms will be easily recognizable while providing the user with the information they need to make an informed decision. The alarms may be displayed on the LCD 28, provided audibly through the speaker 30 and/or using the vibration alarm 16. An alert will sound when the plunger reaches the point where approximately 20 units of insulin (U-100) remain. In alternative embodiments, more or fewer remaining units may be used, and/or the units remaining may be programmable by the user or healthcare professional. An icon indicating "Low Volume" will appear on the main screen, and/or other alarms may be provided, until the condition is corrected.

Abbott Ex. 1002 - 536/1438

[0095] Preferred embodiments will include an alarm clock. The user will determine and set an amount of time, preferably from 30 minutes to 24 hours, although longer or shorter periods may be set. The external infusion device 10 unit will provide an alarm and will prompt the user to repeat the same alarm frequency or cancel the alarm. The alarm will assist in warning the user on when to test blood glucose levels, inject insulin or the like. Alternative embodiments may include multiple alarms and different tones to permit more precise control and monitoring.

[0096] In preferred embodiments, all alarms will gradually escalate in frequency or volume so that the user can terminate them as soon as they are noticed. In alternative embodiments, the alarms may change tones or intermittently stop to draw attention to the alarm condition. In further alternatives, the external infusion device 10 may use the transmitter/receiver 26 to transmit the alarm to a remotely located device, such as a Communication-Station, modem or the like to summon help.

[0097] In preferred embodiments, there is also a maximum number of external infusion device 10 strokes for the drive mechanism 32 that may occur in one hour based on the maximum basal rate and bolus amounts. The external infusion device 10 will sound (or vibrate) and the external infusion device 10 will not be able to deliver more than *((2.5* maximum bolus) + maximum basal + 1)* strokes in one hour. Preferably, the external infusion device 10 will deliver medication in 0.1 units volume increments (although other increments may be used). The actual amount of insulin or medication in a given stroke depends on the insulin or medication concentration, stroke length and delivery reservoir diameter or cross-sectional area. In preferred embodiments, the delivery rates are scrolled by the amount of insulin per stroke. The rate delivery pattern will be calculated by dividing the number of strokes required for the rate into 3600 (the number of seconds in one hour). The result is the number of seconds between each stroke. The rate will be delivered evenly over the hour, each stroke on a one-second boundary. Rates that do not divide evenly into 3600 will not have any accumulating error. For example, consider a rate of 3.0 units per hour and a concentration of U-100. 3.0 U/hr at U-100 will require 30 strokes per hour. This translates to a pump stroke every 3600/30=120 seconds, or one stroke every two minutes. In alternative embodiments, the drive mechanism 32 may provide for continuous flow rather than incremental or pulsed flow rates. Further alternatives may omit strokes and utilize hydraulics, pneumatics, step motors, continuous motors, or the like.

[0098] The external infusion device 10 will support drug delivery in U-400, U-250, U-200, U-100, U-50 and U-40 concentrations of insulin. In alternative embodiments, the external infusion device 10 will support drug delivery in insulin concentrations below U-40 and above U-400, such as U-500 and U-1000. The amount of insulin delivered per pump stroke depends upon the concentration. If the concentration is changed, the constant factors which convert pump strokes into units of insulin are changed accordingly. Preferably, when a new concentration is selected, all settings except the time of day and day of week return to the factory default settings. The default concentration is U-100. In alternative embodiments, different default concentrations may be set being dependent on the type of fluid to be infused, and different or no settings will return to the factory defaults. Preferred embodiments of the external infusion device 10 will utilize a conventional plastic (such as the MiniMed MMT-103) reservoir. Alternative embodiments may use reservoirs formed out of other materials, such as glass, metal or the like; and the reservoir may be pre-filled or filled by the user prior to use in the external infusion device 10.

[0099] Preferred embodiments of the external infusion device 10 can be dropped in water without causing damage to the pump. (IEC601-1 IPX7 watertight standard - although other levels of water resistance or standards may be used). The external infusion device 10 may be resilient to being dropped, such as withstanding a 1500 g force with a 0.5 msec half-sine pulse duration (although other levels of impact resistance may be used). The infusion pump 10 will not be damaged by normal chemicals it may encounter: soap, insulin, suntan lotion, alcohol, betadine, Comet cleanser, 409 cleaner, Windex, Joy dish soap, 25% bleach mixture.

[0100] Preferred embodiments will utilize a cylindrical Li/MnO_2 primary battery.

Part Number	Manufacturer
PX28L (1406LC NEDA/ANSI: IEC)	Duracell

[0101] Alternative embodiments may use multiple batteries, or batteries having different chemical compositions or characteristics. For instance, embodiments may use silver-oxide based batteries, such as Energizer 357 batteries, mercury oxide, or other lithium chemistries. Further embodiments may include rechargeable batteries using either a DC powerport, induction, solar cells, or the like, for recharging.

