infusion device is capable of being concealed from view when being remotely commanded,

wherein the processor controls the external infusion device in accordance with the selected one of the at least two personal delivery patterns.

[0159] 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 basal rate profiles;
a keypad coupled to the housing and used in conjunction with the processor to program the at least two basal rate profiles; and
an indication device to indicate the basal rate profiles during programming,

wherein the processor controls the external infusion device in accordance with the programmed at least two basal rate profiles.

[0160] 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 bolus types;
a keypad coupled to the housing and used in conjunction with the processor to select one of the at least two bolus types; and
an indication device to indicate the selected bolus type,

wherein the processor controls the external infusion device in accordance with the selected one of the at least two bolus types.

Claims

1. An external infusion device (10) for infusion of a liquid into a body from a reservoir (34), the external infusion device (10) comprising:

   a reservoir (34) of liquid to be infused into a body;
   a drive mechanism (32) operatively coupled with the reservoir (34) to infuse the liquid into the body;
   a housing (20) adapted for use on an exterior of the body, wherein the housing (20) contains at least a portion of the reservoir (34), wherein the drive mechanism (32) is at least partially contained within the housing (20), and wherein the drive mechanism (32) operatively couples with the at least a portion of the reservoir (34) within the housing;
   a processor (18) coupled to the housing (20)
   an audible alarm (30) to provide primarily audible indication and which is coupled to the processor (18); and
   a separate vibration alarm (16) to provide primarily tactile indications that are used in conjunction with the processor (18) and the audible alarm (30) to provide an alarm;

   characterized in that the processor (18) is programmed to be able to select, to activate one or more of the audible alarm (30) and vibration alarm (16) independently of the unselected alarm in response to a choice made by the user such that the user determines that the alarms are given as either audible indications, tactile indications or a combination of audible and tactile indications.

2. An external infusion device according to claim 1, wherein the processor (18) is programmed to activate the vibration alarm to agitate the fluid in the reservoir in between successive delivery periods of the fluid by the external infusion device.

3. An external infusion device according to claim 1, wherein the processor (18) is programmed to activate the vibration alarm to agitate the fluid in the reservoir during delivery of the fluid by the external infusion device.

4. An external infusion device (10) according to claim 1 wherein said alarms escalate in volume or frequency until acknowledged by the user.

Abbott Ex. 1002 - 541/1438

5. An external infusion device (10) according to claim 1 wherein said alarm is indicative of low liquid level in the reservoir (34), a low battery condition, or a malfunction of the system such as an occlusion of the outlet that restricts delivery of liquid from the reservoir.

Patentansprüche

1. Externe Infusionseinrichtung (10) zur Infusion einer Flüssigkeit aus einem Reservoir (34) in einen Körper, wobei die externe Infusionseinrichtung (10) umfasst:

   ein Reservoir (34) mit Flüssigkeit zur Infusion in einen Körper;
   einen Antriebsmechanismus (32), der operativ mit dem Reservoir (34) verbunden ist, um die Flüssigkeit in den Körper zu infundieren;
   ein Gehäuse (20), das zur Verwendung an der Außenseite des Körpers geeignet ist, wobei das Gehäuse (20) zumindest einen Teil des Reservoirs (34) enthält, wobei der Antriebsmechanismus (32) zumindest zu einem Teil in dem Gehäuse (20) enthalten ist, und wobei sich der Antriebsmechanismus (32) mit zumindest einem Teil des Reservoirs (34) innerhalb des Gehäuses operativ verbindet;
   einen Prozessor (18), der mit dem Gehäuse (20) verbunden ist;
   einen hörbaren Alarm (30), um vornehmlich eine hörbare Anzeige bereitzustellen, (und) der mit dem Prozessor (18) verbunden ist; und
   einen separaten Vibrationsalarm (16), um vornehmlich taktile Hinweise bereitzustellen, die in Verbindung mit dem Prozessor (18) und dem hörbaren Alarm (30) verwendet werden, um einen Alarm bereitzustellen;

   dadurch gekennzeichnet, dass der Prozessor (18) programmiert ist, in der Lage zu sein, einen oder mehrere des hörbaren Alarms (30) und des Vibrationsalarms (16) unabhängig von dem ungewählten Alarm ansprechend auf eine vom Nutzer getroffene Auswahl so zu aktivieren, dass der Nutzer bestimmt, dass die Alarme entweder als hörbare Anzeigen, taktile Hinweise oder eine Kombination von hörbaren und taktilen Hinweisen gegeben werden.

2. Externe Infusionseinrichtung nach Anspruch 1, bei der der Prozessor (18) programmiert ist, den Vibrationsalarm zu aktivieren, um die Flüssigkeit in dem Reservoir zwischen aufeinanderfolgenden Abgabeperioden der Flüssigkeit durch die externe Infusionseinrichtung zu agitieren.

3. Externe Infusionseinrichtung nach Anspruch 1, bei der der Prozessor (18) programmiert ist, den Vibrationsalarm zu aktivieren, um die Flüssigkeit in dem Reservoir während der Abgabe der Flüssigkeit durch die externe Infusionseinrichtung zu agitieren.

4. Externe Infusionseinrichtung (10) nach Anspruch 1, bei der sich die Alarme in der Lautstärke oder der Frequenz erhöhen bis sie vom Nutzer quittiert werden.

5. Externe Infusionseinrichtung (10) nach Anspruch 1, bei der der Alarm ein niedriges Flüssigkeitsniveau in dem Reservoir (34), einen niedrigen Batteriestand oder eine Fehlfunktion des Systems angezeigt, wie etwa eine Okklusion des Auslasses, die die Abgabe von Flüssigkeit aus dem Reservoir begrenzt.

Revendications

1. Dispositif de perfusion externe (10) pour une perfusion d'un liquide dans un corps à partir d'un réservoir (34), le dispositif de perfusion externe (10) comprenant :

   un réservoir (34) de liquide à perfuser dans un corps ;
   un mécanisme d'entraînement (32) couplé de manière fonctionnelle au réservoir (34) afin de perfuser le liquide dans le corps ;
   un boîtier (20) adapté pour une utilisation sur un extérieur du corps, dans lequel le boîtier (20) contient au moins une partie du réservoir (34), dans lequel le mécanisme d'entraînement (32) est au moins partiellement contenu à l'intérieur du boîtier (20), et dans lequel le mécanisme d'entraînement (32) est couplé de manière fonctionnelle avec la au moins une partie du réservoir (34) à l'intérieur du boîtier ;
   un processeur (18) couplé au boîtier (20) ;
   une alarme sonore (30) pour donner une indication principalement sonore et qui est couplée au processeur

Abbott Ex. 1002 - 542/1438

(18) ; et
une alarme vibrante séparée (16) pour donner des indications principalement tactiles qui sont utilisées conjointement avec le processeur (18) et l'alarme sonore (30) pour produire une alarme ;

caractérisé en ce que le processeur (18) est programmé pour pouvoir sélectionner afin d'activer une ou plusieurs alarmes parmi l'alarme sonore (30) et l'alarme vibrante (16) indépendamment de l'alarme non sélectionnée en réponse à un choix effectué par l'utilisateur de sorte que l'utilisateur détermine que les alarmes sont données soit sous forme d'indications sonores, d'indications tactiles ou d'une combinaison d'indications sonores et tactiles.

2. Dispositif de perfusion externe selon la revendication 1, dans lequel le processeur (18) est programmé pour activer l'alarme vibrante afin d'agiter le fluide dans le réservoir entre des périodes successives d'administration du fluide par le dispositif de perfusion externe.

3. Dispositif de perfusion externe selon la revendication 1, dans lequel le processeur (18) est programmé pour activer l'alarme vibrante afin d'agiter le fluide dans le réservoir pendant une administration du fluide par le dispositif de perfusion externe.

4. Dispositif de perfusion externe (10) selon la revendication 1, dans lequel lesdites alarmes s'intensifient en volume ou en fréquence jusqu'à ce qu'elles soient acquittées par l'utilisateur.

5. Dispositif de perfusion externe (10) selon la revendication 1, dans lequel ladite alarme est indicative d'un niveau de liquide bas dans le réservoir (34), d'un état de batterie faible ou d'un dysfonctionnement du système tel qu'une obstruction de la sortie qui restreint l'administration de liquide à partir du réservoir.

Abbott Ex. 1002 - 543/1438

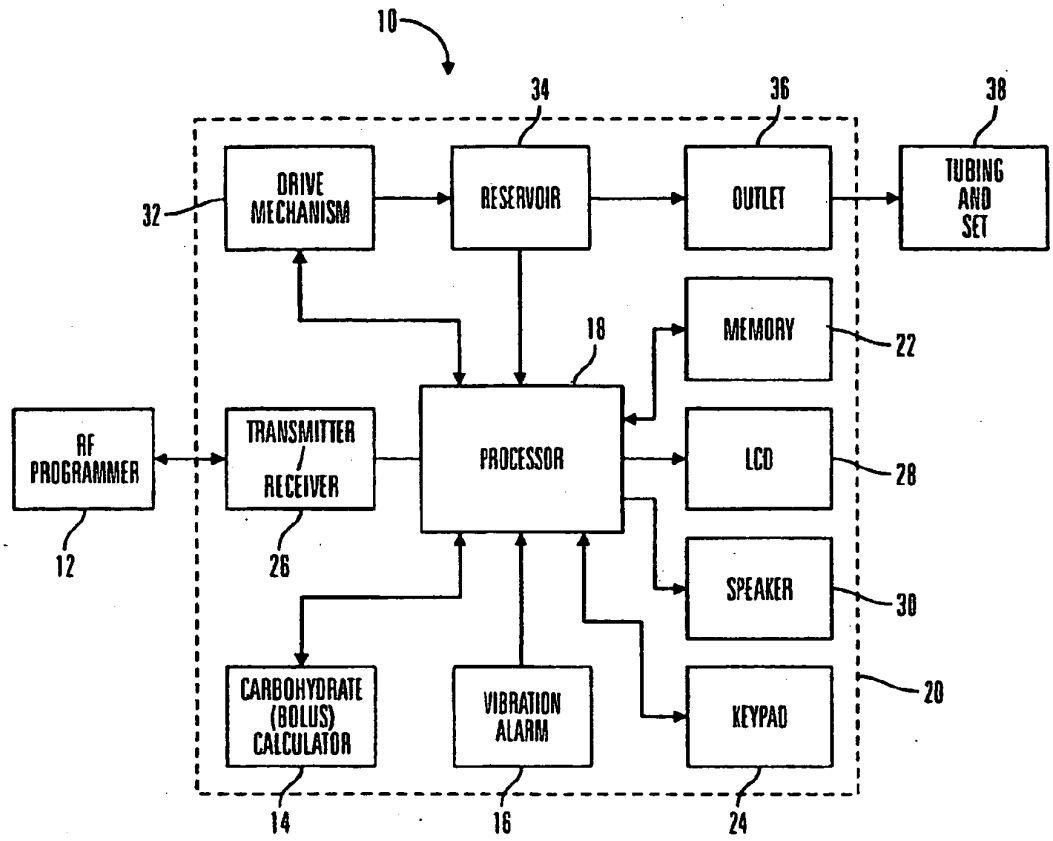


FIG. 1

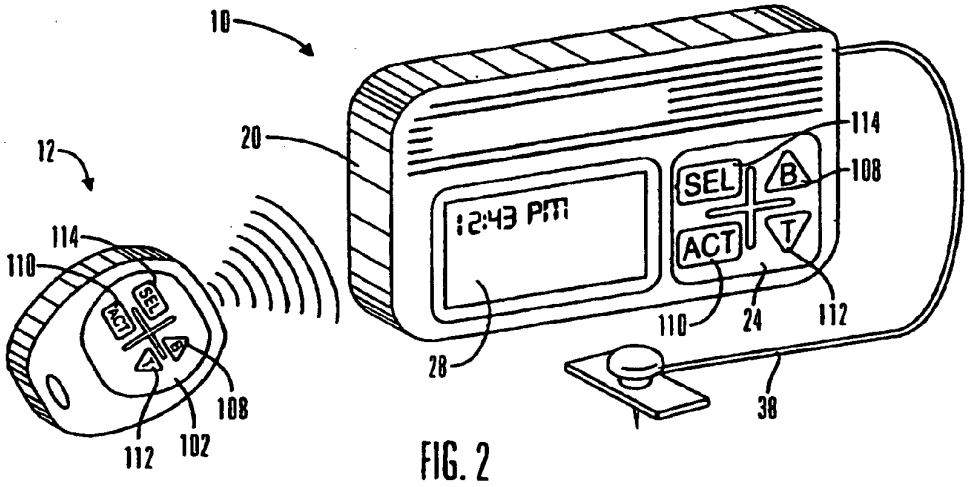


FIG. 2

Abbott Ex. 1002 - 544/1438

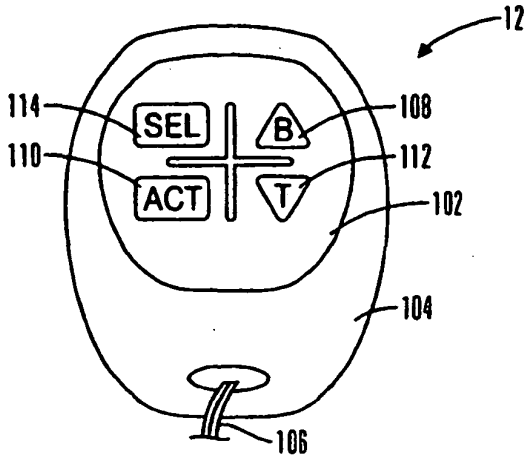


FIG. 3

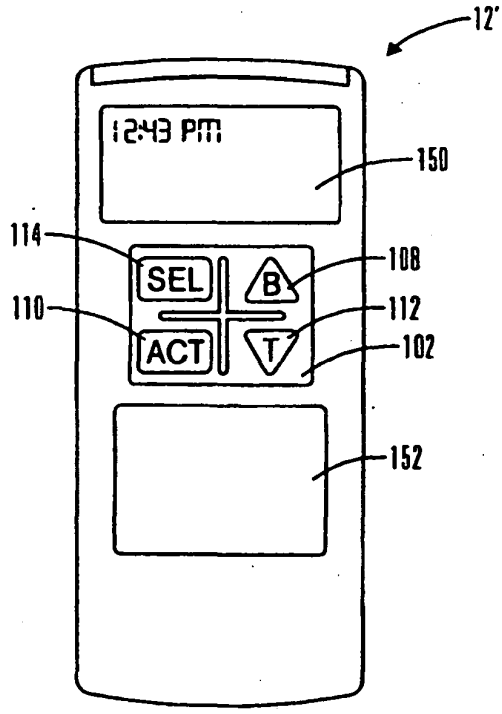


FIG. 4

Abbott Ex. 1002 - 545/1438

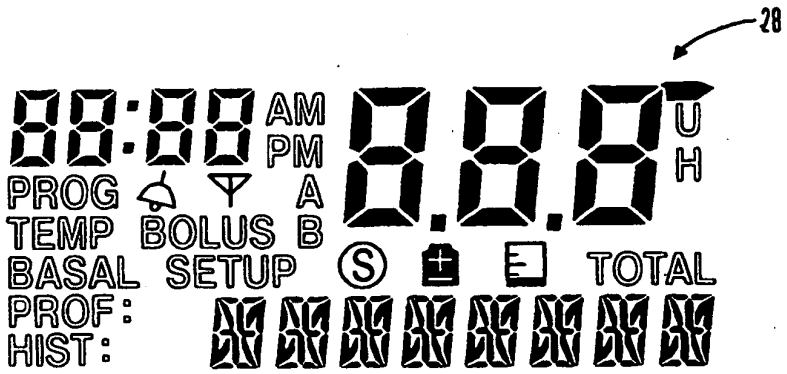


FIG. 5

NO.	SETUP II MENU OPTIONS
1	VARIABLE BOLUS MODE ON/OFF SCREEN
2	BOLUS ESTIMATOR ON/OFF SCREEN
3	MAXIMUM BOLUS SCREEN
4	MAXIMUM BASAL SCREEN
5	ALARM REVIEW SCREEN
6	RF DEVICE ID SCREEN
7	AUDIO BOLUS MODE ON/OFF SCREEN
8	PERSONAL DELIVERY PATTERN SCREEN
9	ALARM MODE (AUDIO/VIBRATE) SCREEN
10	CHILD BLOCK ON/OFF SCREEN
11	TIME DISPLAY SCREEN
12	INSULIN CONCENTRATION SCREEN
13	SETUP I SCREEN
14	SETUP EXIT SCREEN

FIG. 6

Abbott Ex. 1002 - 546/1438

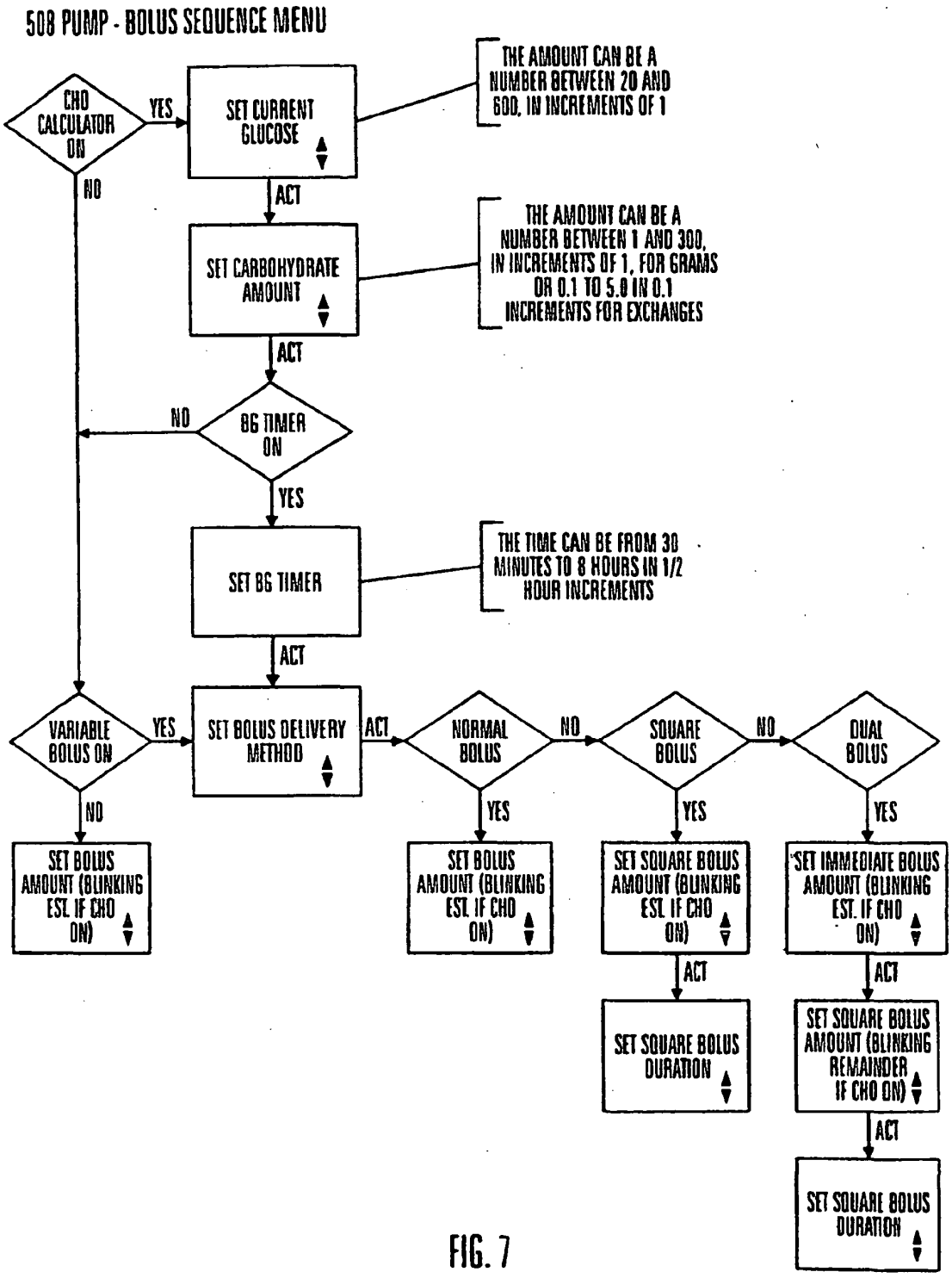


FIG. 7

Abbott Ex. 1002 - 547/1438

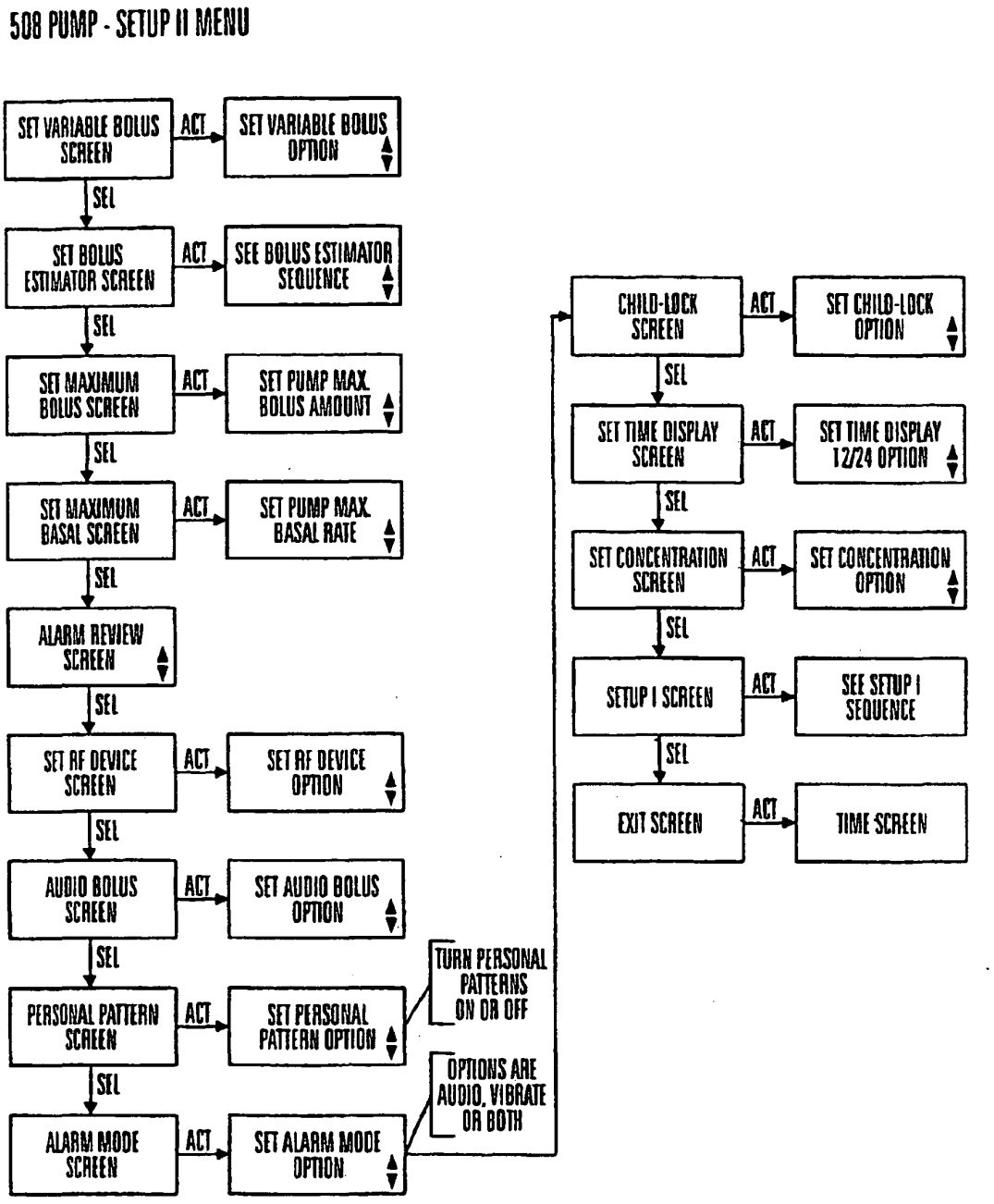


FIG. 8(a)

Abbott Ex. 1002 - 548/1438

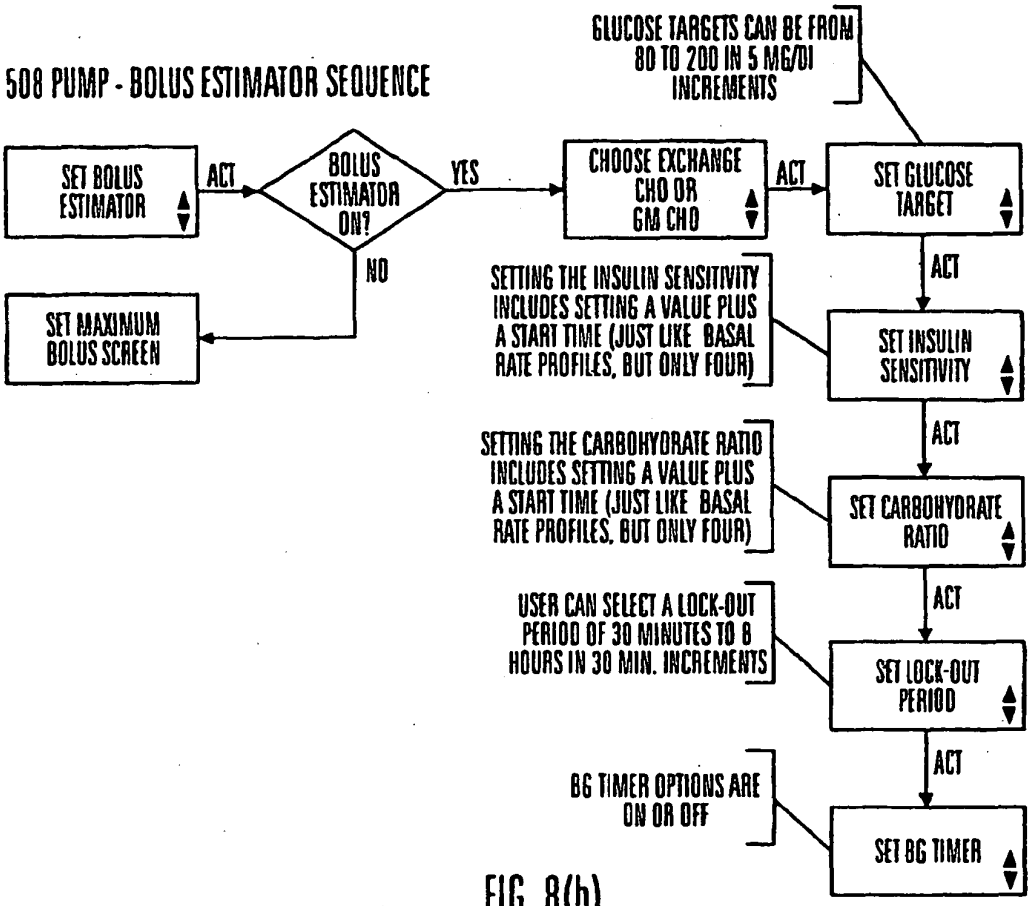


FIG. 8(b)

NO.	MAIN MENU OPTIONS
1	TIME SCREEN
2	BOLUS & BOLUS HISTORY SCREEN
3	SUSPEND/RESUME PUMP SCREEN
4	BASAL RATE SCREEN
5	TEMP. BASAL RATE SCREEN
6	DAILY TOTALS REVIEW SCREEN
7	PRIME BOLUS SCREEN
8	SETUP I SCREEN
9	SETUP II SCREEN

FIG. 9

Abbott Ex. 1002 - 549/1438

NO.	SETUP I MENU OPTIONS
1	TIME & DATE ADJUSTMENT SCREEN
2	AUTO-OFF SCREEN
3	BEEP VOLUME SCREEN
4	SELF-TEST SCREEN
5	SETUP II SCREEN
6	SETUP EXIT SCREEN

FIG. 10

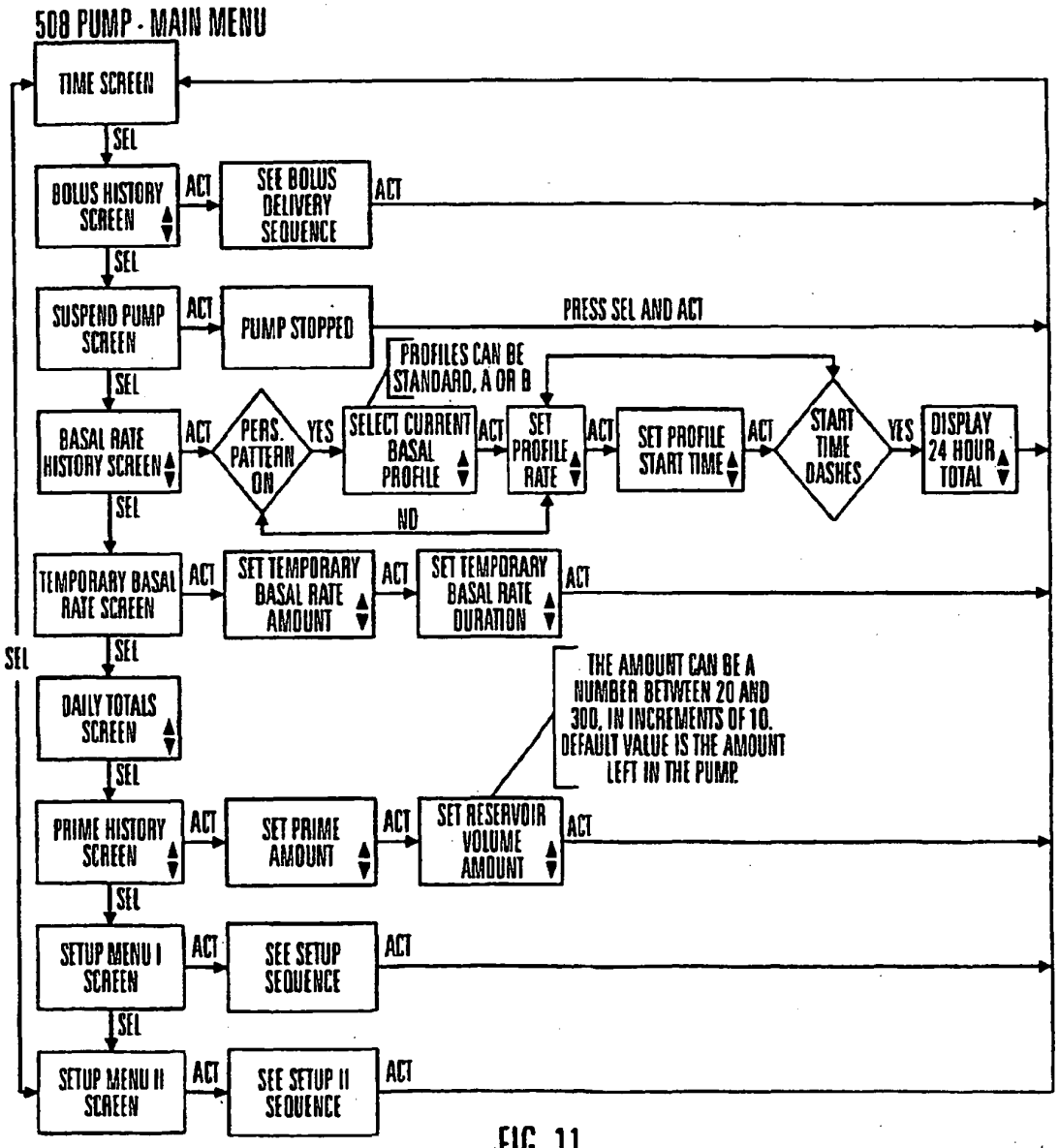


FIG. 11

Abbott Ex. 1002 - 550/1438

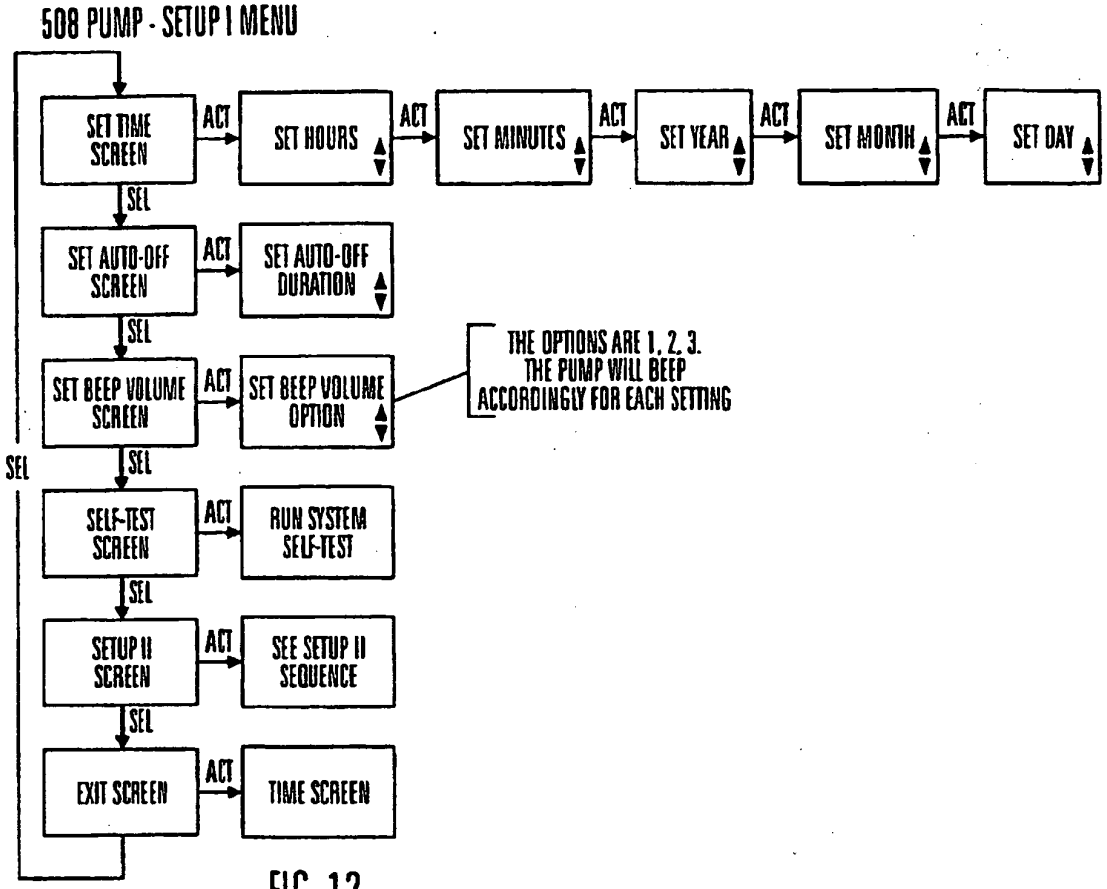


FIG. 12

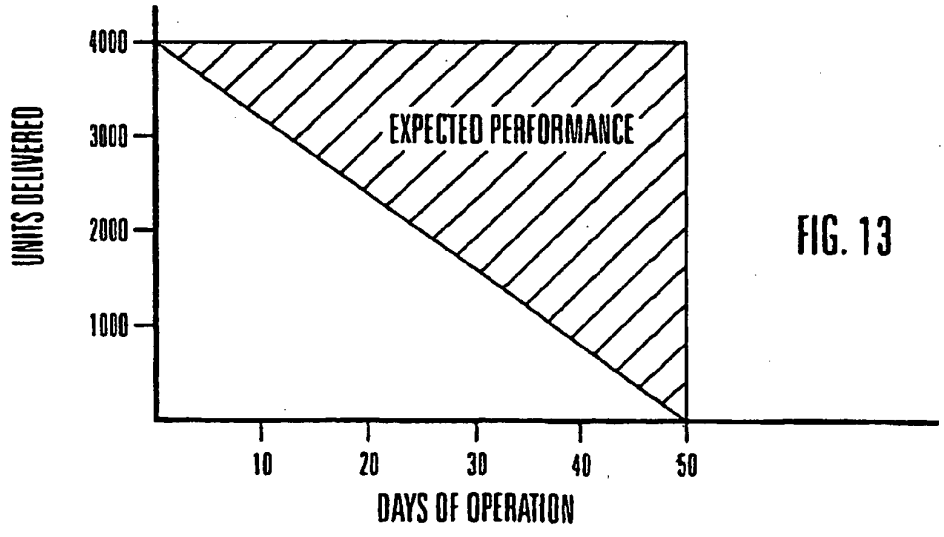


FIG. 13

Abbott Ex. 1002 - 551/1438

PARAMETER	FACTORY DEFAULT
INSULIN CONCENTRATION	U100
BASAL RATE PROFILES	PROFILE 1, 0.0 U/H (PERSONAL PATTERNS 2 AND 3 ARE ALSO SET TO PROFILE 1 OF 0.0 U/H). PERSONAL PATTERN 1 IS THE DEFAULT
MAXIMUM MEAL BOLUS	10.0 U
MAXIMUM BASAL RATE	2.0 U/H
TIME	12:00 AM, JAN 1, 1998 AT TIME OF PUMP POWER ON RESET (E-01)
TIME DISPLAY FORMAT	12 HOUR (FOR U.S.A.), 24 HOUR (FOR EUROPE)
AUDIO BOLUS MODE	OFF
AUDIO BOLUS INCREMENT	0.5 U (U100)
BEEP VOLUME	2 (MEDIUM)
AUTOMATIC OFF DURATION	– (DISABLED)
DAILY TOTALS	ALL 90 DAYS 0.0 U (USER CAN REVIEW LAST 7 ONLY)
BOLUS HISTORY	ALL 450 BOLUSES 0.0 U (USER CAN REVIEW LAST 24 ONLY)
PRIME BOLUS HISTORY	ALL 50 BOLUSES 0.0 U (USER CAN REVIEW LAST 9)
ALARM MODE	AUDIO
LOW VOLUME ALERT	OFF
ALARM CLOCK	OFF
CHILD LOCK	OFF
BOLUS ESTIMATOR	OFF
TARGET BLOOD GLUCOSE	100 MG/DL
INSULIN SENSITIVITY	30
CARBOHYDRATE RATIO	15
EXCHANGE RATIO	1.0
BOLUS ESTIMATOR LOCKOUT	1 HR
BLOOD GLUCOSE TIMER	OFF
RF-DEVICE	OFF
ALARM HISTORY	BLANKS (USER CAN REVIEW LAST 12 ONLY)

FIG. 14

Abbott Ex. 1002 - 552/1438

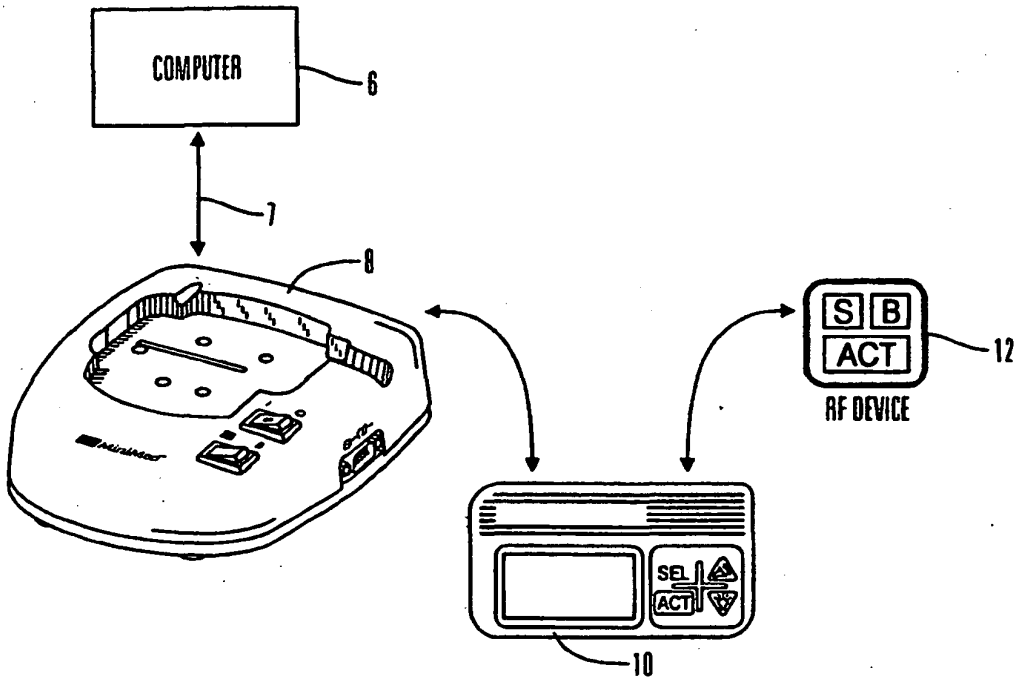


FIG. 15

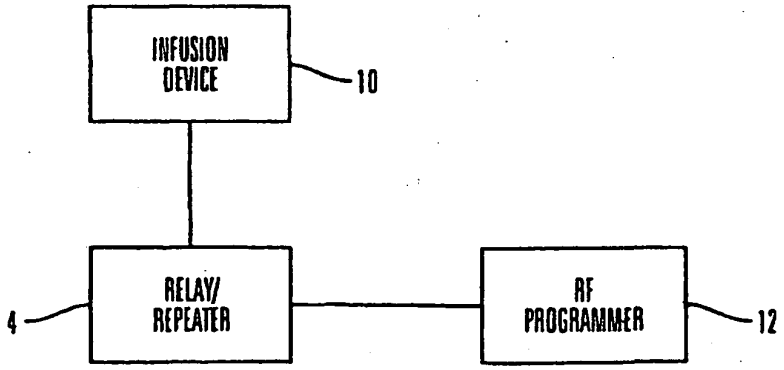


FIG. 16

Abbott Ex. 1002 - 553/1438

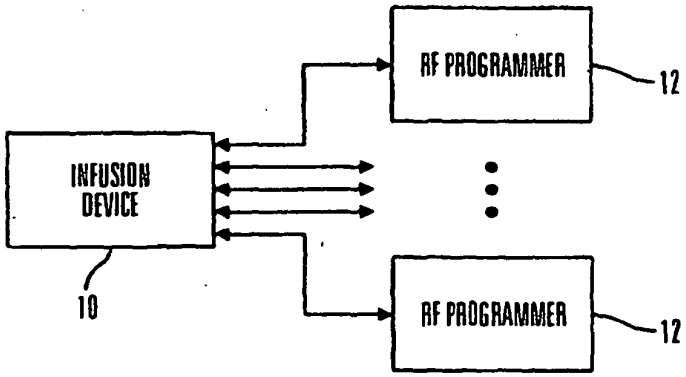


FIG. 17

Abbott Ex. 1002 - 554/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 5582593 A **[0003] [0004]**
- US 5376070 A **[0016] [0079]**
- US 5569186 A **[0049]**
- US 5665065 A **[0049]**

Abbott Ex. 1002 - 555/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 503 660 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
17.01.2007 Bulletin 2007/03

(21) Application number: **03726510.5**

(22) Date of filing: **29.04.2003**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/US2003/013199

(87) International publication number:
WO 2003/094714 (20.11.2003 Gazette 2003/47)

(54) **REAL TIME SELF-ADJUSTING CALIBRATION ALGORITHM**

SELBSTEINSTELLENDES KALIBRIERUNGSALGORITHMUS IN ECHTZEIT

ALGORITHME D'ETALONNAGE A AJUSTEMENT AUTOMATIQUE EN TEMPS REEL

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR

(30) Priority: **08.05.2002 US 141375**

(43) Date of publication of application:
09.02.2005 Bulletin 2005/06

(73) Proprietor: **Medtronic MiniMed, Inc.**
Northridge, CA 91325-1219 (US)

(72) Inventors:
- **SHIN, John, J.**
  Glendale, CA 91207 (US)
- **HOLTZCLAW, Kris, R.**
  Santa Clarita, CA 91350 (US)
- **DANGUI, Nandita, D.**
  Los Angeles, CA 90049 (US)
- **KANDERIAN, Sami, Jr.**
  Northridge, CA 91325 (US)
- **MASTROTOTARO, John, J.**
  Los Angeles, CA 90024 (US)
- **HONG, Peter, I.**
  Santa Clarita, CA 91350 (US)

(74) Representative: **Ruschke, Hans Edvard et al**
RUSCHKE HARTMANN MADGWICK & SEIDE
Patent- und Rechtsanwälte
Postfach 86 06 29
81633 München (DE)

(56) References cited:
WO-A-00/49941
WO-A-99/29230
US-A- 5 497 772

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 1 503 660 B1

Printed by Jouve, 75001 PARIS (FR)

Description

FIELD OF THE INVENTION

[0001] This invention relates to glucose monitor systems and, in particular embodiments, to calibration methods for glucose monitoring systems.

BACKGROUND OF THE INVENTION

[0002] Over the years, body characteristics have been determined by obtaining a sample of bodily fluid. For example, diabetics often test for blood glucose levels. Traditional blood glucose determinations have utilized a painful finger prick using a lancet to withdraw a small blood sample. This results in discomfort from the lancet as it contacts nerves in the subcutaneous tissue. The pain of lancing and the cumulative discomfort from multiple needle pricks is a strong reason why patients fail to comply with a medical testing regimen used to determine a change in a body characteristic over a period of time. Although non-invasive systems have been proposed, or are in development, none to date have been commercialized that are effective and provide accurate results. In addition, all of these systems are designed to provide data at discrete points and do not provide continuous data to show the variations in the characteristic between testing times.

[0003] A variety of implantable electrochemical sensors have been developed for detecting and/or quantifying specific agents or compositions in a patient's blood. For instance, glucose sensors are being developed for use in obtaining an indication of blood glucose levels in a diabetic patient. Such readings are useful in monitoring and/ or adjusting a treatment regimen which typically includes the regular administration of insulin to the patient. Thus, blood glucose readings improve medical therapies with semi-automated medication infusion pumps of the external type, as generally described in U. S. Patent Nos. 4,562, 751; 4,678, 408; and 4,685, 903; or automated implantable medication infusion pumps, as generally described in U. S. Patent No. 4,573, 994, which are herein incorporated by reference. Typical thin film sensors are described in U. S. Patent Nos. 5,390,671; 5,391, 250; 5,482, 473; and 5,586, 553. See also U. S. Patent No. 5,299, 571.

[0004] Document WO 00/49941 describes a method of calibrating a glucose monitor data by collecting data over a period of time and comparing it with at least two reference values taken within the period of time by a blood glucose meter. Various computational techniques are described to obtain the calibration characteristics of the glucose monitor. An error signal is generated if the measured sensibility is outside a given valid range which has previously been determined by in vitro measurements. This document forms the basis for the precharacterizing part of claim 1. Such arrangements can take into account minor changes in sensitivity but are not very reliable at detecting sensor failure.

[0005] An object of the present invention is to realize a calibration method that can detect sensor failure, as well as a change in sensitivity.

SUMMARY OF THE INVENTION

[0006] The invention is as set out in claim 1 and claim 13 below.

[0007] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] 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 is a perspective view illustrating a subcutaneous glucose sensor insertion set and glucose monitor device;
FIG. 2 is a cross-sectional view of the sensor set and glucose monitor device as shown along the line 2-2 of FIG. 1;
FIG. 3 is a cross-sectional view of a slotted insertion needle used in the insertion set of FIGs. 1 and 2;
FIG. 4 is a cross-sectional view as shown along line 4-4 of FIG. 3;
FIG. 5 is a cross-sectional view as shown along line 5-5 of FIG. 3;
FIG. 6 is a partial cross-sectional view corresponding generally with the encircled region 6 of FIG. 2;
FIG. 7 is a cross- sectional view as shown along line 7-7 of FIG. 2;
FIGs.8(a-c) are diagrams showing a relationship between sampled values, interval values and memory storage values;
FIG. 9 is a chart showing clipping limits;
FIG. 10 is a sample computer screen image of a post processor analysis of glucose monitor data;

Abbott Ex. 1002 - 557/1438

FIG. 11 is a chart illustrating the pairing of a blood glucose reference reading with glucose monitor data;
FIG. 12 is a chart illustrating an example of a single-point calibration;
FIG. 13 is a block diagram of a single-point calibration technique;
FIG. 14 is a chart illustrating an example of a linear regression calibration.
FIG. 15 is a block diagram of a linear regression calibration technique;
FIG. 16 is a flowchart of a self-adjusting calibration technique in accordance with an embodiment of the present invention;
FIGs. 17a and 17b are charts illustrating an example of the self-adjusting calibration technique in accordance with FIG. 16; and
FIGS. 18a and 18b are further charts illustrating an example of the self-adjusting calibration technique in accordance with FIG. 16.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0009] As shown in the drawings for purposes of illustration there are described calibration methods for a glucose monitor that is coupled to a sensor set to provide continuous data recording of readings of glucose levels from a sensor for a period of time. Typically the sensor and monitor are a glucose sensor and a glucose monitor for determining glucose levels in the blood and/or bodily fluids of a user. However, it will be recognized that the invention may be used in the calibration of sensors to determine the levels of other body characteristics including analytes or agents, compounds or compositions, such as hormones, cholesterol, medications concentrations, viral loads (e.g., HIV), bacterial levels, or the like. The glucose sensor is primarily adapted for use in subcutaneous human tissue. One or more sensors may be placed in other tissue types, such as muscle, lymph, organ tissue, veins, arteries or the like, and used in animal tissue to measure body characteristics. Readings from the sensor may be recorded on an intermittent, periodic, on-demand, continuous, or analog basis.

[0010] FIGs. 1-7 illustrate a glucose monitor system 1 for use with the calibration methods. The glucose monitor system 1 includes a subcutaneous glucose sensor set 10 and a glucose monitor 100. In preferred embodiments, the glucose monitor 100 is of the type described in U.S. Patent Application Serial No. 60/121,664, filed on February 25, 1999, entitled "Glucose Monitor System" In alternative embodiments, The glucose monitor may be of the type described in WO 00/19887 entitled "Telemetered Characteristic Monitor System.

[0011] Preferably, the glucose monitor 100 is worn by the user and is connected to a surface mounted glucose sensor set 10 that is attached to a user's body by an electrically conductive cable 102, of the type described in WO 00/49942 entitled "Test Plug and Cable for a Glucose Monitor". The sensor interface may be configured in the form of a jack to accept different types of cables that provide adaptability of the glucose monitor 100 to work with different types of subcutaneous glucose sensors and/or glucose sensors placed in different locations of the user's body. However, in alternative embodiments, the sensor interface is permanently connected to the cable 102. A characteristic monitor may be connected to one or more sensor sets to record data of one or more body characteristics from one or more locations on or in the user's body.

[0012] The glucose sensor set 10 is of the type described in published U.S. Patent Application 2002/23852 or WO 98/56293 entitled "Insertion Set For A Transcutaneous Sensor". The glucose sensor 12, which may be of the type described in U.S. Patent Nos. 5,390,671; 5,391,250; 5,482,473; and 5,586,553 extends from the glucose sensor set 10 into the user's body with electrodes 20 of the glucose sensor 12 terminating in the user's subcutaneous tissue. See also U.S. Patent No. 5,299,571. However, the glucose sensor 12 may use other types of sensors, such as chemical based, optical based, or the like. The sensors may be of a type that is used on the external surface of the skin or placed below the skin layer of the user for detecting body characteristics.

[0013] The glucose monitor 100 generally includes the capability to record and store data as it is received from the glucose sensor 12, and includes either a data port (not shown) or wireless transmitter and/or receiver (also not shown) for transferring data to and/or from a data processor 200 such as a computer, communication station, a dedicated processor designed specifically to work with the glucose monitor, or the like. The glucose monitor is generally of the type described in WO 00/19887, 1999, entitled "Telemetered Characteristic Monitor System"

[0014] Preferably, the glucose monitor system 1 minimizes inconvenience by separating complicated monitoring process electronics into two separate devices; the glucose monitor 100, which attaches to the glucose sensor set 10; and the data processor 200, which contains the software and programming instructions to download and evaluate data recorded by the glucose monitor 100. In addition, the use of multiple components (e.g., glucose monitor 100 and data processor 200) facilitates upgrades or replacements, since one module, or the other, can be modified, re-programmed, or replaced without requiring complete replacement of the monitor system 1. Further, the use of multiple components can improve the economics of manufacturing, since some components may require replacement on a more frequent basis, sizing requirements may be different for each module, different assembly environment requirements, and modifications can be made without affecting the other components.

Abbott Ex. 1002 - 558/1438

[0015] The glucose monitor 100 takes raw glucose sensor data from the glucose sensor 12 and assesses it during real-time and/or stores it for later processing or downloading to the data processor 200, which in turn analyzes, displays, and logs the received data. The data processor 200 utilizes the recorded data from the glucose monitor 100 to analyze and review the blood glucose history. In particular embodiments, the glucose monitor 100 is placed into a com-station which facilitates downloading data to a personal computer for presentation to a physician. A software is used to download the data, create a data file, calibrate the data, and display the data in various formats including charts, forms, reports, graphs, tables, lists, and the like. In further embodiments, the glucose monitor system 1 may be used in a hospital environment or the like.

[0016] The glucose monitor may include at least portions of the software described as contained within the data processor 200 above. The glucose monitor might contain the necessary software to calibrate glucose sensor signals, display a real-time blood glucose value, show blood glucose trends, activate alarms and the like. A glucose monitor with these added capabilities is useful for patients that might benefit from real-time observations of their blood glucose characteristics even while they're not in close proximity to a computer, communication device or dedicated independent data processor.

[0017] As shown in FIG. 2, the data processor 200, may include a display 214 that is used to display the calculated results of the raw glucose sensor data received via a download from the glucose monitor 100. The results and information displayed includes, but is not limited to, trending information of the characteristic (e.g., rate of change of glucose), graphs of historical data, average characteristic levels (e.g., glucose), stabilization and calibration information, raw data, tables (showing raw data correlated with the date, time, sample number, corresponding blood glucose level, alarm messages, and more), and the like. Alternative embodiments include the ability to scroll through the data. The display 214 may also be used with buttons (not shown) on the data processor 200, computer, communication station, characteristic monitor, or the like, to program or update data. In preferred embodiments, the glucose monitor 104 includes a display 132 to assist the user in programming the glucose monitor 100, entering data, stabilizing, calibrating, downloading data, or the like.

[0018] There may be included one or more buttons 122, 124, 126 and 128 on the glucose monitor 100 to program the monitor 100, to record data, insert flags to correlate data with external events for later analysis, input calibration values, or the like. In addition, the glucose monitor 100 may include an on/off button 130 for compliance with safety standards and regulations to temporarily suspend transmissions or recording. The glucose monitor 100 may also be combined with other medical devices to accept other patient data through a common data network and/or telemetry system. The glucose monitor 100 may be combined with a blood glucose meter to directly import or correlate glucose calibration reference values such as described in WO 00/78210 entitled "Characteristic Monitor for use with analyte sensor". The glucose monitor 100 may also be combined with semi-automated medication infusion pumps of the external type, as generally described in U.S. Patent Nos. 4,562,751; 4,678,408; and 4,685,903; or automated implantable medication infusion pumps, as generally described in U.S. Patent No. 4,573,994.

[0019] The glucose monitor 100 may record data from the infusion pumps and/or may process data from both the glucose sensor 12 and an infusion pump to establish a closed loop system to control the infusion pump based on glucose sensor measurements. In other embodiments, other body characteristics are monitored, and the monitor may be used to provide feedback in a closed loop system to control a drug delivery rate. In further alternative embodiments, the glucose monitor 100 can be combined with a glucose sensor set 10 as a single unit.

[0020] Glucose sensors are replaced periodically to avoid infection, decaying enzyme coating and therefore sensor sensitivity, deoxidization of the electrodes, and the like. The user will disconnect the glucose sensor set 10 from the cable 102 and glucose monitor 100. A needle 14 is used to install another glucose sensor set 10 and then the needle 14 is removed. Further description of the needle 14 and the sensor set 10 are found in U.S. Patent No. 5,536,553, entitled "Transcutaneous Sensor Insertion Set"; published U.S. Patent Application US 2002/81971 entitled "Insertion Set For A Transcutaneous Sensor"; and U.S. Patent No. 5,951,521, entitled "A Subcutaneous Implantable Sensor Set Having The Capability To Remove Or Deliver Fluids To An Insertion Site,"

[0021] The user connects the connection portion 24 of the glucose sensor set 10 through the cable 102 to the glucose monitor 100, so that the glucose sensor 12 can then be used over a prolonged period of time. An initial reading may be downloaded from the glucose sensor set 10 and the glucose monitor 100 to the data processor 200, to verify proper operation of the glucose sensor 10 and the glucose monitor 100. In preferred embodiments, the glucose sensor set 10 provides data to the glucose monitor 100 for one to seven days before replacement. Glucose sensors 12 may last in the user's body for longer or shorter periods of time depending on the quality of the installation, cleanliness, the durability of the enzyme coating, deoxidization of the sensor, user's comfort, and the like.

[0022] After installation into the body, the glucose sensor 12 is initialized to achieve a steady state of operation before starting a calibration process. Preferably, power supplied by three series silver oxide 357 battery cells 110 in the glucose monitor 100 is used to speed the initialization of the glucose sensor 12. Alternatively, other power supplies may be used such as, different battery chemistries including lithium, alkaline, or the like, and different numbers of batteries, solar cells, a DC converter plugged into an AC socket (provided with proper electrical isolation), or the like.

Abbott Ex. 1002 - 559/1438

[0023] The use of an initialization process can reduce the time for glucose sensor 12 stabilization from several hours to an hour or less. The preferred initialization procedure uses a two step process. First, a high voltage (preferably between 1.0-1.1 volts - although other voltages may be used) is applied between electrodes 20 of the sensor 12 for one to two minutes (although different time periods may be used) to allow the sensor 12 to stabilize. Then, a lower voltage (preferably between 0.5-0.6 volts - although other voltages may be used) is applied for the remainder of the initialization process (typically 58 minutes or less). Other stabilization/initialization procedures using differing currents, currents and voltages, different numbers of steps, or the like, may be used. Other arrangements may omit the initialization/stabilization process, if not required by the body characteristic sensor or if timing is not a factor. Alternatively, the characteristic monitor or the data processor 200 may apply an algorithm to the sensor data to determine when initial transients are sufficiently diminished and the sensor is at a significantly stable state to begin calibration.

[0024] The arrangement may be such that data is not considered valid until a sensor initialization event flag (ESI) is set in the data indicating that stabilization is complete. Preferably, stabilization is complete after 60 minutes or when a user enters a sensor initialization flag using one or more buttons on the glucose monitor 100. After stabilization/initialization is complete the glucose monitor 100 is calibrated to accurately interpret readings from the newly installed glucose sensor 12.

[0025] Beginning with the stabilization process, the glucose monitor 100 measures a continuous electrical current signal (ISIG) generated by the glucose sensor 12 relative to a concentration of glucose present in the subcutaneous tissue of the user's body. In preferred embodiments, the glucose monitor 100 samples the ISIG from the glucose sensor 12 at a sampling rate of once every 10 seconds, as shown in FIGs.8a-c. Examples of sampled values are labeled A-AD in FIG. 8a. At an interval rate of once per minute, the highest and lowest of the sampled values (shown in FIG. 8a as circled sampled values A, E, G, I, M, R, V, W, Y, and AB) are ignored, and the remaining 4 sampled values from an interval are averaged to create interval values (shown in FIG. 8b as values F', L', R', X', and AD'). At a glucose monitor memory storage rate of once every 5 minutes, the highest and lowest of the interval values (shown in FIG. 8b as values L' and X') are ignored and the remaining 3 interval values are averaged and stored in a glucose monitor memory as memory values (shown in FIG. 8c as point AD"). The memory values are retained in memory and may be downloaded to the data processor 200. The memory values are used to calibrate the glucose monitor 100 and/or the post processor 200 and to analyze blood glucose levels. The sampling rate, interval rate and the memory storage rate may be varied as necessary to capture data with sufficient resolution to observe transients or other changes in the data depending on the rate at which sensor values can change, which is affected by the sensor sensitivity, the body characteristic being measured, the physical status of the user, and the like. In other arrangements, all of the sampled values are included in the average calculations of memory storage values. In alternative arrangements more or less sampled values or interval values are ignored depending on the signal noise, sensor stability, or other causes of undesired transient readings. Finally, in still other arrangements, all sampled values and/or interval values are stored in memory.

[0026] Clipping limits may be used to limit the signal magnitude variation from one value to the next thereby reducing the effects of extraneous data, outlying data points, or transients. Clipping limits may be applied to the interval values. For instance, interval values that are above a maximum clipping limit or below a minimum clipping limit are replaced with the nearest clipping limit value.

[0027] In alternative arrangements interval values that are outside of the clipping limits are ignored and not used to calculate the next memory storage value. In particular embodiments, the detection of interval values outside of the clipping limits is considered a calibration cancellation event In further particular arrangements more than one value must be deemed outside of clipping limits to constitute a calibration cancellation event. (Calibration cancellation events are discussed below).

[0028] In preferred arrangements the clipping limits are shifted after each data point. The level that the clipping limits are set to is dependent on an acceptable amount of change from the previous interval value to the present interval value, which is affected by the sensor sensitivity, signal noise, signal drift, and the like. In preferred embodiments, the clipping limits are calculated based on the magnitude of the previous interval value. For example, for a previous interval value from 0 up to but not including 15 Nano-Amps, the clipping limits are set at plus and minus 0.5 Nano-Amps about the previous interval value. For a previous interval value from 15 up to but not including 25 Nano-Amps, the clipping limits are set at plus and minus 3% of the previous interval value, about the previous interval value. For a previous interval value from 25 up to but not including 50 Nano-Amps, the clipping limits are set at plus and minus 2% of the previous interval value, about the previous interval value. And for a previous interval value of 50 Nano-Amps and greater, the clipping limits are set at plus and minus 1% about the previous interval value. In alternative embodiments, different clipping limits may be used.

[0029] FIG. 9 shows a typical clipping limit example in which a previous interval value 500, associated with interval N-1, has a magnitude of 13.0 Nano-Amps, which is less than 15.0 Nano-Amps. Therefore, the maximum clipping limit 502 for the present interval value 506 is set at 13.5 Nano-Amps, which is 0.5 Nano-Amps greater than the magnitude of the previous interval value 500. And the minimum clipping limit 504 is set at 12.5 Nano-Amps which is 0.5 Nano-Amps below the previous interval value 500. The present interval value 506, associated with interval N, is between the maximum

Abbott Ex. 1002 - 560/1438

clipping limit 502 and the minimum clipping limit 504, and is therefore acceptable.

[0030] In another example shown in FIG. 9, the present interval value 508, associated with interval M, has a value of 25.0 Nano-Amps which is outside of the clipping limit 514 and will therefore be clipped. The previous interval value 510, associated with interval M-1, is 26.0 Nano-Amps, which is included in the range from 25.0 up to but not including 50.0 Nano-Amps as discussed above. Therefore the clipping limits are ± 2%. The maximum clipping limit 512 is 2% greater than the previous interval value 510,

$$26.0 + 26.0 * 0.02 = 26.5 \text{ Nano-Amps.}$$

Similarly the minimum clipping limit 514 is 2% less than the previous interval value 510,

$$26.0 - 26.0 * 0.02 = 25.5 \text{ Nano-Amps.}$$

Since the present interval value 508 of 25.0 Nano-Amps is less than the minimum clipping limit 514 of 25.5 Nano-Amps, it will be clipped, and 25.5 Nano-Amps will be used in place of 25.0 Nano-Amps to calculate a memory storage value. For further illustration, FIG. 8 shows interval value R', which is calculated by averaging sampled values N through Q, is outside of the clipping limits 412 and 414, which result from the previous interval value L'. Therefore, the magnitude of interval value R' is not used to calculate memory value AD", instead R", which is the magnitude of the minimum clipping limit 414, is used.

[0031] In other arrangements the clipping limits may be a smaller or larger number of Nano-Amps or a smaller or larger percentage of the previous interval value based on the sensor characteristics mentioned above. Alternatively, the clipping limits are calculated as plus or minus the same percent change from every previous interval value. Other algorithms use several interval values to extrapolate the next interval value and set the clipping limits to a percentage higher and lower than the next anticipated interval value. In further, alternatives, clipping may be applied to the sampled values, interval values, memory values, calculated glucose values, estimated values of a measured characteristic, or any combination of the values.

[0032] All interval values may be compared to an out-of-range limit of 200 Nano-Amps. If three consecutive interval values are equal to or exceed the out-of-range limit, the sensor sensitivity is deemed to be too high and an alarm is activated to notify the user that re-calibration is required or the sensor may need replacing. The out-of range limit may be set at higher or lower values depending on the range of sensor sensitivities, the expected working life of the sensor, the range of acceptable measurements, and the like. The out of range limit may be applied to the sampled values. In other arrangments the out-of-range limit is applied to the memory storage values.

[0033] Unstable signal alarm limits may be set to detect when memory storage values change too much from one to another. The signal alarm limits are established similarly to the clipping limits described above for the interval values, but allow for a larger change in value since there is more time between memory storage values than between interval values. Re-calibration or replacement of the glucose sensor 12 is required once an unstable signal alarm is activated. In essence, the glucose monitor 100 has detected too much noise in the ISIG from the glucose sensor 12.

[0034] Each memory storage value is considered valid (Valid ISIG value) unless one of the following calibration cancellation events occurs: an unstable signal alarm (as discussed above), a sensor initialization event (as discussed above), a sensor disconnect alarm, a power on/off event, an out-of-range alarm (as discussed above), or a calibration error alarm. Only Valid ISIG values are used to calculate blood glucose levels by the glucose monitor 100 or post processor 200, as shown in FIG: 10. Once a calibration cancellation event occurs, the successive memory storage values are not valid, and therefore are not used to calculate blood glucose, until the glucose monitor 100 or post processor 200 is recalibrated. FIG. 10 shows an explanatory computer screen in which cell P3 indicates a sensor disconnect alarm with the abbreviation "SeDi". As shown, blood glucose values do not appear in column K, titled "Sensor Value", and Valid ISIG values do not appear in column J until after the sensor is initialized, as indicated by the "ESI" flag in cell N17. One exception however, is the power on/off event. If the glucose monitor 100 is turned off for a short enough period of time, generally up to 30 minutes, the memory storage values are considered Valid ISIG values as soon as the power is turned back on. If the power is off for longer than 30 minutes, the glucose monitor must be re-calibrated before ISIG values are considered valid. Alternatively, the power may be off 30 minutes up to indefinitely and once the power is restored, the memory storage values are Valid ISIG values. The sensor disconnect alarm is activated when the glucose monitor 100 does not detect a signal. In preferred arrangements when 2 or more out of 5 interval values collected within a given memory storage rate are less than 1.0 Nano-Amp, the disconnect alarm is triggered. In alternative embodiments, more or less values need be below a particular amperage to trigger the disconnect alarm depending of the acceptable

Abbott Ex. 1002 - 561/1438

range or sensor readings and the stability of the sensor signal. The remaining two calibration cancellation events, the calibration error and an alternative embodiment for the out-of-range alarm, are discussed in conjunction with the calibration process below.

[0035] The described calibration techniques that may be used by either glucose monitors 100 during real-time measurements of one or more signals from the glucose sensor 12, or post processors 200 during post-processing of data that has been previously recorded and downloaded (as shown in FIG. 10).

[0036] To calibrate the glucose monitor 100, the calibration factor called a sensitivity ratio (SR) (blood glucose level/ Valid ISIG value) is calculated for a particular glucose sensor 12. The SR is a calibration factor used to convert the Valid ISIG value (Nano-Amps) into a blood glucose level (mg/dℓ or mmol/ℓ). In alternative embodiments, the units for the SR may vary depending on the type of signal available from the sensor (frequency, amplitude, phase shift, delta, current, voltage, impedance, capacitance, flux, and the like), the magnitude of the signals, the units to express the characteristic being monitored, or the like.

[0037] The user may obtain a blood glucose reference reading from a common glucose meter, or another blood glucose measuring device, and immediately enters the blood glucose reference reading into the glucose monitor 100. The blood glucose reference reading is assumed to be accurate and is used as a reference for calibration The glucose monitor 100, or a post processor 200, must temporally correlate the blood glucose reference reading with a Valid ISIG value to establish a paired calibration data point. Since the glucose level in the interstitial body fluid tends to lag behind the blood glucose level, the glucose monitor 100 or post processor 200 applies a delay time and then pairs the blood glucose reference reading with a Valid ISIG value as shown in FIG. 11. An empirically derived 10 minute delay may be used. Since Valid ISIG values are averaged and stored every 5 minutes, the glucose monitor 100 correlates the blood glucose reference reading with the third Valid ISIG stored in memory after the blood glucose reference reading is entered (resulting in an effective delay of 10 to 15 minutes). FIG. 11 illustrates an example, in which a blood glucose reference reading 600 of 90 mg/dℓ is entered into the glucose monitor 100 at 127 minutes. The next Valid ISIG value 602 is stored at 130 minutes. Given a 10 minute delay, the glucose reference reading 600 is paired with the Valid ISIG value 604 which is stored at 140 minutes with a value of 30 Nano-amps. Note that two numbers are needed to establish one paired calibration data point, a blood glucose reference reading and a Valid ISIG.

[0038] Other delay times may be used depending on the user's metabolism, the response time of the sensor, the delay time required for the glucose meter to calculate a reading and for the reading to be entered into the glucose monitor 100 the type of analyte being measured, the tissue that the sensor is placed into, environmental factors, whether the previous glucose Valid ISIG value (or the trend of the Valid ISIG values) was higher or lower than current Valid ISIG value, or the like. Once paired calibration data is available, the appropriate calibration process may be applied dependent on how many paired calibration data points are available since the last calibration, the total period of time that the glucose sensor 12 has been in use, and the number of times the glucose sensor 12 has been calibrated.

[0039] Blood glucose reference readings may be entered into the glucose monitor 100 periodically through out each day of use. Preferably calibration is conducted immediately after the initialization/stabilization of a glucose sensor 12 and once a day thereafter. However, calibration may be conducted more or less often depending on whether a glucose sensor 12 has been replaced, whether a calibration cancellation event has occurred, the stability of the glucose sensor 12 sensitivity over time, or the like.

[0040] In preferred arrangements blood glucose reference readings may be collected several times per day but a new calibration factor is calculated only once per day. Therefore, typically more than one paired calibration data point is collected between calibrations. In alternative embodiments, the glucose monitor is calibrated every time a new paired calibration data point is collected.

[0041] Preferred arrangements use a single-point calibration technique (shown in a block diagram of FIG. 13) to calculate the SR when only one paired calibration data point is available, such as immediately after initialization/stabilization. And a modified linear regression technique (shown in a block diagram in FIG. 15) is used when two or more paired calibration data points are available. Particular embodiments use a single-point calibration technique whether or not more than one paired calibration data point is available.

[0042] A single-point calibration equation is based on the assumption that the Valid ISIG will be 0 when the blood glucose is 0. As shown in FIG.12, a single paired calibration point 700 is used with the point (0,0) to establish a line 702. The slope of the line from the origin (0,0) and passing through the single paired calibration point 700 is the single-point sensitivity ratio (SPSR). The single-point calibration equation to calculate the calibration factor SPSR is as follows:

$$\text{SPSR} = \frac{\text{Blood Glucose Reference Reading}}{\text{Valid ISIG}}$$

Where SPSR = a Single-Point Sensitivity Ratio.

Abbott Ex. 1002 - 562/1438

Therefore, the calibrated blood glucose level is,

$$\text{Blood Glucose Level} = \text{Valid ISIG} * \text{SPSR}.$$

As an example, using the values of 20.1 Nano-Amps and 102 mg/dℓ from the paired calibration data point shown in FIG. 12, the calculation of SPSR is:

$$\text{SPSR} = 102 / 20.1 = 5.07 \text{ mg/d}\ell \text{ per Nano-amp.}$$

[0043] To continue the example, once the calibration is complete, given a glucose sensor reading of 15.0 Nano-Amps, the calculated blood glucose-level is:

$$\text{Blood Glucose Level} = 15.0 * 5.07 = 76.1 \text{ mg/d}\ell.$$

[0044] Additionally, particular arrangements use an offset value in a calibration equation to compensate for the observation that more sensitive glucose sensors 12 (i.e. glucose sensors 12 that generate higher ISIG values compared to other glucose sensors 12 at the same blood glucose level, which result in lower SR values) often have a less linear performance at very high blood glucose levels when compared to glucose sensors 12 with lower sensitivity (and therefore relatively higher SR values). If the SPSR for a particular glucose sensor 12, as calculated above, is less than a sensitivity threshold value, then a modified SPSR (MSPSR) is calculated using an offset value included in a modified single-point calibration equation. In preferred arrangements, the threshold value is 7. When the initial calculation of the SPSR (shown above) is less than 7, an offset value of 3 is used to calculate the MSPSR. If the initial calculation of SPSR yields a value of 7 or greater, then the offset value is 0. Thus, the calibration factor (MSPSR) is calculated using the offset value in the modified single-point calibration equation, as follows:

$$\text{MSPSR} = \frac{\text{Blood Glucose Reference Reading}}{\text{(Valid ISIG-offset)}}$$

Therefore, the calibrated blood glucose level is,

$$\text{Blood Glucose Level} = \text{(Valid ISIG-offset)} * \text{MSPSR}.$$

Continuing the above example since the SPSR is 5.07, which is less than 7, the sensitivity ratio is recalculated using the MSPSR equation as:

$$\text{MSPSR} = 102 / (20.1 - 3) = 5.96 \text{ mg/d}\ell \text{ per Nano-amp.}$$

And given a glucose sensor reading of 15.0 Nano-Amps after calibration the calculated blood glucose level is:

$$\text{Blood Glucose Level} = (15.0 - 3) * 5.96 = 71.5 \text{ mg/d}\ell.$$

Abbott Ex. 1002 - 563/1438

[0045] In another example, given a blood glucose reference reading of 95 from a typical blood glucose meter and a Valid ISIG value of 22.1, the resulting SPSR is 95/22.1 = 4.3. Since SR < 7, the offset = 3. Therefore, the MSPSR is 95 / [22.1 - 3] = 5.0. Note that when the SPSR is greater than or equal to 7 the offset value is 0 and therefore the MSPSR = SPSR.

[0046] In alternative arrangements, the offset value is eliminated from the equation for calculating the blood glucose value as follows:

$$\text{Blood Glucose Level} = \text{Valid ISIG} * \text{MSPSR}.$$

[0047] The threshold value of 7 and the associated offset of 3 have been empirically selected based on the characteristics observed from testing a particular type of glucose sensors 12, such as those described in U.S. Patent 5,391,250 entitled "Method of Fabricating Thin Film Sensors", and U.S. Patent Application Serial Number 60/121,655 filed on February 25, 1999, entitled "Glucose Sensor Set"; incorporated by reference herein. Other threshold values may be used in conjunction with other offset values to optimize the accuracy of the calculated MSPSR for various types of glucose sensors 12 and sensors used to detect other body characteristics. In fact, many threshold values may be used to select between many offset values. An example using two different threshold values (4 and 7) to select between three different offset values (5, 3 and 0) follows:

$$\begin{gathered}\text{If the SPSR} < 4, \text{ then use an offset value of 5, else} \\ \text{if } 4 <= \text{SPSR} < 7, \text{ then use an offset value of 3, else} \\ \text{if SPSR} >= 7 \text{ use an offset value of 0.}\end{gathered}$$

[0048] In preferred arrangements the MSPSR is compared to a valid sensitivity range to determine if the newly calculated MSPSR is reasonable. In order to identify potential system problems, a valid MSPSR range of 1.5 to 15 is employed. This range has been determined based upon valid glucose sensor sensitivity measurements made *in-vitro.* MSPSR values outside this range result in a calibration error alarm (CAL ERROR) to notify the user of a potential problem. Other valid sensitivity ranges may be applied depending on the types of sensors to be calibrated, the range of acceptable sensitivity levels for the various sensor types, the manufacturing consistency expected for the sensors, environmental conditions, how long the sensor has been in use, or the like.

[0049] Preferred arrangements augment the single-point calibration technique using a modified linear regression technique (shown in a block diagram in FIG. 15) when more than one paired calibration data point is available. As shown in FIG. 14, the paired calibration data points 800 are linearly regressed by a least squares method to calculate the best fit straight line 802 correlated with paired calibration data points 800. The slope of the line resulting from the linear regression is the linear regression sensitivity ratio (LRSR) used as the calibration factor to calibrate the glucose monitor 100. The linear regression calibration equation is as follows:

$$LRSR = \frac{\sum_{i=1}^{N}\left[X_i Y_i\right]}{\sum_{i=1}^{N}\left[X_i^2\right]}$$

Where X_i is the ith Valid ISIG value of paired calibration data points,
Y_i is the ith Blood Glucose Reference Reading of paired calibration data points and,
N is the total number of paired calibration data points used for calibration.
i is the identification number of a particular paired calibration data point.

[0050] Therefore, the calibrated blood glucose level is,

$$\text{Blood Glucose Level} = \text{Valid ISIG} * \text{LRSR}.$$

Abbott Ex. 1002 - 564/1438

Note that this linear regression uses a fixed intercept of zero (in other words, when the Valid ISIG is 0 the blood glucose value is 0) and therefore the linear regression method estimates only one regression parameter, the slope. In alternative embodiments, other linear regression methods may be used that estimate additional regression parameters such as an offset value.

[0051] Additionally, particular arrangements use an offset value in a modified linear regression calibration equation. The purpose of the offset value, as described above for the single-point calibration, is to compensate for the observation that more sensitive glucose sensors 12 often have a less linear performance at very high blood glucose levels. If the LRSR for a particular glucose sensor 12, as calculated in the linear regression calibration equation above, is less than a sensitivity threshold value, then a modified linear regression sensitivity ratio (MLRSR) is calculated using an offset value included in a modified linear regression calibration equation. In preferred arrangements the threshold value is 7. When the initial calculation of the LRSR is less than 7, an offset value of 3 is used to calculate the MLRSR. If the initial calculation of LRSR yields a value of 7 or greater, then the offset value is 0. Thus, the MLRSR is calculated using the offset value in the modified linear regression calibration equation, thus:

$$MLRSR = \frac{\sum_{i=1}^{N}\left[\left(X_i - offset\right)Y_i\right]}{\sum_{i=1}^{N}\left(X_i - offset\right)^2}$$

Therefore, the calibrated blood glucose level is,

$$\text{Blood Glucose Level} = (\text{Valid ISIG} - \text{offset}) * \text{MLRSR}.$$

[0052] Just as in the case of single-point calibration techniques described above, other threshold values may be used in conjunction with other offset values in the modified linear regression calibration equation to optimize the accuracy of the calculated MLRSR for various types of glucose sensors 12 and other characteristic sensors.

[0053] In preferred arrangements the MLRSR is compared to a valid sensitivity range to determine if the newly calculated MLRSR is reasonable. In order to identify potential system problems, a valid MLRSR range of 2.0 to 10.0 is employed. MLRSR values outside this range result in a calibration error alarm (CAL ERROR) to notify the user of a potential problem. As described above for the single-point calibration techniques, other valid sensitivity ranges may be applied.

[0054] In preferred arrangements the glucose monitor data is linearly regressed over a 24 hour period (or window), and new sensitivity ratios are used for each 24 hour time period. In alternative arrangements, the time period may be reduced to only a few hours or enlarged to cover the entire monitoring period with the glucose sensor (i.e., several days- or even weeks with implanted sensors). In further arrangements, the time window may be fixed at a predetermined size, such as 24 hours, 12 hours, 6 hours, or the like, and the window is moved along over the operational life of the sensor.

[0055] In particular arrangements, paired calibration data points from measurements taken before the last calibration may be used to calculate a new sensitivity ratio. For example, to calibrate the glucose monitor every 6 hours, a paired calibration data point is established every 6 hours. And the linear regression technique described above is executed using 4 paired calibration data points, the most recently acquired point and points from 6, 12 and 18 hours before. Alternatively, the number of paired calibration data points used in the calibration may be as few as one or as large as the total number of paired calibration data points collected since the glucose sensor was installed. In alternative embodiments, the number of paired calibration data points used in a calibration equation may grow or shrink during the life of the glucose sensor due to glucose sensor anomalies.

[0056] In still other arrangements the decay characteristics of the glucose sensor 12 over time may be factored into the equation to account for typical degradation characteristics of the glucose sensor 12 due to site characteristics, enzyme depletion, body movement, or the like. Considering these additional parameters in the calibration equation will more accurately tailor the calibration equation used by the glucose monitor 100 or post processor 200. In particular arrangements other parameters may be measured along with the blood glucose such as, temperature, pH, salinity, and the like. And these other parameters are used to calibrate the glucose sensor using non-linear techniques.

[0057] In a system embody is the present invention, real-time calibration adjustment can be performed to account for changes in the sensor sensitivity during the lifespan of the glucose sensor 12 and to detect when a sensor fails. FIG. 16 (in conjunction with FIGs. 17 and 18) describes the logic of a self-adjusting calibration technique to adjust the calibration

Abbott Ex. 1002 - 565/1438

formula or detect a sensor failure in accordance with an embodiment of the present invention.

[0058] At block 1000, the user obtains a blood glucose reference from a common glucose meter, or another blood glucose measuring device, and immediately enters the blood glucose reference reading into the glucose monitor 100. For every meter blood glucose entry, an instantaneous calibration check is performed and compared to an expected range of the value of the calibration check, as in block 1010. In preferred embodiments, the Calibration Factor current is calculated (i.e. CFc = Meter BG/current ISIG value) to determine if the CFc (Calibration Factor current) ratio is between 1.5 to 12 ("Criteria 1"), a minimum criteria for an accurate ISIG value. If data is outside this range, raising the likelihood of a sensor failure or incorrect determination/entry of the meter BG value, a Cal Error alarm is triggered at block 1030 and the Recalibration Variable (Recal), which is originally set at NOFAIL is changed to FAILC1. At this point, another blood glucose reference reading is requested and entered into the glucose monitor 100 to determine whether there was indeed a sensor failure or the Meter Blood Glucose value was incorrectly inputted. The previous MBGc that generated the error can be thrown out completely. If Criteria 1 is again not satisfied at block 1010, an end of the sensor life message will be generated at block 1040 since then the Recal variable would be recognized as FAILC1 at block 1020. However, if Criteria 1 is met at block 1010, then the logic proceeds to block 1200, where a check of the Recal Variable is made to see if Recal variable is not equal to FAILC2. The Recal variable is set to FAILC2 only if Criteria 2a is not met, which will be discussed below. Given that the Recal variable at this point would only be set a NOFAIL or FAILC1, the logic proceeds to block 1210.

[0059] At block 1210, a check is performed if the existing calibration slope estimation (Previous Estimated Slope or PES) is much different from the instantaneous calibration check (CFc) performed using the new meter blood glucose value. A significant difference can indicate a sensor failure. In the preferred embodiment, a difference between the previous estimated slope (PES) and the current calibration check (CFc) in terms of percentage (threshold 1) and mg/dl (threshold 2) is performed. Threshold 1 and 2 can be set depending on the particular sensor characteristics. An example of checking the changes between the PES and CFc is as follows:

$$\text{Abs (1-PES/CFc) * 100} = \text{Threshold 1}$$

and

$$\text{Abs (CFc-PES) * Isig} = \text{Threshold 2}$$

If the percentage and/or absolute difference exceeds threshold 1 and/or threshold 2 (collectively "Criteria 2a"), then depending on the Recal variable (at block 1220), either trigger an end of sensor message at block 1040 (if the Recal variable is equal to FAILC1 or FAILC2 at block 1220) or a Cal Error alarm will be generated at block 1230 (if the Recal variable is equal to NOFAIL at block 1220). If a Cal Error alarm is generated at block 1230, the Recal variable is set to FAILC2, the current meter blood glucose reading will be stored as MBGp (Meter Blood Glucose previous), and another blood glucose reference is requested and entered into the glucose monitor 100 (as MBGc) at block 1000. By requesting a new meter blood glucose reading, a comparison can be made between the last meter blood glucose reading stored at block 1230 and the new meter blood glucose reading entered at block 1000 to determine whether there was a sensor failure. The logic follows the same paths as described above after block 1000 until the logic reaches block 1200. At block 1200, since Recal variable is now set to FAILC2 at block 1230, the difference between the previous calibration check (CFp), which generated the FAILC2 alert, and the current calibration check (CFc) is performed at block 1300. In preferred embodiments, the difference between the previous calibration check and the current calibration check in terms of percentage (threshold 1) and mg/dl (threshold 2) is performed. In addition, a check is performed on whether there has been a directional change between the CFp and CFc (collectively "criteria 2b"). An example of criteria 2b is as follows:

$$\text{Abs (1-CFp/CFc) * 100} = \text{Threshold 1}$$

and

$$\text{Abs (CFc-CFp) * Isig} = \text{Threshold 2}$$

and

Abbott Ex. 1002 - 566/1438

$$(CFp\text{-}PES) * (CFc\text{-}CFp) > 0$$

If the percentage and absolute difference exceeds threshold 1 and threshold 2, and there is no directional change in the slope with the second blood glucose meter reading, then an end of sensor message will be triggered at block 1040. If criteria 2b is met, then the logic proceeds to block 1310. At block 1310, the logic then determines whether the difference between the previous value and the current value was due to a change in sensitivity of the sensor or whether the reading is merely noise. In the preferred embodiment, the determination of change in sensitivity versus noise is made by using Criteria 3b. Criteria 3b compares the difference between (the previous estimated slope (PES) and the current calibration check (CFc)) and (the previous calibration check (CFp) versus the current calibration check (CFc)) at block 1420. For example:

$$Abs\ (PES\text{-}CFc) < Abs\ (CFp\text{-}CFc)$$

As illustrated in FIG. 17a, if the difference between the estimated slope (PES) and the current calibration check (CFc) is less than the difference between the previous calibration check (CFp) and the current calibration check (CFc), criteria 3b will be met, indicating that the previous CFp is an outlier reading (i.e. an anomaly). Then, the MBGp (Meter Blood Glucose previous) is removed at block 1320 and only the MBGc paired with a valid ISIG is used in the slope calculation, which is resumed at block 1430 and applied in interpreting the sensor readings at block 1130.

[0060] As illustrated in FIG. 17b, if criteria 3b shows that difference between the estimated slope (PES) and the current calibration check (CFc) is greater than the difference between the previous calibration check (CFp) and the current calibration check (CFc), criteria 3b would not be met, indicating a change in sensor sensitivity. The slope calculation is then fine-tuned by creating a new (artificial) meter blood glucose value (MBGN) with a paired ISIG according to the last slope (Seeding) at block 1330. Using the new paired MBG (MBGN) with the paired MBGp and MBGc, the slope calculation is restarted (or reset) at block 1340, as seen in FIG. 17b. The sensor calculation is then performed using the new slope calculation at block 1130. By resetting the slope calculation, the slope calculation can thus be modified automatically to account for changes in sensor sensitivity.

[0061] Continuing the logic from block 1210, if the percentage and/or absolute difference between the PES and CFc is within threshold 1 and/or threshold 2 at block 1210, indicating a valid calibration, the Recal variable is again checked at block 1400. If the Recal variable is equal to FAILC1 (indicating that the meter BG was checked twice), any fine-tuning determination is skipped and the MBGc paired with a valid ISIG is used to update the slope calculation at block 1430 and applied in interpreting the sensor readings at block 1130. If the Recal Variable is not equal to FAILC1, then the logic will decide whether fine-tuning the slope calculation is needed at blocks 1410 and 1420. In the preferred embodiments, the decision to fine-tune is first made by comparing the percentage and/or absolute difference between the PES and CFc (as done in block 1210) with a threshold 3 and/or a threshold 4 ("Criteria 4") at block 1410. For example:

$$Abs\ (1\text{-}PES/CFc) * 100 < Threshold\ 3$$

and

$$Abs\ (CFc\text{-}PES) * ISIG < Threshold\ 4$$

Again, threshold 3 and 4 can be determined based on the particular sensor characteristics. If the percentage and/or absolute difference between the PES and CFc is less than threshold 3 and/or threshold 4 at block 1410 (i.e. Criteria 4 met), then the slope calculation can simply be updated with the new MBGc and paired ISIG value at block 1430 and applied in interpreting the sensor readings at block 1130.

[0062] On the other hand, if the Criteria 4 is not-met-at-block 1410, the logic then determines at block 1420 whether the difference between the expected value and the current value was due to a change in sensitivity of the sensor or whether the reading is merely noise. In the preferred embodiment, the determination of change in sensitivity versus noise is made by using Criteria 3a. Criteria 3a compares the difference between (the previous estimated slope (PES) and the previous calibration check (CFp)) and (the current calibration check (CFc) versus the previous calibration check (CFp)) at block 1420. For example:

Abbott Ex. 1002 - 567/1438

Abs (PES-CFp) < Abs (CFc-CFp)

As seen in FIG. 18a, if the difference between the estimated slope (PES) and the previous calibration check (CFp) is less than the difference between the current calibration check (CFc) and the previous calibration check (CFp), criteria 3a will be met, indicating that the error between the predicted value and the actual value for the CFc was due to noise in previous calibrations or beginning of a change in sensor sensitivity which will be picked up at the next calibration performance. The slope calculation is then simply updated with the new paired blood glucose entry (MBGc) at block 1430 and applied in interpreting the sensor readings at block 1130.

[0063] As seen in FIG. 18b, if criteria 3a shows that difference between the estimated slope (PES) and the previous valid calibration check is greater than the difference between the previous valid calibration check (CFp) and the current calibration check (CFc), criteria 3b would not be met, indicating a change in the sensor sensitivity and fine tuning is performed. Typically, fine tuning is performed when two MBG entry in succession indicate a change in slope. The slope calculation is fine-tuned by creating a new (artificial) meter blood glucose value (MBGN) with a paired ISIG according to the last slope (Seeding) at block 1330. Using the new paired MBG (MBGN) with the paired MBGp and MBGc, the slope calculation is restarted (or reset) at block 1340, as seen in FIG. 18b. The sensor calculation is then performed using the new slope calculation at block 1130. Again, by resetting the slope calculation, the slope calculation can thus be modified automatically to account for changes in sensor sensitivity.

Alternative Calibration Techniques

[0064] Although the above description described the primary calibration techniques in the preferred embodiments, many modifications can be made to the above described calibration techniques. For example, in alternative arrangements the calibration factor may be calculated by first using a single-point technique to calculate the MSPSR for each paired calibration data point and then averaging them together, either unweighted or weighted by temporal order of by elapsed time. In other alternative arrangements other straight line curve fitting techniques may be used to calculate a slope to be used as the SR. In additional alternative embodiments, other non-regressive curve fitting techniques may be used to generate equations that express the blood glucose level relative to the Valid ISIG. The equations may be polynomial, parabolic, hyperbolic, asymptotic, logarithmic, exponential, Gaussian or the like. In these embodiments, the SR is not a single value (such as a slope) but rather an equation representing a curve that is used to convert the Valid ISIG from the glucose sensor 12 to a blood glucose value in the glucose monitor 100 or a post processor 200. In addition, in using a more robust formula for approximating the slope, the different ISIG can be given different weights, as to weigh the more recent ISIGs more than the older ISIGs. For example where there are contiguous 8 ISIGs (i.e. n=8) are available:

$$\text{Filtered ISIG}_{(i)} = \frac{\sum_{i=i-7}^{i} W_i * RawISIGi}{\sum_{i=i-7}^{i} W_i}$$

where Weights (i)=W=[0.9231 0.7261 0.4868 0.2780 0.1353 0.0561 0.0198 0.0060]

When contiguous 8 ISIGs are not available (n<8) (i.e. after initialization or after triple skips in transmission, the weighting formula would be as follows:

$$\text{Filtered ISIG}_{(i)} = \frac{\sum_{i=i-(n-1)}^{i} W_i * RawISIGi}{\sum_{i=i-(n-1)}^{i} W_i},$$

where n = number of contiguous ISIGs.

[0065] Once all paired meter BGs/ISIGs (Pairing weights) have been weight distributed, the modified regression

Abbott Ex. 1002 - 568/1438

equation shall generate the slope. In a preferred alternative embodiment, a Gaussian function $\frac{1}{\sqrt{2\pi}} e^{\frac{-x^2}{2\sigma^2}}$ is used to curve fit the sensor data, including the weighting functions, the Gaussian Slope is calculated using a modified regression model such as:

$$\text{Gaussian\_slope} = \frac{\sum PW_i \times (Filtered\_Isig_i) \times MBG_i}{\sum PW_i \times (Filtered\_Isig_i)^2}$$

where i = number of pairs in Gaussian buffer and $PW_i = e^{\frac{-(Ti-Tc)^2}{2\sigma^2}}$

where Tc is the current time, Ti is Paired MBG/Filiered ISIG Times and σ = 15 hours (or 180 records, which is the width of the Gaussian profile).

[0066] As discussed, preferred arrangements utilize a least squares linear regression equation to calibrate the glucose monitor 100 or post-processor 200 to analyze the sensor data. However, alternative arrangements, may utilize a multiple' component linear regression, or equations with more variables than just the paired calibration data points, to account for additional calibration effecting parameters, such as environment, the individual user's characteristics, sensor lifetime, manufacturing characteristics (such as lot characteristics), deoxidization, enzyme concentration fluctuation or degradation, power supply variations, or the like: Still other alternative embodiments may utilize singular and multiple, non-linear regression techniques.

[0067] In preferred arrangements after the first calibration is performed on a particular glucose sensor 12, subsequent calibrations employ a weighted average using a sensitivity ratio (SPSR, MSPSR, LRSR, or MLRSR) calculated from data collected since the last calibration, and previous sensitivity ratios calculated for previous calibrations. So the initial sensitivity ratio (SR1) is calculated immediately after initialization/stabilization using a paired calibration data point and is used by the glucose monitor 100 or the post processor 200 until the second sensitivity ratio (SR2) is calculated. The second sensitivity ratio (SR2) is an average of SR1 and the sensitivity ratio as calculated using the paired calibration data points since the initial calibration (SRdayl). The equation is as follows:

$$\mathbf{SR2 = \frac{(SR1 + SRday1)}{2}}$$

The third sensitivity ratio (SR3) is an average of SR2 and the sensitivity ratio as calculated using the paired calibration data points since the second calibration (SRday2). The equation is as follows:

$$\mathbf{SR3 = \frac{(SR2 + SRday2)}{2}}$$

The sensitivity ratios for successive days use the same format, which is expressed below in generic terms:

$$SR_n = \frac{\left(SR_{(n-1)} + SRday_{(n-1)}\right)}{2}$$

Where SR_n is the new sensitivity ratio calculated at the beginning of time period, *n*, using data from time period (*n*-1), to be used by a real time glucose monitor 100, to convert Valid ISIGs to blood glucose readings throughout time period, *n*. $SR_{(n-1)}$ is the previous sensitivity ratio calculated at the beginning of time period, *n-1*, using data from time period (*n*-2). $SRday_{(n-1)}$ is the sensitivity ratio calculated using paired calibration data points collected since the last calibration.

[0068] Alternatively, the previous sensitivity ratios may be ignored and the SR is calculated using only the paired calibration data points since the last calibration. Another alternative is to equally average all previous SRs with the latest SR calculated using only the paired calibration data points since the last calibration. In alternative embodiments, the paired calibration data points are used to establish an equation for a curve representing SR over time. The curve is then

Abbott Ex. 1002 - 569/1438

used to extrapolate SR to be used until the next paired calibration data point is entered.

[0069] In arrangements that use a post processor 200 to evaluate the sensitivity that use a post processor 200 to evaluate the sensitivity ratio, the sensitivity ratio is calculated using paired calibration data points over a period of time since the last calibration and is not averaged with previous SRs. The sensitivity ratio for a period of time can then be applied to the same period of time over which the paired calibration data points were collected. This is more accurate than the real-time case described above for the glucose monitor 100 because, in the real-time case, sensitivity ratios from a previous time period must be used to calculate the blood glucose level in the present time period. If the sensitivity ratio has changed over time, the calculation of blood glucose using an old sensitivity ratio introduces an error.

[0070] In particular arrangements, once calibration is complete, Valid ISIG values are converted to blood glucose readings based on a particular version of the sensitivity ratio, and the resulting blood glucose readings are compared to an out-of-range limit. If the resulting calculated blood glucose level is greater than a maximum out-of-range limit of 200 mg/dℓ (or equivalently 3600 mmol/ℓ), the out-of-range alarm is activated. This is a calibration cancellation event, therefore, ISIG values are no longer valid once this alarm is activated. The blood glucose readings are either not calculated, or at least not considered reliable, until the glucose monitor 100 or post processor 200 is re-calibrated. The user is notified of the alarm and that re-calibration is needed.

[0071] In alternative arrangements higher or lower maximum out-of-range limits may be used depending on the sensor characteristics, the characteristic being measured, the user's body characteristics, and the like. In particular embodiments, a minimum out-of-range limit may be used or both a maximum and a minimum out-of-range limits may be used. In other particular arrangements, the out-of-range limits do not cause the blood glucose readings to become invalid and/or re-calibration is not required; however, an alarm could still be provided. In additional particular arrangements, more than one ISIG value must exceed an out-of-range limit before an alarm is activated of a calibration cancellation event is triggered. The ISIG values that are out-of-range are not used to display a blood glucose value.

[0072] In alternative arrangements, calibration is conducted by injecting a fluid containing a known value of glucose into the site around the glucose sensor set 10, and then one or more glucose sensor readings are sent to the glucose monitor 100. The readings are processed (filtered, smoothed, clipped, averaged, and the like) and used along with the known glucose value to calculate the SR for the glucose sensor 12. Particular alternative arrangements, use a glucose sensor set of the type described in U.S. Patent 5,951,521 entitled "A Subcutaneous Implantable Sensor Set Having the Capability To Remove Or Deliver Fluids To An Insertion Site".

[0073] In other alternative embodiments, the glucose sensor 12 is supplied with a vessel containing a solution with a known glucose concentration to be used as a reference, and the glucose sensor 12 is immersed into the reference glucose solution during calibration. The glucose sensor 12 may be shipped in the reference glucose solution. As described above, the glucose sensor readings are used to calculate a sensitivity ratio given the known glucose concentration of the solution.

[0074] In another alternative arrangement, the glucose sensors 12 are calibrated during the manufacturing process. Sensors from the same manufacturing lot, that have similar properties, are calibrated using a sampling of glucose sensors 12 from the population and a solution with a known glucose concentration. The sensitivity ratio is provided with the glucose sensor 12 and is entered into the glucose monitor 100 or the post processor 200 by the user or another individual.

[0075] In addition, although he preferred logic of FIG. 18 described specific operations occurring in a particular order, in alternative embodiments, certain of the logic operations may be performed in a different order, modified, or removed and still implement the preferred arrangements. Moreover, steps may be added to the above described logic and still conform to the preferred embodiments. For example, although in the preferred embodiment of FIG. 16, the Recal variable is never reset to no fail, potentially, an additional step of can be added to reset the Recal variable to no fail if no cal error alarms are triggered after a predetermined number of calibrations.

[0076] Therefore, 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 invention as defined by the appended claims.

[0077] 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.

Claims

1. A method of calibrating sensor data collected from a sensor (12), wherein a calibration formula based on past calibrations is used to interpret the sensor data, the method comprising the steps of:

   obtaining a calibration reference value for the sensor;
   calculating a current calibration factor based on the calibration reference value and a current sensor data point;

Abbott Ex. 1002 - 570/1438

identifying either a possible error or change in sensitivity in the sensor (12) from the current calibration factor; and confirming a sensor failure or recognizing a change in sensor sensitivity **characterized in that** said confirming comprises:

comparing the current calibration factor with an estimated value for the current calibration factor to determine whether the current calibration factor was unexpected, wherein the estimated value for the current calibration factor is determined from the calibration formula and a past calibration factor; and
confirming the sensor failure when at least two unexpected calibration factors are received in succession without supporting each other.

2. The method of claim 1, further comprising:

updating the calibration formula with the calibration reference value if the sensor failure is not confirmed and no change in sensor sensitivity is recognized; and
interpreting the collected sensor data using the updated calibration formula.

3. The method of claim 1, wherein the step of confirming a sensor failure or recognizing a change in sensor sensitivity further comprises:

recognizing a change in sensor sensitivity when an unexpected past calibration factor is supported by a subsequent current calibration factor in succession;
restarting the calibration formula calculation when a change in sensor sensitivity is recognized.

4. The method of claim 3, further comprising:

interpreting the collected sensor data using the restarted calibration formula.

5. The method of claim 3, wherein the step of restarting the calibration formula calculation further comprises:

creating an artificial calibration reference value; and
formulating the calibration formula using the artificial calibration reference value, a past calibration reference value and a current calibration reference value.

6. The method of claim 2, wherein the calibration formula is a modified regression method.

7. The method of claim 6, wherein the modified regression method is Gaussian regression method.

8. The method of claim 6, wherein the calibration formula weights past calibrations based on how recent the calibration was performed.

9. The method of claim 2, wherein the calibration is performed while obtaining the sensor data.

10. The method of claim 1, wherein the sensor is a glucose sensor.

11. The method of claim 1, wherein the current sensor data point is obtained by the steps of:

sampling characteristic sensor data at a predetermined rate from a sensor over time;
deriving at least one current sensor data point from the sampled characteristic sensor data at a predetermined memory storage rate.

12. The method of claim 1, wherein the current sensor data point is obtained by the steps of:

sampling characteristic sensor data;
deriving interval values by applying dipping limits and averaging the post-clipped sampled characteristic sensor data over a predetermined interval rate; and
deriving at least one current sensor data point by averaging the derived interval values at a predetermined memory storage rate.

Abbott Ex. 1002 - 571/1438

13. An apparatus for calibrating sensor data collected from a sensor (12), wherein a calibration formula based on past calibrations is used to interpret the sensor data, the apparatus comprising:

means for obtaining a calibration reference value for the sensor (12);
means for calculating a current calibration factor based on the calibration reference value and a current sensor data point;
means for identifying either a possible error or change in sensitivity in the sensor (12) from the current calibration factor; and
means for confirming a sensor failure or recognizing a change in sensor sensitivity

characterized in that said means for confirming a sensor failure or recognizing a change in sensor sensitivity has a means for comparing the current calibration factor with an estimated value for the current calibration factor to determine whether the current calibration factor was unexpected, wherein the estimated value for the current calibration factor is determined from the calibration formula and a past calibration factor; and
means for confirming the sensor failure when at least two unexpected calibration factors are received in succession without supporting each other.

14. The apparatus of claim 13, further comprising:

means for updating the calibration formula with the calibration reference value if the sensor failure is not confirmed and no change in sensor sensitivity is recognized; and
means for interpreting the collected sensor data using the updated calibration formula.

15. The apparatus of claim 13, wherein the means for confirming a sensor failure or recognizing a change in sensor sensitivity further comprises:

means for recognizing a change in sensor sensitivity when an unexpected past calibration factor is supported by a subsequent current calibration factor in succession;
means for restarting the calibration formula calculation when a change in sensor sensitivity is recognized.

16. The apparatus of claim 15, further comprising:

means for interpreting the collected sensor data using the restarted calibration formula.

17. The apparatus of claim 15, wherein the means for restarting the calibration formula calculation further comprises:

means for creating an artificial calibration reference value; and
means for formulating the calibration formula using the artificial calibration reference value, a past calibration reference value and a current calibration reference value.

18. The apparatus of claim 14, wherein the calibration formula is a modified regression method.

19. The apparatus of claim 18, wherein the modified regression method is Gaussian regression method.

20. The apparatus of claim 18, wherein the calibration formula weights past calibrations based on how recent the calibration was performed.

21. The apparatus of claim 14, wherein the calibration is performed while obtaining the sensor data.

22. The apparatus of claim 13, wherein the sensor is a glucose sensor.

23. The apparatus of claim 13, wherein the current sensor data point is obtained by:

means for sampling characteristic sensor data at a predetermined rate from a sensor over time;
means for deriving at least one current sensor data point from the sampled characteristic sensor data at a predetermined memory storage rate.

24. The apparatus of claim 14, wherein the current sensor data point is obtained by:

Abbott Ex. 1002 - 572/1438

means for sampling characteristic sensor data;
means for deriving interval values by applying clipping limits and averaging the post-clipped sampled characteristic sensor data over a predetermined interval rate; and
means for deriving at least one current sensor data point by averaging the derived interval values at a predetermined memory storage rate.

25. An article of manufacture containing code for calibrating sensor data collected from a sensor, wherein a calibration formula based on past calibrations is used to interpret the sensor data, comprising a computer usable media including at least one embedded computer programme that is capable of causing at least one computer to perform the method according to any of claims 1 to 12.

Patentansprüche

1. Verfahren zum Kalibrieren von aus einem Sensor (12) aufgenommenen Sensordaten, bei dem zur Interpretation der Sensordaten eine Kalibrierformel angewandt wird, die auf früheren Kalibrierungen basiert, und das folgende Schritte aufweist:

Aufnehmen eines Kalibrier-Bezugswertes für den Sensor;
Berechnen eines aktuellen Kalibrierfaktors auf Grund des Kalibrier-Bezugswertes und eines aktuellen Sensordatenpunkts;
Identifizieren entweder eines möglichen Fehlers oder einer Änderung der Empfindlichkeit des Sensors (12) aus dem aktuellen Kalibrierfaktor; und
Bestätigen eines Sensorausfalls oder Erkennen einer Änderung der Sensorempfindlichkeit;

dadurch gekennzeichnet, dass der Bestätigungsschritt aufweist:

Vergleichen der aktuellen Kalibrierfaktors mit einem Schätzwert für denselben, um zu bestimmen, ob der aktuelle Kalibrierfaktor unerwartet war, wobei der Schätzwert für den aktuellen Kalibrierfaktor mit der Kalibrierformel und einem früheren Kalibrierfaktor bestimmt wird; und
Bestätigen des Sensorausfalls, wenn mindestens zwei unerwartete Kalibrierfaktoren in Folge ohne gegenseitige Stützung empfangen werden.

2. Verfahren nach Anspruch 1 weiterhin mit folgenden Schritten:

Aktualisieren der Kalibrierformel mit dem Kalibrier-Bezugswert, falls der Sensorausfall nicht bestätigt und keine Änderung der Sensorempfindlichkeit erkannt wird; und
Interpretieren der aufgenommenen Sensordaten unter Verwendung der aktualisierten Kalibrierformel.

3. Verfahren nach Anspruch 1, bei dem der Schritt des Bestätigens eines Sensorausfalls oder des Erkennens einer Änderung der Sensorempfindlichkeit weiterhin aufweist:

Erkennen einer Änderung der Sensorempfindlichkeit, wenn ein unerwarteter früherer von einem nachfolgenden aktuellen Kalibrierfaktor erneut gestützt wird; und
Neustarten der Kalibrierformelberechnung, wenn eine Änderung der Sensorempfindlichkeit erkannt wird.

4. Verfahren nach Anspruch 3, das weiterhin aufweist:

Interpretieren der aufgenommenen Sensordaten unter Verwendung der neu gestarteten Kalibrierformel.

5. Verfahren nach Anspruch 3, bei dem das Neustarten der Kalibrierformelberechnung weiterhin aufweist:

Erzeugen eines künstlichen Kalibrierbezugswerts; und
Formulieren der Kalibrierformel unter Verwendung des künstlichen, eines früheren und eines aktuellen Kalibrierbezugswerts.

6. Verfahren nach Anspruch 2, bei dem die Kalibrierformel ein modifiziertes Regressionsverfahren ist.

Abbott Ex. 1002 - 573/1438

7. Verfahren nach Anspruch 6, bei dem das modifizierte Regressionsverfahren ein Gauss'sches Regressionsverfahren ist.

8. Verfahren nach Anspruch 6, bei dem die Kalibrierformel frühere Kalibrierungen danach gewichtet, wie aktuell die Kalibrierung durchgeführt wurde.

9. Verfahren nach Anspruch 2, bei dem die Kalibrierung während der Aufnahme der Sensordaten durchgeführt wird.

10. Verfahren nach Anspruch 1, bei dem der Sensor ein Glucosesensor ist.

11. Verfahren nach Anspruch 1, bei dem man den aktuellen Sensordatenpunkt mit folgenden Schritten erhält:

probenmäßiges Erfassen charakteristischer Sensordaten mit vorbestimmter Häufigkeit an einem Sensor;
Ableiten mindestens eines aktuellen Sensordatenpunkts aus den erfassten Sensordaten mit einer vorbestimmten Speicherhäufigkeit.

12. Verfahren nach Anspruch 1, bei dem der aktuelle Sensordatenpunkt mit folgenden Schritten erhalten wird:

probenmäßiges Erfassen charakteristische Sensordaten;
Ableiten von Intervallwerten, indem man Klippwerte anwendet und die erfassten charakteristischen Sensordaten nach dem Klippen über eine vorbestimmte Intervallhäufigkeit mittelt; und
Ableiten mindestens eines aktuellen Sensordatenpunkts durch Mitteln der abgeleiteten Intervallwerte mit einer vorbestimmten Speicherhäufigkeit.

13. Vorrichtung zum Kalibrieren von an einem Sensor (12) aufgenommenen Sensordaten, bei der eine Kalibrierformel basierend auf früheren Kalibrierungen zur Interpretation der Sensordaten dient und die aufweist:

eine Einrichtung, mit der ein Kalibrierbezugswert für den Sensor (12) bereit stellbar ist;
eine Einrichtung, mit der ein aktueller Kalibrierfaktor basierend auf dem Kalibrierbezugswert und einem aktuellen Sensordatenpunkt berechenbar ist;
eine Einrichtung, mit der aus dem aktuellen Kalibrierfaktor entweder ein möglicher Fehler oder eine Änderung der Empfindlichkeit des Sensors (12) identifizierbar ist; und
eine Einrichtung, mit der ein Sensorausfall bestätigbar oder eine Änderung der Sensorempfindlichkeit erkennbar ist;

dadurch gekennzeichnet, dass die Einrichtung, mit der ein Sensorausfall bestätigbar oder eine Änderung der Sensorempfindlichkeit erkennbar ist, Einrichtungen aufweist, mittels deren der aktuelle Kalibrierfaktor mit einem Schätzwert für denselben vergleichbar ist, um zu bestimmen, ob der aktuelle Kalibrierfaktor unerwartet war, wobei der Schätzwert für den aktuellen Kalibrierfaktor aus der Kalibrierformel und einem früheren Kalibrierfaktor bestimmt wird; und
eine Einrichtung vorgesehen ist, mit der der Sensorausfall bestätigbar ist, wenn mindestens zwei unerwartete Kalibrierfaktoren in Folge empfangen werden, die einander nicht stützen.

14. Vorrichtung nach Anspruch 13 weiterhin mit:

einer Einrichtung, mit der die Kalibrierformel mit dem Kalibrierbezugswert aktualisierbar ist, falls der Sensorausfall nicht bestätigt und keine Änderung der Sensorempfindlichkeit erkannt wird; und
einer Einrichtung, mit der die aufgenommenen Sensordaten unter Anwendung der aktualisierten Kalibrierformel interpretierbar sind.

15. Vorrichtung nach Anspruch 13, bei der die Einrichtung zum Bestätigen eines Sensorausfalls oder Erkennen einer Änderung der Sensorempfindlichkeit weiterhin aufweist:

eine Einrichtung, mit der eine Änderung der Sensorempfindlichkeit erkennbar ist, wenn ein unerwarteter früherer von einem nachfolgenden aktuellen Kalibrierfaktor in Folge gestützt wird; und
eine Einrichtung, mit der die Kalibrierformelberechnung neu startbar ist, wenn eine Änderung der Sensorempfindlichkeit erkannt wird.

Abbott Ex. 1002 - 574/1438

16. Vorrichtung nach Anspruch 15 weiterhin mit einer Einrichtung, mit der die aufgenommenen Sensordaten unter Anwendung der neugestarteten Kalibrierformel interpretierbar sind.

17. Vorrichtung nach Anspruch 15, bei der die Einrichtung zum Neustarten der Kalibrierformel weiterhin aufweist:

    eine Einrichtung, mit der ein künstlicher Kalibrierbezugswert generierbar ist; und
    eine Einrichtung, mit der die Kalibrierformel unter Anwendung des künstlichen Kalibrierbezugswertes, eines früheren und eines aktuellen Kalibrierbezugswertes formulierbar ist.

18. Vorrichtung nach Anspruch 14, bei der die Kalibrierformel ein modifiziertes Regressionsverfahren ist.

19. Vorrichtung nach Anspruch 18, bei der das modifizierte Regressionsverfahren ein Gauss'sches Regressionsverfahren ist.

20. Vorrichtung nach Anspruch 18, bei der die Kalibrierformel frühere Kalibrierungen danach gewichtet, wie aktuell die Kalibrierung durchgeführt wurde.

21. Vorrichtung nach Anspruch 14, bei der die Kalibrierung während des Aufnehmens der Sensordaten erfolgt.

22. Vorrichtung nach Anspruch 13, bei der der Sensor ein Glucosesensor ist.

23. Vorrichtung nach Anspruch 13, bei dem der aktuelle Sensordatenpunkt erhalten wird durch:

    eine Einrichtung, mit der charakteristische Sensordaten mit vorbestimmter Häufigkeit zeitlich verteilt probenmäßig erfassbar sind; und
    eine Einrichtung, mit der aus den probenmäßig erfassten charakteristischen Sensordaten mit vorbestimmter Speicherhäufigkeit mindestens ein aktueller Sensordatenunkt ableitbar ist.

24. Vorrichtung nach Anspruch 14, bei der der aktuelle Sensordatenpunkt erhalten wird durch:

    eine Einrichtung, mit der charakteristische Sensordaten probenmäßig erfassbar sind; und
    eine Einrichtung, mit der durch Anwenden von Klippgrenzen und durch Mitteln der erfassten und geklippten charakteristischen Sensordaten mindestens ein aktueller Sensordatenpunkt mit vorbestimmter Speicherhäufigkeit ableitbar ist.

25. Gefertigter Artikel, der Kode zum Kalibrieren von an einem Sensor aufgenommenen Sensordaten enthält, in dem zum Interpretieren der Sensordaten eine auf früheren Kalibrierungen basierende Kalibrierformel angewandt wird und der einen von einem Rechner nutzbaren Aufzeichnungsträger aufweist, der mindestens ein eingebettetes Computerprogramm enthält, das in der Lage ist, mindestens einen Rechner zur Ausführung des Verfahrens nach einem der Ansprüche 1 bis 12 zu veranlassen.

Revendications

1. Procédé de calibrage de données de capteur recueillies d'un capteur (12), dans lequel une formule de calibrage basée sur les calibrages passés est utilisée pour interpréter les données de capteur, le procédé comportant les étapes consistant à :

    obtenir une valeur de référence de calibrage pour le capteur ;
    calculer un facteur de calibrage actuel sur la base de la valeur de référence de calibrage et d'un point de données de calibrage actuel ;
    identifier une erreur possible ou un changement de sensibilité dans le capteur (12) à partir du facteur de calibrage actuel ; et
    confirmer une défaillance de capteur ou reconnaître un changement de sensibilité de capteur

    caractérisé en ce que ladite confirmation comporte les étapes consistant à :

    comparer le facteur de calibrage actuel avec une valeur estimée du facteur de calibrage actuel pour déterminer

Abbott Ex. 1002 - 575/1438

si le facteur de calibrage actuel est inattendu, dans lequel la valeur estimée pour le facteur de calibrage actuel est déterminée à partir de la formule de calibrage et d'un facteur de calibrage passé; et
confirmer la défaillance de capteur lorsque au moins deux facteurs de calibrage inattendus ont été reçus à la suite sans se conforter l'un l'autre.

2. Procédé selon la revendication 1, comportant en outre les étapes consistant à :

mettre à jour les formules de calibrage avec la valeur de référence de calibrage si la défaillance de capteur n'est pas confirmée et qu'aucun changement de sensibilité de capteur n'est reconnu ; et
interpréter les données de capteur recueillies en utilisant les formules de calibrage mises à jour.

3. Procédé selon la revendication 1, dans lequel l'étape de confirmation d'une défaillance de capteur ou de reconnaissance d'un changement de sensibilité de capteur comporte en outre les étapes consistant à :

reconnaître un changement de sensibilité de capteur lorsqu'un facteur de calibrage passé inattendu est conforté par un facteur de calibrage actuel ultérieur à la suite ;
redémarrer le calcul de formule de calibrage lorsqu'un changement de sensibilité de capteur est reconnu.

4. Procédé selon la revendication 3, comportant en outre l'étape consistant à :

interpréter les données de capteur recueillies en utilisant la formule de calibrage redémarrée.

5. Procédé selon la revendication 3, dans lequel l'étape de redémarrage de calcul de formule de calibrage comporte en outre les étapes consistant à :

créer une valeur de référence de calibrage artificielle ; et
formuler la formule de calibrage en utilisant la valeur de référence de calibrage artificielle, une valeur de référence de calibrage passée et une valeur de référence de calibrage actuelle.

6. Procédé selon la revendication 2, dans lequel la formule de calibrage est un procédé de régression modifié.

7. Procédé selon la revendication 6, dans lequel le procédé de régression modifié est le procédé de régression gaussienne.

8. Procédé selon la revendication 6, dans lequel la formule de calibrage pondère les calibrages passés sur la base de la proximité dans le temps de la réalisation du calibrage.

9. Procédé selon la revendication 2, dans lequel le calibrage est effectué tout en obtenant les données de capteur.

10. Procédé selon la revendication 1, dans lequel le capteur est un capteur de glucose.

11. Procédé selon la revendication 1, dans lequel le point de données de calibrage actuel est obtenu par les étapes consistant à :

échantillonner des données de capteur caractéristiques à une cadence prédéterminée provenant d'un capteur au cours du temps ; et
déduire au moins un point de données de capteur actuel à partir des données de capteur caractéristiques échantillonnées à une cadence de mémorisation prédéterminée.

12. Procédé selon la revendication 1, dans lequel le point de données de capteur actuel est obtenu par les étapes consistant à :

échantillonner des données de capteur caractéristiques ;
déduire des valeurs d'intervalle en appliquant des limites d'écrêtage et en effectuant la moyenne des données de capteur caractéristiques échantillonnées après écrêtage sur une cadence d'intervalle prédéterminée ; et
déduire au moins un point de données de capteur actuel en faisant la moyenne des valeurs d'intervalle déduites à une cadence de mémorisation prédéterminée.

Abbott Ex. 1002 - 576/1438

13. Appareil pour calibrer des données de capteur recueillies d'un capteur (12), dans lequel une formule de calibrage basée sur des calibrages passés est utilisée pour interpréter les données de capteur, le dispositif comportant :

des moyens pour obtenir une valeur de référence de calibrage pour le capteur (12) ;
des moyens pour calculer un facteur de calibrage actuel sur la base de la valeur de référence de calibrage et d'un point de données de calibrage actuel;
des moyens pour identifier une erreur possible ou un changement de sensibilité dans le capteur (12) à partir du facteur de calibrage actuel ; et
des moyens pour confirmer une défaillance de capteur ou reconnaître un changement de sensibilité de capteur

caractérisé en ce que lesdits moyens pour confirmer une défaillance de capteur ou reconnaître un changement de sensibilité de capteur ont des moyens pour comparer le facteur de calibrage actuel avec une valeur estimée du facteur de calibrage actuel pour déterminer si le facteur de calibrage actuel est inattendu, dans lequel la valeur estimée du facteur de calibrage actuel est déterminée à partir de la formule de calibrage et d'un facteur de calibrage passé ; et
des moyens pour confirmer la défaillance de capteur lorsqu'au moins deux facteurs de calibrage inattendus sont reçus à la suite sans se conforter l'un l'autre.

14. Appareil selon la revendication 13, comportant en outre :

des moyens pour mettre à jour la formule de calibrage avec la valeur de référence de calibrage si la défaillance de capteur n'est pas confirmée et qu'aucun changement de sensibilité de capteur n'est reconnu ; et
des moyens pour interpréter les données de capteur recueillies en utilisant la formule de calibrage mise à jour.

15. Appareil selon la revendication 13, dans lequel les moyens pour confirmer une défaillance de capteur ou reconnaître un changement de sensibilité de capteur comportent en outre :

des moyens pour reconnaître un changement de sensibilité de capteur lorsqu'un facteur de calibrage passé inattendu est conforté par un facteur de calibrage actuel ultérieur à la suite ;
des moyens pour redémarrer le calcul de formule de calibrage lorsqu'un changement de sensibilité de capteur est reconnu.

16. Appareil selon la revendication 15, comportant en outre :

des moyens pour interpréter les données de capteur recueillies en utilisant la formule de calibrage redémarrée.

17. Appareil selon la revendication 15, dans lequel les moyens pour redémarrer le calcul de formule de calibrage comportent en outre :

des moyens pour créer une valeur de référence de calibrage artificielle ; et
des moyens pour formuler la formule de calibrage en utilisant la valeur de référence de calibrage artificielle, une valeur de référence de calibrage passée et une valeur de référence de calibrage actuelle.

18. Appareil selon la revendication 14, dans lequel la formule de calibrage est un procédé de régression modifié.

19. Appareil selon la revendication 18, dans lequel le procédé de régression modifié est le procédé de régression gaussienne.

20. Appareil selon la revendication 18, dans lequel la formule de calibrage pondère des calibrages passés sur la base de la proximité dans le temps de la réalisation du calibrage.

21. Appareil selon la revendication 14, dans lequel le calibrage est effectué tout en obtenant les données de capteur.

22. Appareil selon la revendication 13, dans lequel le capteur est un capteur de glucose.

23. Appareil selon la revendication 13, dans lequel le point de données de capteur actuel est obtenu par :

des moyens pour échantillonner des données de capteur caractéristiques à une cadence prédéterminée à partir

Abbott Ex. 1002 - 577/1438

d'un capteur au cours du temps ; et
des moyens pour déduire au moins un point de données de capteur actuel des données de capteur caractéristiques échantillonnées à une cadence de mémorisation prédéterminée.

24. Appareil selon la revendication 14, dans lequel le point de données de capteur actuel est obtenu par :

des moyens pour échantillonner des données de capteur caractéristiques ;
des moyens pour déduire des valeurs d'intervalle en appliquant des limites d'écrêtage et en faisant la moyenne des données de capteur caractéristiques échantillonnées après écrêtage sur une cadence d'intervalle prédéterminée ; et
des moyens pour déduire au moins un point de données de capteur actuel en faisant la moyenne des valeurs d'intervalle déduites à une cadence de mémorisation prédéterminée.

25. Un article de manufacture contenant un code pour calibrer des données de capteur recueillies d'un capteur, dans lequel une formule de calibrage basée sur des calibrages passés est utilisée pour interpréter les données de capteur, comportant un support pouvant être utilisé par ordinateur incluant au moins un programme informatique intégré qui est capable de faire mettre en oeuvre le procédé selon l'une quelconque des revendications 1 à 12 par au moins un ordinateur.

Abbott Ex. 1002 - 578/1438

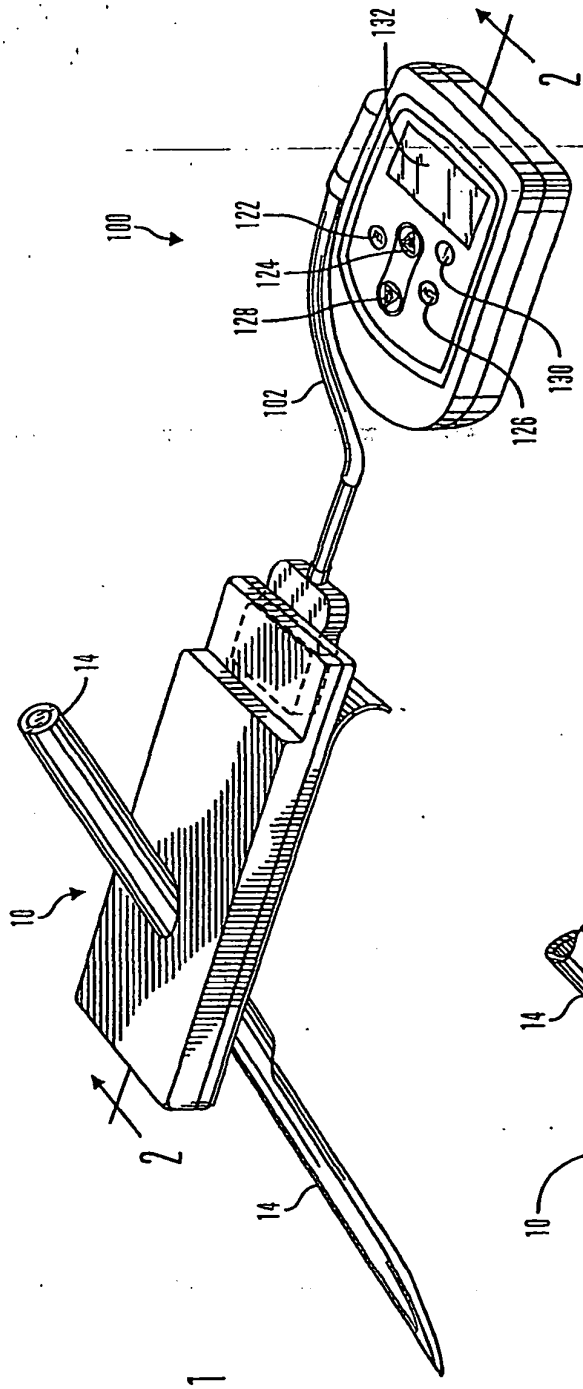


FIG. 1

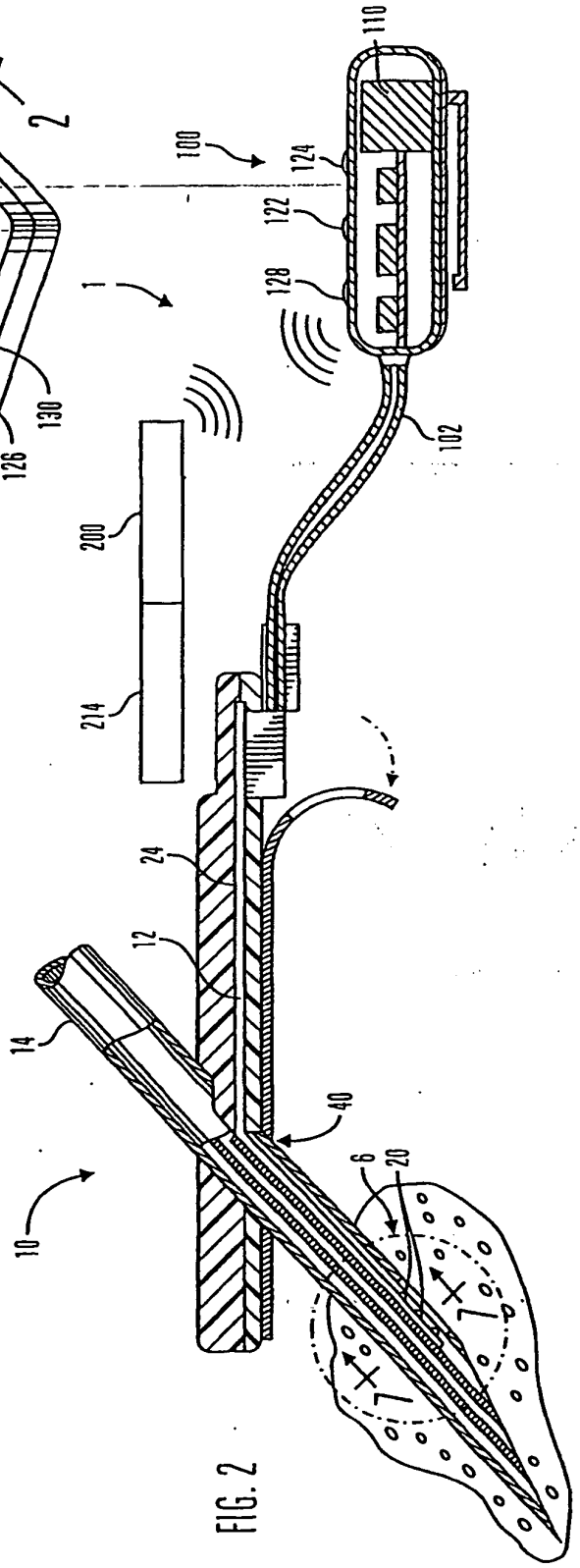


FIG. 2

Abbott Ex. 1002 - 579/1438

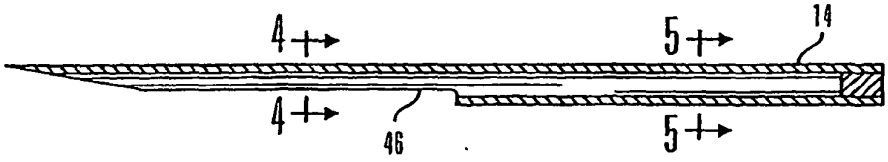


FIG. 3

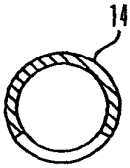


FIG. 4

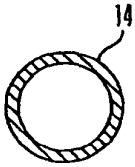


FIG. 5

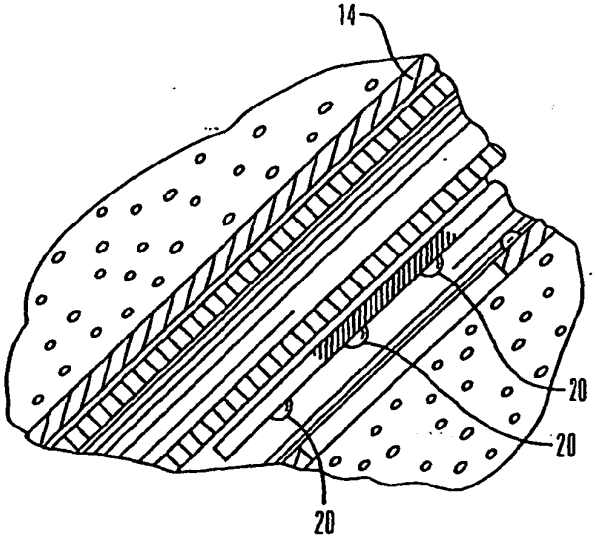


FIG. 6

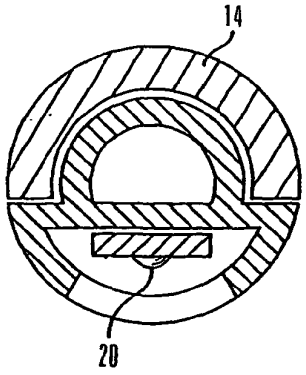


FIG. 7

Abbott Ex. 1002 - 580/1438

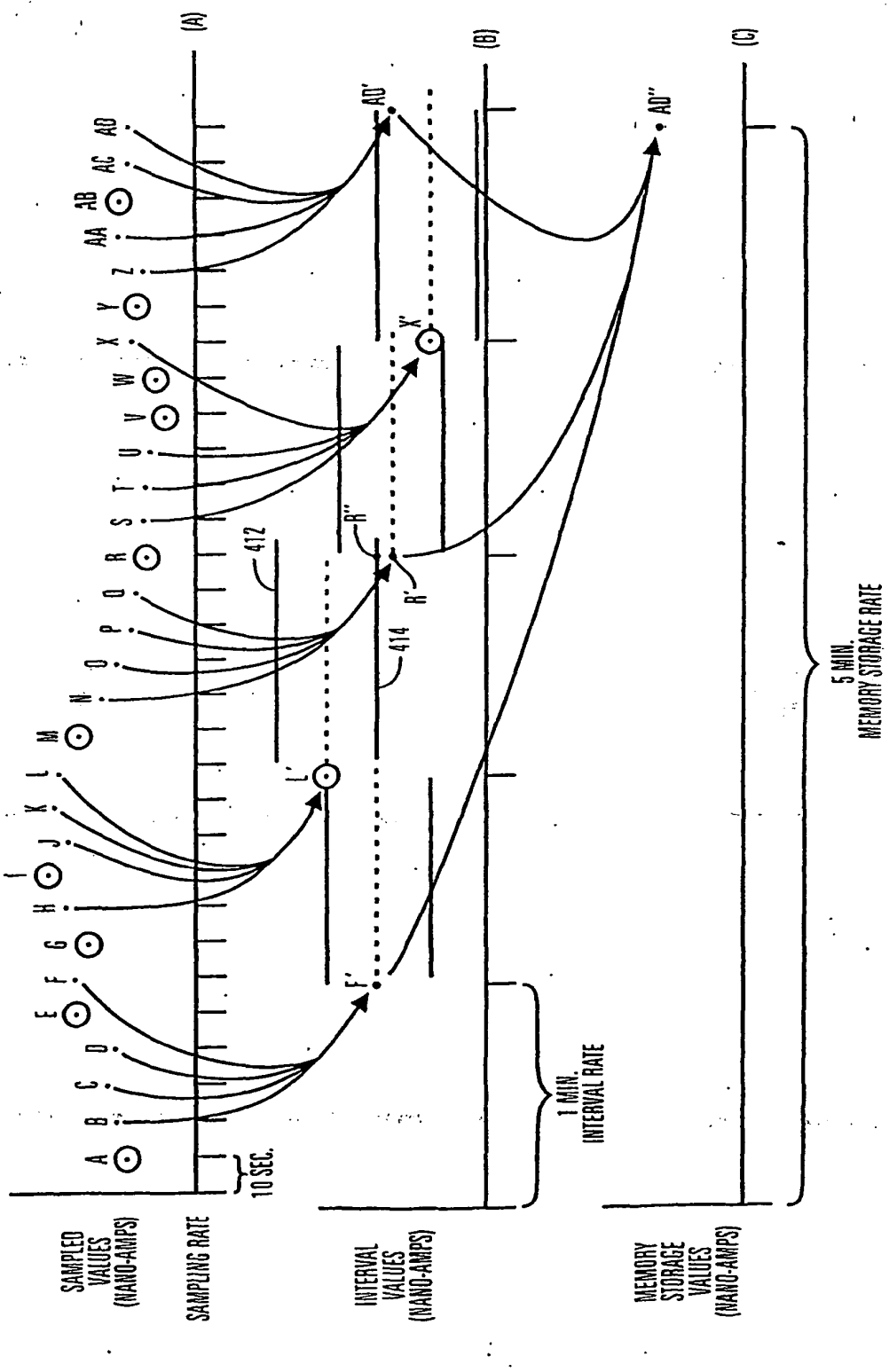


FIG. 8

Abbott Ex. 1002 - 581/1438

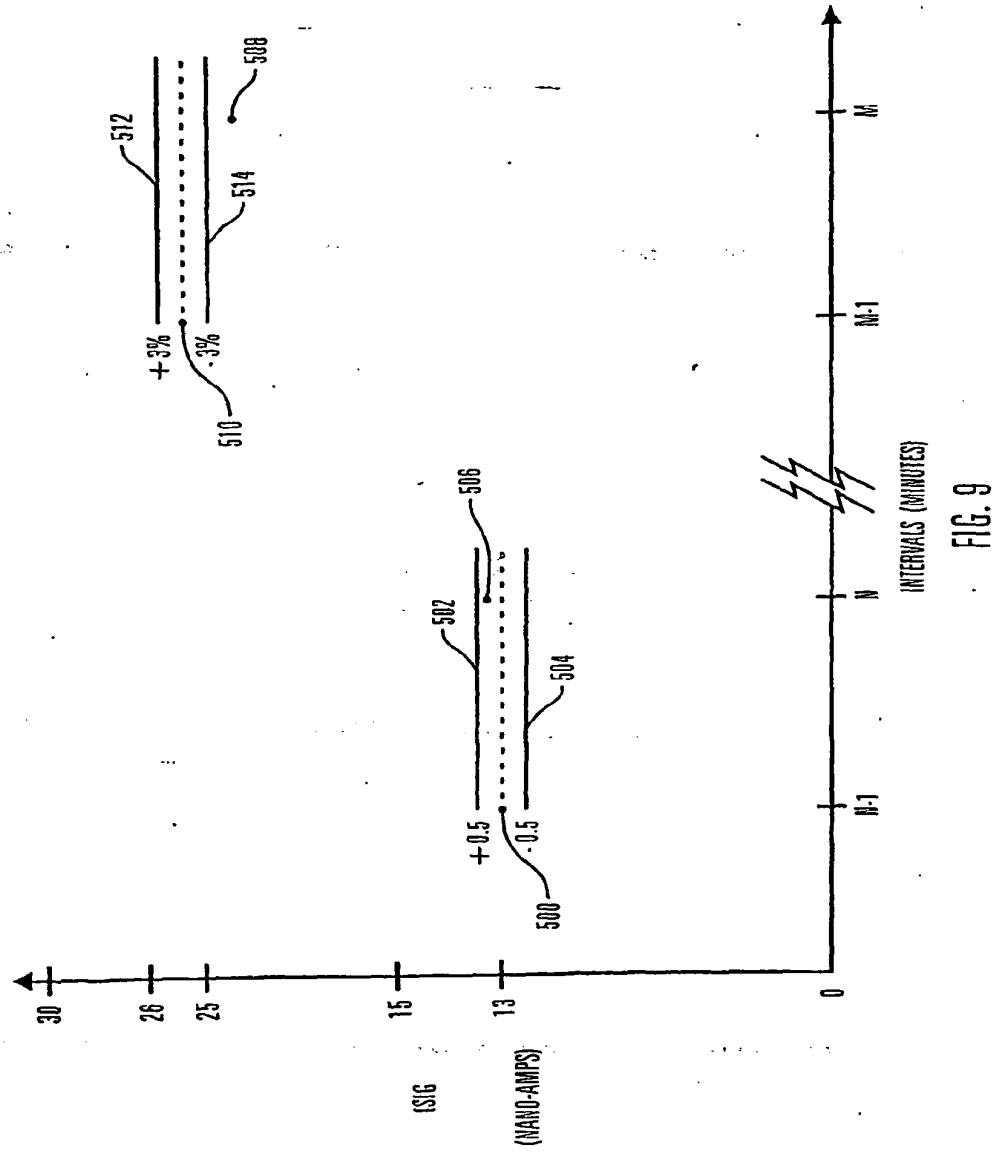


FIG. 9

Abbott Ex. 1002 - 582/1438

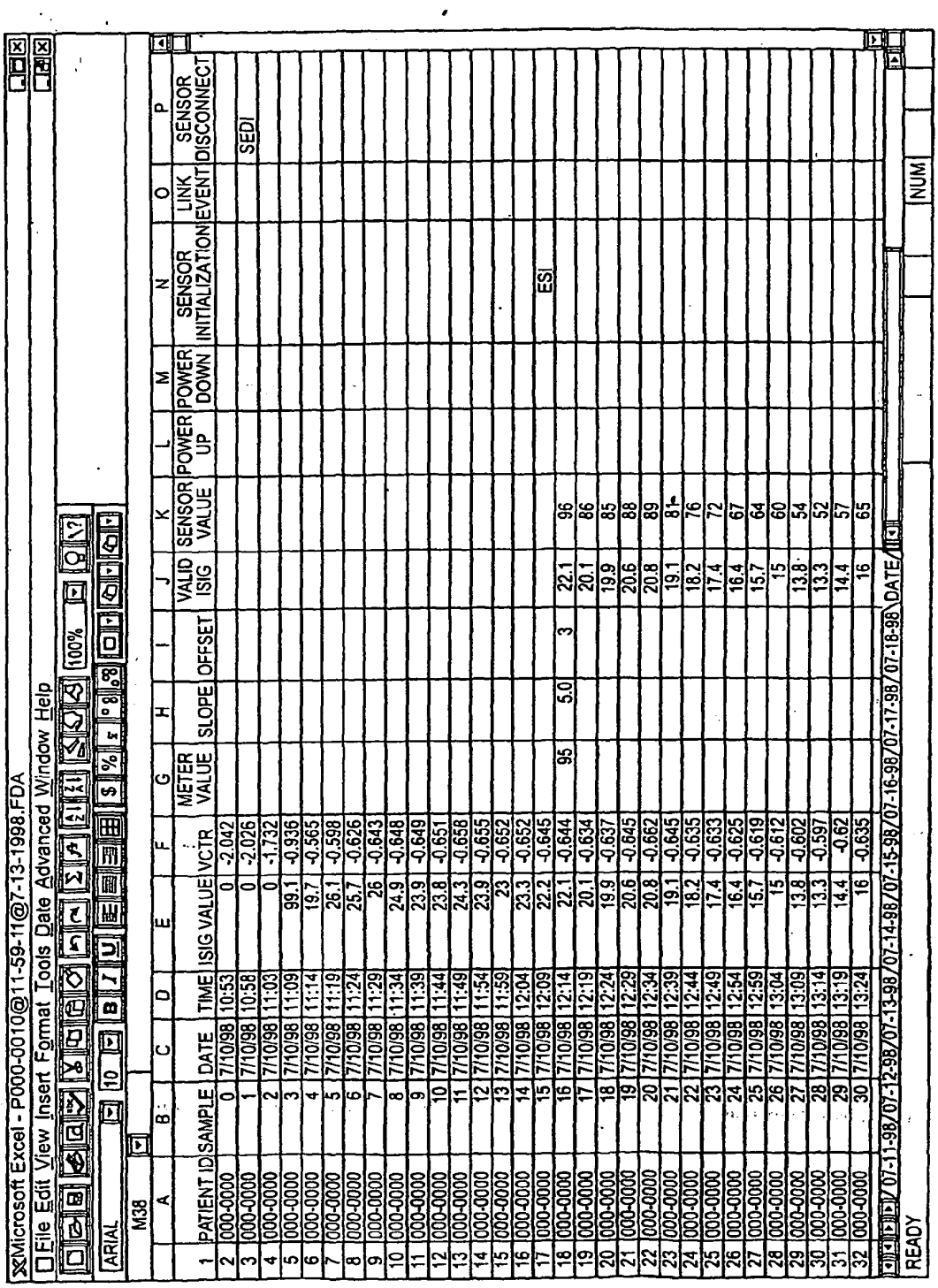


FIG. 10

Abbott Ex. 1002 - 583/1438

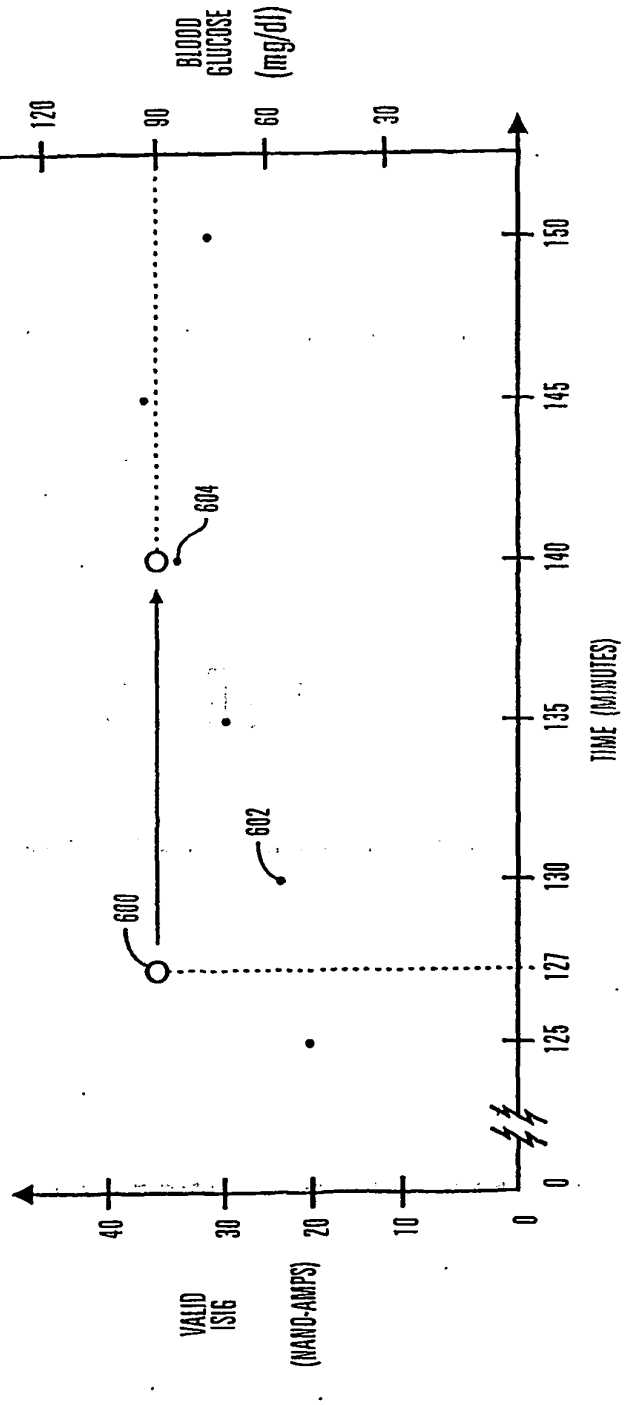


FIG. 11

Abbott Ex. 1002 - 584/1438

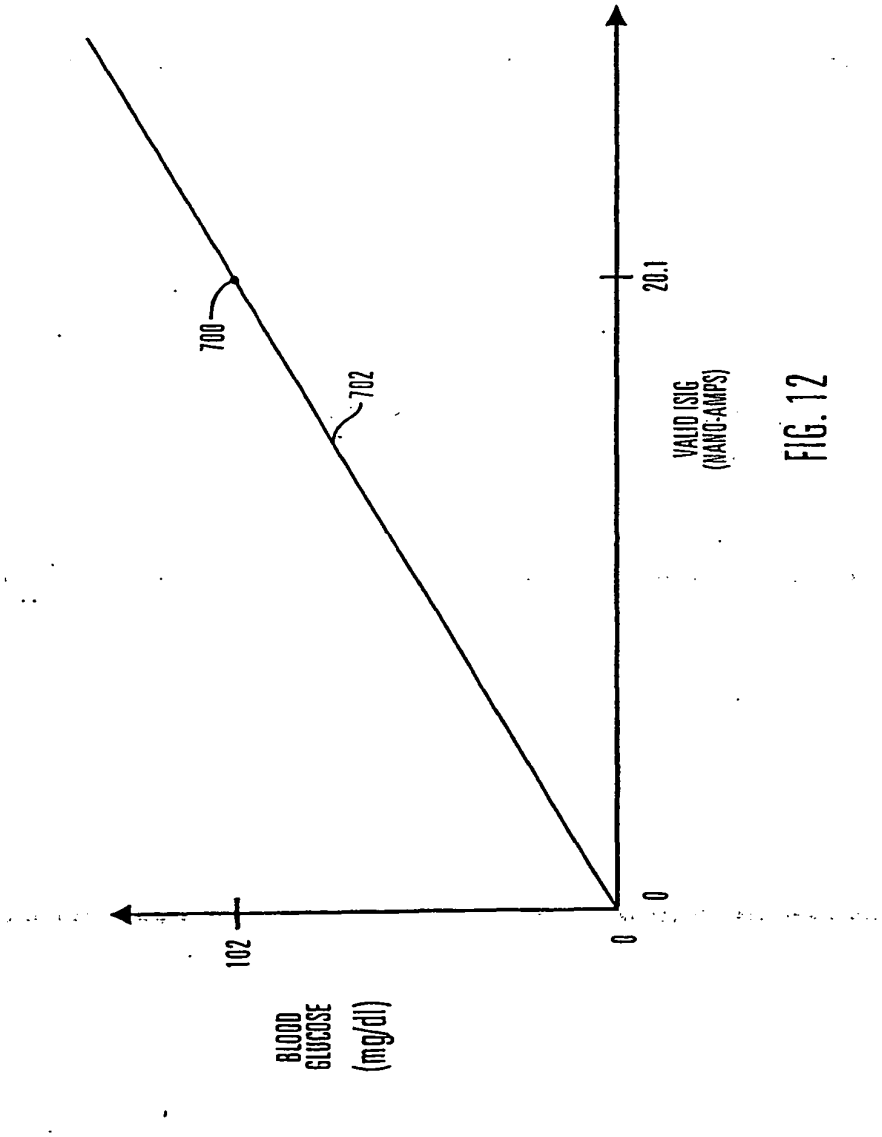


FIG. 12

Abbott Ex. 1002 - 585/1438

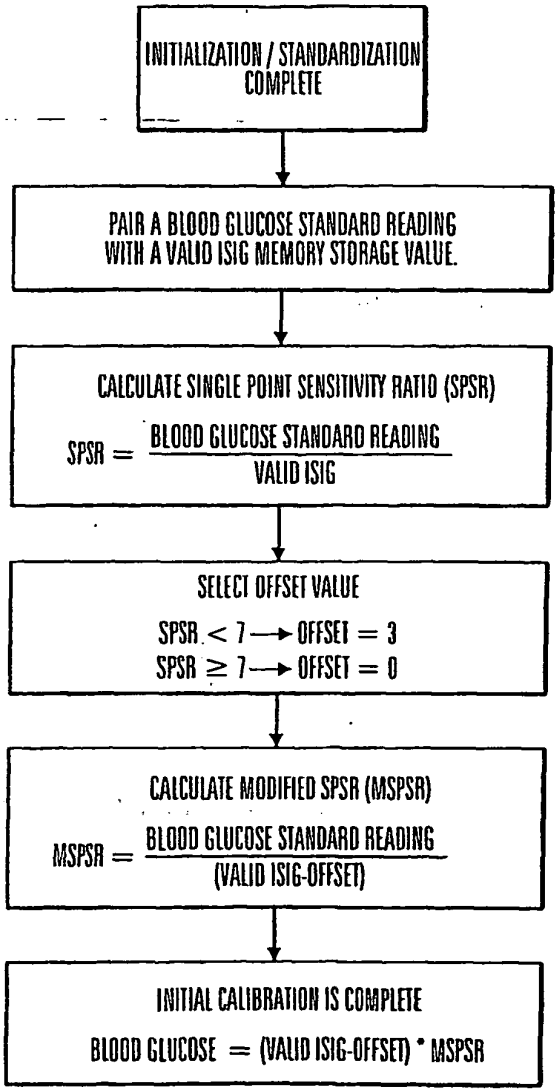


FIG. 13

Abbott Ex. 1002 - 586/1438

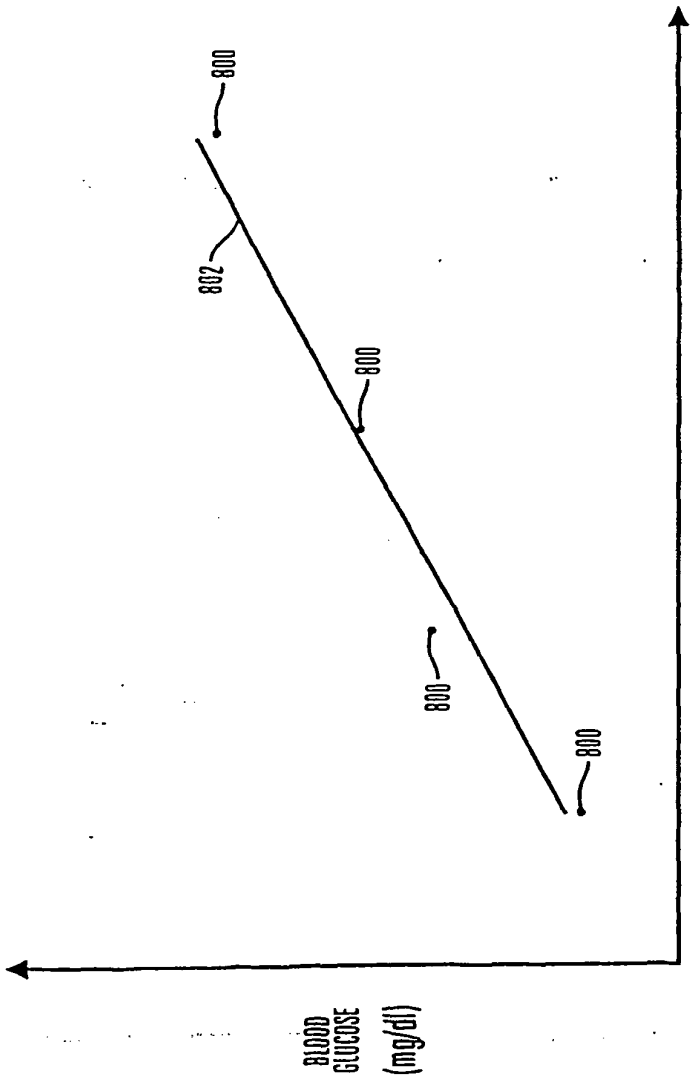


FIG. 14

Abbott Ex. 1002 - 587/1438

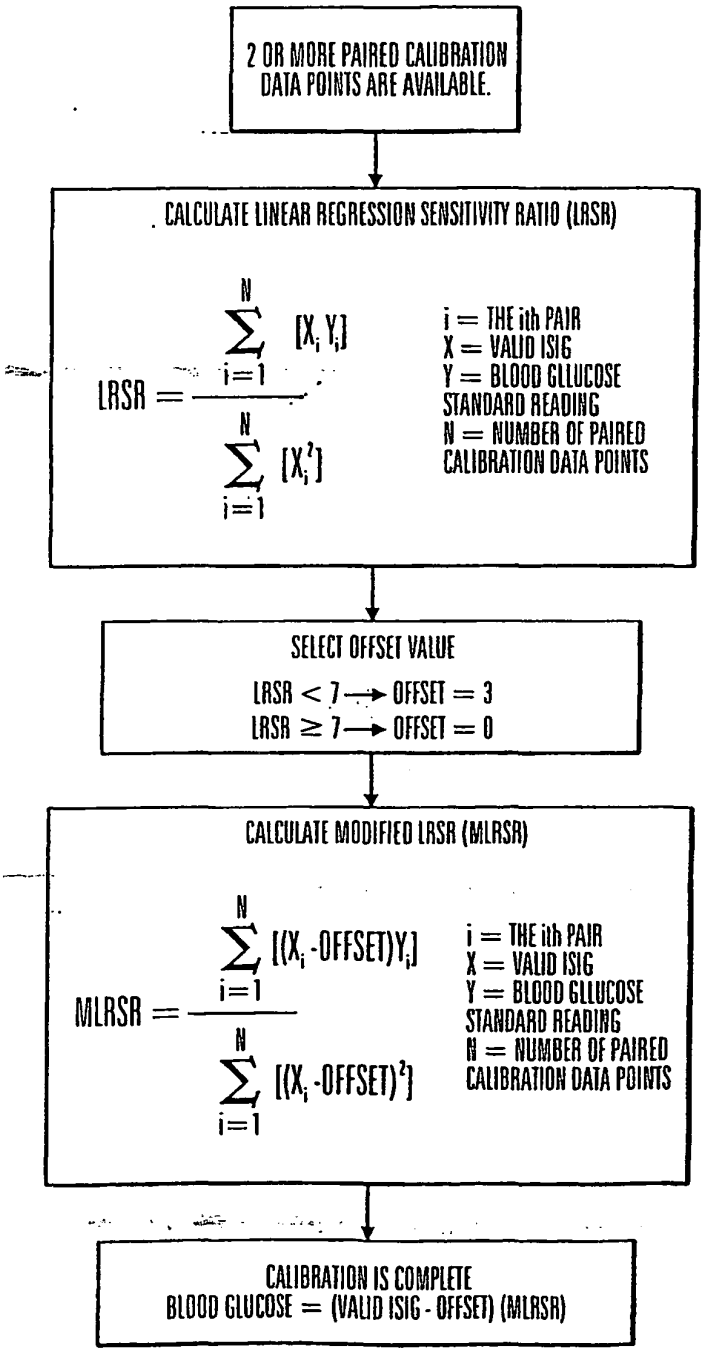
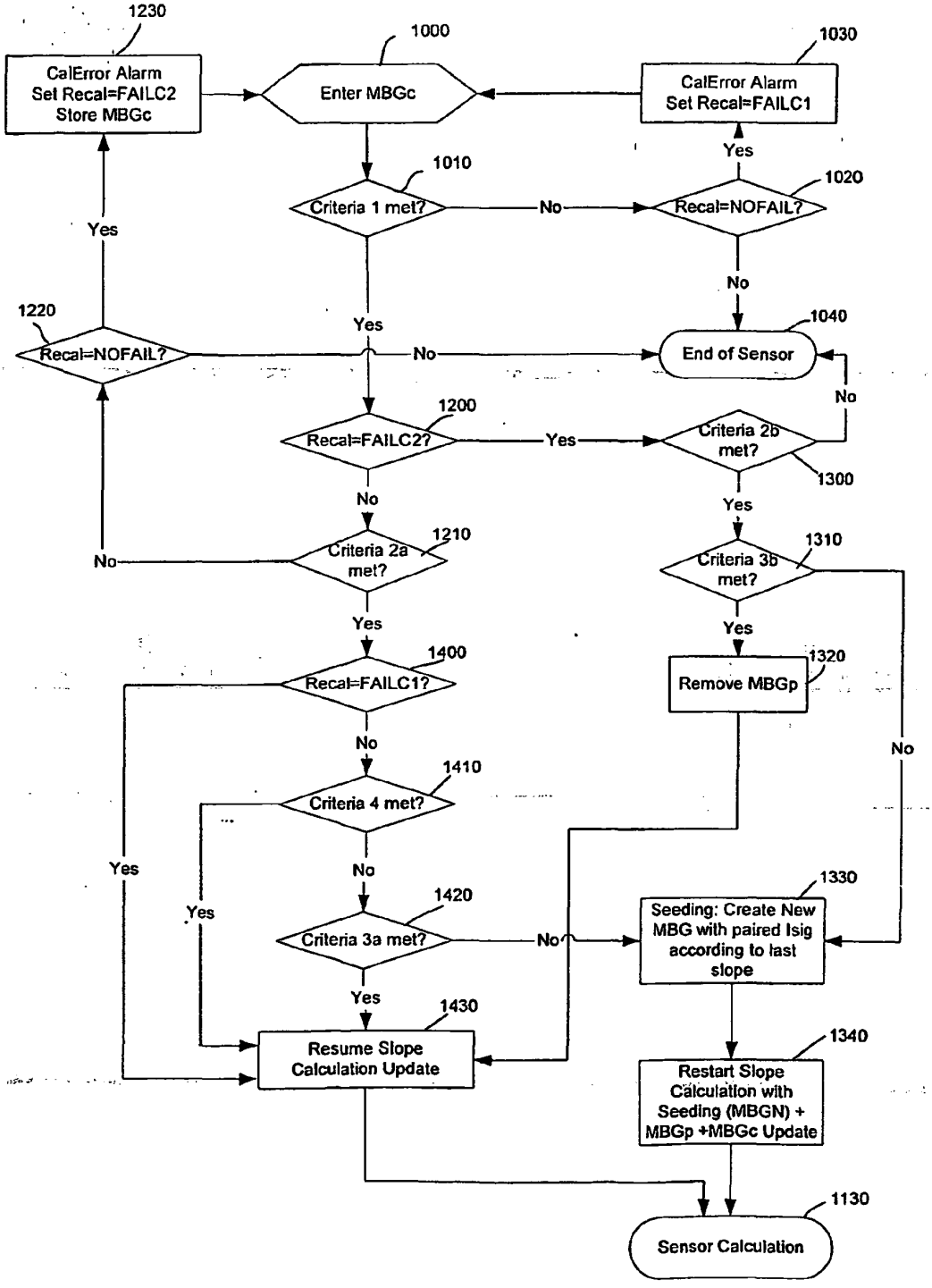


FIG. 15

Abbott Ex. 1002 - 588/1438

FIG. 16



Abbott Ex. 1002 - 589/1438

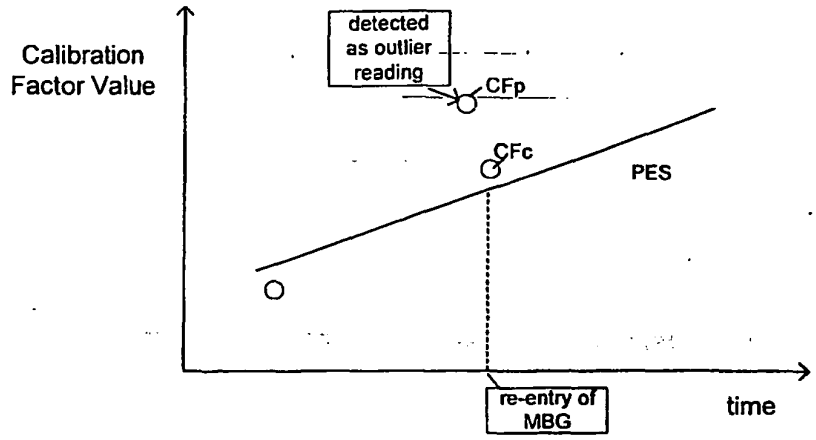


FIG. 17a

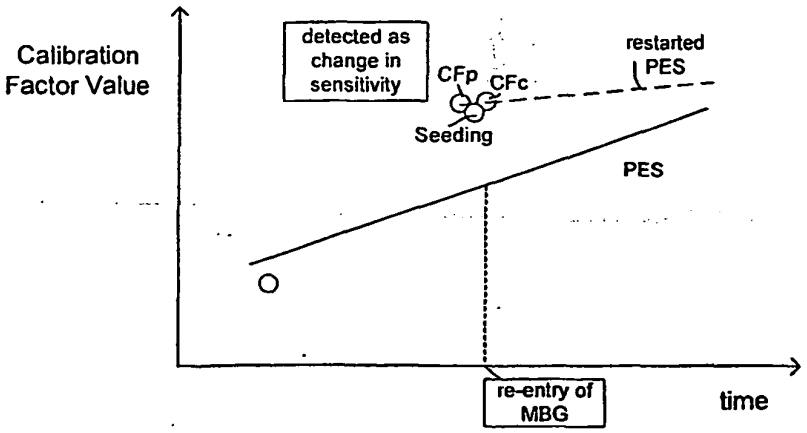


FIG. 17b

Abbott Ex. 1002 - 590/1438

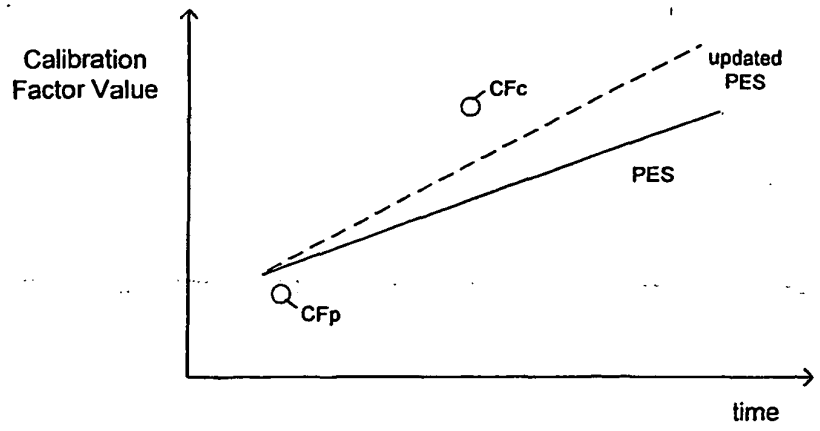


FIG. 18a

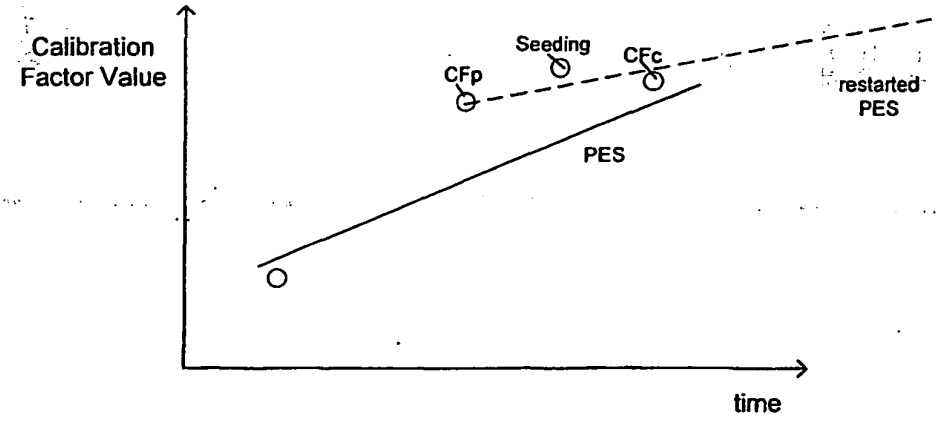


FIG. 18b

Abbott Ex. 1002 - 591/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 518 495 B1

(12) **EUROPÄISCHE PATENTSCHRIFT**

(45) Veröffentlichungstag und Bekanntmachung des Hinweises auf die Patenterteilung:
31.03.2010 Patentblatt 2010/13

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(21) Anmeldenummer: **04021094.0**

(22) Anmeldetag: **04.09.2004**

(54) **Verfahren und Gerät zur laufenden Überwachung der Konzentration eines Analyten**

Method and device for continuous monitoring of analyte concentration

Procédé et dispositif de surveillance continue de la concentration d'un analyte

(84) Benannte Vertragsstaaten:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

(30) Priorität: **23.09.2003 DE 10343863**

(43) Veröffentlichungstag der Anmeldung:
30.03.2005 Patentblatt 2005/13

(73) Patentinhaber:
- **Roche Diagnostics GmbH**
  68305 Mannheim (DE)
  Benannte Vertragsstaaten:
  DE
- **F. Hoffmann-La Roche AG**
  4070 Basel (CH)
  Benannte Vertragsstaaten:
  AT BE BG CH CY CZ DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

(72) Erfinder:
- **Kotulla, Reinhard, Dr.**
  67245 Lambsheim (DE)
- **Staib, Arnulf, Dr.**
  64380 Rossdorf (DE)
- **Gillen, Ralph**
  26871 Papenburg (DE)

(74) Vertreter: **Pfeifer, Hans-Peter et al**
Durm & Partner
Patentanwälte
Moltkestrasse 45
76133 Karlsruhe (DE)

(56) Entgegenhaltungen:
WO-A-02/24065 **WO-A-98/42249**
US-B1- 6 519 705

- **MYERS K A; TAPLEY B D: "Adaptive sequential estimation with unknown noise statistics" IEEE TRANS AUTOM CONTROL AUG 1976, Bd. AC-21, Nr. 4, August 1976 (1976-08), Seiten 520-523, XP002310881**

Anmerkung: Innerhalb von neun Monaten nach Bekanntmachung des Hinweises auf die Erteilung des europäischen Patents im Europäischen Patentblatt kann jedermann nach Maßgabe der Ausführungsordnung beim Europäischen Patentamt gegen dieses Patent Einspruch einlegen. Der Einspruch gilt erst als eingelegt, wenn die Einspruchsgebühr entrichtet worden ist. (Art. 99(1) Europäisches Patentübereinkommen).

EP 1 518 495 B1

Printed by Jouve, 75001 PARIS (FR)

Beschreibung

[0001] Die Erfindung bezieht sich auf ein Verfahren und ein Gerät zur laufenden Überwachung der Konzentration eines Analyten durch Bestimmung von dessen zeitlichem Verlauf im lebenden Körper eines Menschen oder Tieres. Nachfolgend wird hierfür die Bezeichnung "continuous monitoring (CM)" verwendet.

[0002] Ein CM-Verfahren und -Gerät ist beispielsweise in
(1) US-Patent 5,507,288
beschrieben. Es geht dabei insbesondere um die kontinuierliche Überwachung der Konzentration von Glucose im Körper eines Patienten. Sie ist von größter medizinischer Bedeutung. Studien haben zu dem Ergebnis geführt, daß äußerst schwerwiegende langfristige Folgen des Diabetes Mellitus (beispielsweise Erblinden aufgrund einer Retinopathie) vermieden werden können, wenn der zeitliche Verlauf der Konzentration der Glucose in vivo kontinuierlich überwacht wird. Dadurch besteht die Möglichkeit, die erforderliche Medikation (Insulin) zu jedem Zeitpunkt exakt zu dosieren und den Blutzuckerspiegel ähnlich wie bei einer gesunden Person ständig innerhalb enger Grenzen zu halten.

[0003] Die Erfindung bezieht sich insbesondere auf Glucose-CM. Ergänzend wird auf das Dokument (1) und die darin zitierten weiteren Literaturstellen bezug genommen.

[0004] Die Erfindung ist jedoch generell auch für andere Anwendungsfälle geeignet, bei denen der zeitliche Verlauf eines Analyten im lebenden Körper (Nutzsignal) aus einem Meßsignal abgeleitet wird, welches aus zu aufeinanderfolgenden Zeitpunkten gemessenen Meßwerten einer mit der gesuchten Konzentration korrelierenden Meßgröße besteht. Das Meßsignal kann dabei sowohl invasiv als auch nichtinvasiv gemessen werden.

[0005] Ein invasives Meßverfahren wird beispielsweise in
(2) US-Patent 6,584,335
beschrieben. Dabei wird eine Hohlnadel mit einer dünnen optischen Faser in die Haut eingestochen, Licht durch die optische Faser unter die Hautoberfläche eingestrahlt und eine Modifikation des Lichts durch Wechselwirkung mit interstitieller Flüssigkeit, die die optische Faser umgibt, gemessen. Das Meßsignal besteht hier aus Meßwerten, die an Licht gewonnen werden, welches nach der Wechselwirkung mittels der optischen Faser in ein Meßgerät zurückgeführt wird. Beispielsweise kann das Meßsignal aus Spektren des Lichts bestehen, die zu aufeinanderfolgenden Zeitpunkten gemessen werden.

[0006] Ein anderes Beispiel invasiver Meßverfahren sind Konzentrationsüberwachungen mittels eines in die Haut einstechbaren elektrochemischen Sensors, wobei in diesem Fall eine elektrische Meßgröße, in der Regel ein Strom, als mit der Konzentration des Analyten korrelierende Meßgröße bestimmt wird.

[0007] Verschiedene nichtinvasive Verfahren werden in dem Dokument (1) diskutiert. Hierzu gehören spektroskopische Verfahren, bei denen Licht unmittelbar (also ohne Verletzung der Haut) durch die Hautoberfläche in den Körper eingestrahlt und das dabei diffus reflektierte Licht detektiert wird. Derartige Verfahren haben zur Kontrolle des Verlaufs der Sauerstoffsättigung im Blut eine gewisse Bedeutung erlangt. Im Hinblick auf die Analyse von Glucose sind alternative Verfahren bevorzugt, bei denen Licht streng lokalisiert (in der Regel punktförmig) in die Haut eingestrahlt und das Nutzsignal (Verlauf der Glucosekonzentration) aus der räumlichen Verteilung des in der Umgebung der Einstrahlungsstelle aus der Haut austretenden Sekundärlichts gewonnen wird. In diesem Fall wird das Meßsignal also durch das zu aufeinanderfolgenden Zeitpunkten gemessene Intensitätsprofil des Sekundärlichts in der Umgebung der Einstrahlungsstelle gebildet.

[0008] Ein gemeinsames Merkmal aller derartigen Verfahren ist, daß die Ermittlung des zeitlichen Verlaufs der Konzentration (Nutzsignal) aus den zu aufeinanderfolgenden Zeitpunkten gemessenen Meßwerten (Meßsignal) mittels eines Mikroprozessorsystems und eines geeigneten Algorithmus erfolgt. Dieser Auswertealgorithmus schließt folgende Teil-Algorithmen ein:

a) einen Filteralgorithmus, durch den Fehler des Nutzsignals reduziert werden, die aus in dem Meßsignal enthaltenen Signalstörungen resultieren und b) einen Umrechnungsalgorithmus, bei dem ein durch Kalibration bestimmter funktionaler Zusammenhang, der die Korrelation zwischen Meßsignal und Nutzsignal beschreibt, verwendet wird.

[0009] In der Regel werden diese Teile des Auswertealgorithmus in der genannten Reihenfolge ausgeführt, d.h. aus einem Roh-Meßsignal wird zunächst durch Filterung ein gefiltertes Meßsignal gewonnen und dieses wird in das Nutzsignal umgerechnet. Diese Reihenfolge ist jedoch nicht zwingend. Es kann auch zunächst eine Umrechnung des Roh-Meßsignals in ein Roh-Nutzsignal und dann eine Filterung zu dem endgültigen Nutzsignal erfolgen. Der Auswertealgorithmus kann auch weitere Schritte umfassen, bei denen Zwischengrößen ermittelt werden. Im Rahmen der Erfindung erforderlich ist nur, daß an irgendeiner Stelle des Auswertealgorithmus, die beliebig gewählt werden kann, die beiden genannten Teilalgorithmen a) und b) ablaufen.

[0010] Die Erfindung bezieht sich auf Fälle, bei denen Filteralgorithmen in der Zeitdomäne verwendet werden. Gebräuchlich sind insbesondere Kalman-Filteralgorithmen. Nähere Informationen zu derartigen Filteralgorithmen können aus folgenden Literaturzitaten entnommen werden, die teilweise auch chemische und medizinische Anwendungen

Abbott Ex. 1002 - 593/1438

beschreiben:

(3) S. D. Brown: The Kalman filter in analytical chemistry, Analytica Chimica Acta 181 (1986), 1-26.

(4) K. Gordon: The multi-state Kalman filter in medical monitoring, Computer Methods and Programs in Biomedicine 23 (1986), 147-154.

(5) K. Gordon, A.F.M. Smith: Modelling and monitoring biomedical time series, Journal of the American Statistical Association 85 (1990), 328-337.

(6) US-Patent 5,921,937

(7) EP 0 910 023 A2

(8) WO 01/38948 A2

(9) US-Patent 6,317,662

(10) US-Patent 6,575,905 B2 und WO 02/24065

(11) US-Patent 6,519,705

[0011] Wie erwähnt dient der Filteralgorithmus dazu, Störsignale zu entfernen, die in dem Roh-Meßsignal enthalten sind und das Nutzsignal verfälschen würden. Ziel jedes Filteralgorithmus ist es, diese Störungen möglichst vollständig zu eliminieren, gleichzeitig aber eine Verfälschung des Meßsignals zu vermeiden. Dieses Ziel ist bei der in-vivo-Überwachung von Analyten besonders schwer zu erreichen, weil die Meßsignale in der Regel sehr schwach und von starken Störungen überlagert sind. Besondere Probleme werden dadurch verursacht, daß das Meßsignal in der Regel zwei Typen von Störungen enthält, die sich hinsichtlich der Anforderungen an den Filteralgorithmus wesentlich unterscheiden:

- Meßrauschen: Diese Störsignalanteile folgen einer Normalverteilung mit konstanter Standardabweichung um das richtige (physiologische) Meßsignal

- nichtphysiologische Signaländerungen, die beispielsweise durch Bewegungen des Patienten und damit verbundene Änderungen der Ankopplung eines Meßsensors an die Haut verursacht werden. Sie sind in der Regel weder um das physiologische Meßsignal normalverteilt, noch ist die Standardabweichung von dem physiologischen Meßsignal konstant. Für solche Störbeiträge des Rohsignals wird nachfolgend die Bezeichnung NNNC (Non Normal Non Constant) - Noise verwendet.

[0012] Der Erfindung liegt das technische Problem zugrunde, eine Erhöhung der Genauigkeit von CM-Verfahren durch Verbesserung der Filterung von Störsignalen zu erreichen, insbesondere wenn die erwähnten nicht-physiologischen Signaländerungen auftreten, die weder um das physiologische Meßsignal normalverteilt sind noch eine konstante Standardabweichung von dem physiologischen Meßsignal haben.

[0013] Dies wird erfindungsgemäß mittels eines Filteralgorithmus erreicht, der eine Operation einschließt, bei der der Einfluß eines aktuellen Meßwertes auf das Nutzsignal mittels eines Gewichtungsfaktors gewichtet wird ("steuerbarer Filteralgorithmus"), der die Merkmale des Anspruchs 1 aufweist.

[0014] Die Erfindung einschließlich bevorzugter Ausführungsformen wird nachfolgend anhand der Figuren näher erläutert. Die darin dargestellten und nachfolgend beschriebenen Besonderheiten können einzeln oder in Kombination verwendet werden, um bevorzugte Ausgestaltungen der Erfindung zu schaffen. Es zeigen:

Fig. 1 ein Blockdiagramm eines erfindungsgemäßen Geräts

Fig. 2 ein Prinzipskizze eines für die Erfindung geeigneten Sensors

Fig. 3 ein Meßsignal eines Sensors gemäß Fig. 2 und

Fig. 4 ein symbolisches Ablaufdiagramm zur Erläuterung des im Rahmen der Erfindung verwendeten Algorithmus

Fig. 5 eine graphische Darstellung typischer Signalverläufe zur Erläuterung des von der Erfindung gelösten Problems

Abbott Ex. 1002 - 594/1438

Fig. 6 eine graphische Darstellung von experimentell gewonnenen Meßergebnissen

[0015] In Fig. 1 sind die wesentlichen Komponenten eines erfindungsgemäßen Geräts dargestellt. Ein Sensor 1 mißt zu aufeinanderfolgenden Zeitpunkten Meßwerte. Dieses Meßsignal wird - im dargestellten Fall drahtlos - an einen Empfänger 2 übertragen, von dem das Meßsignal an eine Auswerteeinheit 3 weitergeleitet wird, die einen Mikroprozessor 4 und einen Datenspeicher 5 enthält. Daten und Befehle können auch über eine Eingabeeinheit 6 an die Auswerteeinheit 3 übermittelt werden. Die Ausgabe von Resultaten erfolgt mittels einer Ausgabeeinheit 7, die ein Display und andere übliche Ausgabemittel einschließen kann. Selbstverständlich erfolgt die Datenverarbeitung in der Auswerteeinheit 3 digital und es sind entsprechende Wandler zur Umwandlung analoger Signale in Digitalsignale vorgesehen. Nähere Erläuterungen hierzu sind nicht erforderlich, weil der grundsätzliche Aufbau derartiger Geräte (beispielsweise aus dem Dokument 1) bekannt ist und die Erfindung für ganz unterschiedliche Meßtechniken geeignet ist, bei denen - wie einleitenden erläutert - unterschiedliche mit dem gewünschten Nutzsignal korrelierende Meßsignale gemessen werden.

[0016] Fig. 2 zeigt in Form einer Prinzipskizze einen Sensor 1, bei dem ein implantierbarer Katheter 10 verwendet wird, um aus dem Unterhaut-Fettgewebe interstitielle Flüssigkeit mittels einer Pumpe 11 abzusaugen und durch eine photometrische Meßeinheit 12 in einen Abfallbehälter 13 zu saugen. Die Leitung 14, durch die die interstitielle Flüssigkeit transportiert wird, enthält in der photometrischen Meßeinheit 12 eine transparente Meßzelle 15, in die von einem Lichtsender 16 ausgehendes Primärlicht eingestrahlt wird. Das nach Passieren der Meßzelle 15 resultierende Sekundärlicht wird mittels eines Photodetektors 17 gemessen und mittels einer nicht dargestellten Meßelektronik ein Rohsignal erzeugt, das - wie in Figur 1 beispielhaft dargestellt - an eine Auswerteeinheit 3 weitergeleitet wird.

[0017] Fig. 3 zeigt als Kurve A den typischen Verlauf eines mit einem Sensor gemäß Figur 2 gewonnenen Roh-Meßsignals, wobei die bei einer bestimmten Wellenlänge gemessene Intensität des Sekundärlichts I gegen die Zeit in Minuten aufgetragen ist. Der Darstellung liegt ein CM-Versuch an einem Probanden zugrunde, wobei das Meßsignal A aus im Abstand von jeweils einer Sekunde gemessenen Meßwerten besteht.

[0018] Flußschwankungen des Stroms der interstitiellen Flüssigkeit aus dem Körper in die photometrische Meßeinheit 12 führen zu regelmäßigen relativ kleinen Signalschwankungen, die als "Fluidik-Modulation" bezeichnet werden. Zu dem mit dem Pfeil 18 bezeichneten Zeitpunkt nach etwa drei Minuten tritt eine Hemmung der Flüssigkeitsströmung ein, die beispielsweise durch eine Bewegung des Probanden oder durch das Eindringen eines Zellpartikels in den Katheter 10 verursacht sein kann. Diese Hemmung des Flusses führt zu einem massiven Einbruch des Roh-Meßsignals A. Dies zeigt beispielhaft, daß nicht nur Störsignale auftreten, die als Normalverteilung mit weitgehend konstanter Standardabweichung um das dem tatsächlichen physiologischen Meßwert entsprechende Signal verteilt sind, sondern auch Störbeiträge der hier dargestellten Art, für die diese Bedingung nicht gilt (NNNC-Noise). Ziel der Erfindung ist es, auch in derartigen Fällen die erforderliche Filterung so durchzuführen, daß das in Figur 3 als dünne Linie B gezeichnete Nutzsignal resultiert, welches möglichst genau der tatsächlichen physiologischen Konzentration des Analyten entspricht.

[0019] Grundlage eines Filteralgorithmus in der Zeitdomäne, auf den sich die Erfindung bezieht, ist ein Systemmodell, das die zeitliche Entwicklung der interessierenden Variablen und deren Beziehung zueinander beschreibt. Der funktionale Zusammenhang, der die Entwicklung des Systems vom Zeitpunkt t zum Zeitpunkt t+1 beschreibt, lautet:

$$\mathbf{y}_{t+1} = f_t(\mathbf{y}_t, \mathbf{y}_{t-1}, \ldots, \mathbf{u}_t, \mathbf{u}_{t-1}, \ldots) . \qquad (1)$$

[0020] Darin sind $\mathbf{y}_t$ und $\mathbf{u}_t$ Vektoren, die als Zustandsvektor bzw. als Vektor von Input-Variablen bezeichnet werden. Der Zustandsvektor $\mathbf{y}_t$ enthält die physiologisch interessierenden Variablen sowie eventuell Kontrollvariablen, die eine Kontrolle der Messung ermöglichen, wie weiter unten noch näher erläutert wird. Bei CM-Verfahren gehört hierzu die gesuchte Analytkonzentration, also beispielsweise die Glucose-Konzentration g_t im Blut. Als Kontrollvariable eignet sich die Änderungsgeschwindigkeit der Analytkonzentration $g_t' = dg_t/dt$. Der Zustandsvektor $\mathbf{y}_t$ kann auch meßverfahrensbezogene Modellvariablen enthalten. Beispielsweise ist es im Falle eines Meßergebnisses der in Figur 3 dargestellten Art vorteilhaft, die Fluidik-Modulation in dem Systemmodell zu berücksichtigen. Diese Modulation läßt sich mittels ihrer zeitlich veränderlichen Frequenz ω_t und der ebenfalls zeitlich veränderlichen Amplitude A_t beschreiben. Damit ergeben sich für das anhand der Figuren 2 und 3 beschriebene Experiment vier Systemvariable: g_t, A_t, ω_t, g_t'.

[0021] In dem Vektor $\mathbf{u}_t$ werden Input-Variablen zusammengefaßt, die in der Regelungstechnik Stellgrößen entsprechen und somit nicht selbst gemessen werden. Im Fall des Glukose-Monitorings ist es beispielsweise zweckmäßig, die gegebene Insulinmenge und zugeführte Broteinheiten als Input-Variablen in diesem Sinne zu berücksichtigen, weil sie die Glukose-Konzentration im Blut beeinflussen. Werden diese Input-Variablen berücksichtigt, hat der Vektor $\mathbf{u}_t$ zwei Elemente: Insulindosis und Broteinheiten. Charakteristisch für die Input-Variablen ist, daß für sie im Rahmen des Filteralgorithmus keine Vorhersage zukünftiger Werte erforderlich ist.

[0022] Die genannten Variablen des Zustandsvektors $\mathbf{y}_t$ und des Input-Vektors $\mathbf{u}_t$ sind selbstverständlich nur als

Abbott Ex. 1002 - 595/1438

Beispiele zu verstehen. Die Erfindung bezieht sich auf sehr unterschiedliche Systeme, die unterschiedliche Systemmodelle erfordern. Ebenso ist es nicht erforderlich, besagte Modelle in diskreter Form zu benutzen: die bekannte alternative kontinuierliche Formulierung unter Verwendung der entsprechenden Differentialgleichungen kann ebenfalls benutzt werden.

[0023] Charakteristisch für Filteralgorithmen in der Zeitdomäne, auf die sich die Erfindung bezieht, ist, daß sie eine alternierende Folge von Vorhersagen des Systemzustandes ("Prediktorschritt") und anschließender Korrektur dieser Vorhersage auf Basis eines zusätzlich bestimmten Meßwertes ("Korrektorschritt") einschließen.

[0024] In einem Prediktorschritt erfolgt eine Vorhersage des zum Zeitpunkt t aktuellen Wertes der Zustandsvariablen $\mathbf{y}_t$ unter Verwendung der Systemgleichung (1):

$$(2) \qquad \hat{\mathbf{y}}_t = f_{t-1}(\mathbf{y}_{t-1}, \mathbf{y}_{t-2}, \ldots; \mathbf{u}_{t-1}, \mathbf{u}_{t-2}, \ldots) + \mathbf{W}_{t-1}$$

[0025] Darin bezeichnet $\hat{\mathbf{y}}_t$ den mit den Daten des vorherigen Zeitpunktes (t-1) geschätzten (vorhergesagten) Wert des Zustandsvektors zum Zeitpunkt t; $\mathbf{W}_t$ bezeichnet einen Systemfehlervektor.

[0026] Im Falle eines rekursiven Filteralgorithmus erfolgt die Berechnung in dem Prediktorschritt nicht jeweils neu unter Berücksichtigung sämtlicher vorhergehender Zeitpunkte (t-1, t-2, t-3...), sondern unter Verwendung einer gewichteten Summe geglätteter Signalwerte. Im Beispiel eines linearen Kalman-Algorithmus kann man die entsprechende Gleichung wie folgt schreiben:

$$(2a) \qquad \hat{\mathbf{y}}_t = \mathbf{A}_{t-1}\mathbf{y}_{t-1} + \mathbf{B}\mathbf{u}_{t-1} + \mathbf{w}_{t-1}$$

[0027] Darin ist $\mathbf{A}_t$ die Systemmatrix und $\mathbf{B}$ die Inputmatrix. Im allgemeinen (nichtlinearen) Fall ist f_t vorzugeben oder aus bislang ermittelten Daten zu berechnen.

[0028] In dem Korrektorschritt erfolgt eine Korrektur der Vorhersage auf der Grundlage eines aktuellen Meßwertes gemäß

$$(3) \qquad \mathbf{y}_t = \alpha_t \hat{\mathbf{y}}_t + \beta_t \Delta_t$$

[0029] Darin ist Δ_t eine Größe, die ein Maß für die Abweichung eines aktuellen Meßwertes z_t von dem vorhergesagten Wert darstellt und als "Innovation" bezeichnet wird.

$$(4) \qquad \Delta_t = \mathbf{z}_t - \mathbf{h}(\hat{\mathbf{y}}_t)$$

[0030] Dabei ist berücksichtigt, daß in der Regel die Systemvariablen nicht unmittelbar beobachtet werden können. Die Verknüpfung zwischen den Meßwerten und den Zustandsvariablen wird über ein Meßmodell (Meßfunktion $\mathbf{h}_t$) hergestellt gemäß:

$$(5) \qquad \mathbf{z}_t = \mathbf{h}_t(\mathbf{y}_t) + \mathbf{v}_t$$

[0031] Durch $\mathbf{v}_t$ wird das Rauschen der Meßwerte berücksichtigt.

[0032] Für den Fall eines linearen Kalman-Algorithmus (vgl. Gleichung 2a), lautet die Meßgleichung

$$(5a) \qquad \mathbf{z}_t = \mathbf{H}_t \cdot \mathbf{y}_t + \mathbf{V}_t,$$

wobei $\mathbf{H}_t$ die Meßmatrix bezeichnet.

[0033] Beispielsweise wird bei der kontinuierlichen Überwachung der Glucose mittels eines elektrochemischen Sen-

Abbott Ex. 1002 - 596/1438

sors ein Strom gemessen, der mit der Glucosekonzentration g_t korreliert. In diesem Fall beschreibt $\mathbf{h}_t$ die Korrelation der Zustandsvariablen g_t mit der Meßgröße i (Strom), die ein Element des Vektors $\mathbf{z}_t$ ist.

[0034] In dem beschriebenen Beispiel der photometrischen Detektion von Glukose mit filtergestützter Kompensation der Fluidik-Modulation liegt ein nichtlineares Meßmodell vor, das das photometrische Meßsignal z_t mit den Systemvariablen Glukosekonzentration g_t, Amplitude A_t sowie Frequenz ω_t der Fluidikmodulation verknüpft:

$$z_t = g_t + A_t \cdot \sin(\omega_t \cdot t).$$

[0035] Gemäß Gleichung (3) wird der Einfluß des aktuellen Meßwertes (in der Innovation Δ_t enthalten) auf den gefilterten Nutzsignalwert $\mathbf{y}_t$ durch die Faktoren α_t und β_t gewichtet, so daß ein steuerbarer Filteralgorithmus vorliegt.

[0036] Im Falle eines Kalman-Filters ist $\alpha_t = 1$ für jeden Zeitpunkt und $\beta_t = \mathbf{K}_t$. $\mathbf{K}_t$ bezeichnet den Kalman-Gain. Demzufolge lautet die Korrektorgleichung:

$$\mathbf{y}_t = \hat{\mathbf{y}}_t + \mathbf{K}_t\Delta_t \qquad (3a)$$

[0037] Die Bedeutung des Kalman-Gain $\mathbf{K}_t$ und nähere Informationen zu dem Algorithmus können der einschlägigen Literatur, wie weiter oben zitiert, entnommen werden. Anschaulich ausgedrückt bildet der Kalman-Gain ein Maß dafür, wie stark zusätzlich gewonnene Meßwerte berücksichtigt werden. Er wird bei jedem Iterationsschritt des Filteralgorithmus neu berechnet gemäß einer Formel, die sich vereinfachend (für den linearen Fall) wie folgt schreiben läßt:

$$\mathbf{K}_t = \mathbf{P}_t \cdot \mathbf{H}_t \cdot (\mathbf{P}_t \cdot \mathbf{H}_t + \mathbf{V})^{-1} \qquad (6)$$

[0038] Dabei bezeichnet $\mathbf{P}_t$ die Kalmanfehlerkovarianzmatrix. $\mathbf{V}$ bezeichnet die Meßfehlerkovarianzmatrix im konventionellen Kalman-Algorithmus.

[0039] Gleichung (6) zeigt, daß die Elemente von $\mathbf{K}_t$ Werte größer 0 und kleiner 1 annehmen können. Ist der angenommene Meßfehler $\mathbf{V}$ relativ groß gegenüber der Kalmanfehlerkovarianz $\mathbf{P}_t$, so ist $\mathbf{K}_t$ klein, d.h. der jeweils aktuelle Meßwert wird relativ gering gewichtet. Ist hingegen $\mathbf{V}$ klein gegen $\mathbf{P}_t$ (multipliziert mit $\mathbf{H}_t$), so erfolgt eine starke Korrektur durch den aktuellen Meßwert.

[0040] In Figur 4 ist die dem Filtervorgang zugrundeliegende Iterationsschleife 20 graphisch dargestellt. Alternierend erfolgt ein Korrektorschritt, beispielsweise gemäß Gleichung (3) oder (3a), unter Berücksichtigung eines aktuellen Meßwertes $\mathbf{z}_t$ und nach einem Zeitschritt dt ein Prediktorschritt für einen neuen Zeitpunkt, beispielsweise gemäß Gleichung (2) oder (2a). Dieser Teil des Algorithmus wird als Filterkern 22 bezeichnet. Wie erläutert kann er auf unterschiedliche Weise realisiert sein, sofern es sich um einen Algorithmus in der Zeitdomäne handelt und er eine Operation einschließt, bei der der Einfluß eines aktuellen Meßwertes $\bar{\mathbf{z}}_t$ auf das gefilterte Nutzsignal $\mathbf{y}_t$ mittels eines Gewichtungsfaktors α_t,β_t bzw. $\mathbf{K}_t$ gewichtet wird.

[0041] Ein wesentlicher Beitrag zur Verbesserung der Filterung wird im Rahmen der Erfindung dadurch erreicht, daß auf Basis von in engem zeitlichem Zusammenhang mit der Messung des aktuellen Meßwertes $\mathbf{z}_t$ detektierten Signalschwankungen ein hier mit σ_t bezeichneter Signalschwankungsparameter ermittelt wird und die Gewichtung des Einflusses des aktuellen Meßwertes $\mathbf{z}_t$ im Rahmen des Korrektorschrittes in Abhängigkeit von σ_t dynamisch adaptiert wird. Dies wird in Figur 4 graphisch verdeutlicht: Das Feld 23 symbolisiert die Ermittlung des Schwankungsparameters σ_t als Funktion des Meßsignals in einem vorausgehenden Zeitraum (Meßwerte $z_{t-n}...z_t$). Das Feld 24 symbolisiert die Berechnung des in dem Korrektorschritt berücksichtigten Gewichtungsfaktors (hier beispielhaft die Meßfehlerkovarianz $\mathbf{V}$, die den Kalman-Gain beeinflußt) als Funktion des Signalschwankungsparameters σ_t. Der Gewichtsfaktor ist eine zeitlich veränderliche (dynamisch adaptierte) Größe (hier $\mathbf{V}_t$).

[0042] Die Erfindung zielt nicht darauf ab, unterschiedliche Filtertypen - im Sinne einer Filterbank - durch Anwendung von Gewichtungsfaktoren zu gewichten. Dazu wären nämlich eine Reihe von Systemmodellen analog zu Gleichung (2) zu definieren und zwar für jeden Filter der Filterbank ein Modell. Dies ist in der vorliegenden Erfindung nicht erforderlich und resultiert in geringerer Komplexität des Verfahrens.

[0043] Für die in den Schritten 23 und 24 verwendeten funktionalen Zusammenhänge können keine konkreten mathematischen Regeln angegeben werden, weil sie jeweils auf den Einzelfall angepaßt werden müssen. Allgemein gilt jedoch folgendes:

Abbott Ex. 1002 - 597/1438

- der Signalschwankungsparameter wird als Funktion von Meßwerten ermittelt, die in engem zeitlichem Zusammenhang mit dem jeweils aktuellen Meßwert stehen. Dadurch wird erreicht, daß die dynamische Adaption des Filters hinreichend rasch erfolgt. Vorzugsweise basiert die Bestimmung des Signalschwankungsparameters auf Meßwerten, die weniger als 30 Minuten, vorzugsweise weniger als 15 Minuten und besonders bevorzugt weniger als 5 Minuten vor der Messung des aktuellen Meßwertes gemessen wurden. Zumindest sollten in dem Algorithmus zur Ermittlung des Signalschwankungsparameters Meßwerte aus den genannten Zeiträumen mitverwendet werden.

- Unabhängig von den im konkreten Fall eingesetzten Formeln gilt das Prinzip, daß bei abnehmender Signalqualität (also beispielsweise Zunahme der Standardabweichung des Meßsignales) der Signalschwankungsparameter und damit der Gewichtungsfaktor (bzw. gegebenenfalls die Gewichtungsfaktoren) in der Richtung verändert werden, daß der Einfluß des jeweils aktuellen Meßwertes vermindert wird.

[0044] Als Signalschwankungsparameter eignet sich beispielsweise die Standardabweichung, die wie folgt berechnet werden kann.

[0045] Geht man davon aus, daß die Ermittlung der Standardabweichung auf dem aktuellen Meßwert z und vier vorausgehenden Meßwerten z_1 bis z_4 beruht und bezeichnet man die Differenz zwischen z und den vorausgehenden Werten mit δz ($\delta z_n = z\text{-}z_n$), so berechnet sich der Mittelwert ε zu

$$(7) \qquad \varepsilon = \frac{1}{4} (\delta z_1 + \delta z_2 + \delta z_3 + \delta z_4)$$

und die Steigung φ einer Ausgleichsgeraden zu

$$(8) \qquad \varphi = \frac{3(\delta z_1 - \delta z_4) + \delta z_2 - \delta z_3}{10}$$

[0046] Die Standardabweichung der vier Differenzwerte bezüglich dieser Ausgleichsgeraden ist

$$(9) \qquad \sigma_t = \left[\frac{1}{3} (\delta z_1 - (\varepsilon + 1{,}5\varphi))^2 + \frac{1}{3} (\delta z_2 - (\varepsilon + 0{,}5\varphi))^2 + \frac{1}{3} (\delta z_3 - (\varepsilon - 0{,}5\varphi))^2 + \frac{1}{3} (\delta z_4 - (\varepsilon - 1{,}5\varphi))^2 \right]^{1/2}$$

[0047] Auf Basis dieser Standardabweichung läßt sich eine dynamische (zeitabhängige) Meßfehlerkovarianz V_t, die in einen Filterkern mit Kalman-Algorithmus eingeht, beispielsweise berechnen gemäß

$$(10) \qquad V_t = (\sigma_o + \sigma_t)^\gamma$$

[0048] Dabei sind σ_o und y konstante, den Filter charakterisierende Parameter, mit deren Einstellung das zeitliche Verhalten des Filters, insbesondere seine Adaptinität, an den jeweiligen Anwendungszweck angepaßt werden kann.

[0049] Im Beispiel eines steuerbaren rekursiven Filters hängen die Gewichtungsfaktoren α_t, β_t aus Gleichung (3) derart vom Signalschwankungsparameter ab, daß mit zunehmendem σ_t der Faktor α_t größer und der Faktor β_t kleiner wird.

[0050] Wie bereits erläutert, stellen die Gleichungen (7) bis (10) nur eine von zahlreichen Möglichkeiten dar, einen

Abbott Ex. 1002 - 598/1438

Signalschwankungsparameter und auf dessen Basis eine Gewichtungsfaktor für einen steuerbaren Filteralgorithmus in der Zeitdomäne zu ermitteln. Statt der Standardabweichung, die selbstverständlich mit einer abweichenden Anzahl von Meßwerten berechnet werden kann, können auch andere Größen verwendet werden, die ein Maß für die Signalschwankungen in dem einem aktuellen Meßwert vorausgehenden Zeitraum darstellen. Der Begriff "Signalschwankungsparameter" dient allgemein zur Bezeichnung einer mathematischen Größe, die diese Anforderungen erfüllt.

[0051] In Figur 5 sind drei typische Verläufe eines Signals S gegen die Zeit t aufgetragen, nämlich:

a) als durchgezogene Linie ein Rohsignal, das in dem mit dem Kreis 25 umrahmten Zeitabschnitt starken nichtphysiologischen Schwankungen unterliegt und in dem mit dem Rechteck 26 umrahmten Zeitabschnitt wesentlich weniger schwankt, wobei diese Schwankungen im wesentlichen physiologisch bedingt sind.
b) in gestrichelter Darstellung ein Nutzsignal, das aus dem Rohsignal a) mittels eines Kalman-Filters gewonnen wurde, dessen Meßfehlerkovarianz entsprechend der Schwankung des Rohsignals in dem Kreis 25 eingestellt war.
c) in gepunkteter Darstellung ein Nutzsignal, das aus dem Rohsignal a) mittels eines Kalman-Filters gewonnen wurde, dessen Meßfehlerkovarianz gemäß dem Verlauf des Rohsignals in dem Rechteck 26 eingestellt war.

[0052] Man erkennt, daß bei der Kurve b die starken Schwankungen innerhalb des Kreises 25 gut gefiltert werden, jedoch in dem Rechteck 26 das Signal b den physiologischen Schwankungen des Rohsignals völlig unzureichend folgt. Das Nutzsignal c folgt hingegen den physiologischen Schwankungen in dem Bereich 26 gut während die Filterung der unphysiologischen Schwankungen in dem von dem Bereich 25 unzureichend ist. Der konventionelle Kalman-Filteralgorithmus erlaubt demzufolge keine Einstellung, die bei den dargestellten unterschiedlichen Bedingungen zu einer optimalen Filterung führt. Die Erfindung hingegen erfordert nicht einmal die Kenntnis der maximalen Meßwertschwankungen. Der Filteralgorithmus adaptiert sich selbständig an die Änderungen im Signalverlauf und liefert ein gefiltertes Signal, das in dem Kreis 25 der Kurve b und in dem Rechteck 26 der Kurve c entspricht.

[0053] Figur 6 zeigt entsprechende experimentelle Ergebnisse aus einem CM-Versuch zum Glucose-Monitoring an einem Probanden. Dargestellt ist ein bei konventioneller Filterung resultierendes Nutzsignal als durchgezogene Kurve A (Glucosekonzentration in mg/dl) gegen die Zeit in Stunden. Die gestrichelte Kurve B ist das erfindungsgemäß gefilterte Nutzsignal. Zu dem mit dem Pfeil 28 markierten Zeitpunkt beginnt der Proband mit Bewegungen, die den Signalverlauf stören. Die tatsächliche Analytkonzentration ändert sich kaum, aber die durch die Bewegung verursachten Störungen (NNNC-Noise) können von dem konventionellen Filter nicht herausgefiltert werden. Mit der erfindungsgemäßen Filterung erhält man hingegen ein Nutzsignal, das dem physiologischen Glucoseverlauf in sehr guter Näherung folgt.

[0054] Eine erhebliche zusätzliche Sicherheit läßt sich erreichen, wenn sich die Filterung nicht nur auf die gesuchte Analytkonzentration, sondern zusätzlich auf mindestens eine weitere Variable erstreckt, die als Kontrollvariable bezeichnet wird. Dies kann eine aus der Analytkonzentration abgeleitete Größe, insbesondere deren erste, zweite oder höhere zeitliche Ableitung sein. Alternativ kommt auch eine zusätzlich gemessene Größe, wie beispielsweise der Fluß der interstitiellen Flüssigkeit bei dem Sensor gemäß Figur 2 in Betracht. Diese Kontrollvariable kann, wie oben (für g_t', A_t und ω_t) erläutert, als Systemvariable in dem Filteralgorithmus mitgeführt werden. Die Filterung erstreckt sich dann auch auf die Kontrollvariable, für die als Ergebnis der Filterung entsprechend zuverlässige geglättete Nutzsignalwerte zur Verfügung stehen. Diese können dann mit Grenzwerten verglichen werden, um beispielsweise Plausibilitätskontrollen durchzuführen. Im Falle der Glucosekonzentration ist zum Beispiel bekannt, daß Änderungsgeschwindigkeiten der Glucosekonzentration von mehr als 3 mg/dl min physiologisch unter gewöhnlichen Bedingungen nicht vorkommen. Wenn der gefilterte Wert der zeitlichen Ableitung g_t' einen höheren Wert annimmt, ist dies ein Zeichen für eine Fehlfunktion. Dies kann durch die in Figur 4 dargestellte Abfrage 30 benutzt werden, bei der der Wert von y_t' mit einem Minimal- und einem Maximalwert verglichen und y_t nur dann als richtig angenommen wird, wenn y_t' innerhalb dieser Grenzen liegt. Ein solcher Vergleich wäre mit dem Nutzsignal A in Figur 6 nicht möglich, weil die unzureichend gefilterten unphysiologischen Schwankungen zu Fehlalarmen führen würden.

Patentansprüche

1. Verfahren zur laufenden Überwachung der Konzentration eines Analyten durch Bestimmung von dessen zeitlichem Verlauf im lebenden Körper eines Menschen oder Tieres,
bei welchem zu aufeinanderfolgenden Zeitpunkten Meßwerte einer mit der gesuchten Konzentration korrelierenden Meßgröße als Meßsignal ($\mathbf{z_t}$) gemessen werden und der zeitliche Verlauf der Konzentration als Nutzsignal ($\mathbf{y_t}$) aus dem Meßsignal mittels einer Kalibration ermittelt wird,
wobei
die Ermittlung des Nutzsignals ($\mathbf{y_t}$) aus dem Meßsignal ($\mathbf{z_t}$) einen Filteralgorithmus in der Zeitdomäne einschließt, durch den Fehler des.Nutzsignals reduziert werden, die aus in dem Meßsignal enthaltenen Störungen resultieren und der Filteralgorithmus eine Operation einschließt, bei der der Einfluß eines aktuellen Meßwertes auf das Nutzsignal

Abbott Ex. 1002 - 599/1438

mittels eines Gewichtungsfaktors (V) gewichtet wird,
dadurch gekennzeichnet, daß
während der laufenden Überwachung auf Basis von in engem zeitlichem Zusammenhang mit der Messung des aktuellen Meßwertes detektierten Signalschwankungen des Messsignals ein zeitlich veränderlicher Signalschwankungsparameter (σ_t), jeweils für den aktuellen Zeitpunkt, ermittelt wird,
wobei der Signalschwankungsparameter ein Maß für Signalschwankungen des Messsignals in einem dem aktuellen Meßwert vorausgehenden Zeitraum ist und zu dessen Bestimmung Meßwerte verwendet werden, die weniger als 30 Minuten vor der Messung des aktuellen Meßwertes gemessen wurden,
und
der Gewichtungsfaktor dynamisch in Abhängigkeit von dem für den Zeitpunkt der aktuellen Messung ermittelten Signalschwankungsparameters adaptiert wird, wobei der Gewichtungsfaktor in der Richtung verändert wird, dass der Einfluß des jeweils aktuellen Meßwertes bei Zunahme der Standardabweichung der für die Bestimmung des Signalschwankungsparameters verwendeten Meßwerte vermindert wird.

2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** bei der Bestimmung der Signalschwankungen Meßwerte verwendet werden, die weniger als 15 Minuten, bevorzugt weniger als 5 Minuten vor der Messung des aktuellen Meßwertes gemessen wurden.

3. Verfahren nach einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet, daß** der Filteralgorithmus ein rekursiver Filteralgorithmus ist.

4. Verfahren nach Anspruch 3, **dadurch gekennzeichnet, daß** der Filteralgorithmus ein Kalman-Filteralgorithmus ist.

5. Verfahren nach Anspruch 4, **dadurch gekennzeichnet, daß** der Filteralgorithmus ein linearer Kalman-Filteralgorithmus ist.

6. Verfahren nach einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet, daß** zu den Variablen eines dem Filteralgorithmus zugrundeliegenden Systemmodells eine Kontrollvariable gehört.

7. Verfahren nach Anspruch 6, **dadurch gekennzeichnet, daß** die Kontrollvariable eine zeitliche Ableitung, vorzugsweise die erste zeitliche Ableitung der Analytkonzentration ist.

8. Gerät zur laufenden Überwachung der Konzentration eines Analyten durch Bestimmung von dessen zeitlichem Verlauf im lebenden Körper eines Menschen oder Tieres,
mit einer Meßeinheit (12), durch die zu aufeinanderfolgenden Zeitpunkten Meßwerte einer mit der gesuchten Konzentration korrelierenden Meßgröße als Meßsignal **(z_t)** gemessen werden und mit einer Auswerteeinheit (3), durch die der zeitliche Verlauf der Konzentration als Nutzsignal **(y_t)** aus dem Meßsignal mittels einer Kalibration ermittelt wird,
wobei
die Ermittlung des Nutzsignals **(y_t)** aus dem Meßsignal **(z_t)** einen Filteralgorithmus in der Zeitdomäne einschließt, durch den Fehler des Nutzsignals reduziert werden, die aus in dem Meßsignal enthaltenen Störungen resultieren und der Filteralgorithmus eine Operation einschließt, bei der der Einfluß eines aktuellen Meßwertes auf das Nutzsignal mittels eines Gewichtungsfaktors (V) gewichtet wird,
dadurch gekennzeichnet, daß
während der laufenden Überwachung auf Basis von in engem zeitlichem Zusammenhang mit der Messung des aktuellen Meßwertes detektierten Signalschwankungen des Messsignals ein zeitlich veränderlicher Signalschwankungsparameter (σ_t), jeweils für den aktuellen Zeitpunkt, ermittelt wird, wobei der Signalschwankungsparameter ein Maß für Signalschwankungen des Messsignals in einem dem aktuellen Meßwert vorausgehenden Zeitraum ist und zu dessen Bestimmung Meßwerte verwendet werden, die weniger als 30 Minuten vor der Messung des aktuellen Meßwertes gemessen wurden,
und
der Gewichtungsfaktor dynamisch in Abhängigkeit von dem für den Zeitpunkt der aktuellen Messung ermittelten Signalschwankungsparameters adaptiert wird, wobei der Gewichtungsfaktor in der Richtung verändert wird, dass der Einfluß des jeweils aktuellen Meßwertes bei Zunahme der Standardabweichung der für die Bestimmung des Signalschwankungsparameters verwendeten Meßwerte vermindert wird.

Abbott Ex. 1002 - 600/1438

Claims

1. Method for continuous monitoring of the concentration of an analyte by determining its change over time in the living body of a human or animal,
in which, at sequential points in time, measurement values of a measurement variable correlating with the desired concentration are measured as a measurement signal **(z_t)** and the change over time of the concentration is determined from the measurement signal as a useful signal **(y_t)** by means of a calibration,
wherein
the determination of the useful signal **(y_t)** from the measurement signal **(z_t)** includes a filter algorithm in the time domain, by which errors of the useful signal resulting from noise contained in the measurement signal are reduced, and
the filter algorithm includes an operation in which the influence of an actual measurement value on the useful signal is weighted by means of a weighting factor (V),
characterized in that,
during the continuous monitoring, a time dependent signal variation parameter (σ_t), related to the actual point in time, is determined on the basis of signal variations of the measurement signal detected in close chronological relation to the measurement of the actual measurement value,
wherein the signal variation parameter is a measure for signal variations of the measurement signal for a period of time preceding an actual measurement value and is determined on the basis of measurement values including values which were measured less than 30 minutes before the measurement of the actual value; and
the weighting factor is dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement, the weighting factor being changed in such a direction that the influence of the actual measurement value is reduced with increasing standard deviation of the measurement signal.