[0102] Preferably, the external infusion device 10 will report a low battery condition at a battery voltage of 4.2 volts with a 1.0 milliamp load. The absolute maximum current that may be delivered by the battery will be less than 60 milliamps for a maximum of 10 seconds. To maximize battery life, each delivery of 0.1 unit of insulin will consume less than 0.025 millijoules of battery energy. The average continuous battery current will not exceed 65 uA, excluding charging for insulin delivery. Preferably, the external infusion device 10 will indicate relative battery longevity. This information can be conveyed in a concept similar to a cellular phone's battery status indicator. Fig. 13 illustrates expected battery performance in days of operation versus units of medication delivered.

Abbott Ex. 1002 - 537/1438

[0103] Fig. 14 illustrates a table of typical factory default values used by an external infusion device 10. Alternative embodiments, may use other default values with the selection being dependent on the types of medication or fluid to be infused.

[0104] While the description above refers to particular embodiments of the present invention, it will be understood that many modifications may be made without departing from the scope thereof. The accompanying claims are intended to cover such modifications as would fall within the true scope of the present invention.

[0105] The presently disclosed embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims, rather than the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

[0106] Further embodiments include:

[0107] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing;
a receiver coupled to the housing for receiving remotely generated commands;
a processor coupled to the housing and the receiver to receive remotely generated commands and to control the external infusion device in accordance with the commands; and
an indication device to indicate when a command has been received and indicate when the command is being utilized to control the external infusion device such that the external infusion device is capable of being concealed from view when being remotely commanded.

[0108] The external infusion device may include a memory for storing programs, and the receiver may be capable of receiving software updates and facilitating remote programming of external infusion device capabilities.

[0109] The external infusion device may include a memory for storing a patient infusion history and pump activity.

[0110] The remotely generated commands may be capable of programming and activating an audio bolus delivery of the liquid by the external infusion device.

[0111] The remotely generated commands may be capable of programming and activating a vibration bolus delivery of the liquid by the external infusion device.

[0112] The remotely generated commands may be capable of programming and activating a temporary basal rate delivery of the liquid by the external infusion device.

[0113] The remotely generated commands may be capable of programming and suspending delivery of the liquid by the external infusion device.

[0114] The remotely generated commands may be capable of programming and activating an extended bolus delivery of the liquid by the external infusion device.

[0115] The remotely generated commands may be capable of programming and activating a dual wave bolus delivery of the liquid by the external infusion device.

[0116] The remotely generated commands may be capable of programming and activating a profiled bolus delivery of the liquid by the external infusion device.

[0117] An infusion system for infusing a liquid into a body, the infusion system comprising:

an external infusion device including:

a housing;
a receiver coupled to the housing and for receiving remotely generated commands;
a processor coupled to the housing and the receiver to receive remotely generated commands and to control the external infusion device in accordance with the commands; and
an indication device to indicate when a command has been received and indicate when the command is being utilized to control the external infusion device such that the external infusion device is capable of being concealed when being remotely commanded; and
a remote commander including:

a commander housing;
a keypad coupled to the commander housing for inputting commands; and
a transmitter coupled to the keypad for transmitting commands to the receiver of the external infusion device.

[0118] The external infusion device may further include a device transmitter to verify receipt of commands from the remote commander, and the remote commander may further include a remote receiver to receive the verification from the device transmitter of the external infusion device, and the remote commander may further include a remote indication

Abbott Ex. 1002 - 538/1438

device to indicate receipt of the verification from the external infusion device.

[0119] The remote commander may be sized to fit on a key ring.

[0120] The remote commander may use RF frequencies to transmit remote commands to the external infusion device.

[0121] The remote commander may use IR frequencies to transmit remote commands to the external infusion device.

[0122] The remote commander may use optical frequencies to transmit remote commands to the external infusion device.

[0123] The remote commander may use ultrasonic frequencies to transmit remote commands to the external infusion device.

[0124] The remote commander may use audio frequencies to transmit remote commands to the external infusion device.

[0125] The remote commander may use magnetic effects to transmit remote commands to the external infusion device.

[0126] The remote commander may be capable of providing remote commands at a distance greater than 1 inch.

[0127] The processor of the external infusion device may have a unique identification code, the remote commander may include the capability to read and learn the unique identification code of the external infusion device, and the remote commander and the external infusion device may use the unique identification code to substantially avoid interference with other external infusion devices.

[0128] The remote commander may have a unique identification code, the processor of the external infusion device may include the capability to read and learn the unique identification code of the remote commander, and the remote commander and the external infusion device may use the unique identification code to substantially avoid interference with other remote commanders.