2. The method according to Claim 1,
characterized in that measurement values, which were measured less than 15 minutes, and preferably less than 5 minutes before the measurement of the actual measurement value, are used in the determination of the signal variations.

3. The method according to one of the preceding claims,
characterized in that the filter algorithm is a recursive filter algorithm.

4. The method according to Claim 3,
characterized in that the filter algorithm is a Kalman filter algorithm.

5. The method according to Claim 4,
characterized in that the filter algorithm is a linear Kalman filter algorithm.

6. The method according to one of the preceding claims,
characterized in that the variables of a system model upon which the filter algorithm is based comprise a check variable.

7. The method according to Claim 6,
characterized in that the check variable is a time derivative, preferably the first time derivative of the analyte concentration.

8. A device for continuous monitoring of the concentration of an analyte by determining its change over time in the living body of a human or animal,
comprising a measurement unit (12), by which measurement values of a measurement variable correlating with the desired concentration are measured as the measurement signal (z_t) at sequential points in time, and comprising an analysis unit (3), by which the change over time of the concentration is determined by means of a calibration as a useful signal (y_t) from the measurement signal,
the determination of the useful signal (y_t) from the measurement signal (z_t) includes a filter algorithm in the time domain, by which errors of the useful signal, which result from noise contained in the measurement signal, are reduced, and
the filter algorithm includes operations, in which the influence of an actual measurement value on the useful signal is weighted using a weighting factor (V),
characterized in that,

Abbott Ex. 1002 - 601/1438

during the continuous monitoring, a time dependent signal variation parameter (σ_t), related to the actual point in time, is determined on the basis of signal variations of the measurement signal detected in close chronological relation to the measurement of the actual measurement value,
wherein the signal variation parameter is a measure for signal variations of the measurement signal for a period of time preceding an actual measurement value and is determined on the basis of measurement values including values which were measured less than 30 minutes before the measurement of the actual value; and
the weighting factor is dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement, the weighting factor being changed in such a direction that the influence of the actual measurement value is reduced with increasing standard deviation of the measurement signal.

Revendications

1. Procédé de surveillance continue de la concentration d'un analyte par détermination de sa variation temporelle dans le corps vivant d'un homme ou d'un animal,
dans lequel on mesure à des instants successifs des valeurs de mesure d'une grandeur de mesure en corrélation avec la concentration recherchée en tant que signal de mesure ($\mathbf{z_t}$) et on détermine à partir dudit signal de mesure, au moyen d'une calibration, la variation temporelle de la concentration en tant que signal utile ($\mathbf{y_t}$),
la détermination du signal utile ($\mathbf{y_t}$) à partir du signal de mesure ($\mathbf{z_t}$) incluant un algorithme de filtrage dans le domaine temporel, qui permet de réduire des erreurs du signal utile résultant de perturbations contenues dans le signal de mesure, et
l'algorithme de filtrage incluant une opération consistant à pondérer l'influence d'une valeur de mesure actuelle sur le signal utile au moyen d'un facteur de pondération (V),
caractérisé en ce que
on détermine au cours de la surveillance continue, sur la base de variations de signal du signal de mesure détectées en rapport temporel étroit avec la mesure de la valeur de mesure actuelle, un paramètre de variation de signal (σ_t) variable dans le temps pour l'instant actuel,
ledit paramètre de variation de signal étant une mesure des variations de signal du signal de mesure dans un intervalle de temps précédant la valeur de mesure actuelle et pour la détermination duquel étant utilisées des valeurs de mesure, qui ont été mesurées moins de 30 minutes avant la mesure de la valeur de mesure actuelle,
et
on adapte le facteur de pondération de manière dynamique en fonction du paramètre de variation de signal déterminé pour l'instant de la mesure actuelle, le facteur de pondération étant modifié dans le sens de diminuer l'influence de la valeur de mesure actuelle lorsque l'écart type des valeurs de mesure utilisées pour la détermination du paramètre de variation de signal augmente.

2. Procédé selon la revendication 1, **caractérisé en ce que** l'on utilise lors de la détermination des variations de signal des valeurs de mesure, qui ont été mesurées moins de 15 minutes, de préférence moins de 5 minutes avant la mesure de la valeur de mesure actuelle.

3. Procédé selon l'une des revendications précédentes, **caractérisé en ce que** l'algorithme de filtrage est un algorithme de filtrage récursif.

4. Procédé selon la revendication 3, **caractérisé en ce que** l'algorithme de filtrage est un algorithme de filtrage de Kalman.

5. Procédé selon la revendication 4, **caractérisé en ce que** l'algorithme de filtrage est un algorithme de filtrage linéaire de Kalman.

6. Procédé selon l'une des revendications précédentes, **caractérisé en ce qu**'une variable de contrôle fait partie des variables d'un modèle de système sur lequel est basé l'algorithme de filtrage.

7. Procédé selon la revendication 6, **caractérisé en ce que** la variable de contrôle est une dérivée temporelle, de préférence la première dérivée temporelle de la concentration d'analyte.

8. Appareil de surveillance continue de la concentration d'un analyte par détermination de sa variation temporelle dans le corps vivant d'un homme ou d'un animal,
avec une unité de mesure (12), permettant de mesurer à des instants successifs des valeurs de mesure d'une

Abbott Ex. 1002 - 602/1438

grandeur de mesure en corrélation avec la concentration recherchée en tant que signal de mesure ($\mathbf{z_t}$), et avec une unité d'évaluation (3), permettant de déterminer à partir dudit signal de mesure, au moyen d'une calibration, la variation temporelle de la concentration en tant que signal utile ($\mathbf{y_t}$),
la détermination du signal utile ($\mathbf{y_t}$) à partir du signal de mesure ($\mathbf{z_t}$) incluant un algorithme de filtrage dans le domaine temporel, qui permet de réduire des erreurs du signal utile résultant de perturbations contenues dans le signal de mesure, et
l'algorithme de filtrage incluant une opération consistant à pondérer l'influence d'une valeur de mesure actuelle sur le signal utile au moyen d'un facteur de pondération (V),
caractérisé en ce que
au cours de la surveillance continue, sur la base de variations de signal du signal de mesure détectées en rapport temporel étroit avec la mesure de la valeur de mesure actuelle, un paramètre de variation de signal (σ_t) variable dans le temps est déterminé pour l'instant actuel,
ledit paramètre de variation de signal étant une mesure des variations de signal du signal de mesure dans un intervalle de temps précédant la valeur de mesure actuelle et pour la détermination duquel étant utilisées des valeurs de mesure, qui ont été mesurées moins de 30 minutes avant la mesure de la valeur de mesure actuelle,
et
le facteur de pondération est adapté de manière dynamique en fonction du paramètre de variation de signal déterminé pour l'instant de la mesure actuelle, le facteur de pondération étant modifié dans le sens de diminuer l'influence de la valeur de mesure actuelle lorsque l'écart type des valeurs de mesure utilisées pour la détermination du paramètre de variation de signal augmente.

Abbott Ex. 1002 - 603/1438

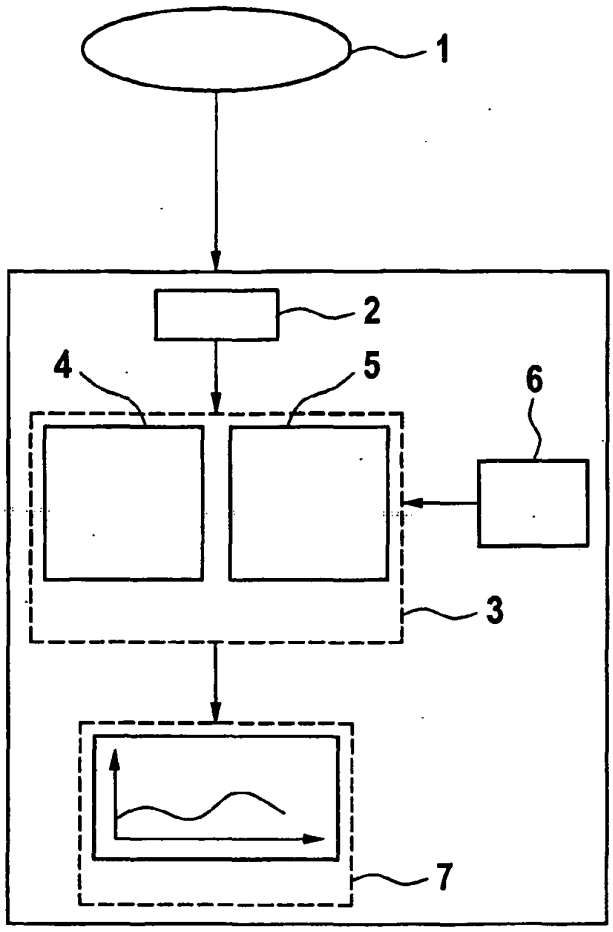


Fig. 1

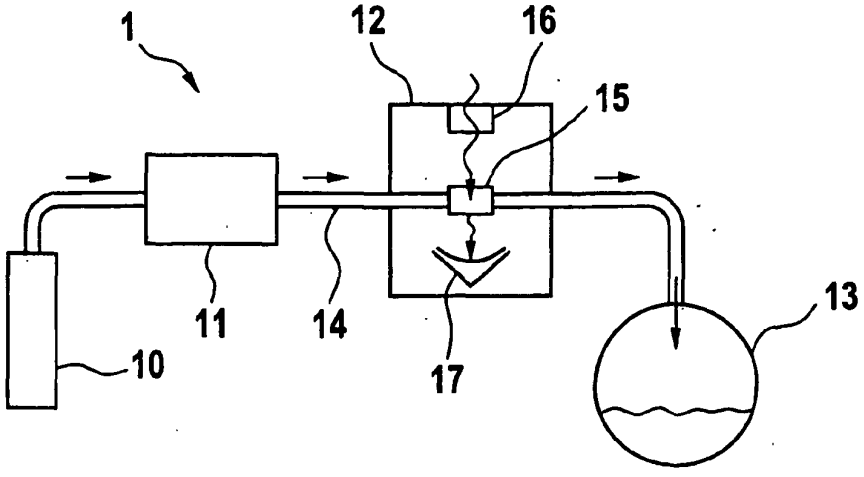


Fig. 2

Abbott Ex. 1002 - 604/1438

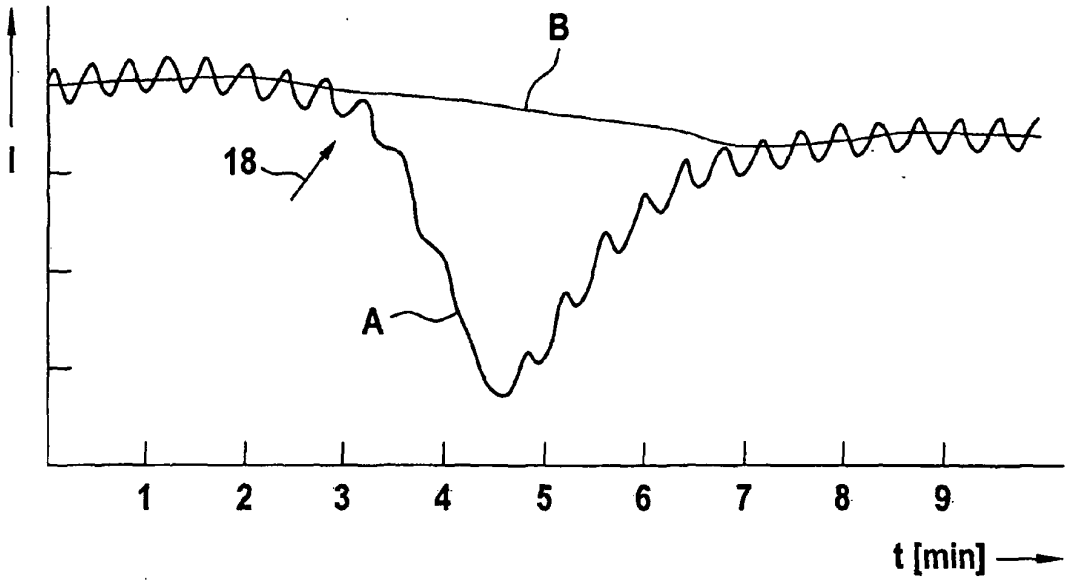


Fig. 3

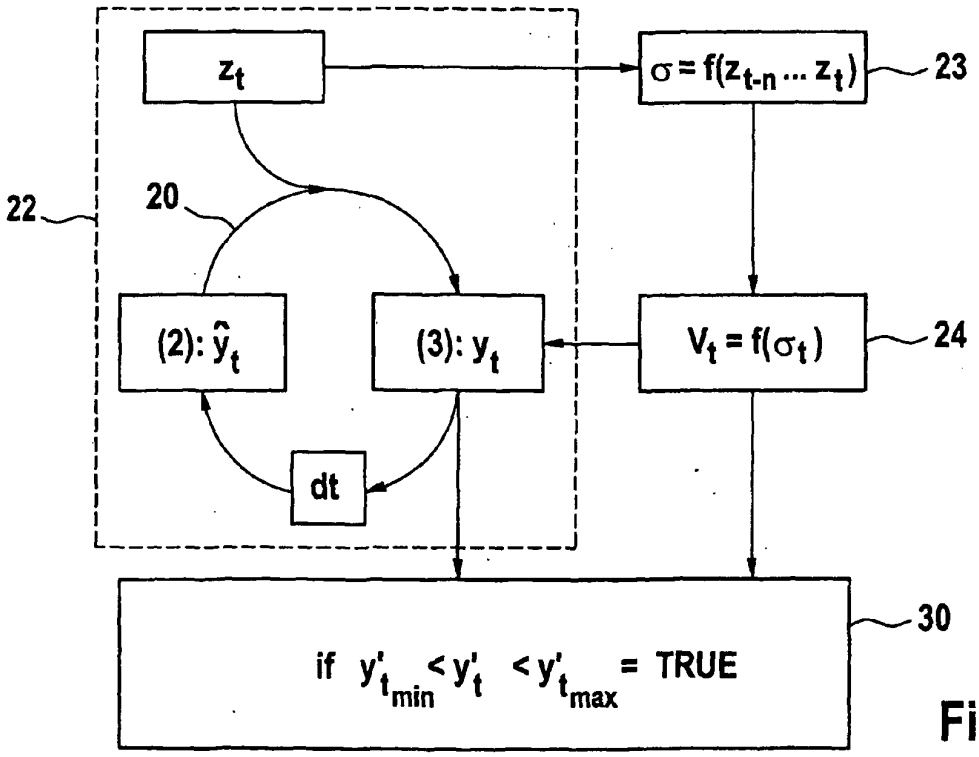


Fig. 4

Abbott Ex. 1002 - 605/1438

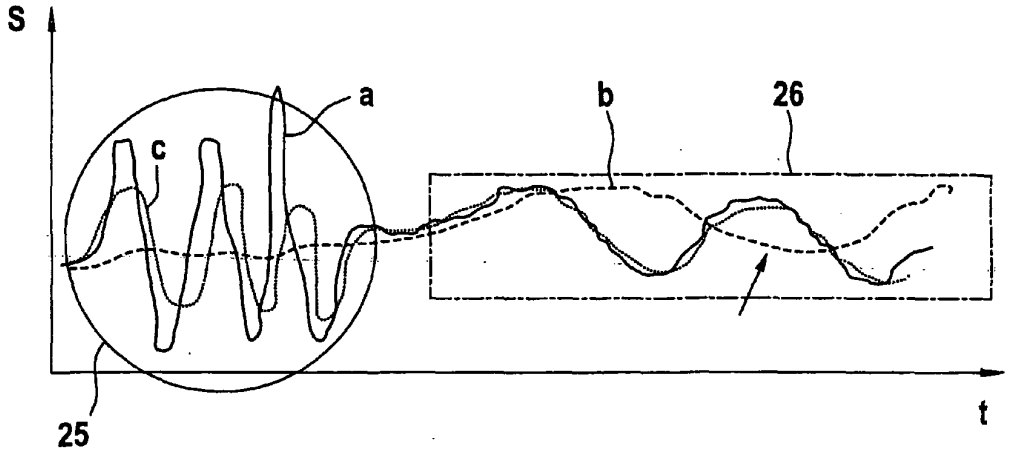


Fig. 5

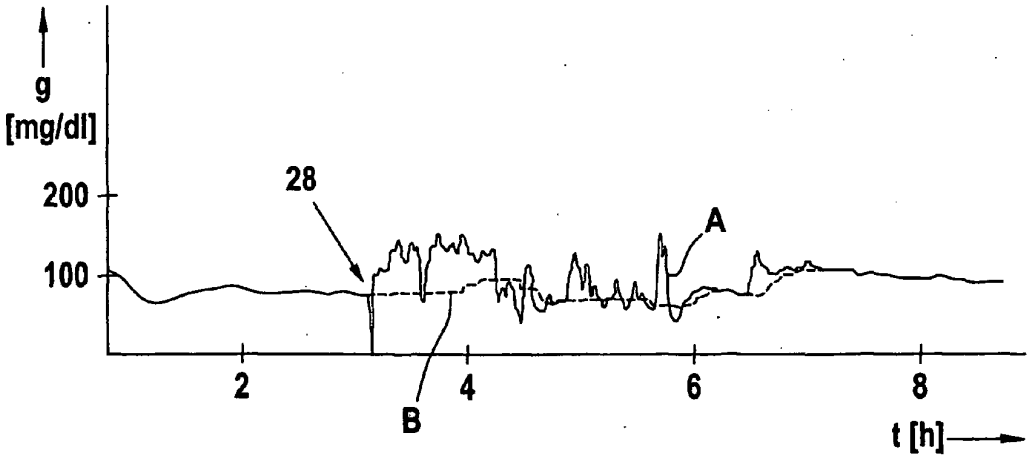


Fig. 6

Abbott Ex. 1002 - 606/1438

IN DER BESCHREIBUNG AUFGEFÜHRTE DOKUMENTE

Diese Liste der vom Anmelder aufgeführten Dokumente wurde ausschließlich zur Information des Lesers aufgenommen und ist nicht Bestandteil des europäischen Patentdokumentes. Sie wurde mit größter Sorgfalt zusammengestellt; das EPA übernimmt jedoch keinerlei Haftung für etwaige Fehler oder Auslassungen.

In der Beschreibung aufgeführte Patentdokumente

- US 5507288 A **[0002]**
- US 6584335 B **[0005]**
- US 5921937 B **[0010]**
- EP 0910023 A2 **[0010]**
- WO 0138948 A2 **[0010]**
- US 6317662 B **[0010]**
- US 6575905 B2 **[0010]**
- WO 0224065 A **[0010]**
- US 6519705 B **[0010]**

In der Beschreibung aufgeführte Nicht-Patentliteratur

- **S. D. Brown.** *The Kalman filter in analytical chemistry, Analytica Chimica Acta,* 1986, vol. 181, 1-26 **[0010]**
- **K. Gordon.** *The multi-state Kalman filter in medical monitoring, Computer Methods and Programs in Biomedicine,* 1986, vol. 23, 147-154 **[0010]**
- **K. Gordon ; A.F.M. Smith.** *Modelling and monitoring biomedical time series, Journal of the American Statistical Association,* 1990, vol. 85, 328-337 **[0010]**

Abbott Ex. 1002 - 607/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 703 839 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
08.02.2012 Bulletin 2012/06

(21) Application number: **04814197.2**

(22) Date of filing: **15.12.2004**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/US2004/041985

(87) International publication number:
WO 2005/065538 (21.07.2005 Gazette 2005/29)

(54) SYSTEM FOR MONITORING PHYSIOLOGICAL CHARACTERISTICS

SYSTEM ZUR ÜBERWACHUNG VON PHYSIOLOGISCHEN GRÖSSEN

SYSTEME PERMETTANT DE CONTROLER DES CARACTERISTIQUES PHYSIOLOGIQUES

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR

(30) Priority: **31.12.2003 US 750080**

(43) Date of publication of application:
27.09.2006 Bulletin 2006/39

(73) Proprietor: **Medtronic MiniMed, Inc.**
Northridge, CA 91325-1291 (US)

(72) Inventors:
- **SIDDIQUI, Uzair**
  Stevenson Ranch, CA 91381 (US)
- **PATEL, Himanshu, P.**
  Northridge, CA 91326 (US)
- **MASTROTOTARO, John, J.**
  Los Angeles, CA 90024 (US)
- **FREDRICKSON, Linda, P.**
  Sunland, CA 91040 (US)
- **HOLTZCLAW, Kris, R.**
  Valencia, CA 91325 (US)
- **WENHOLZ, Bruce, R.**
  Burbank, CA 91505 (US)
- **ESTES, Mark, C.**
  Simi Valley, CA 93065 (US)
- **SAIDARA, Frank**
  Los Angeles, CA 90067 (US)

(74) Representative: **Ruschke, Hans Edvard**
RUSCHKE HARTMANN MADGWICK & SEIDE
Patent- und Rechtsanwälte
Postfach 86 06 29
81633 München (DE)

(56) References cited:
US-A1- 2003 125 612 **US-A1- 2003 211 617**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 703 839 B1

Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] This invention relates generally to medical monitoring systems. More specifically, this invention relates to methods and systems for monitoring physiological characteristics in individuals including those associated with physiological conditions (e.g. monitoring blood glucose levels in diabetics).

2. Description of the Related Art

[0002] A variety of electrochemical sensors have been developed for detecting and/or quantifying specific agents or compositions in a patient's blood. Notably, glucose sensors have been developed for use in obtaining an indication of blood glucose levels in a diabetic patient. Such readings are useful in monitoring and/or adjusting a treatment program which typically includes the regular administration of insulin to the patient. Periodic blood glucose readings significantly improve medical therapies using semi-automated medication infusion devices. Some exemplary external infusion devices are described in U.S. Patent Nos. 4,562,751, 4,678,408 and 4,685,903, while some examples of automated implantable medication infusion devices are described in U.S. Patent No. 4,573,994.

[0003] Electrochemical sensors can be used to obtain periodic measurements over an extended period of time. Such sensors can include a plurality of exposed electrodes at one end for subcutaneous placement in contact with a user's interstitial fluid, blood, or the like. A corresponding plurality of conductive contacts can be exposed at another end for convenient external electrical connection with a suitable monitoring device through a wire or cable. Exemplary sensors are described in U.S. Patent Nos. 5,299,571; 5,390,671; 5,391,250; 5,482,473; and 5,586,553, which are all incorporated by reference herein.

[0004] Conventional glucose monitoring systems are somewhat limited in features that they provide to facilitate the monitoring of blood glucose levels. Typically, a glucose monitor will take readings as directed by the user and might provide a warning if a reading is deemed at an unsafe level (e.g., a hyper- or hypoglycemic condition). However, by the time the warning occurs, the user may already be experiencing negative symptoms. Furthermore, it may be unacceptable to address this by simply reducing (or raising) the value which triggers an indicator (e.g. a display, an alarm or the like) of an unsafe condition, because this may prompt a user to take "remedial" action (such as administering an additional bolus) when no unsafe condition would have actually materialized. Such an approach merely increases the occurrence of false positive alarms. As a consequence, the unnecessary "remedial" action can actually provoke an unsafe condition. As described above, although existing glucose monitors adequately detect blood glucose levels upon entering the hyperglycemic (or hypoglycemic) range, they do not anticipate these conditions.

[0005] As is known in the art, a glucose crash occurs when blood glucose levels of an individual are in a state of rapid decline and its symptoms are similar to those associated with hypoglycemia. The symptoms are caused by the dynamics of a declining glucose level and not by an absolute glucose level. Specific symptoms can include a feeling of light headedness, sweating, tremors, nervousness and/or disorientation. Disorientation is a particular risk to the patient. If the patient becomes disoriented while operating machinery, the patient could harm himself or others. A glucose crash can be caused by any of the following events: excess insulin administration; an unexpected increase in insulin sensitivity; a fall of free fatty acids in the blood; heavy exercise; or mental or physical stress. As previously mentioned, ordinary glucose monitors provide only for detection of hypoglycemic and hyperglycemic levels.

[0006] Impaired fasting glucose (IFG) is another condition which is not predicted by conventional glucose monitors. The American Diabetes Association (ADA) identifies IFG as an undesirable glucose condition, defined as a 126 mg/dL or higher blood glucose level at wakeup. Repeated IFG events can contribute to diabetic morbidity. One cause of IFG is an inadequate nocturnal insulin basal infusion rate. Although a patient can deal with the IFG after waking by administering an insulin bolus, it is preferable for the patient to avoid IFG incidents entirely.

[0007] Conventional monitors are designed to alert the user of unsafe conditions; however, many other factors and situations are also important to the user in managing treatment. For example, events such as meals or exercise, as well as entering calibration values are not tied to reminders issued by conventional monitors. Typical monitors provide only a single alarm to call attention to the user. This can be problematic in contexts of varying physiological states because a user is not made aware of the specific condition and/or the appropriate degree of urgency. In conventional alarm systems, until the user investigates, there is often no indication of the reason for the alarm or the severity of the situation.

[0008] Furthermore, the alarm settings and features for many monitoring systems are very limited. Such systems can provide duplicative warnings that can frustrate users and become ignored if they are excessive. In addition, typical monitoring systems will alarm during predictable periods during which a user does not wish to be disturbed.

US 2003/125612 discloses apparatuses and methods for medical monitoring physiological characteristics values such

Abbott Ex. 1002 - 609/1438

as blood glucose levels for the treatment of diabetes, wherein dynamic glucose monitoring functions are provided that perform predictive analysis to anticipate harmful conditions for a patient or to maximize athletic performance and warn of inadequate nocturnal basal rate. For this purpose, sensors and processors are used for sensing a physiological characteristic value of a user and for operating an alarm, resp.

US 2003/211617 discloses methods, a program product, and an apparatus for implementing a blood glucose meter that will remind the user to test the blood glucose after a programmable wait when a hypoglycemic event is detected, wherein the user may program the meter with an appropriate waiting period to wait following a low blood glucose reading. At the end of this period, the meter will alert the user by way of an audible or tactile warning.

[0009] Thus, conventional glucose monitoring systems are somewhat limited in features they provide to facilitate the monitoring of blood glucose levels. There is a need for monitoring systems for a physiological characteristic (such as blood glucose levels) with convenient features and settings that allow users flexibility in tailoring the system's operation to their personal needs and lifestyle. Particularly, there is a need for such systems that provide advanced alarm functions to reduce or eliminate redundant alarms. In addition, there is a need for monitoring systems that allow a convenient review of measurement and alarm histories. These and other needs are met by the present invention.

SUMMARY OF THE INVENTION

[0010] The invention as embodied and disclosed herein is defined in the claims and pertains to apparatuses and methods for monitoring blood glucose levels. Embodiments of the invention include dynamic monitoring functions that can perform predictive analyses to anticipate harmful conditions, such as hyperglycemic (or hyperglycemic) incidents, before they occur. These dynamic functions can be used to monitor normal physiological functions, as well as in a variety of other contexts including the optimization of athletic performance. Other embodiments of the invention include advanced alarm and reminder functions, as well as advanced data presentation tools. Embodiments of the invention disclosed herein facilitate the convenient and efficient management of diseases such as diabetes.

[0011] One embodiment of the invention includes a method of monitoring a physiological characteristic of a user using a device including an input element capable of receiving a signal from a sensor that is based on a sensed physiological characteristic value of the user, and a processor for analyzing the received signal. In typical embodiments of the invention, the processor determines a dynamic behavior of the physiological characteristic value and provides an observable indicator based upon the dynamic behavior of the physiological characteristic value so determined. In a preferred embodiment, the physiological characteristic value is a measure of the concentration of blood glucose in the user. In another embodiment, the process of analyzing the received signal and determining a dynamic behavior includes repeatedly measuring the physiological characteristic value to obtain a series of physiological characteristic values to determine how the physiological characteristic is changing over time.

[0012] In some embodiments of the invention, each of the series of physiological characteristic values includes a smoothing filtered group of repeated physiological characteristic value readings. In such embodiments, a slope of a line fit to the series of physiological characteristic values can be calculated if a most recent of the series of physiological characteristic values is within a qualifying range. In some embodiments of the invention, the physiological characteristic value readings may be decreasing and the slope is negative. Typically, the indicator can also include a warning alarm that is responsive to the dynamic behavior profile of the physiological characteristic value. The warning alarm can also announce an anticipated glucose crash or merely low glucose levels, depending on the operating parameters of the particular dynamic analysis, including comparison of the slope to a threshold rate (e.g., 1% to 3% per minute) and comparison of the current measured value to a qualifying range (e.g., 60 to 150 mg/dL). In typical embodiments, the series of values analyzed is taken from a defined span of time (e.g., ten to thirty minutes).

[0013] In other typical embodiments of the invention, an anticipated physiological characteristic value is determined from an extrapolated curve based upon the series of physiological characteristic values. In such embodiments the indicator can provide a warning of an anticipated morning glucose incident. In preferred embodiments, the series of values analyzed can also be taken from a defined span of time (e.g. one hour). In one embodiments, the extrapolated curve is determined from a slope of a line fit to the series of physiological characteristic values and an average of the series of physiological characteristic values. In another illustrative embodiment, the anticipated physiological characteristic value can be determined approximately three hours before an anticipated wakeup time. In addition, in certain embodiments, the indicator can be provided if the anticipated value is outside a qualifying range (e.g., approximately 60 mg/dL to 126 mg/dL).

[0014] In related embodiments of the invention, a slope of a line fit to the series of physiological characteristic values is calculated if a most recent of the series of physiological characteristic values exceeds a threshold value and the slope is positive. In such embodiments, the indicator can provide a warning of an anticipated hyperglycemic incident. In an illustrative embodiment, the series of physiological characteristic values spans a time period of approximately thirty minutes and the indicator will be provided if the slope is steeper than a threshold rate. In this context a typical threshold rate can be approximately 3% per minute and the threshold value can be approximately 180 mg/dL. In such other

Abbott Ex. 1002 - 610/1438

embodiments, the indicator can provide a warning of an anticipated hypoglycemic incident. In an illustrative embodiment, the series of physiological characteristic values spans a time period of approximately thirty minutes and the indicator will be provided if the slope is steeper than a threshold rate. In this context a typical threshold rate can be approximately 3% per minute and the threshold value can be approximately 70 mg/dL.

[0015] Another embodiment of the invention includes a physiological characteristic monitor (and corresponding methods for its use) including an input device capable of receiving a signal from a sensor and a processor capable of analyzing the received signal and providing multiple alarms, each of which can be based upon different conditions associated with the physiological characteristic value of the user. In preferred embodiments, the signal is based on a physiological characteristic value of a user. In some embodiments, the multiple alarms are distinguishable from each other and can include any one of a wide variety of signals such as audible signals, visual signals, tactile signals, displays, and/or the like.

[0016] In some embodiments of the invention, the processor determines a physiological characteristic value from the received signal and the multiple alarms are based upon that value. In such embodiments, each of the multiple alarms can then be triggered if the physiological characteristic value exceeds an associated threshold value.

[0017] In other embodiments of the invention, one of a first pair of the multiple alarms can be triggered when a narrow range of physiological characteristic values is exceeded. The first pair of the multiple alarms is typically associated with a first upper threshold value and a first lower threshold value, respectively. In further embodiments, a second pair of multiple alarms can be triggered by events a wide range of physiological characteristic values (e.g. exceeding a predetermined value). The second pair of the multiple alarms can be associated with a second upper threshold value and a second lower threshold value, respectively.

[0018] In yet another embodiment of the invention, a physiological characteristic monitoring method and device are disclosed which include an input device capable of receiving a signal from a sensor and a processor for analyzing the received signal. Typically, the signal is based on a physiological characteristic value of a user. In preferred embodiments, the processor initiates a timer based upon a condition associated with the physiological characteristic value of the user and provides a reminder to the user following expiration of the timer. In some embodiments of the invention, the reminder can include an alarm signal selected from the group consisting of an audible signal, a visual signal, a tactile signal, a display, and/or the like. Typically, the duration of the timer is preset based upon the specific initiating condition.

[0019] In preferred embodiments of the invention, conditions which trigger the one or more alarms can vary. For example, the conditions which trigger the one or more alarms can be an event marker such as meal markers, exercise markers, high blood glucose markers and low blood glucose markers. The condition(s) which trigger the one or more alarms can further be a reference value that is entered into the monitor and the reminder can indicate that a new reference value should be entered.

[0020] In other embodiments of the invention, the processor can determine a physiological characteristic value from the received signal and the triggering condition is then based upon that physiological characteristic value. For example, the triggering condition can be situations where the physiological characteristic value exceeds a predetermined threshold value.

[0021] Other embodiments of the invention include a physiological characteristic monitor including an input device capable of receiving a signal from a sensor, a processor for analyzing the received signal and determining physiological characteristic value data of the user from the received signal, a memory for storing the physiological characteristic value data of the user and a display. Typically, the signal is based on a physiological characteristic value of a user. In preferred embodiments, the display provides a retrospective display of the physiological characteristic value data. In some embodiments of the invention, the stored physiological characteristic value data includes a minimum and maximum blood glucose value and the retrospective display shows the minimum and maximum blood glucose value with a respective time and date. In other embodiments, the stored physiological characteristic value data can include a first number of excursions above an upper blood glucose value and a second number of excursions below a lower blood glucose value and the retrospective display shows the first and second number.

[0022] In other embodiments of the invention, the stored physiological characteristic value data can include a distribution of blood glucose values and the retrospective display shows a first portion of the blood glucose values above an upper blood glucose value, a second portion of the blood glucose values below a lower blood glucose value and a third portion of the blood glucose values between the upper value and the lower value. In preferred embodiments, the portions can be shown as percentages, times or numbers of readings. The display can include a total time for the physiological characteristic value data as well as the total number of readings for the physiological characteristic value data. In preferred embodiments of the invention, the first portion and the second portion can be shown as integrated values. The integrated values can be based on the sums of magnitude differences from the upper blood glucose value and the lower blood glucose value for the first and second portion, respectively. In such embodiments, the integrated values can be divided by a respective duration of sensor use.

[0023] In yet other embodiments of the invention, further advanced alarm functions are employed such as an alarm repeat delay to prevent redundant alarms for a specified period and an alarm snooze function to prevent alarms generally for a specified period. In addition, embodiments of the invention include a monitor that performs a status check routine

Abbott Ex. 1002 - 611/1438

based on sensor activity, sensor calibration and telemetry. Other embodiments of the invention include a measurement entry time and value display for a monitor as well as a real-time and historical measurement display function.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Referring now to the drawings in which like reference numbers represent corresponding parts throughout:
[0025] FIG. 1A is a block diagram of a characteristic monitor embodiment of the present invention;
[0026] FIG. 1B is a block diagram of a telemetered characteristic monitor embodiment of the present invention;
[0027] FIG. 2A is a flowchart of a status check algorithm for a characteristic monitor embodiment of the present invention;
[0028] FIG. 2B is a flowchart of screens for entering a reference value to calibrate a characteristic monitor embodiment of the present invention;
[0029] FIG. 3A is a flowchart of a method for anticipating a glucose crash;
[0030] FIG. 3B is a flowchart of a method for detecting an inadequate nocturnal basal rate;
[0031] FIG. 3C is a flowchart of a method for anticipating a hyperglycemic incident;
[0032] FIG. 3D is a flowchart of a method for maximizing athletic performance;
[0033] FIG. 4A illustrates a multiple alarm function of the invention;
[0034] FIGS. 4B and 4C illustrate respectively hypoglycemia and hyperglycemia alarm screens;
[0035] FIGS. 4D and 4E illustrate respectively flowcharts of screens for setting hypoglycemia and hyperglycemia alarms (Underlined text indicates one that's blinking on the current screen, awaiting to be changed by the user. From screens 1-8, SEL aborts and goes to the next major screen);
[0036] FIG. 4F illustrates a flowchart of screens for setting a hyperglycemia alarm snooze (Underlined text indicates one that's blinking on the current screen, awaiting to be changed by the user. From screens 1-2, SEL aborts and goes to the next major screen);
[0037] FIG. 4G illustrates a flowchart of screens for reviewing a history of glycemia alarms in accordance with an embodiment of the invention;
[0038] FIG. 5 illustrates a reminder function of an embodiment of the invention;
[0039] FIG. 6A illustrates minimum and maximum data presentation;
[0040] FIG. 6B illustrates excursion data presentation;
[0041] FIG. 6C illustrates characteristic value distribution data presentation;
[0042] FIG. 6D illustrates integrated characteristic value data presentation; and
[0043] FIG. 7 illustrates screens for viewing real-time and historical measurements of a physiological characteristic value in an embodiment of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

1. Overview

[0044] Embodiments of the present invention encompass methods and systems for the convenient operation of monitoring physiological characteristics ("characteristic monitoring systems"). The description provided here encompasses the architecture of the apparatus as well as its control and convenience features. The control and convenience features of the present invention can be implemented in a wide range of detailed characteristic monitoring system designs. Although embodiments of the present invention are primarily described in the context of glucose monitors used in the treatment of diabetes, the embodiments of the invention are applicable to a wide variety of patient treatment programs where a physiological characteristic is periodically monitored to use in estimating the responsive treatment. For example, embodiments of the invention can be used to determine the status and/or levels of a variety of characteristics including those associated with agents such as hormones, cholesterol, medication concentrations, pH, oxygen saturation, viral loads (e.g., HIV), or the like. As is known in the art, a sensor for the characteristic monitor can be implanted in and/or through subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue. Such sensors typically communicate a signal from the sensor set to the characteristic monitor.
[0045] General embodiments of the invention include a physiological characteristic monitor coupled to a sensor set. The sensor set and monitor are for determining glucose levels in the blood and/or body fluids of the user without the use of, or necessity of, a wire or cable connection between the transmitter and the monitor.
[0046] Embodiments of the characteristic monitor system of the invention are primarily adapted for use in subcutaneous human tissue. Alternatively, embodiments of the invention can be placed in a variety of other types of physiological milieus, such as muscle, lymph, organ tissue, veins, arteries or the like, as well as being used in related environments such as animal tissue. Embodiments of the invention can provide sensor readings on an intermittent, near-continuous or continuous basis.

Abbott Ex. 1002 - 612/1438

[0047] Embodiments of the invention include sensing and advanced predictive functions of the monitor which are designed to anticipate unsafe conditions for a user before they occur. In addition, predictive functions can be employed so that a user can obtain feedback to obtain a desired physical objective, such as maximizing athletic performance. Other functions of the monitor include multiple programmable alarms and reminders and diagnostic functions. Advanced alarm functions also include an alarm repeat delay function and a snooze function that can be set by a user. Embodiments of the invention can include advanced display tools to facilitate easy and quick interpretation of information related to the user's condition, including a display function for an alarm history as well as a history of measurements.

2. Glucose Monitor

[0048] FIG. 1A is a block diagram of a characteristic monitoring system 100 in accordance with an embodiment of the present invention. The characteristic monitoring system 100 generally includes a sensor set 102 that employs a sensor that produces a signal that corresponds to a measured characteristic of the user, such as a blood glucose level. The sensor set 102 communicates these signals to a characteristic monitor 104 that is designed to interpret these signals to produce a characteristic reading or value for the user, i.e. a measurement of the characteristic. The sensor signals enter the monitor 104 through a sensor input 106 and through the sensor input 106 the signals are conveyed to a processor 108. The processor 108 determines and manipulates the sensor readings within the monitor 104. In addition, but not limited to, the characteristic monitor 104 provides additional functions that will aid in the treatment regime to which the characteristic reading applies. For example, but not limited to, the monitor may track meals, exercise and other activities which affect the treatment of diabetes. These additional functions can be combined with or independent from the characteristic readings determined by the monitor 104.

[0049] Other components of the monitor 104 support the processor 108 in performing functions. A memory 110 is used to store data and instructions used by the processor 108. A data entry device 112 such as a keypad is used to receive direct input from the user and a display 114 such as a liquid crystal display (LCD), or the like, is used to relate information to the user. In addition, the monitor 104 includes a data port 116, such as a digital input/output (I/O) port.

[0050] The data port 116 can be used for the monitor 104 to communicate with a computer 118. To facilitate communication, the monitor 104 may interface with the computer 118 through a communication station 120 that can serve as a docking station for the monitor 104, for example. In some embodiments, the data port 116 within the monitor 104 can be directly connected to the computer 118. Through the communication link, data may be downloaded from the monitor 104, such as stored characteristic readings, settings, programs and other information related to the monitor's function. Thus, advanced analysis can be performed on the computer 118, freeing memory 110 within the monitor 104. Data such as characteristic readings, settings and programs can also be downloaded to the monitor 104. In this way, the monitor 104 can be conveniently reprogrammed without requiring tedious manual entry by the user.

[0051] FIG. 1B is a block diagram of a telemetered characteristic monitoring system embodiment of the invention. In this system embodiment 200, the sensor input 106 of the monitor 104 is a wireless receiver, such as a radio frequency (RF) receiver. The sensor set 102 provides a signal via wired link to a telemetered monitor transmitter 202, where the signal is interpreted and converted to an RF signal. The wireless receiver sensor input 106 of the monitor 104 converts the signal to data understandable to the monitor processor. With some advantages, the telemetered characteristic monitoring system can perform any or all the functions of the characteristic monitoring system of FIG. 1A.

[0052] A characteristic monitoring system 100, in accordance with a preferred embodiment of the present invention, includes a sensor set 102 and characteristic monitor device 104. The sensor set 102 generally utilizes an electrode-type sensor. However, in alternative embodiments, the system can use other types of sensors, such as electrically based sensors, chemically based sensors, optically based sensors, or the like. In further alternative embodiments, the sensors can be of a type that is used on the external surface of the skin or placed below the skin layer of the user. Preferred embodiments of a surface mounted sensor utilize interstitial fluid harvested from underneath the skin. The sensor set 102 is connected to the monitor device 104 and provides a signal based upon the monitored characteristic (e.g., blood glucose). The characteristic monitor device 104 utilizes the received signal to determine the characteristic reading or value (e.g., a blood glucose level). In still other embodiments, the sensor may be placed in other parts of the body, such as, but not limited to, subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue

[0053] The telemetered characteristic monitor transmitter 202 generally includes the capability to transmit data. In alternative embodiments, the telemetered characteristic monitor transmitter 202 can include a receiver, or the like, to facilitate two-way communication between the sensor set 102 and the characteristic monitor 104. In alternative embodiments, the characteristic monitor 104 can be replaced with a data receiver, storage and/or transmitting device for later processing of the transmitted data or programming of the telemetered characteristic monitor transmitter 202. In addition, a relay or repeater (not shown) can be used with a telemetered characteristic monitor transmitter 202 and a characteristic monitor 104 to increase the distance that the telemetered characteristic monitor transmitter 202 can be used with the characteristic monitor 104. For example, the relay can be used to provide information to parents of children using the telemetered characteristic monitor transmitter 202 and the sensor set 102 from a distance. The information can be used

Abbott Ex. 1002 - 613/1438

when children are in another room during sleep or doing activities in a location remote from the parents. In further embodiments, the relay can include the capability to sound an alarm. In addition, the relay can be capable of providing telemetered characteristic monitor transmitter 202 data from the sensor set 102, as well as other data, to a remotely located individual via a modem connected to the relay for display on a monitor, pager or the like. The data can also be downloaded through the communication station 120 to a remotely located computer 118 such as a PC, laptop, or the like, over communication lines, by modem or wireless connection. As disclosed herein, some embodiments of the invention can omit the communication station 120 and use a direct modem or wireless connection to the computer 118. In further embodiments, the telemetered characteristic monitor transmitter 202 transmits to an RF programmer, which acts as a relay, or shuttle, for data transmission between the sensor set 102 and a PC, laptop, communication station 118, a data processor, or the like. In further alternatives, the telemetered characteristic monitor transmitter 202 can transmit an alarm to a remotely located device, such as a communication station 118, modem or the like to summon help.

[0054] In addition, further embodiments can include the capability for simultaneous monitoring of multiple sensors and/or include a sensor for multiple measurements.

[0055] A purpose of the characteristic monitoring system 100 is to provide for better treatment and control in an outpatient or a home use environment. For example, the monitoring systems 100, 200 can provide indications of glucose levels, a hypoglycemia/hyperglycemia alarm and outpatient diagnostics. Embodiments of the invention are also useful as an evaluation tool under a physician's supervision.

[0056] The characteristic monitor device 104 receives characteristic information, such as glucose data or the like, from the sensor set 102 and displays and/or logs the received glucose readings. Logged data can be downloaded from the characteristic monitor 104 to a PC, laptop, or the like, for detailed data analysis. In further embodiments, the characteristic monitoring system 100, 200 can be used in a hospital environment, or the like. Still further embodiments of the present invention can include one or more buttons to record data and events for later analysis, correlation, or the like. Further buttons can include a sensor on/off button to conserve power and to assist in initializing the sensor set 102. The characteristic monitoring system 200 can also be employed with other medical devices to combine other patient data through a common data network system.

[0057] Further embodiments of the sensor set 102 can monitor the temperature of the sensor set 102, which can then be used to improve the calibration of the sensor. For example, for a glucose sensor, the enzyme reaction activity may have a known temperature coefficient The relationship between temperature and enzyme activity can be used to adjust the sensor values to more accurately reflect the actual characteristic levels. In addition to temperature measurements, the oxygen saturation level can be determined by measuring signals from the various electrodes of the sensor set 102. Once obtained, the oxygen saturation level can be used in calibration of the sensor set 102 due to changes in the oxygen saturation levels and its effects on the chemical reactions in the sensor set 102. For example, as the oxygen level goes lower, the sensor sensitivity can be lowered. In alternative embodiments, temperature measurements can be used in conjunction with other readings to determine the required sensor calibration.

[0058] In preferred embodiments, the sensor set 102 facilitates accurate placement of a flexible thin film electrochemical sensor of the type used for monitoring specific blood parameters representative of a user's condition. Preferably, the sensor monitors glucose levels in the body, and can be used in conjunction with automated or semi-automated medication infusion devices of the external or implantable type as described in U.S. Pat Nos. 4,562,751; 4,678,408; 4,685,903 or 4,573,994, to control delivery of insulin to a diabetic patient

[0059] Embodiments of the flexible electrochemical sensor can be constructed in accordance with thin film mask techniques to include elongated thin film conductors embedded or encased between layers of a selected insulative material, such as polyimide film or sheet, and membranes. The sensor electrodes at a tip end of the sensing portion are exposed through one of the insulative layers for direct contact with patient blood or other body fluids, when the sensing portion (or active portion) of the sensor is subcutaneously placed at an insertion site. The sensing portion is joined to a connection portion that terminates in conductive contact pads, or the like, which are also exposed through one of the insulative layers. In alternative embodiments, other types of implantable sensors, such as chemical based, optical based, or the like, can be used. Further description of flexible thin film sensors of this general type are be found in U.S. Patent. No. 5,391,250, entitled "METHOD OF FABRICATING THIN FILM SENSORS". The connection portion can be conveniently connected electrically to the monitor 104 or a telemetered characteristic monitor transmitter 202 by a connector block (or the like) as shown and described in U.S. Pat. No. 5,482,473, entitled "FLEX CIRCUIT CONNECTOR". Thus, in accordance with embodiments of the present invention, subcutaneous sensor sets 102 are configured or formed to work with either a wired or a wireless characteristic monitoring system 100, 200.

A. Glucose Monitor Status Checks

[0060] The physiological characteristic monitoring system 100, 200 can perform a status check to confirm that the monitor 104 is operating properly and calibrated to take glucose measurements. The processor 108 determines the status of the monitor for receiving the signal from the sensor set 102. The monitor status is based upon at least one of

Abbott Ex. 1002 - 614/1438

a plurality of conditions including the sensor activity condition, the sensor calibration condition and the telemetry condition. The display 114 shows different observable indicators depending upon the status of the monitor 104.

[0061] FIG. 2A is a flowchart 220 of an exemplary status check algorithm for a characteristic monitor embodiment of the present invention. Beginning at the default time screen 222 showing the current time, a user can press a key (e.g. the UP key) to initiate the status check. The processor 108 first performs a sensor activity condition check 224 to determine if there is an expired or dead sensor. If the sensor is determined to be dead, the display 114 shows a sensor "REPLACE" prompt 226 with the current time, which indicates that the sensor has expired and replacement of the sensor set 102 is required immediately. If the sensor is determined to be active by the sensor activity check 224, the processor 108 performs a telemetry condition check 228 to determine if the monitor 104 is synchronized with the telemetered monitor transmitter 202 coupled to the sensor set 102. If the monitor 104 and the transmitter 202 are not synchronized, a "NO SYNC" indicator 230 is shown on the display 114. If the devices are synchronized, a calibration condition check 232 is performed by the processor 108 to determine first whether a calibration of the sensor set 102 is pending (i.e., whether the monitor 104 is currently processing a previously entered blood glucose reference value, for example from a meter, to calibrate the sensor set 102). If a calibration is pending, the display 114 shows a "PENDING" indicator 234. If a calibration is not pending, the processor 108 checks whether the sensor calibration is currently valid 236. If the calibration is not valid, the display shows an "ENTER BG" indicator 242 with the current time, which indicates that a blood glucose reference value (e.g., from a blood glucose meter) is required by the monitor 104 to calibrate the sensor set 102. If the calibration is valid, the processor 108 then checks that the sensor expiration time is after the next calibration due time 238, and the display 114 shows a "BG DUE" indicator 240 with the time that the next calibration is due. If the sensor expiration time is before the next calibration due time, the display 114 shows the "REPLACE" prompt 226 with the time that the sensor will expire and replacement of the sensor set 102 will be required.

B. Glucose Monitor Calibration Reference Value Entry

[0062] FIG. 2B is an exemplary flowchart 250 of screens for entering a reference value to calibrate a characteristic monitoring system 100, 200 in accordance with an embodiment of the present invention. While a calibration is pending or valid as a result of entry of a calibration reference value (e.g., a blood glucose value measured by a blood glucose meter), the display 114 shows the calibration reference value and time of the most recent valid entry in the meter screen 252. In particular embodiments, the time of the most recent valid entry is unaffected by a change in a system time setting of the monitor 104. In other embodiments, the time of the most recent valid entry may be shifted in accordance with a change in a system time setting of the monitor 104. From the meter screen 252, pressing a button (e.g., the ACT/activate button) allows entry of a new calibration reference value in the entry screen 254. After entry of the new value (e.g., using the up and down arrow buttons and then pressing the ACT/activate button), the display 114 shows a confirmation screen 256, which requires confirmation of the value entered (e.g., by pressing the ACT/activate button) to release the display to the default time screen 258.

3. Dynamic Glucose Monitoring Functions

[0063] Embodiments of the present invention include different types of continuous glucose monitors that identify trends in blood glucose dynamics to facilitate enhanced treatment of diabetes. In general, a first illustrative monitor can be used to anticipate a glucose "crash" (or other hypoglycemic incident) before the onset of debilitating symptoms. Another illustrative monitor can be used to detect an inadequate nocturnal basal rate and alert the patient in order to avoid an impaired fasting glucose incident. Another illustrative monitor can anticipate hyperglycemic (or hypoglycemic) incidents by detecting trends toward those levels and help the patient avoid such incidents. Another illustrative monitor can assist a patient in maximizing athletic performance in endurance type activities (e.g., a marathon race) by detecting trends toward hypoglycemic levels.

[0064] The disclosed embodiments monitor the dynamics of a physiological characteristic such as blood glucose levels. These embodiments utilize this dynamic monitoring to provide functionality including the anticipation of glucose crash and alerting the patient, the detection of inadequate nocturnal basal rate, the anticipation of hyperglycemic (or hypoglycemic) incidents and maximizing athletic performance. All of these features can be implemented in software operating in the monitor's microprocessor and/or designed into an application specific integrated circuit (ASIC) or other specialized circuitry. Also, dynamic glucose monitoring functions use periodic measurements of a glucose level.

A. Monitor for Anticipating a Glucose Crash

[0065] In one embodiment of the invention, a monitor anticipates a glucose crash by monitoring trends in glucose levels. For example, the monitor can alert the patient when glucose levels are rapidly decreasing. By monitoring such trends or a rate information of measured glucose levels, the monitor can provide a much better warning system to alert

Abbott Ex. 1002 - 615/1438

the user with enough time to stabilize and reverse a dangerous physiological condition.

[0066] In some embodiments of the invention, the monitor measures glucose more frequently than typical glucose monitoring devices. For example, one embodiment of the invention measures approximately every minute, whereas other monitors measure at a lower rate (e.g., but not limited to, once per 5 minutes). Frequent measurements are taken because of the short time intervals which are evaluated. Alternative embodiments may utilize more frequent measurements, such as, but not limited to, 10 seconds, 1 second, or the like.

[0067] In an illustrative embodiment, the monitor periodically measures glucose, analyzes the present trend, determines whether a glucose crash incident is probable and appropriately alerts the patient At some frequent interval (e.g., but not limited to, once per minute), the device measures the glucose level, applies a smoothing filter to the result, and records the filtered value. The smoothing filter may take a weighted sum of past sensor values (so called finite impulse response- FIR -filter), a weighted sum of past sensor values and past filtered values (so called infinite impulse response - IIR -filters), may use simple clipping algorithms (e.g. limit the percent change in filtered output), or employ models to predict the output (e.g. Weiner and Kalman filter designs). For example, if the most recent (filtered) value is in the "qualifying range", the monitor can calculate the slope of a line fit to the most recent values (most likely, but not limited to, using a Saritzky gulag filter) and determine if the slope is steeper than a selected threshold rate (e.g., but not limited to, 3% or declining at more than 30 mg/dL in ten minutes). If the slope equals or exceeds the threshold rate, a glucose crash incident is likely and the monitor alerts the patient accordingly.

[0068] Those skilled in the art will understand that in some embodiments the qualifying range can be a closed range (e.g., but not limited to, between 100 and 150 mg/dL) and in other embodiments the qualifying range can be an open range (e.g., but not limited to, greater than 100 mg/dL). By first identifying whether a most recent value is within the qualifying range, further calculation of the dynamic behavior of the physiologic characteristic can be avoided. Thus, the determination of a glucose crash can be unconcerned with rate magnitudes occurring when the current characteristic value is outside of the range (of course, other alarms, which merely monitor the current characteristic value, can be triggered when the reading is too high or too low). However, in alternate embodiments, the slope can be calculated and compared to the threshold rate with every new value. In further embodiments, multiple qualifying ranges and threshold rates can be applied to evaluate the glucose dynamics and determine triggering a glucose crash warning.

[0069] In one preferred embodiment, the monitor determines that a glucose crash is likely if three criteria are met The criteria are as follows. The first, dG/dT (the rate of glucose level change) is negative, can be considered for example in situations where blood glucose levels are dropping (e.g., but not limited to, when a value pertaining to the rate of glucose change is negative). The second, |dG/dT| exceeds a threshold rate, can be considered in contexts, for example where a specified blood glucose change rate is exceeded for a specified sustained period (e.g., but not limited to, greater than 3% per minute for 10 minutes). The third, G, the glucose level, can be considered for example, when this value begins dropping starting within a specified range, (e.g., but not limited to, 100 - 150 mg/dL).

[0070] In some embodiments, these criteria can be parameterized to allow the user to customize the values. The qualifying range, threshold rate and period can be general values, applied to all users, or determined from factors specific to the individual user. For example, the monitor can include a feature to adjust the qualifying glucose level range, the maximum rate of glucose change, or in some embodiments, the sustained time period length. In addition, in some embodiments, any or all of the dynamic glucose monitoring functions can enabled or disabled, selectively or together.

[0071] The following control program pseudo code provides an example of a programming routine performed by the processor of the monitor to implement an embodiment of the invention.

Abbott Ex. 1002 - 616/1438

```
REPEAT every minute)
    {
        Measure glucose level   g_i
        Filter g_i and store the filtered value g '_i
        IF(g '_i is in range 100 - 150 mg/dL)
            THEN
                Fit a line to the most recent 10 filtered (or, alternatively, unfiltered) values
                IF (dG/dT for that line < ( - 3% per minute )
                    THEN
                        Alert the patient and record in history
                ENDIF
        ENDIF
    }
END REPEAT
```

[0072] FIG. 3A is a flowchart of a method for anticipating a glucose crash 300. At block 302, a characteristic level is repeatedly measured to obtain a group of characteristic level values. Following this at block 304, a smoothing filter can be applied to the group of characteristic level values to produce a filtered measurement value. The filtered measurement value is recorded at block 306. At block 308 it is determined if the recorded value falls within a qualifying range (e.g., but not limited to, between 100 to 150 mg/dL). If not, the process returns to block 302. If the recorded measurement is within the range, a slope of a line fit to a recent series of recorded filtered values is calculated at block 310. The calculated slope is compared to a threshold rate (e.g., but not limited to, -3% per minute) at block 312. If the calculated slope is not steeper than the threshold rate the process returns to block 302. If the slope exceeds the threshold rate, an anticipated glucose crash is indicated at block 314. Alternative embodiments may utilize similar logic for when the glucose level is already outside of the range and continues to drop. In addition in an alternative preferred embodiment of the invention, one can utilize a raw data measurement (e.g. a group of characteristic level values) to determine a derivative as an alternative to using a filtered measurement value to determine a derivative.

B. Monitor for Detecting an Inadequate Nocturnal Basal Rate

[0073] In another embodiment of the invention, the characteristic monitor can be used to detect an inadequate nocturnal basal rate. This embodiment generally applies to diabetic patients using an insulin infusion device that continually administers insulin at a patient controlled basal rate. The monitor detects an inadequate basal rate (i.e., but not limited to, "low basal rate" or a "high basal rate"), by monitoring trends in glucose levels. The monitor then alerts a patient in the early morning, when glucose levels are high and relatively steady, low and relatively stable or changing rapidly. This gives the patient time to adjust the basal rate of the infusion device upward or downward to and avoid an impaired fasting glucose incident

[0074] The monitor operates to track the characteristic level rate. For example, every 5 minutes the monitor measures and records the glucose level. Once a day (e.g., but not limited to, 3 hours before to the anticipated wakeup time), the monitor calculates the average blood glucose and the rate of blood glucose change for the previous hour. The monitor can then determine a prediction of the "morning glucose" level at wake up based upon the calculated average blood glucose and the rate of blood glucose change. In one embodiment the "morning glucose" is predicted assuming that the rate of change remains constant, however in other embodiments nonlinear characteristic curves and functions can be applied in making the prediction. If the anticipated "morning glucose" level is greater than a high threshold value (e.g., but not limited to, 126 mg/dL), or less than a low threshold value (e.g., but not limited to, 60 mg/dL), an alarm is sounded. This will allow time for the infusion device basal rate to be adjusted appropriately. In alternative embodiments, different

Abbott Ex. 1002 - 617/1438

times before anticipated wakeup, different high threshold values, or different low threshold values, may be used.

[0075] In some embodiments, the triggering criteria can also be parameterized to allow the user to customize the values. In some embodiments, the user is allowed to set the values for the controlling parameters. For example, the user can set the qualifying low and high glucose levels as well as the anticipated waking time. For each of the settings a default value can be used in the absence of a user setting. For example, a default low glucose level of 60 mg/dL, a default high glucose level of 126 mg/dL and an anticipated waking time of 7:00 AM can be used. In addition, the entire function can be enabled and disabled.

[0076] FIG. 3B is a flowchart of a method for detecting an inadequate nocturnal basal rate 320. At block 322, the method begins by measuring a characteristic level to obtain a measurement value. The value is recorded at block 324. Measuring and recording is repeated periodically to obtain a series of values at block 326. At block 328, the average of the series of values is calculated. At block 330, a slope of a line fit to the series of values is calculated. The calculated slope and average of the series of values are then used to determine a predictive curve at block 332. At block 334, the curve is extrapolated to predict a glucose level at wakeup. Those skilled in the art understand that such calculations are not limited to slope y = mx + b, and that, in this context, one can use alternative filtered arrangements as are known in the art. The extrapolation is performed some time before wakeup (e.g., but not limited to, 3 hours prior) to provide enough time to correct any impending negative condition. The predicted glucose level is compared to an acceptable range at block 336. If the predicted glucose value falls within the range, the process ends. If the predicted glucose value falls outside the range, a morning glucose incident is reported at block 338.

C. Monitor for Anticipating Hyperglycemic Incidents

[0077] In another embodiment of the invention, a glucose monitor anticipates a hyperglycemic (or hypoglycemic) incident by monitoring trends in glucose levels. The monitor alerts the patient when a "relatively steady increase" (or decrease) in glucose levels occurs. The monitor periodically measures glucose, analyzes the present trend, determines whether a hyperglycemic (or hypoglycemic) incident is probable and appropriately alerts the patient.

[0078] In one embodiment, the device measures glucose values at a specific time interval (e.g. once every minute), and then, e.g. at 5 minute intervals, applies a smoothing filter to this group of values and records the filtered value. If the most recent (filtered) value exceeds a threshold value (e.g., but not limited to, 180 mg/dL), the monitor calculates the slope of a line fit to a recent series of recorded values (for example, but not limited to, six values). If the slope is greater than a threshold rate (e.g., but not limited to, 3% per minute), a hyperglycemic incident is likely and the monitor alerts the patient. For hypoglycemic incidents, values and thresholds corresponding to low glucose levels would be used.

[0079] The threshold value is applied in a similar manner to the "qualifying range" applied in determining a glucose crash previously discussed. The threshold value effectively operates as an open range (e.g., but not limited to, greater than 180 mg/dL). In other embodiments, the threshold value can be a closed range. Therefore, determining a hyperglycemic incident can be unconcerned with values below the threshold value (as determining a hypoglycemic incident can be unconcerned with values above a threshold value). In one embodiment, a slope calculation can be avoided if the current reading is outside the range. However, in alternate embodiments, the slope can be calculated and compared to the threshold rate with every new reading. In further embodiments, multiple qualifying ranges and threshold rates can be applied to evaluate the glucose dynamics and determine triggering a hyperglycemic (or hypoglycemic) incident warning.

[0080] Here again, in some embodiments the criteria can be parameterized to allow the user to customize the controlling values for anticipating hyperglycemic (or hypoglycemic) incidents. For example, some embodiments can allow the user to set the glucose threshold level and/or the threshold rate. Embodiments of the invention can also use default parameters if no user settings are provided (e.g., but not limited to, a threshold level of 180 mg/dL and a maximal rate of 3% per minute). Embodiments of the invention can also enable and disable this function.

[0081] FIG. 3C is a flowchart of a method for anticipating a hyperglycemic incident 350. The method begins at block 352 by repeatedly measuring a characteristic level to obtain a group of values. At block 354, a smoothing filter is applied to the group of values to obtain a filtered measurement value. The filtered value is recorded at block 356. The recorded value is compared to a threshold value at block 358. If the recorded value does not exceed the threshold value (e.g., but not limited to, 180 mg/dL), the process returns to block 352. If the recorded value does exceed the threshold value, a slope of a line fit to a recent series of values is calculated at block 354. The calculated slope is compared to a threshold rate (e.g., but not limited to, +3% per minute) at block 362. If the slope is not steeper than the threshold rate, the process returns to block 352. If the slope is steeper than the threshold rate, an anticipated hyperglycemic incident is reported at block 364. For hypoglycemic incidents, corresponding steps for low glucose levels would be used. As noted previously, estimates of dG/dt may be calculated by a variety of methods known in the art including the slope (and that such calculations are not limited to, for example, determinations based on y = mx + b).

Abbott Ex. 1002 - 618/1438

D. Monitor for Maximizing Athletic Performance

[0082] Dynamic monitoring can also be used to provide feedback based upon the engaged activity of the user. For example, the monitor can be used to maximize performance during an endurance type activity (e.g., but not limited to, a marathon race). The endurance athlete strives to burn glucose rather than fat and accordingly needs to anticipate low glucose levels and ingest carbohydrates early enough to avoid low glucose levels.

[0083] In such embodiments, the monitor anticipates low glucose levels and alerts the athlete to ingest carbohydrates. It is important to note that this embodiment is not strictly anticipating hypoglycemic incidents. Instead it is anticipating low glucose levels where it would otherwise be too late for the athlete to compensate by ingesting carbohydrates and still perform effectively and/or at full capacity.

[0084] In one embodiment, once a minute, the device measures a glucose level, applies a smoothing filter and records the filtered value at 5-minute intervals. If the most recent recorded (i.e., filtered) value is in a qualifying range (e.g., but not limited to, 60 - 140 mg/dL), the processor calculates the slope of a line fit to the most recent six filtered values and determines if the slope is steeper than -1 % (i.e., but not limited to, 30 mg/dL in 30 minutes). If the rate of decline exceeds this threshold, a low glucose level is likely and the monitor alerts the athlete accordingly. Thus, for example, but not limited to, to trigger an alarm, the glucose level rate, dG/dT, is negative with a magnitude greater than 1% per minute for 30 minutes beginning in range 60 - 140 mg/dL.

[0085] Similar to the glucose crash monitor, in embodiments for maximizing athletic performance, the qualifying range can be a closed range (e.g., but not limited to, between 60 and 140 mg/dL) or an open range (e.g., but not limited to, less than 140 mg/dL). By first identifying whether a most recent value is within the qualifying range, further calculation of the dynamic behavior of the physiologic characteristic is avoided. However, other alarms which merely monitor the current characteristic value can be triggered when the reading is too high or too low. In alternate embodiments, the slope can be calculated and compared to the threshold rate with every new value. In further embodiments, multiple qualifying ranges and threshold rates can be applied to evaluate the glucose dynamics and determine triggering a low glucose warning.

[0086] Here too, these criteria can be parameterized to allow the user to customize the values. Typically, the monitor will allow a user to set the qualifying glucose range and/or enable and disable the function. A default qualifying range (e.g., but not limited to, 60-140 mg/dL) can be used.

[0087] FIG. 3D is a flowchart of a method for maximizing athletic performance 370. The process begins at block 372, where a characteristic level is repeatedly measured to obtain a group of characteristic level values. Following this at block 374, a smoothing filter can be applied to the group of characteristic level values to produce a filtered measurement value. The filtered measurement value is recorded at block 376. At block 378 it is determined if the recorded value falls within a qualifying range (e.g., but not limited to, between 60 to 140 mg/dL). If not, the process returns to block 372. If the recorded measurement is within the range, a slope of a line fitted to a recent series of recorded filtered values is calculated at block 380. The calculated slope is compared to a threshold rate (e.g., but not limited to, -1% per minute) at block 382. If the calculated slope is not steeper than the threshold rate the process returns to block 372. If the slope exceeds the threshold rate, an anticipated low glucose level is indicated at block 384. As noted previously, estimates of dG/dt may be calculated by slope as well as other methods known in the art.

4. Glucose Alarm Functions

[0088] Embodiments of the invention can utilize various advanced alarm functions. For example, in some embodiments multiple alarms can be independently set by the user. In further embodiments, user input can direct review of the alarm history and also alter the alarm display to suit the user's preference. Alarm settings for embodiments of the invention can also include an alarm snooze or "blackout" period as well as an alarm repeat delay.

A. Multiple Glucose Alarm Functions

[0089] Embodiments of the invention can employ multiple alarms that can be independently set by the user. For example, a continuous glucose monitoring system can have multiple alarms for different glucose values. The system can allow a user to set threshold glucose values that define a "narrow" glucose range (as compared to the ordinary alarm limits). If the user's glucose level passes outside the "narrow" range, an alarm can sound. This alarm alerts the user to monitor his glucose levels more closely. The system can sound a second alarm (preferably having a sound distinguishable from the first "arrow" range alarm) in the event the user's glucose level reaches a more dangerous condition requiring immediate action. Alarm indications may be audible, tactile, vibratory, visual, combinations of alarm indications, or the like. In the case of visual alarm indications, but not limited to, green lights can be displayed while the user's glucose level remains within the defined "narrow" range; yellow for the first alarm level; and red for the second alarm level. The visual alarm indications may flash and/or also be combined with other alarm indications.

Abbott Ex. 1002 - 619/1438

[0090] Although the above example describes a two-layer alarm system, further embodiments of the invention can incorporate multiple alarm layers. In addition, the alarms can be set in ranges, or separate high and low glucose level alarms can be set. Distinctive sounds can be used for each alarm. For example, each successive high glucose level alarm can have, but is not limited to having, a higher pitch. Successive low glucose level alarms can each have, but are not limited to having, lowering pitches. Alternately, intermittent or wavering volumes that also increase in pitch according to the severity of the condition can be used. In still other embodiments, the user can select or program alarm tones and other sounds and assign them to the various alarms. Also, in some embodiments, these distinguishable alarms can also be set at different volume levels. In addition, as discussed above, the alarms are not limited to audible signals; some embodiments of the invention can also utilize visual alarms, such as flashing lights or displays, or tactile alarms, such as vibrating indicators.

[0091] In still further embodiments, threshold values and associated alarms can be set according to a schedule. For example, but not limited to, particular alarms can be set to be active only during selected portions of the day.

[0092] FIG. 4A illustrates a multiple alarm function of the invention. A plot of the monitored characteristic value 400 (e.g., blood glucose) changing over time is shown. A typical wide alarm range 402 is defined by an upper threshold value 404 and a lower threshold value 406. If the monitored characteristic value 400 should exceed the defined range and cross either threshold, an alarm is initiated to indicate to the user to check his blood glucose. In one embodiment, a distinctive alarm can be associated with the alarm range 402. Thus, the same alarm is produced whether the range 402 is exceeded by passing the upper threshold value 404 or the lower threshold value 406. In other embodiments, distinctive alarms can be assigned to each threshold value 404, 406. In further embodiments of the invention, other alarm ranges can also be set. For example, a second narrower range 408 can be set with a lower upper threshold value 410 than that of the wider range 402; and a higher lower threshold value 412 than that of the wider range 402. As with the wider range 402, an alarm is initiated if the narrower range is exceeded by the monitored characteristic value 400. Here also, alarms can be the same or different for each threshold value 410, 412.

[0093] The ability to set different ranges and associated alarms allows the monitor to immediately convey some information about the condition of the user even before checking the actual readings. Particularly, using the narrower range 408 and associated alarms allows the user to know of a negative trend that does not require the same urgency as an alarm triggered by the wider range 402. In effect, the user is able to set multiple alarms, each indicating a different level of urgency and/or different conditions. In some embodiments, threshold values for alarms can also be set independent from ranges.

[0094] In still further embodiments, alarms or indicators can be set according to the direction in which a threshold value is crossed by the monitored characteristic value 400. For example, as the monitored characteristic value 400 crosses a lower threshold value 412 from the narrow range (e.g., but not limited to, at point 414), one type of alarm can be provided. However, when the monitored characteristic value 400 crosses a lower threshold value 412 from the wider range 402 (e.g., but not limited to, at point 416), another type of alarm can be provided. The difference in the alarms is appropriate because only the former case indicates a worsening of the user's condition. In the latter case, the transition actually indicates an improvement in the user's condition. Thus, in some embodiments of the invention, alarms will only be given when crossing a threshold indicates a worsening of the user's condition. In other embodiments, an indicator will also be given when a threshold has been crossed in an improving direction. In these cases, either the same indicator (sound, light, display or other) or different indicators can be used. In a similar manner, reminders can be set to indicate to a user various conditions (not necessarily negative) that will aid in convenient therapy management.

[0095] The multiple alarm function of the invention can be readily incorporated with any of the individual alarm functions and settings such as discussed hereafter.

B. Individual Alarm Functions and Settings

[0096] In further embodiments of the invention, a physiological characteristic monitor can incorporate various individual alarm functions and settings to enhance convenient operation by a user. As typical of the monitoring system 100, 200 shown in FIGS. 1A and 1B, the monitor includes a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user, and a processor for operating an alarm based on user input from an input device. The alarm indicates an alarm condition where the sensed physiological characteristic value exceeds a set range. In preferred embodiments of the invention, the physiological characteristic value is a measurement related to a blood glucose level in the user and the alarm indicates a glycemic condition. Operating the alarm comprises setting parameters of the alarm based on the user input from the input device. For example, the blood glucose level or value that will activate a hypoglycemia or hyperglycemia alarm may be set by the user utilizing the input device. The hypoglycemia alarm may be set to trigger if the user's blood glucose level is less than or equal to 60, 65, or 70 mg/dl (or any other desired level), and the hyperglycemia alarm may be set to trigger if the user's blood glucose level is greater than or equal to 150, 160, or 175 mg/dl (or any other desired level).

[0097] FIGS. 4B and 4C illustrate the hypoglycemia and hyperglycemia alarm screens, respectively. In each case,

Abbott Ex. 1002 - 620/1438

the display shows the measurement of the concentration of blood glucose indicating the glycemic condition, preferably until the alarm is acknowledged by the user. Furthermore, the display shows a time of the alarm. In particular embodiments, the alarm indicates the glycemic condition only if the monitor is calibrated, although in alternative embodiments, the alarm may indicate the glycemic condition regardless if the monitor is calibrated.

[0098] In the illustrated embodiment, the display shows a LOW indicator when the measurement of the concentration of blood glucose is below a specified level for a hypoglycemia alarm, such as 60 mg/dl. Similarly, the display shows a HIGH indicator when the measurement of the concentration of blood glucose is above a specified level for a hyperglycemia alarm, such as 150 mg/dl. In some embodiments, alarm indications may be other visual indicators (e.g., lights, flashing displays, or the like), audible, tactile, and/or vibratory. A hypoglycemia alarm is indicated by at least two audible descending tones, or a hyperglycemia alarm is indicated by at least two audible ascending tones.

[0099] In further embodiments of the invention, an alarm repeat delay period is employed. Subsequent alarms are prevented for the alarm repeat delay period after the measurement of the concentration of blood glucose first indicates a glycemic condition. For example, the alarm repeat delay period can be less than 20 minutes (e.g. approximately 17.5 minutes) for the glycemic condition comprising a hypoglycemic condition. In another example, the alarm repeat delay period is less than 1 hour (e.g. approximately 52.5 minutes) for the glycemic condition comprising a hyperglycemic condition. In alternative embodiments, the alarm repeat delay period may be other time periods, such as 10 minutes, 15 minutes, 30 minutes, 1½ hours, 2 hours, or the like.

[0100] In particular embodiments, the level of the measurement of the concentration of blood glucose from the sensor that will trigger a low limit (or hypoglycemia) alarm or a high limit (or hyperglycemia) alarm can be set based upon input from the user. Particularly, these two alarm levels can be separately set. FIGS. 4D and 4E show exemplary hypoglycemia and hyperglycemia alarm setting algorithms, respectively. FIG. 4D shows an exemplary hypoglycemia alarm setting flowchart 420. To begin setting the hypoglycemia alarm, from the hypoglycemia alarm setting screen 422, the ACT/activate button is pressed, and the hypoglycemia alarm activation screen 424 is entered. From this screen 424, the user can select setting the hypoglycemia alarm on, off or entering the alarm repeat setting function menu. If the user sets the hypoglycemia alarm off and presses the ACT/activate button, an alarm off confirmation screen 426 is presented. If the hypoglycemia alarm is set on and the ACT/activate button is pressed, the low limit entry screen 428 is presented. The low limit entry screen 428 allows the user to scroll through low limit alarm level settings using up and down arrow buttons to specify that the hypoglycemia alarm will trigger if the user's blood glucose level is less than or equal to 60, 65, or 70 mg/dl, or any other desired level. After setting the low limit alarm level, pressing the ACT/activate button again presents a hypoglycemia low limit alarm level confirmation screen 430 for confirming the specified hypoglycemic blood glucose level.

[0101] From the hypoglycemia alarm activation screen 424, if the alarm repeat setting function is selected, the alarm repeat display screen 432 is entered, which allows the user to set a period for delaying a repeated check of the hypoglycemia alarm condition. The current alarm repeat delay period is shown in the alarm repeat display screen 432. Pressing the ACT/activate button allows the user to enter the repeat time select screen 434. Alternatively, the alarm repeat display screen 432 may be omitted, and the repeat time select screen 434 is entered once the alarm repeat setting function is selected. In the repeat time select screen 434, the alarm repeat delay period blinks while being set by the user utilizing the input device. The user can scroll through a list of delay increments and select the desired alarm repeat delay period from the list of delay increments. The alarm repeat delay period has a default value of 20 minutes for the hypoglycemia (low limit) alarm level. For convenience, the scrolled list of delay increments can wrap around, beginning again when one end of the list is reached. For the low limit alarm level, the alarm repeat delay period can be selected from a group of values differing in 10 minute increments. For example, the alarm repeat delay period can be selected from 20, 30, 40, 50 and 60 minutes for the low limit alarm level. In alternative embodiments, the alarm repeat delay period may be selected from a group of values differing in other time increments, such as 5, 15, or 20 minutes, or further, may be specified using up and down arrow buttons and then pressing the ACT/activate button. After selecting the alarm repeat delay period, pressing the ACT/activate button displays the alarm repeat delay confirmation screen 436 for confirming the period selection.

[0102] FIG. 4E shows an exemplary hyperglycemia alarm setting flowchart 440. From the hyperglycemia alarm setting screen 442, if the ACT/activate button is pressed, the hyperglycemia alarm activation screen 444 is entered. From this screen 444, the user can select setting the hyperglycemia alarm on, off or entering the alarm repeat setting function menu. If the user sets the hyperglycemia alarm off and presses the ACT/activate button, an alarm off confirmation screen 446 is presented. If the hyperglycemia alarm is set on and the ACT/activate button is pressed, the high limit entry screen 448 is presented. The high limit entry screen 448 allows the user to scroll through high limit alarm level settings using up and down arrow buttons to specify that the hyperglycemia alarm will trigger if the user's blood glucose level is greater than or equal to 150, 160, 170, 175, or 180 mg/dl, or any other desired level. After setting the high limit alarm level, pressing the ACT/activate button again presents a hyperglycemia high limit alarm level confirmation screen 450 for confirming the specified hyperglycemic blood glucose level.

[0103] The alarm repeat delay period for the hyperglycemia alarm is set in the same manner as that for the hypoglycemia

Abbott Ex. 1002 - 621/1438

alarm described above with respect to FIG. 4D; however, the alarm repeat delay period is typically set separately for a low limit alarm level and a high limit alarm level because the desired delays are different in each case. In general, the hyperglycemia alarm repeat delay period may be longer than that of the hypoglycemia alarm. From the hyperglycemia alarm activation screen 444, if the alarm repeat setting function is selected, the alarm repeat display screen 452 is entered, which allows the user to set a period for delaying a repeated check of the hyperglycemia alarm condition. The current alarm repeat delay period is shown in the alarm repeat display screen 452. Pressing the ACT/activate button allows the user to enter the repeat time select screen 454. Alternatively, the alarm repeat display screen 452 may be omitted, and the repeat time select screen 454 is entered once the alarm repeat setting function is selected. In the repeat time select screen 454, the hyperglycemia alarm repeat delay period is selected in a manner similar to the hypoglycemia alarm repeat delay period described above with respect to FIG. 4D, and then pressing the ACT/activate button displays the alarm repeat delay confirmation screen 456 for confirming the period selection. The alarm repeat delay period can have a default value of 1 hour for the hyperglycemia (high limit) alarm level. For the high limit alarm level, the alarm repeat delay period can be selected from a group of values differing in 30 minute increments. For example, the alarm repeat delay period can be selected from 1, 1½, 2, 2½ and 3 hours for the hyperglycemia alarm level. In alternative embodiments, the alarm repeat delay period may be selected from a group of values differing in other time increments, such as 15 or 20 minutes or 1 hour, or further, may be specified using up and down arrow buttons and then pressing the ACT/activate button.

[0104] As noted above, the multiple alarm function of the invention can be incorporated with various specific alarm features. For example, the alarm repeat delay function can be set differently for hypoglycemic alarms and hyperglycemic alarms of different severities. If a lower threshold hyperglycemic alarm is triggered, a relatively long repeat delay may be invoked. However, if a higher threshold hyperglycemic alarm is triggered, a shorter repeat delay may be used so that the user is warned more frequently because of the severity of his condition.

[0105] FIG. 4F illustrates a hyperglycemia alarm snooze setting flowchart 460. The hyperglycemia alarm snooze function sets an alarm snooze period for temporarily disabling the alarm. The snooze function is set by the user utilizing the input device. In some embodiments, the alarm snooze period is only available for a hyperglycemia alarm, although in other embodiments, the alarm snooze period may also be available for a hypoglycemia alarm. Generally, the snooze function is available only when the snooze period is running and the monitor is calibrated, although in alternative embodiments, the snooze function may be available regardless if the monitor is calibrated. Further, the alarm snooze period is preferably deactivated upon any adjustment of the hyperglycemia alarm setting described above with respect to FIG. 4E. The snooze setting flowchart 460 begins at the snooze display screen 462, which can be entered by scrolling past the default time screen 464 and the BG due screen 466. From the snooze display screen 462, pressing the ACT/activate button will produce the snooze time select screen 468. In this screen 468, a user can select the desired period for the snooze function to operate, and the alarm snooze period blinks while being set by the user utilizing the input device. The alarm snooze period can be set by the user scrolling through a list of snooze period increments and selecting the desired alarm snooze period from the list of snooze period increments. For example, the list of snooze period increments can include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours, and for convenience, the list of snooze period increments wraps around as it is scrolled by the user. In alternative embodiments, the snooze period may be selected from a list of other time increments, such as 15 or 30 minutes, or further, may be specified using up and down arrow buttons and then pressing the ACT/activate button. When the snooze function is activated, the display shows time remaining of the alarm snooze period and an indicator (e.g. an "S") showing that the snooze function is active.

[0106] It may be instructive to note that, although both the alarm repeat delay function and the alarm snooze function prevent alarms for specified periods, they are not the same. One difference between the two functions can generally be identified by how each function is initiated. The alarm repeat delay is initiated (assuming the function is activated and set by the user) in response to a first alarm. In contrast, the alarm snooze function is activated by the user directly, either by directing the monitor to snooze immediately or scheduling a snooze at a specified time. For example, a user may schedule a snooze during sleeping hours that occur at some known time.

[0107] Just as with the alarm repeat delay, the multiple alarm function of the invention can also be incorporated with the alarm snooze function. For example, the snooze function can be set differently for hypoglycemic alarms and hyperglycemic alarms of different severities. The snooze function can function normally when a lower threshold hyperglycemic alarm is set (i.e. ignore the alarm). However, when a higher threshold hyperglycemic alarm is set, the snooze function may be overridden due to the severity of the user's condition.

[0108] FIG. 4G illustrates glycemia alarm history review in accordance with an embodiment of the invention. Operating the alarm history review can allow a user to review a historical list of the alarms indicating a glycemic condition occurrence. The alarm history review flowchart 470 shows the alarm history is entered by pressing the ACT/activate button from the alarms menu screen 472. If no alarm history exists, a screen 474 indicating "NONE" will be displayed. However, if at least one alarm event has occurred, the entries will be displayed in a historical list 476. In one embodiment, the display shows a single glycemic alarm in the historical list at a time. The display shows a physiological characteristic value (e.g. blood glucose value) and time of the glycemic condition occurrence indicated for each alarm in the historical list. The

Abbott Ex. 1002 - 622/1438

time of the glycemic condition occurrence can also include a date of the alarm. Further, the display can show at least a portion of the time of the glycemic condition occurrence in blinking text. The historical list typically includes a limited number of stored entries. For example, the historical list can comprise the 20 most recent alarms indicating a glycemic condition occurrence. In alternative embodiments, the historical list may include more or less alarms, such as the 10, 15, 30, or 50 most recent alarms.

[0109] As part of the display of the historical list, the display can show the blood glucose measurements only within a specified range. For example, the specified range can be the operational range of the sensor, such as from 40 to 400 mg/dl, although the range may span other values, such as from 20 to 600 mg/dl. When a measurement in the historical list is above the specified range, the display shows a HI indicator. Similarly, the display shows a LO indicator for the measurements below the specified range.

5. Advanced Blood Glucose Reminder Functions

[0110] Another aspect of the invention allows the user to set reminders that will be provided by the monitor. The reminders can be alarm signals (including, but not limited to, auditory, visual, tactile, etc.) that are initiated after a timer has run to prompt the user to take action or merely inform the user of a particular status. The reminder is started (i.e. the timer is initiated), when an event occurs and/or certain conditions are met. The alarm signals can be the same or different based upon the triggering events or conditions. These reminders can be used to further assist the user in managing insulin delivery for optimum results. For example, but not limited to, reminders can be set for event markers, blood glucose values, reference values, high or low sensor measurements.

[0111] Characteristic monitors and infusion devices can use event markers that place tags in the data for events the user experiences (e.g., but not limited to, meals, exercise, and high or low blood glucose). For example, but not limited to, when an infusion device identifies a high or low blood glucose event marker, it can start a timer that reminds the user to check blood glucose levels. This is intended to make therapy safer by encouraging more frequent checks during times that the patient may be at risk from hypoglycemia or hyperglycemia. In addition, this feature can also be applied to characteristic monitors. For example, but not limited to, a characteristic monitor that is used to show low or high blood glucose tags can have a timer set to remind a user to check their blood glucose levels at a later time.

[0112] In addition, a reminder timer can be set that is triggered if a blood glucose value is entered. For example, but not limited to, the reminder can be if the user enters a low or high blood glucose value into the monitor as a reference or calibration value.

[0113] A reminder timer can also be triggered by a user providing a reference value to the monitor. Thus, the user can be reminded to supply a new reference value after a minimum time period has elapsed. In this way calibration of the monitor is assured.

[0114] A blood glucose reminder can also be triggered by high or low measurement from the sensor. Thus, the monitor will request a blood glucose reference value during an excursion away from the normal range of values. The trigger for this reminder can be tempered by setting a minimum time between reminders to avoid pestering the user. This reminder can be used to provide more robust data for curve fitting as correlation improves with variability in the data pairs. The reminder promotes more frequent data collection during more critical periods (e.g., but not limited to, when blood glucose is too high or too low) and therefore the interpolated curve for this period is more reliably representative of the true curve.

[0115] One aspect behind the use of these reminders is that they also serve to prevent redundant and excessive alarms for the user. For example, if the timer is removed from the previously described high or low measurement reminder, the result would be a simple hypoglycemia or hyperglycemia alarm. Using a reminder, however, the message is not that the user's blood glucose is out of range. Rather, the reminder's message is to check the user's blood glucose with a meter, or the like. If a user's blood glucose is very near an alarm triggering threshold, an alarm might be triggered repeatedly as the value passes back and forth across the threshold. A reminder will set a timer, preventing duplicative warnings for a short period of time, but reminding the user to check blood glucose again when that period has expired. This can provide a better or easier path through the regulatory process. Thus, reminders are less likely to become a nuisance to the user and also prompt more useful data collection. In alternative embodiments, the alarm is triggered again, regardless of the presence of a time, if the glucose level continues to change in the direction of the trend.

[0116] FIG. 5 illustrates a reminder function of the invention triggered by high or low characteristic values. A plot of a monitored characteristic value 500 (such as, but not limited to, blood glucose) is shown. One or more ranges 502, 504 define safe characteristic values (e.g., but not limited to, a first range 502 being a warning range and a second range 504 being a critical range), such as can be employed using multiple alarms as previously described. When a range is exceeded (e.g., but not limited to, at time 506), an alarm can be triggered but also a timer is started such that a reminder is also initiated after its expiration (e.g., but not limited to, at time 508). Over the timer period further occurrences of exceeding the threshold (e.g., but not limited to, at point 510) will not result in a duplicative alarm.

[0117] However, the situation can be somewhat different when the intervening triggering event is not identical to the first triggering event. For example, if a first range 502 is exceeded (e.g., but not limited to, at time 512) and a timer is

Abbott Ex. 1002 - 623/1438

started, but before a reminder can be issued (e.g., but not limited to, at time 514) a second range 504 is exceeded (e.g., but not limited to, at time 516), then the second alarm will be issued and the timer will be restarted. No reminder will be indicated at the theoretical expiration of the first timer (e.g., but not limited to, at time 514), but a reminder will be issued at the expiration of the second timer (e.g., but not limited to, at time 518). In this case, exceeding the second range overrides the first reminder because the second alarm is a different, albeit related, condition. As previously described, however, the use of reminders is not limited to monitoring high and low characteristic values. In a similar manner, reminders can be triggered by user's supplied reference values for calibration as well as event markers entered into the monitor.

6. Glucose Monitoring Information Management

[0118] Another aspect of the invention is to provide meaningful retrospective information to the patient using the sensor. In particular, a retrospective display of one or more physiological values can provide significantly useful data. As disclosed, the retrospective displays can be designed in a variety of ways to provide various useful information. For example, but not limited to, as the sleeping user receives no benefit from a real-time display, a retrospective view of data is important. While a simple listing of previous values has value, it can be time consuming to review, provides information that is difficult to visualize and comprehend and requires significant memory space within the device. Providing useful information that is easy to understand and that can be stored within a small memory space is very important. The ability to review data from the previous sleep period is particularly helpful to a user with nocturnal hypoglycemia or "dawn effect", as there is typically no witness to the real-time display. These measures can be even more important in cases where the alarm system can exhibit many false positives and/or false negatives, which might otherwise frustrate the user and lead to non-use of the monitor.

[0119] The following advanced data presentation tools can be used to conveniently and efficiently store and display useful information on a screen for a user to review while the monitor is in use. The tools provide useful information while requiring only a minimal amount memory space. These data presentation tools can also be used in any retrospective analysis package, such as software running on a computer or network designed to analyze trends and provide advise regarding a treatment regime.

[0120] The tools operate by processing that compares actual reading to high and low value limits (e.g., but not limited to, acceptable blood glucose ranges). For example, but not limited to, the limits can be the adjustable hypoglycemic and hyperglycemic alarm thresholds of a monitor. Alternately, for standardization, the tools can be applied to a fixed definition of a target blood glucose range that is independent of the hyperglycemic and hypoglycemic alarm thresholds for the particular user/monitor.

[0121] FIG. 6A illustrates one minimum and maximum data presentation. A display of the minimum and maximum values 600 of the characteristic monitor that have been measured for the user can be displayed on the monitor. The minimum value and maximum values can be conveniently displayed along with the date and time of their occurrence. Such a display 600 is useful, but becomes more useful when combined with an excursion count, a distribution of values, and/or integrated values as discussed below

[0122] FIG. 6B illustrates an excursion data presentation. The number of excursions above or below the respective blood glucose limits is also very useful to have summarized for the user. An excursion display 602 provides good information, particularly when there are no alarms active on the monitor (either because the monitor is not turned on or alarms are not being employed by the user). A display 602 of the number of excursions above the hyperglycemic limit and the number of excursions below hypoglycemic limit give the user an idea of performance of a treatment program at a glance. A high number of incidents exceeding either limit indicate a need for improvements.

[0123] FIG. 6C illustrates a characteristic value distribution data presentation. A simple distribution of sensor values offers a very powerful tool. In a preferred embodiment, the distribution is described in percentages that are automatically scaled with the duration of monitor use. Optionally, a monitor can include the total time of use with a percentage distribution. Awareness of a total time provides perspective for reviewing the percentage distribution. A time based distribution can also be used, but requires the total time to be included in the analysis as a reference. A distribution can also be presented based upon the total number of readings, but requires the total time is required in the analysis.

[0124] For example, but not limited to, the display can show a percentage of readings above a hyperglycemic alarm level, a percentage of readings below a hypoglycemic alarm level and a percentage of readings of readings within alarm range as shown in FIG. 6C. Optionally, the total time covered in the analysis can also be displayed. Similarly, an alternate display can show the time spent above a hyperglycemic alarm level, the time spent below a hypoglycemic alarm level and the time spent within alarm range (not shown). As mentioned, the time base display requires a known total time as part of the analysis. Finally, a display can also include the number of readings above hyperglycemic alarm level, the number of readings below a hypoglycemic alarm level and the number of readings within alarm range (not shown).

[0125] FIG. 6D illustrates an integrated characteristic value data presentation. Performing an integration of the readings outside the alarm levels with respect to time can provide a measure of the hypoglycemic and hyperglycemic events'

Abbott Ex. 1002 - 624/1438

severity. In addition, these results can also be scaled these by a total sensor time to provide a measure that is duration independent

[0126] For example, a "hyperglycemic area" can be calculated as the sum of the differences between the readings and the hyperglycemic alarm limit. A "hypoglycemic area" can be calculated from the sum of all the differences between the hypoglycemic alarm limit and the readings. A "hyperglycemic index" is calculated by taking the "hyperglycemic area" and dividing it by the duration of sensor use. Similarly, the "hypoglycemic index" can be calculated by taking the "hypoglycemic area" divided by the duration of sensor use.

[0127] Various alarms and/or monitoring aspects discussed above may be combined or utilized with other alarms and/or monitoring aspects. The possible embodiments and/or combinations should not be limited to the specific embodiments described above.

7. Real-Time Glucose Display and History

[0128] In other embodiments of the invention, a physiological characteristic monitor 104 is used for reviewing a history of measurements of the sensed characteristic value based on user input from an input device with a display for showing the history of the measurements of the sensed characteristic value. As discussed above with respect to the alarm history, the display may show the measurements only within a specified range, such as the operational range of the sensor (e.g. 40 to 400 or 20 to 600 mg/dl). Outside the specified range, a HI or LO indicator is shown.

[0129] FIG. 7 illustrates the real-time and history display 700 of an embodiment of the invention. Three exemplary screens 702, 704, 706 are shown for the display of real-time or historical measurement data. The in-range screen 702 is used when the measurement is within the specified range; the actual measurement is shown. The high screen 704 (showing a HI indicator) is used when the measurement is above the specified range, and the low screen 706 (showing a LO indicator) is used when the measurement is below the specified range. The display shows a no measurement indicator where no value was recorded in the history.

[0130] The user input also directs scrolling through a history of the measurements of the sensed characteristic value. In a typical embodiment, the display shows a single measurement at a time. The display shows a time of acquisition by the sensor for each measurement in the history. In the example in-range screen 702, the current measurement is being shown, indicated by the "NOW" indicator. The time of acquisition can be shown as a value relative to a most recent measurement of the history. For example, the high and low screens 704, 706 each show values measured 5 hours and 25 minutes before the current time interval. Alternatively, the actual date and time of the measurement may be shown.

[0131] The history of the measurements of the sensed characteristic value can be scrolled through in even time increments. In further embodiments, the even time increment can have a selectable size (e.g. selectable between 5 minute or 30 minute increments), and the selected time increment can be indicated on the display as the history is reviewed. The history itself can comprise a fixed total period from the present backward. For convenience, scrolling through the history wraps around after an end of the history is reached.

[0132] In further embodiments of the invention, when no measurement is currently available, the NOW indicator can be replaced by a status message indicating no calibration, noise or a missed measurement.

[0133] This concludes the description including the preferred embodiments of the present invention. The foregoing description including the preferred embodiment of the invention has been presented for the purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed. Many equivalent modifications and variations are possible in light of the above teaching.

[0134] It is intended that the scope of the invention be limited not by this detailed description, but rather by the claims appended hereto. The above specification, examples and information provide a description of the manufacture and use of the apparatus and method of the invention. Since many embodiments of the invention can be made without departing from the scope of the invention, the invention resides in the claims hereinafter appended.

Claims

1. A physiological characteristic monitor (104), comprising:

a sensor input (106) capable of receiving a signal from a sensor (102), the signal being based on a measurement of the concentration of blood glucose in a user; and
a processor (108) for operating an alarm based on user input from an input device (112); wherein:

operating the alarm comprises setting parameters of the alarm based on the user input from the input device; the alarm indicates a glycemic condition condition when the concentration of blood glucose in the user exceeds a set range;

Abbott Ex. 1002 - 625/1438

characterized in that
the glycemic condition comprises a hypoglycemic condition, and the alarm is indicated by at least two audible descending tones
or
the glycemic condition comprises a hyperglycemic condition, and the alarm is indicated by at least two audible ascending tones.

2. The physiological characteristic monitor (104) of claim 1, wherein subsequent alarms are inhibited for an alarm repeat delay period after the measurement of the concentration of blood glucose indicates the glycemic condition.

3. The physiological characteristic monitor (104) of claim 1, wherein an alarm repeat delay period for delaying a repeated check of the alarm condition is set by the user input

4. The physiological characteristic monitor (104) of claim 3, wherein the alarm repeat delay period is different based upon an alarm threshold triggering the alarm, and wherein multiple alarm thresholds are used to indicate different severities of the glycemic condition.

5. The physiological characteristic monitor (104) of claim 3, wherein the alarm repeat delay period is set by the user scrolling through a list of delay increments and selecting the desired alarm repeat delay period from the list of delay increments.

6. The physiological characteristic monitor (104) of claim 3, wherein the alarm repeat delay period is set separately for the glycemic condition comprising a hypoglycemic condition and a hyperglycemic condition.

7. The physiological characteristic monitor (104) of claim 6, wherein the alarm repeat delay period has a default value of approximately 20 minutes for the glycemic condition comprising the hypoglycemic condition.

8. The physiological characteristic monitor (104) of claim 6, wherein the alarm repeat delay period has a default value of approximately 1 hour for the glycemic condition comprising the hyperglycemic condition.

9. The physiological characteristic monitor (104) of claim 1, wherein an alarm snooze period for temporarily disabling the alarm is set by the user input.

10. The physiological characteristic monitor (104) of claim 9, wherein the alarm snooze period is different based upon an alarm threshold triggering the alarm, and wherein multiple alarm thresholds are used to indicate different severities of the glycemic condition.

11. The physiological characteristic monitor (104) of claim 9, wherein the alarm snooze period is only available for a glycemic condition comprising a hyperglycemic condition.

12. The physiological characteristic monitor (104) of claim 9, wherein the alarm snooze period is deactivated upon adjusting a hyperglycemic alarm setting.

13. The physiological characteristic monitor (104) of claim 9, wherein the display shows a snooze indicator when the snooze period is running and the monitor is calibrated.

14. The physiological characteristic monitor (104) of claim 9, wherein the display shows time remaining of the alarm snooze period.

15. The physiological characteristic monitor (104) of claim 9, wherein the alarm snooze period is set by the user scrolling through a list of snooze period increments and selecting the desired alarm snooze period from the list of snooze period increments.

16. The physiological characteristic monitor (104) of claim 9, wherein the alarm snooze period is set by the user utilizing up arrow and down arrow buttons.

Abbott Ex. 1002 - 626/1438

Patentansprüche

1. Monitor (104) zur Überwachung einer physiologischen Eigenschaft, mit:

einem Sensoreingang (106), der aus einem Sensor (102) ein Signal aufnehmen kann, dem eine Messung der Blut-Glucose-Konzentration in einem Benutzer zu Grunde liegt; und
einem Prozessor (108), mit dem auf Grund einer Eingabe des Benutzers aus einer Eingabeeinrichtung (112) ein Alarm auslösbar ist; wobei
das Auslösen des Alarms das Setzen von Parametern desselben auf Grund der Eingabe des Benutzers an der Eingabeeinrichtung beinhaltet, und
der Alarm einen glycemischen Zustand anzeigt, wenn die Blut-Glucose-Konzentration im Benutzer aus einem voreingestellten Bereich fällt;
dadurch gekennzeichnet, dass
der glycemische Zustand eine Unterzuckerung beinhaltet und der Alarm durch mindestens zwei in der Tonhöhe absteigende hörbare Töne angezeigt wird, oder
der glycemische Zustand eine Überzuckerung beinhaltet und der Alarm durch mindestens zwei in der Tonhöhe aufsteigend hörbare Töne angezeigt wird.

2. Monitor (104) nach Anspruch 1, bei dem nachfolgende Alarme für die Dauer einer Wiederholungsverzögerung gesperrt werden, nachdem die Messung der Blut-Glucose-Konzentration den glycemischen Zustand angezeigt hat.

3. Monitor (104) nach Anspruch 1, bei dem durch die Benutzereingabe eine Alarm-Wiederholungsverzögerung zum Verzögern einer wiederholten Prüfung des Alarmzustands gesetzt wird.

4. Monitor (104) nach Anspruch 3, bei dem die Alarm-Wiederholungsverzögerung auf Grund der Auslösung des Alarms an einem Alarm-Schwellenwert differiert und mehrere Alarm-Schwellenwerte angesetzt werden, um unterschiedliche Schweregrade des glycemischen Zustands anzuzeigen.

5. Monitor (104) nach Anspruch 3, bei dem die Alarm-Wiederholungsverzögerung gesetzt wird, indem der Benutzer durch Auf- oder Abwärtsrollen in einer Liste abgestufter Verzögerungsschritte eine gewünschte Alarm-Wiederholungsverzögerung auswählt.

6. Monitor (104) nach Anspruch 3, bei dem die Alarm-Wiederholungsverzögerung für eine Unter- oder Überzuckerung getrennt gesetzt wird.

7. Monitor (104) nach Anspruch 6, bei dem bei Unterzuckerung die Alarm-Wiederholungsverzögerung einen Standard- bzw. Vorgabewert von etwa 20 Minuten hat.

8. Monitor (104) nach Anspruch 6, bei dem bei Überzuckerung die Alarm-Wiederholungsverzögerung einen Standard- bzw. Vorgabewert von etwa einer Stunde hat.

9. Monitor (104) nach Anspruch 1, bei dem durch Eingabe des Benutzers ein Schlummerintervall zum zeitweiligen Deaktivieren des Alarms setzbar ist.

10. Monitor (104) nach Anspruch 9, bei dem das Schlummerintervall auf Grund eines den Alarm auslösenden Alarm-Schwellenwerts unterschiedlich ist und mehrere Alarm-Schwellenwerte angesetzt sind, um unterschiedliche Schweregrade des glycemischen Zustands anzuzeigen.

11. Monitor (104) nach Anspruch 9, bei dem das Alarm-Schlummerintervall nur bei Überzuckerung verfügbar ist.

12. Monitor (104) nach Anspruch 9, bei dem das Alarm-Schlummerintervall bei Neueinstellung des Überzuckerungsalarms deaktiviert wird.

13. Monitor (104) nach Anspruch 9, bei dem auf dem Sichtfeld eine Schlummer-Anzeige ausgegeben wird, wenn das Schlummerintervall läuft und der Monitor abgeglichen ist.

14. Monitor (104) nach Anspruch 9, auf dessen Sichtfeld die verbleibende Restdauer des Alarm-Schlummerintervalls angezeigt wird.

Abbott Ex. 1002 - 627/1438

15. Monitor (104) nach Anspruch 9, bei dem das Alarm-Schlummerintervall vom Benutzer durch Auf- und Abwärtsrollen in einer Liste von Intervallstufen auswähl- bar ist und gesetzt wird.

16. Monitor (104) nach Anspruch 9, bei dem das Alarm-Schlummerintervall vom Benutzer mittels Aufwärts- und Abwärts-Pfeiltasten auswählbar ist.

Revendications

1. Moniteur de caractéristiques physiologiques (104), comprenant :

une entrée de capteur (106) capable de recevoir un signal en provenance d'un capteur (102), le signal étant basé sur une mesure de la concentration de glucose dans le sang d'un utilisateur ; et
un processeur (108) pour actionner une alarme sur la base d'une entrée d'utilisateur depuis un dispositif d'entrée (112) ; dans lequel :

l'actionnement de l'alarme comprend le réglage de paramètres de l'alarme sur la base de l'entrée d'utilisateur depuis le dispositif d'entrée ;
l'alarme indique un état glycémique lorsque la concentration de glucose dans le sang de l'utilisateur dépasse une plage définie ;
caractérisé en ce que
l'état glycémique comprend un état hypoglycémique, et l'alarme est indiquée par au moins deux tonalités descendantes audibles
ou
l'état glycémique comprend un état hyperglycémique, et l'alarme est indiquée par au moins deux tonalités ascendantes audibles.

2. Moniteur de caractéristiques physiologiques (104) selon la revendication 1, dans lequel des alarmes ultérieures sont inhibées pendant une période de retard de répétition d'alarme une fois que la mesure de la concentration de glucose dans le sang indique l'état glycémique.

3. Moniteur de caractéristiques physiologiques (104) selon la revendication 1, dans lequel une période de retard de répétition d'alarme pour différer un contrôle répété de l'état d'alarme est réglée par l'entrée d'utilisateur.

4. Moniteur de caractéristiques physiologiques (104) selon la revendication 3, dans lequel la période de retard de répétition d'alarme est différente sur la base d'un seuil d'alarme déclenchant l'alarme, et dans lequel de multiples seuils d'alarme sont utilisés pour indiquer différentes sévérités de l'état glycémique.

5. Moniteur de caractéristiques physiologiques (104) selon la revendication 3, dans lequel la période de retard de répétition d'alarme est réglée par l'utilisateur en faisant défiler une liste d'incréments de retard et en sélectionnant la période de retard de répétition d'alarme désirée à partir de la liste d'incréments de retard.

6. Moniteur de caractéristiques physiologiques (104) selon la revendication 3, dans lequel la période de retard de répétition d'alarme est réglée séparément pour l'état glycémique comprenant un état hypoglycémique et un état hyperglycémique.

7. Moniteur de caractéristiques physiologiques (104) selon la revendication 6, dans lequel la période de retard de répétition d'alarme a une valeur par défaut d'approximativement 20 minutes pour l'état glycémique comprenant l'état hypoglycémique.

8. Moniteur de caractéristiques physiologiques (104) selon la revendication 6, dans lequel la période de retard de répétition d'alarme a une valeur par défaut d'approximativement une heure pour l'état glycémique comprenant l'état hyperglycémique.

9. Moniteur de caractéristiques physiologiques (104) selon la revendication 1, dans lequel une période de rappel d'alarme pour désactiver temporairement l'alarme est réglée par l'entrée d'utilisateur.

10. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel la période de rappel d'alarme

Abbott Ex. 1002 - 628/1438

est différente sur la base d'un seuil d'alarme déclenchant l'alarme, et dans lequel de multiples seuils d'alarme sont utilisés pour indiquer différentes sévérités de l'état glycémique.

11. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel la période de rappel d'alarme est uniquement disponible pour un état glycémique comprenant une état hyperglycémique.

12. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel la période de rappel d'alarme est désactivée lors du réglage d'un paramétrage d'alarme hyperglycémique.

13. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel l'affichage montre un indicateur de rappel d'alarme lorsque la période de rappel d'alarme est en cours d'exécution et que le moniteur est calibré.

14. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel l'affichage montre le temps restant de la période de rappel d'alarme.

15. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel la période de rappel d'alarme est réglée par l'utilisateur en faisant défiler une liste d'incréments de période de rappel d'alarme et en sélectionnant la période de rappel d'alarme désirée à partir de la liste d'incréments de période de rappel d'alarme.

16. Moniteur de caractéristiques physiologiques (104) selon la revendication 9, dans lequel la période de rappel d'alarme est définie par l'utilisateur en utilisant des touches de flèche vers le haut et de flèche vers le bas.

Abbott Ex. 1002 - 629/1438

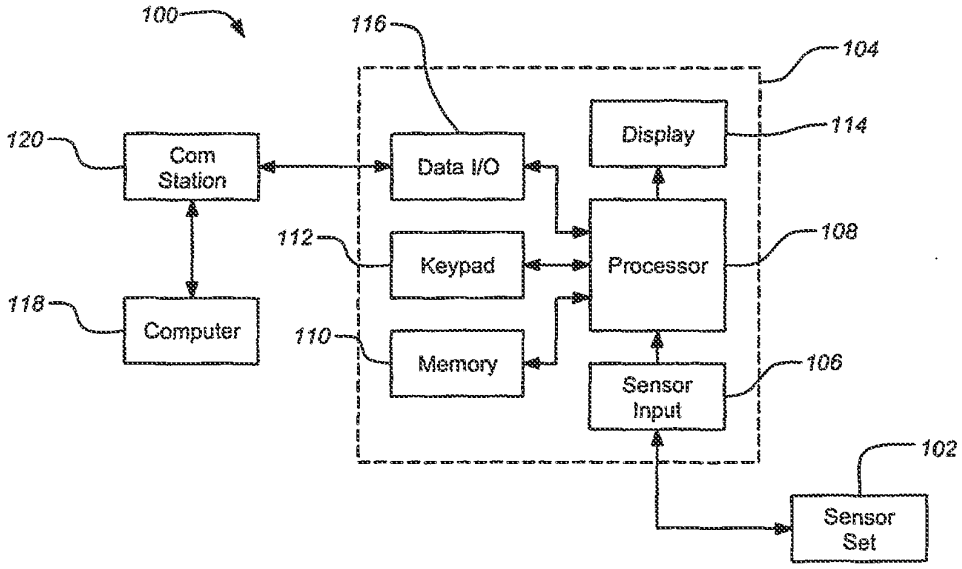


FIG. 1A

Abbott Ex. 1002 - 630/1438

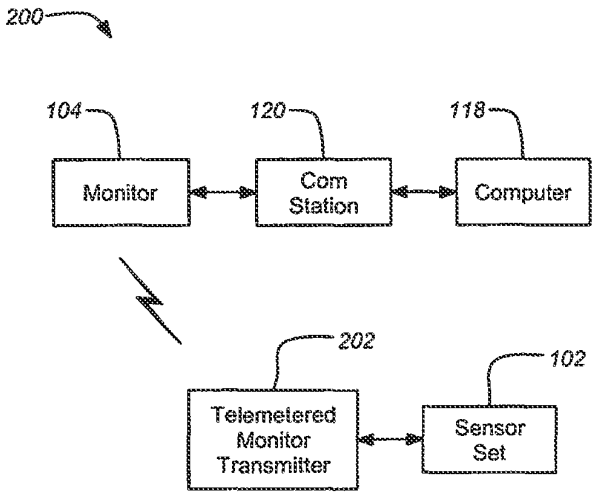


FIG. 1B

Abbott Ex. 1002 - 631/1438

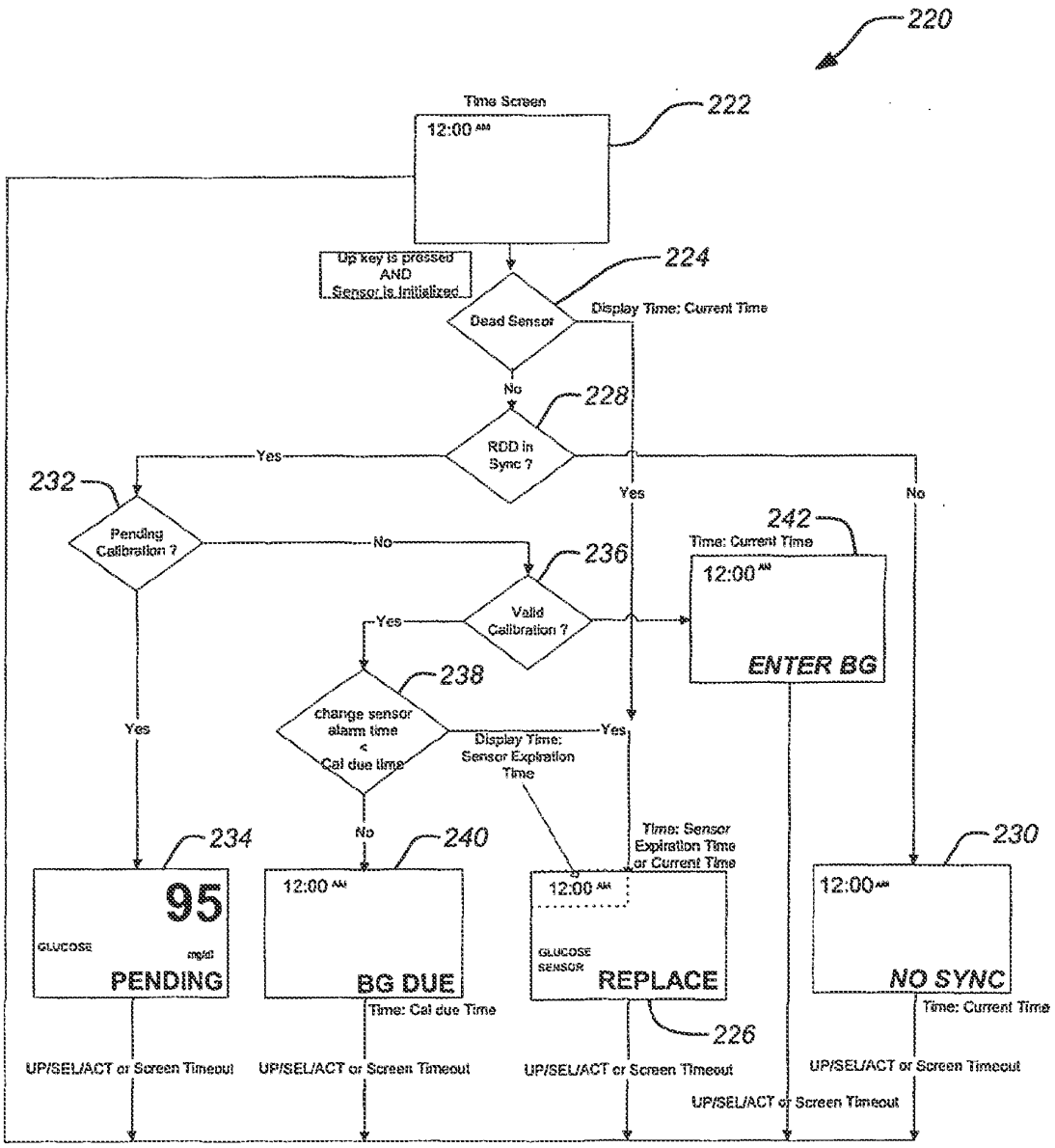


FIG. 2A

Abbott Ex. 1002 - 632/1438

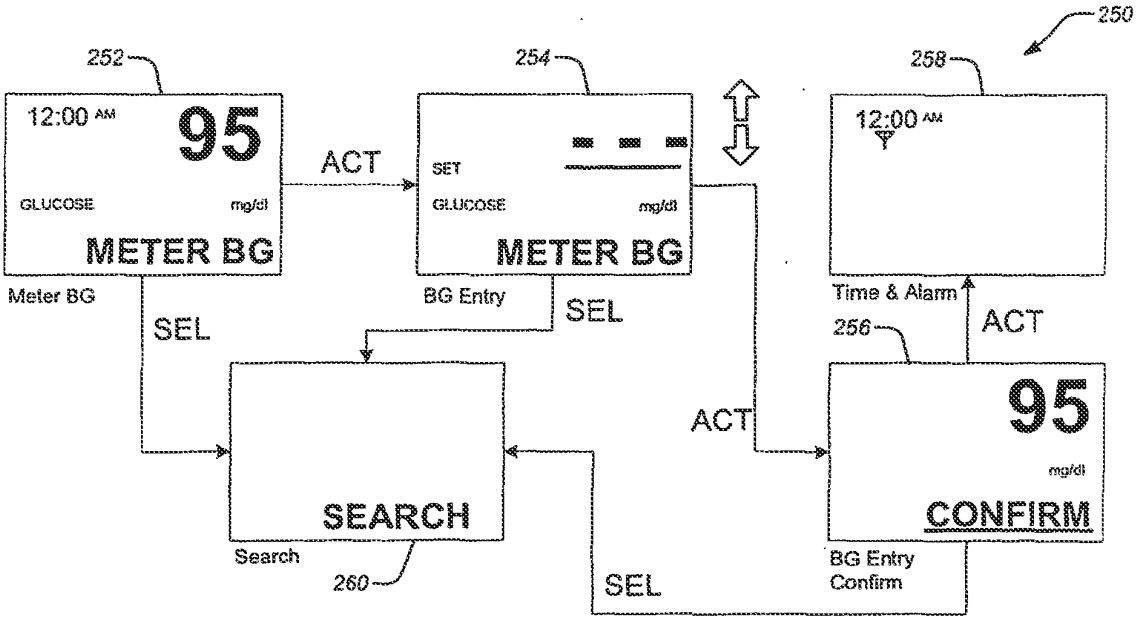


FIG. 2B

Abbott Ex. 1002 - 633/1438

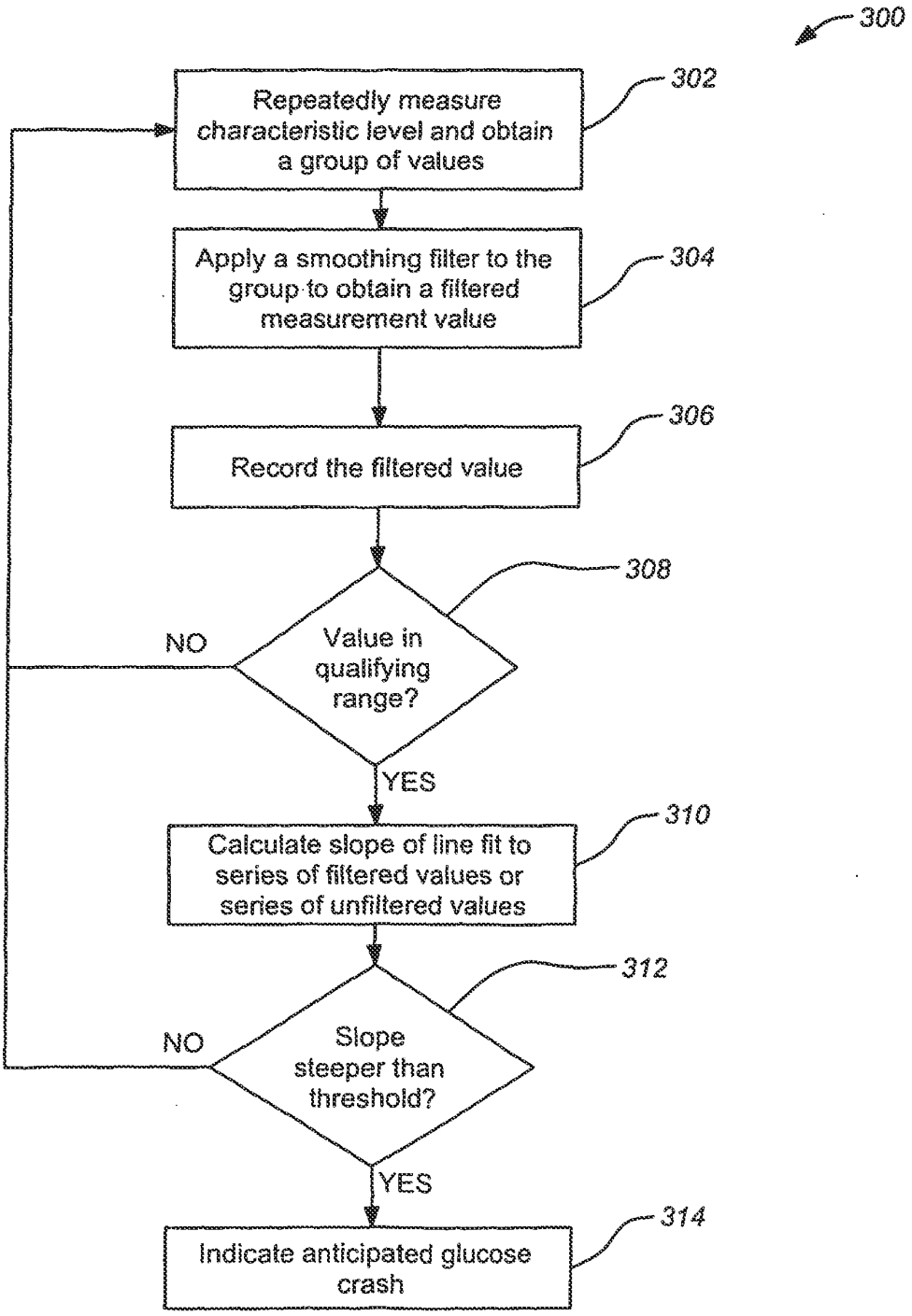


FIG. 3A

Abbott Ex. 1002 - 634/1438

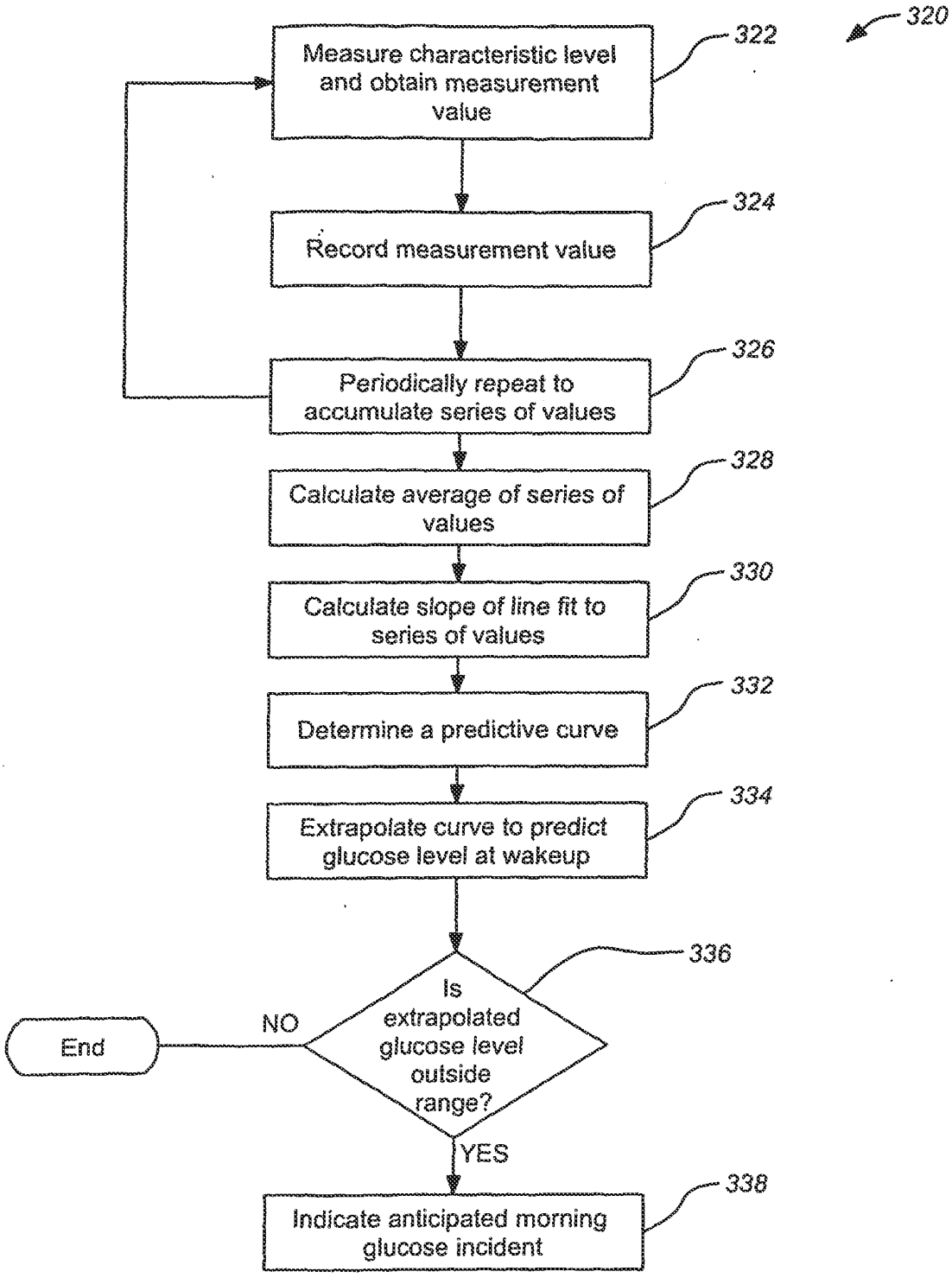


FIG. 3B

Abbott Ex. 1002 - 635/1438

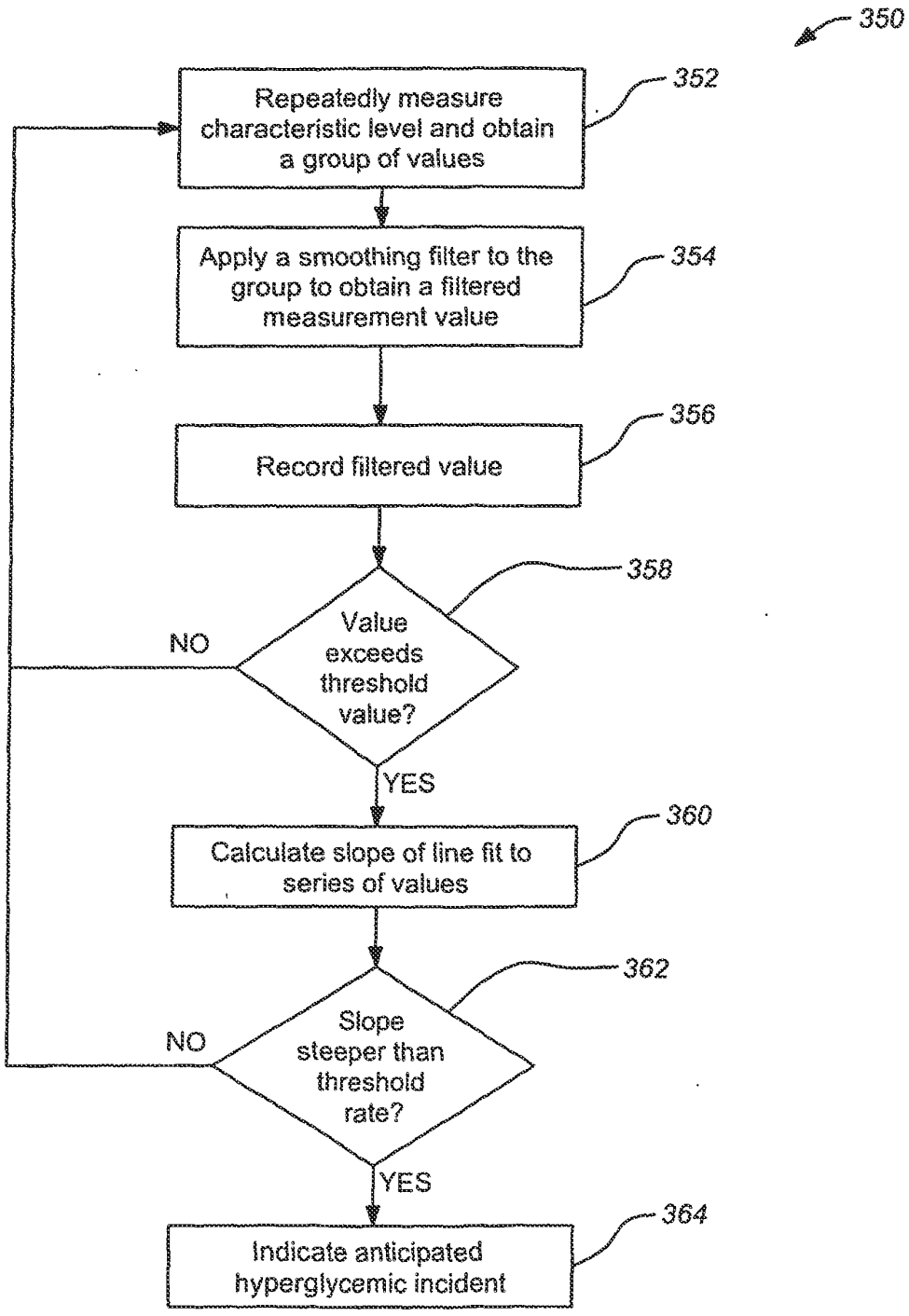


FIG. 3C

Abbott Ex. 1002 - 636/1438

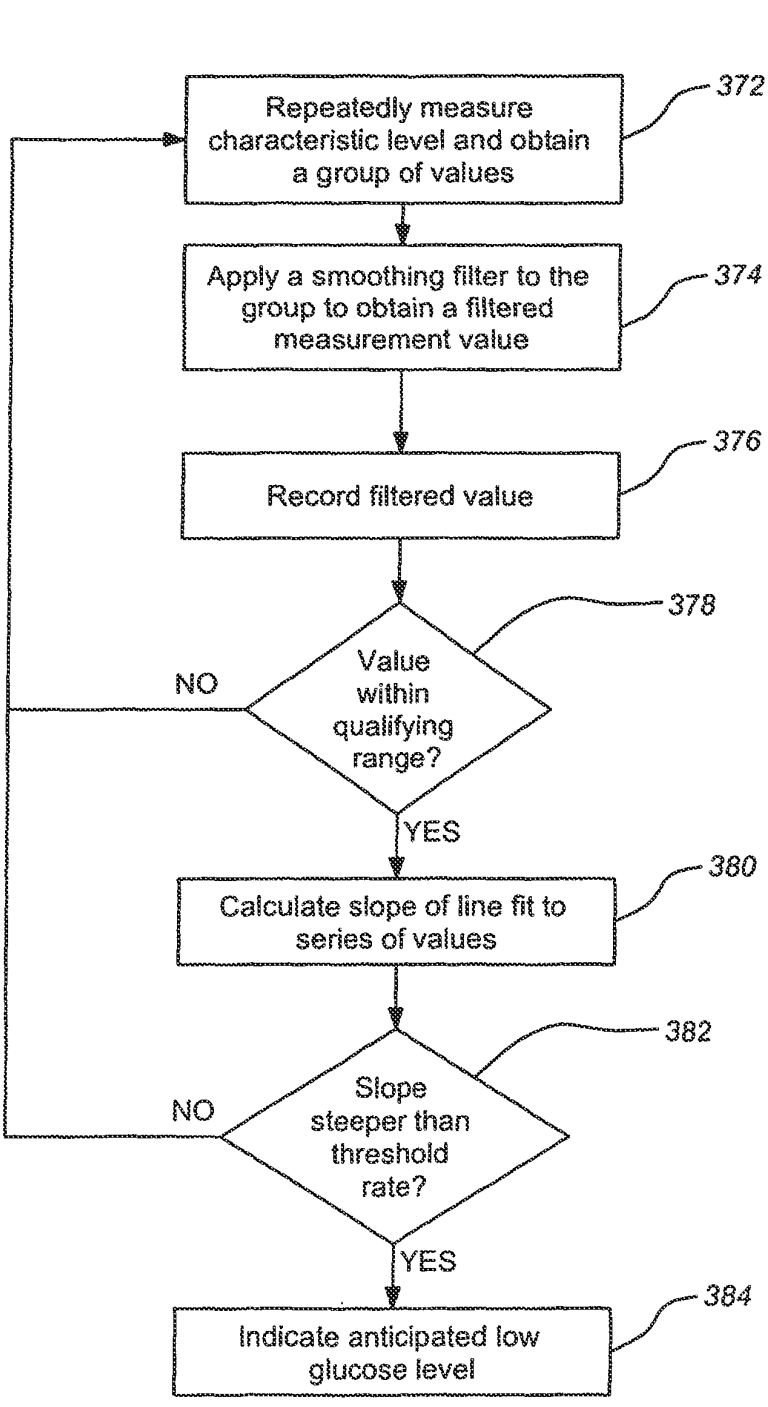


FIG. 3D

Abbott Ex. 1002 - 637/1438

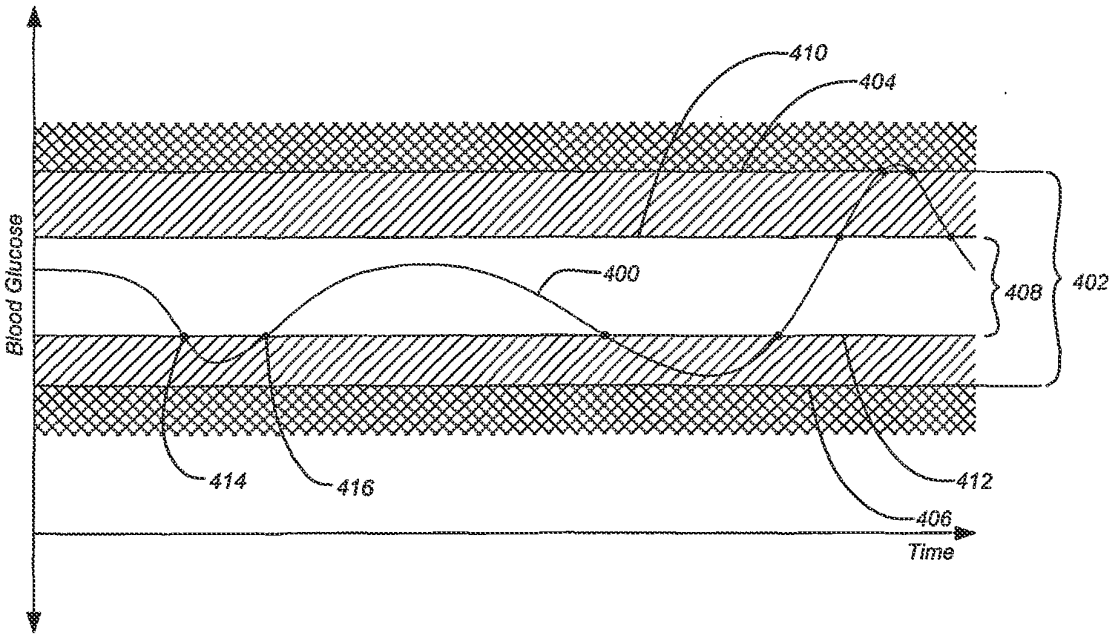


FIG. 4A

Abbott Ex. 1002 - 638/1438

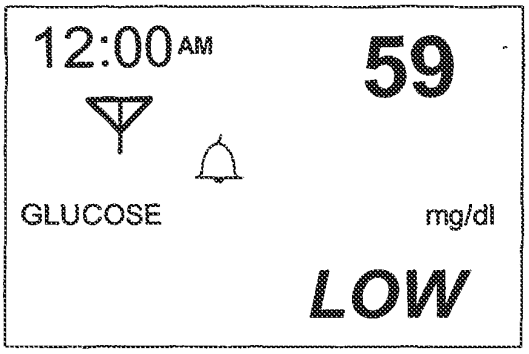


FIG. 4B

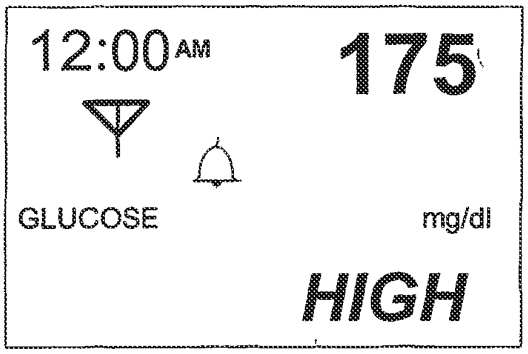


FIG. 4C

Abbott Ex. 1002 - 639/1438

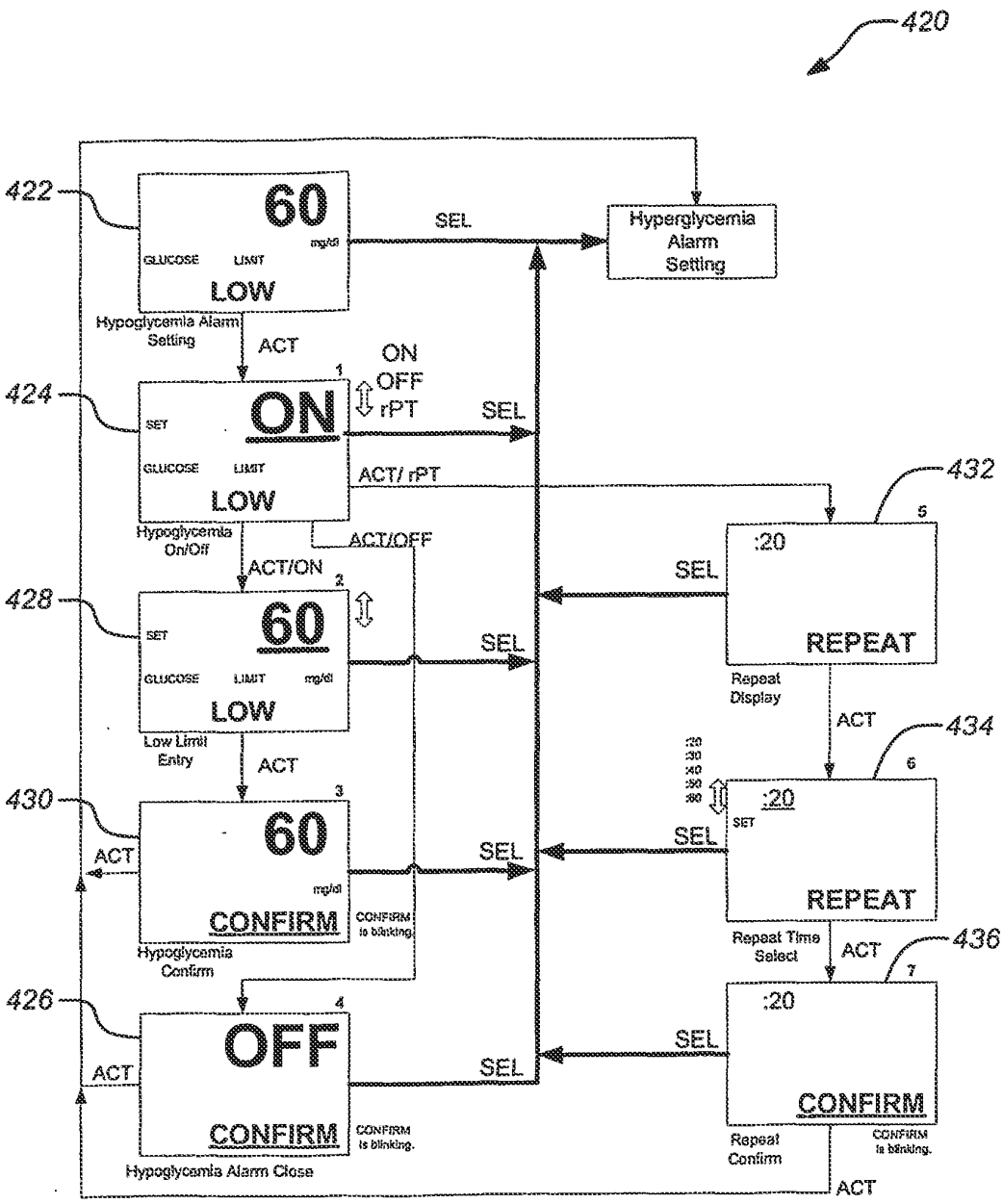


FIG. 4D

Abbott Ex. 1002 - 640/1438

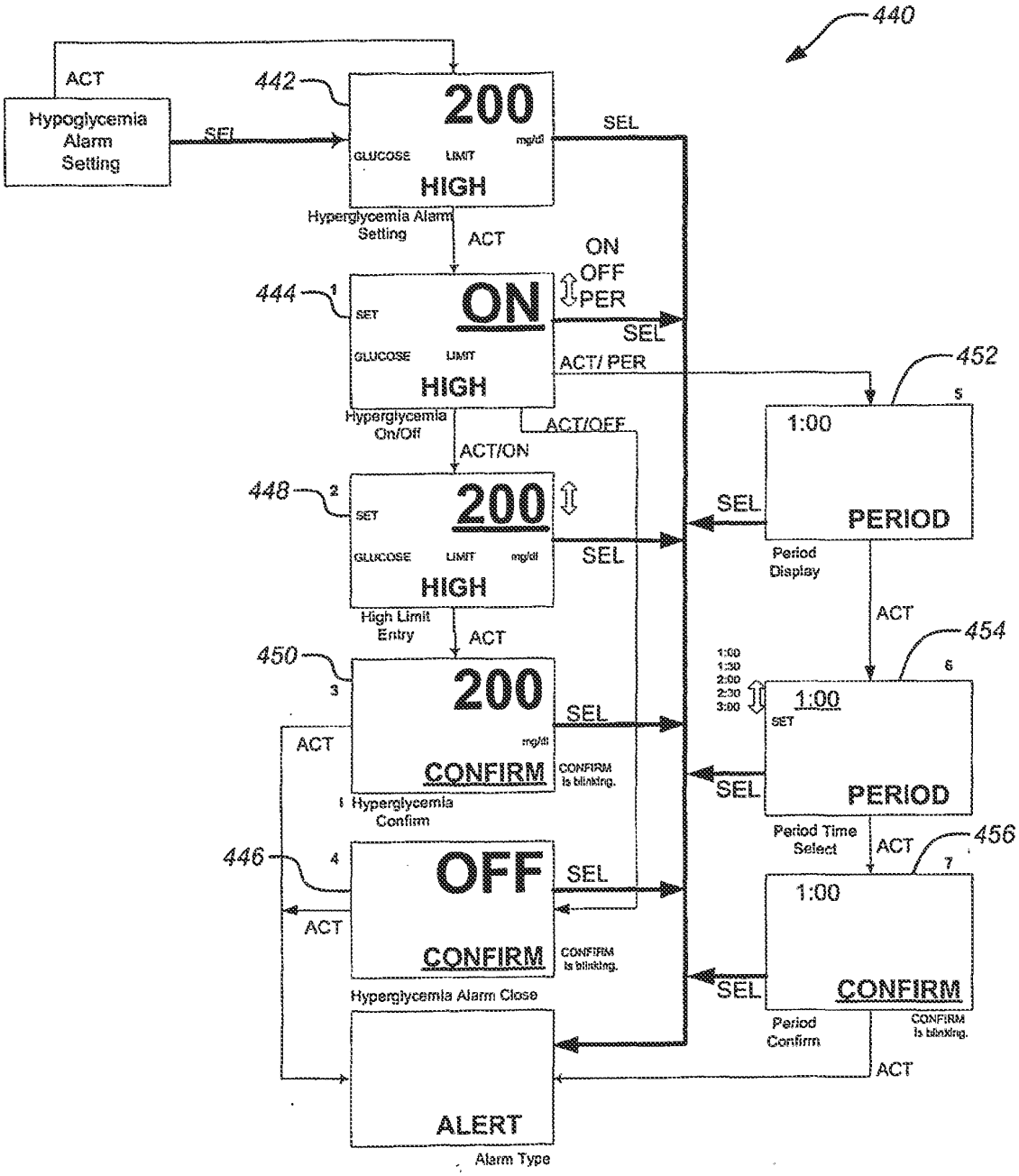


FIG. 4E

Abbott Ex. 1002 - 641/1438

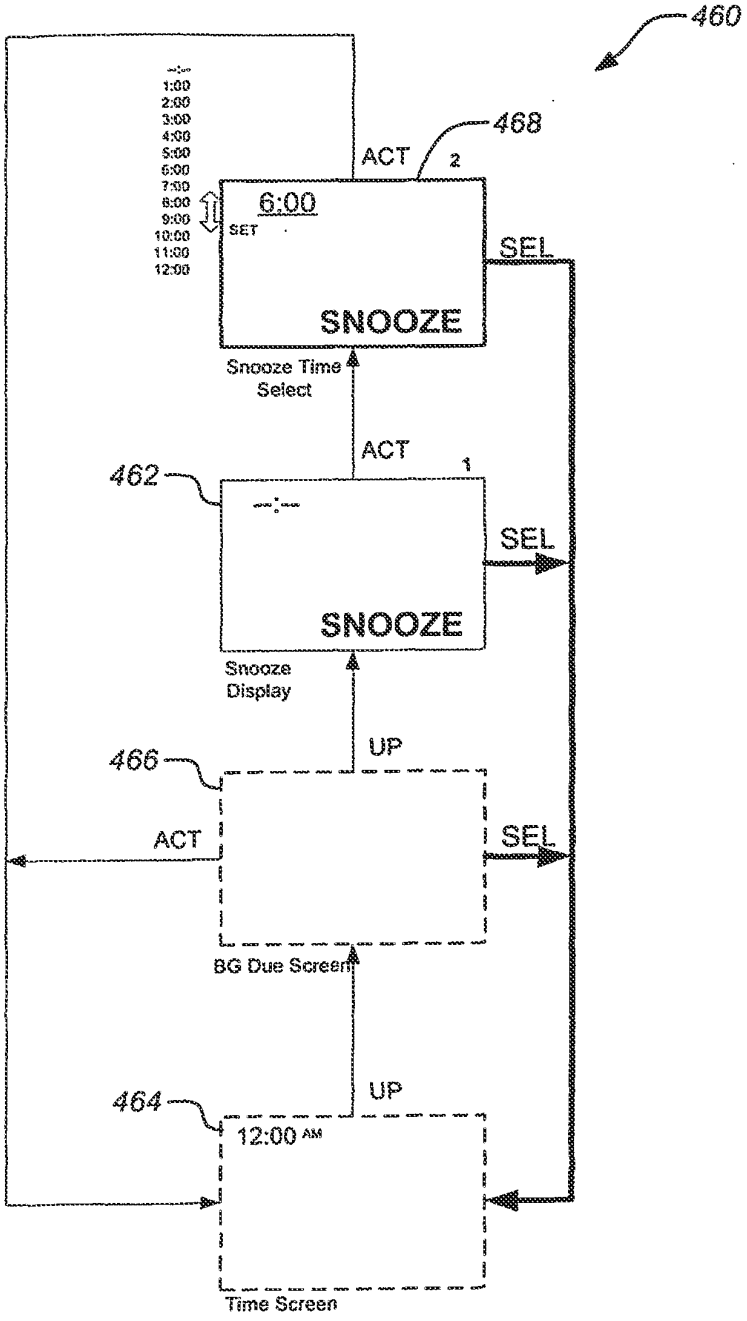


FIG. 4F

Abbott Ex. 1002 - 642/1438

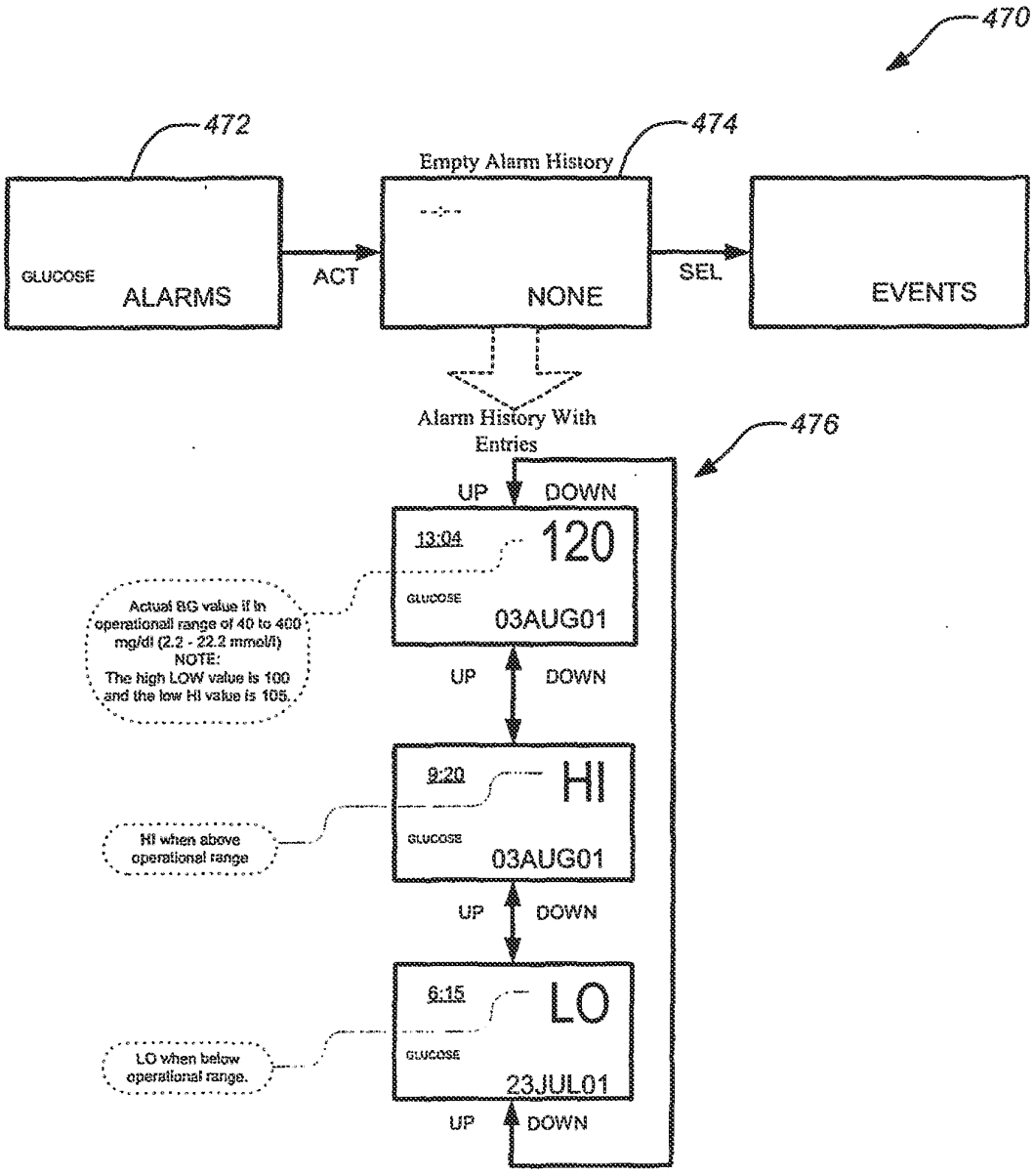


FIG. 4G

Abbott Ex. 1002 - 643/1438

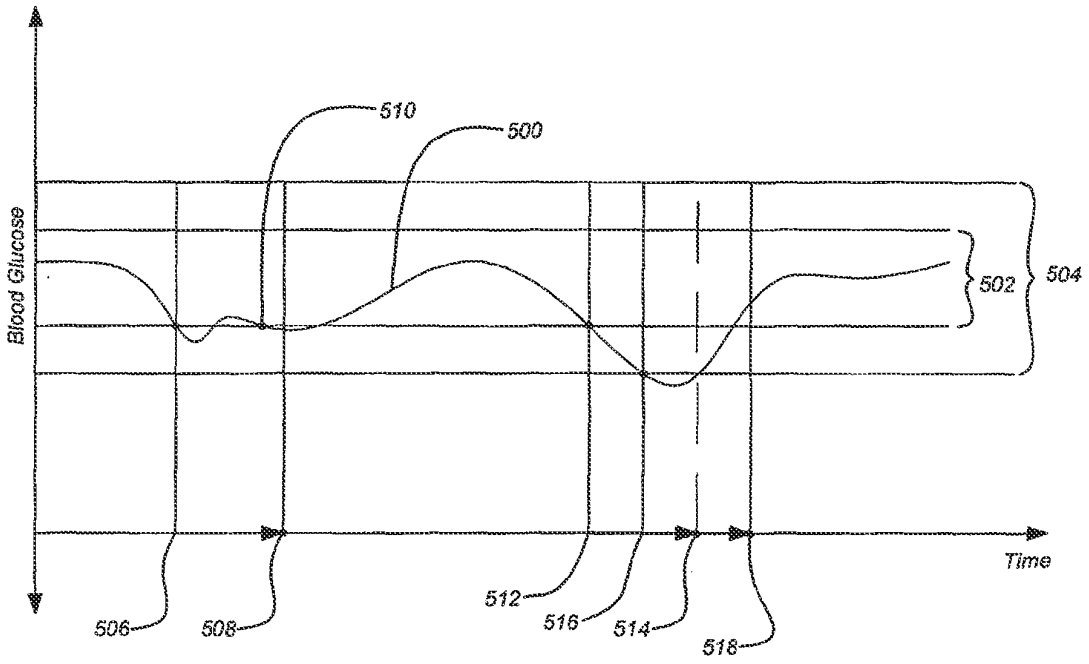


FIG. 5

Abbott Ex. 1002 - 644/1438

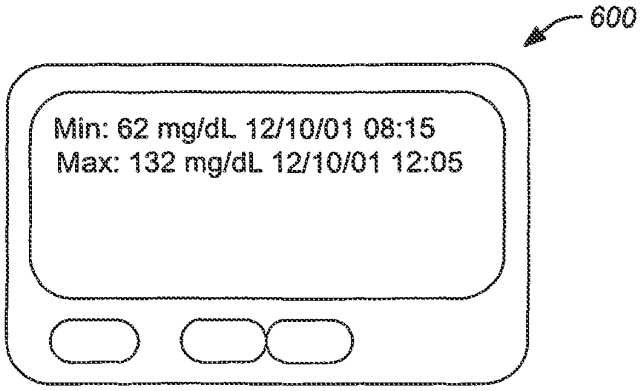


FIG. 6A

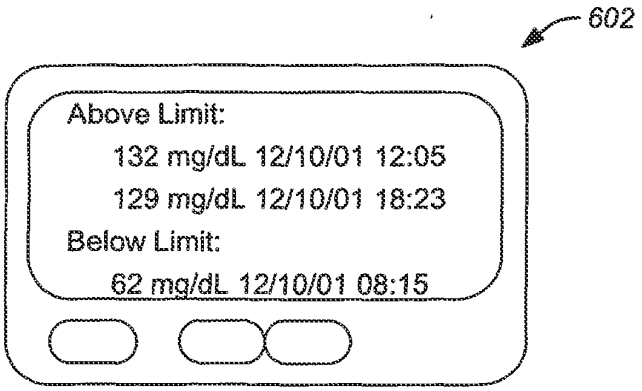


FIG. 6B

Abbott Ex. 1002 - 645/1438

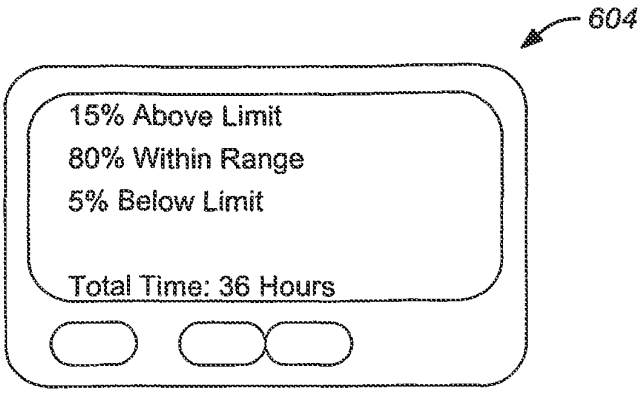


FIG. 6C

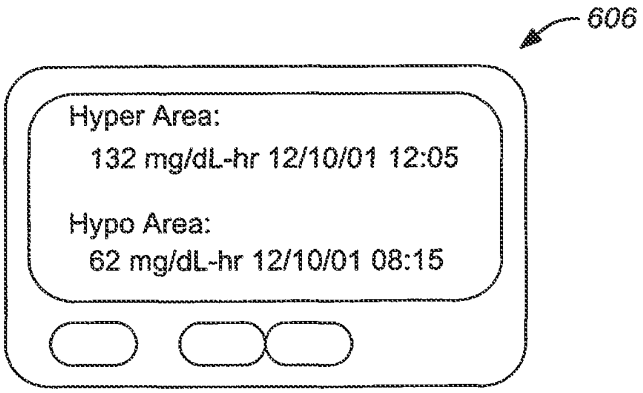


FIG. 6D

Abbott Ex. 1002 - 646/1438

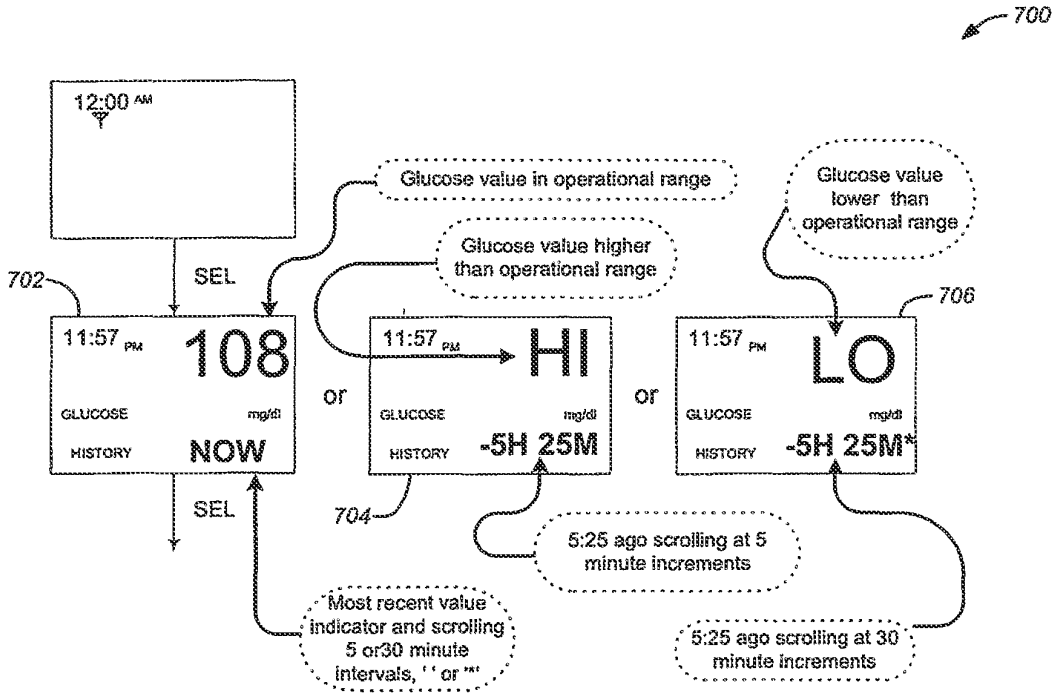


FIG. 7

Abbott Ex. 1002 - 647/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 4562751 A **[0002] [0058]**
- US 4678408 A **[0002] [0058]**
- US 4685903 A **[0002] [0058]**
- US 4573994 A **[0002] [0058]**
- US 5299571 A **[0003]**
- US 5390671 A **[0003]**
- US 5391250 A **[0003] [0059]**
- US 5482473 A **[0003] [0059]**
- US 5586553 A **[0003]**
- US 2003125612 A **[0008]**
- US 2003211617 A **[0008]**

Abbott Ex. 1002 - 648/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 706 022 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
29.10.2008 Bulletin 2008/44

(21) Application number: **04814084.2**

(22) Date of filing: **15.12.2004**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/US2004/041856

(87) International publication number:
WO 2005/065535 (21.07.2005 Gazette 2005/29)

(54) **SYSTEM AND METHOD FOR SENSOR RECALIBRATION**

SYSTEM UND VERFAHREN ZUR SENSORREKALIBRIERUNG

SYSTEME ET PROCEDE DE REETALONNAGE DE CAPTEUR

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR

(30) Priority: **30.12.2003 US 751327**

(43) Date of publication of application:
04.10.2006 Bulletin 2006/40

(73) Proprietor: **Medtronic MiniMed, Inc.**
Northridge, CA 91325 (US)

(72) Inventors:
- **ZHANG, Yanan**
  Valencia, CA 91355 (US)
- **WANG, Lu**
  Pasadena, CA 91106 (US)
- **SHAH, Rajiv**
  Rancho Palos Verdes, CA 90275 (US)

(74) Representative: **Ruschke, Hans Edvard**
RUSCHKE HARTMANN MADGWICK & SEIDE
Patent- und Rechtsanwälte
Postfach 86 06 29
81633 München (DE)

(56) References cited:
WO-A-98/58250
US-A1- 2003 153 821
US-A1- 2003 187 338
US-B1- 6 387 048

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 706 022 B1

Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND

1. Field of the Invention

[0001] The present invention relates to recalibration techniques and, in particular, to recalibration techniques for implantable sensors.

2. Description of Related Art

[0002] The accuracy of a sensing system is generally limited by the drift characteristics of the sensing element over time and the amount of environmental noise introduced into the output of the sensing element. To accommodate the drift inherent in the sensing element and the noise inherent in the system environment, the sensing system is periodically calibrated, or recalibrated.

[0003] A typical recalibration routine is performed at regular intervals. Generally, a technician will measure an output of the sensing system in response to a known, accurate input. The sensing system is then adjusted, or recalibrated, so that the output of the sensing system matches that of the known, accurate input to within an acceptable error margin.

[0004] Typical recalibration routines are often inadequate for many sensing systems. Many sensing systems include sensing elements that exhibit non-linear outputs or outputs that change in a non-linear fashion over time. Thus, a simple linear adjustment during a recalibration procedure to force an output of the sensing system back to acceptable output values often fails to account for the true nature of many sensing elements. The result of simple linear adjustments may be a sensing system that is accurate only over a small range of the sensing elements capabilities or a sensing system that may not maintain acceptable levels of accuracy for extended periods of time.

SUMMARY

[0005] According to an embodiment of the present invention, method for calibrating a sensor may include compiling an array of data relating to the sensor; adjusting a nominal output current a first time based on data in the array; adjusting a curve shape representing the sensor output based on data in the array; and adjusting the nominal output current a second time based on data in the array. Also, the method may further include establishing a new sensor output based on the adjusted curve and the twice adjusted sensor parameter.

[0006] The array may include historical data and empirical data. The historical data may include measured blood glucose readings. The recent data may include blood glucose concentrations and electrode readings, such as, for example, glucose electrode readings and oxygen electrode readings.

[0007] According to embodiments of the present invention, adjusting a nominal output current a first time may include adjusting a nominal glucose current based on a shift of measured data points with respect to blood glucose readings. The shift may be a mean shift.

[0008] Adjusting the curve representing the sensor output may include performing a linear regression on data in the array. The result of the linear regression may determine a first calibration point. The first calibration point may be used to determine a plurality of calibration points.

[0009] According to an embodiment of the present invention, adjusting the curve representing the sensor output may include adjusting the curve in a piecewise linear fashion. The number of pieces in the piecewise linear adjustment may be five.

[0010] Adjusting a nominal output current a second time may include adjusting a nominal glucose current based on a shift of measured data points with respect to blood glucose readings. The shift may be a mean shift.

[0011] According to an embodiment of the present invention, an implantable sensing system may include a sensor for sensing a biological parameter; a processor connected to the sensor for processing the parameter; and a drug delivery unit connected to the processor for responding to the processor based on the parameter. The processor may be programmed to adjust an output of the sensor by compiling an array of data relating to the sensor; adjusting a nominal output current a first time based on data in the array; adjusting a curve shape representing the sensor output based on data in the array; and adjusting the nominal output current a second time based on data in the array.

[0012] The sensor may be a glucose sensor. The drug delivery unit may be an insulin pump. The insulin pump may deliver insulin in response to the sensed parameter.

[0013] A method for calibrating a sensor may include generating a calibration curve based on *a priori* empirical values; compiling a plurality of data values from the sensor; compiling independent historical values of a parameter sensed by the sensor; and reconciling the plurality of data values from the sensor to the calibration curve using the independent historical values. The sensor may be a glucose sensor. The independent historical values of a parameter sensed by the

Abbott Ex. 1002 - 650/1438

sensor may be metered blood glucose values.

[0014] Generating a calibration curve may include compiling *a priori* empirical values of sensors similar to the sensor being calibrated. Generating a calibration curve may also include generating a calibration curve representing a sensor having a plurality of phases.

[0015] Reconciling the plurality of data values may include adjusting an output current of the sensor. The output current of the sensor may be a nominal glucose current. Also, the nominal glucose current may be adjusted based on a shift of the plurality of data values from the sensor with respect to metered blood glucose values. Reconciling the plurality of data values may also include performing a linear regression on the plurality of data values. In addition, reconciling the plurality of data values may be performed in a piecewise linear fashion.

[0016] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] 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.

[0018] Figure 1 shows a cross-sectional view of an exemplary sensor according to an embodiment of the present invention.

[0019] Figure 2 shows a graph of a normalized calibration curve for the three phases of a sensor life according to an embodiment of the present invention.

[0020] Figure 3 shows a graph of a piecewise linear approximation technique for the calibration curve according to an embodiment of the present invention.

[0021] Figure 4 shows a detailed method for calibrating a sensor according to an embodiment of the present invention.

[0022] Figure 5a-d shows a resulting adjustment of a recalibrated sensor output according to an embodiment of the present invention.

[0023] Figure 6 shows an implanted sensing system in which embodiments of the invention may be used according to embodiments of the present invention.

DETAILED DESCRIPTION

[0024] In the following description of embodiments of the invention, reference is made to the accompanying drawings which form a part hereof, and in which are shown by way of illustration specific embodiments in which the invention may be practiced. It is to be understood that other embodiments may be utilized and structural changes may be made without departing from the scope of the preferred embodiments of the present invention.

[0025] Embodiments of the present invention are directed to calibration techniques for use with implantable sensors that measure a characteristic of a patient's body. In preferred embodiments, the characteristic is the glucose level, and the implantable sensor is placed in an artery or a vein. Although embodiments of the present invention are primarily described in the context of glucose sensors used in the treatment of diabetes, the embodiments of the invention are applicable to a wide variety of patient treatment programs where a physiological characteristic is monitored. For example, embodiments of the invention can be used to determine the status and/or levels of a variety of characteristics including those associated with agents such as hormones, cholesterol, medication concentrations, pH, oxygen saturation, viral loads (e.g., HIV), or the like. Also embodiments of the present invention are not limited to implantation in an artery or vein, but can be implanted in and/or through subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue. Such sensors typically communicate a signal from the implantable sensor to either an internal or external monitor. The implantable sensor is primarily adapted for use with blood. However, still further embodiments of the implantable sensor may be used in other bodily fluids, such as interstitial fluid, spinal fluid, saliva, urine, tears, sweat, or the like.

[0026] FIG. 1 is a cross-sectional view of an exemplary sensor in accordance with the embodiments of the present invention. The sensor generally includes, in one preferred form, an implantable enzyme electrode of the general type described in U.S. Pat. Nos. 4,650,547; 4,671,288; 4,781,798; 4,703,756; and 4,890,620. Such enzyme electrodes can be used in a sensor for direct contact with patient fluids, such as blood. In the preferred embodiments, a glucose oxygen sensor 20 is used to detect the level of glucose in the blood by measuring the depletion of oxygen as the glucose oxidase enzyme catalyzes a reaction between glucose and oxygen present in the blood according to the following reaction:

[0027]

Abbott Ex. 1002 - 651/1438

$$\text{Glucose} + O_2 \xrightarrow{\text{Glucose Oxidase}} \text{Gluconic Acid} + H_2O_2$$

[0028] Typically, the glucose sensor 20 has at least two electrodes 110, 120 to detect the level of oxygen in the blood. Preferably, the first electrode is an oxygen sensing electrode 110 to detect the level of oxygen in the patient fluid (e.g. blood) as a reference point for the second electrode. The second electrode is a glucose sensing electrode 120 placed in the proximity of glucose oxidase to ascertain the oxygen depletion during the electrochemical reaction between oxygen and the glucose around the area of the glucose sensing electrode 120. The glucose oxygen sensor 20 is designed to send a particular current depending on the amount of oxygen present near the electrodes 110, 120. Given that the amount of current flowing to the electrodes has a fairly linear relationship the amount oxygen present in the area surrounding the electrodes 110, 120, a measurement of the currents can be used to determine the amount of glucose present in the blood, as described in Application Serial Number 10/034,338 entitled "Implantable Sensor Electrodes and Electronic Circuitry," filed on December 28, 2001.

[0029] In alternative embodiments, different sensors technology may be used, such as, but not limited to a hydrogen peroxide sensor or an optical sensor. A hydrogen peroxide sensor would work similar to an oxygen sensor, except that rather than measuring the amount of oxygen depleted in the presence of the glucose oxidase enzyme, the hydrogen peroxide sensor would measure the amount of hydrogen peroxide produced as a result of the reaction between oxygen and glucose in the presence of the glucose oxidase enzyme. Alternatively, an implantable optical sensor would include a photo-reactive substance or compound that optically changes, fluoresces, or the like, or other suitable compounds that detect changing properties in the presence of a bodily fluid analyte, such as glucose or the like. The compounds can also be used to detect the level of an analyte that has been ingested, injected or placed inside the body, such as marker substances, or the like. For example, possible compounds that produce a fluorescent change in the presence of a bodily fluid analyte are disclosed in U.S. Patent No. 5,503,770 issued April 2, 1996 to James et al. and entitled "Fluorescent Compound Suitable For Use In The Detection Of Saccharides"; U.S. Patent No. 5,512,246 issued April 30, 1996 to Russell et al. and entitled "Method and Means for Detecting Polyhydroxyl Compounds"; U.S. Provisional Application Serial No. 60/007,515 to Van Antwerp et al. and entitled "Minimally Invasive Chemically Amplified Optical Glucose Sensor"; and U.S. Patent No. 6,011,984 to Van Antwerp et al. and entitled "Detection of Biological Molecules Using Chemical Amplification". Other compounds using Donor Acceptor fluorescent techniques may be used, such as is disclosed in U.S. Patent No. 5,628,310 issued May 13, 1997 to Rao et al. and entitled " Method and Apparatus to Perform Trans-cutaneous Analyte Monitoring"; U.S. Patent No. 5,342,789 issued August 30, 1994 to Chick et al. and entitled "Method and Device for Detecting and Quantifying Glucose in body Fluids"; and U.S. Patent No. 5,246,867 issued September 21, 1993 to Lakowicz et al. and entitled "Determination and Quantification of Saccharides by Luminescent Lifetimes and Energy Transfer".

[0030] Therefore, the generalized method for recalibration of a sensor according to an embodiment of the present invention may be applied to a variety of sensors, including, but not limited to, biological parameter sensors, physical parameter sensors and the like. For example, the generalized method may be applied to a variety of glucose sensors used in conjunction with implantable insulin pumps. Sensors and related systems of this type are disclosed in U.S. Patent Application No. 10/036,093, entitled, "Sensing Apparatus and Process," filed December 28, 2001, and U.S. Patent Application No. 10/038,276, filed January 2, 2002, entitled, "Sensor Substrate and Method of Fabricating Same".

[0031] Sensors typically exhibit different characteristics during the useful life of the sensor. Specifically, sensors typically have three phases: (1) initialization phase, (2) stable phase, and (3) end of life phase. For example, after a sensor has been implanted into a patient, readings from the sensor needs to be adjusted for the first phase of the sensor life as the sensor becomes used to its environment. As the sensor begins to mature and the sensor enters its second phase of life, readings from the sensor need to be adjusted for its second phase of life. Lastly, as the sensor approaches its end of life and enters its third phase of life, the readings from the sensor need to be adjusted for its third phase of life. According to embodiments of the present invention, a calibration scheme is described which can be used to properly calibrate the sensor regardless of the phase of the sensor life and to identify which phase the sensor is in.

[0032] According to embodiments of the present invention, a normalized calibration curve for the three phases of the sensor life is shown in Figure 2. The curve shapes 20, 30, and 40 are the calibration curve shapes of each phase of the sensor life as determined based on empirical data collected from the use of sensors. Arrow 5a, 5b represent a typical life cycle of the calibration curves as the sensor changes from one phase to another phase, as will be described in greater detail below. Although the normalized calibration curves in Figure 2 were originally derived based on glucose sensors, further research has proved that most sensors behave similarly and these calibration curves can be used with other type of sensors. According to embodiments of the present invention, sensor recalibrations will be performed not only based on independent characteristic values (e.g., blood meter values) but with use of the expected normalized

Abbott Ex. 1002 - 652/1438

calibration curves as will be described in greater detail below with respect to Figures 4 and 5.

[0033] In Figure 2, the vertical axis, designated as I_g/I_{g0}, represents the ratio of real time glucose current to an imaginary glucose current in the absence of glucose. I_g represents a sensor current output modulated by real time glucose measurements. I_{g0} represents a nominal value of the sensor output current when no glucose is present for measurement. I_{g0} can be calculated using the following formula:

[0034]

$$I_{g0} = R * I_o,$$

[0035] where R is a conversion factor that is based on blood meter values to calibrate the sensor and I_o is oxygen electrode output current. Since the presence of glucose lowers the glucose current, I_g should never exceed I_{g0}. Therefore, the highest point along Y axis is 1, when $I_g=I_{g0}$. The horizontal axis, designated by C_g/C_o, represents the ratio of measured glucose concentration versus a nominal glucose concentration. C_g represents the glucose concentration. C_o may be calculated by multiplying a nominal sensor oxygen electrode output current I_o by a constant. In other words,

[0036]

$$C_o = K \times I_o. \qquad (1)$$

[0037] In equation (1), the value "K" is a constant based on the ratio of the oxygen concentration to the oxygen electrode current.

[0038] As described previously, phase 1 of the sensor's life may be viewed as a sensitivity period during the initial output of the sensor current with respect to glucose concentration. As can be seen in Figure 2, line 20 is virtually completely linear during the first phase. This linearity represents the sensor output when it is initially placed in a patient. However, as the sensor stabilizes and enters phase 2, the current output of the sensor with respect to glucose concentration tends to become non-linear. The curve shape moves from line 20 to curve 30, as shown by the arrow 5a, as the sensor gets used to its environment and the enzyme or other mechanism on the sensor proceeds towards stabilization and settles into its environment.

[0039] The curve shift between line 20 and curve 30, represented by arrow 5a, represent a continuum of change in the sensor output current with respect to glucose concentration As the sensor finally stabilizes in its environment, it reaches a period of stabilization, represented by curve 30. According to embodiments of the present invention, the sensor may remain in this stabilized state for periods of one year or more.

[0040] Toward the end of the sensor life, the sensor output current tends to change less and less with respect to glucose concentration. Curve 30 moves toward curve 40 as represented by arrow 5b. Eventually, at the sensor's end of life, curve 40 is relatively flat for higher glucose concentrations, thereby rendering the sensor essentially ineffective for measurement. In other words, at the end of the sensor's life, the change in sensor output current with respect to a change in glucose concentration is minimal.

[0041] As described above, the present invention adjusts the calibration curve throughout the life of the sensor. Having a constantly updated calibration curve assures that accurate sensor readings are obtained regardless of the phase of the sensor. In further embodiments of the invention, a five-point piecewise linear approximation is used each time to approximate the calibration curve. In other words, instead of using a smooth curve, the curve is broken into five points and the line between each two consecutive points is assumed to be linear, as illustrated in Figure 3. The piecewise linear approximation has been shown to reduce the complexity of the performed calculations while maintaining accurate results. In alternative embodiments, other mathematical approximations can be used to get the value of the calibration curve, including using a larger or smaller number of piecewise linear approximations.

[0042] Figure 4 shows a more detailed method for calibrating a sensor according to an embodiment of the present invention. At Step 50, a calibration array is compiled from independent glucose readings, such as readings from a blood glucose meter taken simultaneously during the life of the sensor. The calibration array may be compiled from blood glucose meter readings, which have been taken and recorded for a particular sensor over a period of time, such as, for example, three weeks.

[0043] Each recalibration of the sensor uses historically measured glucose points and corresponding sensor data. The reference glucose points and corresponding sensor data may be placed into the calibration array. According to embodiments of the present invention, the calibration array may include the following elements: time, independently measured glucose points (M_g), measured blood glucose concentrations (C_o), glucose electrode readings (I_g) and oxygen

Abbott Ex. 1002 - 653/1438

electrode readings (I_o).

[0044] At Step 52, the nominal glucose current I_{g0} may be adjusted. For example, under certain conditions it is possible that there may be a base line shift in the nominal glucose current, I_{g0},. Thus, the normalized nominal glucose current may not be exactly equal to "one." For the nominal glucose current adjustment, data may be used to adjust the current over a period of time. For example, according to an embodiment of the present invention, data over the last three weeks from the glucose sensor may be used to adjust the value of the nominal glucose current.

[0045] According to embodiments of the present invention, the nominal glucose current (I_{g0}) may be adjusted by calculating a shift of each measured data point with respect to the blood glucose meter readings . A mean shift may be determined and the value of the nominal glucose current adjusted accordingly, for example, either by adjusting the nominal glucose current by the amount of the mean shift or by adjusting the nominal glucose current by an amount corresponding to or dependent upon the mean shift. To calculate the mean shift, the shift to the calibration curve in the y-direction" the coordinates, X_m and Y_m, may be calculated as follows:

[0046]

$$X_m = M_g(t) / C_o(t + a) \qquad (2)$$

[0047]

$$Y_m = I_g(t + a) /(R * I_o(t + a)) \qquad (3)$$

[0048] X_m and Y_m represent the x-y coordinates to map the meter values to the calibration curve graph. The constant a is an empirically derived time shift to correlate the sensor reading with the blood glucose meter. The time shift, a, has been found to be approximately 15 minutes.

[0049] Y_shift=Y_m/Y_c, in which Y_c is the corresponding point on the calibration curve with the same X_m value. In the first I_{g0} adjustment (i.e. step 52), the Y_shift is calculated for only the Y_m and X_m values corresponding to glucose values less than 120 mg/dl. The mean shift of I_{g0} is then calculated by:

[0050]

$$\text{mean\_shift} = \Sigma(Y\_shift)/N,$$

[0051] where N is the total number of calibration points (i.e., meter readings).

[0052] Once the mean shift has been determined, the value "R" may be adjusted as follows:

[0053]

$$R' = R * \text{mean shift} \qquad (4)$$

[0054] Once the new value of R is calculated, the Y_m values of each calibration point may be adjustment according to the new value of R:

[0055]

$$Y_m' = I_g(t+a)/(R'*I_o(t+a))$$

[0056] Thus, adjusting the nominal glucose current effectively changes the value of "R" in equation (4), above. Once

Abbott Ex. 1002 - 654/1438

the new Y_m (Y_m') is determined, adjustment on the shape of the calibration curve can be determined.

[0057] At Step 54, adjustments may be made to the shape of the measured curve, i.e., the shape of the sensor calibration curve. The adjustments to the calibration curve may be used to provide calculation of the sensor output.

[0058] The difference between the new Y_m (Y_m') is then calculated and the result is stored in array Y_d such that $Y_d = Y_m'-Y_c$.

[0059] Y_d is then regressed against the corresponding x coordinates, X_m, by performing a standard weighted linear regression. The slope and intercept of the regression results may be calculated as follows:

[0060]

$$Slope = \frac{(\sum w_i)(\sum w_i x_i Yd_i) - (\sum w_i x_i)(\sum w_i Yd_i)}{\Delta} \qquad (6)$$

[0061]

$$Intercept = \frac{(\sum w_i x_i^{\,2})(\sum w_i Yd_i) - (\sum w_i x_i)(\sum w_i x_i Yd_i)}{\Delta} \qquad (7)$$

where

[0062]

$$\Delta = (\sum w_i)(\sum w_i x_i^{\,2}) - (\sum w_i x_i)^2$$

[0063] The weights, w_i, are determined according to the time at which that glucose measurement point is taken. According to an embodiment of the present invention, the weight declines linearly as the reference point is further back in history from the time the calibration:

[0064]

$$w_i = (T - i),$$

[0065] in which T is the time of calibration and i is the time at which the glucose measurement point is taken.

[0066] The result of the linear regression is used to determine the last recalibration point. The last recalibration point is one of the five points on the calibration curve corresponding to the highest glucose concentration. The last calibration point, Y(5), is determined as follows:

[0067]

$$Y'(5) = Y(5)+slope*X(4)+Intercept.$$

[0068] The slope and intercept are determined by equations 6 and 7.

[0069] The remaining calibration points can then be determined as follows:

[0070]

Abbott Ex. 1002 - 655/1438

$$\Delta Y\ (i)/(1\text{-}y(i)) = H^{*}\ \Delta Y\ (i+1)/(1\text{-}y(i+1))$$

[0071] in which ΔY is the amount of change for calibration point Y and the variable H is set to 0.9 if the sensor is gaining sensitivity and 0.7 when the sensor losing sensitivity. The variable H may be different in different phases of sensor life.

[0072] The new calibration curve, therefore, becomes:

[0073]

$$Y'(i)=Y(i)+\Delta Y(i)$$

[0074] Once the new curve shape is determined, a second I_{g0} adjustment can be made to ensure the maximum accuracy. The second I_{g0} adjustment is identical to the first I_{g0} adjustment, except that all calibration points, as opposed to only the low glucose value points (i.e., Y_m and X_m coordinates corresponding to glucose values under 120 mg/dl), will be used. At Step 58, a new nominal glucose current and new calibration curve may be set for the sensor. Thus, after recalibration, the sensor output can be calculated using the new calibration curve derived from the recalibration procedure of Figure 4.

[0075] Figures 5a-d summarize the step-by-step change of the calibration curve. Figure 5a shows the calibration curve before the recalibration. The reference points mapped on the calibration graph are significantly deviant from the calibration curve. In Figure 5b, the sensor has undergone first I_{g0} adjustment; the low end points are lined up with the new calibration curve. In Figure 5c, the sensor has undergone curve shape adjustment, and the high-end points are also lined up with the calibration curve. In Figure 5d, the sensor has undergone the second I_{g0} adjustment for fine tuning purposes. As seen in Figure 5d, the curve is likely to change only slightly with respect to the reference points during the second I_{g0} adjustment.

[0076] Figure 6 shows an implanted sensing system in which embodiments of the present invention may be used. In Figure 6, an implanted sensing system 90 may include, but is not limited to, a pump 96, a catheter 94 having one end attached to the pump 96, and a sensor 92 disposed at another end of the catheter 94. The pump 96 may be an insulin pump and the sensor 92 may be a glucose sensor. The sensor 92 may be calibrated using embodiments of the present invention. A properly calibrated sensor 92 may send signals to the pump 96, enabling the pump 96 to accurately deliver medication or other fluids, such as insulin, for example, through the catheter 94 to a patient.

[0077] Thus, according to embodiments of the present invention, a non-linear curve may be adjusted using a linear regression. Using a linear regression rather than a non-linear regression provides many advantages. For example, the amount of processing power saved by using a linear regression rather than a non-linear regression is dramatic. Processing power is critical in battery operated or otherwise powered implantable systems. Moreover, linear regressions are far more stable than non-linear regressions when input data varies widely. Stability is critical in medical diagnostic and treatment systems such as an implantable insulin pump, for example.

[0078] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that the invention is not limited to the particular embodiments shown and described and that changes and modifications may be made without departing from the spirit and scope of the appended claims. Thus, embodiments of the present invention may be used to recalibrate any sensor that exhibits nonlinear characteristics. Generally, embodiments of the present invention may be adapted for use with any type of sensor in any type of environment where calibration of the sensor over its lifetime is desired.

Claims

1. A method for calibrating a sensor comprising:

   compiling an array of data relating to the sensor;
   adjusting a nominal output current of the sensor a first time based on data in the array;
   adjusting a curve shape representing the sensor output based on data in the array and the adjusted value of the nominal output current; and

Abbott Ex. 1002 - 656/1438

adjusting the nominal output current of the sensor a second time based on data in the array.

2. The method of Claim 1, wherein compiling an array comprises compiling historical data.

3. The method of Claim 2, wherein the historical data comprises measured blood glucose readings.

4. The method of Claim 1, wherein compiling an array comprises compiling recent data.

5. The method of Claim 4, wherein the recent data comprises electrode readings.

6. The method of Claim 5, wherein the electrode readings comprise glucose electrode readings and oxygen electrode readings.

7. The method of Claim 4, wherein the recent data comprises measured blood glucose concentrations.

8. The method of Claim 7, wherein the nominal output current is a nominal glucose current.

9. The method of Claim 8, wherein the nominal glucose current is adjusted based on a shift of measured data points with respect to blood glucose readings.

10. The method of Claim 9, wherein the shift is a mean shift.

11. The method of Claim 1, wherein adjusting the curve representing the sensor output comprises performing a linear regression on data in the array.

12. The method of Claim 11, wherein a result of the linear regression determines a first calibration point.

13. The method of Claim 12, wherein the first calibration point is used to determine a plurality of calibration points.

14. The method of Claim 1, wherein adjusting the curve representing the sensor output comprises adjusting the curve in a piecewise linear fashion.

15. The method of Claim 14, wherein a number of pieces in the piecewise linear adjustment is five.

16. The method of Claim 1, wherein the nominal output current is a nominal glucose current.

17. The method of Claim 16, wherein the nominal glucose current is adjusted based on a shift of measured data points with respect to blood glucose readings.

18. The method of Claim 17, wherein the shift is a mean shift.

19. The method of Claim 1, further comprising establishing a new sensor output based on the adjuster curve and the twice adjusted sensor parameter.

20. A sensor calibration system comprising:

means for compiling an array of data relating to the sensor;
means for adjusting a nominal output current a first time based on data in the array;
means for adjusting a curve shape representing the sensor output based on data in the array; and
means for adjusting the sensor parameter a second time based on data in the array.

21. An implantable sensing system comprising:

a sensor for sensing a biological parameter;
a processor connected to the sensor for processing the parameter; and
a drug delivery unit connected to the processor for responding to the processor based on the parameter,
wherein the processor is programmed to adjust an output of the sensor by

Abbott Ex. 1002 - 657/1438

compiling an array of data relating to the sensor;
adjusting a nominal output current a first time based on data in the array;
adjusting a curve shape representing the sensor output based on data in the array; and
adjusting the sensor parameter a second time based on data in the array.

22. The system of Claim 21, wherein the sensor is a glucose sensor.

23. The system of Claim 21, wherein the drug delivery unit is an insulin pump.

24. The system of Claim 21, wherein the insulin pump delivers insulin in response to the sensed parameter.

25. The system of Claim 21, wherein compiling an array comprises compiling historical data.

26. The system of Claim 25, wherein the historical data comprises measured blood glucose readings.

27. The system of Claim 21, wherein compiling an array comprises compiling recent data.

28. The system of Claim 27, wherein the recent data comprises glucose electrode readings and oxygen electrode readings.

29. The system of Claim 27, wherein the recent data comprises measured blood glucose concentrations.

30. The system of Claim 21, wherein adjusting a sensor parameter a first time comprise adjusting a nominal glucose current.

31. The system of Claim 21, wherein adjusting the curve representing the sensor output comprises performing a linear regression on data in the array.

32. The system of Claim 21, wherein adjusting the curve representing the sensor output comprises adjusting the curve in a piecewise linear fashion.

Patentansprüche

1. Verfahren zur Kalibrierung eines Sensors, bei dem man
einen Satz Daten betreffend den Sensor zusammenstellt;
einen Nenn-Ausgangsstrom des Sensors auf Grund von Daten im Datensatz ein erstes Mal einstellt;
einen Kurvenverlauf, der das Sensorausgangssignal auf Grund der Daten im Datensatz darstellt, sowie den eingestellten Wert des Nenn-Ausgangsstroms einstellt; und
den Nenn-Ausgangsstrom des Sensors auf Grund von Daten im Datensatz ein zweites Mal einstellt.

2. Verfahren nach Anspruch 1, bei dem das Zusammenstellen eines Datensatzes das Zusammenstellen von Hintergrund- bzw. Verlaufsdaten beinhaltet.

3. Verfahren nach Anspruch 2, bei dem die Verlaufsdaten BlutglukoseMesswerte beinhalten.

4. Verfahren nach Anspruch 1, bei dem das Zusammenstellen eines Datensatzes das Zusammenstellen aktueller Daten beinhaltet.

5. Verfahren nach Anspruch 4, bei dem die aktuellen Daten Elektrodenmesswerte beinhalten.

6. Verfahren nach Anspruch 5, bei dem die Elektrodenmesswerte Glukose-und Sauerstoff-Elektrodenmesswerte beinhalten.

7. Verfahren nach Anspruch 4, bei dem die aktuellen Daten gemessene Blutglukosekonzentrationen beinhalten.

8. Verfahren nach Anspruch 7, bei dem der Nenn-Ausgangsstrom ein Nenn-Glukosestrom ist.

Abbott Ex. 1002 - 658/1438

9. Verfahren nach Anspruch 8, bei dem der Nenn-Glukosestrom auf Grund einer Verschiebung gemessener Datenpunkte bezüglich Blutglukose-Messwerten nachgestellt wird.

10. Verfahren nach Anspruch 9, bei dem die Verschiebung ein Mittelwert ist.

11. Verfahren nach Anspruch 1, bei dem das Einstellen der die Sensorausgangsgröße darstellenden Kurve eine lineare Regression von Daten im Datensatz beinhaltet.

12. Verfahren nach Anspruch 11, bei dem ein Ergebnis der linearen Regression einen ersten Kalibrationspunkt bestimmt.

13. Verfahren nach Anspruch 12, bei dem der erste Kalibrationspunkt dazu dient, eine Vielzahl von Kalibrationspunkten zu bestimmen.

14. Verfahren nach Anspruch 1, bei dem das Einstellen der die Sensorausgangsgröße darstellenden Kurve das stückweise lineare Einstellen der Kurve beinhaltet.

15. Verfahren nach Anspruch 14, bei dem eine Anzahl von Stücken in der stückweise linearen Einstellung gleich fünf ist.

16. Verfahren nach Anspruch 1, bei dem der Nenn-Ausgangsstrom ein Nenn-Glukosestrom ist.

17. Verfahren nach Anspruch 16, bei dem der Nenn-Glukosestrom auf Grund einer Verschiebung gemessener Datenpunkte bezüglich Blutglukosemesswerten eingestellt wird.

18. Verfahren nach Anspruch 17, bei dem die Verschiebung ein Mittelwert ist.

19. Verfahren nach Anspruch 1, bei dem man weiterhin auf Grund der nachgestellten Kurve und des zweimal nachgestellten Sensorparameters ein neues Sensorausgangssignal festlegt.

20. Sensorkalibriersystem mit:

einer Einrichtung zum Zusammenstellen eines Satzes von Daten betreffend den Sensor;
einer Einrichtung zum erstmaligen Einstellen eines Nenn-Ausgangsstroms auf Grund von Daten in dem Datensatz;
einer Einrichtung zum Einstellen eines das Sensor-Ausgangssignal darstellenden Kurvenverlaufs auf Grund von Daten im Datensatz; und
einer Einrichtung zu einem zweiten Einstellen des Sensorparameters auf Grund der Daten im Datensatz.

21. Implantierbares Sensorsystem mit:

einem Sensor zum Erfassen eines biologischen Parameters;
einem Prozessor, der mit dem Sensor verbunden ist, um den Parameter zu verarbeiten; und
einer Medikamentenausgabeeinheit, die an den Prozessor angeschlossen ist und auf Grund des Parameters auf ihn anspricht;
wobei der Prozessor programmiert ist, eine Ausgangsgröße des Sensors einzustellen, indem

ein Satz von Daten über den Sensor zusammengestellt wird;
ein Nenn-Ausgangsstrom auf Grund von Daten im Datensatz ein erstes Mal eingestellt wird;
ein das Sensorausgangssignal darstellender Kurvenverlauf auf Grund von Daten im Datensatz nachgestellt wird; und
der Sensorparameter auf Grund von Daten im Datensatz ein zweites Mal nachgestellt wird.

22. System nach Anspruch 21, bei dem der Sensor ein Glukosesensor ist.

23. System nach Anspruch 21, bei dem die Medikamentenausgabeeinheit eine Insulinpumpe ist.

24. System nach Anspruch 21, bei dem die Insulinpumpe das Insulin ansprechend auf den erfassten Parameter ausgibt.

25. System nach Anspruch 21, bei dem zum Zusammenstellen eines Datensatzes Hintergrund- bzw. Verlaufsdaten

Abbott Ex. 1002 - 659/1438

zusammengestellt werden.

26. System nach Anspruch 25, bei dem die Hintergrund- bzw. Verlaufsdaten Blutglukosemesswerte beinhalten.

27. System nach Anspruch 21, bei dem zum Zusammenstellen eines Datensatzes aktuellere Daten zusammengestellt werden.

28. System nach Anspruch 27, bei dem die aktuelleren Daten Glukose- und Sauerstoff-Elektrodenmesswerte beinhalten.

29. System nach Anspruch 27, bei dem die aktuelleren Daten Messwerte der Blutglukosekonzentration beinhalten.

30. System nach Anspruch 21, bei dem das erstmalige Einstellen eines Sensorparameters das Einstellen eines Nenn-Glukosestroms beinhaltet.

31. System nach Anspruch 21, bei dem das Nachstellen der das Sensorausgangssignal darstellenden Kurve das Ausführen einer linearen Regression auf Daten im Datensatz beinhaltet.

32. System nach Anspruch 21, bei dem das Nachstellen der die Sensorausgangsgröße darstellenden Kurve das stückweise lineare Nachstellen derselben beinhaltet.

Revendications

1. Procédé pour étalonner un capteur comprenant :

la compilation d'un tableau de données concernant le capteur ;
le réglage une première fois d'un courant de sortie nominal du capteur sur la base des données du tableau ;
le réglage d'une forme de courbe représentant la sortie du capteur sur la base des données du tableau et de la valeur réglée du courant de sortie nominal ; et
le réglage une seconde fois du courant de sortie nominal du capteur sur la base des données du tableau.

2. Procédé selon la revendication 1, dans lequel la compilation d'un tableau comprend la compilation de données d'historique.

3. Procédé selon la revendication 2, dans lequel les données d'historique comprennent des lectures de glycémie mesurée.

4. Procédé selon la revendication 1, dans lequel la compilation d'un tableau comprend la compilation de données récentes.

5. Procédé selon la revendication 4, dans lequel les données récentes comprennent des lectures d'électrode.

6. Procédé selon la revendication 5, dans lequel les lectures d'électrode comprennent des lectures d'électrode de glucose et des lectures d'électrode d'oxygène.

7. Procédé selon la revendication 4, dans lequel les données récentes comprennent des concentrations de glucose sanguin mesurées.

8. Procédé selon la revendication 7, dans lequel le courant de sortie nominal est un courant de glucose nominal.

9. Procédé selon la revendication 8, dans lequel le courant de glucose nominal est réglé sur la base d'un décalage de points de données mesurés par rapport à des lectures de glycémie.

10. Procédé selon la revendication 9, dans lequel le décalage est un décalage moyen.

11. Procédé selon la revendication 1, dans lequel le réglage de la courbe représentant la sortie du capteur comprend l'exécution d'une régression linéaire sur des données du tableau.

Abbott Ex. 1002 - 660/1438

12. Procédé selon la revendication 11, dans lequel un résultat de la régression linéaire détermine un premier point d'étalonnage.

13. Procédé selon la revendication 12, dans lequel le premier point d'étalonnage est utilisé pour déterminer une pluralité de points d'étalonnage.

14. Procédé selon la revendication 1, dans lequel le réglage de la courbe représentant la sortie du capteur comprend le réglage de la courbe de manière linéaire par morceaux.

15. Procédé selon la revendication 14, dans lequel un nombre de morceaux dans le réglage linéaire par morceaux est égal à cinq.

16. Procédé selon la revendication 1, dans lequel le courant de sortie nominal est un courant de glucose nominal.

17. Procédé selon la revendication 16, dans lequel le courant de glucose nominal est réglé sur la base d'un décalage de points de données mesurés par rapport à des lectures de glycémie.

18. Procédé selon la revendication 17, dans lequel le décalage est un décalage moyen.

19. Procédé selon la revendication 1, comprenant en outre l'établissement d'une nouvelle sortie de capteur sur la base de la courbe réglée et du paramètre de capteur réglé deux fois.

20. Système d'étalonnage de capteur comprenant :

des moyens pour compiler un tableau de données concernant le capteur ;
des moyens pour régler une première fois un courant de sortie nominal sur la base des données du tableau ;
des moyens pour régler une forme de courbe représentant la sortie du capteur sur la base des données du tableau ; et
des moyens pour régler une seconde fois le paramètre de capteur sur la base des données du tableau.

21. Système de détection implantable comprenant :

un capteur pour détecter un paramètre biologique ;
un processeur relié au capteur pour traiter le paramètre ; et
une unité de distribution de médicament reliée au processeur pour répondre au processeur sur la base du paramètre,

dans lequel le processeur est programmé pour régler une sortie du capteur en :

compilant un tableau de données concernant le capteur ;
réglant une première fois un courant de sortie nominal sur la base des données du tableau ;
réglant une forme de courbe représentant la sortie du capteur sur la base des données du tableau ; et
réglant une seconde fois le paramètre du capteur sur la base des données du tableau.

22. Système selon la revendication 21, dans lequel le capteur est un capteur de glucose.

23. Système selon la revendication 21, dans lequel l'unité de distribution de médicament est une pompe à insuline.

24. Système selon la revendication 21, dans lequel la pompe à insuline distribue de l'insuline en réponse au paramètre détecté.

25. Système selon la revendication 21, dans lequel la compilation d'un tableau comprend la compilation de données d'historique.

26. Système selon la revendication 25, dans lequel les données d'historique comprennent des lectures de glycémie mesurée.

27. Système selon la revendication 21, dans lequel la compilation d'un tableau comprend la compilation de données

Abbott Ex. 1002 - 661/1438

récentes.

28. Système selon la revendication 27, dans lequel les données récentes comprennent des lectures d'électrode de glucose et des lectures d'électrode d'oxygène.

29. Système selon la revendication 27, dans lequel les données récentes comprennent des concentrations de glucose sanguin mesurées.

30. Système selon la revendication 21, dans lequel le premier réglage d'un paramètre de capteur comprend le réglage d'un courant de glucose nominal.

31. Système selon la revendication 21, dans lequel le réglage de la courbe représentant la sortie du capteur comprend l'exécution d'une régression linéaire sur des données du tableau.

32. Système selon la revendication 21, dans lequel le réglage de la courbe représentant la sortie du capteur comprend le réglage de la courbe de manière linéaire par morceaux.

Abbott Ex. 1002 - 662/1438

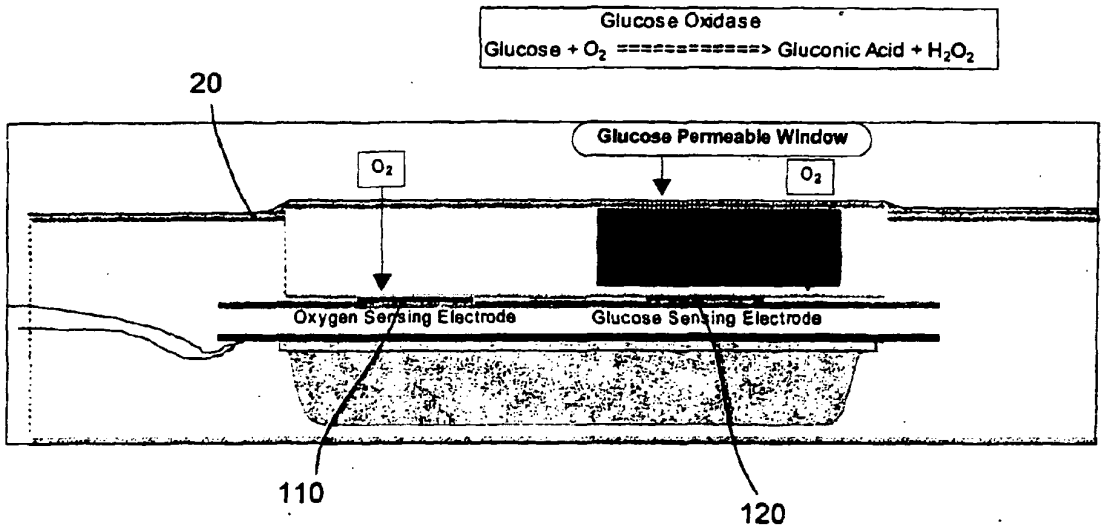


FIG. 1

Abbott Ex. 1002 - 663/1438

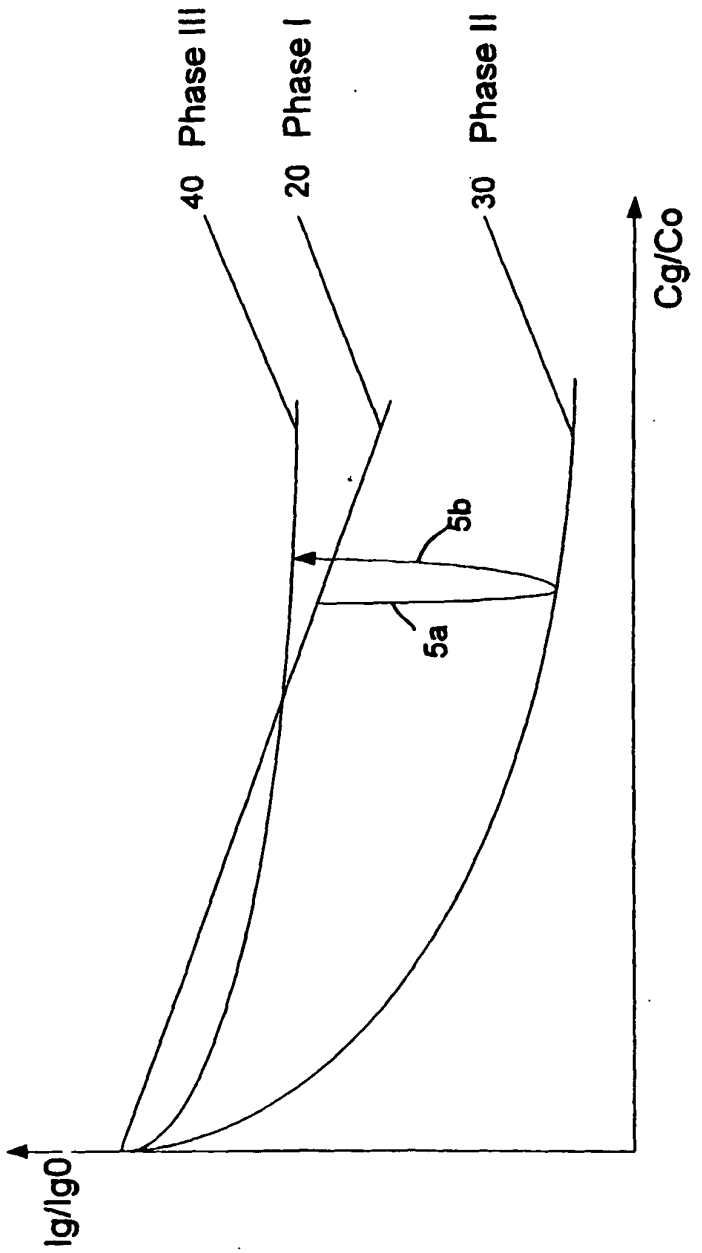


FIG. 2

Abbott Ex. 1002 - 664/1438

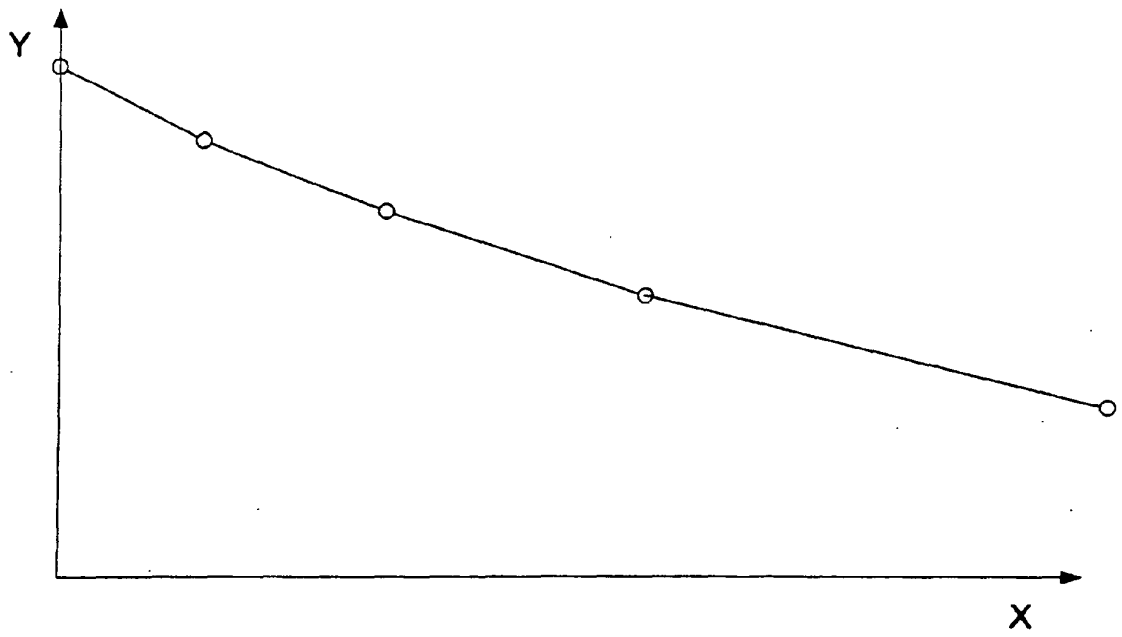


FIG. 3

Abbott Ex. 1002 - 665/1438

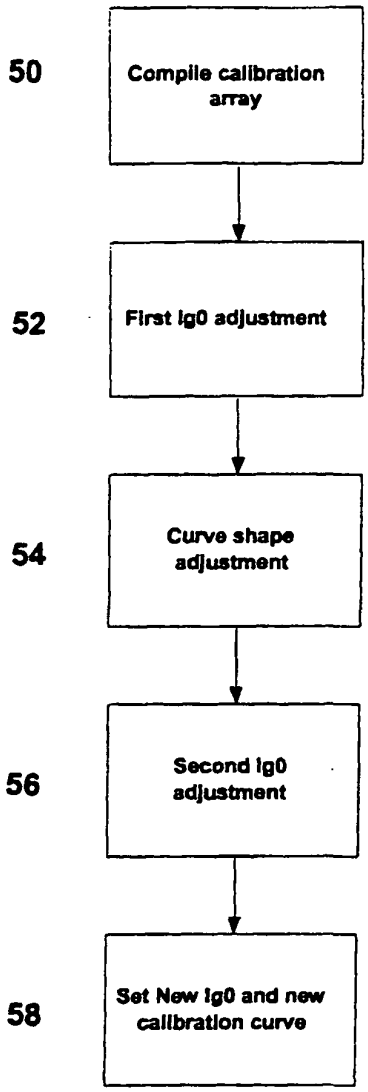


FIG. 4

Abbott Ex. 1002 - 666/1438

FIG. 5a

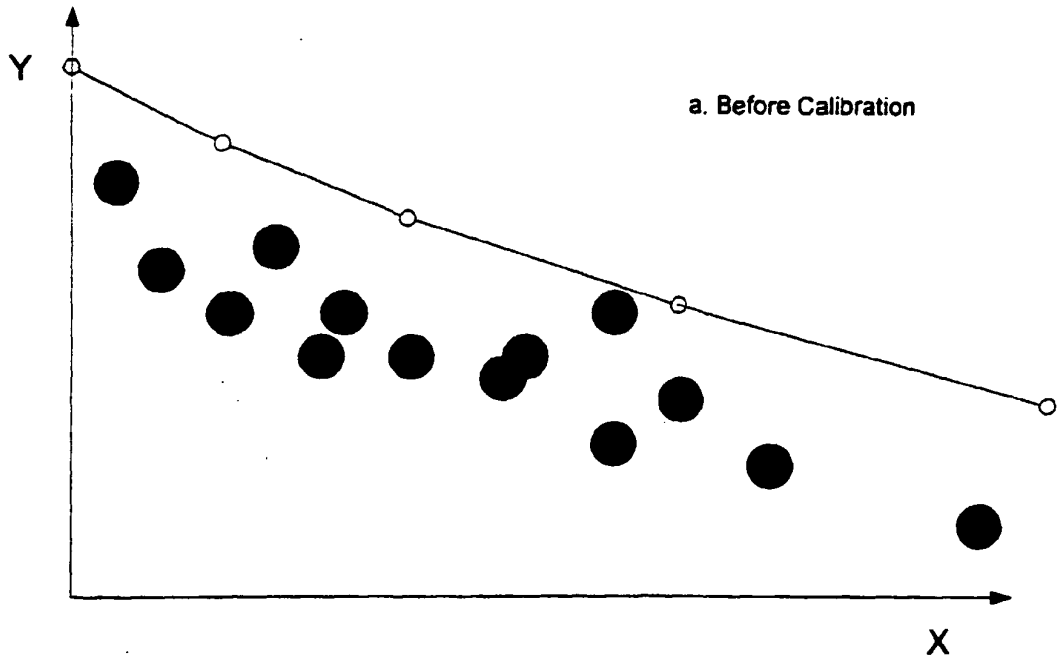
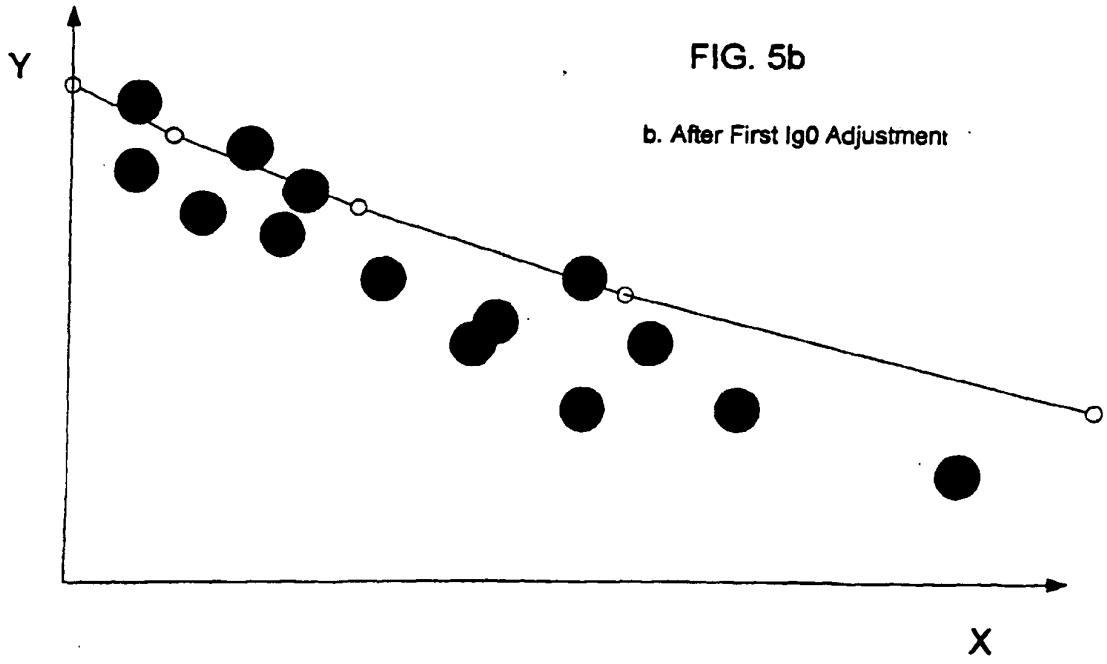


FIG. 5b



Abbott Ex. 1002 - 667/1438

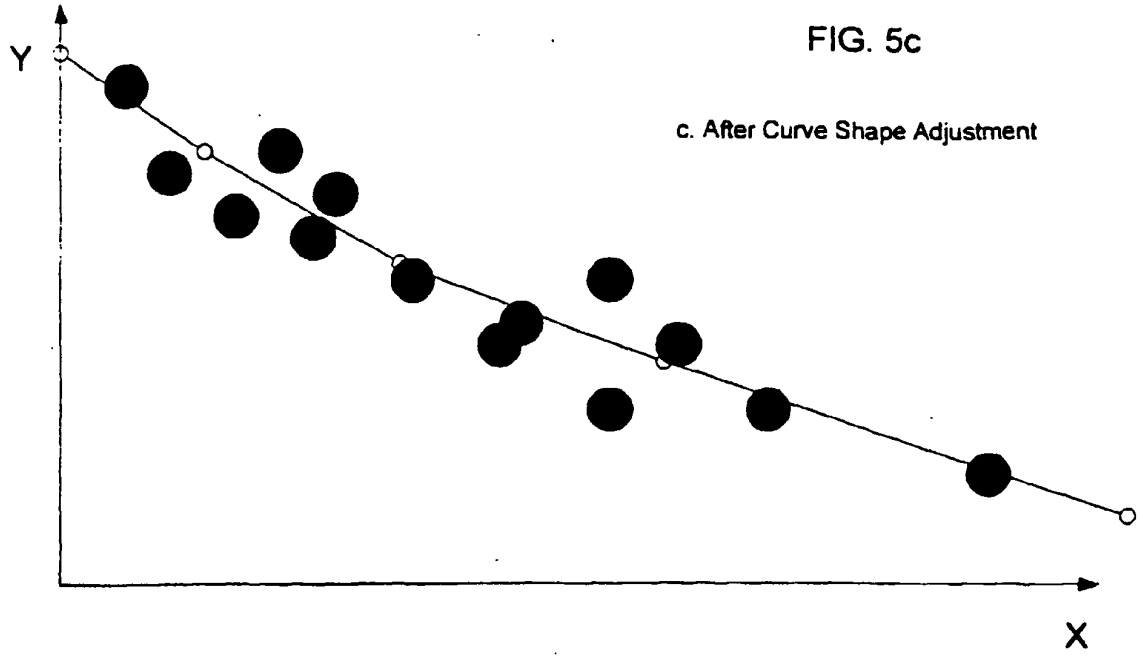


FIG. 5c

c. After Curve Shape Adjustment

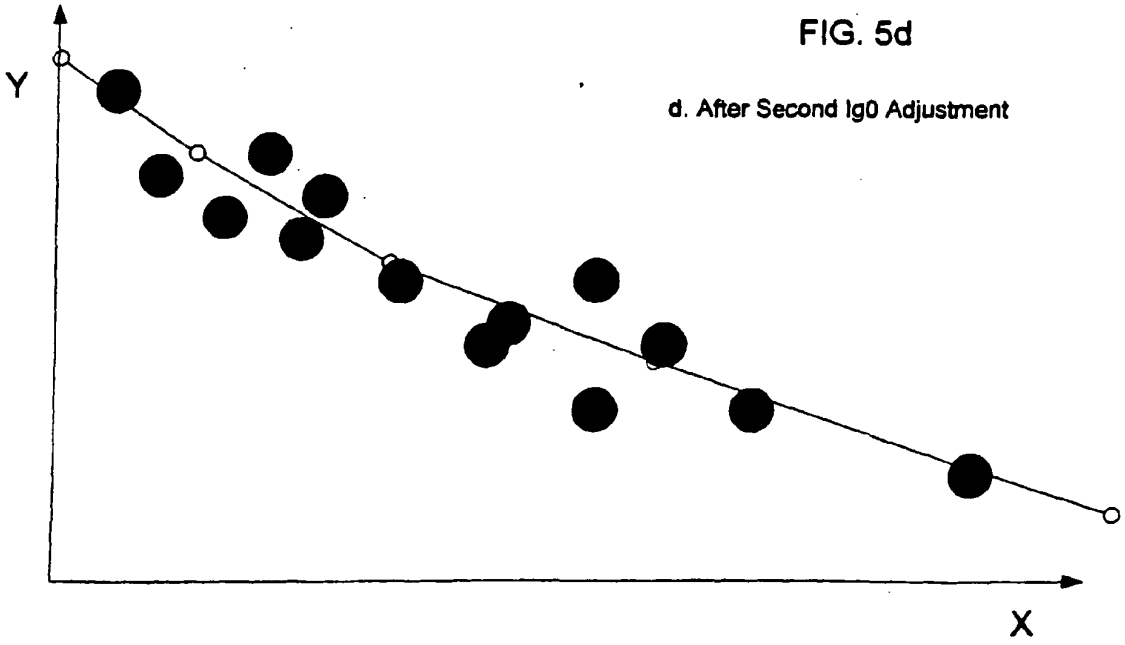


FIG. 5d

d. After Second Ig0 Adjustment

Abbott Ex. 1002 - 668/1438

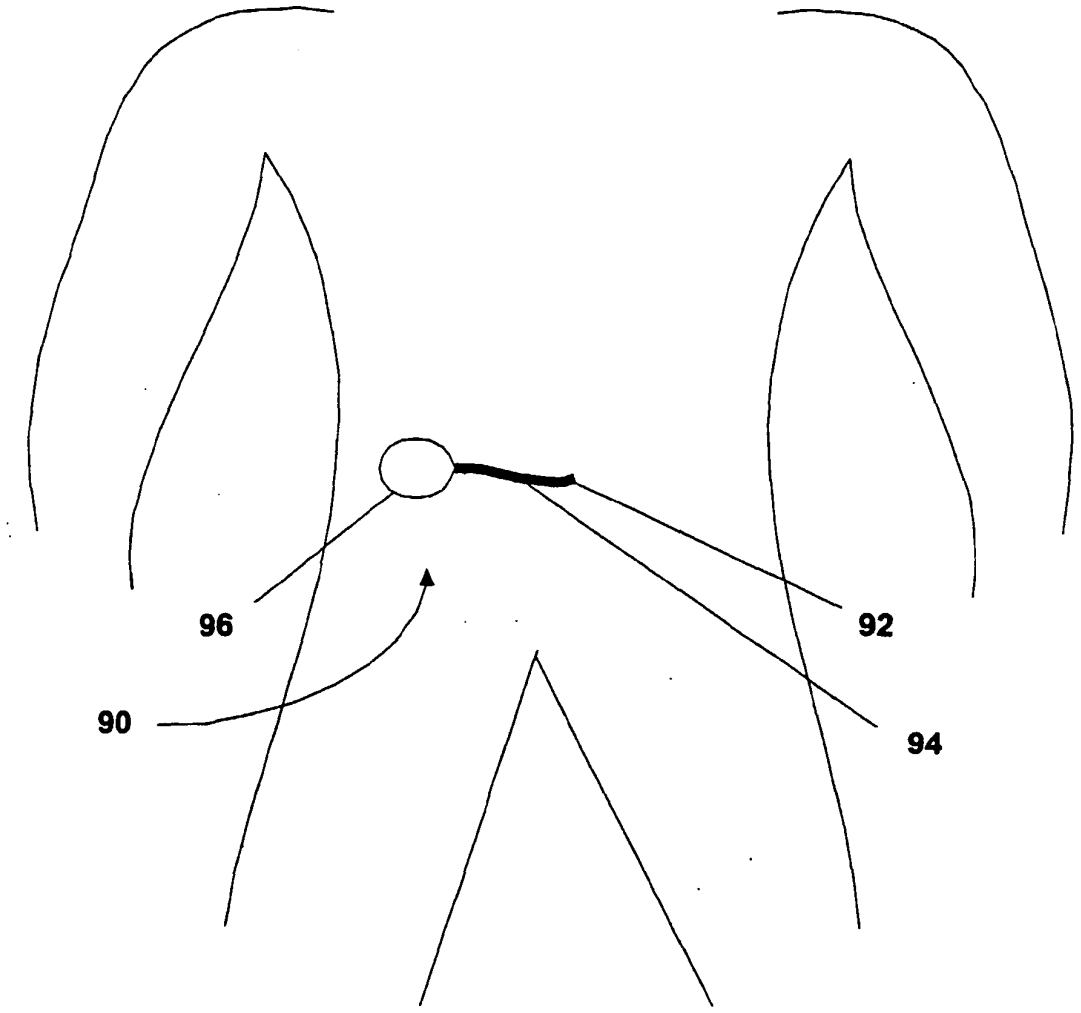


FIG. 6

Abbott Ex. 1002 - 669/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 4650547 A **[0026]**
- US 4671288 A **[0026]**
- US 4781798 A **[0026]**
- US 4703756 A **[0026]**
- US 4890620 A **[0026]**
- US 10034338 B **[0028]**
- US 5503770 A, James **[0029]**
- US 5512246 A, Russell **[0029]**
- US 007515 P, Van Antwerp **[0029]**
- US 6011984 A, Van Antwerp **[0029]**
- US 5628310 A, Rao **[0029]**
- US 5342789 A, Chick **[0029]**
- US 5246867 A, Lakowicz **[0029]**
- US 03609301 A **[0030]**
- US 03827602 A **[0030]**

Abbott Ex. 1002 - 670/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 706 022 B2

(12) **NEW EUROPEAN PATENT SPECIFICATION**
After opposition procedure

(45) Date of publication and mention of the opposition decision:
23.11.2011 Bulletin 2011/47

(45) Mention of the grant of the patent:
29.10.2008 Bulletin 2008/44

(21) Application number: **04814084.2**

(22) Date of filing: **15.12.2004**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/US2004/041856

(87) International publication number:
WO 2005/065535 (21.07.2005 Gazette 2005/29)

(54) **SYSTEM AND METHOD FOR SENSOR RECALIBRATION**

SYSTEM UND VERFAHREN ZUR SENSORREKALIBRIERUNG

SYSTEME ET PROCEDE DE REETALONNAGE DE CAPTEUR

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR

(30) Priority: **30.12.2003 US 751327**

(43) Date of publication of application:
04.10.2006 Bulletin 2006/40

(73) Proprietor: **Medtronic MiniMed, Inc.**
Northridge, CA 91325 (US)

(72) Inventors:
- **ZHANG, Yanan**
  Valencia, CA 91355 (US)
- **WANG, Lu**
  Pasadena, CA 91106 (US)
- **SHAH, Rajiv**
  Rancho Palos Verdes, CA 90275 (US)

(74) Representative: **Ruschke, Hans Edvard**
RUSCHKE HARTMANN MADGWICK & SEIDE
Patent- und Rechtsanwälte
Postfach 86 06 29
81633 München (DE)

(56) References cited:
WO-A-98/58250
WO-A1-03/094714
US-A- 4 436 812
US-A- 5 507 288
US-A- 6 088 608
US-A1- 2003 153 821
US-A1- 2003 187 338
US-B1- 6 275 717
US-B1- 6 387 048

EP 1 706 022 B2

Abbott Ex. 1002 - 671/1438

Description

BACKGROUND

1. Field of the Invention

[0001] The present invention relates to recalibration techniques and, in particular, to recalibration techniques for implantable sensors.