[0129] The remote commander may include a mode that permits physician controlled programming of specific capabilities of the external infusion device to the exclusion of the user.

[0130] The remote commander may also include a link to a computer to allow computer programming to initiate or alter available capabilities of the external infusion device.

[0131] The external infusion device may include a memory for storing programs, and the receiver may be capable of receiving software updates to facilitate remote programming of external infusion device capabilities.

[0132] The remote commander may be capable of receiving data from another medical device and relaying the received data to the external infusion device.

[0133] The remote commander may be capable of remotely commanding and controlling the other medical device.

[0134] The remote commander may be capable of programming and activating an audio bolus delivery of the liquid by the external infusion device.

[0135] The remote commander may be capable of programming and activating a vibration bolus delivery of the liquid by the external infusion device.

[0136] The remote commander may be capable of programming and activating a temporary basal rate delivery of the liquid by the external infusion device.

[0137] The remote commander may be capable of programming and suspending delivery of the liquid by the external infusion device.

[0138] The remote commander may be capable of programming and activating an extended bolus delivery of the liquid by the external infusion device.

[0139] The remote commander may be capable of programming and activating a profiled bolus delivery of the liquid by the external infusion device.

[0140] The remote commander may be capable of programming and activating a dual wave bolus delivery of the liquid by the external infusion device.

[0141] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing;
a processor coupled to the housing;
a bolus estimator used in conjunction with the processor and externally supplied values to estimate an amount of liquid to be infused based upon an estimate of a material to be taken in by the body; and
an indication device to indicate when an amount of fluid to be infused has been calculated.

[0142] The bolus estimator may include the capability to calculate a correction bolus based upon a current characteristic value and a target characteristic value.

[0143] The bolus estimator may include a liquid sensitivity that is used to determine the amount of liquid to be infused to calculate the correction bolus.

[0144] The liquid to be infused may be insulin, and the material to be taken in may be carbohydrates.

[0145] The bolus estimator may include a lockout to prevent the calculation of a bolus for a predetermined period of time after a bolus estimated by the bolus estimator.

Abbott Ex. 1002 - 539/1438

[0146] The supplied values may be codes representing a carbohydrate value of specific foods.

[0147] The supplied values may be codes representing a carbohydrate value of specific meals.

[0148] The external infusion device may further include a duration factor to determine a value of how long a previously infused amount of liquid will remain active in the body, and the determined value may be used to adjust the amount of the fluid to be infused.

[0149] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing containing a reservoir;
a processor coupled to the housing; and
a vibration alarm used in conjunction with the processor to provide an alarm, and to generate sufficient vibration to assist in removing gas bubbles from the fluid in the reservoir during priming of the external infusion device.

[0150] The vibration alarm may be used to agitate the fluid in the reservoir in between successive delivery periods of the fluid by the external infusion device.

[0151] The vibration alarm may be used to agitate the fluid in the reservoir during delivery of the fluid by the external infusion device.

[0152] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing containing a reservoir;
a processor coupled to the housing;
an audible alarm coupled to the processor; and
a vibration alarm used in conjunction with the processor and the audible alarm to provide an alarm.

[0153] The vibration alarm may also used to agitate the fluid in the reservoir in between successive delivery periods of the fluid by the external infusion device.

[0154] The vibration alarm may also used to agitate the fluid in the reservoir during delivery of the fluid by the external infusion device.

[0155] The processor may select to activate one of the audible alarm and vibration alarm independently of the unselected alarm.

[0156] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing;
a processor coupled to the housing;
a keypad coupled to the housing and used in conjunction with the processor to determine an estimate of remaining battery power; and
an indication device to indicate the estimate of remaining battery power.

[0157] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing;
a processor coupled to the housing;
a memory coupled to and used in conjunction with the processor to store at least two personal delivery patterns;
a keypad coupled to the housing and used in conjunction with the processor to select one of the at least two personal delivery patterns; and
an indication device to indicate the selected personal delivery pattern, wherein the processor controls the external infusion device in accordance with the selected one of the at least two personal delivery patterns.

[0158] An external infusion device for infusion of a liquid into a body, the external infusion device comprising:

a housing;
a receiver coupled to the housing for receiving remotely generated commands;
a processor coupled to the housing;
a memory coupled to and used in conjunction with the processor to store at least two personal delivery patterns, wherein the processor is coupled to the receiver to receive the remotely generated commands and to control the external infusion device in accordance with the commands to select one of the at least two personal delivery patterns; and
an indication device to indicate the selected personal delivery pattern and when a command has been received to control the external infusion device in accordance with the selected personal delivery pattern such that the external

Abbott Ex. 1002 - 540/1438