2. Description of Related Art

[0002] The accuracy of a sensing system is generally limited by the drift characteristics of the sensing element over time and the amount of environmental noise introduced into the output of the sensing element. To accommodate the drift inherent in the sensing element and the noise inherent in the system environment, the sensing system is periodically calibrated, or recalibrated.

[0003] A typical recalibration routine is performed at regular intervals. Generally, a technician will measure an output of the sensing system in response to a known, accurate input. The sensing system is then adjusted, or recalibrated, so that the output of the sensing system matches that of the known, accurate input to within an acceptable error margin.

[0004] Typical recalibration routines are often inadequate for many sensing systems. Many sensing systems include sensing elements that exhibit non-linear outputs or outputs that change in a non-linear fashion over time. Thus, a simple linear adjustment during a recalibration procedure to force an output of the sensing system back to acceptable output values often fails to account for the true nature of many sensing elements. The result of simple linear adjustments may be a sensing system that is accurate only over a small range of the sensing elements capabilities or a sensing system that may not maintain acceptable levels of accuracy for extended periods of time.

[0005] The invention in its broadest form is defined in independent claims 1, 20 and 21 below.

SUMMARY

[0006] A method for calibrating a sensor may include compiling an array of data relating to the sensor; adjusting a nominal output current a first time based on data in the array; adjusting a curve shape representing the sensor output based on data in the array; and adjusting the nominal output current a second time based on data in the array. Also, the method may further include establishing a new sensor output based on the adjusted curve and the twice adjusted sensor parameter.

[0007] The array may include historical data and empirical data. The historical data may include measured blood glucose readings. The recent data may include blood glucose concentrations and electrode readings, such as, for example, glucose electrode readings and oxygen electrode readings.

[0008] Adjusting a nominal output current a first time may include adjusting a nominal glucose current based on a shift of measured data points with respect to blood glucose readings. The shift may be a mean shift.

[0009] Adjusting the curve representing the sensor output may include performing a linear regression on data in the array. The result of the linear regression may determine a first calibration point. The first calibration point may be used to determine a plurality of calibration points.

[0010] Adjusting the curve representing the sensor output may include adjusting the curve in a piecewise linear fashion. The number of pieces in the piecewise linear adjustment may be five.

[0011] Adjusting a nominal output current a second time may include adjusting a nominal glucose current based on a shift of measured data points with respect to blood glucose readings. The shift may be a mean shift.

[0012] An implantable sensing system may include a sensor for sensing a biological parameter; a processor connected to the sensor for processing the parameter; and a drug delivery unit connected to the processor for responding to the processor based on the parameter. The processor may be programmed to adjust an output of the sensor by compiling an array of data relating to the sensor; adjusting a nominal output current a first time based on data in the array; adjusting a curve shape representing the sensor output based on data in the array; and adjusting the nominal output current a second time based on data in the array.

[0013] The sensor may be a glucose sensor. The drug delivery unit may be an insulin pump. The insulin pump may deliver insulin in response to the sensed parameter.

[0014] A method for calibrating a sensor may include generating a calibration curve based on *a priori* empirical values; compiling a plurality of data values from the sensor; compiling independent historical values of a parameter sensed by the sensor; and reconciling the plurality of data values from the sensor to the calibration curve using the independent historical values. The sensor may be a glucose sensor. The independent historical values of a parameter sensed by the sensor may be metered blood glucose values.

Abbott Ex. 1002 - 672/1438

[0015] Generating a calibration curve may include compiling *a priori* empirical values of sensors similar to the sensor being calibrated. Generating a calibration curve may also include generating a calibration curve representing a sensor having a plurality of phases.

[0016] Reconciling the plurality of data values may include adjusting an output current of the sensor. The output current of the sensor may be a nominal glucose current. Also, the nominal glucose current may be adjusted based on a shift of the plurality of data values from the sensor with respect to metered blood glucose values. Reconciling the plurality of data values may also include performing a linear regression on the plurality of data values. In addition, reconciling the plurality of data values may be performed in a piecewise linear fashion.

[0017] Other features and advantages 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] A detailed description will be made with reference to the accompanying drawings, wherein like numerals designate corresponding parts in the several figures.

[0019] Figure 1 shows a cross-sectional view of an exemplary sensor according to an embodiment of the present invention.

[0020] Figure 2 shows a graph of a normalized calibration curve for the three phases of a sensor life.

[0021] Figure 3 shows a graph of a piecewise linear approximation technique for the calibration curve.

[0022] Figure 4 shows a detailed method for calibrating a sensor.

[0023] Figure 5a-d shows a resulting adjustment of a recalibrated sensor output.

[0024] Figure 6 shows an implanted sensing system in which examples of the invention may be used.

DETAILED DESCRIPTION

[0025] In the following description, reference is made to the accompanying drawings which form a part hereof, and in which are shown by way of illustration specific examples in which the invention may be practiced. It is to be understood that other embodiments may be utilized and structural changes may be made.

[0026] Embodiments of the present invention are directed to calibration techniques for use with implantable sensors that measure a characteristic of a patient's body. In preferred embodiments, the characteristic is the glucose level, and the implantable sensor is placed in an artery or a vein. Although embodiments of the present invention are primarily described in the context of glucose sensors used in the treatment of diabetes, the embodiments of the invention are applicable to a wide variety of patient treatment programs where a physiological characteristic is monitored. For example, embodiments of the invention can be used to determine the status and/or levels of a variety of characteristics including those associated with agents such as hormones, cholesterol, medication concentrations, pH, oxygen saturation, viral loads (e.g., HIV), or the like. Also embodiments of the present invention are not limited to implantation in an artery or vein, but can be implanted in and/or through subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue. Such sensors typically communicate a signal from the implantable sensor to either an internal or external monitor. The implantable sensor is primarily adapted for use with blood. However, still further embodiments of the implantable sensor may be used in other bodily fluids, such as interstitial fluid, spinal fluid, saliva, urine, tears, sweat, or the like.

[0027] FIG. 1 is a cross-sectional view of an exemplary sensor in accordance with the embodiments of the present invention. The sensor generally includes, in one preferred form, an implantable enzyme electrode of the general type described in U.S. Pat. Nos. 4,650,547; 4,671,288; 4,781,798; 4,703,756; and 4,890,620. Such enzyme electrodes can be used in a sensor for direct contact with patient fluids, such as blood. In the preferred embodiments, a glucose oxygen sensor 20 is used to detect the level of glucose in the blood by measuring the depletion of oxygen as the glucose oxidase enzyme catalyzes a reaction between glucose and oxygen present in the blood according to the following reaction:

[0028]

$$\text{Glucose} + O_2 \xrightarrow{\text{Glucose Oxidase}} \text{Gluconic Acid} + H_2O_2$$

[0029] Typically, the glucose sensor 20 has at least two electrodes 110, 120 to detect the level of oxygen in the blood. Preferably, the first electrode is an oxygen sensing electrode 110 to detect the level of oxygen in the patient fluid (e.g. blood) as a reference point for the second electrode. The second electrode is a glucose sensing electrode 120 placed in the proximity of glucose oxidase to ascertain the oxygen depletion during the electrochemical reaction between oxygen and the glucose around the area of the glucose sensing electrode 120. The glucose oxygen sensor 20 is designed to

Abbott Ex. 1002 - 673/1438

send a particular current depending on the amount of oxygen present near the electrodes 110, 120. Given that the amount of current flowing to the electrodes has a fairly linear relationship the amount oxygen present in the area surrounding the electrodes 110, 120, a measurement of the currents can be used to determine the amount of glucose present in the blood, as described in Application Serial Number 10/034,338 entitled "Implantable Sensor Electrodes and Electronic Circuitry," filed on December 28, 2001.

[0030] In alternative embodiments, different sensors technology may be used, such as, but not limited to a hydrogen peroxide sensor or an optical sensor. A hydrogen peroxide sensor would work similar to an oxygen sensor, except that rather than measuring the amount of oxygen depleted in the presence of the glucose oxidase enzyme, the hydrogen peroxide sensor would measure the amount of hydrogen peroxide produced as a result of the reaction between oxygen and glucose in the presence of the glucose oxidase enzyme. Alternatively, an implantable optical sensor would include a photo-reactive substance or compound that optically changes, fluoresces, or the like, or other suitable compounds that detect changing properties in the presence of a bodily fluid analyte, such as glucose or the like. The compounds can also be used to detect the level of an analyte that has been ingested, injected or placed inside the body, such as marker substances, or the like. For example, possible compounds that produce a fluorescent change in the presence of a bodily fluid analyte are disclosed in U.S. Patent No. 5,503,770 issued April 2, 1996 to James et al. and entitled "Fluorescent Compound Suitable For Use In The Detection Of Saccharides"; U.S. Patent No. 5,512,246 issued April 30, 1996 to Russell et al. and entitled "Method and Means for Detecting Polyhydroxyl Compounds"; U.S. Provisional Application Serial No. 60/007,515 to Van Antwerp et al. and entitled "Minimally Invasive Chemically Amplified Optical Glucose Sensor"; and U.S. Patent No. 6,011,984 to Van Antwerp et al. and entitled "Detection of Biological Molecules Using Chemical Amplification". Other compounds using Donor Acceptor fluorescent techniques may be used, such as is disclosed in U.S. Patent No. 5,628,310 issued May 13, 1997 to Rao et al. and entitled " Method and Apparatus to Perform Trans-cutaneous Analyte Monitoring"; U.S. Patent No. 5,342,789 issued August 30, 1994 to Chick et al. and entitled "Method and Device for Detecting and Quantifying Glucose in body Fluids"; and U.S. Patent No. 5,246,867 issued September 21, 1993 to Lakowicz et al. and entitled "Determination and Quantification of Saccharides by Luminescent Lifetimes and Energy Transfer".

[0031] Therefore, the generalized method for recalibration of a sensor according to an embodiment of the present invention may be applied to a variety of sensors, including, but not limited to, biological parameter sensors, physical parameter sensors and the like. For example, the generalized method may be applied to a variety of glucose sensors used in conjunction with implantable insulin pumps. Sensors and related systems of this type are disclosed in U.S. Patent Application No. 10/036,093, entitled, "Sensing Apparatus and Process," filed December 28, 2001, and U.S. Patent Application No. 10/038,276, filed January 2, 2002, entitled, "Sensor Substrate and Method of Fabricating Same".

[0032] Sensors typically exhibit different characteristics during the useful life of the sensor. Specifically, sensors typically have three phases: (1) initialization phase, (2) stable phase, and (3) end of life phase. For example, after a sensor has been implanted into a patient, readings from the sensor needs to be adjusted for the first phase of the sensor life as the sensor becomes used to its environment. As the sensor begins to mature and the sensor enters its second phase of life, readings from the sensor need to be adjusted for its second phase of life. Lastly, as the sensor approaches its end of life and enters its third phase of life, the readings from the sensor need to be adjusted for its third phase of life. According to embodiments of the present invention, a calibration scheme is described which can be used to properly calibrate the sensor regardless of the phase of the sensor life and to identify which phase the sensor is in.

[0033] According to embodiments of the present invention, a normalized calibration curve for the three phases of the sensor life is shown in Figure 2. The curve shapes 20, 30, and 40 are the calibration curve shapes of each phase of the sensor life as determined based on empirical data collected from the use of sensors. Arrow 5a, 5b represent a typical life cycle of the calibration curves as the sensor changes from one phase to another phase, as will be described in greater detail below. Although the normalized calibration curves in Figure 2 were originally derived based on glucose sensors, further research has proved that most sensors behave similarly and these calibration curves can be used with other type of sensors. According to embodiments of the present invention, sensor recalibrations will be performed not only based on independent characteristic values (e.g., blood meter values) but with use of the expected normalized calibration curves as will be described in greater detail below with respect to Figures 4 and 5.

[0034] In Figure 2, the vertical axis, designated as I_g/I_{g0}, represents the ratio of real time glucose current to an imaginary glucose current in the absence of glucose. I_g represents a sensor current output modulated by real time glucose measurements. I_{g0} represents a nominal value of the sensor output current when no glucose is present for measurement. I_{g0} can be calculated using the following formula:

[0035]

$$I_{g0} = R * I_o,$$

Abbott Ex. 1002 - 674/1438

[0036] where R is a conversion factor that is based on blood meter values to calibrate the sensor and I_o is oxygen electrode output current. Since the presence of glucose lowers the glucose current, I_g should never exceed I_{g0}. Therefore, the highest point along Y axis is 1, when $I_g=I_{g0}$. The horizontal axis, designated by C_g/C_o, represents the ratio of measured glucose concentration versus a nominal glucose concentration. C_g represents the glucose concentration. C_o may be calculated by multiplying a nominal sensor oxygen electrode output current I_o by a constant. In other words,

[0037]

$$C_o = K \times I_o. \qquad (1)$$

[0038] In equation (1), the value "K" is a constant based on the ratio of the oxygen concentration to the oxygen electrode current.

[0039] As described previously, phase 1 of the sensor's life may be viewed as a sensitivity period during the initial output of the sensor current with respect to glucose concentration. As can be seen in Figure 2, line 20 is virtually completely linear during the first phase. This linearity represents the sensor output when it is initially placed in a patient. However, as the sensor stabilizes and enters phase 2, the current output of the sensor with respect to glucose concentration tends to become non-linear. The curve shape moves from line 20 to curve 30, as shown by the arrow 5a, as the sensor gets used to its environment and the enzyme or other mechanism on the sensor proceeds towards stabilization and settles into its environment.

[0040] The curve shift between line 20 and curve 30, represented by arrow 5a, represent a continuum of change in the sensor output current with respect to glucose concentration As the sensor finally stabilizes in its environment, it reaches a period of stabilization, represented by curve 30. According to embodiments of the present invention, the sensor may remain in this stabilized state for periods of one year or more.

[0041] Toward the end of the sensor life, the sensor output current tends to change less and less with respect to glucose concentration. Curve 30 moves toward curve 40 as represented by arrow 5b. Eventually, at the sensor's end of life, curve 40 is relatively flat for higher glucose concentrations, thereby rendering the sensor essentially ineffective for measurement. In other words, at the end of the sensor's life, the change in sensor output current with respect to a change in glucose concentration is minimal.

[0042] As described above, the present invention adjusts the calibration curve throughout the life of the sensor. Having a constantly updated calibration curve assures that accurate sensor readings are obtained regardless of the phase of the sensor. In further embodiments of the invention, a five-point piecewise linear approximation is used each time to approximate the calibration curve. In other words, instead of using a smooth curve, the curve is broken into five points and the line between each two consecutive points is assumed to be linear, as illustrated in Figure 3. The piecewise linear approximation has been shown to reduce the complexity of the performed calculations while maintaining accurate results. In alternative embodiments, other mathematical approximations can be used to get the value of the calibration curve, including using a larger or smaller number of piecewise linear approximations.

[0043] Figure 4 shows a more detailed method for calibrating a sensor according to an embodiment of the present invention. At Step 50, a calibration array is compiled from independent glucose readings, such as readings from a blood glucose meter taken simultaneously during the life of the sensor. The calibration array may be compiled from blood glucose meter readings, which have been taken and recorded for a particular sensor over a period of time, such as, for example, three weeks.

[0044] Each recalibration of the sensor uses historically measured glucose points and corresponding sensor data. The reference glucose points and corresponding sensor data may be placed into the calibration array. According to embodiments of the present invention, the calibration array may include the following elements: time, independently measured glucose points (M_g), measured blood glucose concentrations (C_o), glucose electrode readings (I_g) and oxygen electrode readings (I_o).

[0045] At Step 52, the nominal glucose current I_{g0} may be adjusted. For example, under certain conditions it is possible that there may be a base line shift in the nominal glucose current, I_{g0},. Thus, the normalized nominal glucose current may not be exactly equal to "one." For the nominal glucose current adjustment, data may be used to adjust the current over a period of time. For example, according to an embodiment of the present invention, data over the last three weeks from the glucose sensor may be used to adjust the value of the nominal glucose current.

[0046] According to the present invention, the nominal glucose current (I_{g0}) may be adjusted by calculating a shift of each measured data point with respect to the blood glucose meter readings . A mean shift may be determined and the value of the nominal glucose current adjusted accordingly, for example, either by adjusting the nominal glucose current by the amount of the mean shift or by adjusting the nominal glucose current by an amount corresponding to or dependent upon the mean shift. To calculate the mean shift, the shift to the calibration curve in the y-direction" the coordinates, X_m and Y_m, may be calculated as follows:

Abbott Ex. 1002 - 675/1438

[0047]

$$X_m = M_g(t) / C_o(t + a) \quad (2)$$

[0048]

$$Y_m = I_g(t + a) /(R * I_o(t + a)) \quad (3)$$

[0049] X_m and Y_m represent the x-y coordinates to map the meter values to the calibration curve graph. The constant a is an empirically derived time shift to correlate the sensor reading with the blood glucose meter. The time shift, a, has been found to be approximately 15 minutes.

[0050] $Y\_shift=Y_m/Y_c$, in which Y_c is the corresponding point on the calibration curve with the same X_m value. In the first I_{g0} adjustment (i.e. step 52), the Y_shift is calculated for only the Y_m and X_m values corresponding to glucose values less than 120 mg/dl. The mean shift of I_{g0} is then calculated by:

[0051]

$$mean\_shift = \Sigma(Y\_shift)/N,$$

[0052] where N is the total number of calibration points (i.e., meter readings).

[0053] Once the mean shift has been determined, the value "R" may be adjusted as follows:

[0054]

$$R' = R * mean\ shift \quad (4)$$

[0055] Once the new value of R is calculated, the Y_m values of each calibration point may be adjustment according to the new value of R:

[0056]

$$Y_m' = I_g(t+a)/(R'*I_o(t+a))$$

[0057] Thus, adjusting the nominal glucose current effectively changes the value of "R" in equation (4), above. Once the new Y_m (Y_m') is determined, adjustment on the shape of the calibration curve can be determined.

[0058] At Step 54, adjustments are made to the shape of the measured curve, i.e., the shape of the sensor calibration curve. The adjustments to the calibration curve may be used to provide calculation of the sensor output.

[0059] The difference between the new Y_m (Y_m') is then calculated and the result is stored in array Y_d such that $Y_d = Y_m'-Y_c$.

[0060] Y_d is then regressed against the corresponding x coordinates, X_m, by performing a standard weighted linear regression. The slope and intercept of the regression results may be calculated as follows:

[0061]

$$Slope = \frac{(\sum w_i)(\sum w_i x_i Yd_i) - (\sum w_i x_i)(\sum w_i Yd_i)}{\Delta} \quad (6)$$

Abbott Ex. 1002 - 676/1438

[0062]

$$Intercept = \frac{(\sum w_i x_i^2)(\sum w_i Yd_i) - (\sum w_i x_i)(\sum w_i x_i Yd_i)}{\Delta} \quad (7)$$

where

[0063]

$$\Delta = (\sum w_i)(\sum w_i x_i^2) - (\sum w_i x_i)^2$$

[0064] The weights, w_i, are determined according to the time at which that glucose measurement point is taken. According to an embodiment of the present invention, the weight declines linearly as the reference point is further back in history from the time the calibration:

[0065]

$$w_i = (T - i),$$

[0066] in which T is the time of calibration and i is the time at which the glucose measurement point is taken.

[0067] The result of the linear regression is used to determine the last recalibration point. The last recalibration point is one of the five points on the calibration curve corresponding to the highest glucose concentration. The last calibration point, Y(5), is determined as follows:

[0068]

$$Y'(5) = Y(5) + slope * X(4) + Intercept.$$

[0069] The slope and intercept are determined by equations 6 and 7.

[0070] The remaining calibration points can then be determined as follows:

[0071]

$$\Delta Y(i)/(1-y(i)) = H * \Delta Y(i+1)/(1-y(i+1))$$

[0072] in which ΔY is the amount of change for calibration point Y and the variable H is set to 0.9 if the sensor is gaining sensitivity and 0.7 when the sensor losing sensitivity. The variable H may be different in different phases of sensor life.

[0073] The new calibration curve, therefore, becomes:

[0074]

$$Y'(i) = Y(i) + \Delta Y(i)$$

[0075] Once the new curve shape is determined, a second I_{g0} adjustment is made to ensure the maximum accuracy. The second I_{g0} adjustment is identical to the first I_{g0} adjustment, except that all calibration points, as opposed to only the low glucose value points (i.e., Y_m and X_m coordinates corresponding to glucose values under 120 mg/dl), will be used. At Step 58, a new nominal glucose current and new calibration curve may be set for the sensor. Thus, after recalibration, the sensor output can be calculated using the new calibration curve derived from the recalibration procedure

Abbott Ex. 1002 - 677/1438

of Figure 4.

[0076] Figures 5a-d summarize the step-by-step change of the calibration curve. Figure 5a shows the calibration curve before the recalibration. The reference points mapped on the calibration graph are significantly deviant from the calibration curve. In Figure 5b, the sensor has undergone first I_{g0} adjustment; the low end points are lined up with the new calibration curve. In Figure 5c, the sensor has undergone curve shape adjustment, and the high-end points are also lined up with the calibration curve. In Figure 5d, the sensor has undergone the second I_{g0} adjustment for fine tuning purposes. As seen in Figure 5d, the curve is likely to change only slightly with respect to the reference points during the second I_{g0} adjustment.

[0077] Figure 6 shows an implanted sensing system in which embodiments of the present invention may be used. In Figure 6, an implanted sensing system 90 may include, but is not limited to, a pump 96, a catheter 94 having one end attached to the pump 96, and a sensor 92 disposed at another end of the catheter 94. The pump 96 may be an insulin pump and the sensor 92 may be a glucose sensor. The sensor 92 may be calibrated using embodiments of the present invention. A properly calibrated sensor 92 may send signals to the pump 96, enabling the pump 96 to accurately deliver medication or other fluids, such as insulin, for example, through the catheter 94 to a patient.

[0078] Thus, according to embodiments of the present invention, a non-linear curve may be adjusted using a linear regression. Using a linear regression rather than a non-linear regression provides many advantages. For example, the amount of processing power saved by using a linear regression rather than a non-linear regression is dramatic. Processing power is critical in battery operated or otherwise powered implantable systems. Moreover, linear regressions are far more stable than non-linear regressions when input data varies widely. Stability is critical in medical diagnostic and treatment systems such as an implantable insulin pump, for example.

[0079] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that the invention is not limited to the particular embodiments shown and described and that changes and modifications may be made without departing from the spirit and scope of the appended claims. Thus, embodiments of the present invention may be used to recalibrate any sensor that exhibits nonlinear characteristics. Generally, embodiments of the present invention may be adapted for use with any type of sensor in any type of environment where calibration of the sensor over its lifetime is desired.

Claims

1. A method for calibrating a sensor comprising:

   compiling a calibration array of data relating to the sensor;
   adjusting a nominal output current of the sensor a first time based on data in the array, wherein only calibration points from the calibration array corresponding to glucose values less than 120 mg/dl are used;
   adjusting a curve shape representing the sensor output based on data in the array and the adjusted value of the nominal output current; and
   adjusting the nominal output current of the sensor a second time based on data in the array, wherein all calibration points from the calibration array are used.

2. The method of claim 1, wherein compiling an array comprises compiling historical data.

3. The method of claim 2, wherein the historical data comprises measured blood glucose readings.

4. The method of claim 1, wherein compiling an array comprises compiling recent data.

5. The method of claim 4, wherein the recent data comprises electrode readings.

6. The method of claim 5, wherein the electrode readings comprise glucose electrode readings and oxygen electrode readings.

7. The method of claim 4, wherein the recent data comprises measured blood glucose concentrations.

8. The method of claim 7, wherein the nominal output current is a nominal glucose current.

9. The method of claim 8, wherein the nominal glucose current is adjusted based on a shift of measured data points with respect to blood glucose readings.

Abbott Ex. 1002 - 678/1438

10. The method of claim 9, wherein the shift is a mean shift.

11. The method of claim 1, wherein adjusting the curve representing the sensor output comprises performing a linear regression on data in the array.

12. The method of claim 11, wherein a result of the linear regression determines a first calibration point.

13. The method of claim 12, wherein the first calibration point is used to determine a plurality of calibration points.

14. The method of claim 1, wherein adjusting the curve representing the sensor output comprises adjusting the curve in a piecewise linear fashion.

15. The method of claim 14, wherein a number of pieces in the piecewise linear adjustment is five.

16. The method of claim 1, wherein the nominal output current is a nominal glucose current,

17. The method of claim 16, wherein the nominal glucose current is adjusted based on a shift of measured data points with respect to blood glucose readings.

18. The method of claim 17, wherein the shift is a mean shift.

19. The method of claim 1, further comprising establishing a new sensor output based on the adjusted curve and the twice adjusted sensor parameter

20. A sensor calibration system comprising:

means for compiling a calibration array of data relating to the sensor;
means for adjusting a nominal output current a first time based on data in the array, wherein only calibration points from the calibration array corresponding to glucose values less than 120 mg/dl are used;
means for adjusting a curve shape representing the sensor output based on data in the array; and
means for adjusting the nominal output current a second time based on data in the array, wherein all calibration points from the calibration array are used.

21. An implantable sensing system comprising:

a sensor for sensing a biological parameter;
a processor connected to the sensor for processing the parameter; and
a drug delivery unit connected to the processor for responding to the processor based on the parameter,
wherein the processor is programmed to adjust an output of the sensor by
compiling a calibration array of data relating to the sensor;
adjusting a nominal output current a first time based on data in the array, wherein only calibration points from the calibration array corresponding to glucose values less than 120 mg/dl are used;
adjusting a curve shape representing the sensor output based on data in the array; and
adjusting the nominal output current a second time based on data in the array, wherein all calibration points from the calibration array are used.

22. The system of claim 21, wherein the sensor is a glucose sensor.

23. The system of claim 21, wherein the drug delivery unit is an insulin pump.

24. The system of claim 21, wherein the insulin pump delivers insulin in response to the sensed parameter.

25. The method of claim 21, wherein compiling an array comprises compiling historical data.

26. The method of claim 25, wherein the historical data comprises measured blood glucose readings.

27. The method of claim 21, wherein compiling an array comprises compiling recent data.

Abbott Ex. 1002 - 679/1438

28. The method of claim 27, wherein the recent data comprises glucose electrode readings and oxygen electrode readings.

29. The method of claim 27, wherein the recent data comprises measured blood glucose concentrations.

30. The method of claim 21, wherein adjusting a sensor parameter a first time comprises adjusting a nominal glucose current.

31. The method of claim 21, wherein adjusting the curve representing the sensor output comprises performing a linear regression on data in the array.

32. The method of claim 21, wherein adjusting the curve representing the sensor output comprises adjusting the curve in a piecewise linear fashion.

Patentansprüche

1. Verfahren zur Kalibrierung eines Sensors, bei dem man
einen Kalibrierungs-Satz Daten betreffend den Sensor zusammenstellt;
einen Nenn-Ausgangsstrom des Sensors auf Grund von Daten im Datensatz ein erstes Mal einstellt, wobei nur Kalibrierungspunkte von dem Kalibrierungs-Satz entsprechend den Glukose-Werten unterhalb von 120 mg/dl verwendet werden;
einen Kurvenverlauf, der das Sensorausgangssignal auf Grund der Daten im Datensatz darstellt, sowie den eingestellten Wert des Nenn-Ausgangsstroms einstellt; und
den Nenn-Ausgangsstrom des Sensors auf Grund von Daten im Datensatz ein zweites Mal einstellt, wobei alle Kalibrierungspunkte vom Kalibrierungs-Satz verwendet werden.

2. Verfahren nach Anspruch 1, bei dem das Zusammenstellen eines Datensatzes das Zusammenstellen von Hintergrund- bzw. Verlaufsdaten beinhaltet.

3. Verfahren nach Anspruch 2, bei dem die Verlaufsdaten BlutglukoseMesswerte beinhalten.

4. Verfahren nach Anspruch 1, bei dem das Zusammenstellen eines Datensatzes das Zusammenstellen aktueller Daten beinhaltet.

5. Verfahren nach Anspruch 4, bei dem die aktuellen Daten Elektrodenmesswerte beinhalten.

6. Verfahren nach Anspruch 5, bei dem die Elektrodenmesswerte Glukose- und Sauerstoff-Elektrodenmesswerte beinhalten.

7. Verfahren nach Anspruch 4, bei dem die aktuellen Daten gemessene Blutglukosekonzentrationen beinhalten.

8. Verfahren nach Anspruch 7, bei dem der Nenn-Ausgangsstrom ein Nenn-Glukosestrom ist.

9. Verfahren nach Anspruch 8, bei dem der Nenn-Glukosestrom auf Grund einer Verschiebung gemessener Datenpunkte bezüglich Blutglukose-Messwerten nachgestellt wird.

10. Verfahren nach Anspruch 9, bei dem die Verschiebung ein Mittelwert ist.

11. Verfahren nach Anspruch 1, bei dem das Einstellen der die Sensorausgangsgröße darstellenden Kurve eine lineare Regression von Daten im Datensatz beinhaltet.

12. Verfahren nach Anspruch 11, bei dem ein Ergebnis der linearen Regression einen ersten Kalibrationspunkt bestimmt.

13. Verfahren nach Anspruch 12, bei dem der erste Kalibrationspunkt dazu dient, eine Vielzahl von Kalibrationspunkten zu bestimmen.

14. Verfahren nach Anspruch 1, bei dem das Einstellen der die Sensorausgangsgröße darstellenden Kurve das stück-

Abbott Ex. 1002 - 680/1438

weise lineare Einstellen der Kurve beinhaltet.

15. Verfahren nach Anspruch 14, bei dem eine Anzahl von Stücken in der stückweise linearen Einstellung gleich fünf ist.

16. Verfahren nach Anspruch 1, bei dem der Nenn-Ausgangsstrom ein Nenn-Glukosestrom ist.

17. Verfahren nach Anspruch 16, bei dem der Nenn-Glukosestrom auf Grund einer Verschiebung gemessener Datenpunkte bezüglich Blutglukosemesswerten eingestellt wird.

18. Verfahren nach Anspruch 17, bei dem die Verschiebung ein Mittelwert ist.

19. Verfahren nach Anspruch 1, bei dem man weiterhin auf Grund der nachgestellten Kurve und des zweimal nachgestellten Sensorparameters ein neues Sensorausgangssignal festlegt.

20. Sensorkalibriersystem mit:

einer Einrichtung zum Zusammenstellen eines Kalibrierungs-Satzes von Daten betreffend den Sensor;
einer Einrichtung zum erstmaligen Einstellen eines Nenn-Ausgangsstroms auf Grund von Daten in dem Datensatz, wobei nur Kalibrierungspunkte von dem Kalibrierungs-Satz entsprechend den Glukose-Werten unterhalb von 120 mg/ dl verwendet werden;
einer Einrichtung zum Einstellen eines das Sensor-Ausgangssignal darstellenden Kurvenformverlaufs auf Grund von Daten im Datensatz; und
einer Einrichtung zu einem zweiten Einstellen des Nenn-Ausgangsstroms auf Grund der Daten im Datensatz, wobei alle Kalibrierungspunkte vom Kalibrierungs-Satz verwendet werden.

21. Implantierbares Sensorsystem mit:

einem Sensor zum Erfassen eines biologischen Parameters;
einem Prozessor, der mit dem Sensor verbunden ist, um den Parameter zu verarbeiten; und
einer Medikamentenausgabeeinheit, die an den Prozessor angeschlossen ist und auf Grund des Parameters auf ihn anspricht;
wobei der Prozessor programmiert ist, eine Ausgangsgröße des Sensors einzustellen, indem

ein Kalibrierungs-Satz von Daten über den Sensor zusammengestellt wird;
ein Nenn-Ausgangsstrom auf Grund von Daten im Datensatz ein erstes Mal eingestellt wird, wobei nur Kalibrierungspunkte vom Kalibrierungs-Satz entsprechend Glukose-Werten unterhalb von 120 mg/ dl verwendet werden;
ein das Sensorausgangssignal darstellender Kurvenformverlauf auf Grund von Daten im Datensatz nachgestellt wird; und
der Nenn-Ausgangsstrom auf Grund von Daten im Datensatz ein zweites Mal nachgestellt wird, wobei alle Kalibrierungspunkte vom Kalibrierungs-Satz verwendet werden.

22. System nach Anspruch 21, bei dem der Sensor ein Glukosesensor ist.

23. System nach Anspruch 21, bei dem die Medikamentenausgabeeinheit eine Insulinpumpe ist.

24. System nach Anspruch 21, bei dem die Insulinpumpe das Insulin ansprechend auf den erfassten Parameter ausgibt.

25. System nach Anspruch 21, bei dem zum Zusammenstellen eines Datensatzes Hintergrund- bzw. Verlaufsdaten zusammengestellt werden.

26. System nach Anspruch 25, bei dem die Hintergrund- bzw. Verlaufsdaten Blutglukosemesswerte beinhalten.

27. System nach Anspruch 21, bei dem zum Zusammenstellen eines Datensatzes aktuellere Daten zusammengestellt werden.

28. System nach Anspruch 27, bei dem die aktuelleren Daten Glukose- und Sauerstoff-Elektrodenmesswerte beinhalten.

Abbott Ex. 1002 - 681/1438

29. System nach Anspruch 27, bei dem die aktuelleren Daten Messwerte der Blutglukosekonzentration beinhalten.

30. System nach Anspruch 21, bei dem das erstmalige Einstellen eines Sensorparameters das Einstellen eines Nenn-Glukosestroms beinhaltet.

31. System nach Anspruch 21, bei dem das Nachstellen der das Sensorausgangssignal darstellenden Kurve das Ausführen einer linearen Regression auf Daten im Datensatz beinhaltet.

32. System nach Anspruch 21, bei dem das Nachstellen der die Sensorausgangsgröße darstellenden Kurve das stückweise lineare Nachstellen derselben beinhaltet.

Revendications

1. Procédé pour étalonner un capteur comprenant :

   la compilation d'un tableau d'étalonnage de données concernant le capteur ;
   le réglage une première fois d'un courant de sortie nominal du capteur sur la base des données du tableau, dans lequel on utilise uniquement des points d'étalonnage provenant du tableau d'étalonnage et correspondant à des valeurs de glucose inférieures à 120 mg/dl ;
   le réglage d'une forme de courbe représentant la sortie du capteur sur la base des données du tableau et de la valeur réglée du courant de sortie nominal ; et
   le réglage une seconde fois du courant de sortie nominal du capteur sur la base des données du tableau, dans lequel on utilise tous les points d'étalonnage provenant du tableau d'étalonnage.

2. Procédé selon la revendication 1, dans lequel la compilation d'un tableau comprend la compilation de données d'historique.

3. Procédé selon la revendication 2, dans lequel les données d'historique comprennent des lectures de glycémie mesurée.

4. Procédé selon la revendication 1, dans lequel la compilation d'un tableau comprend la compilation de données récentes.

5. Procédé selon la revendication 4, dans lequel les données récentes comprennent des lectures d'électrode.

6. Procédé selon la revendication 5, dans lequel les lectures d'électrode comprennent des lectures d'électrode de glucose et des lectures d'électrode d'oxygène.

7. Procédé selon la revendication 4, dans lequel les données récentes comprennent des concentrations de glucose sanguin mesurées.

8. Procédé selon la revendication 7, dans lequel le courant de sortie nominal est un courant de glucose nominal.

9. Procédé selon la revendication 8, dans lequel le courant de glucose nominal est réglé sur la base d'un décalage de points de données mesurés par rapport à des lectures de glycémie.

10. Procédé selon la revendication 9, dans lequel le décalage est un décalage moyen.

11. Procédé selon la revendication 1, dans lequel le réglage de la courbe représentant la sortie du capteur comprend l'exécution d'une régression linéaire sur des données du tableau.

12. Procédé selon la revendication 11, dans lequel un résultat de la régression linéaire détermine un premier point d'étalonnage.

13. Procédé selon la revendication 12, dans lequel le premier point d'étalonnage est utilisé pour déterminer une pluralité de points d'étalonnage.

Abbott Ex. 1002 - 682/1438

14. Procédé selon la revendication 1, dans lequel le réglage de la courbe représentant la sortie du capteur comprend le réglage de la courbe de manière linéaire par morceaux.

15. Procédé selon la revendication 14, dans lequel un nombre de morceaux dans le réglage linéaire par morceaux est égal à cinq.

16. Procédé selon la revendication 1, dans lequel le courant de sortie nominal est un courant de glucose nominal.

17. Procédé selon la revendication 16, dans lequel le courant de glucose nominal est réglé sur la base d'un décalage de points de données mesurés par rapport à des lectures de glycémie.

18. Procédé selon la revendication 17, dans lequel le décalage est un décalage moyen.

19. Procédé selon la revendication 1, comprenant en outre l'établissement d'une nouvelle sortie de capteur sur la base de la courbe réglée et du paramètre de capteur réglé deux fois.

20. Système d'étalonnage de capteur comprenant :

des moyens pour compiler un tableau d'étalonnage de données concernant le capteur ;
des moyens pour régler une première fois un courant de sortie nominal sur la base des données du tableau, dans lequel on utilise uniquement des points d'étalonnage provenant du tableau d'étalonnage et correspondant à des valeurs de glucose inférieures à 120 mg/dl ;
des moyens pour régler une forme de courbe représentant la sortie du capteur sur la base des données du tableau ; et
des moyens pour régler une seconde fois le courant de sortie nominal sur la base des données du tableau, dans lequel on utilise tous les points d'étalonnage provenant du tableau d'étalonnage.

21. Système de détection implantable comprenant :

un capteur pour détecter un paramètre biologique ;
un processeur relié au capteur pour traiter le paramètre ; et
une unité de distribution de médicament reliée au processeur pour répondre au processeur sur la base du paramètre,
dans lequel le processeur est programmé pour régler une sortie du capteur en :

compilant un tableau d'étalonnage de données concernant le capteur ;
réglant une première fois un courant de sortie nominal sur la base des données du tableau, dans lequel on utilise uniquement des points d'étalonnage provenant du tableau d'étalonnage et correspondant à des valeurs de glucose inférieures à 120 mg/dl ;
réglant une forme de courbe représentant la sortie du capteur sur la base des données du tableau ; et
réglant une seconde fois le courant de sortie nominal sur la base des données du tableau, dans lequel on utilise tous les points d'étalonnage provenant du tableau d'étalonnage.

22. Système selon la revendication 21, dans lequel le capteur est un capteur de glucose.

23. Système selon la revendication 21, dans lequel l'unité de distribution de médicament est une pompe à insuline.

24. Système selon la revendication 21, dans lequel la pompe à insuline distribue de l'insuline en réponse au paramètre détecté.

25. Système selon la revendication 21, dans lequel la compilation d'un tableau comprend la compilation de données d'historique.

26. Système selon la revendication 25, dans lequel les données d'historique comprennent des lectures de glycémie mesurée.

27. Système selon la revendication 21, dans lequel la compilation d'un tableau comprend la compilation de données récentes.

Abbott Ex. 1002 - 683/1438

28. Système selon la revendication 27, dans lequel les données récentes comprennent des lectures d'électrode de glucose et des lectures d'électrode d'oxygène.

29. Système selon la revendication 27, dans lequel les données récentes comprennent des concentrations de glucose sanguin mesurées.

30. Système selon la revendication 21, dans lequel le premier réglage d'un paramètre de capteur comprend le réglage d'un courant de glucose nominal.

31. Système selon la revendication 21, dans lequel le réglage de la courbe représentant la sortie du capteur comprend l'exécution d'une régression linéaire sur des données du tableau.

32. Système selon la revendication 21, dans lequel le réglage de la courbe représentant la sortie du capteur comprend le réglage de la courbe de manière linéaire par morceaux.

Abbott Ex. 1002 - 684/1438

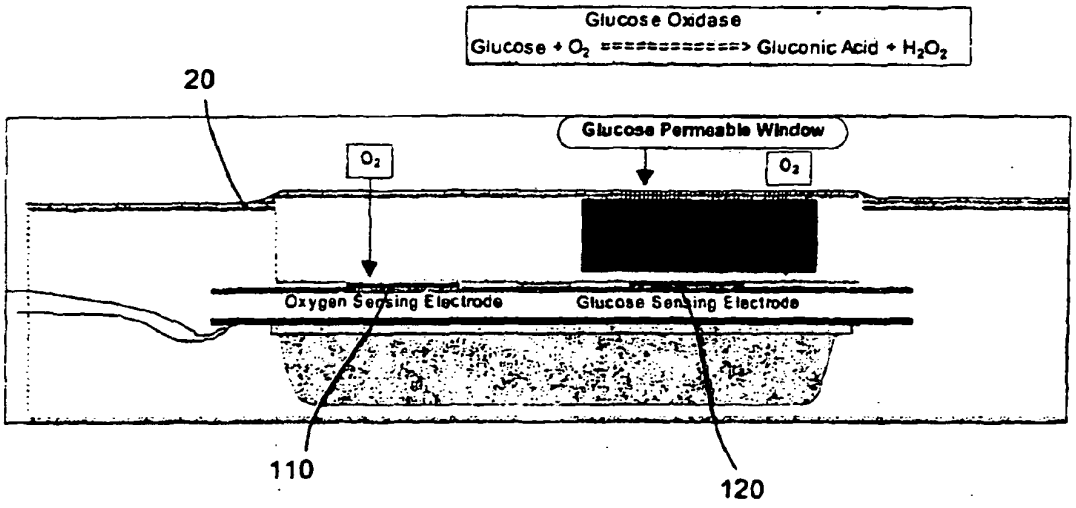


FIG. 1

Abbott Ex. 1002 - 685/1438

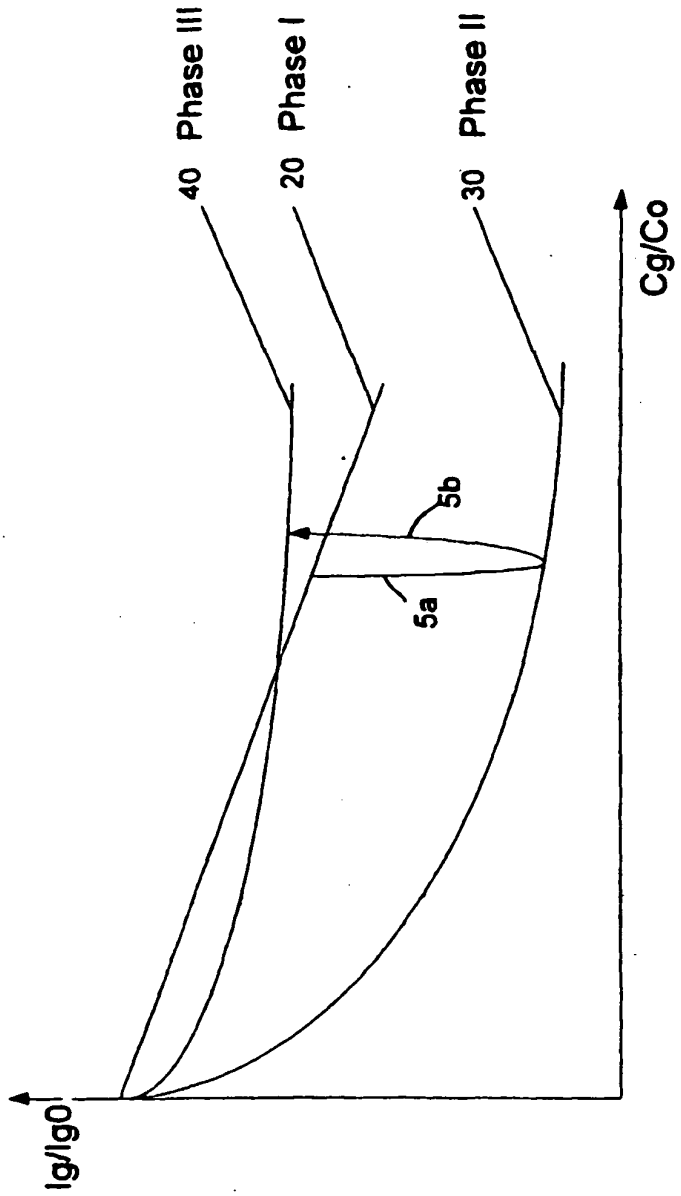


FIG. 2

Abbott Ex. 1002 - 686/1438

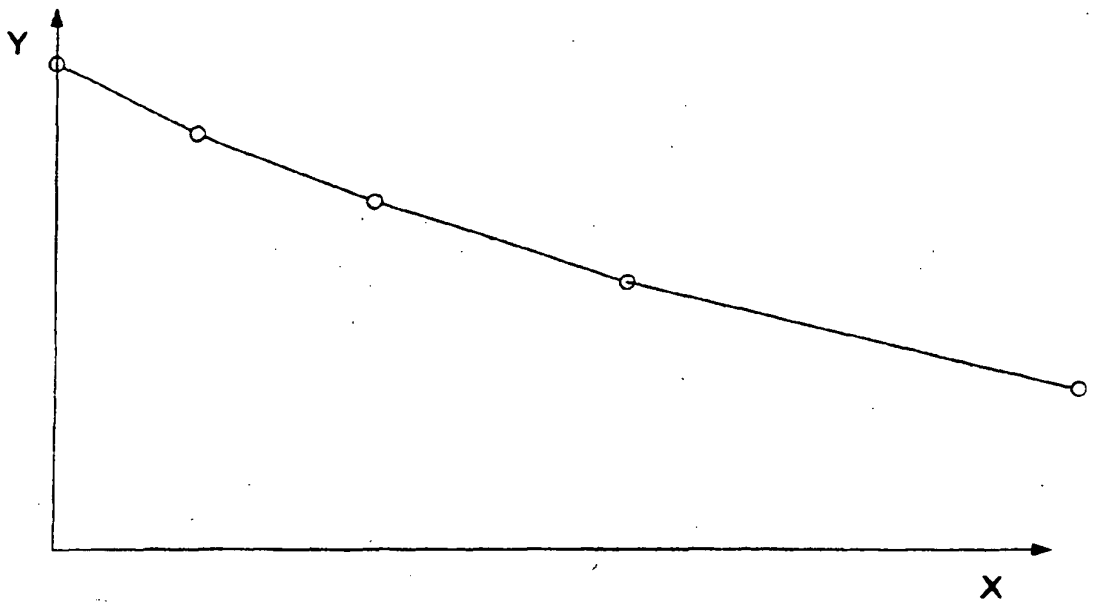


FIG. 3

Abbott Ex. 1002 - 687/1438

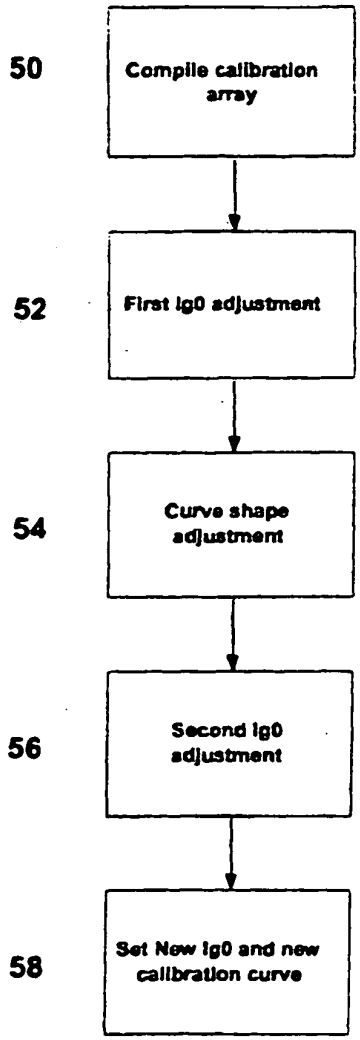


FIG. 4

Abbott Ex. 1002 - 688/1438

FIG. 5a

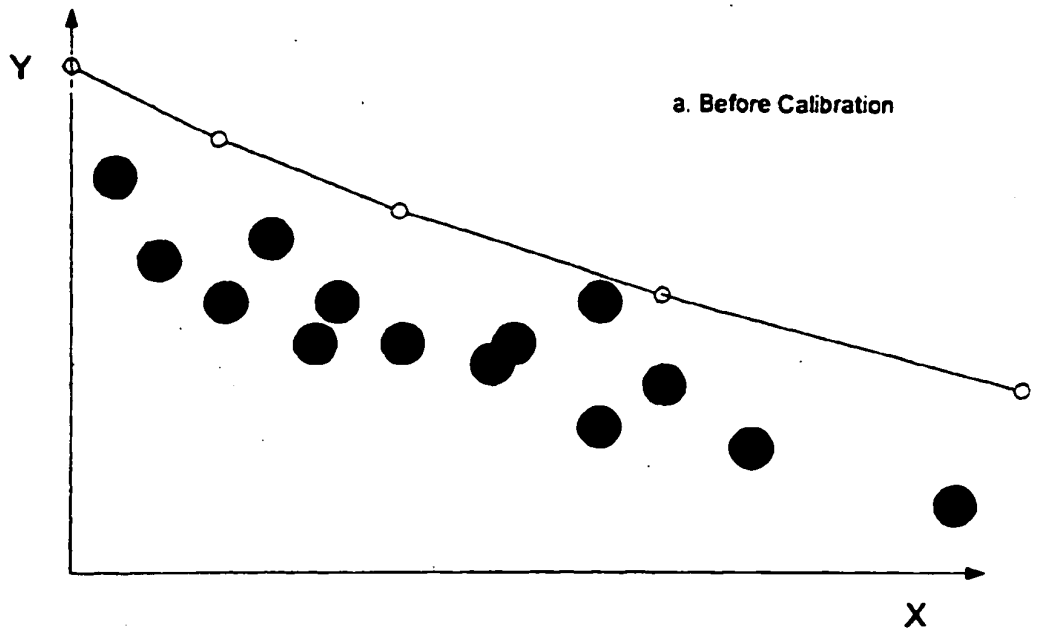
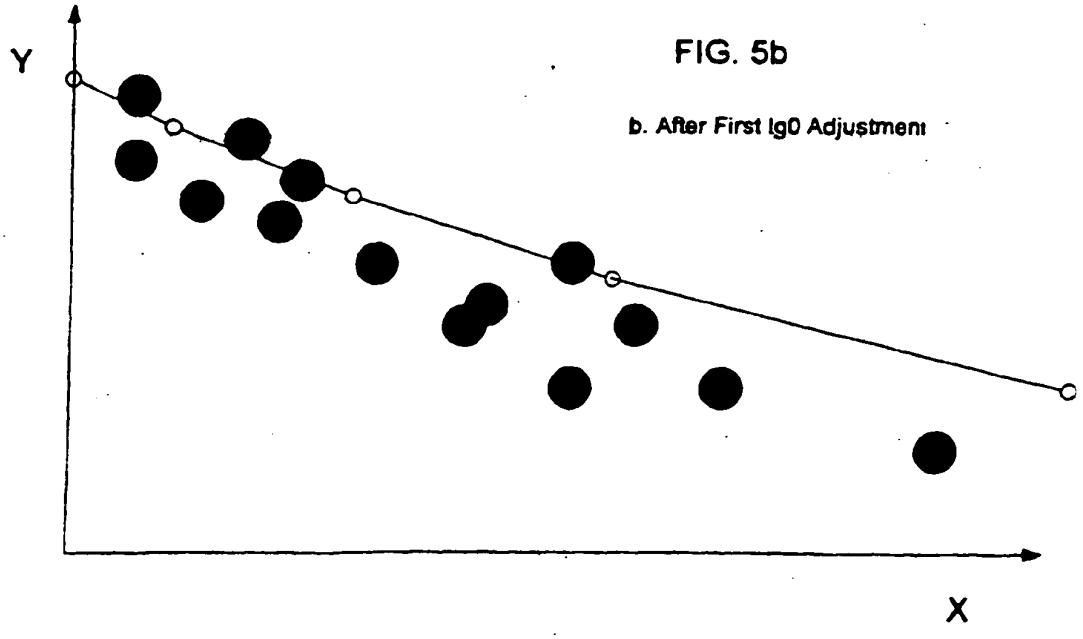


FIG. 5b



Abbott Ex. 1002 - 689/1438

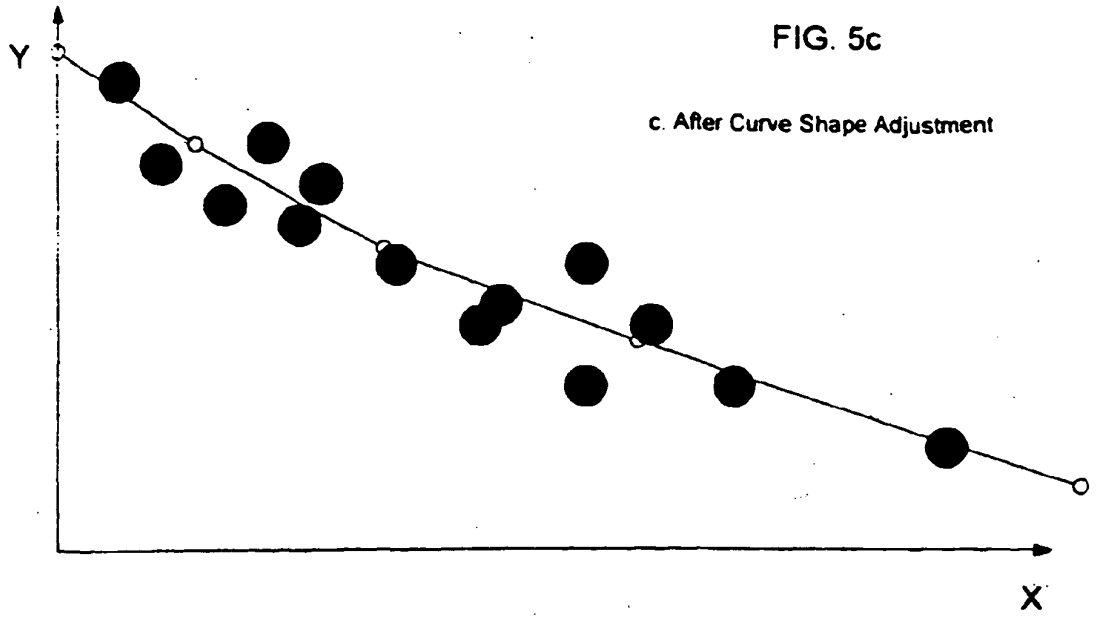


FIG. 5c

c. After Curve Shape Adjustment

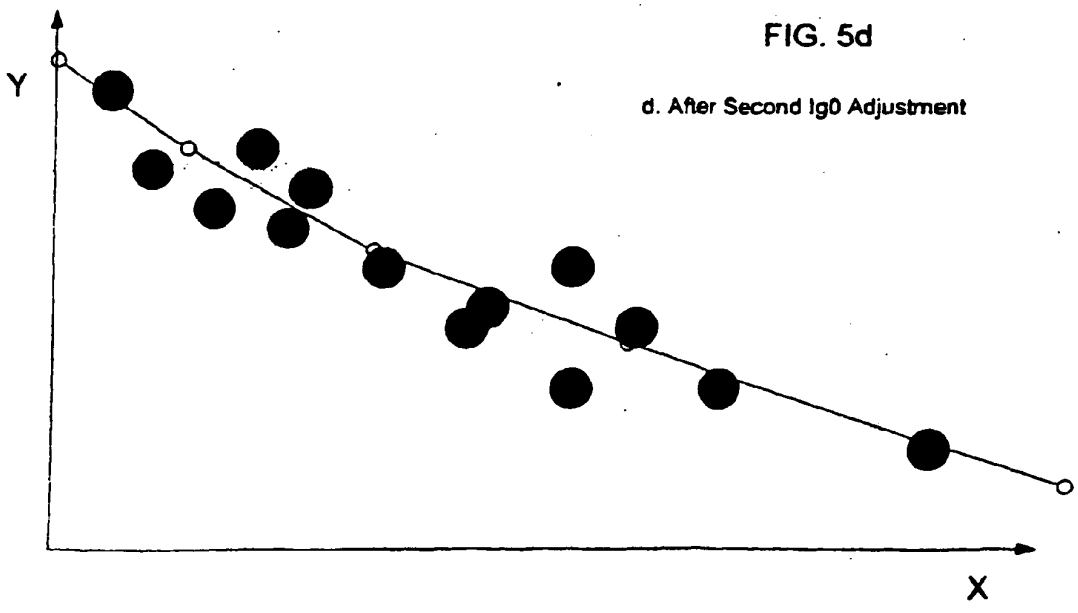


FIG. 5d

d. After Second Ig0 Adjustment

Abbott Ex. 1002 - 690/1438

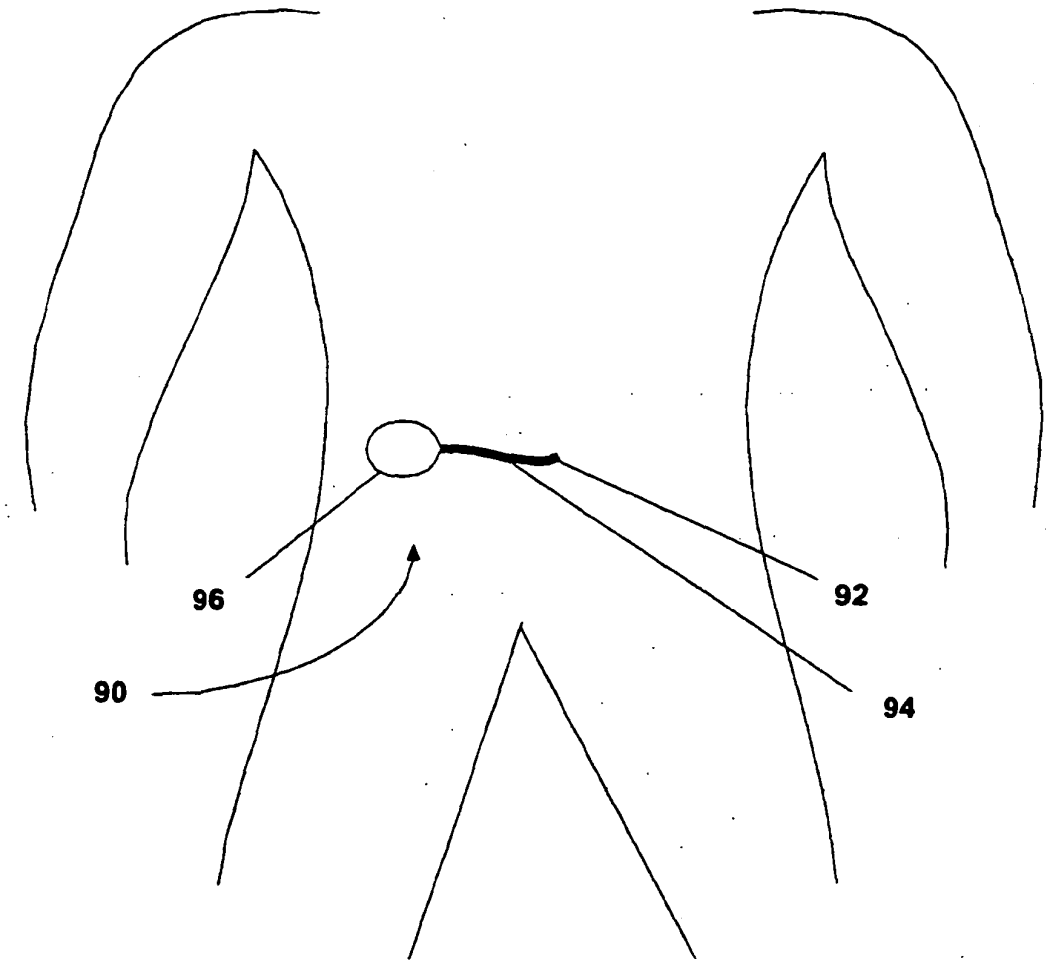


FIG. 6

Abbott Ex. 1002 - 691/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 4650547 A **[0027]**
- US 4671288 A **[0027]**
- US 4781798 A **[0027]**
- US 4703756 A **[0027]**
- US 4890620 A **[0027]**
- US 10034338 B **[0029]**
- US 5503770 A **[0030]**
- US 5512246 A **[0030]**
- US 007515 P **[0030]**
- US 6011984 A **[0030]**
- US 5628310 A **[0030]**
- US 5342789 A **[0030]**
- US 5246867 A **[0030]**
- US 036093 A **[0031]**
- US 03827602 A **[0031]**

Abbott Ex. 1002 - 692/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 759 201 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
13.10.2010 Bulletin 2010/41

(21) Application number: **05755120.2**

(22) Date of filing: **20.05.2005**

(51) Int Cl.:
G01N 33/487 *(2006.01)*

(86) International application number:
PCT/US2005/019106

(87) International publication number:
WO 2005/121785 (22.12.2005 Gazette 2005/51)

(54) SYSTEM FOR MONITORING PHYSIOLOGICAL CHARACTERISTICS ACCORDING TO THE USER BIOLOGICAL STATE

SYSTEM ZUR ÜBERWACHUNG PHYSIOLOGISCHER EIGENSCHAFTEN GEMÄSS DEM BIOLOGISCHEN ZUSTAND DES ANWENDERS

SYSTEME DE SURVEILLANCE DE CARACTERISTIQUES PHYSIOLOGIQUES

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR

(30) Priority: **03.06.2004 US 860114**

(43) Date of publication of application:
07.03.2007 Bulletin 2007/10

(73) Proprietor: **Medtronic MiniMed, Inc.**
Northridge, CA 91325-1219 (US)

(72) Inventors:
- **SAIDARA, Frank**
  Los Angeles, CA 90067 (US)
- **MASTROTOTARO, John, Joseph**
  Los Angeles, CA 90024 (US)
- **TOLLE, Charles, Vallet**
  Van Nuys, CA 91406 (US)
- **MUELLER, John, C., Jr.**
  Simi Valley, CA 93065 (US)
- **SANDERS, Jeff, B.**
  Moorpark, CA 93021 (US)
- **NIELSEN, Edward, S.**
  Castaic, CA 91384 (US)

(74) Representative: **Ruschke, Hans Edvard**
RUSCHKE HARTMANN MADGWICK & SEIDE
Patent- und Rechtsanwälte
Postfach 86 06 29
81633 München (DE)

(56) References cited:
EP-A- 1 127 544
WO-A-02/44865
US-A1- 2003 100 040
US-A1- 2003 125 612
US-A1- 2003 187 336
US-A1- 2003 208 113

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 759 201 B1

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] This invention relates generally to medical monitoring systems. More specifically, this invention relates to a device and a method for monitoring physiological characteristics in individuals including those associated with physiological conditions (e.g. monitoring blood glucose levels in diabetics).

2. Description of the Related Art

[0002] A variety of electrochemical sensors have been developed for detecting and/or quantifying specific agents or compositions in a patient's blood. Notably, glucose sensors have been developed for use in obtaining an indication of blood glucose levels in a diabetic patient. Such readings are useful in monitoring and/or adjusting a treatment program which typically includes the regular administration of insulin to the patient. Periodic blood glucose readings significantly improve medical therapies using semi-automated medication infusion devices. Some exemplary external infusion devices are described in U.S. Patent Nos. 4,562,751, 4,678,408 and 4,685,903, while some examples of automated implantable medication infusion devices are described in U.S. Patent No. 4,573,994.

[0003] Electrochemical sensors can be used to obtain periodic measurements over an extended period of time. Such sensors can include a plurality of exposed electrodes at one end for subcutaneous placement in contact with a user's interstitial fluid, blood, or the like. A corresponding plurality of conductive contacts can be exposed at another end for convenient external electrical connection with a suitable monitoring device through a wire or cable. Exemplary sensors are described in U.S. Patent Nos. 5,299,571; 5,390,671; 5,391,250; 5,482,473; and 5,586,553.

[0004] Conventional glucose monitoring systems are somewhat limited in features that they provide to facilitate the monitoring of blood glucose levels. Typically, a glucose monitor can take readings as directed by the user and might provide a warning if a reading is deemed at an unsafe level (e.g., a hyper- or hypoglycemic condition). However, by the time the warning occurs, the user may already be experiencing negative symptoms. Furthermore, it may be unacceptable to address this by simply reducing (or raising) the value which triggers an indicator (e.g. a display, an alarm or the like) of an unsafe condition, because this may prompt a user to take "remedial" action (such as administering an additional bolus) when no unsafe condition would have actually materialized. Such an approach merely increases the occurrence of false positive alarms. As a consequence, the unnecessary "remedial" action can actually provoke an unsafe condition. As described above, although existing glucose monitors adequately detect blood glucose levels upon entering the hyperglycemic (or hypoglycemic) range, they do not anticipate these conditions.

[0005] As is known in the art, a glucose crash occurs when blood glucose levels of an individual are in a state of rapid decline and its symptoms are similar to those associated with hypoglycemia. The symptoms are caused by the dynamics of a declining glucose level and not by an absolute glucose level. Specific symptoms can include a feeling of light headedness, sweating, tremors, nervousness and/or disorientation. Disorientation is a particular risk to the patient. If the patient becomes disoriented while operating machinery, the patient could harm himself or others. A glucose crash can be caused by any of the following events: excess insulin administration; an unexpected increase in insulin sensitivity; a fall of free fatty acids in the blood; heavy exercise; or mental or physical stress. As previously mentioned, ordinary glucose monitors provide only for detection of hypoglycemic and hyperglycemic levels.

[0006] Impaired fasting glucose (IFG) is another condition which is not predicted by conventional glucose monitors. The American Diabetes Association (ADA) identifies IFG as an undesirable glucose condition, defined as a 126 mg/dL or higher blood glucose level at wakeup. Repeated IFG events can contribute to diabetic morbidity. One cause of IFG is an inadequate nocturnal insulin basal infusion rate. Although a patient can deal with the IFG after waking by administering an insulin bolus, it is preferable for the patient to avoid IFG incidents entirely.

[0007] Conventional monitors are designed to alert the user of unsafe conditions; however, many other factors and situations are also important to the user in managing treatment. For example, events such as meals or exercise, as well as entering calibration values are not tied to reminders issued by conventional monitors. Typical monitors provide only a single alarm to call attention to the user. This can be problematic in contexts of varying physiological states because a user is not made aware of the specific condition and/or the appropriate degree of urgency. In conventional alarm systems, until the user investigates, there is often no indication of the reason for the alarm or the severity of the situation.

[0008] Furthermore, the alarm settings and features for many monitoring systems are very limited. Such systems can provide duplicative warnings that can frustrate users and become ignored if they are excessive. In addition, typical monitoring systems can alarm during predictable periods during which a user does not wish to be disturbed.

[0009] Thus, conventional glucose monitoring systems are somewhat limited in features they provide to facilitate the monitoring of blood glucose levels. There is a need for monitoring systems for a physiological characteristic (such as

Abbott Ex. 1002 - 694/1438

blood glucose levels) with convenient features and settings that allow users flexibility in tailoring the system's operation to their personal needs and lifestyle. Particularly, there is a need for such systems that provide advanced alarm functions to reduce or eliminate redundant alarms. In addition, there is a need for monitoring systems that allow a convenient review of measurement and alarm histories.

[0010] Document US2003/0187336 shows a wearable device which collects information about the wearer partly from a sensor and partly via a series of questions presented to the user. The device also has a keypad to receive user input and a buzzer to attract the user's attention. The pre-characterizing part of claims 1 and 9 are based on this document.

SUMMARY OF THE INVENTION

[0011] The invention is as defined in claims 1 and 9 below.

[0012] The present invention provides a device comprising a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user; and a processor coupled to the sensor input for operating an alarm based on the sensed physiological characteristic value of the user from the received signal from the sensor; wherein the processor activates the alarm and delays accepting input from the user when the alarm awakens the user. In a specific embodiment of the invention, the physiological characteristic value is a blood glucose measurement and delaying accepting input from the user is applied to a low blood glucose alarm or a high blood glucose alarm. In preferred embodiments of the invention, the processor delays accepting input from the user until the user provides a predetermined input such as entering a numeric code or executing a button sequence. Optionally, delaying accepting input from a user who is most likely asleep when the alarm sounds is set according to a schedule based on a time of day, or alternatively, is set by the user before sleeping.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Referring now to the drawings in which like reference numbers represent corresponding parts throughout:

[0014] FIG. 1A is a block diagram of a characteristic monitor;

[0015] FIG. 1B is a block diagram of a telemetered characteristic monitor;

[0016] FIG. 2A is a flowchart of a status check algorithm for a characteristic monitor;

[0017] FIG. 2B is a flowchart of screens for entering a reference value to calibrate a characteristic monitor;

[0018] FIG. 3A is a flowchart of a method for anticipating a glucose crash;

[0019] FIG. 3B is a flowchart of a method for detecting an inadequate nocturnal basal rate;

[0020] FIG. 3C is a flowchart of a method for anticipating a hyperglycemic incident;

[0021] FIG. 3D is a flowchart of a method for maximizing athletic performance;

[0022] FIG. 4A illustrates a multiple alarm function;

[0023] FIGS. 4B and 4C illustrate respectively hypoglycemia and hyperglycemia alarm screens;

[0024] FIGS. 4D and 4E illustrate respectively flowcharts of screens for setting hypoglycemia and hyperglycemia alarms with underlined text indicating that it is blinking on the current screen, awaiting to be changed by the user; from screen 1-8, SEL aborts and goes to the next major screen;

[0025] FIG. 4F illustrates a flowchart of screens for setting a hyperglycemia alarm snooze with underlined text indicating that it is blinking on the current screen, awaiting to be changed by the user; from screen 1-2, SEL aborts and goes to the next major screen;

[0026] FIG. 4G illustrates a flowchart of screens for reviewing a history of glycemia alarms;

[0027] FIG. 5 illustrates a reminder function;

[0028] FIG. 6A illustrates minimum and maximum data presentation;

[0029] FIG. 6B illustrates excursion data presentation;

[0030] FIG. 6C illustrates characteristic value distribution data presentation;

[0031] FIG. 6D illustrates integrated characteristic value data presentation;

[0032] FIG. 7 illustrates screens for viewing real-time and historical measurements of a physiological characteristic value;

[0033] FIG. 8A illustrates a screen employing a graphical display of measurements of a physiological characteristic value with a three hour time scale;

[0034] FIG. 8B illustrates a screen employing a graphical display of measurements of a physiological characteristic value with a twenty-four hour time scale;

[0035] FIG. 8C illustrates control of the graphical display of measurements of a physiological characteristic value;

[0036] FIG. 8D illustrates a screen employing a graphical display of measurements of a physiological characteristic value in a grid display pattern which is further color coded to clearly delineate data which includes both physiological characteristic levels as well as physiological characteristic trends (e.g. high and going down, high and stable, high and going up, in zone going down, in zone in zone stable, in zone going up etc.);

Abbott Ex. 1002 - 695/1438

[0037] FIG. 8E illustrates a screen employing a graphical display of which provides the concentrations of a physiological characteristic over a specific time scale as well as information regarding the physiological significance of that concentration (e.g. too high, in zone, too low etc.) where the information regarding the physiological significance of that concentration is delineated in a row-like display pattern. Alternative arrangements of this type of display pattern include a gradual transition between the stripes of the row-like display pattern as well as arrangements where stripe colors (e.g. yellow and red) can vary over time and represent warning levels that are preselected (e.g. set by the user);

[0038] FIGS. 9A-9G provide a flow chart which illustrates various aspects of a system for monitoring physiological characteristics in individuals including the manner in which various interrelated elements of the system can be designed to interact.

DETAILED DESCRIPTION

1. Overview

[0039] The description that follows encompasses methods and systems for the convenient operation of monitoring physiological characteristics ("characteristic monitoring systems"). The description provided here encompasses the architecture of the apparatus as well as its control and convenience features. The control and convenience features can be implemented in a wide range of detailed characteristic monitoring system designs. Although arrangements are primarily described in the context of glucose monitors used in the treatment of diabetes, they are applicable to a wide variety of patient treatment programs where a physiological characteristic is periodically monitored to use in estimating the responsive treatment. For example, they can be used to determine the status and/or levels of a variety of characteristics including those associated with agents such as hormones, cholesterol, medication concentrations, pH, oxygen saturation, viral loads (e.g., HIV), or the like. As is known in the art, a sensor for the characteristic monitor can be implanted in and/or through subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue. Such sensors typically communicate a signal from the sensor set to the characteristic monitor.

[0040] Arrangements include specific features associated with a physiological characteristic monitoring apparatus (e.g. a continuous glucose monitor, glucose test strip meters and the like) that are designed to facilitate a users monitoring and/or control of a physiological characteristic of interest (e.g. blood glucose concentrations). Typically such physiological characteristic monitoring devices are coupled to one or more complementary medical apparati (e.g. sensor sets, infusion pumps and the like). Preferably, the sensor set and monitor are for determining glucose levels in the blood and/or body fluids of the user without the use of, or necessity of, a wire or cable connection between the transmitter and the monitor. Physiological characteristic monitors can be incorporated in to a wide variety of medical systems known in the art such as with infusion pump systems that designed to control the rate that medication is infused into the body of a user. Such infusion pump systems can include a physiological characteristic monitor which provides information to a user that facilitates the user's subsequent use of a drug delivery system (e.g. one that calculates a dose to be delivered by a medication infusion pump). In such contexts, the meter associated with the physiological characteristic monitor may also transmit commands to, and be used to remotely control, the delivery system. Preferably, the physiological characteristic monitor is used to monitor the glucose concentration in the body of the user, and the therapeutic agent that is infused by the delivery system into the body of the user includes insulin. Illustrative systems are disclosed for example in U. S. Patent Nos. 6,558,351 and 6,551,276; WO 00/19887 and WO 00/18449; as well as WO 2004/008956 and WO 2004/009161.

[0041] The physiological characteristic monitoring apparatus can be used in combination with a wide variety of other devices, for example in a closed loop infusion system designed to control the rate that medication is infused into the body of a user. Such a closed loop infusion system can include a sensor and an associated meter which generates an input to a controller which in turn operates a delivery system (e.g. one that calculates a dose to be delivered by a medication infusion pump). In such contexts, the meter associated with the sensor may also transmit commands to, and be used to remotely control, the delivery system. Such systems can be fully automated with the sensor transmitting information to a processor that determines whether a medication dose is needed, with such processors further being coupled to an infusion pump which then infuses the appropriate medication. Alternatively, the systems can be partially automated, for example where a processor makes a recommendation to the user, with the user's approval then activating the infusion pump. Illustrative systems are disclosed for example in U. S. Patent Nos. 6,558,351 and 6,551,276; WO 00/19887 and WO 00/18449 ; as well as WO 2004/008956 and WO 2004/009161.

[0042] The characteristic monitor system described herein is primarily adapted for use in subcutaneous human tissue. Alternatively, such arrangements can be placed in a variety of other types of physiological milieus, such as muscle, lymph, organ tissue, veins, arteries or the like, as well as being used in related environments such as animal tissue. They can provide sensor readings on an intermittent, near-continuous or continuous basis.

[0043] The described arrangements include sensing and advanced predictive functions of the monitor which are designed to anticipate unsafe conditions for a user before they occur. In addition, predictive functions can be employed

Abbott Ex. 1002 - 696/1438

so that a user can obtain feedback to obtain a desired physical objective, such as maximizing athletic performance. Other functions of the monitor include multiple programmable alarms and reminders and diagnostic functions. Advanced alarm functions also include an alarm repeat delay function and a snooze function that can be set by a user. Arrangements can include advanced display tools to facilitate easy and quick interpretation of information related to the user's condition, including a display function for an alarm history as well as a history of measurements.

2. Glucose Monitor

[0044] FIG. 1A is a block diagram of a characteristic monitoring system 100 as may be used in an embodiment of the present invention. The characteristic monitoring system 100 generally includes a sensor set 102 that employs a sensor that produces a signal that corresponds to a measured characteristic of the user, such as a blood glucose level. The sensor set 102 communicates these signals to a characteristic monitor 104 that is designed to interpret these signals to produce a characteristic reading or value for the user, i.e. a measurement of the characteristic. The sensor signals enter the monitor 104 through a sensor input 106 and through the sensor input 106 the signals are conveyed to a processor 108. The processor 108 determines and manipulates the sensor readings within the monitor 104. In addition, but not limited to, the characteristic monitor 104 provides additional functions that will aid in the treatment regime to which the characteristic reading applies. For example, but not limited to, the monitor may track meals, exercise and other activities which affect the treatment of diabetes. These additional functions can be combined with or independent from the characteristic readings determined by the monitor 104. Monitors can for example be coupled to an infusion pump that can further provide a medication to a user. Optionally the monitor is designed to be inconspicuous, for example a monitor design that resembles a wristwatch.

[0045] Other components of the monitor 104 support the processor 108 in performing functions. A memory 110 is used to store data and instructions used by the processor 108. A data entry device 112 such as a keypad is used to receive direct input from the user and a display 114 such as a liquid crystal display (LCD), or the like, is used to relate information to the user. In addition, the monitor 104 includes a data port 116, such as a digital input/output (I/O) port.

[0046] The data port 116 can be used for the monitor 104 to communicate with a computer 118. To facilitate communication, the monitor 104 may interface with the computer 118 through a communication station 120 that can serve as a docking station for the monitor 104, for example. The data port 116 within the monitor 104 can be directly connected to the computer 118. Through the communication link, data may be downloaded from the monitor 104, such as stored characteristic readings, settings, programs and other information related to the monitor's function. Thus, advanced analysis can be performed on the computer 118, freeing memory 110 within the monitor 104. Data such as characteristic readings, settings and programs can also be downloaded to the monitor 104. In this way, the monitor 104 can be conveniently reprogrammed without requiring tedious manual entry by the user.

[0047] FIG. 1B is a block diagram of a telemetered characteristic monitoring system. In this system 200, the sensor input 106 of the monitor 104 is a wireless receiver, such as a radio frequency (RF) receiver. The sensor set 102 provides a signal via wired link to a telemetered monitor transmitter 202, where the signal is interpreted and converted to an RF signal. The wireless receiver sensor input 106 of the monitor 104 converts the signal to data understandable to the monitor processor. With some advantages, the telemetered characteristic monitoring system can perform any or all the functions of the characteristic monitoring system of FIG. 1A.

[0048] A characteristic monitoring system 100, which may be used is the present invention, includes a sensor set 102 and characteristic monitor device 104. The sensor set 102 generally utilizes an electrode-type sensor. However, in alternative embodiments, the system can use other types of sensors, such as electrically based sensors, chemically based sensors, optically based sensors, or the like. The sensors can be of a type that is used on the external surface of the skin or placed below the skin layer of the user. Preferred surface mounted sensors utilize interstitial fluid harvested from underneath the skin. In this context for example, real-time interstitial sensor glucose values can be correlated with blood glucose values. The sensor set 102 is connected to the monitor device 104 and provides a signal based upon the monitored characteristic (e.g., blood glucose). The characteristic monitor device 104 utilizes the received signal to determine the characteristic reading or value (e.g., a blood glucose level). The sensor may be placed in other parts of the body, such as, but not limited to, subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue

[0049] The telemetered characteristic monitor transmitter 202 generally includes the capability to transmit data. In alternative arrangements the telemetered characteristic monitor transmitter 202 can include a receiver, or the like, to facilitate two-way communication between the sensor set 102 and the characteristic monitor 104. In alternative arrangements, the characteristic monitor 104 can be replaced with a data receiver, storage and/or transmitting device for later processing of the transmitted data or programming of the telemetered characteristic monitor transmitter 202. In addition, a relay or repeater (not shown) can be used with a telemetered characteristic monitor transmitter 202 and a characteristic monitor 104 to increase the distance that the telemetered characteristic monitor transmitter 202 can be used with the characteristic monitor 104.

[0050] For example, a relay can be used to provide information to parents of children using the telemetered charac-

Abbott Ex. 1002 - 697/1438

teristic monitor transmitter 202 and the sensor set 102 from a distance. The information can be used when children are in another room during sleep or doing activities in a location remote from the parents. In a related arrangement, a relay can be used to provide information to medical professional and/or related caregiver regarding the physiological status of a user (e.g. a hypoglycemic event) in a situation where that event has not been acknowledged and/or addressed by the user within a specific time parameter (e.g. 15-45 minutes). In one illustrative embodiment, a physiological characteristic monitoring system includes a relay that automatically dials a predetermined telephone number as part of a notification scheme for an event that has not been acknowledged and/or addressed by the user. The relay can include the capability to sound an alarm. In addition, the relay can be capable of providing telemetered characteristic monitor transmitter 202 data from the sensor set 102, as well as other data, to a remotely located individual via a modem connected to the relay for display on a monitor, pager or the like. The data can also be downloaded through the communication station 120 to a remotely located computer 118 such as a PC, laptop, or the like, over communication lines, by modem, wired or wireless connection. Wireless communication can include for example the reception of emitted radiation signals as occurs with the transmission of signals via RF telemetry, infrared transmissions, optical transmission, sonic and ultrasonic transmissions and the like. As disclosed herein, some arrangements can omit the communication station 120 and use a direct modem or wireless connection to the computer 118. In further arrangements, the telemetered characteristic monitor transmitter 202 transmits to an RF programmer, which acts as a relay, or shuttle, for data transmission between the sensor set 102 and a PC, laptop, communication station 118, a data processor, or the like. In further alternatives, the telemetered characteristic monitor transmitter 202 can transmit an alarm to a remotely located device, such as a communication station 118, modem or the like to summon help.

[0051] In addition, further arrangements can include the capability for simultaneous monitoring of multiple sensors and/or include a sensor for multiple measurements.

[0052] A purpose of the characteristic monitoring system 100 is to provide for better treatment and control in an outpatient or a home use environment. For example, the monitoring systems 100, 200 can provide indications of glucose levels, a hypoglycemia/hyperglycemia alarm and outpatient diagnostics. Embodiments of the invention can be used a part of an evaluation tool under a physician's supervision.

[0053] The characteristic monitor device 104 receives characteristic information, such as glucose data or the like, from the sensor set 102 and displays and/or logs the received glucose readings. Logged data can be downloaded from the characteristic monitor 104 to a PC, laptop, or the like, for detailed data analysis. In further arrangements the characteristic monitoring system 100, 200 can be used in a hospital environment, or the like. Still further arrangements can include one or more buttons to record data and events for later analysis, correlation, or the like. Further buttons can include a sensor on/offbutton to conserve power and to assist in initializing the sensor set 102. The characteristic monitoring system 200 can also be employed with other medical devices to combine other patient data through a common data network system.

[0054] Further arrangements of the sensor set 102 can monitor the temperature of the sensor set 102, which can then be used to improve the calibration of the sensor. For example, for a glucose sensor, the enzyme reaction activity may have a known temperature coefficient. The relationship between temperature and enzyme activity can be used to adjust the sensor values to more accurately reflect the actual characteristic levels. In addition to temperature measurements, the oxygen saturation level can be determined by measuring signals from the various electrodes of the sensor set 102. Once obtained, the oxygen saturation level can be used in calibration of the sensor set 102 due to changes in the oxygen saturation levels and its effects on the chemical reactions in the sensor set 102. For example, as the oxygen level goes lower, the sensor sensitivity can be lowered. In alternative arrangements temperature measurements can be used in conjunction with other readings to determine the required sensor calibration.

[0055] In preferred arrangements the sensor set 102 facilitates accurate placement of a flexible thin film electrochemical sensor of the type used for monitoring specific blood parameters representative of a user's condition. Preferably, the sensor monitors glucose levels in the body, and can be used in conjunction with automated or semi-automated medication infusion devices of the external or implantable type as described in U.S. Pat. Nos. 4,562,751; 4,678,408; 4,685,903 or 4,573,994 to control delivery of insulin to a diabetic patient. In addition, the monitor characteristic monitor 104 may typically be integrated into such a medication infusion device so that medication delivery and monitoring are conveniently provided within a single device.

[0056] The flexible electrochemical sensor may be constructed in accordance with thin film mask techniques to include elongated thin film conductors embedded or encased between layers of a selected insulative material, such as polyimide film or sheet, and membranes. The sensor electrodes at a tip end of the sensing portion are exposed through one of the insulative layers for direct contact with patient blood or other body fluids, when the sensing portion (or active portion) of the sensor is subcutaneously placed at an insertion site. The sensing portion is joined to a connection portion that terminates in conductive contact pads, or the like, which are also exposed through one of the insulative layers. In alternative arrangements, other types of implantable sensors, such as chemical based, optical based, or the like, can be used. Further description of flexible thin film sensors of this general type are be found in U.S. Patent. No. 5,391,250, entitled "METHOD OF FABRICATING THIN FILM SENSORS". The connection portion can be conveniently connected

Abbott Ex. 1002 - 698/1438

electrically to the monitor 104 or a telemetered characteristic monitor transmitter 202 by a connector block (or the like) as shown and described in U.S. Pat. No. 5,482,473, entitled "FLEX CIRCUIT CONNECTOR". Thus the subcutaneous sensor sets 102 may be configured or formed to work with either a wired or a wireless characteristic monitoring system 100, 200.

A. Glucose Monitor Status Checks

[0057] The physiological characteristic monitoring system 100, 200 can perform a status check to confirm that the monitor 104 is operating properly and calibrated to take glucose measurements. The processor 108 determines the status of the monitor for receiving the signal from the sensor set 102. The monitor status is based upon at least one of a plurality of conditions including the sensor activity condition, the sensor calibration condition and the telemetry condition. The display 114 shows different observable indicators depending upon the status of the monitor 104.

[0058] FIG. 2A is a flowchart 220 of an exemplary status check algorithm for a characteristic monitor as can be used in an embodiment of the present invention. Beginning at the default time screen 222 showing the current time, a user can press a key (e.g. the UP key) to initiate the status check. The processor 108 first performs a sensor activity condition check 224 to determine if there is an expired or dead sensor. If the sensor is determined to be dead, the display 114 shows a sensor "REPLACE" prompt 226 with the current time, which indicates that the sensor has expired and replacement of the sensor set 102 is required immediately. If the sensor is determined to be active by the sensor activity check 224, the processor 108 performs a telemetry condition check 228 to determine if the monitor 104 is synchronized with the telemetered monitor transmitter 202 coupled to the sensor set 102. If the monitor 104 and the transmitter 202 are not synchronized, a "NO SYNC" indicator 230 is shown on the display 114. If the devices are synchronized, a calibration condition check 232 is performed by the processor 108 to determine first whether a calibration of the sensor set 102 is pending (i.e., whether the monitor 104 is currently processing a previously entered blood glucose reference value, for example from a meter, to calibrate the sensor set 102). If a calibration is pending, the display 114 shows a "PENDING" indicator 234. If a calibration is not pending, the processor 108 checks whether the sensor calibration is currently valid 236. If the calibration is not valid, the display shows an "ENTER BG" indicator 242 with the current time, which indicates that a blood glucose reference value (e.g., from a blood glucose meter) is required by the monitor 104 to calibrate the sensor set 102. If the calibration is valid, the processor 108 then checks that the sensor expiration time is after the next calibration due time 238, and the display 114 shows a "BG DUE" indicator 240 with the time that the next calibration is due. If the sensor expiration time is before the next calibration due time, the display 114 shows the "REPLACE" prompt 226 with the time that the sensor will expire and replacement of the sensor set 102 can be required.

B. Glucose Monitor Calibration Reference Value Entry

[0059] FIG. 2B is an exemplary flowchart 250 of screens for entering a reference value to calibrate a characteristic monitoring system 100, 200. While a calibration is pending or valid as a result of entry of a calibration reference value (e.g., a blood glucose value measured by a blood glucose meter), the display 114 shows the calibration reference value and time of the most recent valid entry in the meter screen 252. In particular arrangements, the time of the most recent valid entry is unaffected by a change in a system time setting of the monitor 104. In other arrangements, the time of the most recent valid entry may be shifted in accordance with a change in a system time setting of the monitor 104. From the meter screen 252, pressing a button (e.g., the ACT/activate button) allows entry of a new calibration reference value in the entry screen 254. After entry of the new value (e.g., using the up and down arrow buttons and then pressing the ACT/activate button), the display 114 shows a confirmation screen 256, which requires confirmation of the value entered (e.g., by pressing the ACT/activate button) to release the display to the default time screen 258.

3. Dynamic Glucose Monitoring Functions

[0060] Embodiments of the present invention may be used with different types of continuous glucose monitors that identify trends in blood glucose dynamics to facilitate enhanced treatment of diabetes. In general, a first illustrative monitor can be used to anticipate a glucose "crash" (or other hypoglycemic incident) before the onset of debilitating symptoms. Another illustrative monitor can be used to detect an inadequate nocturnal basal rate and alert the patient in order to avoid an impaired fasting glucose incident. Another illustrative monitor can anticipate hyperglycemic (or hypoglycemic) incidents by detecting trends toward those levels and help the patient avoid such incidents. Another illustrative monitor can assist a patient in maximizing athletic performance in endurance type activities (e.g., a marathon race) by detecting trends toward hypoglycemic levels.

[0061] The disclosed arrangements monitor the dynamics of a physiological characteristic such as blood glucose levels. These arrangements utilize this dynamic monitoring to provide functionality including the anticipation of glucose crash and alerting the patient, the detection of inadequate nocturnal basal rate, the anticipation of hyperglycemic (or

Abbott Ex. 1002 - 699/1438

hypoglycemic) incidents and maximizing athletic performance. All of these features can be implemented in software operating in the monitor's microprocessor and/or designed into an application specific integrated circuit (ASIC) or other specialized circuitry. Also, dynamic glucose monitoring functions use periodic measurements of a glucose level.

A. Monitor for Anticipating a Glucose Crash

[0062] In one arrangement a monitor anticipates a glucose crash by monitoring trends in glucose levels. For example, the monitor can alert the patient when glucose levels are rapidly decreasing. By monitoring such trends or a rate information of measured glucose levels, the monitor can provide a much better warning system to alert the user with enough time to stabilize and reverse a dangerous physiological condition.

[0063] In some arrangements, the monitor measures glucose more frequently than typical glucose monitoring devices. For example, one arrangement measures approximately every minute, whereas an other monitors measure at a lower rate (e.g., but not limited to, once per 5 minutes). Frequent measurements are taken because of the short time intervals which are evaluated. Alternative arrangements may utilize more frequent measurements, such as, but not limited to, 10 seconds, 1 second, or the like.

[0064] In an illustrative arrangement, the monitor periodically measures glucose, analyzes the present trend, determines whether a glucose crash incident is probable and appropriately alerts the patient. At some frequent interval (e.g., but not limited to, once per minute), the device measures the glucose level, applies a smoothing filter to the result, and records the filtered value. The smoothing filter may take a weighted sum of past sensor values (so called finite impulse response- FIR -filter), a weighted sum of past sensor values and past filtered values (so called infinite impulse response - IIR -filters), may use simple clipping algorithms (e.g. limit the percent change in filtered output), or employ models to predict the output (e.g. Weiner and Kalman filter designs). For example, if the most recent (filtered) value is in the "qualifying range", the monitor can calculate the slope of a line fit to the most recent values (most likely, but not limited to, using a Saritzky gulag filter) and determine if the slope is steeper than a selected threshold rate (e.g., but not limited to, 3% or declining at more than 30 mg/dL in ten minutes). If the slope equals or exceeds the threshold rate, a glucose crash incident is likely and the monitor alerts the patient accordingly.

[0065] Those skilled in the art will understand that in some arrangements the qualifying range can be a closed range (e.g., but not limited to, between 100 and 150 mg/dL) and in other embodiments the qualifying range can be an open range (e.g., but not limited to, greater than 100 mg/dL). By first identifying whether a most recent value is within the qualifying range, further calculation of the dynamic behavior of the physiologic characteristic can be avoided. Thus, the determination of a glucose crash can be unconcerned with rate magnitudes occurring when the current characteristic value is outside of the range (of course, other alarms, which merely monitor the current characteristic value, can be triggered when the reading is too high or too low). However, in alternate embodiments, the slope can be calculated and compared to the threshold rate with every new value. In further arrangements, multiple qualifying ranges and threshold rates can be applied to evaluate the glucose dynamics and determine triggering a glucose crash warning.

[0066] In one preferred arrangement, the monitor determines that a glucose crash is likely if three criteria are met. The criteria are as follows. The first, dG/dT (the rate of glucose level change) is negative, can be considered for example in situations where blood glucose levels are dropping (e.g., but not limited to, when a value pertaining to the rate of glucose change is negative). The second, |dG/dT| exceeds a threshold rate, can be considered in contexts, for example where a specified blood glucose change rate is exceeded for a specified sustained period (e.g., but not limited to, greater than 3% per minute for 10 minutes). The third, G, the glucose level, can be considered for example, when this value begins dropping starting within a specified range, (e.g., but not limited to, 100 - 150 mg/dL).

[0067] In some arrangements, these criteria can be parameterized to allow the user to customize the values. The qualifying range, threshold rate and period can be general values, applied to all users, or determined from factors specific to the individual user. For example, the monitor can include a feature to adjust the qualifying glucose level range, the maximum rate of glucose change, or in some embodiments, the sustained time period length. In addition, in some arrangements, any or all of the dynamic glucose monitoring functions can enabled or disabled, selectively or together.

[0068] The following control program pseudo code provides an example of a programming routine performed by the processor of the monitor.

Abbott Ex. 1002 - 700/1438

```
REPEAT every minute)
   {
      Measure glucose level   g_i
      Filter g_i and store the filtered value g'_i
      IF(g'_i is in range 100 - 150 mg/dL)
         THEN
            Fit a line to the most recent 10 filtered (or,
alternatively, unfiltered) values
            IF (dG/dT for that line < ( - 3% per minute )
               THEN
                  Alert the patient and record in history
            ENDIF
      ENDIF
   }
END REPEAT
```

[0069] FIG. 3A is a flowchart of a method for anticipating a glucose crash 300. At block 302, a characteristic level is repeatedly measured to obtain a group of characteristic level values. Following this at block 304, a smoothing filter can be applied to the group of characteristic level values to produce a filtered measurement value. The filtered measurement value is recorded at block 306. At block 308 it is determined if the recorded value falls within a qualifying range (e.g., but not limited to, between 100 to 150 mg/dL). If not, the process returns to block 302. If the recorded measurement is within the range, a slope of a line fit to a recent series of recorded filtered values is calculated at block 310. The calculated slope is compared to a threshold rate (e.g., but not limited to, -3% per minute) at block 312. If the calculated slope is not steeper than the threshold rate the process returns to block 302. If the slope exceeds the threshold rate, an anticipated glucose crash is indicated at block 314. Alternative arrangements may utilize similar logic for when the glucose level is already outside of the range and continues to drop. In addition in an alternative preferred arrangement, one can utilize a raw data measurement (e.g. a group of characteristic level values) to determine a derivative as an alternative to using a filtered measurement value to determine a derivative.

B. Monitor for Detecting an Inadequate Nocturnal Basal Rate

[0070] In another arrangement, the characteristic monitor can be used to detect an inadequate nocturnal basal rate. This arrangement generally applies to diabetic patients using an insulin infusion device that continually administers insulin at a patient controlled basal rate. The monitor detects an inadequate basal rate (i.e., but not limited to, "low basal rate" or a "high basal rate"), by monitoring trends in glucose levels. The monitor then alerts a patient in the early morning, when glucose levels are high and relatively steady, low and relatively stable or changing rapidly. This gives the patient time to adjust the basal rate of the infusion device upward or downward to and avoid an impaired fasting glucose incident.

[0071] The monitor operates to track the characteristic level rate. For example, every 5 minutes the monitor measures and records the glucose level. Once a day (e.g., but not limited to, 3 hours before to the anticipated wakeup time), the monitor calculates the average blood glucose and the rate of blood glucose change for the previous hour. The monitor can then determine a prediction of the "morning glucose" level at wake up based upon the calculated average blood glucose and the rate of blood glucose change. In one arrangement the "morning glucose" is predicted assuming that the rate of change remains constant, however in other arrangements nonlinear characteristic curves and functions can be applied in making the prediction. If the anticipated "morning glucose" level is greater than a high threshold value (e.g., but not limited to, 126 mg/dL), or less than a low threshold value (e.g., but not limited to, 60 mg/dL), an alarm is sounded. This will allow time for the infusion device basal rate to be adjusted appropriately. In alternative arrangements, different

Abbott Ex. 1002 - 701/1438

times before anticipated wakeup, different high threshold values, or different low threshold values, may be used.

[0072] In some arrangements, the triggering criteria can also be parameterized to allow the user to customize the values. In some arrangements, the user is allowed to set the values for the controlling parameters. For example, the user can set the qualifying low and high glucose levels as well as the anticipated waking time. For each of the settings a default value can be used in the absence of a user setting. For example, a default low glucose level of 60 mg/dL, a default high glucose level of 126 mg/dL and an anticipated waking time of 7:00 AM can be used. In addition, the entire function can be enabled and disabled.

[0073] FIG. 3B is a flowchart of a method for detecting an inadequate nocturnal basal rate 320. At block 322, the method begins by measuring a characteristic level to obtain a measurement value. The value is recorded at block 324. Measuring and recording is repeated periodically to obtain a series of values at block 326. At block 328, the average of the series of values is calculated. At block 330, a slope of a line fit to the series of values is calculated. The calculated slope and average of the series of values are then used to determine a predictive curve at block 332. At block 334, the curve is extrapolated to predict a glucose level at wakeup. Those skilled in the art understand that such calculations are not limited to slope y = mx + b, and that, in this context, one can use alternative filtered arrangements as are known in the art. The extrapolation is performed some time before wakeup (e.g., but not limited to, 3 hours prior) to provide enough time to correct any impending negative condition. The predicted glucose level is compared to an acceptable range at block 336. If the predicted glucose value falls within the range, the process ends. If the predicted glucose value falls outside the range, a morning glucose incident is reported at block 338.

C. Monitor for Anticipating Hyperglycemic Incidents

[0074] In another arrangement, a glucose monitor anticipates a hyperglycemic (or hypoglycemic) incident by monitoring trends in glucose levels. The monitor alerts the patient when a "relatively steady increase" (or decrease) in glucose levels occurs. The monitor periodically measures glucose, analyzes the present trend, determines whether a hyperglycemic (or hypoglycemic) incident is probable and appropriately alerts the patient.

[0075] In one arrangement, the device measures glucose values at a specific time interval (e.g. once every minute), and then, e.g. at 5 minute intervals, applies a smoothing filter to this group of values and records the filtered value. If the most recent (filtered) value exceeds a threshold value (e.g., but not limited to, 180 mg/dL), the monitor calculates the slope of a line fit to a recent series of recorded values (for example, but not limited to, six values). If the slope is greater than a threshold rate (e.g., but not limited to, 3% per minute), a hyperglycemic incident is likely and the monitor alerts the patient. For hypoglycemic incidents, values and thresholds corresponding to low glucose levels would be used.

[0076] The threshold value is applied in a similar manner to the "qualifying range" applied in determining a glucose crash previously discussed. The threshold value effectively operates as an open range (e.g., but not limited to, greater than 180 mg/dL). In other arrangements, the threshold value can be a closed range. Therefore, determining a hyperglycemic incident can be unconcerned with values below the threshold value (as determining a hypoglycemic incident can be unconcerned with values above a threshold value). In one arrangement, a slope calculation can be avoided if the current reading is outside the range. However, in alternate arrangements, the slope can be calculated and compared to the threshold rate with every new reading. In further arrangements, multiple qualifying ranges and threshold rates can be applied to evaluate the glucose dynamics and determine triggering a hyperglycemic (or hypoglycemic) incident warning.

[0077] Here again, in some arrangements the criteria can be parameterized to allow the user to customize the controlling values for anticipating hyperglycemic (or hypoglycemic) incidents. For example, some arrangements can allow the user to set the glucose threshold level and/or the threshold rate. Some arrangements can also use default parameters if no user settings are provided (e.g., but not limited to, a threshold level of 180 mg/dL and a maximal rate of 3% per minute). Some arrangements can also enable and disable this function.

[0078] FIG. 3C is a flowchart of a method for anticipating a hyperglycemic incident 350. The method begins at block 352 by repeatedly measuring a characteristic level to obtain a group of values. At block 354, a smoothing filter is applied to the group of values to obtain a filtered measurement value. The filtered value is recorded at block 356. The recorded value is compared to a threshold value at block 358. If the recorded value does not exceed the threshold value (e.g., but not limited to, 180 mg/dL), the process returns to block 352. If the recorded value does exceed the threshold value, a slope of a line fit to a recent series of values is calculated at block 354. The calculated slope is compared to a threshold rate (e.g., but not limited to, +3% per minute) at block 362. If the slope is not steeper than the threshold rate, the process returns to block 352. If the slope is steeper than the threshold rate, an anticipated hyperglycemic incident is reported at block 364. For hypoglycemic incidents, corresponding steps for low glucose levels would be used. As noted previously, estimates of dG/dt may be calculated by a variety of methods known in the art including the slope (and that such calculations are not limited to, for example, determinations based on y = mx + b).

Abbott Ex. 1002 - 702/1438

D. Monitor for Maximizing Athletic Performance

[0079] Dynamic monitoring can also be used to provide feedback based upon the engaged activity of the user. For example, the monitor can be used to maximize performance during an endurance type activity (e.g., but not limited to, a marathon race). The endurance athlete strives to burn glucose rather than fat and accordingly needs to anticipate low glucose levels and ingest carbohydrates early enough to avoid low glucose levels.

[0080] In such arrangements, the monitor anticipates low glucose levels and alerts the athlete to ingest carbohydrates. It is important to note that this arrangement is not strictly anticipating hypoglycemic incidents. Instead it is anticipating low glucose levels where it would otherwise be too late for the athlete to compensate by ingesting carbohydrates and still perform effectively and/or at full capacity.

[0081] In one arrangement, once a minute, the device measures a glucose level, applies a smoothing filter and records the filtered value at 5-minute intervals. If the most recent recorded (i.e., filtered) value is in a qualifying range (e.g., but not limited to, 60 - 140 mg/dL), the processor calculates the slope of a line fit to the most recent six filtered values and determines if the slope is steeper than -1 % (i.e., but not limited to, 30 mg/dL in 30 minutes). If the rate of decline exceeds this threshold, a low glucose level is likely and the monitor alerts the athlete accordingly. Thus, for example, but not limited to, to trigger an alarm, the glucose level rate, dG/dT, is negative with a magnitude greater than 1% per minute for 30 minutes beginning in range 60 -140 mg/dL.

[0082] Similar to the glucose crash monitor, in arrangements for maximizing athletic performance, the qualifying range can be a closed range (e.g., but not limited to, between 60 and 140 mg/dL) or an open range (e.g., but not limited to, less than 140 mg/dL). By first identifying whether a most recent value is within the qualifying range, further calculation of the dynamic behavior of the physiologic characteristic is avoided. However, other alarms which merely monitor the current characteristic value can be triggered when the reading is too high or too low. In alternate arrangements, the slope can be calculated and compared to the threshold rate with every new value. In further arrangements, multiple qualifying ranges and threshold rates can be applied to evaluate the glucose dynamics and determine triggering a low glucose warning.

[0083] Here too, these criteria can be parameterized to allow the user to customize the values. Typically, the monitor will allow a user to set the qualifying glucose range and/or enable and disable the function. A default qualifying range (e.g., but not limited to, 60-140 mg/dL) can be used.

[0084] FIG. 3D is a flowchart of a method for maximizing athletic performance 370. The process begins at block 372, where a characteristic level is repeatedly measured to obtain a group of characteristic level values. Following this at block 374, a smoothing filter can be applied to the group of characteristic level values to produce a filtered measurement value. The filtered measurement value is recorded at block 376. At block 378 it is determined if the recorded value falls within a qualifying range (e.g., but not limited to, between 60 to 140 mg/dL). If not, the process returns to block 372. If the recorded measurement is within the range, a slope of a line fitted to a recent series of recorded filtered values is calculated at block 380. The calculated slope is compared to a threshold rate (e.g., but not limited to, -1% per minute) at block 382. If the calculated slope is not steeper than the threshold rate the process returns to block 372. If the slope exceeds the threshold rate, an anticipated low glucose level is indicated at block 384. As noted previously, estimates of dG/dt may be calculated by slope as well as other methods known in the art.

[0085] Glucose Alarm Functions

[0086] The described arrangements can utilize various advanced alarm functions. For example, in some arrangements multiple alarms can be independently set by the user. In further arrangements, user input can direct review of the alarm history and also alter the alarm display to suit the user's preference. Alarm settings can also include an alarm snooze or "blackout" period as well as an alarm repeat delay.

[0087] A. Multiple Glucose Alarm Functions

[0088] The described arrangements can employ multiple alarms that can be independently set by the user. For example, a continuous glucose monitoring system can have multiple alarms for different glucose values. The system can allow a user to set threshold glucose values that define a "narrow" glucose range (as compared to the ordinary alarm limits). If the user's glucose level passes outside the "narrow" range, an alarm can sound. This alarm alerts the user to monitor his glucose levels more closely. The system can sound a second alarm (preferably having a sound distinguishable from the first "narrow" range alarm) in the event the user's glucose level reaches a more dangerous condition requiring immediate action. Alarm indications may be audible, tactile, vibratory, visual, combinations of alarm indications, or the like. In the case of visual alarm indications, but not limited to, green lights can be displayed while the user's glucose level remains within the defined "narrow" range; yellow for the first alarm level; and red for the second alarm level. The visual alarm indications may flash and/or also be combined with other alarm indications.

[0089] Although the above example describes a two-layer alarm system, one can incorporate multiple alarm layers. In addition, the alarms can be set in ranges, or separate high and low glucose level alarms can be set Distinctive sounds can be used for each alarm. For example, each successive high glucose level alarm can have, but is not limited to having, a higher pitch. Successive low glucose level alarms can each have, but are not limited to having, lowering pitches.

Abbott Ex. 1002 - 703/1438

Alternately, intermittent or wavering volumes that also increase in pits according to the severity of the condition can be used. In still other arrangements, the user can select or program alarm tones and other sounds and assign them to the various alarms. Also, in some arrangements, these distinguishable alarms can also be set at different volume levels. In addition, as discussed above, the alarms are not limited to audible signals; some arrangements can also utilize visual alarms, such as flashing lights or displays, or tactile alarms, such as vibrating indicators.

[0090] In still further arrangements, threshold values and associated alarms can be set according to a schedule. For example, but not limited to, particular alarms can be set to be active only during selected portions of the day.

[0091] FIG. 4A illustrates a multiple alarm function. A plot of the monitored characteristic value 400 (e.g., blood glucose) changing over time is shown. A typical wide alarm range 402 is defined by an upper threshold value 404 and a lower threshold value 406. If the monitored characteristic value 400 should exceed the defined range and cross either threshold, an alarm is initiated to indicate to the user to check his blood glucose. In one arrangement, a distinctive alarm can be associated with the alarm range 402. Thus, the same alarm is produced whether the range 402 is exceeded by passing the upper threshold value 404 or the lower threshold value 406. In other embodiments, distinctive alarms can be assigned to each threshold value 404, 406. In further arrangements, other alarm ranges can also be set. For example, a second narrower range 408 can be set with a lower upper threshold value 410 than that of the wider range 402; and a higher lower threshold value 412 than that of the wider range 402. As with the wider range 402, an alarm is initiated if the narrower range is exceeded by the monitored characteristic value 400. Here also, alarms can be the same or different for each threshold value 410,412.

[0092] The ability to set different ranges and associated alarms allows the monitor to immediately convey some information about the condition of the user even before checking the actual readings. Particularly, using the narrower range 408 and associated alarms allows the user to know of a negative trend that does not require the same urgency as an alarm triggered by the wider range 402. In effect, the user is able to set multiple alarms, each indicating a different level of urgency and/or different conditions. In some arrangements, threshold values for alarms can also be set independent from ranges.

[0093] In still further arrangements, alarms or indicators can be set according to the direction in which a threshold value is crossed by the monitored characteristic value 400. For example, as the monitored characteristic value 400 crosses a lower threshold value 412 from the narrow range (e.g., but not limited to, at point 414), one type of alarm can be provided. However, when the monitored characteristic value 400 crosses a lower threshold value 412 from the wider range 402 (e.g., but not limited to, at point 416), another type of alarm can be provided. The difference in the alarms is appropriate because only the former case indicates a worsening of the user's condition. In the latter case, the transition actually indicates an improvement in the user's condition. Thus, in some arrangements, alarms will only be given when crossing a threshold indicates a worsening of the user's condition. Alternatively, an indicator will also be given when a threshold has been crossed in an improving direction. In these cases, either the same indicator (sound, light, display or other) or different indicators can be used. In a similar manner, reminders can be set to indicate to a user various conditions (not necessarily negative) that will aid in convenient therapy management.

[0094] The multiple alarm function of the invention can be readily incorporated with any of the individual alarm functions and settings such as discussed hereafter.

[0095] B. Individual Alarm Functions and Settings

[0096] In further arrangements, a physiological characteristic monitor can incorporate various individual alarm functions and settings to enhance convenient operation by a user. As typical of the monitoring system 100, 200 shown in FIGS. 1A and 1B, the monitor includes a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user, and a processor for operating an alarm based on user input from an input device. The alarm indicates an alarm condition where the sensed physiological characteristic value exceeds a set range. In preferred arrangements, the physiological characteristic value is a measurement related to a blood glucose level in the user and the alarm indicates a glycemic condition. Operating the alarm comprises setting parameters of the alarm based on the user input from the input device. For example, the blood glucose level or value that will activate a hypoglycemia or hyperglycemia alarm may be set by the user utilizing the input device. The hypoglycemia alarm may be set to trigger if the user's blood glucose level is less than or equal to 60, 65, or 70 mg/dl (or any other desired level), and the hyperglycemia alarm may be set to trigger if the user's blood glucose level is greater than or equal to 150,160, or 175 mg/dl (or any other desired level).

[0097] FIGS. 4B and 4C illustrate the hypoglycemia and hyperglycemia alarm screens, respectively. In each case, the display shows the measurement of the concentration of blood glucose indicating the glycemic condition, preferably until the alarm is acknowledged by the user. Furthermore, the display shows a time of the alarm. In particular arrangements, the alarm indicates the glycemic condition only if the monitor is calibrated, although in alternative arrangements, the alarm may indicate the glycemic condition regardless if the monitor is calibrated.

[0098] In the illustrated arrangement, the display shows a LOW indicator when the measurement of the concentration of blood glucose is below a specified level for a hypoglycemia alarm, such as 60 mg/dl. Similarly, the display shows a HIGH indicator when the measurement of the concentration of blood glucose is above a specified level for a hyperglycemia

Abbott Ex. 1002 - 704/1438

alarm, such as 150 mg/dl. In some arrangements, alarm indications may be other visual indicators (e.g., lights, flashing displays, or the like), audible, tactile, and/or vibratory. For example, a hypoglycemia alarm can be indicated by at least two audible descending tones, and a hyperglycemia alarm can be indicated by at least two audible ascending tones.

[0099] In further arrangements of the invention, an alarm repeat delay period is employed. Subsequent alarms are prevented for the alarm repeat delay period after the measurement of the concentration of blood glucose first indicates a glycemic condition. For example, the alarm repeat delay period can be less than 20 minutes (e.g. approximately 17.5 minutes) for the glycemic condition comprising a hypoglycemic condition. In another example, the alarm repeat delay period is less than 1 hour (e.g. approximately 52.5 minutes) for the glycemic condition comprising a hyperglycemic condition. In alternative arrangements, the alarm repeat delay period may be other time periods, such as 10 minutes, 15 minutes, 30 minutes, 1½ hours, 2 hours, or the like.

[0100] In particular arrangements, the level of the measurement of the concentration of blood glucose from the sensor that will trigger a low limit (or hypoglycemia) alarm or a high limit (or hyperglycemia) alarm can be set based upon input from the user. Particularly, these two alarm levels can be separately set. FIGS. 4D and 4E show exemplary hypoglycemia and hyperglycemia alarm setting algorithms, respectively. FIG. 4D shows an exemplary hypoglycemia alarm setting flowchart 420. To begin setting the hypoglycemia alarm, from the hypoglycemia alarm setting screen 422, the ACT/activate button is pressed, and the hypoglycemia alarm activation screen 424 is entered. From this screen 424, the user can select setting the hypoglycemia alarm on, off or entering the alarm repeat setting function menu. If the user sets the hypoglycemia alarm off and presses the ACT/activate button, an alarm off confirmation screen 426 is presented. If the hypoglycemia alarm is set on and the ACT/activate button is pressed, the low limit entry screen 428 is presented. The low limit entry screen 428 allows the user to scroll through low limit alarm level settings using up and down arrow buttons to specify that the hypoglycemia alarm will trigger if the user's blood glucose level is less than or equal to 60, 65, or 70 mg/dl, or any other desired level. After setting the low limit alarm level, pressing the ACT/activate button again presents a hypoglycemia low limit alarm level confirmation screen 430 for confirming the specified hypoglycemic blood glucose level.

[0101] From the hypoglycemia alarm activation screen 424, if the alarm repeat setting function is selected, the alarm repeat display screen 432 is entered, which allows the user to set a period for delaying a repeated check of the hypoglycemia alarm condition. The current alarm repeat delay period is shown in the alarm repeat display screen 432. Pressing the ACT/activate button allows the user to enter the repeat time select screen 434. Alternatively, the alarm repeat display screen 432 may be omitted, and the repeat time select screen 434 is entered once the alarm repeat setting function is selected. In the repeat time select screen 434, the alarm repeat delay period blinks while being set by the user utilizing the input device. The user can scroll through a list of delay increments and select the desired alarm repeat delay period from the list of delay increments. The alarm repeat delay period has a default value of 20 minutes for the hypoglycemia (low limit) alarm level. For convenience, the scrolled list of delay increments can wrap around, beginning again when one end of the list is reached. For the low limit alarm level, the alarm repeat delay period can be selected from a group of values differing in 10 minute increments. For example, the alarm repeat delay period can be selected from 20, 30, 40, 50 and 60 minutes for the low limit alarm level. In alternative arrangements, the alarm repeat delay period may be selected from a group of values differing in other time increments, such as 5, 15, or 20 minutes, or further, maybe specified using up and down arrow buttons and then pressing the ACT/activate button. After selecting the alarm repeat delay period, pressing the ACT/activate button displays the alarm repeat delay confirmation screen 436 for confirming the period selection.

[0102] FIG. 4E shows an exemplary hyperglycemia alarm setting flowchart 440. From the hyperglycemia alarm setting screen 442, if the ACT/activate button is pressed, the hyperglycemia alarm activation screen 444 is entered. From this screen 444, the user can select setting the hyperglycemia alarm on, off or entering the alarm repeat setting function menu. If the user sets the hyperglycemia alarm off and presses the ACT/activate button, an alarm off confirmation screen 446 is presented. If the hyperglycemia alarm is set on and the ACT/activate button is pressed, the high limit entry screen 448 is presented. The high limit entry screen 448 allows the user to scroll through high limit alarm level settings using up and down arrow buttons to specify that the hyperglycemia alarm will trigger if the user's blood glucose level is greater than or equal to 150, 160, 170, 175, or 180 mg/dl, or any other desired level. After setting the high limit alarm level, pressing the ACT/activate button again presents a hyperglycemia high limit alarm level confirmation screen 450 for confirming the specified hyperglycemic blood glucose level.

[0103] The alarm repeat delay period for the hyperglycemia alarm is set in the same manner as that for the hypoglycemia alarm described above with respect to FIG. 4D; however, the alarm repeat delay period is typically set separately for a low limit alarm level and a high limit alarm level because the desired delays are different in each case. In general, the hyperglycemia alarm repeat delay period may be longer than that of the hypoglycemia alarm. From the hyperglycemia alarm activation screen 444, if the alarm repeat setting function is selected, the alarm repeat display screen 452 is entered, which allows the user to set a period for delaying a repeated check of the hyperglycemia alarm condition. The current alarm repeat delay period is shown in the alarm repeat display screen 452. Pressing the ACT/activate button allows the user to enter the repeat time select screen 454. Alternatively, the alarm repeat display screen 452 may be

Abbott Ex. 1002 - 705/1438

omitted, and the repeat time select screen 454 is entered once the alarm repeat setting function is selected. In the repeat time select screen 454, the hyperglycemia alarm repeat delay period is selected in a manner similar to the hypoglycemia alarm repeat delay period described above with respect to FIG. 4D, and then pressing the ACT/activate button displays the alarm repeat delay confirmation screen 456 for confirming the period selection. The alarm repeat delay period can have a default value of 1 hour for the hyperglycemia (high limit) alarm level. For the high limit alarm level, the alarm repeat delay period can be selected from a group of values differing in 30 minute increments. For example, the alarm repeat delay period can be selected from 1, 1½, 2, 2½ and 3 hours for the hyperglycemia alarm level. In alternative arrangements, the alarm repeat delay period may be selected from a group of values differing in other time increments, such as 15 or 20 minutes or 1 hour, or further, may be specified using up and down arrow buttons and then pressing the ACT/activate button.

[0104] As noted above, the multiple alarm function can be incorporated with various specific alarm features. For example, the alarm repeat delay function can be set differently for hypoglycemic alarms and hyperglycemic alarms of different severities. If a lower threshold hyperglycemic alarm is triggered, a relatively long repeat delay may be invoked. However, if a higher threshold hyperglycemic alarm is triggered, a shorter repeat delay may be used so that the user is warned more frequently because of the severity of his condition.

[0105] As disclosed herein, arrangements that incorporate a plurality specific alarm features can be used to optimize the utility of the alarm functions associated with hypoglycemia and/or hyperglycemia. In an alarm associated with hypoglycemic events for example, one can monitor a plurality of relevant physiological characteristic and can further utilize multiple alarm modes for alerting the user as to the status of the one or more characteristics. For example, an illustrative first alarm can be based upon a detection scheme for physiological glucose levels reaching a predetermined concentration (i.e. a dangerously low concentration). An illustrative second alarm can be based upon a detection scheme for a specific rate in which physiological glucose concentrations are changing in the user. In such situations, the arrangements disclosed herein can provide a first alarm based upon the rate of glucose concentration change in advance of a second alarm that is predicated upon physiological glucose concentrations reaching a predetermined threshold concentration. In such arrangements, the physiological characteristic threshold criteria for triggering an alarm can be modulated to for example, modulate the period of time between the first and second alarm functions according to the needs of the user.

[0106] In certain arrangements a user can employ a device that monitors both of the above-noted glucose detection schemes simultaneously. In such arrangements the device can employ a combination of the two alerts where the predetermined triggers for the various alarm functions are different. For example it is observed that when both the rate and specific concentrations of glucose are monitored, the rate change detector usually alerts before the fixed threshold change detector but has a higher false alarm rate. Consequently certain arrangements can employ a combination of the two alerts where the threshold for the physiological parameter that triggers each alert are different. In one such arrangement for example, the fixed concentration threshold parameter can be a higher or more stringent than the rate of concentration change threshold parameter. Such combinations provide devices that exhibit a good sensitivity while minimizing false alerts. In such contexts, one can further use information about both the rate of change and the current value to create a rule or mathematical formula which allows one to maximize the efficiency of detection while minimizing the occurrence of false alerts.

[0107] One such illustrative arrangement is a device, comprising a sensor input capable of receiving at least one signal from a sensor, the signal being based on a plurality of sensed physiological characteristic values of a user of the device; and a processor coupled to the sensor input for operating a plurality of alarms based on the received signal from the sensor; wherein the processor is capable of activating each of the plurality of alarms according to a different sensed physiological characteristic value of the plurality of sensed physiological characteristic values. Preferably, the plurality of sensed physiological characteristic values include the blood glucose concentrations in the user; and the rate of change of blood glucose concentrations in the user over a predetermined time period. In such devices, a first alarm can be activated when glucose concentrations exhibit a predetermined rate of change and a second alarm can be activated when glucose concentrations reach a predetermined value. Optionally the criteria for activating the first alarm are more stringent than the criteria for activating the second alarm. In this context, criteria for activating an alarm are considered to be more stringent when they are based on parameters associated with greater physiological stress (e.g. a higher blood glucose concentration in hyperglycemia and/or a lower blood glucose concentration in hypoglycemia).

[0108] In a preferred arrangement, the processor is capable of activating an alarm based on an evaluation of both the blood glucose concentrations in the user and the rate of change of blood glucose concentrations and the alarm is activated based on a mathematical comparison of the blood glucose concentrations in the user and the rate of change of blood glucose concentrations in the user. In an exemplary arrangement the alarm is activated when the relationship between the blood glucose concentrations in the user and the rate of change of blood glucose concentrations in the user meet a certain criteria. Optionally such criteria are determined by one or more mathematical formulae or algorithms that are based upon calculations that consider the specific the relationship between the blood glucose concentrations in the user and the rate of change of blood glucose concentrations in situations typically considered dangerous to the user.

[0109] FIG. 4F illustrates a hyperglycemia alarm snooze setting flowchart 460. The hyperglycemia alarm snooze

Abbott Ex. 1002 - 706/1438

function sets an alarm snooze period for temporarily disabling the alarm. The snooze function is set by the user utilizing the input device. In some arrangement, the alarm snooze period is only available for a hyperglycemia alarm, although the alarm snooze period may also be available for a hypoglycemia alarm. Generally, the snooze function is available only when the snooze period is running and the monitor is calibrated, although the snooze function may be available regardless if the monitor is calibrated. Further, the alarm snooze period is preferably deactivated upon any adjustment of the hyperglycemia alarm setting described above with respect to FIG. 4E. The snooze setting flowchart 460 begins at the snooze display screen 462, which can be entered by scrolling past the default time screen 464 and the BG due screen 466. From the snooze display screen 462, pressing the ACT/activate button will produce the snooze time select screen 468. In this screen 468, a user can select the desired period for the snooze function to operate, and the alarm snooze period blinks while being set by the user utilizing the input device. The alarm snooze period can be set by the user scrolling through a list of snooze period increments and selecting the desired alarm snooze period from the list of snooze period increments. For example, the list of snooze period increments can include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours, and for convenience, the list of snooze period increments wraps around as it is scrolled by the user. In alternative arrangements, the snooze period may be selected from a list of other time increments, such as 15 or 30 minutes, or further, may be specified using up and down arrow buttons and then pressing the ACT/activate button. When the snooze function is activated, the display shows time remaining of the alarm snooze period and an indicator (e.g. an "S") showing that the snooze function is active.

[0110] It may be instructive to note that, although both the alarm repeat delay function and the alarm snooze function prevent alarms for specified periods, they are not the same. One difference between the two functions can generally be identified by how each function is initiated. The alarm repeat delay is initiated (assuming the function is activated and set by the user) in response to a first alarm. In contrast, the alarm snooze function is activated by the user directly, either by directing the monitor to snooze immediately or scheduling a snooze at a specified time. For example, a user may schedule a snooze during sleeping hours that occur at some known time.

[0111] Just as with the alarm repeat delay, the multiple alarm function can also be incorporated with the alarm snooze function. For example, the snooze function can be set differently for hypoglycemic alarms and hyperglycemic alarms of different severities. The snooze function can function normally when a lower threshold hyperglycemic alarm is set (i.e. ignore the alarm). However, when a higher threshold hyperglycemic alarm is set, the snooze function may be overridden due to the severity of the user's condition.

[0112] FIG. 4G illustrates glycemia alarm history review. Operating the alarm history review can allow a user to review a historical list of the alarms indicating a glycemic condition occurrence. The alarm history review flowchart 470 shows the alarm history is entered by pressing the ACT/activate button from the alarms menu screen 472. If no alarm history exists, a screen 474 indicating "NONE" can be displayed. However, if at least one alarm event has occurred, the entries can be displayed in a historical list 476. In one arrangement, the display shows a single glycemic alarm in the historical list at a time. The display shows a physiological characteristic value (e.g. blood glucose value) and time of the glycemic condition occurrence indicated for each alarm in the historical list. The time of the glycemic condition occurrence can also include a date of the alarm. Further, the display can show at least a portion of the time of the glycemic condition occurrence in blinking text. The historical list typically includes a limited number of stored entries. For example, the historical list can comprise the 20 most recent alarms indicating a glycemic condition occurrence. In alternative arrangements, the historical list may include more or less alarms, such as the 10, 15, 30, or 50 most recent alarms.

[0113] As part of the display of the historical list, the display can show the blood glucose measurements only within a specified range. For example, the specified range can be the operational range of the sensor, such as from 40 to 400 mg/dl, although the range may span other values, such as from 20 to 600 mg/dl. When a measurement in the historical list is above the specified range, the display shows a HI indicator. Similarly, the display shows a LO indicator for the measurements below the specified range.

[0114] C. Interrupted Sleep Alarm and Infusion Device Functions

[0115] Some alarm functions are designed to accommodate anticipated temporary behaviors of the users. For example, in the typical case where the characteristic value is a blood glucose level, it has been observed that when a user of the monitor is awakened from sleep by low blood glucose alarm from the monitor, there is often a period of disorientation. The disorientation may be particularly significant because the effect of low blood glucose level is made more severe at night. Consequently, in such a situation the user may begin pushing buttons on the device somewhat randomly in an attempt to quickly issue a bolus from the infusion device. This can result in an incorrect dosage or settings being altered without being realized by the user. In an embodiment of the invention, special functions are invoked to alleviate the problems associate with this disorientation.

[0116] As mentioned previously, the monitor may be included as part of an infusion device system. In such arrangements, the monitor and the infusion device may both be controlled through the same input device, e.g. keypad 112. In addition, information regarding both the monitor and infusion device may be displayed on the same display 114. The problem of night disorientation described above does not only involve a function of the monitor alarm. The function of the infusion device can also be modified.

Abbott Ex. 1002 - 707/1438

[0117] Any of the functions described below to deal with night disorientation can be set in the monitor and/or infusion device to be invoked in different ways. For example, the user can activate a night mode upon retiring to bed (and deactivate it upon waking). One or more of the functions are activated while in the night mode. Or, one or more of the functions can be automatically set to operate during a specified period designed to correspond with the user's usual sleep. In any case, the function(s) may be divided into two related embodiments. The embodiment according to the present invention delays accepting input from the user when an alarm wakes the user. An additional arrangement provides an earlier warning to the user when sleeping than when awake.

[0118] The embodiment of the invention as noted above operates to eliminate mis-operation of monitor and/or infusion device by requiring preventing input until disorientation of the user has abated somewhat. This may be done by an ordinary delay or, preferably by requiring a predetermined input before normal operation is restored. In one example embodiment, when the night mode is activated and a low blood glucose alarm or shutoff has occurred, operation of the infusion device and/or monitor may be blocked until the user has provided the proper input. Blocking the device(s) operation may be performed by automatically invoking a "block" function that is built into the device (that is normally manually invoked by the user) or a simple keypad/button lockout. Alternately, a separate user "test" can be invoked such that the user must enter a specified key sequence (e.g. a numeric code) before operation of the device(s) is restored. Requiring such user input insures that any disorientation has passed before allowing operations such as delivering medication or altering other settings.

[0119] A typical example of this embodiment is a device comprising a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user of the device; and a processor coupled to the sensor input for operating an alarm based on the received signal from the sensor, wherein the processor activates the alarm according to a first criteria when the user is awake; and a second criteria when the user is asleep. Such devices are designed for example to adapt to a number of situations in which a user may exhibit different behaviors during time periods when they are typically asleep as compared to time periods when they are typically awake. For example, in the typical case where the characteristic value is a blood glucose level, it has been observed that when a user of the monitor is awakened from sleep by low blood glucose alarm from the monitor, there is often a period of disorientation. The disorientation may be particularly significant because the effect of low blood glucose level is made more severe at night.

[0120] In preferred embodiments of the invention, the sensed physiological characteristic is a measurement of glucose and the device provides an alarm warning at an earlier timepoint when the user is asleep as compared to when the user is awake by altering a threshold criteria for the activation an alarm during sleeping hours. Alternatively one can provide an alarm having a different tone or audibility. Exemplary threshold criteria include glucose concentrations reaching a predetermined value; or glucose concentrations exhibiting a predetermined rate of change. Optionally one can provide earlier or different alarm warnings to the user by using multiple alarms. For example the device can activate the alarm to provide earlier alarm warning by monitoring a rate of change in the sensed physiological characteristic value and adjusting an alarm threshold value when the rate exceeds a predetermined rate limit.

[0121] The likelihood night disorientation can be reduced by providing an earlier warning to the user regarding a low blood glucose level. In some arrangements, this may involve a purpose driven application of the multiple alarm function described above. Different alarm thresholds may be set to be active at different times. For example, a higher low blood glucose alarm threshold is set for sleeping hours than for waking hours. Alternately, the night alarm level (e.g. a higher low blood glucose alarm threshold) can be manually activated upon retiring to sleep and cancelled upon waking as mentioned above. Multiple alarm thresholds (e.g. two levels of low blood glucose alarms) may also be applied within the night mode as well.

[0122] The present invention provides a device comprising a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user; and a processor coupled to the sensor input for operating an alarm based on the sensed physiological characteristic value of the user from the received signal from the sensor; wherein the processor activates the alarm and delays accepting input from the user when the alarm awakens the user. In an illustrative embodiment of the invention, the physiological characteristic value is a blood glucose measurement and delaying accepting input from the user is applied to a low blood glucose alarm or a high blood glucose alarm. In preferred embodiments of the invention, the processor delays accepting input from the user until the user provides a predetermined input such as entering a numeric code or executing a button sequence. Optionally, delaying accepting input from a user who is most likely asleep when the alarm sounds is set according to a schedule based on a time of day, or alternatively, is set by the user before sleeping.

[0123] In further examples an early warning regarding a low blood glucose level to the user may be provided through a dynamic measurement, as described above. Employing a dynamic measurement (e.g. monitoring a rate change of the blood glucose level) enables the monitor to better anticipate a low blood glucose level. See section 3, above. In this case, a fast declining blood glucose rate, e.g. -2.0 mg/dL per minute or greater (which may be indicated by a single down arrow on the graphical display) will cause an adjustment in the low blood glucose alarm threshold value. For example, the fast declining blood glucose rate can trigger a low blood glucose threshold value to be raised by 6 mg/dL.

Abbott Ex. 1002 - 708/1438

Thus, the low blood glucose alarm will sound sooner than it otherwise would without the adjustment based on the fast declining blood glucose rate, allowing the user to wake up and make a correction with less chance of disorientation. Similarly, an even greater declining rate, e.g. a -4.0 mg/dL or greater (which may be indicated by a double down arrow on the graphical display) will cause a greater adjustment in the low blood glucose alarm threshold value. For example, this sharp declining blood glucose rate can trigger a blood glucose threshold value to be raised by 12 mg/dL, providing an even earlier warning than the first fast declining blood glucose rate. In the case of multiple alarms with different thresholds, the adjustment(s) may be applied to all of the low blood glucose alarms so that the same set of alarms operate but at adjusted levels.

[0124] As has been previously discussed in section 3, the dynamic measurement is can be applied to anticipate low (or high) blood glucose levels before they actually occur. This is useful whether the user is awake or asleep. In the case of an awakened user, however, it is important to provide somewhat more warning because of the possibility of disorientation as described above. Accordingly, a dynamic measurement and adjustment applied in a night mode may employ either a lower rate level or a greater threshold adjustment or both than that used in a normal (day) mode.

[0125] 5. Advanced Blood Glucose Reminder Functions

[0126] Other arrangements described herein allow the user to set reminders that can be provided by the monitor. The reminders can be alarm signals (including, but not limited to, auditory, visual, tactile, etc.) that are initiated after a timer has run to prompt the user to take action or merely inform the user of a particular status. The reminder is started (i.e. the timer is initiated), when an event occurs and/or certain conditions are met. The alarm signals can be the same or different based upon the triggering events or conditions. These reminders can be used to further assist the user in managing insulin delivery for optimum results. For example, but not limited to, reminders can be set for event markers, blood glucose values, reference values, high or low sensor measurements.

[0127] Characteristic monitors and infusion devices can use event markers that place tags in the data for events the user experiences (e.g., but not limited to, meals, exercise, and high or low blood glucose). For example, but not limited to, when an infusion device identifies a high or low blood glucose event marker, it can start a timer that reminds the user to check blood glucose levels. This is intended to make therapy safer by encouraging more frequent checks during times that the patient may be at risk from hypoglycemia or hyperglycemia. In addition, this feature can also be applied to characteristic monitors. For example, but not limited to, a characteristic monitor that is used to show low or high blood glucose tags can have a timer set to remind a user to check their blood glucose levels at a later time.

[0128] In addition, a reminder timer can be set that is triggered if a blood glucose value is entered. For example, but not limited to, the reminder can be if the user enters a low or high blood glucose value into the monitor as a reference or calibration value.

[0129] A reminder timer can also be triggered by a user providing a reference value to the monitor. Thus, the user can be reminded to supply a new reference value after a minimum time period has elapsed. In this way calibration of the monitor is assured.

[0130] A blood glucose reminder can also be triggered by high or low measurement from the sensor. Thus, the monitor will request a blood glucose reference value during an excursion away from the normal range of values. The trigger for this reminder can be tempered by setting a minimum time between reminders to avoid pestering the user. This reminder can be used to provide more robust data for curve fitting as correlation improves with variability in the data pairs. The reminder promotes more frequent data collection during more critical periods (e.g., but not limited to, when blood glucose is too high or too low) and therefore the interpolated curve for this period is more reliably representative of the true curve.

[0131] One aspect behind the use of these reminders is that they also serve to prevent redundant and excessive alarms for the user. For example, if the timer is removed from the previously described high or low measurement reminder, the result would be a simple hypoglycemia or hyperglycemia alarm. Using a reminder, however, the message is not that the user's blood glucose is out of range. Rather, the reminder's message is to check the user's blood glucose with a meter, or the like. If a user's blood glucose is very near an alarm triggering threshold, an alarm might be triggered repeatedly as the value passes back and forth across the threshold. A reminder will set a timer, preventing duplicative warnings for a short period of time, but reminding the user to check blood glucose again when that period has expired. This can provide a better or easier path through the regulatory process. Thus, reminders are less likely to become a nuisance to the user and also prompt more useful data collection. In alternative arrangements, the alarm is triggered again, regardless of the presence of a time, if the glucose level continues to change in the direction of the trend.

[0132] FIG. 5 illustrates a reminder function triggered by high or low characteristic values. A plot of a monitored characteristic value 500 (such as, but not limited to, blood glucose) is shown. One or more ranges 502, 504 define safe characteristic values (e.g., but not limited to, a first range 502 being a warning range and a second range 504 being a critical range), such as can be employed using multiple alarms as previously described. When a range is exceeded (e.g., but not limited to, at time 506), an alarm can be triggered but also a timer is started such that a reminder is also initiated after its expiration (e.g., but not limited to, at time 508). Over the timer period further occurrences of exceeding the threshold (e.g., but not limited to, at point 510) will not result in a duplicative alarm.

[0133] However, the situation can be somewhat different when the intervening triggering event is not identical to the

Abbott Ex. 1002 - 709/1438

first triggering event. For example, if a first range 502 is exceeded (e.g., but not limited to, at time 512) and a timer is started, but before a reminder can be issued (e.g., but not limited to, at time 514) a second range 504 is exceeded (e.g., but not limited to, at time 516), then the second alarm can be issued and the timer can be restarted. No reminder can be indicated at the theoretical expiration of the first timer (e.g., but not limited to, at time 514), but a reminder can be issued at the expiration of the second timer (e.g., but not limited to, at time 518). In this case, exceeding the second range overrides the first reminder because the second alarm is a different, albeit related, condition. As previously described, however, the use of reminders is not limited to monitoring high and low characteristic values. In a similar manner, reminders can be triggered by user's supplied reference values for calibration as well as event markers entered into the monitor.

[0134] 6. Glucose Monitoring Information Management

[0135] Other arrangements described herein provide meaningful retrospective information to the patient using the sensor. In particular, a retrospective display of one or more physiological values can provide significantly useful data. As disclosed, the retrospective displays can be designed in a variety of ways to provide various useful information. For example, but not limited to, as the sleeping user receives no benefit from a real-time display, a retrospective view of data is important. While a simple listing of previous values has value, it can be time consuming to review, provides information that is difficult to visualize and comprehend and requires significant memory space within the device. Providing useful information that is easy to understand and that can be stored within a small memory space is very important. The ability to review data from the previous sleep period is particularly helpful to a user with nocturnal hypoglycemia or "dawn effect", as there is typically no witness to the real-time display. These measures can be even more important in cases where the alarm system can exhibit many false positives and/or false negatives, which might otherwise frustrate the user and lead to non-use of the monitor.

[0136] The following advanced data presentation tools can be used to conveniently and efficiently store and display useful information on a screen for a user to review while the monitor is in use. The tools provide useful information while requiring only a minimal amount of memory space. These data presentation tools can also be used in any retrospective analysis package, such as software running on a computer or network designed to analyze trends and provide advise regarding a treatment regime.

[0137] The tools operate by processing that compares actual reading to high and low value limits (e.g., but not limited to, acceptable blood glucose ranges). For example, but not limited to, the limits can be the adjustable hypoglycemic and hyperglycemic alarm thresholds of a monitor. Alternately, for standardization, the tools can be applied to a fixed definition of a target blood glucose range that is independent of the hyperglycemic and hypoglycemic alarm thresholds for the particular user/monitor.

[0138] FIG. 6A illustrates one minimum and maximum data presentation. A display of the minimum and maximum values 600 of the characteristic monitor that have been measured for the user can be displayed on the monitor. The minimum value and maximum values can be conveniently displayed along with the date and time of their occurrence. Such a display 600 is useful, but becomes more useful when combined with an excursion count, a distribution of values, and/or integrated values as discussed below

[0139] FIG. 6B illustrates an excursion data presentation. The number of excursions above or below the respective blood glucose limits is also very useful to have summarized for the user. An excursion display 602 provides good information, particularly when there are no alarms active on the monitor (either because the monitor is not turned on or alarms are not being employed by the user). A display 602 of the number of excursions above the hyperglycemic limit and the number of excursions below hypoglycemic limit give the user an idea of performance of a treatment program at a glance. A high number of incidents exceeding either limit indicate a need for improvements.

[0140] FIG. 6C illustrates a characteristic value distribution data presentation. A simple distribution of sensor values offers a very powerful tool. Preferably, the distribution is described in percentages that are automatically scaled with the duration of monitor use. Optionally, a monitor can include the total time of use with a percentage distribution. Awareness of a total time provides perspective for reviewing the percentage distribution. A time based distribution can also be used, but requires the total time to be included in the analysis as a reference. A distribution can also be presented based upon the total number of readings, but requires the total time is required in the analysis.

[0141] For example, but not limited to, the display can show a percentage of readings above a hyperglycemic alarm level, a percentage of readings below a hypoglycemic alarm level and a percentage of readings of readings within alarm range as shown in FIG. 6C. Optionally, the total time covered in the analysis can also be displayed. Similarly, an alternate display can show the time spent above a hyperglycemic alarm level, the time spent below a hypoglycemic alarm level and the time spent within alarm range (not shown). As mentioned, the time base display requires a known total time as part of the analysis. Finally, a display can also include the number of readings above hyperglycemic alarm level, the number of readings below a hypoglycemic alarm level and the number of readings within alarm range (not shown).

[0142] FIG. 6D illustrates an integrated characteristic value data presentation. Performing an integration of the readings outside the alarm levels with respect to time can provide a measure of the hypoglycemic and hyperglycemic events' severity. In addition, these results can also be scaled these by a total sensor time to provide a measure that is duration

Abbott Ex. 1002 - 710/1438

independent.

[0143] For example, a "hyperglycemic area" can be calculated as the sum of the differences between the readings and the hyperglycemic alarm limit. A "hypoglycemic area" can be calculated from the sum of all the differences between the hypoglycemic alarm limit and the readings. A "hyperglycemic index" is calculated by taking the "hyperglycemic area" and dividing it by the duration of sensor use. Similarly, the "hypoglycemic index" can be calculated by taking the "hypoglycemic area" divided by the duration of sensor use.

[0144] Various alarms and/or monitoring aspects discussed above may be combined or utilized with other alarms and/or monitoring aspects. The possible arrangements and/or combinations should not be limited to those specifically described above.

[0145] 7. Real-Time Glucose Display and History

[0146] In other arrangements, a physiological characteristic monitor 104 is used for reviewing a history of measurements of the sensed characteristic value based on user input from an input device with a display for showing the history of the measurements of the sensed characteristic value. As discussed above with respect to the alarm history, the display may show the measurements only within a specified range, such as the operational range of the sensor (e.g. 40 to 400 or 20 to 600 mg/dl). Outside the specified range, a HI or LO indicator is shown.

[0147] FIG. 7 illustrates a real-time and history display 700. Three exemplary screens 702, 704, 706 are shown for the display of real-time or historical measurement data. The in-range screen 702 is used when the measurement is within the specified range; the actual measurement is shown. The high screen 704 (showing a HI indicator) is used when the measurement is above the specified range, and the low screen 706 (showing a LO indicator) is used when the measurement is below the specified range. The display shows a no measurement indicator where no value was recorded in the history.

[0148] The user input also directs scrolling through a history of the measurements of the sensed characteristic value. In a typical arrangement, the display shows a single measurement at a time. The display shows a time of acquisition by the sensor for each measurement in the history. In the example in-range screen 702, the current measurement is being shown, indicated by the "NOW" indicator. The time of acquisition can be shown as a value relative to a most recent measurement of the history. For example, the high and low screens 704, 706 each show values measured 5 hours and 25 minutes before the current time interval. Alternatively, the actual date and time of the measurement may be shown.

[0149] The history of the measurements of the sensed characteristic value can be scrolled through in even time increments. In further arrangements, the even time increment can have a selectable size (e.g. selectable between 5 minute or 30 minute increments), and the selected time increment can be indicated on the display as the history is reviewed. The history itself can comprise a fixed total period from the present backward. For convenience, scrolling through the history wraps around after an end of the history is reached.

[0150] In further arrangements, when no measurement is currently available, the NOW indicator can be replaced by a status message indicating no calibration, noise or a missed measurement.

[0151] 8. Graphical Display of Measurements of Characteristic Values

[0152] In further arrangements, a graphical display is employed in the monitor 104 (which may be combined with an infusion device) to allow for a user to readily apprehend the current and historical measurements of the characteristic value tracked by the monitor 104.

[0153] Devices may be provided which display data from measurements of a sensed physiological characteristic (e.g. blood glucose concentrations) in a manner and format tailored to allow a user of the device to easily monitor and, if necessary, modulate the physiological status of that characteristic (e.g. modulation of blood glucose concentrations via insulin administration). One illustrative arrangement is a device comprising a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user; a memory for storing a plurality of measurements of the sensed physiological characteristic value of the user from the received signal from the sensor; and a display for presenting a text and/or graphical representation of the plurality of measurements of the sensed physiological characteristic value (e.g. text, a line graph or the like, a bar graph or the like, a grid pattern or the like or a combination thereof). Preferably, the graphical representation displays real time measurements of the sensed physiological characteristic value. Such devices can be used in a variety of contexts, for example in combination with other medical apparati. In preferred arrangements, the device is used in combination with at least one other medical device (e.g. a glucose sensor) and receives a signal from this device that is transmitted via a wired or wireless connection. Wireless communication can include for example the reception of emitted radiation signals as occurs with the transmission of signals via RF telemetry, infrared transmissions, optical transmission, sonic and ultrasonic transmissions and the like. Most preferably, the device is an integral part of a medication infusion pump (e.g. an insulin pump). Typically in such devices, the physiological characteristic values includes a plurality of measurements of blood glucose.

[0154] The physiological characteristic value measurement may be displayed in a graphical format, a text format or a combination thereof. For example, the graphical representation can comprise a color coded set of one or more indicators of the status of the physiological characteristic. In a specific arrangement, the graphical representation comprises one or more trend indicators, indicating an approximate rate trend in the sensed physiological characteristic value over a

Abbott Ex. 1002 - 711/1438

recent series of the plurality of measurements (e.g. the four most recent measurements of the sensed physiological characteristic value). Optionally the graphical representation further comprises a vertical cursor which allows a user to alternatively select measurements of a sensed physiological characteristic value from the graphical format or from a text format. For example, the display can include a scrolling vertical cursor, allowing individual Blood Glucose measurements in the graphics plot to be selected, with the Blood Glucose value and the time the measurement was made displayed in a text portion of the screen.

[0155] The display for presenting a graphical representation of the plurality of measurements of the sensed physiological characteristic value can comprise a number of different formats in which to display the various physiological characteristic values. For example where the graphical representation comprises one or more trend indicators, the trend indicators can include an indicator of a past measurement, a current measurement or a combination thereof. Preferably, a continuous screen update is included, with the graphics display updated upon receipt of each telemetered blood glucose value. In certain formats, the trend indicators comprise a color coded set of indicators. The graphical display can be modulated to indicate to the user whether it is day or night. For example, when the time range shows the 24 hour period the graphical plot daytime hours can be displayed with a light background and night time hours can displayed with a dark background. Where the time range shows the 24 hour period, noon and midnight on the graphical plot can each be marked by a vertical line. In such a 24 hour graph, optionally night is indicated by reverse graph (e.g. white dots on black background).

[0156] In a specific illustrative arrangement, the physiological characteristic value can be a blood glucose measurement and the color coded set of indicators can comprise a grid of nine indicators including three rate trend categories including going down, stable and going up and three current measurement categories including low, in zone and high where a single rate trend category and a single current measurement category are indicated simultaneously. Optionally, going down and low and going up and high can be indicated in red; going down and high and going up and low can be indicated in yellow; going down and in zone, going up and in zone, stable and high and stable and low can be indicated in orange; and stable and in zone can be indicated in green.

[0157] In yet another illustrative arrangement, the physiological characteristic value is a blood glucose measurement and the graphical representation comprises a graphical plot of at least a portion of the plurality of measurements of the sensed blood glucose measurement where a horizontal axis comprises a time scale and a vertical axis comprises a blood glucose measurement scale. Optionally, the graphical plot can comprise a color coded set of indicators. For example, a color coded set of indicators can comprise horizontal bands corresponding to various levels of danger (e.g. hyperglycemia or hypoglycemia) corresponding to each of the plurality of measurements of the sensed blood glucose measurement. Optionally, the color coded set of indicators can comprise a color of the graphical plot indicating a current danger level corresponding to a current blood glucose measurement. In certain arrangements, the graphical plot can be continuously updated in real-time such that the shown portion of the plurality of measurements of the sensed blood glucose measurement comprises a most recent period.

[0158] Where a graphical representation comprises one or more trend indicators, the trend indicators can comprise about five symbols indicating for example a fast increasing rate, a moderate increasing rate, a negligible rate change, a moderate decreasing rate and/or a fast decreasing rate, respectively. The symbols can comprise any one of a variety of suitable symbols, for example arrows, with two up arrows, a single up arrow, no indicator, a single down arrow and two down arrows, corresponding respectively to for example, the fast increasing rate, the moderate increasing rate, the negligible rate change, the moderate decreasing rate and the fast decreasing rate. In one such arrangement, the physiological characteristic value is a blood glucose measurement and the fast increasing rate is at least approximately +3 mg/dl, the moderate increasing rate is between approximately +3 mg/dl and +1 mg/dl, the negligible rate change is between approximately +1 mg/dl and -1 mg/dl, the moderate decreasing rate is between approximately -1 mg/dl and -3 mg/dl and the fast decreasing rate equal or exceeding -3 mg/dl. Trend indicators indicate the average glucose rate of change over the last 4 measurements: Double up arrow for an average increase equal to or greater than 3 mg/dl. Single up arrow for an average increase less than 3 and equal to greater than 1 mg/dl. No arrow for an average increase or decrease less then 1 mg/dL. Single down arrow for an average decrease less than 3 and equal to greater than 1 mg/dl. Double down arrow for an average decrease equal to or greater than 3 mg/dl.

[0159] The display may be tailored to a specific set of criteria that are associated with an analyte to be sensed. For example, in a display tailored to provide information on blood glucose, the blood glucose measurement scale can be selectively displayed in mg/dl or mmol/l. In the context of the analyte itself for example, the blood glucose measurement scale can comprise a fixed measurement range from approximately 0 to 310 mg/dl or approximately 0 to 17.2 mmol/l. In addition, the time scale can comprise a time range selectively changed to show different periods of a plurality of blood glucose measurements. In an illustrative example, the time range is selectively changed as either a 3 hour period or a 24 hour period. Optionally, the time range shows the 3 hour period the graphical plot comprises approximately 36 blood glucose measurements, each approximately five minutes apart. In certain arrangements, when the time range shows the 3 hour period each hour of the graphical plot is marked by a vertical line. In a specific embodiment, when the time range shows the 24 hour period the graphical plot comprises approximately 72 blood glucose measurements, each

Abbott Ex. 1002 - 712/1438

approximately 20 minutes apart.

[0160] 9. Illustrative Specific apparatus

[0161] The following describes an insulin infusion device having an monitor that provides a display of physiological glucose values and a user interface.

[0162] Software associated with the device can allow the entry of a number of user values such as a "Sensor ON/OFF" function that allows the user to turn the sensor on or off. When the sensor is turned ON, features such as those described below can be enabled. When the Sensor is turned off, the options will not be displayed in the pump menus. Options include a *Sensor Transmitter ID Number* which allows the user to enter the ID number of the sensor transmitter. Another option is a *Low Glucose Level* which allows the user to select the Low Glucose Alarm Level. This parameter can have a minimum of 50 mg/dl. It can have a maximum equal to 10mg/dl below the High Glucose Level set by the User. The default can be 50 mg/ml. It can provide a visual feedback of the new selection. Another option is a *Low Glucose Snooze* which can define the time period between the first Low Glucose Alarm and any subsequent Low Glucose alarm. It can have a minimum of 5 minutes and a maximum of 60 minutes. The default can be 20 minutes. Another option is a *Low Glucose Suspend* which allows allow the user to select the Low Glucose Suspend Level. The default can be Off. If turned On, this parameter can have a minimum of 40 mg/dl. It can have a maximum equal to 10mg/dl below the Low Glucose Level set by the User (see previous paragraph), up to 120 mg/ml. Once turned on, the default can be 40 mg/ml. It can provide a visual feedback of the new selection. Another option is a *High Glucose Level* which allows allow the user to select the High Glucose Alarm Level. The default can be Off. If turned On, this parameter can have a minimum equal to 10 mg/dl above the Low Glucose Level set by the User (see previous two paragraphs). It can have a maximum of 400 mg/dl. Once turned on, the default can be 200 mg/ml. It can provide a visual feedback of the new selection. Another option is a *High Glucose Snooze* which can define the time period between the first High Glucose Alarm and any subsequent High Glucose alarm. It can have a minimum of 5 minutes and a maximum of 180 minutes. The default can be 60 minutes. Another option is a *Glucose Format* which can allow the user to select glucose values to be displayed in units of mg/dl or mmol/l. The default can be mg/dl. It can provide a visual feedback of the new selection. Another option is a *Communication Failure Alert Period (Missed Data)* which can allow the user to set the time period that will lapse between the loss of communications and a loss of communications alarm. This parameter can have a minimum value of 5 minutes and a maximum value of 40 minutes. After 40 minutes, the pump can re-sync automatically. If the re-sync fails, a Link Error alarm is generated and the communication stops. The default can be 30 minutes. Another option is a *Calibration Reminder,* a value which can define the time before the sensor Calibration is required to remind the user. The minimum value can be Off. The Maximum value can be 4 hours. The default value can be 1 hour.

[0163] The following sensor trend values can be utilized in the glucose calculations. A first sensor trend value is a *High Positive Trend Threshold* which can define the High Positive Trend Threshold limit that will result in a display of two up arrows. The value can be 3mg/dl per minute averaged over 20 minutes. This can be defined as a change between the current glucose value and the 20-minute-old glucose value. Another sensor trend value is a *Low Positive Trend Threshold* which can define the Low Positive Trend Threshold limit that will result in a display of one up arrow. The value can be 1mg/dl per minute. Another sensor trend value is a *Low Negative Trend Threshold* which can define the Low Negative Trend Threshold limit that will result in a display of one down arrow. The value can be -1mg/dl per minute. Another sensor trend value is a *High Negative Trend Threshold* which can define the High Negative Trend Threshold limit that will result in a display of two down arrows. The value can be -3mg/dl per minute. Another sensor trend value is a *Glucose Calibration* / Calculation which can calibrate the glucose value using the raw data from the sensor. Optionally a mathematical formula or algorithm is used in this calculation. For example, the glucose can be calculated by multiplying the glucose raw data value by the calibration factor.

[0164] This apparatus includes a Glucose Graphical History Screen which can be activated by pushing the ESC key, and can stay active for some period of time (e.g. 2 minutes) before transitioning to the default "Idle" screen. This can display information including the current glucose level as measured by the Sensor, displayed in units selected by the user. These can be displayed graphically in 5-minute intervals, with each data point 2 pixels wide. The most recent data can be on the right side of the display. An alphanumeric display of the glucose data or reasons that the data is not displayed can be included. The current value of High Glucose Level set by the user can be displayed as a dashed line on the graph. The current value of Low Glucose Level set by the user can be displayed as a dashed line on the graph. Glucose Trend Indicator: High or Low Glucose Trend can be displayed as a single or double up arrow while the user is viewing the Current Glucose Value.

[0165] The device can compare the trend magnitude received from the sensor with a trend threshold value and display arrows on the screen based on the following rules: if the trend information is greater than or equal to the High Positive Trend Threshold, the screen can display two arrows pointing up; if the trend magnitude is less than the High Positive Trend Threshold and greater than or equal to the Low Positive Trend Threshold, the screen can display one arrow pointing up; if the trend magnitude is less than the Low Positive Trend Threshold and greater than or equal to the Low Negative Trend Threshold, the screen can display no arrows; if the trend magnitude is less than the Low Negative Trend Threshold and greater than or equal to the High Negative Trend Threshold, the screen can display one arrow pointing

Abbott Ex. 1002 - 713/1438

down; if the trend information from the sensor is less than the High Negative Trend Threshold, the screen can display two arrows pointing down.

[0166] The screen can display the time of the sensor value measurement, for example in the form of time markers. There can be a vertical dashed line at each clock hour on the 3-hour display. There can be a vertical dashed line at Noon and Midnight on the 24-hour display. The graphic screen can display a visual indication of data above and below the range of the display screen. The terms "HIGH" and "LOW" can be displayed in the alphanumeric display. The graphic screen can visually display the time of any boluses within the time displayed on the graph. This can be done with a bar at the bottom of the screen.

[0167] The screen can include a cursor. Consequently, the user can scroll a vertical cursor left and right through the points on the graph, and the time, and the glucose value for each data point can be displayed. This can be done using the up and down buttons. When displaying data that is not the current value, the screen can have a different appearance to alert the user that the data is historical, not current. This may be done by flashing the numbers or using an inverse font. It can also display the term "History". The user can be able to change the screen from a 3 hour width to a 24 hour width by pushing a single button. In this mode, the screen can display 24 hours of data at 20-minute intervals. In this display, each time period can be only one pixel wide. The display can incorporate features to identify to the user that this is a 24-hour display, not the three-hour display. This may be done by putting the night hours (6pm to 6am) in inverse font, placing the terms "3 hour" or "24 hour" on the display, both, or another method. There can be a vertical line at Noon and Midnight.

[0168] The device can further include a calibration glucose entry which allows the user to enter the reference glucose values from an external meter reading. The frequency of this entry can be based on the sensor calibration requirements. The User can get a reminder at a user selectable time period prior to the required entry time. The measurement can be entered manually or can be communicated to the device via a wired or wireless connection. Wireless communication can include for example the reception of emitted radiation signals as occurs with the transmission of signals via RF telemetry, infrared transmissions, optical transmission, sonic and ultrasonic transmissions and the like. When the Paradigm™ Link meter is used, the glucose measurement is sent to the pump automatically via RF. Alternatively, one can use the described arrangements in combination with any one of the wide variety of other medical devices known in the art such as those produced by Therasense, Roche, Bayer or Abbot laboratories.

[0169] The device can have a number of alarm functions. When an alarm condition occurs, the pump can display the alarm to the user on the pump screen and via the selected alert mechanism. The pump can provide the ability to clear the display and return to the action previously in progress. A cleared sensor or glucose alarm can not be reissued for a user specified time after the user clears the alarm. Alarm conditions include a communications error alarm where the alarm can be set when the pump doesn't receive valid data for the time period specified by the use, a sensor low battery alarm which can activate when the sensor transmitter sends a low battery signal, a sensor dead battery alarm which can activate when the sensor transmitter sends a dead battery signal, a low glucose alarm which can be set when the current glucose level is equal to or below the low glucose level set by the user, and a shutoff limit alarm which can be set when the current glucose level is equal to or below the shutoff limit level set by the user and which can suspend pumping and warn the user following the alarm protocol. The error message can be similar to " low glucose - pumping suspended", a high glucose alarm which can be set when the current glucose level is equal to or above the high glucose level set by the user, a calibration required alarm which can be set when 12 hours have elapsed since the last reference glucose value has been entered (this time period can be determined based on the sensor calibration requirements), a sensor end of life alarm which can be set when the pump calculates that the sensor has reached its end of life, a calibration needed alarm which can inform the user a calibration is needed in short period of time. The user can set the time delay between this alarm and the calibration required alarm. The device also includes a glucose alarm history where the pump can display the sensor glucose alarm values as a tabular display of time and alarm information, with the ability to scroll forward and backward in time. This function can be combined with other history tables.

[0170] The Pump can also display the user entered glucose calibration values as a tabular display of time and alarm information, with the ability to scroll forward and backward in time. This can include user entered values as well as the values sent automatically via RF. The device sending the value can be a device such as a Paradigm link meter or any one of the wide variety of other appropriate medical devices known in the art such as those produced by Therasense, Roche, Bayer or Abbot laboratories. This function may be combined with other history tables. The pump can allow the user to conveniently access sensor information and settings. The sensor status screen can include the following information: communication status; next calibration; sensor age; sensor isig value; transmitter battery status; transmitter software version; transmitter serial number; and pump serial number. The sensor settings screen can include the following information: sensor is on or off; high glucose setting; high glucose snooze time; low glucose setting; low glucose snooze time; low glucose shutoff limit; alarm snooze; calibration required reminder time; BG units selection; and transmitter serial number.

[0171] The pump can store the most recent 3 days of sensor raw data, and computed glucose values of the last 30 days. The pump can support the download of either the complete database of memory or selected block specific sections

Abbott Ex. 1002 - 714/1438

of data via the comlink or meter. The download time can be minimized with a goal that it can not exceed two (2) minutes for the sensor data. The pump can download either its complete database of memory or selected block specific sections of memory via the comlink or meter. The download time can be minimized with a goal that it can not exceed four (4) minutes for the pump. The pump can communicate using telemetry.

Claims

1. A device, comprising:

   a sensor input (106) capable of receiving a sensor signal from a sensor (102), the sensor signal being based on a sensed physiological characteristic value of a user;
   an alarm output capable of transmitting an alarm signal to an alarm device to awaken a user; and
   a processor (108) coupled to the sensor input (106) and to the alarm output to generate the alarm signal for operating the alarm based on the sensed physiological characteristic value of the user from the received sensor signal from the sensor;
   a data entry port (112) for connection to a user operable data entry device (112) to accept input from the user;
   characterized in that the processor (108) is configured such that when it applies the alarm signal to the alarm output to activate the alarm and awaken the user it also delays accepting input from the user at the data entry port (112).

2. The device of claim 1, wherein the physiological characteristic value is a blood glucose measurement and the alarm signal indicates a low blood glucose.

3. The device of claim 1, wherein the physiological characteristic value is a blood glucose measurement and the alarm signal indicates a high blood glucose.

4. The device of claim 1, wherein delaying accepting input from the user is applied to a plurality of alarms based on a plurality of sensed physiological characteristic values.

5. The device of claim 1, wherein delaying accepting input from the user is set according to a schedule based on a time of day.

6. The device of claim 1, wherein delaying accepting input from the user is set by the user before sleeping.

7. The device of claim 1, wherein the processor delays accepting input from the user until the user provides a predetermined input, preferably comprising entering a numeric code or executing a button sequence.

8. The device of claim 1, wherein the processor activates the alarm to provide earlier warning to the user when sleeping than when the user is awake.

9. A method for operating an alarm of a device, the device comprising:

   a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user; and
   a processor coupled to the sensor input for operating the alarm based on the sensed physiological characteristic value of the user from the received signal from the sensor;
   wherein the method comprises the processor activating the alarm and delaying acceptance input from the user when the alarm awakens the user.

10. The method of claim 9, wherein the physiological characteristic value is a blood glucose measurement and delaying accepting input from the user is applied to one of a low blood glucose alarm, and a high blood glucose alarm.

11. The method of claim 9, wherein delaying accepting input from the user is applied to a plurality of alarms based on a plurality of sensed physiological characteristic values.

12. The method of claim 9, wherein delaying accepting input from the user is set according to a schedule based on a time of day.

Abbott Ex. 1002 - 715/1438

13. The method of claim 9, wherein delaying accepting input from the user is set by the user before sleeping.

14. The method of claim 9, wherein the processor delays accepting input from the user until the user provides a predetermined input, preferably comprising entering a numeric code or executing a button sequence.

15. The method of claim 9, wherein the processor activates the alarm to provide earlier warning to the user when sleeping than when the user is awake.

Patentansprüche

1. Gerät mit:

einem Sensoreingang (106), der geeignet ist, ein Sensorsignal von einem Sensor (102) zu empfangen, wobei das Sensorsignal auf einer abgefühlten physiologischen Kenngröße eines Nutzers basiert;
einem Alarmausgang, der geeignet ist, ein Alarmsignal an ein Alarmgerät zu übermitteln, um einen Nutzer aufzuwecken; und
einem Prozessor (108), der mit dem Sensoreingang (106) und dem Alarmausgang verbunden ist, um das Alarmsignal zu erzeugen, um den Alarm auf der Basis der abgefühlten physiologischen Kenngröße des Nutzers aus dem empfangenen Sensorsignal des Sensors zu betreiben;
einem Dateneingabeanschluss (112) zur Verbindung mit einem benutzerbedienbaren Dateneingabegerät (112), um eine Eingabe von dem Nutzer anzunehmen;
dadurch gekennzeichnet, dass der Prozessor (108) so ausgebildet ist, dass er auch die Annahme einer Eingabe von dem Nutzer am Dateneingabeanschluss (112) verzögert, wenn er das Alarmsignal am Alarmausgang anlegt, um den Alarm zu aktivieren und den Nutzer zu wecken.

2. Gerät nach Anspruch 1, bei dem die physiologische Kenngröße eine Blutzuckermessung ist und das Alarmsignal niedrigen Blutzucker anzeigt.

3. Gerät nach Anspruch 1, bei dem die physiologische Kenngröße eine Blutzuckermessung ist und das Alarmsignal hohen Blutzucker anzeigt.

4. Gerät nach Anspruch 1, bei dem das Verzögern der Annahme einer Eingabe von dem Nutzer auf der Basis einer Vielzahl von abgefühlten physiologischen Kenngrößen auf eine Vielzahl von Alarmen angewandt wird.

5. Gerät nach Anspruch 1, bei dem das Verzögern des Annehmens einer Eingabe von dem Nutzer gemäß einem Plan auf der Basis einer Tageszeit eingestellt wird.

6. Gerät nach Anspruch 1, bei dem das Verzögern des Annehmens einer Eingabe von dem Nutzer durch den Nutzer vor dem Schlafen eingestellt wird.

7. Gerät nach Anspruch 1, bei dem der Prozessor das Annehmen einer Eingabe von dem Nutzer verzögert bis der Nutzer eine vorbestimmte Eingabe bereitstellt, die vorzugsweise das Eingeben eines numerischen Codes oder das Anwenden einer Tastenabfolge umfasst.

8. Gerät nach Anspruch 1, bei dem der Prozessor den Alarm aktiviert, um dem Nutzer eine frühere Warnung bereitzustellen, wenn er schläft, als wenn der Nutzer wach ist.

9. Verfahren zum Betreiben eines Alarms eines Geräts, wobei das Gerät umfasst:

einen Sensoreingang, der geeignet ist ein Sensorsignal von einem Sensor zu empfangen, wobei das Signal auf einer abgefühlten physiologischen Kenngröße des Nutzers basiert; und
einen Prozessor, der mit dem Sensoreingang verbunden ist, um den Alarm auf der Basis der abgefühlten physiologischen Kenngröße aus dem empfangenen Signal des Sensors zu betreiben;
wobei das Verfahren das Aktivieren des Alarms durch den Prozessor und das Verzögern der Annahme einer Eingabe von dem Nutzer umfasst, wenn der Alarm den Nutzer aufweckt.

10. Verfahren nach Anspruch 9, bei dem die physiologische Kenngröße eine Blutzuckermessung ist und das Verzögern

Abbott Ex. 1002 - 716/1438

der Annahme einer Eingabe des Nutzers entweder auf einen Niedrigblutzuckeralarm oder einen Hochblutzuckeralarm angewendet wird.

11. Verfahren nach Anspruch 9, bei dem das Verzögern des Annehmens einer Eingabe des Nutzers auf eine Vielzahl von Alarmen auf der Basis einer Vielzahl von abgefühlten physiologischen Kenngrößen angewendet wird.

12. Verfahren nach Anspruch 9, bei dem das Verzögern des Annehmens einer Eingabe des Nutzers gemäß einem Plan auf der Basis einer Tageszeit eingestellt wird.

13. Verfahren nach Anspruch 9, bei dem das Verzögern des Annehmens einer Eingabe durch den Nutzer durch den Nutzer vor dem Schlafen eingestellt wird.

14. Verfahren nach Anspruch 9, bei dem der Prozessor eine Eingabe des Nutzers verzögert, bis der Nutzer eine vorbestimmte Eingabe bereitstellt, die vorzugsweise das Eingeben eines numerischen Codes oder das Anwenden einer Tastenabfolge umfasst.

15. Verfahren nach Anspruch 9, bei dem der Prozessor den Alarm aktiviert, um dem Nutzer eine frühere Warnung bereitzustellen, wenn er schläft, als wenn der Nutzer wach ist.

Revendications

1. Dispositif comprenant :

une entrée de capteur (106) capable de recevoir un signal de capteur provenant d'un capteur (102), le signal de capteur étant basé sur une valeur de caractéristique physiologique détectée d'un utilisateur ;
une sortie d'alarme capable d'émettre un signal d'alarme vers un dispositif d'alarme pour réveiller un utilisateur ; et
un processeur (108) couplé à l'entrée de capteur (106) et à la sortie d'alarme afin de générer le signal d'alarme pour actionner l'alarme sur la base de la valeur de caractéristique physiologique détectée de l'utilisateur à partir du signal de capteur reçu du capteur ;
un port de saisie de données (112) pour une connexion à un dispositif opérationnel de saisie de données (112) par un utilisateur pour accepter une entrée de l'utilisateur ;
caractérisé en ce que le processeur (108) est configuré de sorte que lorsqu'il applique le signal d'alarme à la sortie d'alarme pour activer l'alarme et réveiller l'utilisateur, il retarde aussi l'acceptation de l'entrée de l'utilisateur au port de saisie de données (112).

2. Dispositif selon la revendication 1, dans lequel la valeur de caractéristique physiologique est une mesure de glycémie sanguine et le signal d'alarme indique une glycémie sanguine faible.

3. Dispositif selon la revendication 1, dans lequel la valeur de caractéristique physiologique est une mesure de glycémie sanguine et le signal d'alarme indique une glycémie sanguine élevée.

4. Dispositif selon la revendication 1, dans lequel le retardement de l'acceptation d'une entrée de l'utilisateur est appliqué à une pluralité d'alarmes sur la base d'une pluralité de valeurs de caractéristiques physiologiques détectées.

5. Dispositif selon la revendication 1, dans lequel le retardement de l'acceptation d'une entrée de l'utilisateur est établi en fonction d'un programme basé sur une heure du jour.

6. Dispositif selon la revendication 1, dans lequel le retardement de l'acceptation d'une entrée de l'utilisateur est établi par l'utilisateur avant de s'endormir.

7. Dispositif selon la revendication 1, dans lequel le processeur retarde l'acceptation d'une entrée de l'utilisateur jusqu'à ce que l'utilisateur fournisse une entrée prédéterminée, comprenant de préférence la saisie d'un code numérique ou l'exécution d'une séquence de touches.

8. Dispositif selon la revendication 1, dans lequel le processeur active l'alarme pour donner à l'utilisateur une alerte plus tôt lors du sommeil que lorsque l'utilisateur est réveillé.

Abbott Ex. 1002 - 717/1438

9. Procédé pour actionner une alarme d'un dispositif, le dispositif comprenant :

une entrée de capteur capable de recevoir un signal provenant d'un capteur, le signal étant basé sur une valeur de caractéristique physiologique détectée d'un utilisateur ; et
un processeur couplé à l'entrée de capteur pour actionner l'alarme sur la base de la valeur de caractéristique physiologique détectée de l'utilisateur à partir du signal reçu du capteur ;
dans lequel le procédé comprend l'activation de l'alarme par le processeur et le retardement de l'acceptation d'une entrée de l'utilisateur lorsque l'alarme réveille l'utilisateur.

10. Procédé selon la revendication 9, dans lequel la valeur de caractéristique physiologique est une mesure de glycémie sanguine et le retardement de l'acceptation d'une entrée de l'utilisateur est appliqué à l'une d'une alarme de glycémie sanguine faible et d'une alarme de glycémie sanguine élevée.

11. Procédé selon la revendication 9, dans lequel le retardement de l'acceptation d'une entrée de l'utilisateur est appliqué à une pluralité d'alarmes sur la base d'une pluralité de valeurs de caractéristiques physiologiques détectées.

12. Procédé selon la revendication 9, dans lequel le retardement de l'acceptation d'une entrée de l'utilisateur est établi en fonction d'un programme basé sur une heure du jour.

13. Procédé selon la revendication 9, dans lequel le retardement de l'acceptation d'une entrée de l'utilisateur est établi par l'utilisateur avant de s'endormir.

14. Procédé selon la revendication 9, dans lequel le processeur retarde l'acceptation d'une entrée de l'utilisateur jusqu'à ce que l'utilisateur fournisse une entrée prédéterminée, comprenant de préférence la saisie d'un code numérique ou l'exécution d'une séquence de touches.

15. Procédé selon la revendication 9, dans lequel le processeur active l'alarme pour donner à l'utilisateur une alerte plus tôt lors du sommeil que lorsque l'utilisateur est réveillé.

Abbott Ex. 1002 - 718/1438

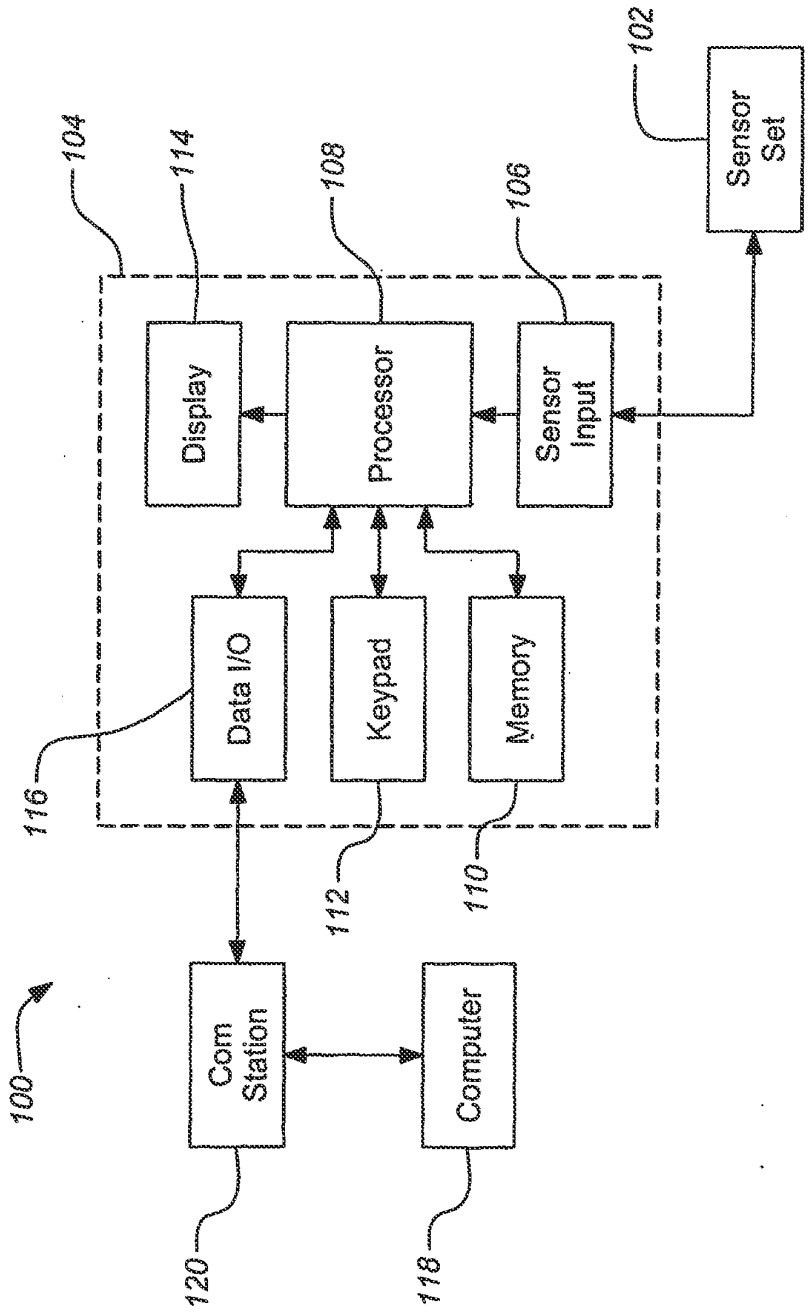


FIG. 1A

Abbott Ex. 1002 - 719/1438

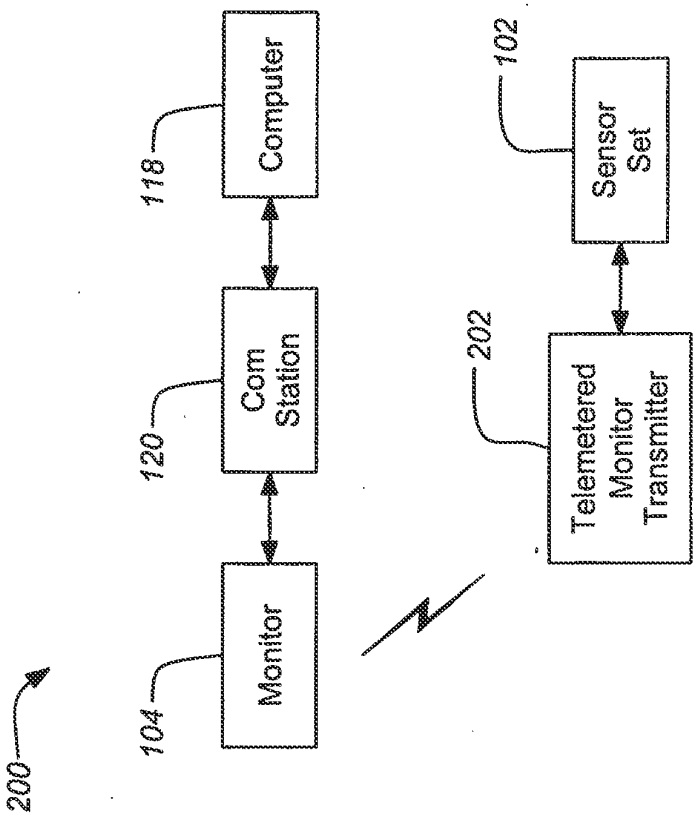


FIG. 1B

Abbott Ex. 1002 - 720/1438

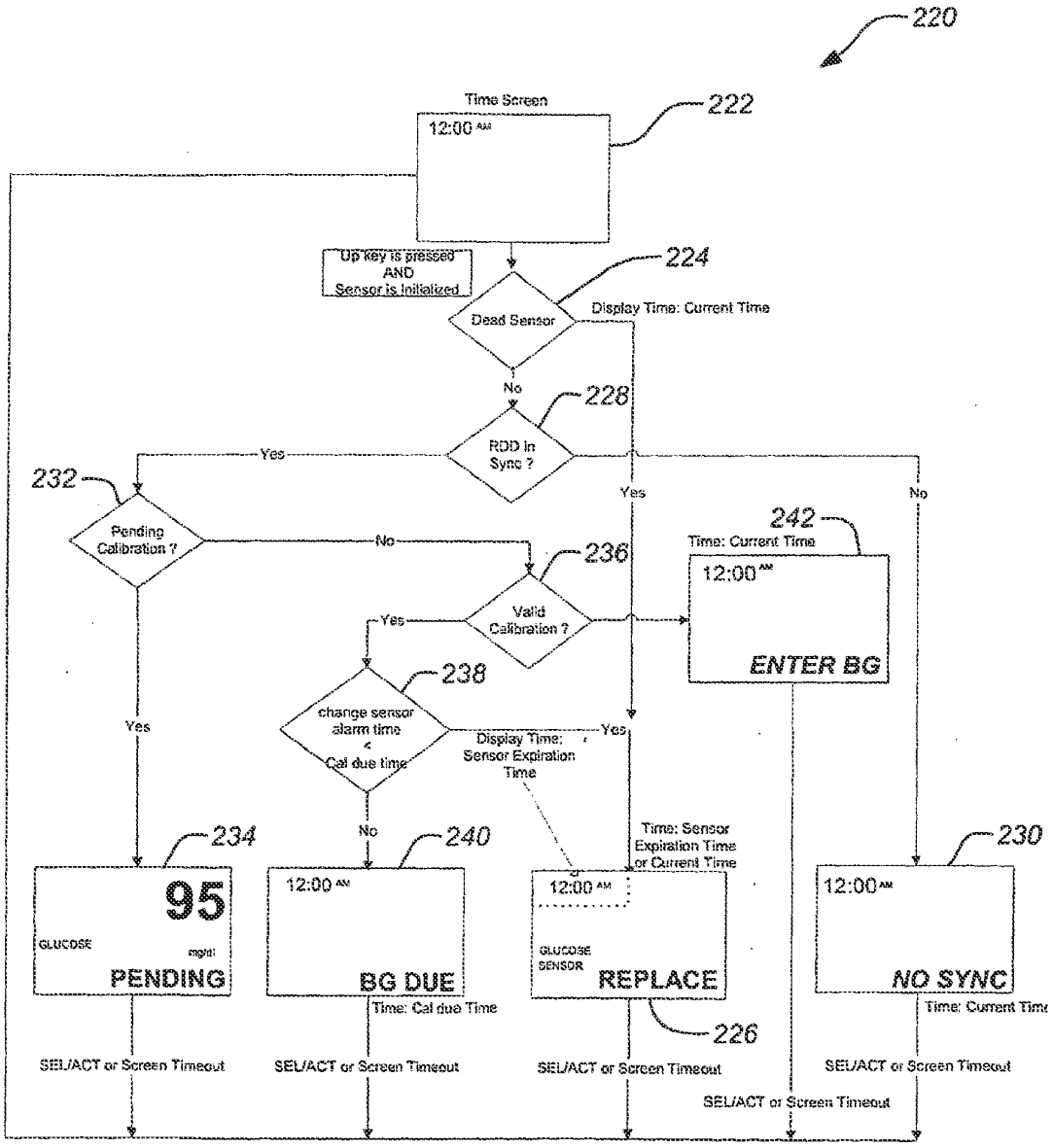


FIG. 2A

Abbott Ex. 1002 - 721/1438

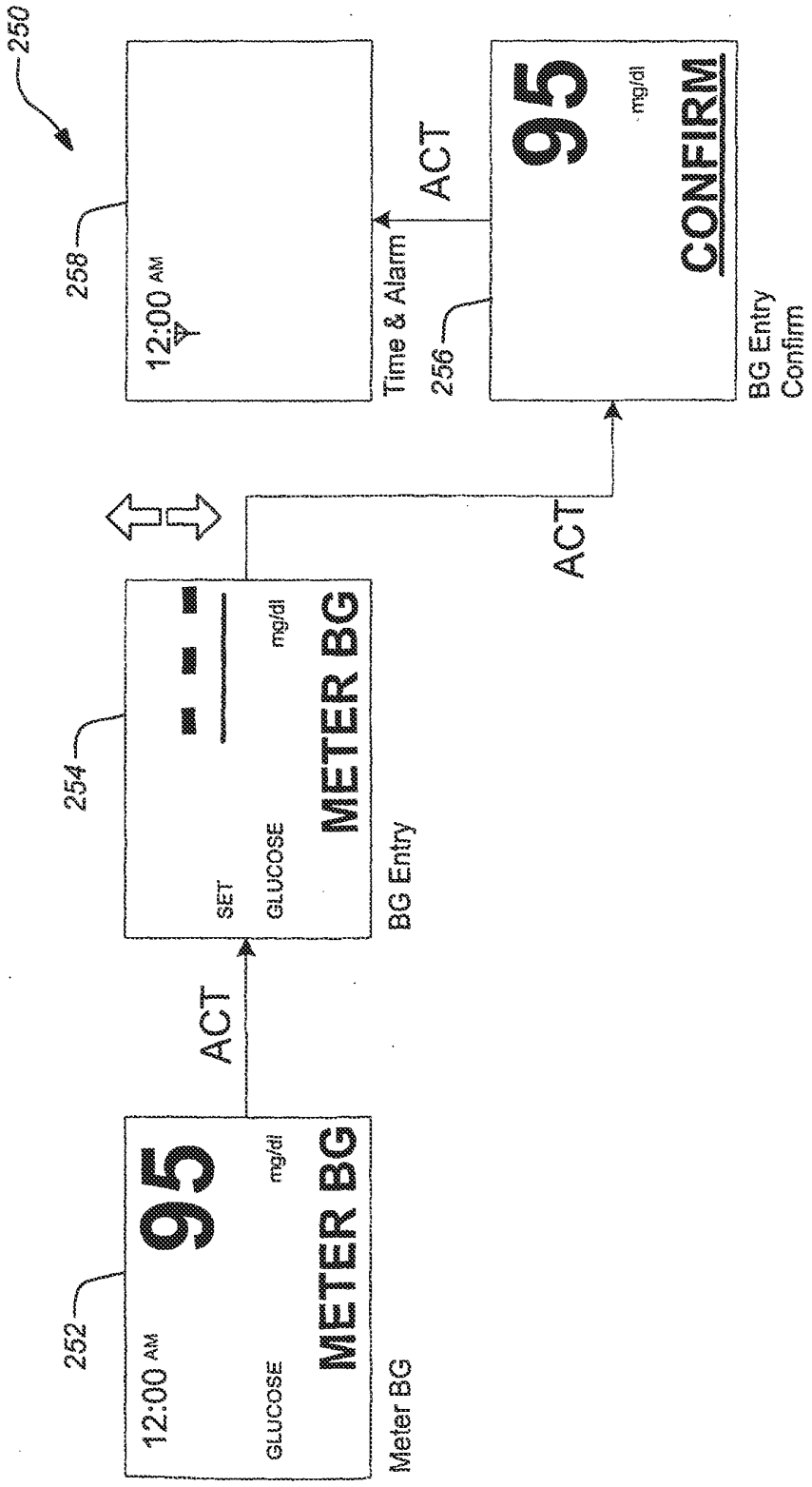


FIG. 2B

Abbott Ex. 1002 - 722/1438

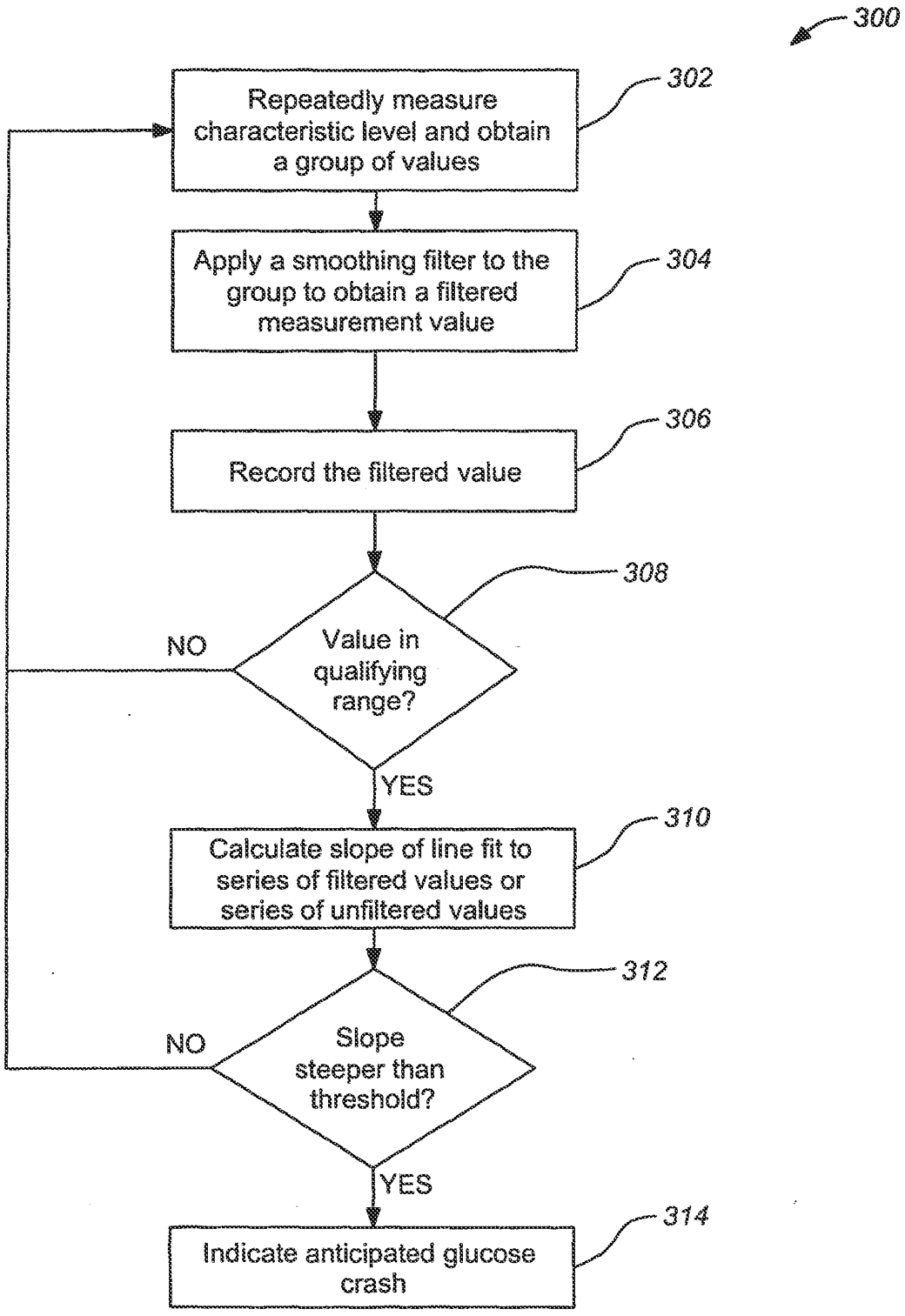


FIG. 3A

Abbott Ex. 1002 - 723/1438

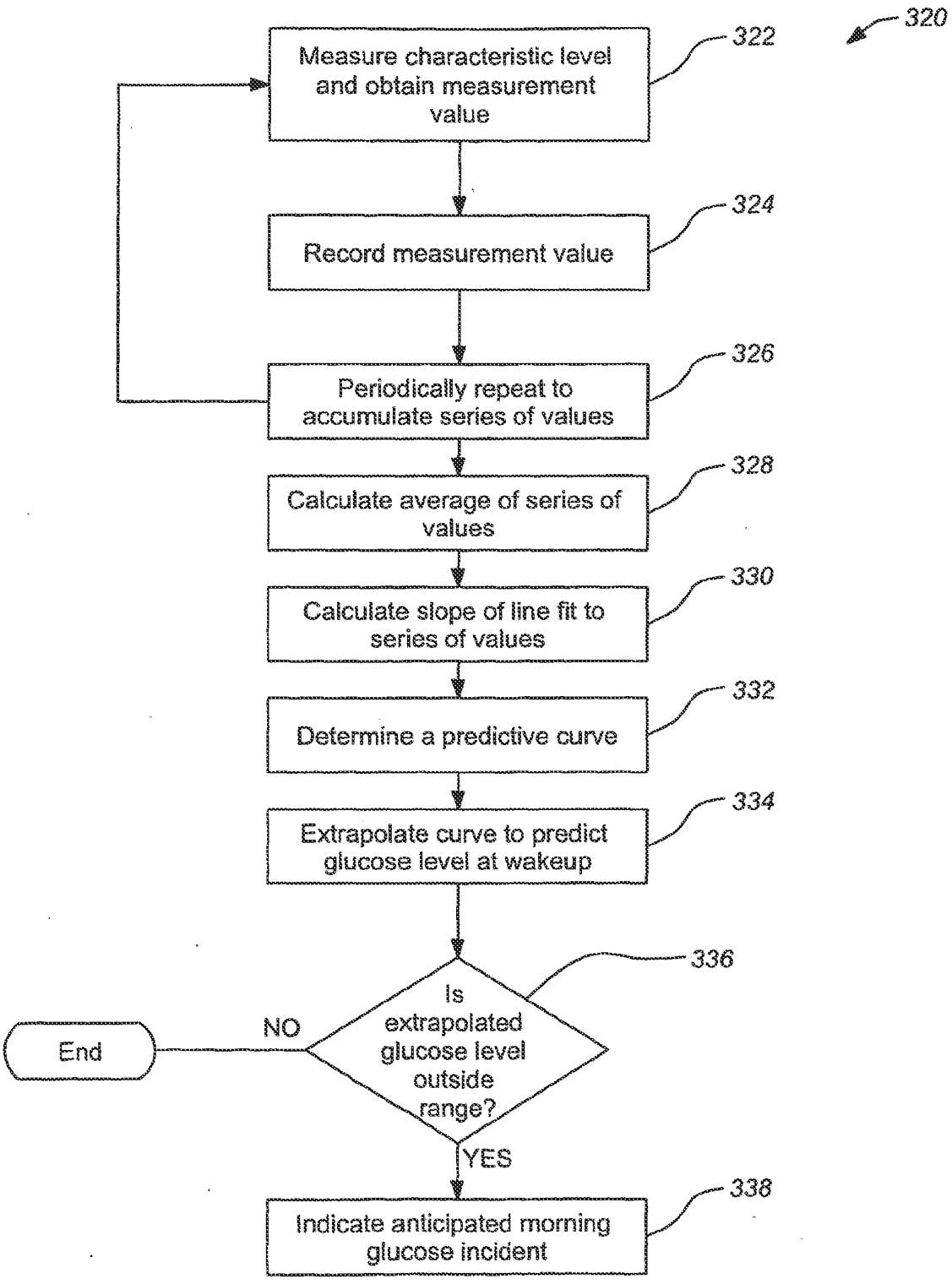


FIG. 3B

Abbott Ex. 1002 - 724/1438

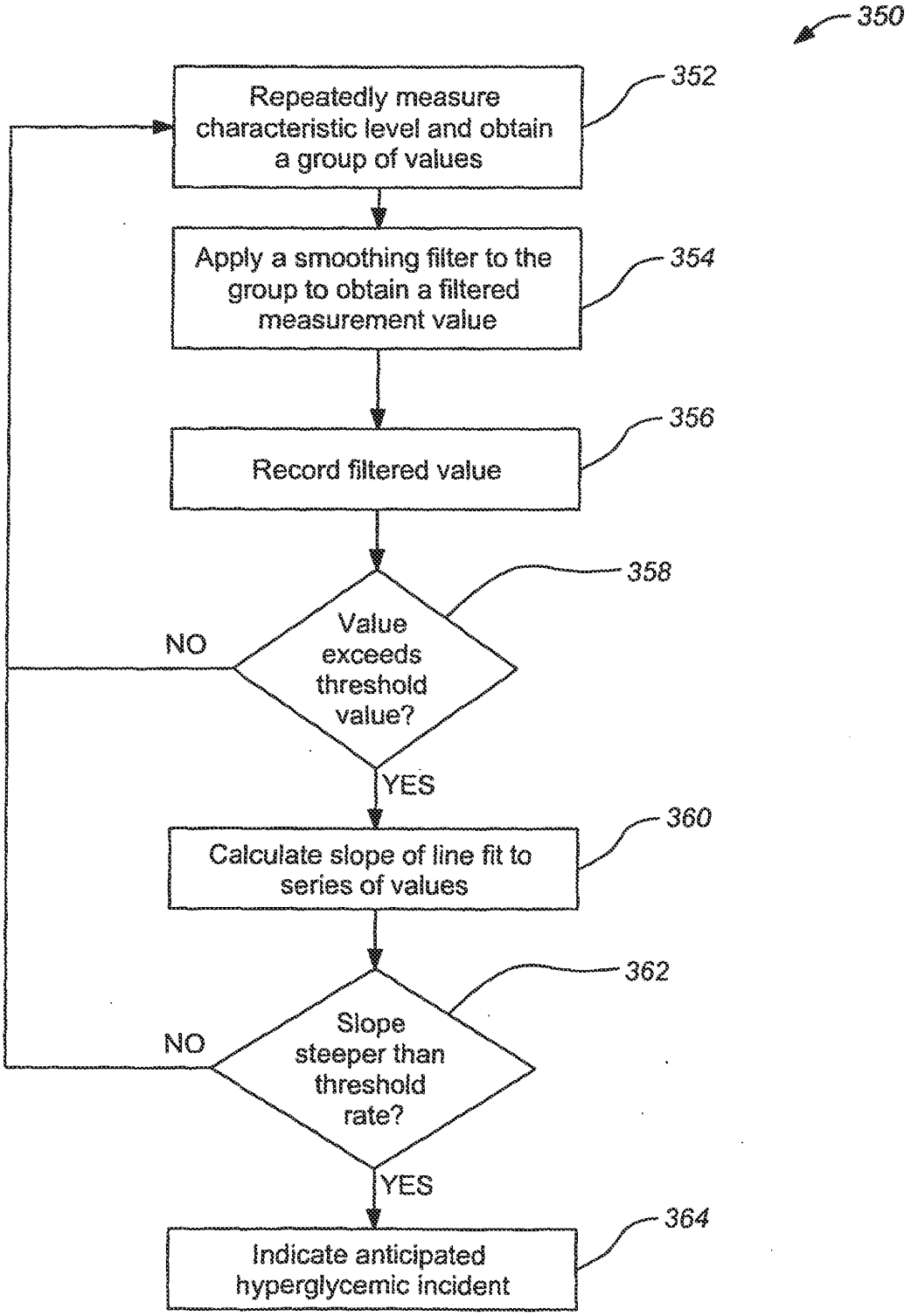


FIG. 3C

Abbott Ex. 1002 - 725/1438

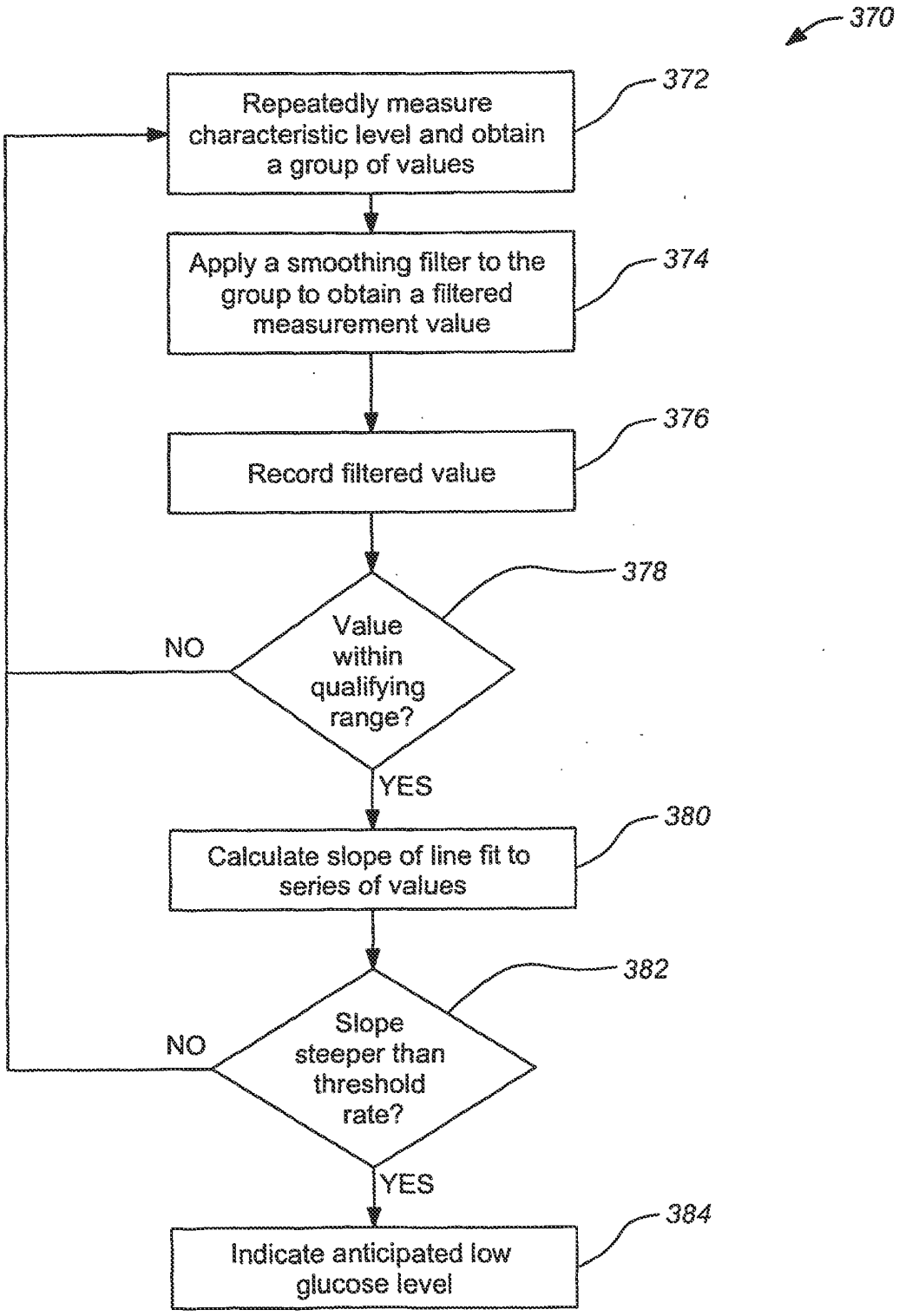


FIG. 3D

Abbott Ex. 1002 - 726/1438

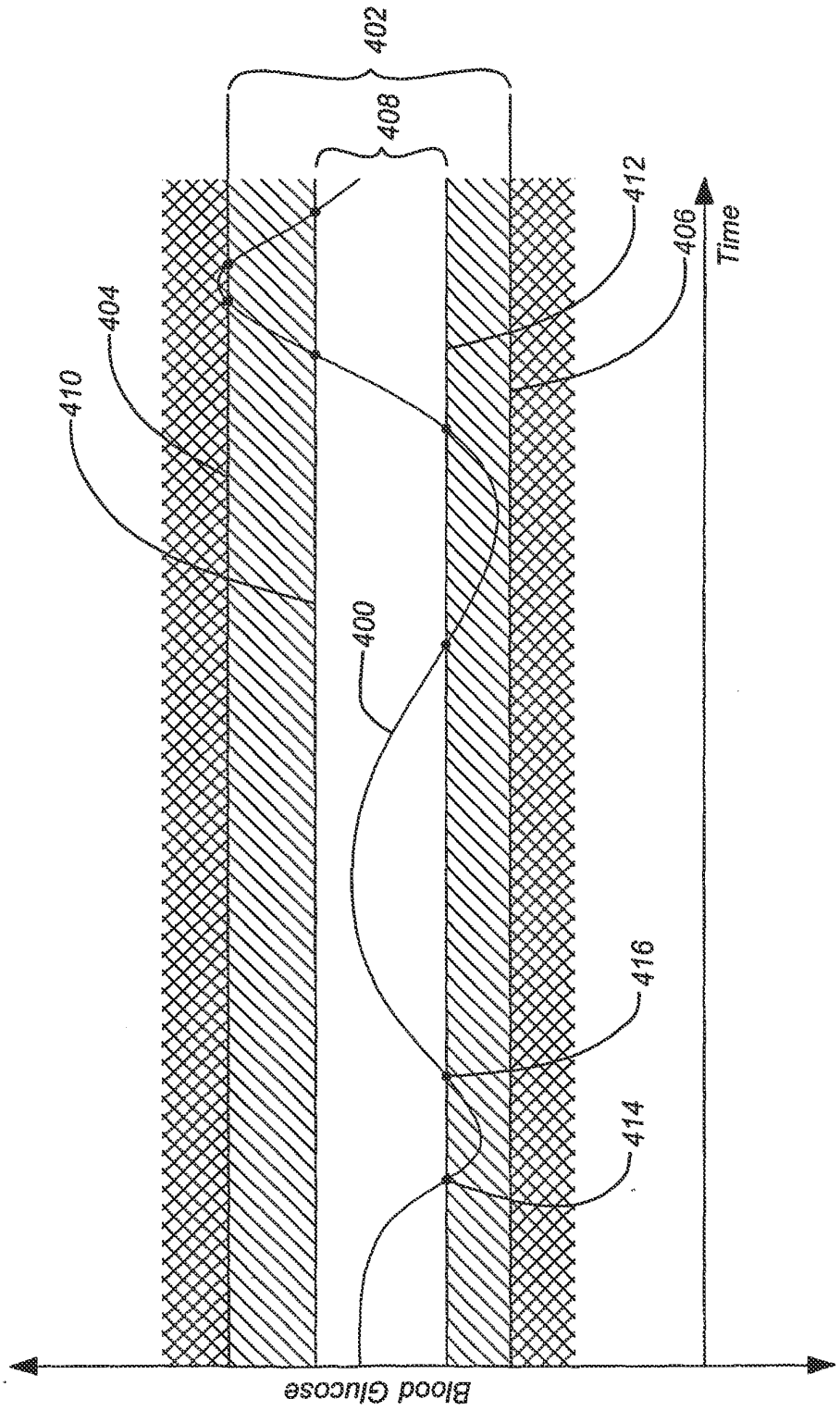


FIG. 4A

Abbott Ex. 1002 - 727/1438

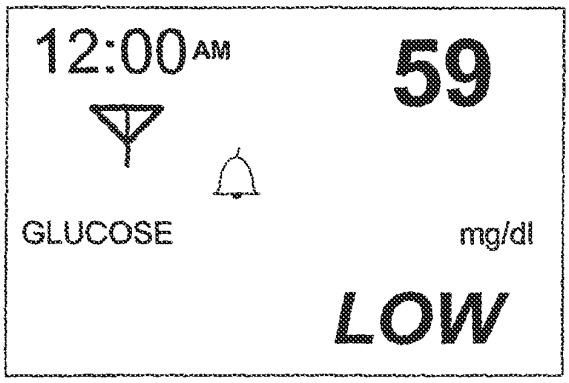


FIG. 4B

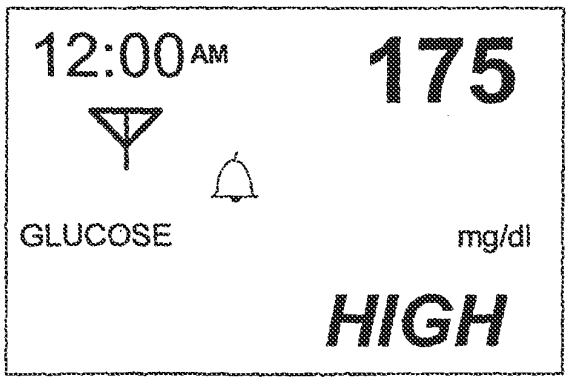


FIG. 4C

Abbott Ex. 1002 - 728/1438

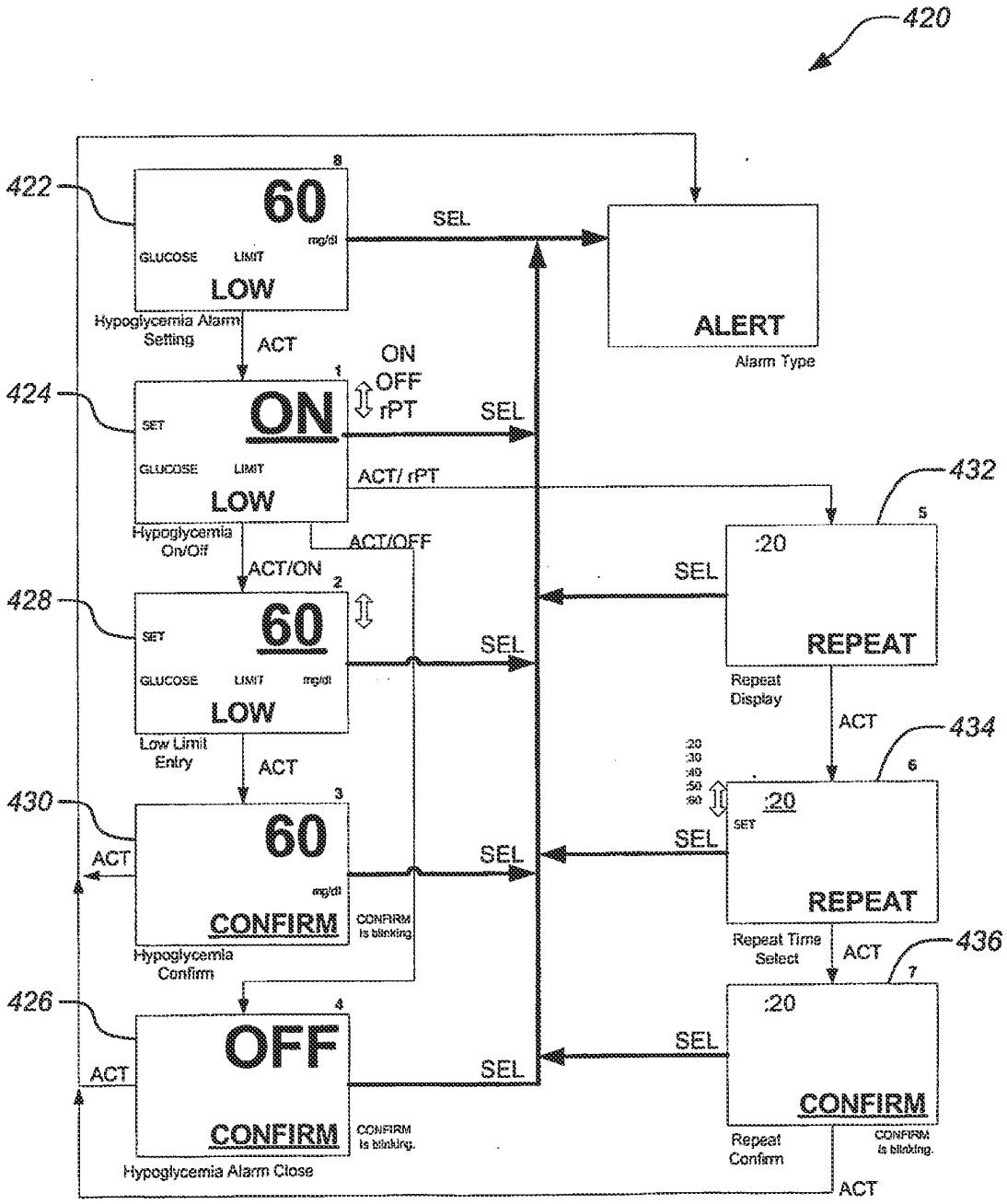


FIG. 4D

Abbott Ex. 1002 - 729/1438

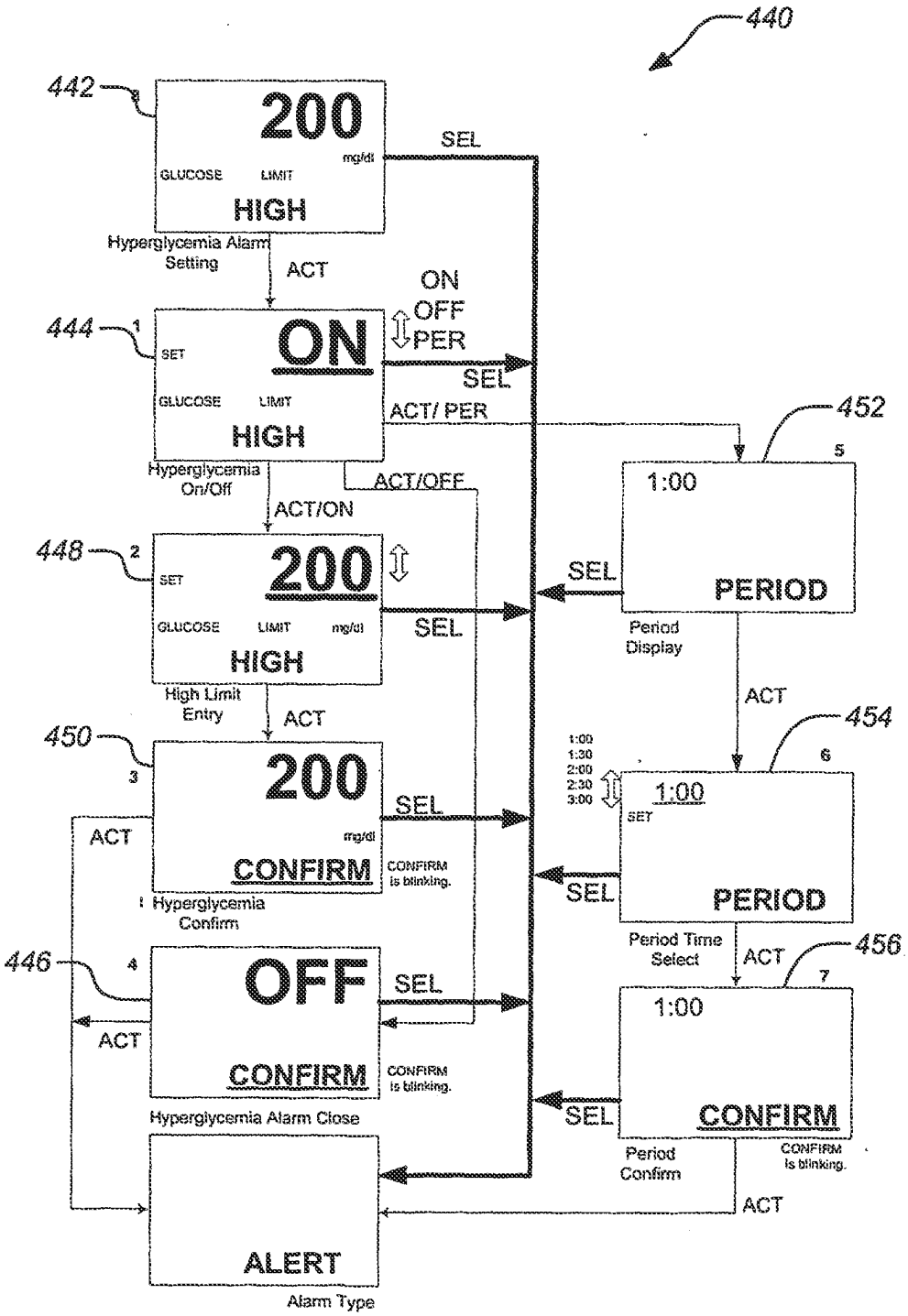


FIG. 4E

Abbott Ex. 1002 - 730/1438

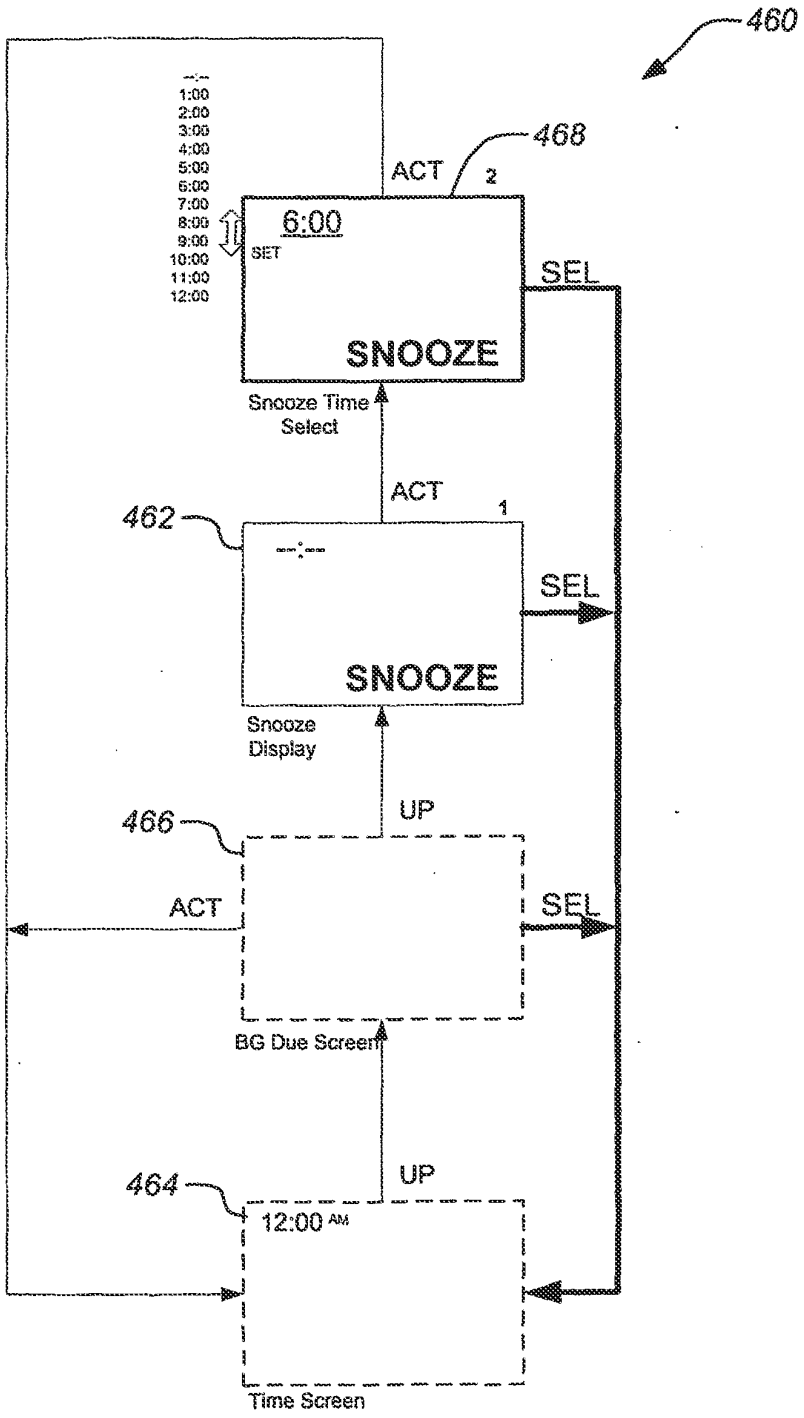


FIG. 4F

Abbott Ex. 1002 - 731/1438

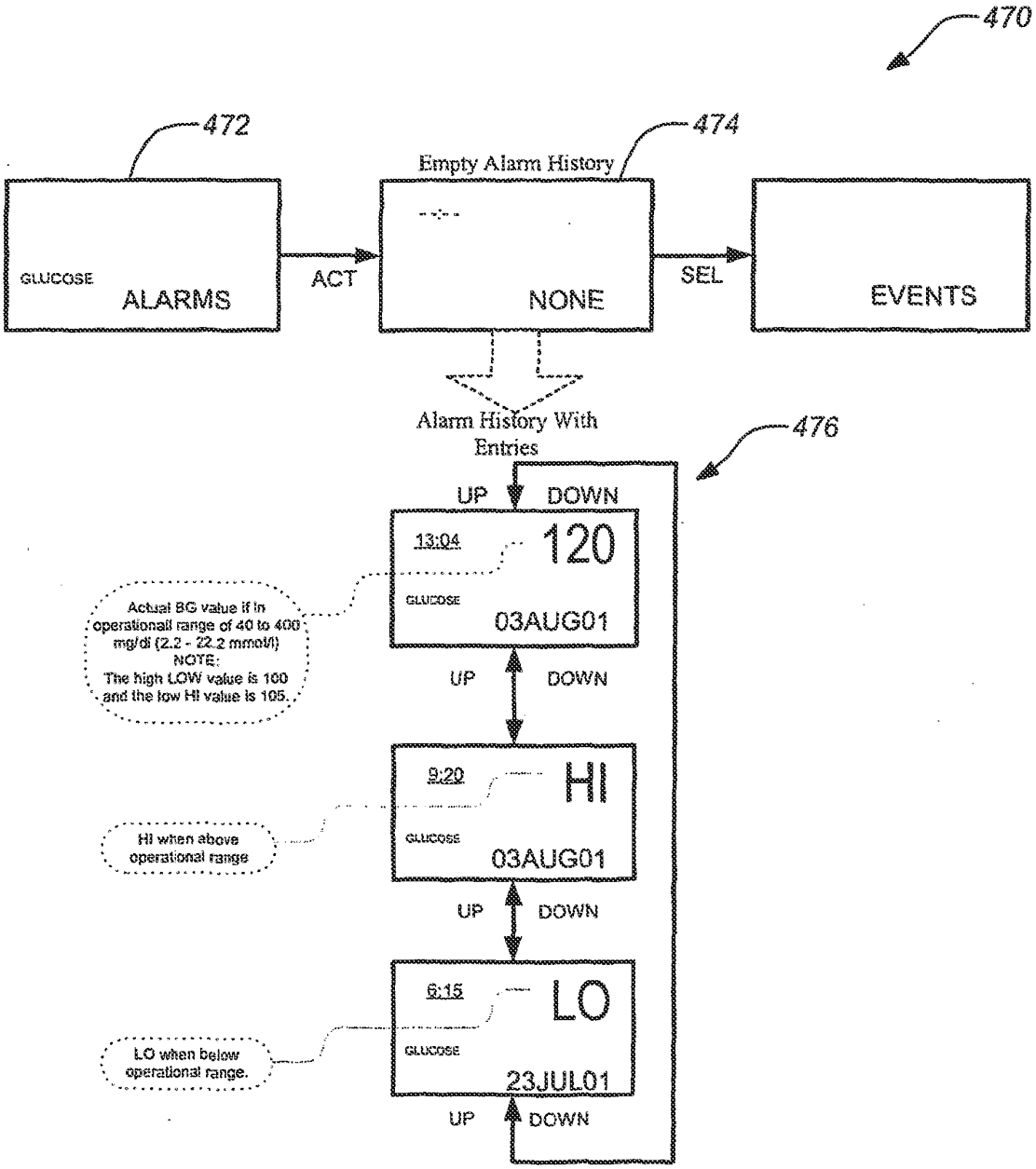


FIG. 4G

Abbott Ex. 1002 - 732/1438

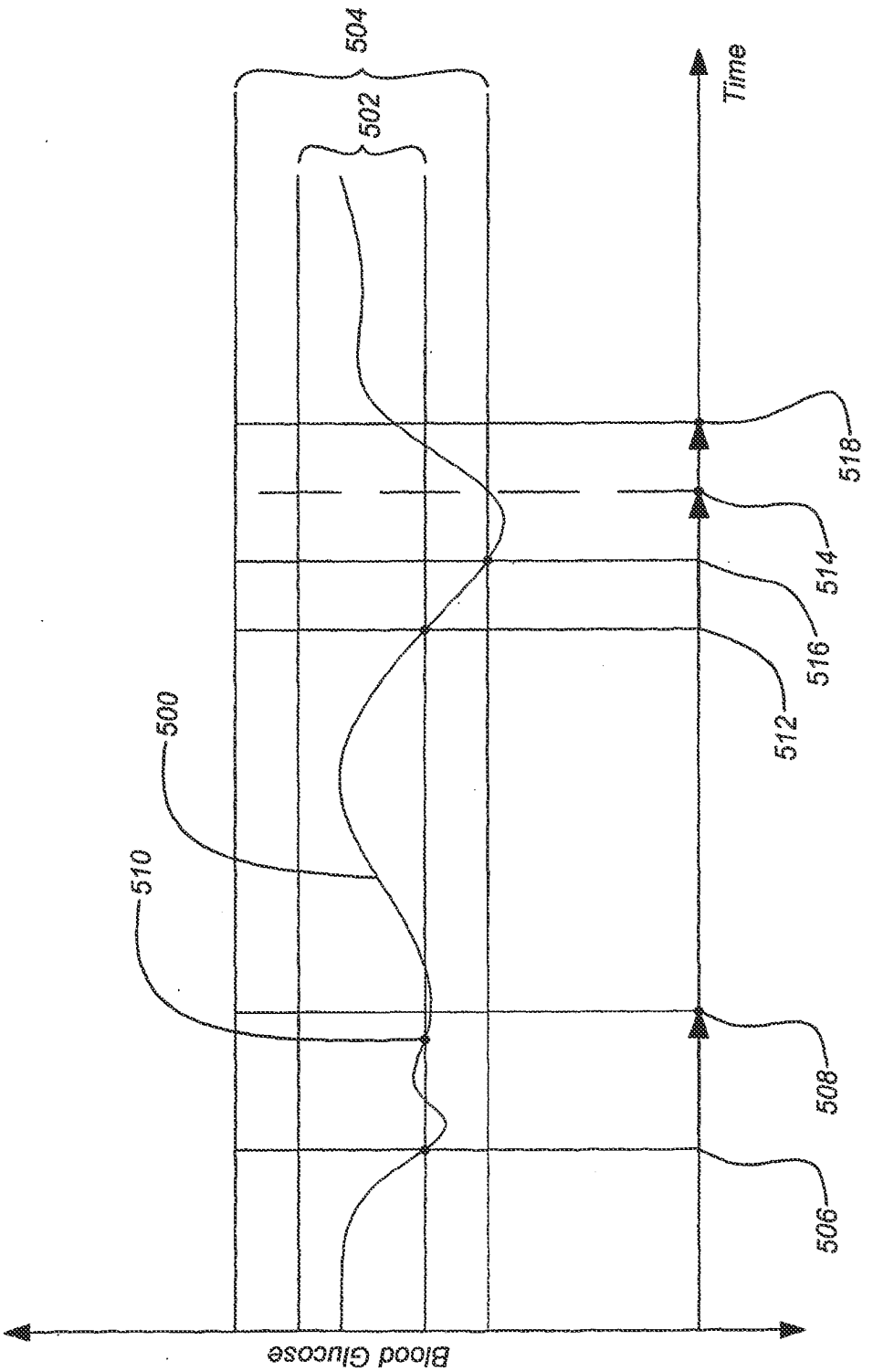


FIG. 5

Abbott Ex. 1002 - 733/1438

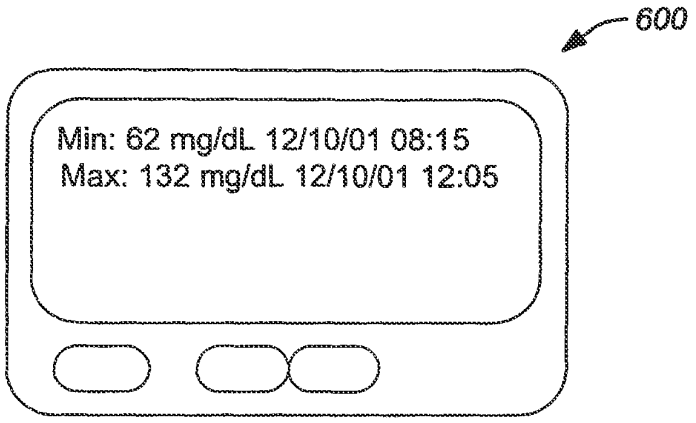


FIG. 6A

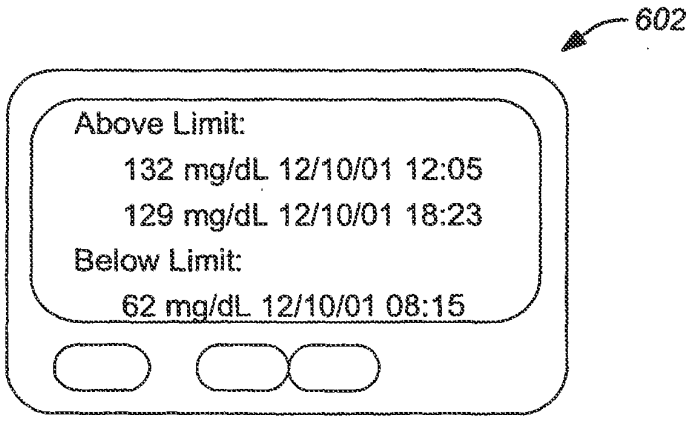


FIG. 6B

Abbott Ex. 1002 - 734/1438

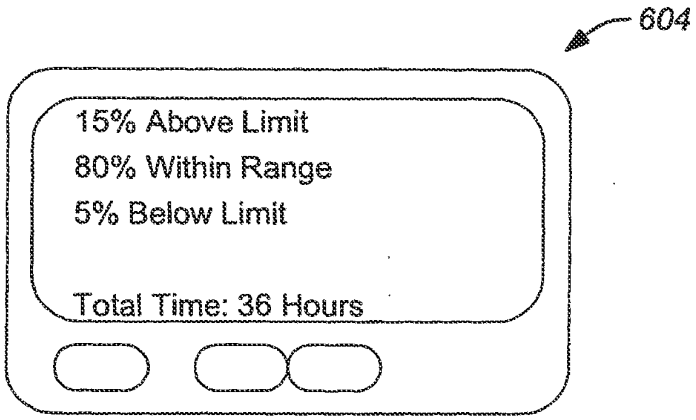


FIG. 6C

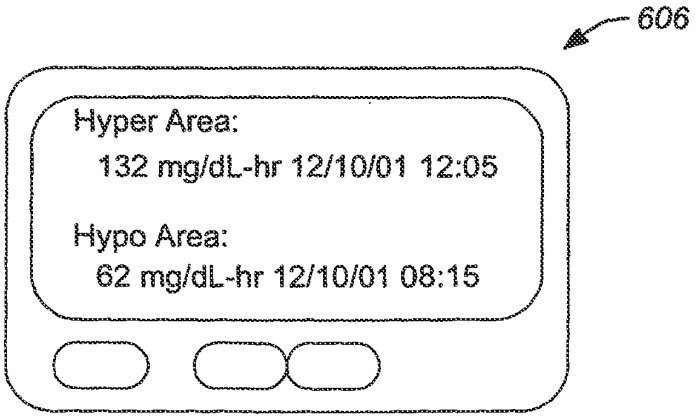


FIG. 6D

Abbott Ex. 1002 - 735/1438

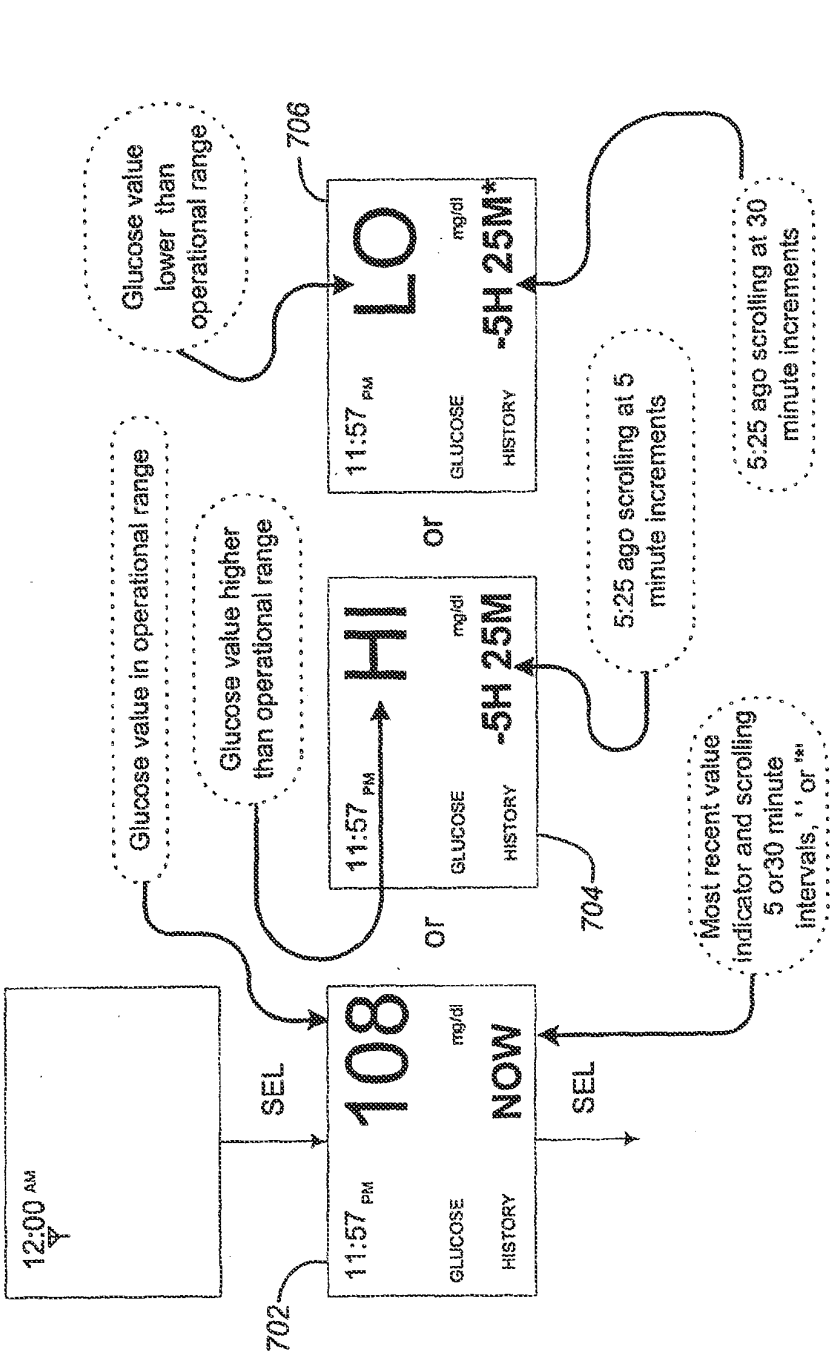


FIG. 7

Abbott Ex. 1002 - 736/1438

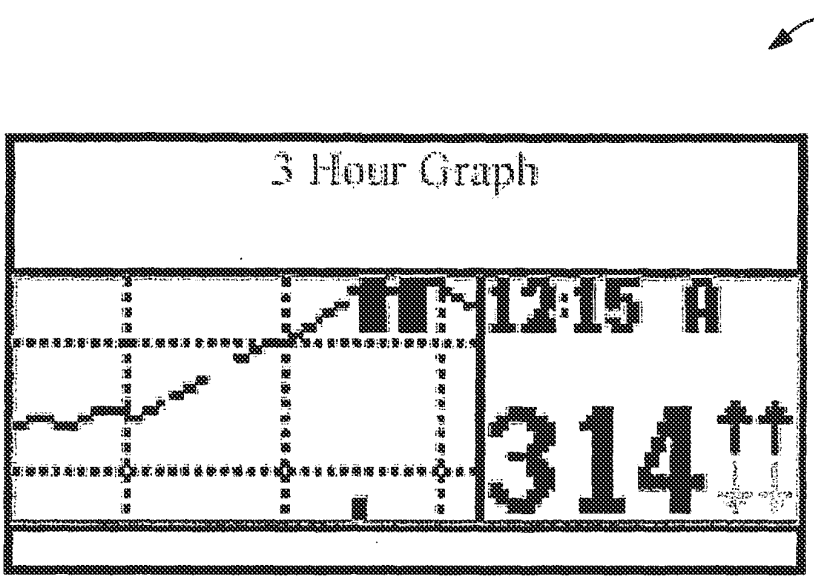


FIG. 8A

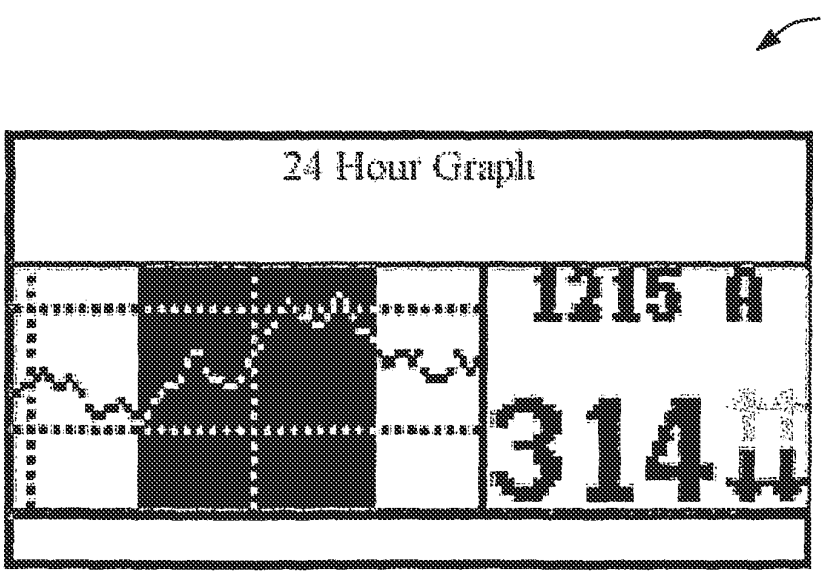


FIG. 8B

Abbott Ex. 1002 - 737/1438

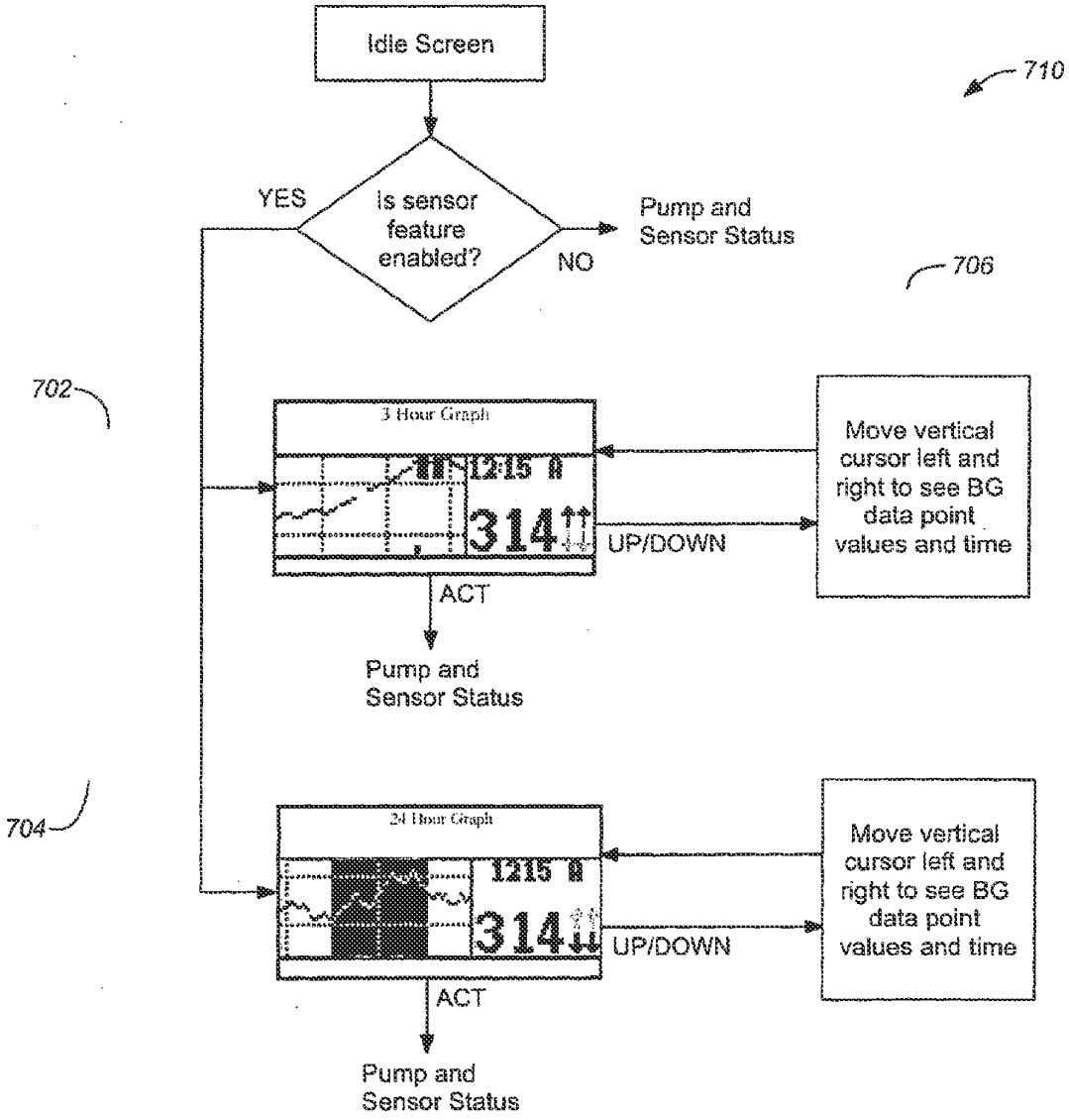


FIG. 8C

Abbott Ex. 1002 - 738/1438

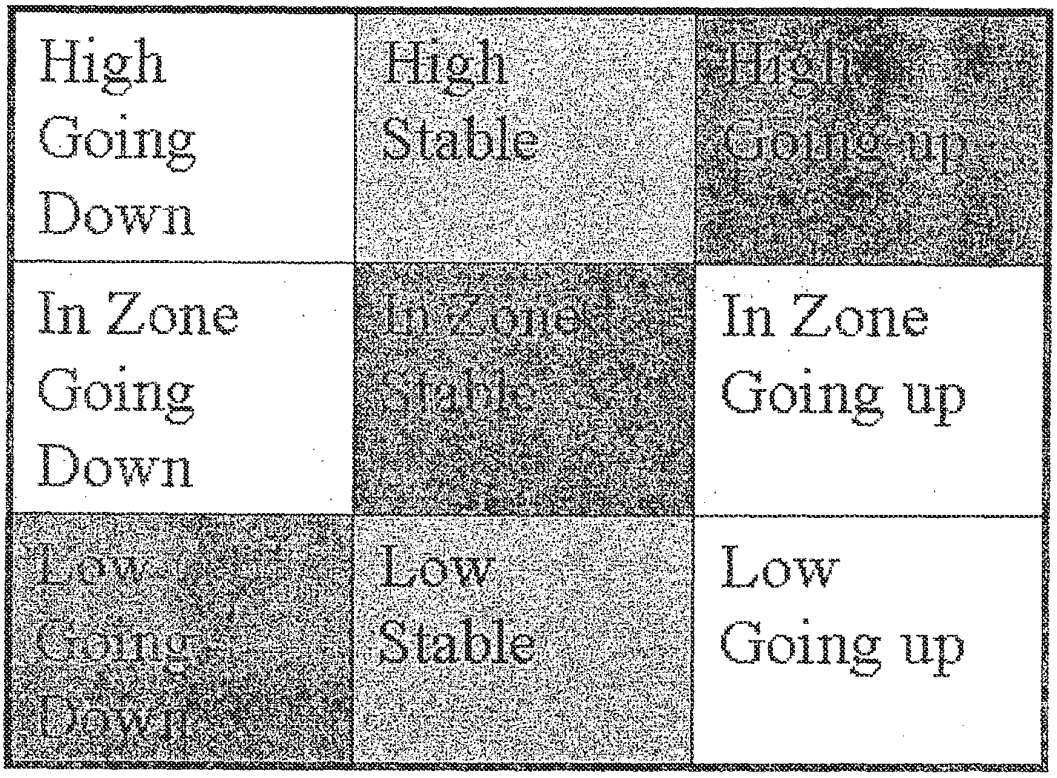


FIG. 8D

Abbott Ex. 1002 - 739/1438

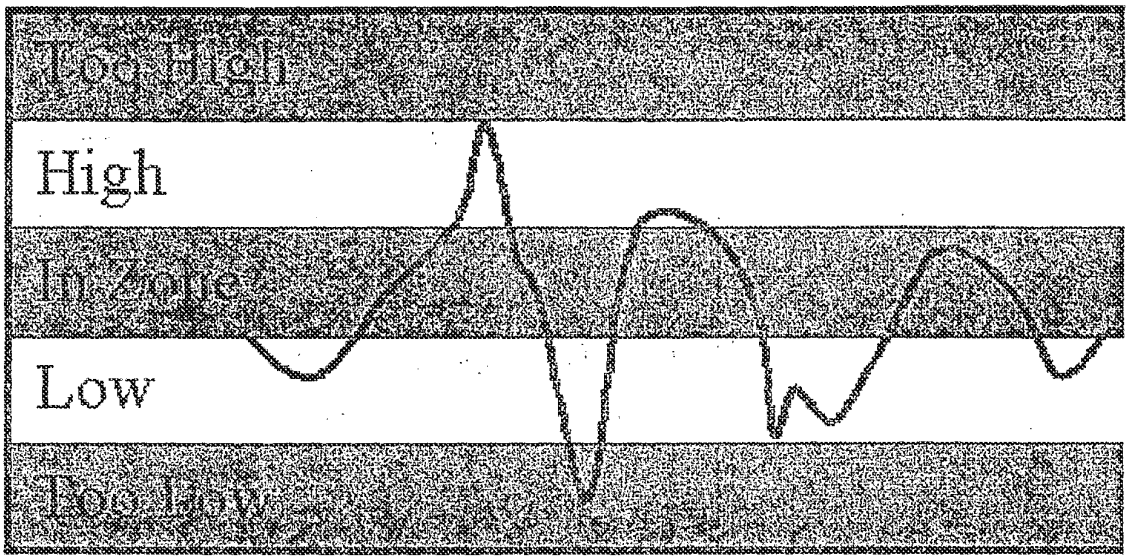


FIG. 8E

Abbott Ex. 1002 - 740/1438

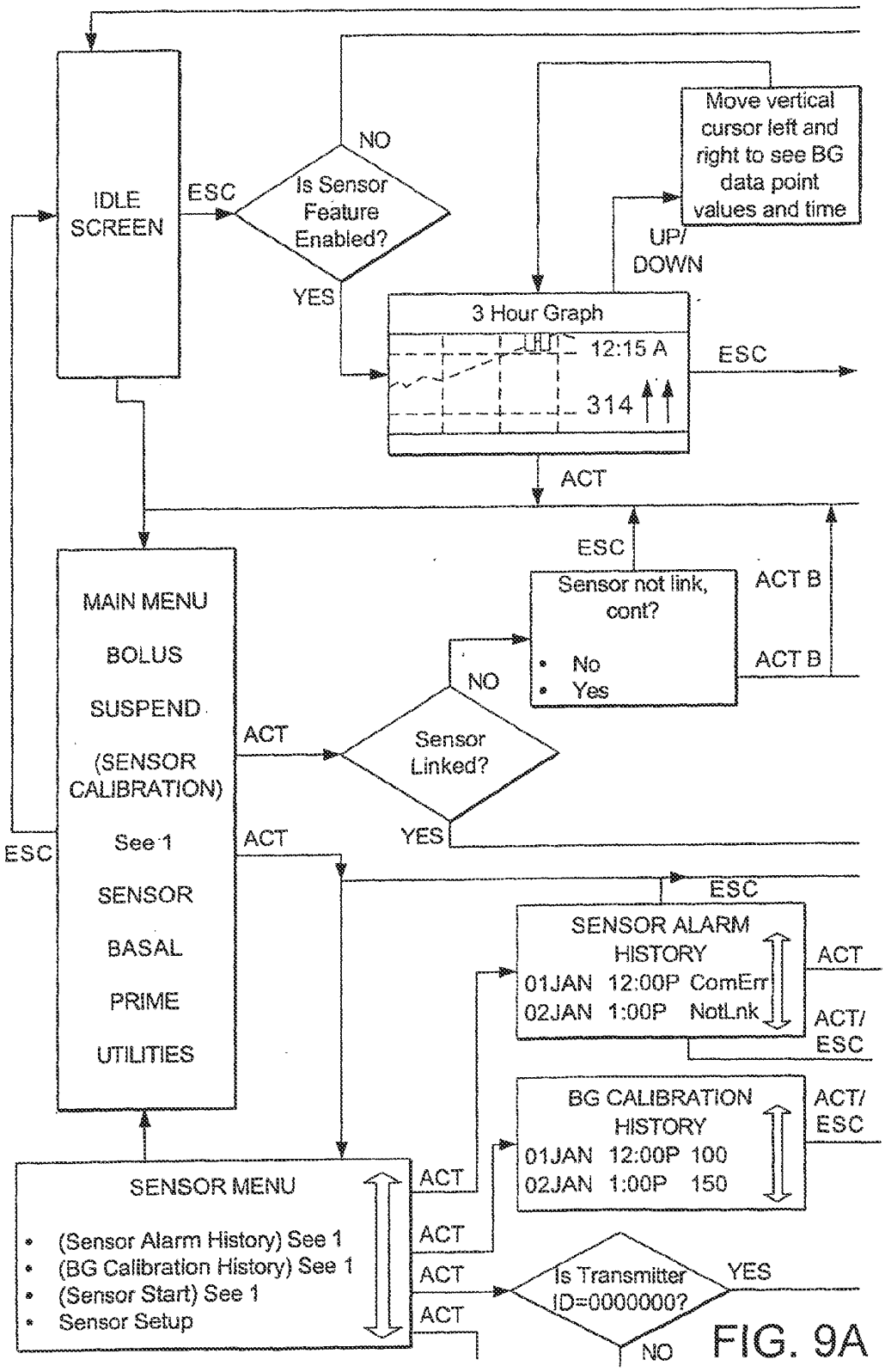


FIG. 9A

Abbott Ex. 1002 - 741/1438

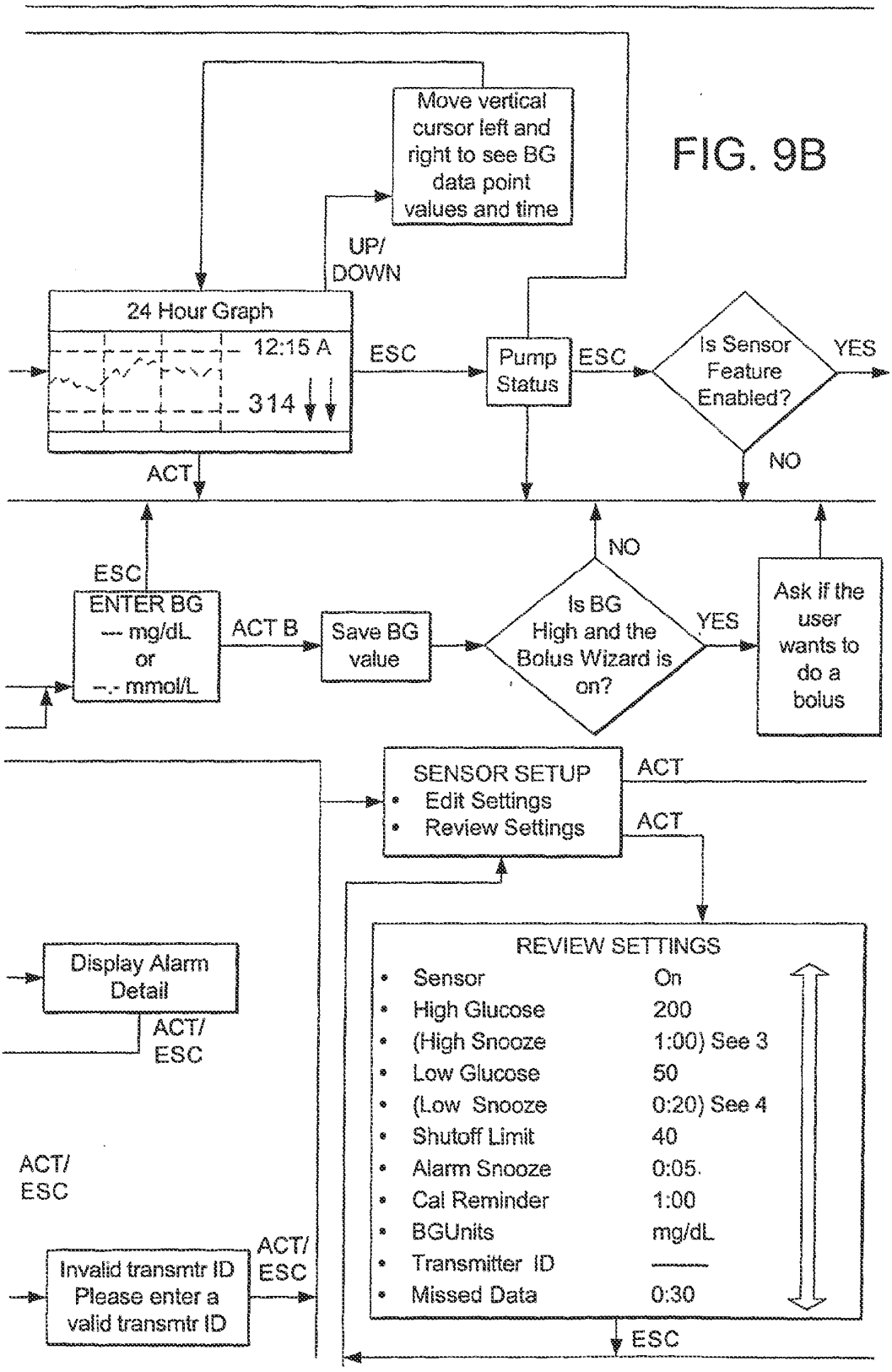


FIG. 9B

Abbott Ex. 1002 - 742/1438

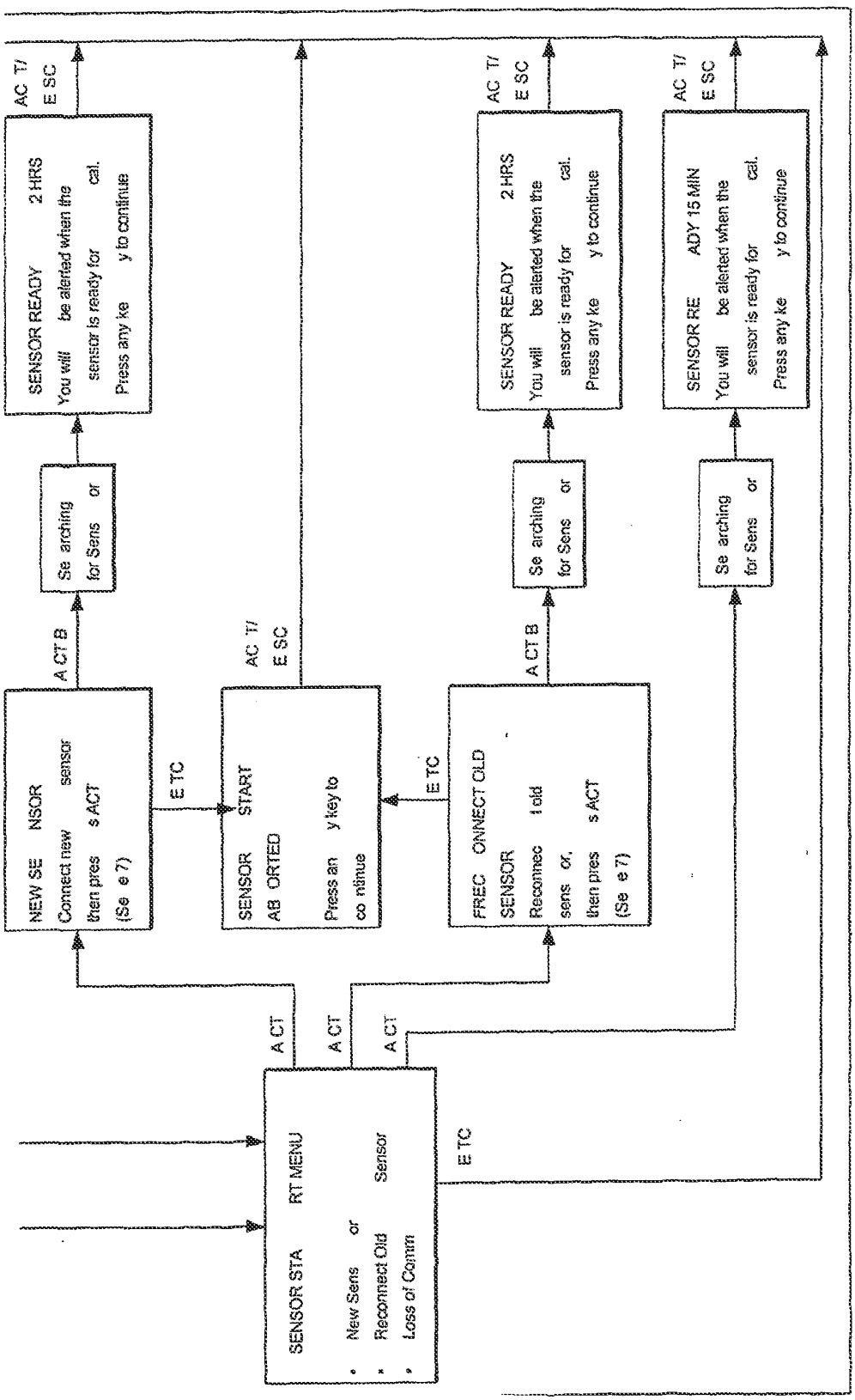


FIG. 9C

Abbott Ex. 1002 - 743/1438

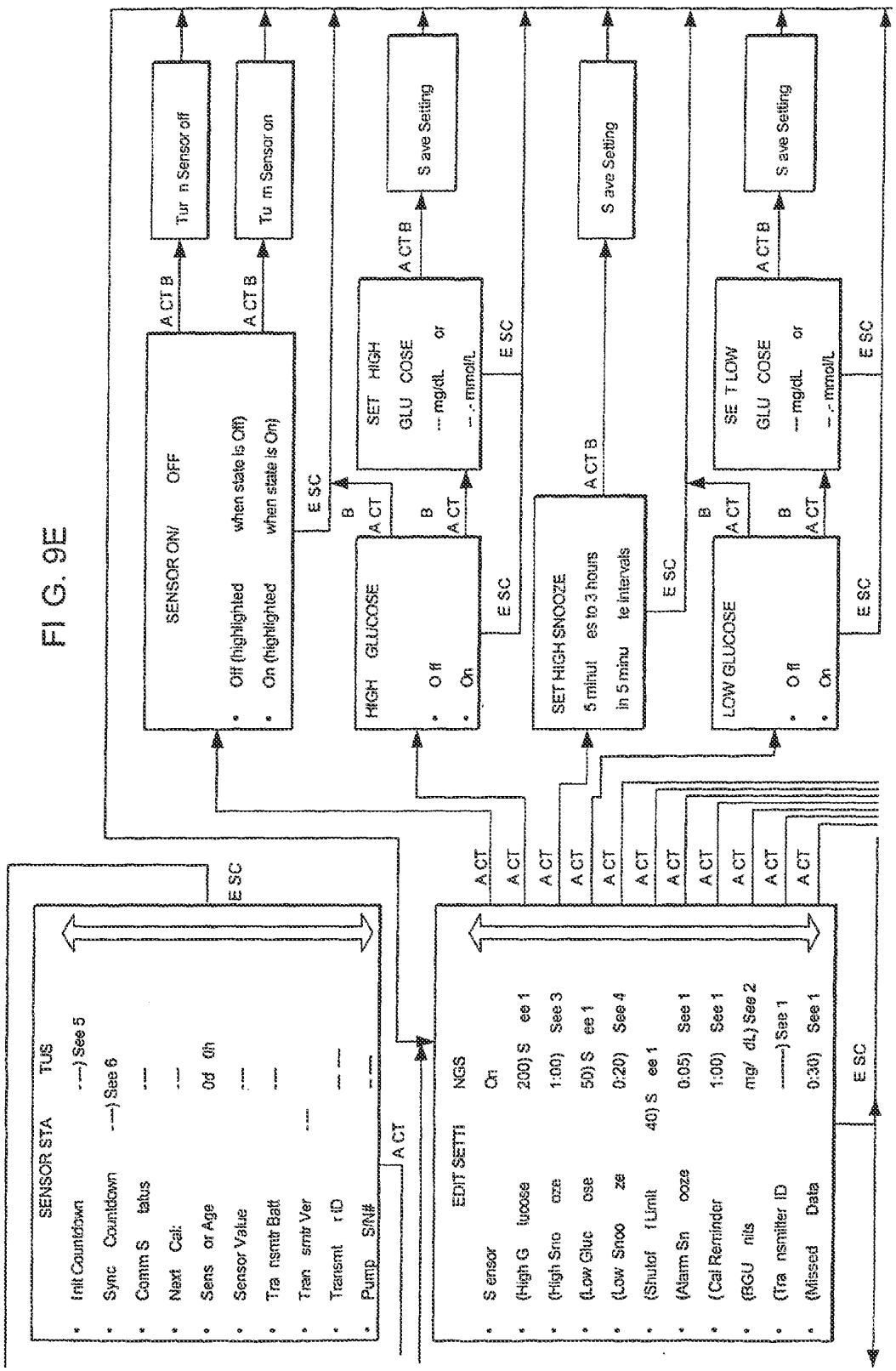
NOTES
1. Appears only if the Sensor Feature is on.
2. Appears only if the Bolus Wizard is enabled and the Sensor Feature is on.
3. Appears only when High Glucose Limit and Sensor Feature is enabled.
4. Appears only when Low Glucose Limit and Sensor Feature is enabled.
5. Appears only when a new sensor has been connected.
6. Appears only when an old sensor has been reconnected.
7. When this screen times out it returns to the idle screen. Pressing any key on the idle returns you to this screen.

Name	Default Value	Limit	Warning	Step Size	Max Entries
Sensor On/Off	Off	N/A	N/A	N/A	1
High Glucose	200 mg/dL	Low Glucose +10 mg/dL to 400 mg/dL Max range is 60 mg/dL to 400 mg/dL.	N/A	1 mg/dL	1
High Snooze	1:00	0:05 - 3:00	N/A	0:05	1
Low Glucose	50 mg/dL	Shutoff Limit +10 mg/dL to High Glucose -10 mg/dL. Max range is 50 mg/dL to 390 mg/dL.	N/A	1 mg/dL	1
Low Snooze	0:20	0:05 - 1:00	N/A	0:05	1
Shutoff Limit	40 mg/dL	40 mg/dL to Low Glucose -10 mg/dL. Max range is 40 mg/dL to 120 mg/dL.	N/A	1 mg/dL	1
Alarm Snooze	0:05	0:05 - 1:00	N/A	0:05	1
Cal Reminder	1:00	0:05 - 4:00	N/A	0:05	1
Missed Data	0:20	0:05 - 0:40	N/A	0:05	1

FIG. 9D

Abbott Ex. 1002 - 744/1438

FIG. 9E



Abbott Ex. 1002 - 745/1438

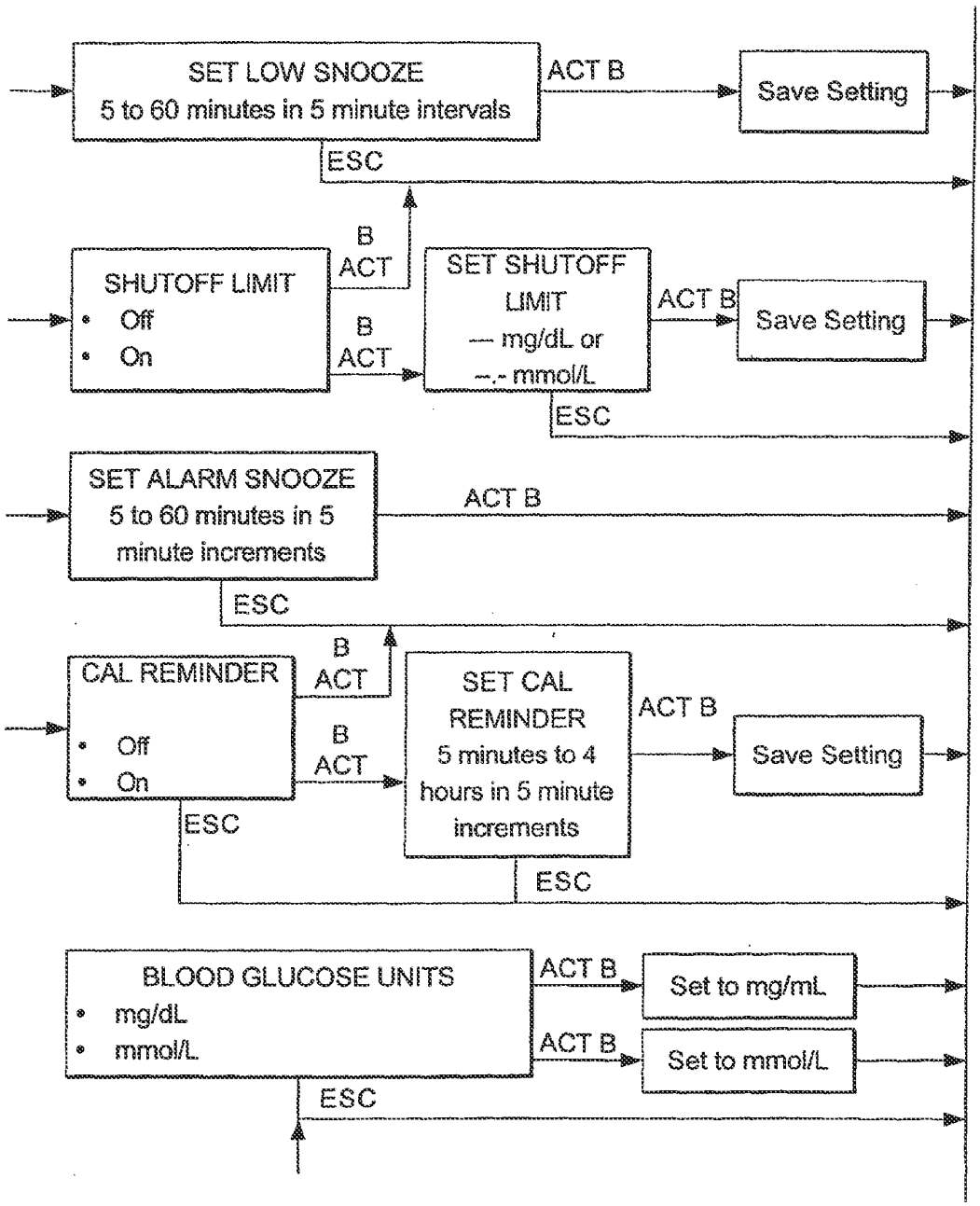


FIG. 9F

Abbott Ex. 1002 - 746/1438

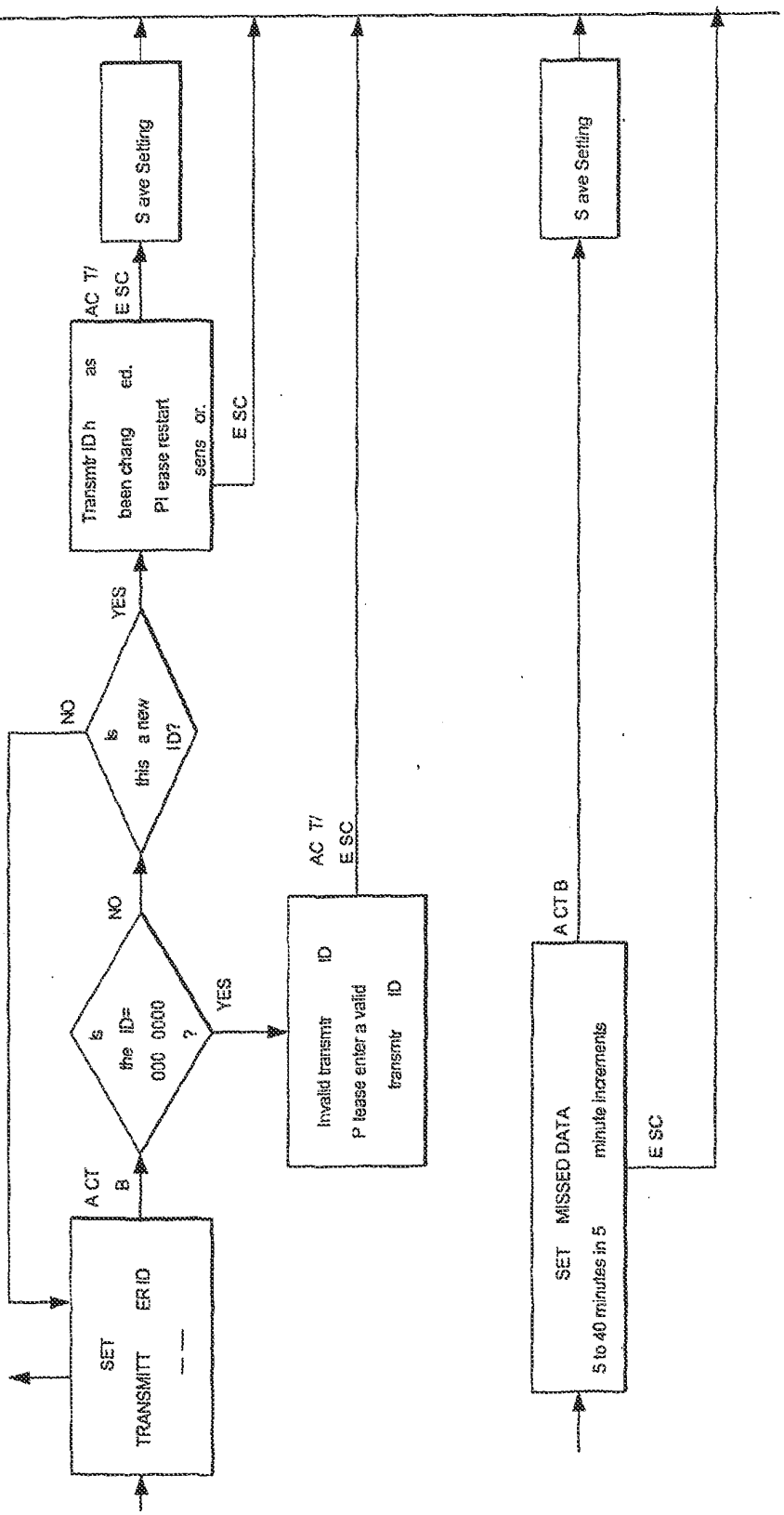


FIG. 9G

Abbott Ex. 1002 - 747/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 4562751 A **[0002] [0055]**
- US 4678408 A **[0002] [0055]**
- US 4685903 A **[0002] [0055]**
- US 4573994 A **[0002] [0055]**
- US 5299571 A **[0003]**
- US 5390671 A **[0003]**
- US 5391250 A **[0003] [0056]**
- US 5482473 A **[0003] [0056]**
- US 5586553 A **[0003]**
- US 20030187336 A **[0010]**
- US 6558351 B **[0040] [0041]**
- US 6551276 B **[0040] [0041]**
- WO 0019887 A **[0040] [0041]**
- WO 0018449 A **[0040] [0041]**
- WO 2004008956 A **[0040] [0041]**
- WO 2004009161 A **[0040] [0041]**

Abbott Ex. 1002 - 748/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 890 597 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
22.02.2012 Bulletin 2012/08

(21) Application number: **06760592.3**

(22) Date of filing: **31.05.2006**

(51) Int Cl.:
A61B 5/05 *(2006.01)* ***A61B 5/00*** *(2006.01)*

(86) International application number:
PCT/US2006/021113

(87) International publication number:
WO 2006/132884 (14.12.2006 Gazette 2006/50)

(54) METHOD AND APPARATUS FOR PROVIDING RECHARGEABLE POWER IN DATA MONITORING AND MANAGEMENT SYSTEMS

VERFAHREN UND GERÄT ZUR LIEFERUNG VON WIEDER AUFLADBARER ENERGIE IN DATENÜBERWACHUNGS- UND VERWALTUNGSSYSTEMEN

PROCEDE ET APPAREIL POUR LA FOURNITURE D'ENERGIE RECHARGEABLE DANS DES SYSTEMES DE CONTROLE ET DE GESTION DE DONNEES

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

(30) Priority: **03.06.2005 US 145048**

(43) Date of publication of application:
27.02.2008 Bulletin 2008/09

(73) Proprietor: **Abbott Diabetes Care Inc.**
Alameda, CA 94502 (US)

(72) Inventor: **REGGIARDO, Christopher, V.**
Castro Valley, CA 94546 (US)

(74) Representative: **Horton, Andrew Robert Grant**
Bowles Horton
Felden House
Dower Mews
High Street
Berkhamsted, Hertfordshire HP4 2BL (GB)

(56) References cited:
US-A- 6 144 869
US-A1- 2003 168 335
US-A1- 2005 277 844
US-B1- 6 185 452
US-B2- 7 136 704

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 890 597 B1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] The present invention relates to data monitoring and management systems. More specifically, the present invention relates to a method and apparatus for providing rechargeable power used in data monitoring systems such as glucose monitoring systems.

[0002] Glucose monitoring systems including continuous and discrete monitoring systems generally include a small, lightweight battery powered and microprocessor controlled system which is configured to detect signals proportional to the corresponding measured glucose levels using an electrometer, and RF signals to transmit the collected data. One aspect of such glucose monitoring systems include a sensor configuration which is, for example, mounted on the skin of a subject whose glucose level is to be monitored. The sensor cell may use a three-electrode (work, reference and counter electrodes) configuration driven by a controlled potential (potentiostat) analog circuit connected through a contact system.

[0003] The battery providing power to the microprocessor controlled system is typically configured for a limited duration usage, and thus would require periodic replacement Furthermore, given the compact size of the system, as well as the need for water tight seals, it is not desirable to have removable components such as battery covers or additional electrical contacts that may be exposed to the environment or to the patient's skin without the addition of seals and covers.

[0004] In view of the foregoing, it would be desirable to have an approach to readily and easily provide rechargeable power to the battery in the microprocessor controlled system.

[0005] The invention is defined by the independent claims 1 and 5, which are partitioned relative to the document US-B1-0185452.

[0006] In view of the foregoing, in accordance with the various embodiments of the present invention, there is provided a method and apparatus for charging the battery through the existing analog electrical contacts (electrodes) using the ESD protection circuitry.

[0007] More specifically, in one embodiment of the present invention, using the guard and the counter electrodes coupled to the transmitter unit of the data monitoring and management system, the power supply of the transmitter unit may be recharged so that the power supply need not be repeatedly replenished when it has been depleted of power and can not support reliable system operation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008]

FIG. 1 illustrates a block diagram of a data monitoring and management system for practicing one embodiment of the present invention;

FIG. 2 is a block diagram of the transmitter of the data monitoring and management system shown in FIG. 1 in accordance with one embodiment of the present invention;

FIG. 3 illustrates the front end section of the analog interface of the transmitter in accordance with one embodiment of the present invention;

FIGS. 4A-4B respectively show detailed illustrations of the current to voltage circuit and the counter-reference servo circuit of the analog interface shown in FIG. 3 in accordance with one embodiment of the present invention;

FIG. 5 illustrates the battery recharging circuit in accordance with one embodiment of the present invention;

FIG. 6 illustrates the battery recharging circuit in accordance with another embodiment of the present invention; and

FIGS. 7A-7B illustrates inductive battery recharging in accordance with alternate embodiments of the present invention.

DETAILED DESCRIPTION

[0009] FIG. 1 illustrates a data monitoring and management system such as, for example, a glucose monitoring system 100 in accordance with one embodiment of the present invention. In such embodiment, the glucose monitoring system 100 includes a sensor 101, a transmitter 102 coupled to the sensor 101, and a receiver 104 which is configured to communicate with the transmitter 102 via a communication link 103. The receiver 104 may be further configured to transmit data to a data processing terminal 105 for evaluating the data received by the receiver 104. Only one sensor 101, transmitter 102, communication link 103, receiver 104, and data processing terminal 105 are shown in the embodiment of the glucose monitoring system 100 illustrated in FIG. 1. However, it will be appreciated by one of ordinary skill in the art that the glucose monitoring system 100 may include one or more sensor 101, transmitter 102, communication link 103, receiver 104, and data processing terminal 105, where each receiver 104 is uniquely synchronized with a respective transmitter 102. Moreover, within the scope of the present invention, the glucose monitoring system 100 may be a continuous monitoring system, or a semi-continuous or discrete monitoring system.

[0010] In one embodiment of the present invention, the sensor 101 is physically positioned on the body of a user whose glucose level is being monitored. The sensor 101 may be configured to continuously sample the glucose level of the user and convert the sampled glucose level into a corresponding data signal for transmission by the transmitter 102. In one embodiment, the transmitter 102 is mounted on the sensor 101 so that both devices are positioned on the user's body. The transmitter 102 performs data processing such as filtering and encoding on data signals, each of which corresponds to a sampled

Abbott Ex. 1002 - 750/1438

glucose level of the user, for transmission to the receiver 104 via the communication link 103.

[0011] In one embodiment, the glucose monitoring system 100 is configured as a one-way RF communication path from the transmitter 102 to the receiver 104. In such embodiment, the transmitter 102 transmits the sampled data signals received from the sensor 101 without acknowledgement from the receiver 104 that the transmitted sampled data signals have been received. For example, the transmitter 102 may be configured to transmit the encoded sampled data signals at a fixed rate (e.g., at one minute intervals) after the completion of the initial power on procedure. Likewise, the receiver 104 may be configured to detect such transmitted encoded sampled data signals at predetermined time intervals. Alternatively, the glucose monitoring system 10 may be configured with a bi-directional RF communication between the transmitter 102 and the receiver 104.

[0012] Additionally, in one aspect, the receiver 104 may include two sections. The first section is an analog interface section that is configured to communicate with the transmitter 102 via the communication link 103. In one embodiment, the analog interface section may include an RF receiver and an antenna for receiving and amplifying the data signals from the transmitter 102, which are thereafter, demodulated with a local oscillator and filtered through a band-pass filter. The second section of the receiver 104 is a data processing section which is configured to process the data signals received from the transmitter 102 such as by performing data decoding, error detection and correction, data clock generation, and data bit recovery.

[0013] In operation, upon completing the power-on procedure, the receiver 104 is configured to detect the presence of the transmitter 102 within its range based on, for example, the strength of the detected data signals received from the transmitter 102 or a predetermined transmitter identification information. Upon successful synchronization with the corresponding transmitter 102, the receiver 104 is configured to begin receiving from the transmitter 102 data signals corresponding to the user's detected glucose level. More specifically, the receiver 104 in one embodiment is configured to perform synchronized time hopping with the corresponding synchronized transmitter 102 via the communication link 103 to obtain the user's detected glucose level.

[0014] Referring again to FIG. 1, the data processing terminal 105 may include a personal computer, a portable computer such as a laptop or a handheld device (e.g., personal digital assistants (PDAs)), and the like, each of which may be configured for data communication with the receiver via a wired or a wireless connection. Additionally, the data processing terminal 105 may further be connected to a data network (not shown) for storing, retrieving and updating data corresponding to the detected glucose level of the user.

[0015] Within the scope of the present invention, the data processing terminal 105 may include an infusion device such as an insulin infusion pump, which may be configured to administer insulin to patients, and which is configured to communicate with the receiver unit 104 for receiving, among others, the measured glucose level. Alternatively, the receiver unit 104 may be configured to integrate an infusion device therein so that the receiver unit 104 is configured to administer insulin therapy to patients, for example, for administering and modifying basal profiles, as well as for determining appropriate boluses for administration based on, among others, the detected glucose levels received from the transmitter 102.

[0016] FIG. 2 is a block diagram of the transmitter of the data monitoring and detection system shown in FIG. 1 in accordance with one embodiment of the present invention. Referring to the Figure, the transmitter 102 in one embodiment includes an analog interface 201 configured to communicate with the sensor 101 (FIG. 1), a user input 202, and a temperature detection section 203, each of which is operatively coupled to a transmitter processor 204 such as a central processing unit (CPU). As can be seen from FIG. 2, there are provided four contacts, three of which are electrodes - work electrode (W) 210, guard contact (G) 211, reference electrode (R) 212, and counter electrode (C) 213, each operatively coupled to the analog interface 201 of the transmitter 102 for connection to the sensor unit 201 (FIG. 1). In one embodiment, each of the work electrode (W) 210, guard contact (G) 211, reference electrode (R) 212, and counter electrode (C) 213 may be made using a conductive material that is either printed or etched, for example, such as carbon which may be printed, or metal foil (e.g., gold) which may be etched.

[0017] Further shown in FIG. 2 are a transmitter serial communication section 205 and an RF transmitter 206, each of which is also operatively coupled to the transmitter processor 204. Moreover, a power supply 207 such as a battery, including a rechargeable battery, is also provided in the transmitter 102 to provide the necessary power for the transmitter 102 where the guard contact (G) 211 and the counter electrode (C) 213 are configured to couple to the power supply 207 through ESD clamp diodes (in the analog interface 201). Additionally, as can be seen from the Figure, clock 208 is provided to, among others, supply real time information to the transmitter processor 204. As discussed in further detail below, the power supply 207 may be configured to be recharged via a select pair of the plurality of electrodes 210-213 such as the guard contact 211 and counter electrode 213, when the transmitter unit 102 is not mounted to a patient and configured for periodic transmission of measured data to the receiver unit 103. As further discussed below, the power supply 207 may be coupled or docked to a battery charging station or unit during the recharge process, where the power supply 207 is recharged and, thereafter, when the transmitter unit 102 is mounted to the patient and coupled to the sensor 101, the power supply 207 may be configured to provide the necessary power to reliably operate the transmitter unit 102.

Abbott Ex. 1002 - 751/1438

[0018] Referring back to the Figures, in one embodiment, a unidirectional input path is established from the sensor 101 (FIG. 1) and/or manufacturing and testing equipment to the analog interface 201 of the transmitter 102, while a unidirectional output is established from the output of the RF transmitter 206 of the transmitter 102 for transmission to the receiver 104. In this manner, a data path is shown in FIG. 2 between the aforementioned unidirectional input and output via a dedicated link 209 from the analog interface 201 to serial communication section 205, thereafter to the processor 204, and then to the RF transmitter 206. As such, in one embodiment, via the data path described above, the transmitter 102 is configured to transmit to the receiver 104 (FIG. 1), via the communication link 103 (FIG. 1), processed and encoded data signals received from the sensor 101 (FIG. 1). Additionally, the unidirectional communication data path between the analog interface 201 and the RF transmitter 206 discussed above allows for the configuration of the transmitter 102 for operation upon completion of the manufacturing process as well as for direct communication for diagnostic and testing purposes.

[0019] As discussed above, the transmitter processor 204 is configured to transmit control signals to the various sections of the transmitter 102 during the operation of the transmitter 102. In one embodiment, the transmitter processor 204 also includes a memory (not shown) for storing data such as the identification information for the transmitter 102, as well as the data signals received from the sensor 101. The stored information may be retrieved and processed for transmission to the receiver 104 under the control of the transmitter processor 204. Furthermore, the power supply 207 may include a commercially available non-rechargeable battery or a proprietary or commercially available rechargeable battery.

[0020] The transmitter 102 is also configured such that the power supply section 207 does not significantly affect the battery life after having been stored for 18 months in a low-power (non-operating) mode. In one embodiment, this may be achieved by the transmitter processor 204 operating in low power modes in the non-operating state, for example, drawing no more than approximately 1 μA of current. Indeed, in one embodiment, the final step during the manufacturing process of the transmitter 102 may place the transmitter 102 in the lower power, non-operating state (i.e., post-manufacture sleep mode). In this manner, the shelf life of the transmitter 102 may be significantly improved.

[0021] Referring yet again to FIG. 2, the temperature detection section 203 of the transmitter 102 is configured to monitor the temperature of the skin near the sensor insertion site. The temperature reading is used to adjust the glucose readings obtained from the analog interface 201. The RF transmitter 206 of the transmitter 102 may be configured for operation in the frequency band of 315 MHz to 322 MHz, for example, in the United States. Further, in one embodiment, the RF transmitter 206 is configured to modulate the carrier frequency by performing Frequency Shift Keying and Manchester encoding. In one embodiment, the data transmission rate is 19,200 symbols per second, with a minimum transmission range for communication with the receiver 104.

[0022] Additional detailed description of the continuous glucose monitoring system, its various components including the functional descriptions of the transmitter are provided in U.S. Patent No. 6,175,752 issued January 16, 2001 entitled "Analyte Monitoring Device and Methods of Use", and in application No. 10/745,878 filed December 26, 2003 entitled "Continuous Glucose Monitoring System and Methods of Use", each assigned to the Assignee of the present application, and the disclosures of each of which are incorporated herein by reference for all purposes.

[0023] FIG. 3 illustrates the front end section of the analog interface of the transmitter in accordance with one embodiment of the present invention. Referring to the Figure, the front end section of the analog interface 201 includes a current to voltage circuit 301 which is configured to operatively couple to the work electrode 210 and the guard contact 211, and a counter-reference servo circuit 302 which is configured to operatively couple to the reference electrode 212 and the counter electrode 213.

[0024] FIGS. 4A-4B illustrate detailed illustrations of the current to voltage circuit and the counter-reference servo circuit, respectively, of the analog interface shown in FIG. 3 in accordance with one embodiment of the present invention. Referring to FIG. 4A, the current to voltage circuit 301 (FIG. 3) in one embodiment includes an operational amplifier 402 having a non-inverting input terminal 405, and an inverting input terminal 404. Also shown in the Figure is a resistor 401 operatively coupled to the inverting input terminal 404 of the operational amplifier 402, and an output terminal 406.

[0025] Referring again to FIG. 4A, the work electrode 210 is operatively coupled to the inverting input terminal 404 of the operational amplifier 402, while the guard contact 211 is operatively coupled to the non-inverting input terminal 405 of the operational amplifier 402. It can be further seen that the work voltage source Vw is provided to the non-inverting terminal 405 of the operational amplifier 402. In this manner, in accordance with one embodiment of the present invention, a separate contact, the guard contact 211 is operatively coupled to the analog interface 201 (FIG. 2) of the transmitter 102 (FIG. 2). The guard contact 211 is provided at a substantially equipotential to the work electrode 210 such that any current leakage path to the work electrode 210 (from either the reference electrode 212 or the counter electrode 213, for example) is protected by the guard contact 211 by maintaining the guard contact 211 at substantially the same potential as the work electrode 210.

[0026] Referring now to FIG. 4B, the counter-reference servo unit 302 in accordance with one embodiment includes an operational amplifier 407 having an inverting input terminal 408 and a non-inverting input terminal 409,

Abbott Ex. 1002 - 752/1438

as well as an output terminal 410. In one embodiment, the reference electrode 212 is operatively coupled to the inverting input terminal 408, while the counter electrode 213 is operatively coupled to the output terminal 410 of the operational amplifier 407 in the counter-reference servo unit 302. It can also be seen from FIG. 4B that a reference voltage source Vr is provided to the non-inverting input terminal 409 of the operational amplifier 407 in the counter-reference servo unit 302.

[0027] Referring back to FIGS. 3 and 4A-4B, in accordance with one embodiment of the present invention, the current to voltage circuit 301 and the counter-reference servo unit 302 are operatively coupled to the remaining sections of the analog interface 201 of the transmitter 102, and configured to convert the detected glucose level at the sensor unit 101 (FIG. 1) into an analog signal for further processing in the transmitter unit 102. It should also be noted that, in the manner described, the Poise voltage (for example, at a value of 40 mV) may be determined based on the difference between the voltage signal level of the work voltage source Vw at the non-inverting input terminal 405 of the operational amplifier 402 in the current to voltage circuit 301, and the voltage signal level of the reference voltage source Vr at the non-inverting input terminal 409 of the operational amplifier 407 in the counter-reference servo unit 302.

[0028] FIG. 5 illustrates the battery recharging circuit in accordance with one embodiment of the present invention. Referring to the Figure, in one embodiment of the present invention, the analog interface unit 201 of the transmitter unit 102 includes a pair of electrode contacts 510, 520 which are configured to respectively couple to the electrode contacts of the transmitter unit 102 for example, to the electrode contacts for the guard contact 210 and the counter electrode 213 (FIG. 3). Within the scope of the present invention, the guard contact 210 in one embodiment may not be configured as an electrode with respect to the sensor unit 101, but referred to herein as an electrode. The electrode contact 510 which, in one embodiment is coupled to the counter electrode 213 contact of the transmitter unit 102, for example, is coupled in series to a resistor 511 that is in turn, further coupled to a pair of ESD protection diodes 512, 513. Moreover, in one embodiment, the electrode contact 520 which in one embodiment is coupled to the guard contact 210 contact of the transmitter unit 102, is coupled in series to a resistor 521, that is in turn, further coupled to another pair of EDS protection diodes 522, 523.

[0029] In this manner, in one embodiment of the present invention, during the power supply or battery recharging process (for example, when the transmitter unit 102 is docked or positioned in the power supply recharging unit (not shown)), electrode contact 520 is coupled to the recharging unit's ground terminal potential, while the electrode contact 510 is coupled to the positive charging voltage supply. In this manner, as shown in FIG. 5, current I is configured to flow into the electrode contact 510 through resistor 511, and forward bias the ESD protection diodes 512, and 523, thereby charging the battery 530 of the power supply 207 (FIG. 2) for the transmitter unit 102, and then flow through resistor 521 out to the electrode contact 520 which is held at ground potential as discussed above. Due to symmetry, this process also works when electrode contact 510 is coupled to the recharging unit's ground terminal potential, while the electrode contact 520 is coupled to the positive charging voltage supply such that the ESD protection diodes 513, and 522 become forward biased.

[0030] In the manner described above, in one embodiment of the present invention, the current I may be monitored and the voltage drops across the resistors 511 and 521 and the respective pairs of the EDS protection diodes 512, 513, and 522, 523 may be determined (for example, based on current), so as to control the battery 530 charging voltage level and to ensure that the power supply 207 is properly charged.

[0031] Indeed, in one embodiment of the present invention, a positive charging voltage may be applied to one electrode of the transmitter unit 102 such as the Counter electrode 213 with respect to another electrode such as the guard contact 210, so that current would flow into the electrode contact 510 coupled to the counter electrode 213, through the counter electrode ESD protection resistor 511, and also, through the counter electrode positive clamp diode 512, and through the battery 530 of the power supply 207 thereby charging the battery 530 of the power supply 207. Additionally, the current also flows through the guard contact negative clamp diode 523, and through the guard ESD protection resistor 521, and out the electrode contact 520 coupled to the guard contact 210. In one embodiment, the counter electrode and guard contact ESD protection resistors 511, 521 include nominal resistor values from 50 Ohms to 1KOhm.

[0032] In the embodiment described above, the counter electrode 213 and the guard contact 210 were used for the power supply 207 recharging process because they have lower ESD protection resistors (for example, at 50 Ohms to 1KOhms nominal) as compared to the ESD protection resistors of the work electrode 211 and the reference electrode 212 which may be at 10KOhms nominal. Moreover, the counter electrode 213 and the guard contact 210 have common clamp diodes (For example, having part No. BAV 199) as compared to the low-leakage ESD protection devices that are required for the work electrode 211 and the reference electrode 212 (each of which may use STTRDPAD diodes or alternate ESD protection technology such as the SurgX 0603ESDA). Moreover, they have series resistors (10k nominal) between the clamp diode (ESD protection device) node and the driving circuits.

[0033] Although both the counter electrode 213 and the guard contact 210 signals are outputs, in one embodiment, each has a series resistor (for example, 20KOhms nominal) between the ESD diode clamp node and the associated analog circuitry (not shown) making

Abbott Ex. 1002 - 753/1438

it is acceptable to overdrive each of these signals with the charging voltage without causing damage.

[0034] Moreover, it should be noted that the charging voltage to the power supply charging unit should be limited to 3.6 Volts or less to prevent potential damage to the battery 530 and the transmitter unit 102 circuitry during the recharging process. The voltage limit of 3.6 Volts in one embodiment is the voltage limit of the processor 204 of the transmitter unit 102. For example, if the battery 530 is being recharged with a 10mA current and the voltage across the ESD protection resistors 511 and 521 is modeled as 1 Volt each (assuming 100 Ohm valued resistors) and the voltage across the ESD protection diodes 512 and 523 is modeled as 0.7 Volts each (assuming BAV 199 part numbers), then the charging circuit would limit the charging voltage to 7 Volts, which is a sum of the voltages across the EDS protection resistors 511, 521, the voltages across the two ESD protection diodes 512, 523, and the voltage limit of the processor 204.

[0035] Moreover, while the counter electrode 213 and the guard contact 210 are used for the power supply 207 recharging process in the embodiment discussed above, within the scope of the present invention, the work electrode 211 and the reference electrode 212 may be used for the power supply 207 charging process.

[0036] Additionally, within the scope of the present invention, if the comparator used for data input through the AFE was maintained, then the comparator may be configured to toggle when the transmitter unit 102 is docked or coupled to the power supply charging unit, thus effectively, pulling the electrode contact 520 coupled to the guard contact 211 in one embodiment low with respect to the electrode contact 510 coupled in one embodiment to the counter electrode 213, and further, to revert when the transmitter unit 102 is undocked or removed from the power supply charging unit. In this manner, within the scope of the present invention, it is possible to provide a signal representative of an indication that the transmitter unit 102 is in a recharging process, such that the power supply monitoring algorithm for example, in the processor 204 (FIG. 2) may be updated accordingly. For example, the amount of battery 530 life, which decreases with respect to usage time, may be increased with respect to charging time. This allows an accurate estimate of usable battery 530 life so that a new sensor may not be inserted when the system does not have sufficient battery life to support proper operation for the life of a given sensor 101 (FIG. 1). Moreover, this may allow normal transmitter unit 102 operation and RF transmissions to be suspended when the transmitter unit 102 is being charged to prevent RF contention or collision with a second transmitter unit that may be used when the first transmitter unit 102 is charging.

[0037] In the manner described above, in accordance with one embodiment of the present invention, to maintain the smallest possible size and cost, is a method of recharging the battery or power supply 207 of the transmitter unit 102 through the ESD protection circuitry on two of the four electrodes 210-213. Moreover, in the manner described above, in one embodiment of the present invention, the risk of having a pair of unprotected battery contacts exposed to the patient and the environment is eliminated.

[0038] Indeed, as discussed above, in accordance with the various embodiments of the present invention, when the data monitoring and management system 100 (and in particular, the transmitter unit 102) is not connected to a patient, it can be connected to a battery charging system. This battery charger would hold one of the two electrodes used for charging the battery at the chargers ground potential. The second of the two electrodes used for charging the battery would then be brought to a potential to forward bias the ESD protection diodes causing a current to flow into one electrode, through any series resistance, through an ESD protection diode to the positive battery contact, through the battery - thus charging the battery, out the negative battery contact through another ESD protection diode, through any series resistance, and out the second electrode. By monitoring the current and calculating the voltage drops across any series resistance elements and the ESD protection diodes, the battery voltage can be controlled and proper charging achieved.

[0039] FIG. 6 illustrates a portion of the battery recharging circuit for battery recharging through ESD protection circuitry in accordance with another embodiment of the present invention. Referring to the Figure, a battery recharging unit 610 (such as, for example, a recharging docking station) is provided with a pair of diodes 611, 612 coupled to a resistor 613 as shown in the Figure such that a current I is configured to flow from electrode contact 510, into the transmitter unit 102, and back out through the electrode contact 520, thus creating a recharging current path through the rechargeable battery 530 (for example, FIG. 5) in the transmitter unit 102 power supply 207.

[0040] While the voltage level at the electrode contact 510 (at terminal Vout shown in FIG. 5) may be driven directly, the recharging unit needs to have knowledge of the recharging voltage at the battery, and thus the recharging current through the various ESD components such as the diodes and series resistors as described above. Moreover, most batteries require recharging based on a voltage-current profile over time. Indeed, many batteries require different voltage-current profiles for various stages of the charging process (i.e. one profile for a "fast-charge" portion up to 80% recharge and another profile for the remaining recharge portion, for example). As a result, the charging voltage is often driven through a shunt resistor 613, that is, at the drive node Vr3, with feedback to indicate the charging current and voltage (Vr3 minus Vout and Vout respectively).

[0041] In one embodiment, the battery recharging process through ESD protection circuitry may include driving node Vdrive and determining the feedback at the node Vdrive, node Vr3 and node Vout, to calculate the

Abbott Ex. 1002 - 754/1438

current into and voltage across the rechargeable battery 530, where the diode 611 and the resistor 613 are selected to match the component values of the ESD protection circuitry for the transmitter unit 102 being recharged. Thus the voltage across the diode 612 and the resistor 613 (Vdrive minus Vout) matches the voltage across the resistor 511 (FIG. 5) and the diode 512 (FIG. 5) pair and the voltage across the resistor 521 (FIG. 5) and the diode 523 (FIG. 5) pair giving the battery 530 voltage as Vout - 2 * (Vdrive - Vout) or 3V out - 2Vdrive.

[0042] One advantage of this approach is that there is no need to model the voltage drop across the ESD protection diodes, which are not linear with respect to current, as they match the voltage drop across the diode 612, where the diode 611 is inactive just as, for example the diode 513 (FIG. 5) and the diode 522 are inactive (there is similar component package heating as all components are used in a similar fashion).

[0043] For example, if the transmitter unit 102 being recharged uses BAV 199 ESD protection diodes and 100 Ohm series resistors as described above, then the diode 611 is a BAV 199 diode and the resistor 613 is 100 Ohms (the precision of which is selected as is appropriate) such that the current I = Vr3 - Vout / R3 (resistor 613), which is equal to Vr3 - Vout /100. The voltage at Vdrive is then driven using analog, digital (digital logic such as a microprocessor and a D/A converter) or some combination of mixed signal techniques (analog and digital) to maintain the preferred voltage-current battery recharging profile over time. Moreover, this technique allows the recharging circuitry to be larger and more complex while maintaining the small size and low cost of the unit being recharged.

[0044] FIGS. 7A-7B illustrates inductive battery recharging in accordance with alternate embodiments of the present invention. Referring to FIG. 7A, in one embodiment of the present invention, during the power supply or battery recharging process (for example, when the transmitter unit 102 is docked or positioned in the power supply recharging unit 760), power source 710, such as a wall plug or an external battery, is coupled to a power driver 720 of the power supply recharging unit 760. As shown in the Figure, there is also provided a power circuit 730 in the power supply 207 of the transmitter unit 102 which, together with the power driver 720 comprise a transformer. As can be further seen from FIG. 7A, the power circuit 730 in the power supply 207 of the transmitter unit 102 in one embodiment may be further coupled to the power supply source 740 which is configured to supply power to the transmitter unit 102 when the transmitter is in normal operation, and further, to the rechargeable battery 750.

[0045] In this manner, in one embodiment of the present invention, the power circuit 730 of the power supply 207 in the transmitter unit 102 may be configured to recharge the battery 750 based on a predetermined and/or desired voltage-current recharging profiles whenever power is applied via the power source 710 and power driver 720.

[0046] Referring to FIG. 7B, an alternate embodiment of the inductive power supply recharging schematic is shown, where, there is also provided a separate connection to the rechargeable battery 750 coupled to the power circuit 730, and which, in one embodiment is configured to supply power to the transmitter unit 102 power supply 207 via the power supply source 740, or alternatively, be recharged by the power circuit 730 via the power source 710 when coupled thereto. When recharging, the power supply source 740 may be set to 0 Volts to disable system operation, or alternatively, may be a valid operating voltage provided by the power circuit 730. One advantage of this approach is that the power circuit 730 need not account for power being consumed by the supply source 740 when recharging the battery 750 according to the predetermined and/or desired voltage-current profiles.

[0047] In the manner described above, in accordance with one embodiment of the present invention, inductive power charging is provided using a transformer and receiving power from an external power source during the power supply or battery recharging process (for example, when the transmitter unit 102 is docked or positioned in the power supply recharging unit). Moreover, a rechargeable battery may be provided in the transmitter unit to provide power when the external power source is disconnected. Similar to the approach shown in FIG. 5 above, in one aspect of the present invention, the power circuit 730 may provide a signal representative of an indication that the transmitter unit 102 is in a recharging process, such that the power supply monitoring algorithm for example, in the processor 204 (FIG. 2) may be updated accordingly.

[0048] In this manner, within the scope pf the present invention, there is provided an apparatus for recharging power in a data communication device including a plurality of contacts, a power source operatively coupled to the plurality of contacts, and a rechargeable battery operatively coupled to the plurality of contacts, where the rechargeable battery is configured to receive a predetermined signal from the power source, and further, where the rechargeable battery is configured to recharge based on the predetermined signal from the power source.

[0049] The plurality of contacts may include a guard contact and a counter electrode, and the rechargeable battery and the plurality of contacts may be provided in a data communication device, wherein the rechargeable battery is configured to provide power to the data communication device.

[0050] The data communication device in one embodiment may include a data transmitter, and the data transmitter may be configured to transmit measured glucose data. In one embodiment, the data communication device may be configured for either a uni-directional or bi-directional wireless data communication. Further, in one embodiment, the wireless data communication may include one or more of the following data communication protocols: rf communication, infrared communication, Bluetooth data communication; and 802.11x communication

Abbott Ex. 1002 - 755/1438

protocol.

[0051] In a further aspect, the transmitter may be configured to receive the measured glucose data from a sensor, where the sensor may include one of a subcutaneous sensor and a transcutaneous sensor, configured to detect an analyte level, which in one embodiment includes glucose level.

[0052] An apparatus including a rechargeable power in a glucose monitoring system in a further embodiment of the present invention includes a sensor configured to detect one or more glucose level of a patient, a transmitter unit configured to receive the one or more detected glucose levels, and to transmit one or more data corresponding to the detected one or more glucose levels, and a receiver unit configured to receive the transmitted one or more measured glucose data, where the transmitter unit includes a rechargeable battery, where the sensor includes a plurality of sensor contacts, each of the plurality of sensor contacts coupled to the transmitter unit, and further, where a pair of the plurality of sensor contacts coupled to the transmitter unit is configured to receive a predetermined power signal to charge the rechargeable batter of the transmitter unit.

[0053] In one embodiment, the pair of plurality of sensor contacts configured to receive a predetermined power signal may include a guard contact and a counter electrode, and further, where the predetermined power signal may include a current signal from a power source.

[0054] A method for recharging power in a data communication device in a further embodiment of the present invention includes the steps of providing a plurality of contacts, operatively coupling a power source to the plurality of contacts, and operatively coupling a rechargeable battery to the plurality of contacts, the rechargeable battery configured to receive a predetermined signal from the power source, where the rechargeable battery is configured to recharge based on the predetermined signal from the power source.

[0055] The method in a further embodiment may include the step of providing the rechargeable battery and the plurality of contacts in a data communication device, where the rechargeable battery is configured to provide power to the data communication device.

[0056] Various other modifications and alterations in the structure and method of operation of this invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. It is intended that the following claims define the scope of the present invention and that structures and methods within the scope of these claims and their equivalents be covered thereby.

Claims

1. An apparatus for recharging a rechargeable battery in a data communication device which includes a plurality of contacts (510, 520), a power source operatively coupled to the plurality of contacts and a rechargeable battery (530) operatively coupled to the plurality of contacts, the rechargeable battery being configured to receive and recharge in response to a power signal from the power source, the apparatus including an analyte sensor (101) including a plurality of electrodes (210 - 213) which can be coupled through an analogue interface circuit (201) to a data transmitter (206), ***characterised in that*** the contacts (510, 520) are configured to couple to two of the said electrodes and the contacts are connected to provide a recharging current for the rechargeable battery by way of an electrostatic discharge protection circuit in the analogue interface circuit (201).

2. Apparatus according to claim 1 in which the electrostatic discharge protection circuit comprises for each contact a series resistor (511, 521) and a pair of electrostatic discharge protection diodes (521, 513; 522, 523) arranged so that charging current flows from one of the contacts (510) through one of the diodes in one pair, the battery and a diode in the other pair to the other contact (520).

3. Apparatus according to claim 1 or 2 in which the electrodes are a guard electrode (211) and a counter electrode (213).

4. Apparatus according to claim 1 or 2 in which the electrodes are a work electrode (210) and a reference electrode (212).

5. A method of recharging a rechargeable battery in a data communication device which includes a plurality of contacts (510, 520), a power source operatively coupled to the plurality of contacts and a rechargeable battery (530) operatively coupled to the plurality of contacts, the rechargeable battery being configured to receive and recharge in response to a power signal from the power source, the apparatus including an analyte sensor (101) including a plurality of electrodes (210 - 213) which can be coupled through an analogue interface circuit (201) to a data transmitter (206), ***characterised*** **by** coupling the contacts (510, 520) to two of the said electrodes when the sensor is connected to provide signals for the transmitter, providing electrostatic discharge protection by means of an electrostatic protection circuit in the analogue interface circuit, and coupled to said contacts, providing a recharging current for the rechargeable battery by way of an electrostatic discharge protection circuit in the analogue interface circuit (201).

Abbott Ex. 1002 - 756/1438

6. A method according to claim 5, in which the two electrodes are a guard electrode (211) and a counter electrode (213).

7. A method according to claim 5 or 6, in which the data transmitter (206) is configured to transmit measured glucose data.

8. A method according to any of claims 5 to 7, in which the sensor (101) is a subcutaneous sensor or a transcutaneous sensor, configured to detect an analyte level.

9. A method according to any of claims 5 to 8, further comprising monitoring the recharging current

10. A method according to any of claims 5 to 9, further comprising providing a signal representative of an indication of the charging of the rechargeable battery.

11. A method according to any of claims 5 to 10, in which the recharging of the battery is performed when the transmitter is not configured for the transmission of data.

Patentansprüche

1. Vorrichtung zum Wiederaufladen einer wiederaufladbaren Batterie in einer Datenübertragungsvorrichtung, die eine Vielzahl von Kontakten (510, 520), eine Leistungsquelle, die wirksam mit der Vielzahl von Kontakten gekoppelt ist, und eine wiederaufladbare Batterie (530), die wirksam mit der Vielzahl von Kontakten gekoppelt ist, umfasst, wobei die wiederaufladbare Batterie zum Empfangen und Wiederaufladen in Reaktion auf ein Leistungssignal von der Leistungsquelle ausgelegt ist, wobei die Vorrichtung einen Analytensensor (101) mit einer Vielzahl von Elektroden (210 - 213) umfasst, die durch eine analoge Schnittstellenschaltung (201) mit einem Datensender (206) gekoppelt werden können, **dadurch gekennzeichnet, dass** die Kontakte (510, 520) dazu ausgelegt sind, mit zwei der Elektroden gekoppelt zu werden, und die Kontakte zum Liefern eines Wiederaufladestroms für die wiederaufladbare Batterie über eine in der analogen Schnittstellenschaltung (201) vorgesehene Schaltung zum Schutz vor elektrostatischer Entladung verbunden werden.

2. Vorrichtung nach Anspruch 1, wobei die Schaltung zum Schutz vor elektrostatischer Entladung für jeden Kontakt einen Reihenwiderstand (511, 521) und ein Paar von Dioden (512, 513; 522, 523) zum Schutz vor elektrostatischer Entladung umfasst, die so angeordnet sind, dass ein Aufladestrom von einem der Kontakte (510) durch eine der Dioden in einem Paar, die Batterie und eine Diode im anderen Paar zum anderen Kontakt (520) fließt.

3. Vorrichtung nach Anspruch 1 oder 2, wobei die Elektroden eine Schutzelektrode (211) und eine Gegenelektrode (213) sind.

4. Vorrichtung nach Anspruch 1 oder 2, wobei die Elektroden eine Arbeitselektrode (210) und eine Referenzelektrode (212) sind.

5. Verfahren zum Wiederaufladen einer wiederaufladbaren Batterie in einer Datenübertragungsvorrichtung, die eine Vielzahl von Kontakten (510, 520), eine Leistungsquelle, die wirksam mit der Vielzahl von Kontakten gekoppelt ist, und eine wiederaufladbare Batterie (530), die wirksam mit der Vielzahl von Kontakten gekoppelt ist, umfasst, wobei die wiederaufladbare Batterie zum Empfangen und Wiederaufladen in Reaktion auf ein Leistungssignal von der Leistungsquelle ausgelegt ist, wobei die Vorrichtung einen Analytensensor (101) mit einer Vielzahl von Elektroden (210 - 213) umfasst, die durch eine analoge Schnittstellenschaltung (201) mit einem Datensender (206) gekoppelt werden können, **gekennzeichnet durch** Koppeln der Kontakte (510, 520) mit zwei der Elektroden, wenn der Sensor verbunden wird, um Signale für den Sender zu liefern, Vorsehen eines Schutzes vor elektrostatischer Entladung mittels einer mit den Kontakten gekoppelten Schaltung zum elektrostatischen Schutz, die in der analogen Schnittstellenschaltung vorgesehen ist, Liefern eines Wiederaufladestroms für die wiederaufladbare Batterie über eine in der analogen Schnittstellenschaltung (201) vorgesehene Schaltung zum Schutz vor elektrostatischer Entladung).

6. Verfahren nach Anspruch 5, wobei die zwei Elektroden eine Schutzelektrode (211) und eine Gegenelektrode (213) sind.

7. Verfahren nach Anspruch 5 oder 6, wobei der Datensender (206) dazu ausgelegt ist, Messdaten von Glucose zu übertragen.

8. Verfahren nach einem der Ansprüche 5 bis 7, wobei der Sensor (101) ein subkutaner Sensor oder ein transkutaner Sensor ist, der dazu ausgelegt ist, einen Analytenspiegel zu erfassen.

9. Verfahren nach einem der Ansprüche 5 bis 8, das ferner das Überwachen des Wiederaufladestroms umfasst.

10. Verfahren nach einem der Ansprüche 5 bis 9, das ferner das Liefern eines Signals, das eine Anzeige der Aufladung der wiederaufladbaren Batterie darstellt, umfasst.

Abbott Ex. 1002 - 757/1438

11. Verfahren nach einem der Ansprüche 5 bis 10, wobei das Wiederaufladen der Batterie durchgeführt wird, wenn der Sender nicht für die Übertragung von Daten konfiguriert ist.

Revendications

1. Appareil pour recharger une batterie rechargeable dans un dispositif de communication de données qui comprend une pluralité de contacts (510, 520), une source d'alimentation couplée de manière fonctionnelle à la pluralité de contacts et une batterie rechargeable (530) couplée de manière fonctionnelle à la pluralité de contacts, la batterie rechargeable étant configurée pour recevoir et recharger en réponse à un signal d'alimentation provenant de la source d'alimentation, l'appareil comprenant un capteur d'analytes (101) comprenant une pluralité d'électrodes (210 à 213) qui peuvent être couplées grâce à un circuit d'interface analogique (201) à un transmetteur de données (206), **caractérisé en ce que** les contacts (510, 520) sont configurés pour être couplés à deux desdites électrodes et les contacts sont reliés pour fournir un courant de recharge pour la batterie rechargeable au moyen d'un circuit de protection de décharge électrostatique dans le circuit d'interface analogique (201).

2. Appareil selon la revendication 1, dans lequel le circuit de protection de décharge électrostatique comprend pour chaque contact une résistance en série (511, 521) et une paire de diodes de protection de décharge électrostatique (521, 513 ; 522, 523) agencées de sorte qu'un courant de charge circule à partir de l'un des contacts (510) à travers l'une des diodes dans une paire, la batterie et une diode dans l'autre paire à l'autre contact (520).

3. Appareil selon la revendication 1 ou 2, dans lequel les électrodes sont une électrode de garde (211) et une contre électrode (213).

4. Appareil selon la revendication 1 ou 2, dans lequel les électrodes sont une électrode de travail (210) et une électrode de référence (212).

5. Procédé de recharge d'une batterie rechargeable dans un dispositif de communication de données qui comprend une pluralité de contacts (510, 520), une source d'alimentation couplée de manière fonctionnelle à la pluralité de contacts et une batterie rechargeable (530) couplée de manière fonctionnelle à la pluralité de contacts, la batterie rechargeable étant configurée pour recevoir et recharger en réponse à un signal d'alimentation provenant de la source d'alimentation, l'appareil comprenant un capteur d'analytes (101) comprenant une pluralité d'électrodes (210 à 213) qui peuvent être couplées par un circuit d'interface analogique (201) à un transmetteur de données (206), **caractérisé par** le couplage des contacts (510, 520) à deux desdites électrodes quand le capteur est relié pour fournir des signaux au transmetteur, la fourniture d'une protection de décharge électrostatique au moyen d'un circuit de protection électrostatique dans le circuit d'interface analogique ; et couplé auxdits contacts, la fourniture d'un courant de recharge pour la batterie rechargeable au moyen d'un circuit de protection de décharge électrostatique dans le circuit d'interface analogique (201).

6. Procédé selon la revendication 5, dans lequel les deux électrodes sont une électrode de garde (211) et une contre électrode (213).

7. Procédé selon la revendication 5 ou 6, dans lequel le transmetteur de données (206) est configuré pour transmettre des données concernant le glucose.

8. Procédé selon l'une quelconque des revendications 5 à 7, dans lequel le capteur (101) est un capteur sous-cutané ou un capteur transcutané, configuré pour détecter un niveau d'analytes.

9. Procédé selon l'une quelconque des revendications 5 à 8, comprenant en outre la surveillance du courant de recharge.

10. Procédé selon l'une quelconque des revendications 5 à 9, comprenant en outre la fourniture d'un signal représentatif d'une indication de la charge de la batterie rechargeable.

11. Procédé selon l'une quelconque des revendications 5 à 10, dans lequel la recharge de la batterie est réalisée quand le transmetteur n'est pas configuré pour la transmission de données.

Abbott Ex. 1002 - 758/1438

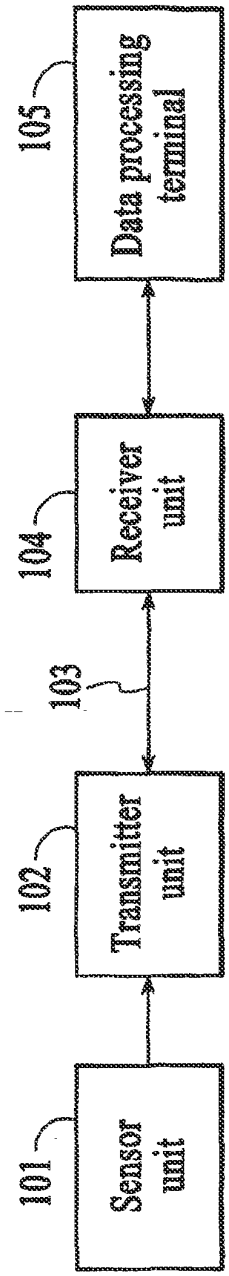


FIG.1

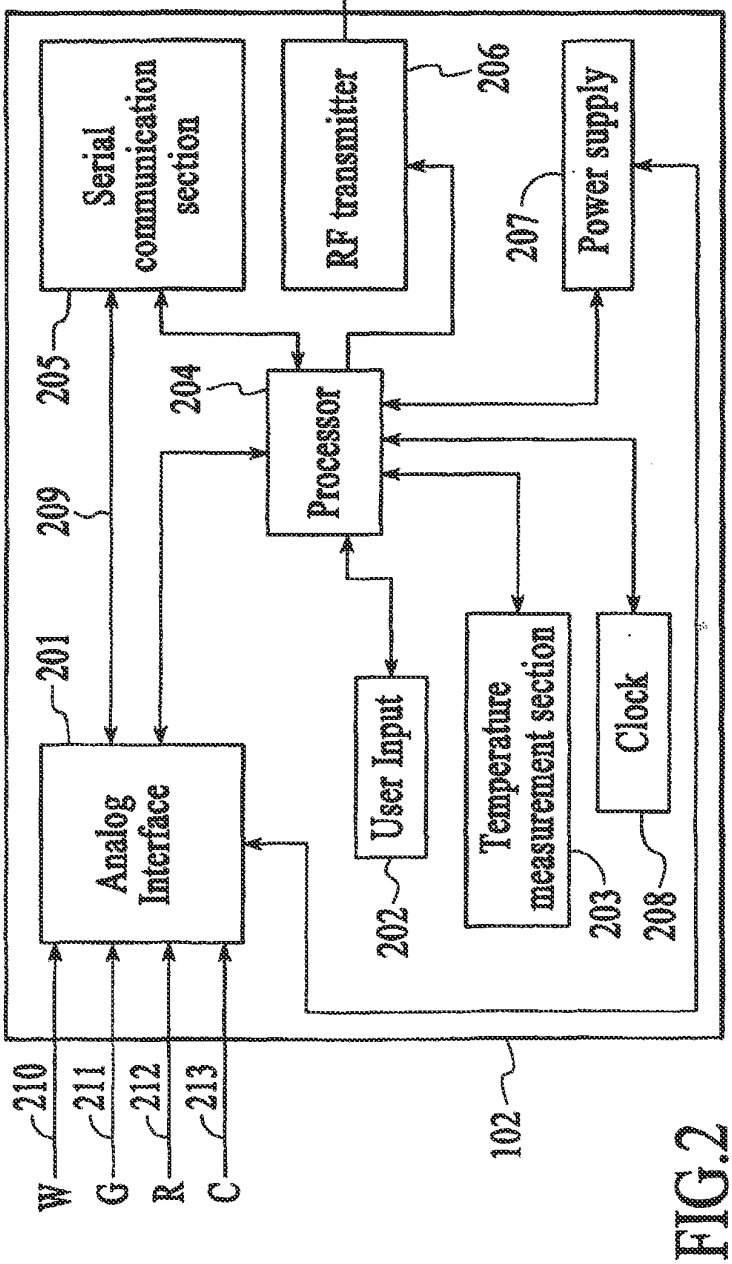


FIG.2

Abbott Ex. 1002 - 759/1438

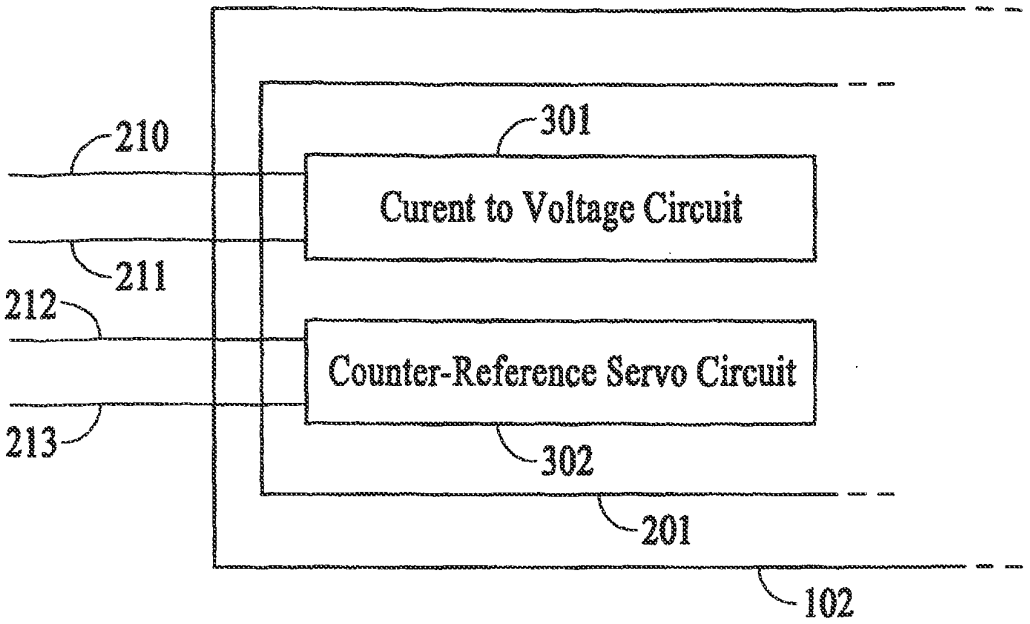


FIG.3

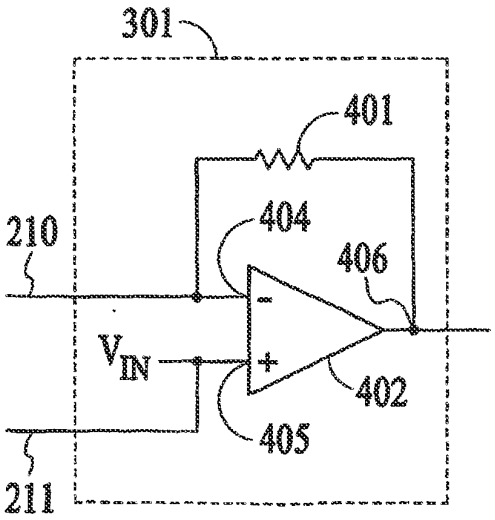


FIG.4A

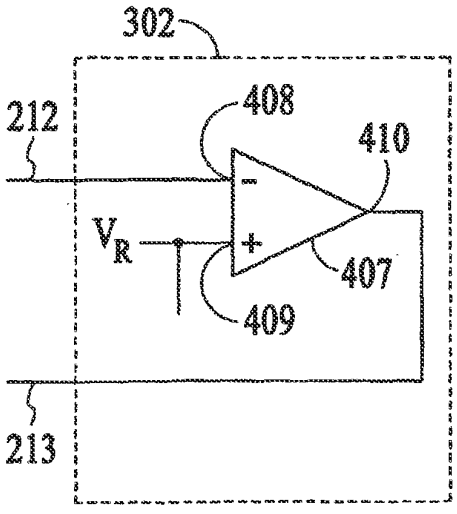
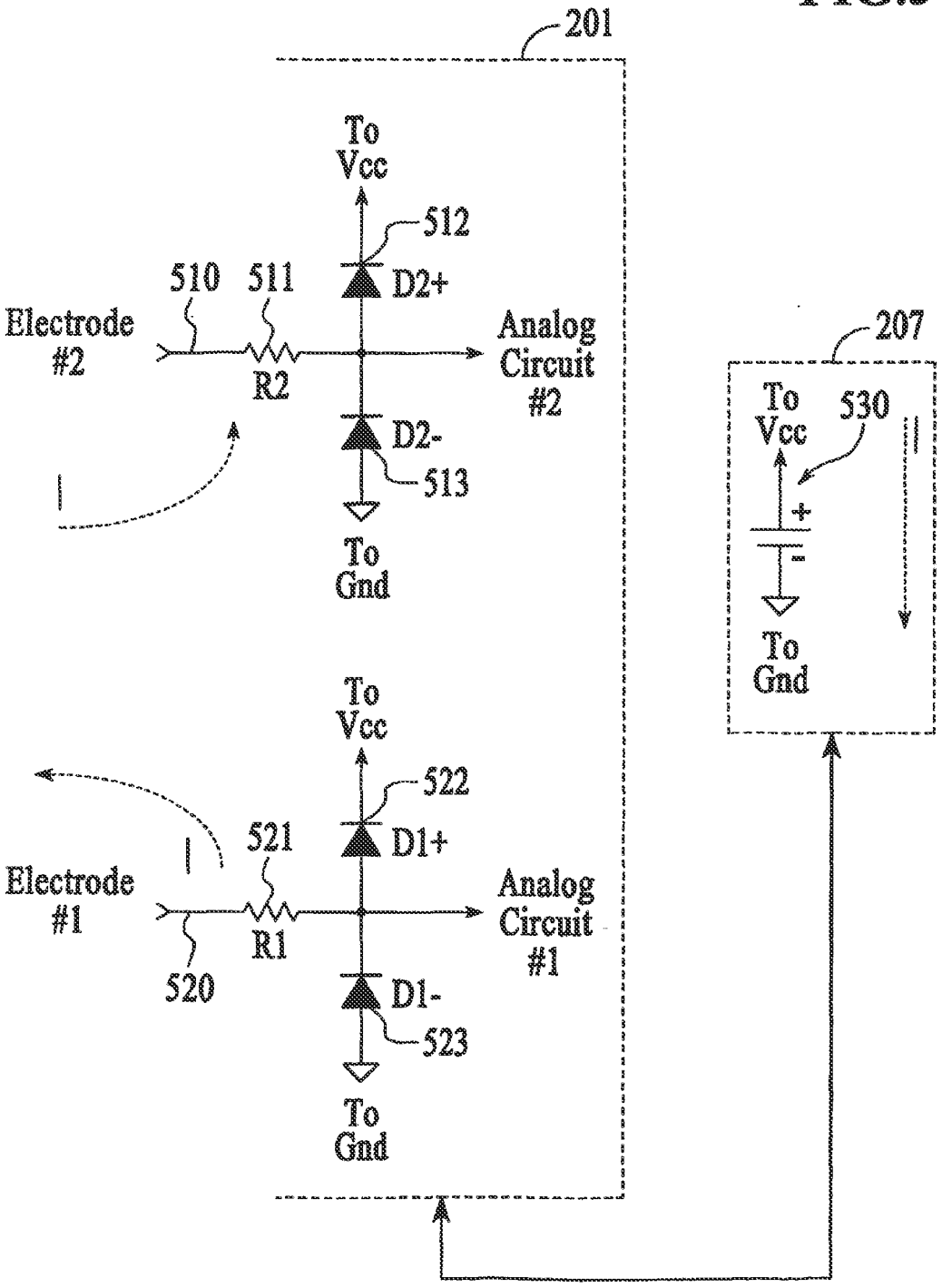


FIG.4B

Abbott Ex. 1002 - 760/1438

FIG.5



Abbott Ex. 1002 - 761/1438

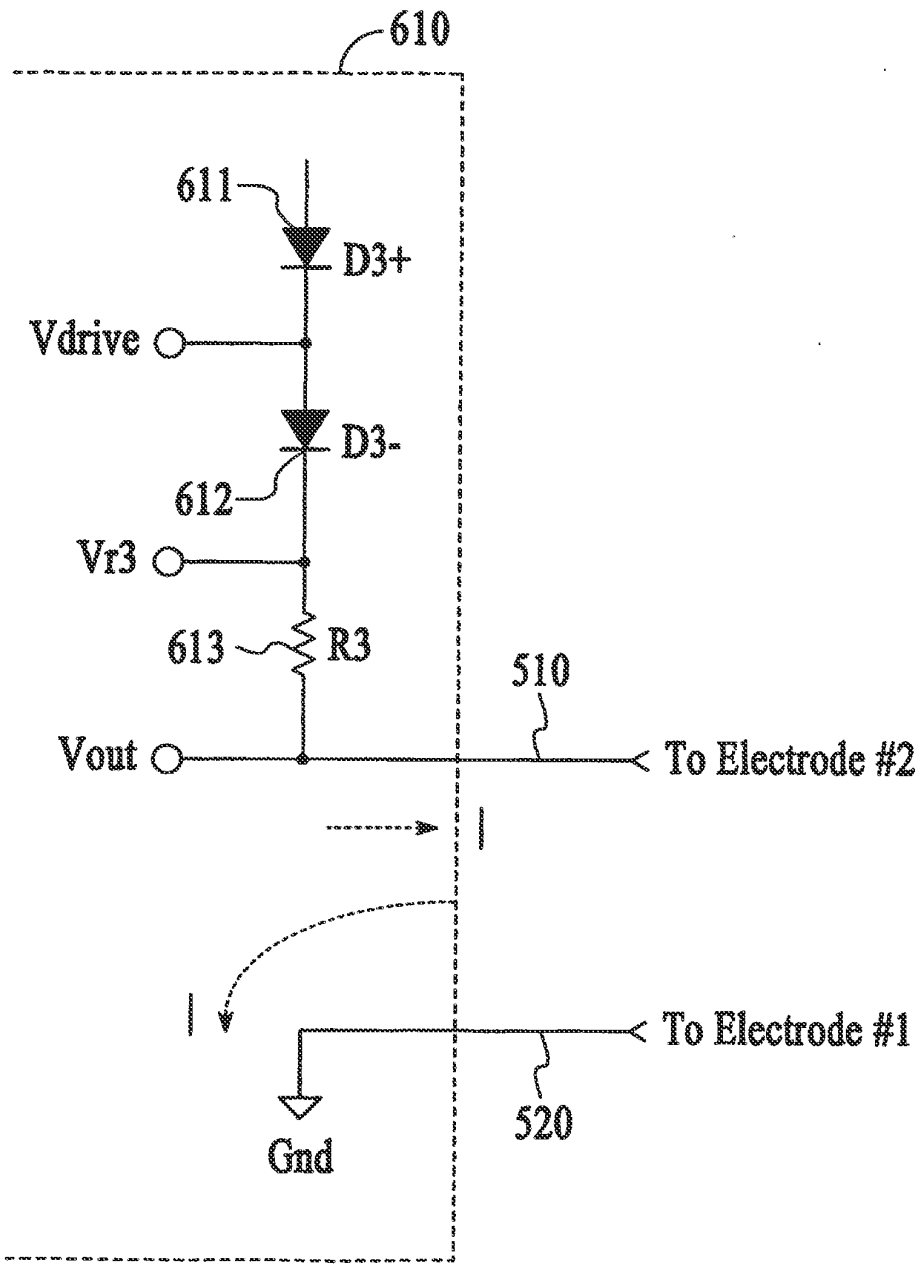


FIG.6

Abbott Ex. 1002 - 762/1438

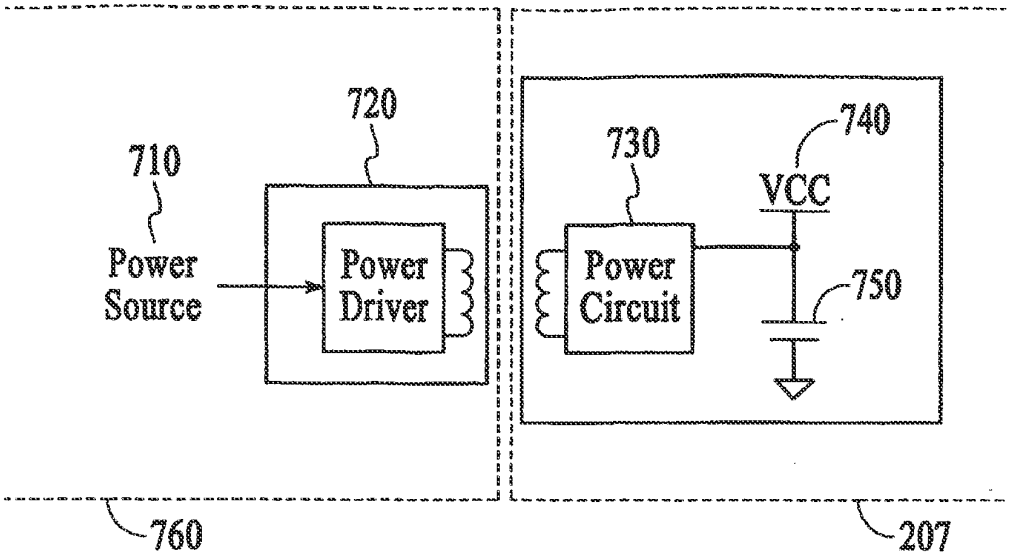


FIG.7A

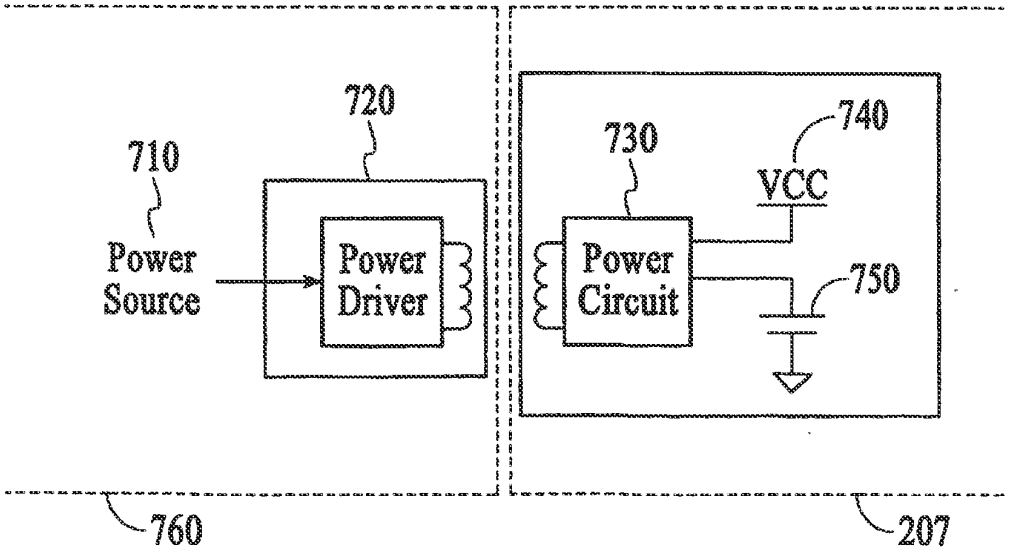


FIG.7B

Abbott Ex. 1002 - 763/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 0185452 B1 **[0005]**
- US 6175752 B **[0022]**
- US 10745878 B **[0022]**

Abbott Ex. 1002 - 764/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 927 602 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
11.01.2012 Bulletin 2012/02

(51) Int Cl.:
C08F 126/06 *(2006.01)* ***G01N 27/40*** *(2006.01)*
C12Q 1/00 *(2006.01)*

(21) Application number: **08004540.4**

(22) Date of filing: **15.05.2002**

(54) Biosensor membranes composed of polymers containing heterocyclic nitrogens

Biosensor-Membranen aus Polymeren mit heterozyklischen Stickstoffen

Membranes de biocapteur composées de polymères contenant de l'azote hétérocyclique

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

(30) Priority: **15.05.2001 US 291215 P**
14.05.2002 US 146518

(43) Date of publication of application:
04.06.2008 Bulletin 2008/23

(60) Divisional application:
10184740.8 / 2 292 671

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
02806821.1 / 1 466 156

(73) Proprietor: **Abbott Diabetes Care Inc.**
Alameda, CA 94502 (US)

(72) Inventors:
- **Mao, Fei**
  Fremont, CA 94555 (US)
- **Cho, Hyun**
  Berkeley, CA 94704 (US)

(74) Representative: **Tollett, Ian**
Williams Powell
Staple Court
11 Staple Inn Buildings
London, WC1V 7QH (GB)

(56) References cited:
WO-A-01/57241 **US-A- 4 929 313**
US-A- 5 543 326

- **KABANOV V A ET AL: "INTERACTION OF POLYIONS WITH CELL-MIMETIC SPECIES: PHYSICO-CHEMICAL AND BIOMEDICAL ASPECTS" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 39, February 1996 (1996-02), pages 173-189, XP002915177 ISSN: 0168-3659**
- **VUILLAUME P Y ET AL: "SYNTHESIS AND SOLID-STATE CHARACTERIZATION OF AMPHIPHILIC TAIL-END PYRIDINIUM POLYMETHACRYLATES" MACROMOLECULES, ACS, WASHINGTON, DC, US, vol. 33, no. 3, 18 February 2000 (2000-02-18), pages 781-790, XP000932314 ISSN: 0024-9297**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 927 602 B1

Printed by Jouve, 75001 PARIS (FR)

Description

Field of the Invention

[0001] This invention generally relates to an analyte-flux-limiting membrane. More particularly, the invention relates to such a membrane composed of polymers containing heterocyclic nitrogens. The membrane is a useful component in biosensors, and more particularly, in biosensors that can be implanted in a living body.

Background of the Invention

[0002] Although biosensors themselves are not in accordance with the present invention, enzyme-based biosensors are devices in which an analyte-concentration-dependent biochemical reaction signal is converted into a measurable physical signal, such as an optical or electrical signal. Such biosensors are widely used in the detection of analytes in clinical, environmental, agricultural and biotechnological applications. Analytes that can be measured in clinical assays of fluids of the human body include, for example, glucose, lactate, cholesterol, bilirubin and amino acids. The detection of analytes in biological fluids, such as blood, is important in the diagnosis and the monitoring of many diseases.

[0003] Biosensors that detect analytes via electrical signals, such as current (amperometric biosensors) or charge (coulometric biosensors), are of special interest because electron transfer is involved in the biochemical reactions of many important bioanalytes. For example, the reaction of glucose with glucose oxidase involves electron transfer from glucose to the enzyme to produce gluconolactone and reduced enzyme. In an example of an amperometric glucose biosensor, glucose is oxidized by oxygen in the body fluid via a glucose oxidase-catalyzed reaction that generates gluconolactone and hydrogen peroxide, whereupon the hydrogen peroxide is electrooxidized and correlated to the concentration of glucose in the body fluid. (Thome-Duret, V., *et al.,* Anal. Chem. 68, 3822 (1996); and U.S. Patent No. 5,882,494 of Van Antwerp.) In another example of an amperometric glucose biosensor, the electrooxidation of glucose to gluconolactone is mediated by a polymeric redox mediator that electrically "wires" the reaction center of the enzyme to an electrode. (Csöregi, *E., et al.,* Anal. Chem. 66, 3131 (1994); Csöregi, *E., et al.,* Anal. Chem. 67, 1240 (1995); Schmidtke, D.W., *et al.,* Anal. Chem. 68, 2845 (1996); Schmidtke, D.W., *et al.,* Anal. Chem. 70, 2149 (1998); and Schmidtke, D.W., *et al.,* Proc. Natl. Acad. Sci. U.S.A. 95, 294 (1998).)

[0004] Amperometric biosensors typically employ two or three electrodes, including at least one measuring or working electrode and one reference electrode. In two-electrode systems, the reference electrode also serves as a counter-electrode. In three-electrode systems, the third electrode is a counter-electrode. The measuring or working electrode is composed of a non-corroding carbon or a metal conductor and is connected to the reference electrode via a circuit, such as a potentiostat.

[0005] Although biosensors themselves are not in accordance with the present invention, some biosensors are designed for implantation in a living animal body, such as a mammalian or a human body, merely by way of example. In an implantable amperometric biosensor, the working electrode is typically constructed of a sending layer, which is in direct contact with the conductive material of the electrode, and a diffusion-limiting membrane layer on top of the sensing layer. The sensing layer typically consists of an enzyme, an enzyme stabilizer such as bovine serum albumin (BSA), and a crosslinker that crosslinks the sensing layer components. Alternatively, the sensing layer consists of an enzyme, a polymeric mediator, and a crosslinker that crosslinks the sensing layer components, as in the above-mentioned "wired-enzyme" biosensor.

[0006] In an implantable amperometric glucose sensor, the membrane is often beneficial or necessary for regulating or limiting the flux of glucose to the sensing layer. By way of explanation, in a glucose sensor without a membrane, the flux of glucose to the sensing layer increases linearly with the concentration of glucose. When all of the glucose arriving at the sensing layer is consumed, the measured output signal is linearly proportional to the flux of glucose and thus to the concentration of glucose. However, when the glucose consumption is limited by the kinetics of chemical or electrochemical activities in the sensing layer, the measured output signal is no longer controlled by the flux of glucose and is no longer linearly proportional to the flux or concentration of glucose. In this case, only a fraction of the glucose arriving at the sensing layer is consumed before the sensor becomes saturated, whereupon the measured signal stops increasing, or increases only slightly, with the concentration of glucose. In a glucose sensor equipped with a diffusion-limiting membrane, on the other hand, the membrane reduces the flux of glucose to the sensing layer such that the sensor does not become saturated and can therefor operate effectively within a much wider range of glucose concentration.

[0007] More particularly, in these membrane-equipped glucose sensors, the glucose consumption rate is controlled by the diffusion or flux of glucose through the membrane rather than by the kinetics of the sensing layer. The flux of glucose through the membrane is defined by the permeability of the membrane to glucose, which is usually constant, and by the concentration of glucose in the solution or biofluid being monitored. When all of the glucose arriving at the sensing layer is consumed, the flux of glucose through the membrane to the sensing layer varies linearly with the concentration of glucose in the solution, and determines the measured conversion rate or signal output such that it is

Abbott Ex. 1002 - 766/1438

also linearly proportional to the concentration of glucose concentration in the solution. Although not necessary, a linear relationship between the output signal and the concentration of glucose in the solution is ideal for the calibration of an implantable sensor.

[0008] Implantable amperometric glucose sensors based on the electrooxidation of hydrogen peroxide, as described above, require excess oxygen reactant to ensure that the sensor output is only controlled by the concentration of glucose in the body fluid or tissue being monitored. That is, the sensor is designed to be unaffected by the oxygen typically present in body fluid or tissue. In body tissue in which the glucose sensor is typically implanted, the concentration of oxygen can be very low, such as from about 0.02 mM to about 0.2 mM, while the concentration of glucose can be as high as about 30 mM or more. Without a glucose-diffusion-limiting membrane, the sensor would become saturated very quickly at very low glucose concentrations. The sensor thus benefits from having a sufficiently oxygen-permeable membrane that restricts glucose flux to the sensing layer, such that the so-called "oxygen-deficiency problem," a condition in which there is insufficient oxygen for adequate sensing to take place, is minimized or eliminated.

[0009] In implantable amperometric glucose sensors that employ wired-enzyme electrodes, as described above, there is no oxygen-deficiency problem because oxygen is not a necessary reactant. Nonetheless, these sensors require glucose-diffusion-limiting membranes because typically, for glucose sensors that lack such membranes, the current output reaches a maximum level around or below a glucose concentration of 10 mM, which is well below 30 mM, the high end of clinically relevant glucose concentration.

[0010] A diffusion-limiting membrane is also of benefit in a biosensor that employs a wired-enzyme electrode, as the membrane significantly reduces chemical and biochemical reactivity in the sensing layer and thus reduces the production of radical species that can damage the enzyme. The diffusion-limiting membrane may also act as a mechanical protector that prevents the sensor components from leaching out of the sensor layer and reduces motion-associated noise.

[0011] There have been various attempts to develop a glucose-diffusion-limiting membrane that is mechanically strong, biocompatible, and easily manufactured. For example, a laminated microporous membrane with mechanical holes has been described (U.S. Patent No. 4,759,828 of Young et al.) and membranes formed from polyurethane are also known (Shaw, G.W., et al., Biosensors and Bioelectronics 6, 401 (1991); Bindra, D.S., et al., Anal. Chem. 63, 1692 (1991); Shichiri, M., et al., Horm. Metab. Res., Suppl. Ser. 20, 17 (1988)). Supposedly, glucose diffuses through the mechanical holes or cracks in these various membranes. Further by way of example, a heterogeneous membrane with discrete hydrophobic and hydrophilic regions (U.S. Patent No. 4,484,987 of Gough) and homogenous membranes with both hydrophobic and hydrophilic functionalities (U.S. Patent Nos. 5,284,140 and 5,322,063 of Allen et al.) have been described. However, all of these known membranes are difficult to manufacture and have inadequate physical properties.

[0012] An improved membrane formed from a complex mixture of a diisocyanate, a diol, a diamine and a silicone polymer has been described in U.S. Patent Nos. 5,777,060 (Van Antwerp), 5,786,439 (Van Antwerp et al.) and 5,882,494 (Van Antwerp). As described therein, the membrane material is simultaneously polymerized and crosslinked in a flask;.the resulting polymeric material is dissolved in a strong organic solvent, such as tetrahydroforan (THF); and the resulting solution is applied onto the sensing layer to form the membrane. Unfortunately, a very strong organic solvent, such as THF, can denature the enzyme in the sensing layer and also dissolve conductive ink materials as well as any plastic materials that may be part of the sensor. Further, since the polymerization and crosslinking reactions are completed in the reaction flask, no further bond-making reactions occur when the solution is applied to the sensing layer to form the membrane. As a result, the adhesion between the membrane layer and sensing layer may not be adequate.

[0013] In the published Patent Cooperation Treaty (PCT) Application bearing International Publication No. WO 01/57241 A2, Kelly and Schiffer describe a method for making a glucose-diffusion-limiting membrane by photolytically polymerizing small hydrophilic monomers. The sensitivities of the glucose sensors employing such membranes are widely scattered, however, indicating a lack of control in the membrane-making process. Further, as the polymerization involves very small molecules, it is quite possible that small, soluble molecules remain after polymerization, which may leach out of the sensor. Thus, glucose sensors employing such glucose-diffusion-limiting membranes may not be suitable for implantation in a living body.

[0014] US 4,929,313 discloses electrochemical devices that can be used to convert an ion flux into an electric current for determination of ion concentration. The devices are operated without the need for a reference electrode and are specific based on known ion transfer agents. Operation of the devices involves the use of pairs of electrodes modified with electroactive redox materials overlaid with ion selective coatings. An applied potential between a pair of appropriately modified electrodes results in the flow of an electric current between the electrodes that is dependent on the concentration of the ion to be sensed. Devices constructed by combining electrodes overlaid with electroactive polymers and different ion selective films allow simultaneous determination of diverse ions. For example, these devices are useful for measuring the concentration of total cations, total anions, H^+, Li^+, K^+, Ca_2^+, Na^+, HCO_3^-, Cl^-, other cations and anions, and combinations thereof. The devices are small and stable enough to be used ***in vivo,*** for example, as blod monitoring means, or in large scale water quality monitoring or purification/separation techniques.

[0015] US 5,543,326 discloses oxidoreductases that are chemically modified so as to change their net charge at a given pH. Through such modification the adsorption of the enzymes on surfaces, their retention in similarly or oppositely

Abbott Ex. 1002 - 767/1438

charged polymer membranes and their binding with similarly or oppositely charged macromolecules, particularly redox macromolecules, is controlled. The modified enzymes, of which modified recombinant glucose oxidase is an example, are useful in biosensors, e.g. for glucose; as marker enzymes of antigens or antibodies in immunosensing; and as labels of nucleotide sequences in probes, e.g. for DNA nucleotide sequences.

[0016] Kabanov *et al.* (1996) *Journal of Controlled Release* 39, 173-189 disclose the interaction of polyions with cell-mimetic species.

[0017] Vuillaume *et al.* (2000) *Macromolecules* 33, 781-790 disclose the synthesis and characterization of amphiphilic tail-end pyridinium polymethacrylates.

Summary of the Invention

[0018] The present invention is directed to membranes composed of crosslinked polymers containing heterocyclic nitrogen groups, particularly polymers of polyvinylpyridine and polyvinylimidazole . The membranes are useful in limiting the flux of an analyte to a working electrode in an electrochemical sensor so that the sensor is linearly responsive over a large range of analyte concentrations and is easily calibrated. Electrochemical sensors equipped with membranes of the present invention demonstrate considerable sensitivity and stability, and a large signal-to-noise ratio, in a variety of conditions.

[0019] According to one aspect of the invention, the membrane is formed by crosslinking *in situ* a polymer, modified with a zwitterionic moiety, a non-pyridine copolymer component, and optionally another moiety that is either hydrophilic or hydrophobic, and/or has other desirable properties, in an alcohol-buffer solution. The modified polymer is made from a precursor polymer containing heterocyclic nitrogen groups. Preferably, the precursor polymer is polyvinylpyridine or polyvinylimidazole. When used in an electrochemical sensor, the membrane limits the flux of an analyte reaching a sensing layer of the sensor, such as an enzyme-containing sensing layer of a "wired enzyme" electrode, and further protects the sensing layer. These qualities of the membrane significantly extend the linear detection range and the stability of the sensor.

[0020] In the membrane formation process, the non-pyridine copolymer component generally enhances the solubility of the polymer and may provide further desirable physical or chemical properties to the polymer or the resulting membrane. Optionally, hydrophilic or hydrophobic modifiers may be used to "fine-tune" the permeability of the resulting membrane to an analyte of interest. Optional hydrophilic modifiers, such as poly(ethylene glycol), hydroxyl or polyhydroxyl modifiers, may be used to enhance the biocompatibility of the polymer or the resulting membrane. In the formation of a membrane of the present invention, the zwitterionic moiety of the polymer is believed to provide an additional layer of crosslinking, via intermolecular electrostatic bonds, beyond the basic crosslinking generally attributed to covalent bonds, and is thus believed to strengthen the membrane.

[0021] Another aspect of the invention concerns the preparation of a substantially homogeneous, analyte-diffusion-limiting membrane that may be used in a biosensor, such as an implantable amperometric biosensor. The membrane is formed *in situ* by applying an alcohol-buffer solution of a crosslinker and a modified polymer over an enzyme-containing sensing layer and allowing the solution to cure for one to two days. The crosslinker-polymer solution may be applied to the sensing layer by placing a droplet or droplets of the solution on the sensor, by dipping the sensor into the solution, or the like. Generally, the thickness of the membrane is controlled by the concentration of the solution, by the number of droplets of the solution applied, by the number of times the sensor is dipped in the solution, or by any combination of the these factors. Amperometric glucose sensors equipped with diffusion-limiting membranes of the present invention demonstrate excellent stability and fast and linear responsivity to glucose concentration over a large glucose concentration range.

Brief Description of the Drawings

[0022] Figure 1 is an illustration of a typical structure of a section of an analyte-diffusion-limiting membrane, according to the present invention.

[0023] Figure 2A is a schematic, side-view illustration of a portion of a two-electrode glucose sensor having a working electrode, a combined counter/reference electrode, and a dip-coated membrane according to the present invention that encapsulates both electrodes. Figures 2B and 2C are schematic top- and bottom-view illustrations, respectively, of the portion of the glucose sensor of Figure 2A. Herein, Figures 2A, 2B and 2C may be collectively referred to as Figure 2.

[0024] Figure 3 is a graph of current versus glucose concentration for sensors having glucose-diffusion-limiting membranes according to the present invention, and for sensors lacking such membranes, based on average values.

[0025] Figure 4 is a graph of current output versus time at fixed glucose concentration for a sensor having a glucose-diffusion-limiting membrane according to the present invention, and for a sensor lacking such a membrane.

[0026] Figure 5 is a graph of current output versus time at different levels of glucose concentration for sensors having glucose-diffusion-limiting membranes according to the present invention, based on average values.

Abbott Ex. 1002 - 768/1438

[0027] Figure 6 is a graph of current output versus time at different levels of glucose concentration, with and without stirring, for a sensor having a glucose-diffusion-limiting membrane according to the present invention, and for a sensor lacking such a membrane.

[0028] Figure 7A is a graph of current output versus glucose concentration for four separately prepared batches of sensors having glucose-diffusion-limiting membranes according to the present invention, based on average values. Figures 7B-7E are graphs of current output versus glucose concentration for individual sensors in each of the four above-referenced batches of sensors having glucose-diffusion-limiting membranes, according to the present invention, respectively. Herein, Figures 7A, 7B, 7C, 7D and 7E may be collectively referred to as Figure 7.

Description of the Invention

[0029] When used herein, the terms in quotation marks are defined as set forth below.

[0030] The term "alkyl" includes linear or branched, saturated aliphatic hydrocarbons. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl and the like. Unless otherwise noted, the term "alkyl" includes both alkyl and cycloalkyl groups.

[0031] The term "alkoxy" describes an alkyl group joined to the remainder of the structure by an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, tert-butoxy, and the like. In addition, unless otherwise noted, the term 'alkoxy' includes both alkoxy and cycloalkoxy groups.

[0032] The term "alkenyl" describes an unsaturated, linear or branched aliphatic hydrocarbon having at least one carbon-carbon double bond. Examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-methyl-1-propenyl, and the like.

[0033] A "reactive group" is a functional group of a molecule that is capable of reacting with another compound to couple at least a portion of that other compound to the molecule. Reactive groups include carboxy, activated ester, sulfonyl halide, sulfonate ester, isocyanate, isothiocyanate, epoxide, aziridine, halide, aldehyde, ketone, amine, acrylamide, thiol, acyl azide, acyl halide, hydrazine, hydroxylamine, alkyl halide, imidazole, pyridine, phenol, alkyl sulfonate, halotriazine, imido ester, maleimide, hydrazide, hydroxy, and photo-reactive azido aryl groups. Activated esters, as understood in the art, generally include esters of succinimidyl, benzotriazolyl, or aryl substituted by electron-withdrawing groups such as sulfo, nitro, cyano, or halo groups; or carboxylic acids activated by carbodiimides.

[0034] A "substituted" functional group (e.g., substituted alkyl, alkenyl, or alkoxy group) includes at least one substituent selected from the following: halogen, alkoxy, mercapto, aryl, alkoxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, -OH,-NH2, alkylamino, dialkylamino, trialkylammonium, alkanoylamino, arylcarboxamido, hydrazino, alkylthio, alkenyl, and reactive groups.

[0035] A "crosslinker" is a molecule that contains at least two reactive groups capable of linking at least two molecules together, or linking at least two portions of the same molecule together. Linking of at least two molecules is called intermolecular crosslinking, while linking of at least two portions of the same molecule is called intramolecular crosslinking. A crosslinker having more than two reactive groups may be capable of both intermolecular and intramolecular crosslinkings at the same time.

[0036] The term "precursor polymer" refers to the starting polymer before the various modifier groups are attached to form a modified polymer.

[0037] The term "heterocyclic nitrogen group" refers to a cyclic structure containing a sp^2 hybridized nitrogen in a ring of the structure.

[0038] The term "polyvinylpyridine" refers to poly(4-vinylpyridine), poly(3-vinylpyridine), or poly(2-vinylpyridine), as well as any copolymer of vinylpyridine and a second or a third copolymer component.

[0039] The term "polyvinylimidazole" refers to poly(1-vinylimidazole), poly(2-vinylimidazole), or poly(4-vinylimidazole).

[0040] A "membrane' solution" is a solution that contains all necessary components for crosslinking and forming the membrane, including a modified polymer containing heterocyclic nitrogen groups, a crosslinker and a buffer or an alcohol-buffer mixed solvent.

[0041] A "biological fluid" or "biofluid" is any body fluid or body fluid derivative in which the analyte can be measured, for example, blood, interstitial fluid, plasma, dermal fluid, sweat, and tears.

[0042] An "electrochemical sensor" is a device configured to detect the presence of or measure the concentration or amount of an analyte in a sample via electrochemical oxidation or reduction reactions. Typically, these reactions can be transduced to an electrical signal that can be correlated to an amount or concentration of analyte.

[0043] A "redox mediator" is an electron-transfer agent for carrying electrons between an analyte, an analyte-reduced or analyte-oxidized enzyme, and an electrode, either directly, or via one or more additional electron-transfer agents. A redox mediator that includes a polymeric backbone may also be referred to as a "redox polymer".

[0044] The term "reference electrode" includes both a) reference electrodes and b) reference electrodes that also function as counter electrodes (i.e., counter/reference electrodes), unless otherwise indicated.

[0045] The term "counter electrode" includes both a) counter electrodes and b) counter electrodes that also function

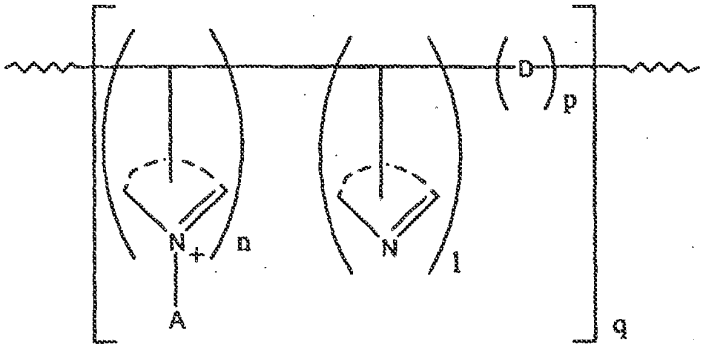
Abbott Ex. 1002 - 769/1438

as reference electrodes (i.e., counter/reference electrodes), unless otherwise indicated.

[0046] In general, membrane of the present invention is formed by crosslinking a modified polymer containing heterocyclic nitrogen groups in an alcohol-buffer mixed solvent and allowing the membrane solution to cure over time. The polymer comprises poly(heterocyclic nitrogen-containing constituent) as a portion of its backbone and additional elements, including a zwitterionic moiety, a hydrophobic moiety, and optionally, a biocompatible moiety. The resulting membrane is capable of limiting the flux of an analyte from one space, such as a space associated with a biofluid, to another space, such as space associated with an enzyme-containing sensing layer. An amperometric glucose sensor constructed of a wired-enzyme sensing layer and a glucose-diffusion-limiting layer of the present invention is very stable and has a large linear detection range.

Heterocyclic-Nitrogen Containing Polymers

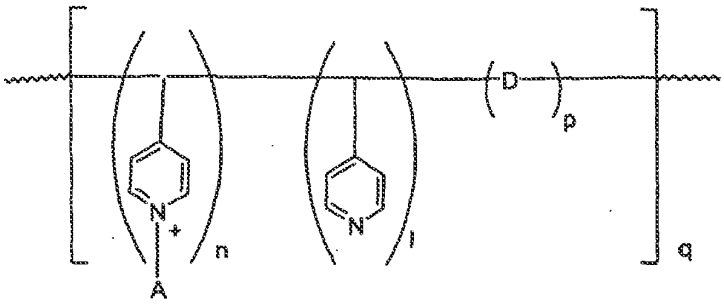
[0047] The polymer of the present invention has the following general formula, Formula 1a:



1a

wherein the horizontal line represents a polymer backbone; A is an alkyl group substituted with a water soluble group, preferably a negatively charged group, such as sulfonate, phosphate, or carboxylate, and more preferably, a strong acid group such as sulfonate, so that the quaternized heterocyclic nitrogen to which it is attached is zwitterionic; D is a copolymer component of the polymer, as further described below; each of n, l, and p is independently an average number of an associated polymer unit or polymer units shown in the closest parentheses to the left; and q is a number of a polymer unit or polymer units shown in the brackets.

[0048] The heterocyclic nitrogen groups of Formula 1a include, but are not limited to, pyridine, imidazole, oxazole, thiazole, pyrazole, or any derivative thereof. Preferably, the heterocyclic nitrogen groups are independently vinylpyridine, such as 2-, 3-, or 4-vinylpyridine, or vinylimidazole, such as 1-, 2-, or 4-vinylimidazole. More preferably, the heterocyclic nitrogen groups are independently 4-vinylpyridine, such that the more preferable polymer is a derivative of poly(4-vinylpyridine). An example of such a poly(4-vinylpyridine) of the present invention has the following general formula, Formula 1b:

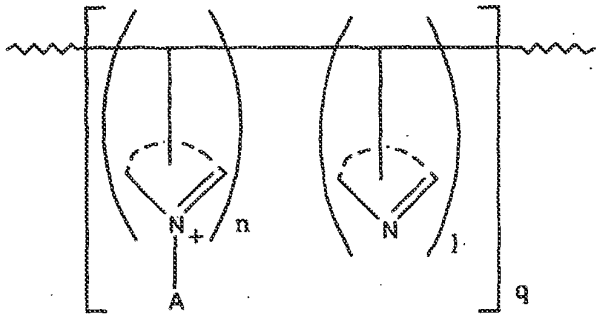


1b

Abbott Ex. 1002 - 770/1438

wherein A, D, n,l, p and q are as described above in relation to Formula 1a.

[0049] While the polymer of the present invention has the general Formula 1a or Formula 1b above, it should be noted that when A is a strong acid, such as a stronger acid than carboxylic acid, the D component is optional, such that p may equal zero. Such a polymer of the present invention has the following general formula, Formula 1c:



1c

wherein A is a strong acid and the heterocyclic nitrogen groups, n, l and q are all as described above. Sulfonate and fluorinated carboxylic acid are examples of suitably strong acids. It is believed that when A is a sufficiently strong acid, the heterocyclic nitrogen to which it is attached becomes zwitterionic and thus capable of forming intermolecular electrostatic bonds with the crosslinker during membrane formation. It is believed that these intermolecular electrostatic bonds provide another level of crosslinking, beyond the covalent bonds typical of crosslinking, and thus make the resulting membrane stronger. As a result, when A is a suitably strong acid, the D component, which is often a strengthening component such as styrene, may be omitted from the polymers of Formulas 1a and 1b above. When A is a weaker acid, such that the heterocyclic nitrogen is not zwitterionic or capable of forming intermolecular electrostatic bonds, the polymer of the present invention does include D, as shown in Formulas 1a and 1b above.

[0050] Examples of A include, but are not limited to, sulfopropyl, sulfobutyl, carboxypropyl, and carboxypentyl. In one embodiment of the invention, group A has the formula -L-G, where L is a C2-C12 linear or branched alkyl linker optionally and independently substituted with an aryl, alkoxy, alkenyl, alkynyl, -F, -Cl, -OH, aldehyde, ketone, ester, or amide group, and G is a negatively charged carboxy or sulfonate group. The alkyl portion of the substituents of L have 1-6 carbons and are preferably an aryl, -OH or amide group.

[0051] A can be attached to the heterocyclic nitrogen group via quaternization with an alkylating agent that contains a suitable linker L and a negatively charged group G, or a precursor group that can be converted to a negatively charged group G at a later stage. Examples of suitable alkylating agents include, but are not limited to, 2-bromoethanesulfonate, propanesultone, butanesultone, bromoacetic acid, 4-bromobutyric acid and 6-bromohexanoic acid. Examples of alkylating agents containing a precursor group include, but are not limited to, ethyl bromoacetate and methyl 6-bromohexanoate. The ethyl and methyl ester groups of these precursors can be readily converted to a negatively charged carboxy group by standard hydrolysis.

[0052] Alternatively, A can be attached to the heterocyclic nitrogen group by quaternizing the nitrogen with an alkylating agent that contains an additional reactive group, and subsequently coupling, via standard methods, this additional reactive group to another molecule that contains a negatively charged group G and a reactive group. Typically, one of the reactive groups is an electrophile and the other reactive group is a nucleophile. Selected examples of reactive groups and the linkages formed from their interactions are shown in Table 1.

Table 1: Examples of Reactive Groups and Resulting Linkages

First Reactive Group	Second Reactive Group	Resulting Linkage
Activated ester*	Amine	Amide
Acrylamide	Thiol	Thioether
Acyl azide	Amine	Amide
Acyl halide	Amine	Amide
Carboxylic acid	Amine	Amide

Abbott Ex. 1002 - 771/1438

(continued)

First Reactive Group	Second Reactive Group	Resulting Linkage
Aldehyde or ketone	Hydrazine	Hydrazone
Aldehyde or ketone	Hydroxyamine	Oxime
Alkyl halide	Amine	Alkylamine
Alkyl halide	Carboxylic acid	Ester
Alkyl halide	Imidazole	Imidazolium
Alkyl halide	Pyridine	Pyridinium
Alkyl halide	Alcohol/phenol	Ether
Alkyl halide	Thiol	Thioether
Alkyl sulfonate	Thiol	Thioether
Alkyl sulfonate	Pyridine	Pyridinium
Alkyl sulfonate	Imidazole	Imidazolium
Alkyl sulfonate	Alcohol/phenol	Ether
Anhydride	Alcohol/phenol	Ester
Anhydride	Amine	Amide
Aziridine	Thiol	Thioether
Aziridine	Amine	Alkylamine
Aziridine	Pyridine	Pyridinium
Epoxide	Thiol	Thioether
Epoxide	Amine	Alkylamine
Epoxide	Pyridine	Pyridinium
Halotriazine	Amine	Aminotriazine
Halotriazine	Alcohol	Triazinyl ether
Imido ester	Amine	Amidine
Isocyanate	Amine	Urea
Isocyanate	Alcohol	Urethane
Isothiocyanate	Amine	Thiourea
Maleimide	Thiol	Thioether
Sulfonyl halide	Amine	Sulfonamide
* Activated esters, as understood in the art, generally include esters of succinimidyl, benzotriazolyl, or aryl substituted by electron-withdrawing groups such as sulfo, nitro, cyano, or halo; or carboxylic acids activated by carbodiimides.		

[0053] By way of example, A may be attached to the heterocyclic nitrogen groups of the polymer by quaternizing the heterocyclic nitrogens with 6-bromohexanoic acid and subsequently coupling the carboxy group to the amine group of 3-amino-1-propanesulfonic acid in the presence of a carbodiimide coupling agent.

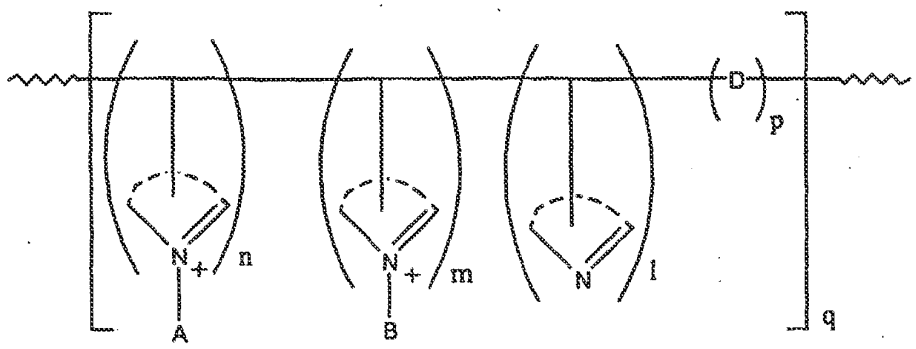
[0054] D is a component of a poly(heterocyclic nitrogen-co-D) polymer of Formula 1a or 1b. Examples of D include, but are not limited to, phenylalkyl, alkoxystyrene, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, and a molecule containing a poly(ethylene glycol) or polyhydroxyl group. Some poly(heterocyclic nitrogen-*co*-D) polymers suitable as starting materials for the present invention are commercially available. For example, poly(2-vinylpyridine-co-styrene), poly(4-vinylpyridine-co-styrene) and poly(4-vinylpyridine-co-butyl methacrylate) are available from Aldrich Chemical Company, Inc. Other poly(heterocyclic nitrogen-coD) polymers can be readily synthesized by anyone skilled in the art of polymer chemistry using well-known methods. Preferably, D is a styrene or a C1-C18 alkyl methacrylate component of a poly-vinylpyridine-poly-D, such as (4-vinylpyrine-co-styrene) or poly(4-vinylpyridine-co-butyl methacrylate), more preferably,

Abbott Ex. 1002 - 772/1438

the former. D may contribute to various desirable properties of the membrane including, but not limited to, hydrophobicity, hydrophilicity, solubility, biocompatibility, elasticity and strength. D may be selected to optimize or "fine-tune" a membrane made from the polymer in terms of its permeability to an analyte and its non-permeability to an undesirable, interfering component, for example.

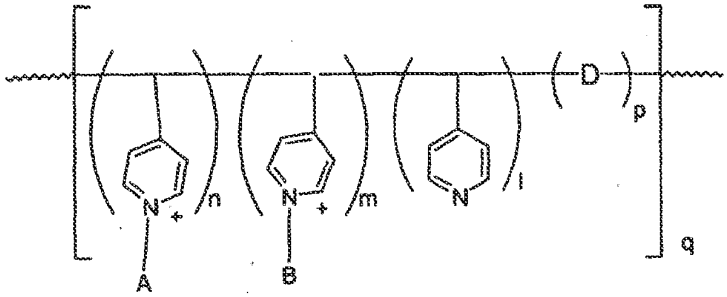
[0055] The letters n, l, and p designate, respectively, an average number of each copolymer component in each polymer unit. The letter q is one for a block copolymer or a number greater than one for a copolymer with a number of repeating polymer units. By way of example, the q value for a polymer of the present invention may be ≥ about 950, where n, l and p are 1, 8 and 1, respectively. The letter q is thus related to the overall molecular weight of the polymer. Preferably, the average molecular weight of the polymer is above about 50,000, more preferably above about 200,000, most preferably above about 1,000,000.

[0056] The polymer of the present invention may comprise a further, optional copolymer, as shown in the following general formula, Formula 2a:



2a

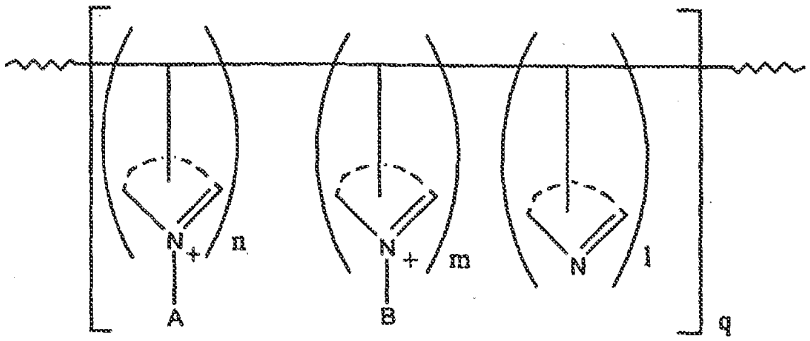
wherein the polymer backbone, A, D, n, l, p and q are as described above in relation to Formulas 1a-1c; m is an average number of an associated polymer unit or polymer units shown in the closest parentheses to the left; and B is a modifier. When the heterocyclic nitrogen groups are 4-substituted pyridine, as is preferred, the polymer of the present invention is derivative of poly(4-vinylpyridine) and has the general formula, Formula 2b, set forth below.



2b

Further, when A is a suitably strong acid, as described above, the D copolymer is optional, in which case the polymer of the present invention has the general formula, Formula 2c:

Abbott Ex. 1002 - 773/1438



2c

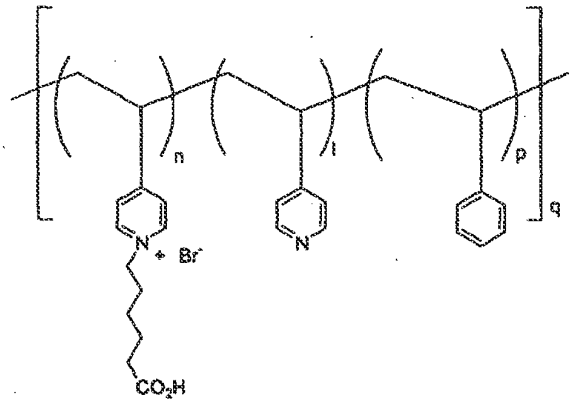
[0057] In any of Formulas 2a-2c, B is a modifier group that may add any desired chemical, physical or biological properties to the membrane. Such desired properties include analyte selectivity, hydrophobicity, hydrophilicity, elasticity, and biocompatibility. Examples of modifiers include the following: negatively charged molecules that may minimize entrance of negatively charged, interfering chemicals into the membrane; hydrophobic hydrocarbon molecules that may increase adhesion between the membrane and sensor substrate material; hydrophilic hydroxyl or polyhydroxy molecules that may help hydrate and add biocompatibility to the membrane; silicon polymers that may add elasticity and other properties to the membrane; and poly(ethylene glycol) constituents that are known to increase biocompatibility of biomaterials (Bergstrom, K., et al., J. Biomed. Mat. Res. 26, 779 (1992)). Further examples of B include, but are not limited to, a metal chelator, such as a calcium chelator, and other biocompatible materials. A poly(ethylene glycol) suitable for biocompatibility modification of the membrane generally has a molecular weight of from about 100 to about 20,000, preferably, from about 500 to about 10,000, and more preferably, from about 1,000 to about 8,000.

[0058] The modifier B can be attached to the heterocyclic nitrogens of the polymer directly or indirectly. In direct attachment, the heterocyclic nitrogen groups may be reacted with a modifier containing an alkylating group. Suitable alkylating groups include, but are not limited to, alkyl halide, epoxide, aziridine, and sulfonate esters. In indirect attachment, the heterocyclic nigrogens of the polymer may be quaternized with an alkylating agent having an additional reactive group, and then attached to a molecule having a desired property and a suitable reactive group.

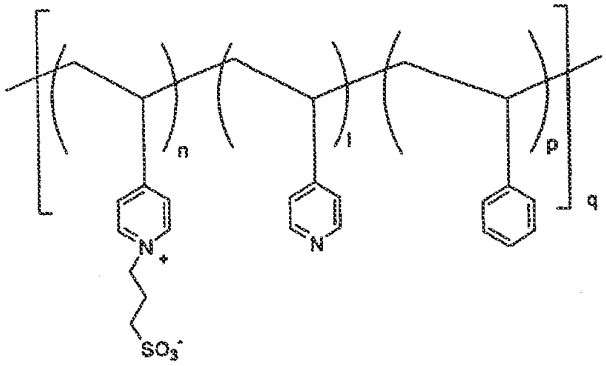
[0059] As described above, the B-containing copolymer is optional in the membrane of the present invention, such that when m of Formula 2a-2c is zero, the membrane has the general formula of Formula 1a-1c, respectively. The relative amounts of the four copolymer components, the heterocyclic nitrogen group containing A, the optional heterocyclic nitrogen group containing B, the heterocyclic nitrogen group, and D, may be expressed as percentages, as follows: [n/(n + m + l+ p)] x 100%, [m/(n + m + l + p)] x 100%, [l/(n + m + l + p)] x 100%, and [p/(n + m + l + p)] x 100%, respectively. Suitable percentages are 1-25%, 0-15% (when the B-containing heterocyclic nitrogen group is optional) or 1-15%, 20-90%, and 0-50% (when D is optional) or 1-50%, respectively, and preferable percentages are 5-20%, 0-10% (when the B-containing heterocyclic nitrogen group is optional) or 1-10%, 60-90%, and 5-20%, respectively.

[0060] Specific examples of suitable polymers have the general formulas, Formulas 3-6, shown below.

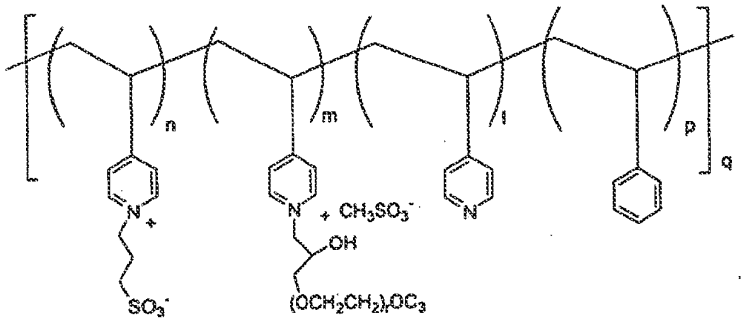
Abbott Ex. 1002 - 774/1438



3

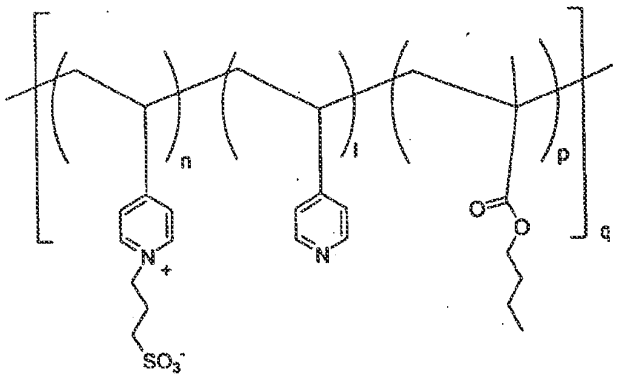


4



5

Abbott Ex. 1002 - 775/1438



6

Examples of Syntheses of Polyvinylpyridine Polymers

[0061] Examples showing the syntheses of various polyvinylpyridine polymers according to the present invention are provided below. Numerical figures provided are approximate.

Example 1: Synthesis of a Polymer of Formula 3

[0062] By way of illustration, an example of the synthesis of a polymer of Formula 3 above, is now provided. A solution of poly(4-vinylpyridine-co-styrene) (~10% styrene content) (20g, Aldrich) in 100 mL of dimethyl formamide (DMF) at 90°C was stirred and 6-bromohexanoic acid (3.7 g) in 15-20 mL of DMF was added. The resulting solution was stirred at 90°C for 24 hours and then poured into 1.5L of ether, whereupon the solvent was decanted. The remaining, gummy solid was dissolved in MeOH (150-200 mL) and suction-filtered through a medium-pore, fritted funnel to remove any undissolved solid. The filtrate was added slowly to rapidly stirred ether (1.5L) in a beaker. The resulting precipitate was collected by suction filtration and dried at 50°C under high vacuum for 2 days. The polymer had the following parameters: [n/(n+l+p)] x 100% ≈ 10%; [l/(n+l+p)] x 100% ≈ 80%; and [p/(n+l+p)] x 100% ≈ 10%.

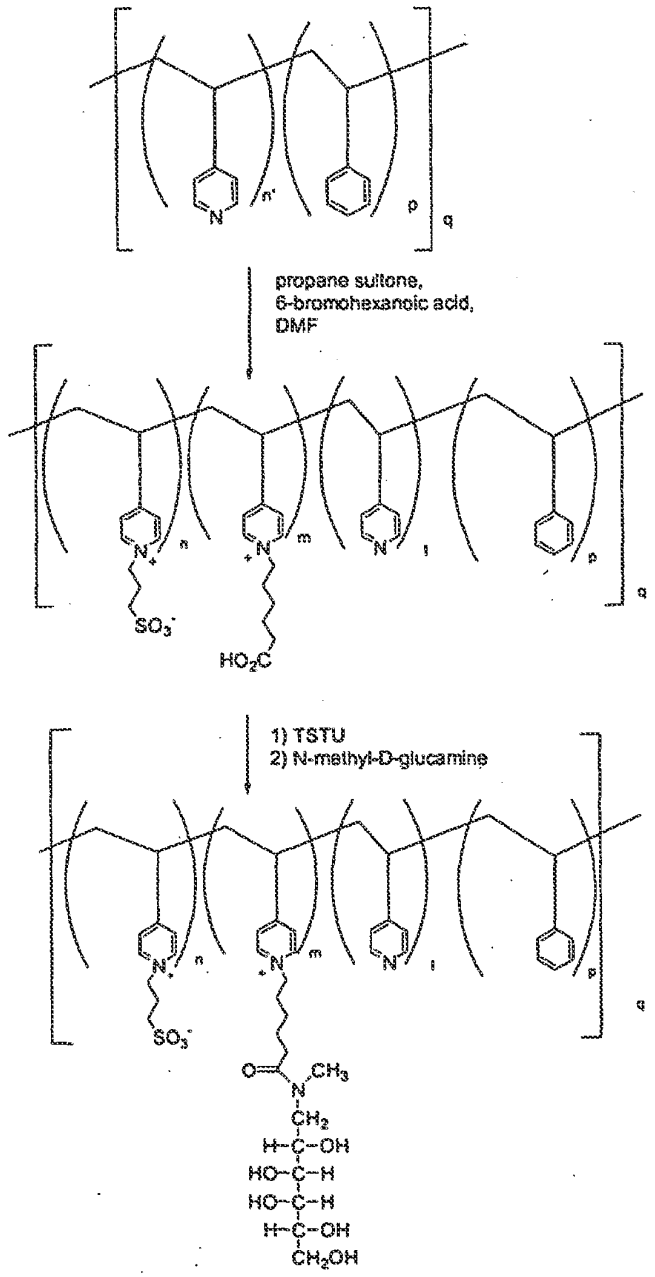
Example 2: Synthesis of a Polymer of Formula 5

[0063] By way of illustration, an example of the synthesis of a polymer of Formula 5 above, is now provided. A solution of poly(4-vinylpyridine-*co*-styrene) (~10% styrene) (20g, Aldrich) in 100 mL of anhydrous DMF at 90°C was stirred, methanesulfonic acid (~80mg) was added, and then 2g of methoxy-PEG-epoxide (molecular weight 5,000) (Shearwater Polymers, Inc.) in 15-20 mL of anhydrous DMF was added. The solution was stirred at 90°C for 24 hours and 1,3-Propane sultone (2.32g) in 10 mL of anhydrous DMF was added. The resulting solution was continuously stirred at 90° for 24 hours, and then cooled to room temperature and poured into 800 mL of ether. The solvent was decanted and the remaining precipitate was dissolved in hot MeOH (~200 mL), suction-filtered, precipitated again from 1 L of ether, and then dried at 50°C under high vacuum for 48 hours. The resulting polymer has the following parameters: [n/(n+m+l+p)] x 100% ≈ 10%; [m/(n+m+l+p)] x 100% ≈ 10%; [l/(n+m+l+p)] x 100% ≈ 70%; and [p/(n+m+l+p)] x 100% ≈ 10%.

Example 3: Synthesis of a Polymer Having a Polyhydroxy Modifier B

[0064] By way of illustration, an example of the synthesis of a polymer having a polyhydroxy modifier B, as schematically illustrated below, is now provided. Various polyhydroxy compounds are known for having biocompatibility properties. (U.S. Patent No. 6,011,077.) The synthesis below illustrates how a modifier group having a desired property may be attached to the polymer backbone via a linker.

Abbott Ex. 1002 - 776/1438



1,3-propane sultone (0.58 g, 4.8 mmoles) and 6-bromohexanoic acid (1.85g, 9.5 mmoles) are added to a solution of poly(4-vinylpyridine-co-styrene) (~10% styrene) (10g) dissolved in 60 mL of anhydrous DMF. The resulting solution is stirred at 90°C for 24 hours and then cooled to room temperature. O-(N-succinimidyl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate (TSTU) (2.86g, 9.5 mmoles) and N,N-diisopropylethylamine (1.65 mL, 9.5 mmoles) are then added in succession to the solution. After the solution is stirred for 5 hours, N-methyl-D-glucamine (2.4g, 12.4 mmoles) is added and the resulting solution is stirred at room temperature for 24 hours. The solution is poured into 500 ml of ether and the precipitate is collected by suction filtration. The collected precipitate is then dissolved in MeOH/H_2O and the resulting solution is subjected to ultra membrane filtration using the same MeOH/H_2O solvent to remove small molecules. The dialyzed solution is evaporated to dryness to give a polymer with the following parameters: [n/(n+m+l+p)] x 100% ≈ 10%; [m/(n+m+l+p)] x 100% ≈ 10%; [l/(n+m+l+p)] x 100% ≈ 70%; and [p/(n+m+l+p)] x 100% ≈ 10%.

Abbott Ex. 1002 - 777/1438

Crosslinkers

[0065] Crosslinkers of the present invention are molecules having at least two reactive groups, such as bi-, tri-, or tetra-functional groups, capable of reacting with the heterocyclic nitrogen groups, pyridine groups, or other reactive groups contained on A, B or D of the polymer. Preferably, the reactive groups of the crosslinkers are slow-reacting alkylating groups that can quaternize the heterocyclic nitrogen groups, such as pyridine groups, of the polymer. Suitable alkylating groups include, but are not limited to, derivatives of poly(ethylene glycol) or poly(propylene glycol), epoxide (glycidyl group), aziridine, alkyl halide, and sulfonate esters. Alkylating groups of the crosslinkers are preferably glycidyl groups. Preferably, glycidyl crosslinkers have a molecular weight of from about 200 to about 2,000 and are water soluble or soluble in a water-miscible solvent, such as an alcohol. Examples of suitable crosslinkers include, but are not limited to, poly(ethylene glycol) diglycidyl ether with a molecular weight of about 200 to about 600, and N,N-diglycidyl-4-glycidyloxyaniline.

It is desirable to have a slow crosslinking reaction during the dispensing of membrane solution so that the membrane coating solution has a reasonable pot-life for large-scale manufacture. A fast crosslinking reaction results in a coating solution of rapidly changing viscosity, which renders coating difficult. Ideally, the crosslinking reaction is slow during the dispensing of the membrane solution, and accelerated during the curing of the membrane at ambient temperature, or at an elevated temperature where possible.

Membrane Formation and Sensor Fabrication

[0066] An example of a process for producing a membrane of the present invention is now described. In this example, the polymer of the present invention and a suitable crosslinker are dissolved in a buffer-containing solvent, typically a buffer-alcohol mixed solvent, to produce a membrane solution. Preferably, the buffer has a pH of about 7.5 to about 9.5 and the alcohol is ethanol. More preferably, the buffer is a 10 mM (2-(4-(2-hydroxyethyl)-1-piperazine)ethanesulfonate) (HEPES) buffer (pH 8) and the ethanol to buffer volume ratio is from about 95 to 5 to about 0 to 100. A minimum amount of buffer is necessary for the crosslinking chemistry, especially if an epoxide or aziridine crosslinker is used. The amount of solvent needed to dissolve the polymer and the crosslinker may vary depending on the nature of the polymer and the crosslinker. For example, a higher percentage of alcohol may be required to dissolve a relatively hydrophobic polymer and/or crosslinker.

[0067] The ratio of polymer to cross-linker is important to the nature of the final membrane. By way of example, if an inadequate amount of crosslinker or an extremely large excess of crosslinker is used, crosslinking is insufficient and the membrane is weak. Further, if a more than adequate amount of crosslinker is used, the membrane is overly crosslinked such that membrane is too brittle and/or impedes analyte diffusion. Thus, there is an optimal ratio of a given polymer to a given crosslinker that should be used to prepare a desirable or useful membrane. By way of example, the optimal polymer to crosslinker ratio by weight is typically from about 4:1 to about 32:1 for a polymer of any of Formulas 3-6 above and a poly(ethylene glycol) diglycidyl ether crosslinker, having a molecular weight of about 200 to about 400. Most preferably, this range is from about 8:1 to about 16:1. Further by way of example, the optimal polymer to crosslinker ratio by weight is typically about 16:1 for a polymer of Formula 4 above, wherein $[n/(n+l+p)] \times 100\% \approx 10\%$, $[l/(n+l+p)] \times 100\% \approx 80\%$, and $[p/(n+l+p)] \times 100\% \approx 10\%$, or for a polymer of Formula 5 above, wherein $[n/(n+m+l+p)] \times 100\% \approx 10\%$, $[m/(n+m+l+p)] \times 100\% \approx 10\%$, $[l/(n+m+l+p)] \times 100\% \approx 70\%$, $[p/(n+m+l+p)] \times 100\% \approx 10\%$, and $r \approx 110$, and a poly(ethylene glycol) diglycidyl ether crosslinker having a molecular weight of about 200.

[0068] The membrane solution can be coated over a variety of biosensors that may benefit from having a membrane disposed over the enzyme-containing sensing layer. Examples of such biosensors include, but are not limited to, glucose sensors and lactate sensors. (See U.S. Patent No. 6,134,461 to Heller *et al.*)

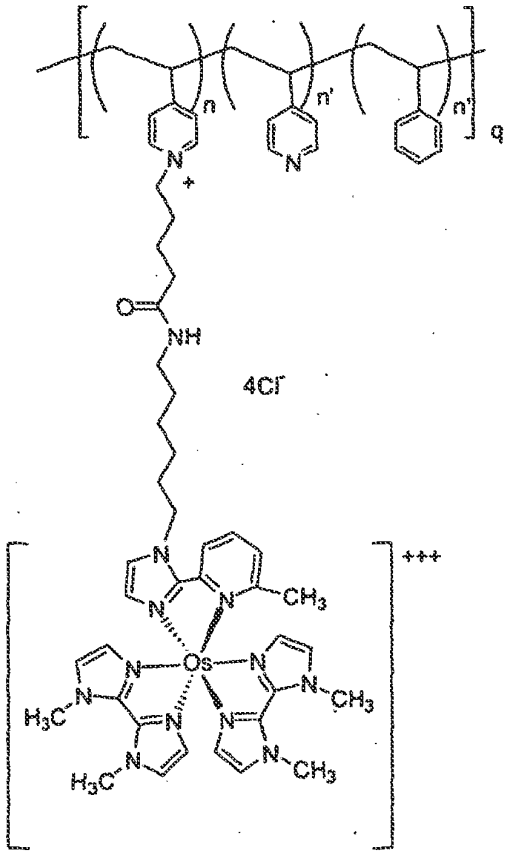
The coating process may comprise any commonly used technique, such as spin-coating, dip-coating, or dispensing droplets of the membrane solution over the sensing layers, and the like, followed by curing under ambient conditions typically for 1 to 2 days. The particular details of the coating process (such as dip duration, dip frequency, number of dips, or the like) may vary depending on the nature (i.e., viscosity, concentration, composition, or the like) of the polymer, the crosslinker, the membrane solution, the solvent, and the buffer, for example. Conventional equipment may be used for the coating process, such as a DSG D1L-160 dip-coating or casting system of NIMA Technology in the United Kingdom.

Example of Sensor Fabrication

[0069] Although sensors themselves are not in accordance with the present invention, sensor fabrication typically consists of depositing an enzyme-containing sensing layer over a working electrode and casting the diffusion-limiting membrane layer over the sensing layer, and optionally, but preferably, also over the counter and reference electrodes. The procedure below concerns the fabrication of a two-electrode sensor, such as that depicted in Figures 2A-2C. Sensors having other configurations such as a three-electrode design can be prepared using similar methods.

Abbott Ex. 1002 - 778/1438

[0070] A particular example of sensor fabrication, wherein the numerical figures are approximate, is now provided. A sensing layer solution was prepared from a 7.5mM HEPES solution (0.5 μL, pH 8), containing 1.7μg of the polymeric osmium mediator compound L, as disclosed in Published Patent Cooperation Treaty (PCT) Application, International Publication No. WO 01/36660 A2;
2:1μg of glucose oxidase (Toyobo); and 1.3μg of poly(ethylene glycol) diglycidyl ether (molecular weight 400). Compound L is shown below.



The sensing layer solution was deposited over carbon-ink working electrodes and cured at room temperature for two days to produce a number of sensors. A membrane solution was prepared by mixing 4 volumes of a polymer of Formula 4 above, dissolved at 64 mg/mL in 80% EtOH / 20% HEPES buffer (10 mM, pH 8), and one volume of poly(ethylene glycol) diglycidyl ether (molecular weight 200), dissolved at 4 mg/mL in 80% EtOH /20% HEPES buffer (10 mM, pH 8). The above-described sensors were dipped three times into the membrane solution, at about 5 seconds per dipping, with about a 10-minute time interval between consecutive dippings. The sensors were then cured at room temperature and normal humidity for 24 hours.

[0071] An approximate chemical structure of a section of a typical membrane prepared according to the present invention is shown in Figure 1. Such a membrane may be employed in a variety of sensors, such as the two- or three-electrode sensors described previously herein. By way of example, the membrane may be used in a two-electrode amperometric glucose sensor, as shown in Figure 2A-2C (collectively Figure 2) and described below.

[0072] The amperometric glucose sensor 10 of Figure 2 comprises a substrate 12 disposed between a working electrode 14 that is typically carbon-based, and a Ag/AgCl counter/reference electrode 16. A sensor or sensing layer 18 is disposed on the working electrode. A membrane or membrane layer 20 encapsulates the entire glucose sensor 10, including the Ag/AgCl counter/reference electrode.

[0073] The sensing layer 18 of the glucose sensor 10 consists of crosslinked glucose oxidase and a low potential polymeric osmium complex mediator, as disclosed in the above-mentioned Published PCT Application, International Publication No. WO 01/36660 A2. The enzyme- and mediator-containing formulation that can be used in the sensing layer, and methods for applying them to an electrode system, are known in the art, for example, from U.S. Patent No. 6,134,461. According to the present invention, the membrane overcoat was formed by thrice dipping the sensor into a

Abbott Ex. 1002 - 779/1438

membrane solution comprising 4 mg/mL poly(ethylene glycol) diglycidyl ether (molecular weight of about 200) and 64mg/mL of a polymer of Formula 4 above, wherein [n/(n+l+p)] x 100% ≈ 10%; [l/(n+l+p)] x 100% ≈ 80%; and [p/(n+l+p)] x 100% ≈ 10%, and curing the thrice-dipped sensor at ambient temperature and normal humidity for at least 24 hours, such as for about 1 to 2 days. The q value for such a membrane overcoat may be ≥ about 950, where n, l and p are 1, 8 and 1, respectively.

Membrane Surface Modification

[0074] Polymers of the present invention have a large number of heterocyclic nitrogen groups, such as pyridine groups, only a few percent of which are used in crosslinking during membrane formation. The membrane thus has an excess of these groups present both within the membrane matrix and on the membrane surface. Optionally, the membrane can be further modified by placing another layer of material over the heterocyclic-nitrogen-group-rich or pyridine-rich membrane surface. For example, the membrane surface may be modified by adding a layer of poly(ethylene glycol) for enhanced biocompatibility. In general, modification may consist of coating the membrane surface with a modifying solution, such as a solution comprising desired molecules having an alkylating reactive group, and then washing the coating solution with a suitable solvent to remove excess molecules. This modification should result in a monolayer of desired molecules.
The membrane 20 of the glucose sensor 10 shown in Figure 2 may be modified in the manner described above.

Experimental Examples

[0075] Examples of experiments that demonstrate the properties and/or the efficacy of sensors having diffusion-limiting membranes according to the present invention are provided below. Numerical figures provided are approximate.

Calibration Experiment

[0076] In a first example, a calibration experiment was conducted in which fifteen sensors lacking membranes were tested simultaneously (Set 1), and separately, eight sensors having diffusion-limiting membranes according to the present invention were tested simultaneously (Set 2), all at 37°C. In Set 2, the membranes were prepared from polymers of Formula 4 above and poly(ethylene glycol) diglycidyl ether (PEGDGE) crosslinkers, having a molecular weight of about 200. In the calibration experiment for each of Set 1 and Set 2, the sensors were placed in a PBS-buffered solution (pH 7) and the output current of each of the sensors was measured as the glucose concentration was increased. The measured output currents (μA for Set 1; nA for Set 2) were then averaged for each of Set 1 and Set 2 and plotted against glucose concentration (mM), as shown in the calibration graph of Figure 3.

[0077] As shown, the calibration curve for the Set 1 sensors lacking membranes is approximately linear over a very small range of glucose concentrations, from zero to about 3 mM, or 5 mM at most. This result indicates that the membrane-free sensors are insufficiently sensitive to glucose concentration change at elevated glucose concentrations such as 10 mM, which is well below the high end of clinically relevant glucose concentration at about 30 mM. By contrast, the calibration curve for the Set 2 sensors having diffusion-limiting membranes according to the present invention is substantially linear over a relatively large range of glucose concentrations, for example, from zero to about 30 mM, as demonstrated by the best-fit line ($y = 1.2502x + 1.1951$; $R^2 \approx 0.997$) also shown in Figure 3. This result demonstrates the considerable sensitivity of the membrane-equipped membranes to glucose concentration, at low, medium, and high glucose concentrations, and of particular relevance, at the high end of clinically relevant glucose concentration at about 30 mM.

Stability Experiment

[0078] In a second example, a stability experiment was conducted in which a sensor lacking a membrane and a sensor having a diffusion-limiting membrane according to the present invention were tested, simultaneously, at 37°C. The membrane-equipped sensor had a membrane prepared from the same polymer and the same crosslinker as those of the sensors of Set 2 described above in the calibration experiment. In this stability experiment, each of the sensors was placed in a PBS-buffered solution (pH 7) having a fixed glucose concentration of 30 mM, and the output current of each of the sensors was measured. The measured output currents (μA for the membrane-less sensor; nA for the membrane-equipped sensor) were plotted against time (hour), as shown in the stability graph of Figure 4.

[0079] As shown, the stability curve for the membrane-less sensor decays rapidly over time, at a decay rate of about 4.69% μA per hour. This result indicates a lack of stability in the membrane-less sensor. By contrast, the stability curve for the sensor equipped with a membrane according to the present invention shows relative constancy over time, or no appreciable decay over time, the decay rate being only about 0.06% nA per hour. This result demonstrates the consid-

Abbott Ex. 1002 - 780/1438

erable stability and reliability of said sensors. That is, at a glucose concentration of 30 mM, while the membrane-less sensor lost sensitivity at a rate of almost 5% per hour over a period of about 20 hours, the sensor equipped with a membrane according to the present invention showed virtually no loss of sensitivity over the same period.

Responsivity Experiment

[0080] Ideally, the membrane of an electrochemical sensor should not impede communication between the sensing layer of the sensor and fluid or biofluid containing the analyte of interest. That is, the membrane should respond rapidly to changes in analyte concentration.

[0081] In a third example, a responsivity experiment was conducted in which eight sensors having diffusion-limiting membranes according to the present invention were tested simultaneously (Set 3), all at 37°C. The sensors of Set 3 had membranes prepared from the same polymers and the same crosslinkers as those of the sensors of Set 2 described in the calibration experiment above. In this responsivity experiment, the eight sensors were placed in a PBS-buffered solution (pH 7), the glucose concentration of which was increased in a step-wise manner over time, as illustrated by the glucose concentrations shown in Figure 5, and the output current of each of the sensors was measured. The measured output currents (nA) were then averaged for Set 3 and plotted against time (real time, hour:minute:second), as shown in the responsivity graph of Figure 5.

[0082] The responsivity curve for the Set 3 sensors having diffusion-limiting membranes according to the present invention has discrete steps that mimic the step-wise increases in glucose concentration in a rapid fashion. As shown, the output current jumps rapidly from one plateau to the next after the glucose concentration is increased. This result demonstrates the considerable responsivity of the sensors equipped with membranes of the present invention. The responsivity of these membrane-equipped electrochemical sensors makes them ideal for analyte sensing, such as glucose sensing.

Motion-Sensitivity Experiment

[0083] Ideally, the membrane of an electrochemical sensor should be unaffected by motion or movement of fluid or biofluid containing the analyte of interest. This is particularly important for a sensor that is implanted in a body, such as a human body, as body movement may cause motion-associated noise and may well be quite frequent.

[0084] In this fourth example, a motion-sensitivity experiment was conducted in which a sensor A lacking a membrane was tested, and separately, a sensor B having a diffusion-limiting membrane according to the present invention was tested, all at 37°C. Sensor B had a membrane prepared from the same polymer and the same crosslinker as those of the sensors of Set 2 described in the calibration experiment above. In this experiment, for each of test, the sensor was placed in a beaker containing a PBS-buffered solution (pH 7) and a magnetic stirrer. The glucose concentration of the solution was increased in a step-wise manner over time, in much the same manner as described in the responsivity experiment above, as indicated by the various mM labels in Figure 6. The stirrer was activated during each step-wise increase in the glucose concentration and deactivated some time thereafter, as illustrated by the "stir on" and "stir off' labels shown in Figure 6. This activation and deactivation of the stirrer was repeated in a cyclical manner at several levels of glucose concentration and the output current of each of the sensors was measured throughout the experiment. The measured output currents (μA for sensor A; nA for sensor B) were plotted against time (minute), as shown in the motion-sensitivity graph of Figure 6.

[0085] As shown, the output current for the membrane-less sensor A is greatly affected by the stir versus no stir conditions over the glucose concentration range used in the experiment. By contrast, the output current for sensor B, having diffusion-limiting membranes according to the present invention, is virtually unaffected by the stir versus no stir conditions up to a glucose concentration of about 10 mM, and only slightly affected by these conditions at a glucose concentration of about 15 mM. This result demonstrates the considerable stability of the sensors equipped with membranes of the present invention in both stirred and non-stirred environments. The stability of these membrane-equipped electrochemical sensors in an environment of fluid movement makes them ideal for analyte sensing within a moving body.

Sensor Reproducibility Experiment

[0086] Dip-coating, or casting, of membranes is typically carried out using dipping machines, such as a DSG D1L-160 of NIMA Technology of the United Kingdom. Reproducible casting of membranes has been considered quite difficult to achieve. (Chen, T., et al., In Situ Assembled Mass-Transport Controlling Micromembranes and Their Application in Implanted Amperometric Glucose Sensors, Anal. Chem., Vol. 72, No. 16, Pp. 3757-3763 (2000).) Surprisingly, sensors equipped with membranes of the present invention can be made quite reproducibly, as demonstrated in the experiment now described.

[0087] Four batches of sensors (Batches 1-4) were prepared separately by dipping the sensors in membrane solution

Abbott Ex. 1002 - 781/1438

three times using casting equipment and allowing them to cure. In each of the four batches, the membrane solutions were prepared from the polymer of Formula 4 and poly(ethylene glycol) digycidyl ether (PEDGE) crosslinker having a molecular weight of about 200 (as in Set 2 and other Sets described above) using the same procedure. The membrane solutions for Batches 1 and 2 were prepared separately from each other, and from the membrane solution used for Batches 3 and 4. The membrane solution for Batches 3 and 4 was the same, although the Batch 3 and Batch 4 sensors were dip-coated at different times using different casting equipment. That is, Batches 1, 2 and 3 were dip-coated using a non-commercial, built system and Batch 4 was dip-coated using the above-referenced DSG D1L-160 system.

[0088] Calibration tests were conducted on each batch of sensors at 37°C. For each batch, the sensors were placed in PBS-buffered solution (pH 7) and the output current (nA) of each of the sensors was measured as the glucose concentration (mM) was increased. For each sensor in each of the four batches, a calibration curve based on a plot of the current output versus glucose concentration was prepared as shown in Figure 7B (Batch 1: 5 sensors), Figure 7C (Batch 2: 8 sensors), Figure 7D (Batch 3: 4 sensors) and Figure 7E (Batch 4: 4 sensors). The average slopes of the calibration curves for each batch were the following:

Batch 1: Average Slope = 1.10 nA/mM (CV = 5%);

Batch 2: Average Slope = 1.27 nA/mM (CV =10%);

Batch 3: Average Slope = 1.15 nA/mM (CV = 5%);

and

Batch 4: Average Slope = 1.14 nA/mM (CV = 7%).

Further, for each batch, the current output for the sensors in the batch was averaged and plotted against glucose concentration, as shown in Figure 7A. The average slope for Batches 1-4 was 1.17 nA/mM (CV = 7.2%).

[0089] The slopes of the curves within each batch and from batch-to-batch are very tightly grouped, showing considerably little variation. The results demonstrate that sensors prepared with membranes according to the present invention give quite reproducible results, both within a batch and from batch-to-batch.

[0090] The foregoing examples demonstrate many of the advantages of the membranes of the present invention and the sensors employing such membranes. Particular advantages of sensors employing the membranes of the present invention include sensitivity, stability, responsivity, motion-compatibility, ease of calibration, and ease and reproducibility of manufacture.

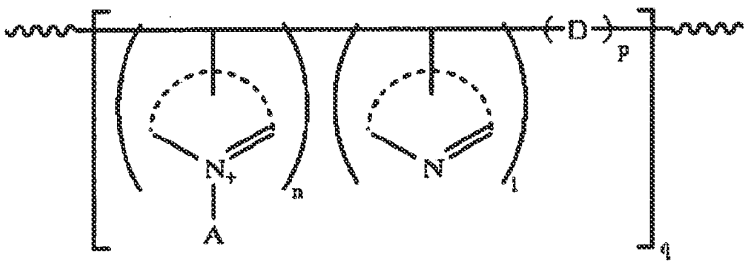
[0091] Various aspects and features of the present invention have been explained or described in relation to beliefs or theories, although it will be understood that the invention is not bound to any particular belief or theory. Various modifications, processes, as well as numerous structures to which the present invention may be applicable will be readily apparent to those of skill in the art to which the present invention is directed upon review of the specification. Although the various aspects and features of the present invention have been described with respect to various embodiments and specific examples herein, it will be understood that the invention is entitled to protection within the full scope of the appended claims.

Claims

1. A crosslinked membrane comprising:

a polymer having the formula:

Abbott Ex. 1002 - 782/1438



wherein the solid horizontal line represents a polymer backbone;
A is an alkyl substituted with a water-soluble constituent;
D is selected from phenylalkyl, alkoxystyrene, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, a poly(ethylene glycol)-containing constituent, and a polyhydroxyl-containing constituent; and
each of n, 1, p and q is independently a positive number.

2. The membrane of claim 1, wherein A is negatively charged.

3. The membrane of claim 1, wherein A is selected from a sulphonate, a carboxylate, and a phosphate.

4. The membrane of claim 1, wherein A is selected from sulphopropyl, sulphobutyl, carboxypropyl, and carboxypentyl.

5. The membrane of claim 1, wherein A is of the formula L-G, where L is a C2-C12 linear or branched alkyl linker and G is a negatively charged carboxy or sulphonate.

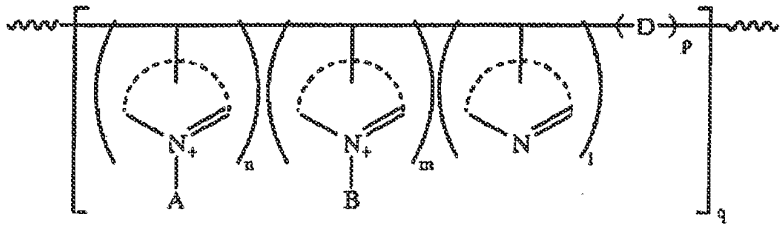
6. The membrane of claim 5, wherein L is substituted with an aryl, alkoxy, alkenyl, alkynyl, --F, --Cl, --OH, aldehyde, ketone, ester, or amide.

7. The membrane of claim 1, wherein D is styrene or C1-C18 alkyl methacrylate.

8. The membrane of claim 1, wherein an average molecular weight of the polymer is above 50,000.

9. The membrane of claim 1, wherein an average molecular weight of the polymer is above 200,000.

10. The membrane of claim 1, wherein the polymer further comprises a B-containing copolymer such that the polymer has the formula:



wherein B is a modifier and m is a positive number.

11. The membrane of claim 10, wherein B is selected from a chelator, a negatively charged constituent, a hydrophobic hydrocarbon constituent, a hydrophilic hydroxyl or polyhydroxy constituent, a silicon polymer, and a poly(ethylene glycol).

12. The membrane of claim 10, wherein B is a poly(ethylene glycol) having a molecular weight of from 100 to 20,000.

Abbott Ex. 1002 - 783/1438

13. The membrane of claim 10, wherein B is a poly(ethylene glycol) having a molecular weight of from 200 to 2000.

14. The membrane of claim 10, wherein [n/(n+m+1+p)]x100% is from 1% to 25%.

15. The membrane of claim 10, wherein [m/(n+m+1+p)]x100% is from 1% to 15%.

16. The membrane of claim 10, wherein [1/(n+m+1+p)]x100% is from 20% to 90%.

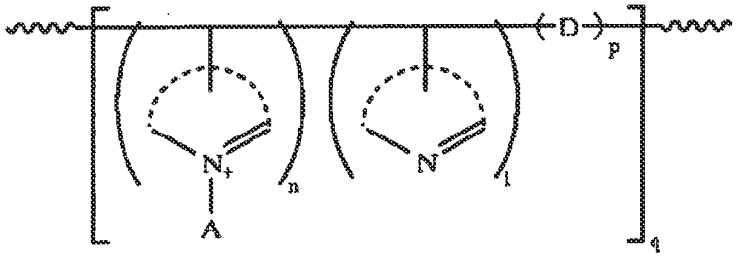
17. The membrane of claim 10, wherein [p/(n+m+1+p)]x100% is from 1% to 50%.

18. The membrane of claim 1, wherein at least one heterocyclic nitrogen constituent of the polymer is independently selected from pyridine, imidazole, oxazole, thiazole, pyrazole, and any derivative thereof.

Patentansprüche

1. Vernetzte Membran umfassend:

ein Polymer der Formel:



wobei die durchgezogene horizontale Linie ein Polymergrundgerüst darstellt;
A ein mit einem wasserlöslichen Bestandteil substituiertes Alkyl ist;
D aus Phenylalkyl, Alkoxystyrol, Hydroxyalkyl, Alkoxyalkyl, Alkoxycarbonylalkyl, einem poly(Ethylenglykol)-enthaltendem Bestandteil und einem poly(Hydroxyl)-enthaltendem Bestandteil ausgewählt ist; und
jedes von n, l, p und q unabhängig eine positive Zahl ist.

2. Membran gemäß Anspruch 1, wobei A negativ geladen ist.

3. Membran gemäß Anspruch 1, wobei A aus einer Gruppe, bestehend aus einem Sulfonat, einem Carboxylat, und einem Phosphat, ausgewählt ist.

4. Membran gemäß Anspruch 1, wobei A aus einer Gruppe, bestehend aus Sulfopropyl, Sulfobutyl , Carboxypropyl, und Carboxypentyl, ausgewählt ist.

5. Membran gemäß Anspruch 1, wobei A der Formel L-G entspricht, worin L ein linear oder verzweigt ausgebildeter C2-C12 Linker ist und G eine negativ geladene Carboxy-oder Sulfonat-Gruppe.

6. Membran gemäß Anspruch 5, wobei L mit einem Aryl, einem Alkoxy, einem Alkenyl, einem Alkinyl, -F, Cl, -OH, Aldehyd, Keton, Ester oder Amid substituiert ist.

7. Membran gemäß Anspruch 1, wobei D Styrol oder C1-C18-Alkylmethacrylat ist.

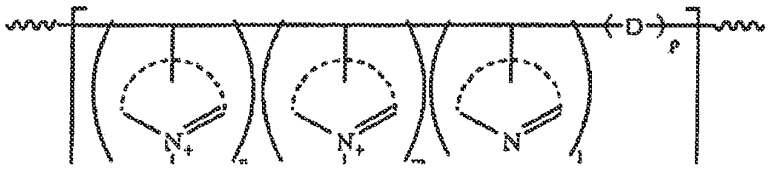
8. Membran gemäß Anspruch 1, wobei ein durchschnittliches Molekulargewicht des Polymers über 50 000 liegt.

9. Membran gemäß Anspruch 1, wobei ein durchschnittliches Molekulargewicht des Polymers über 200 000 liegt.

10. Membran gemäß Anspruch 1, wobei das Polymer weiterhin ein B-enthaltendes Co-Polymer umfasst, so dass das

Abbott Ex. 1002 - 784/1438

Polymer die Formel besitzt:



wobei B ein Modifikator und M eine positive Zahl ist.

11. Membran gemäß Anspruch 10, wobei B ausgewählt ist aus einem Chelator, einem negativ geladenen Bestandteil, einem hydrophoben Kohlenwasserstoffbestandteil, einem hydrophilen Hydroxy- oder Polyhydroxybestandteil, einem Silikonpolymer und einem Poly(ethylenglykol), ausgewählt ist.

12. Membran gemäß Anspruch 10, wobei B ein Poly(ethylenglykol) mit einem Molekulargewicht von 100 bis 20 000 ist.

13. Membran gemäß Anspruch 10, wobei B ein Poly(ethylenglykol) mit einem Molekulargewicht von 200 bis 2 000 ist.

14. Membran gemäß Anspruch 10, wobei [n/(n+m+l+p)]x100 % von 1 % bis 25% ist.

15. Membran gemäß Anspruch 10, wobei [m/(n+m+l+p)]x100 % von 1% bis 15% ist.

16. Membran gemäß Anspruch 10, wobei [l/(n+m+l+p)]x100 % von 20% bis 90% ist.

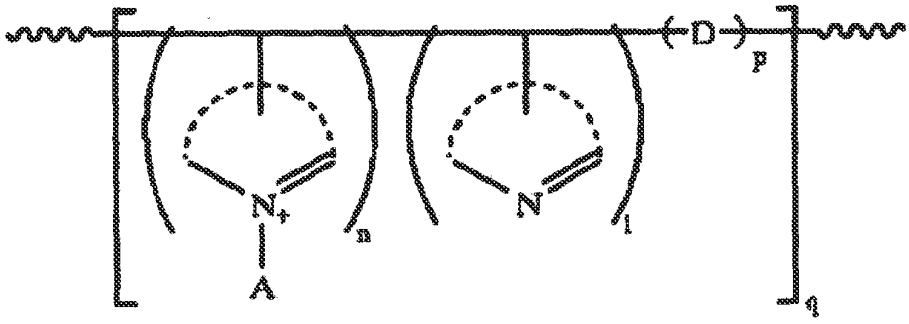
17. Membran gemäß Anspruch 10, wobei [p/(n+m+l+p)]x100 % von 1% bis 50% ist.

18. Membran gemäß Anspruch 1, wobei mindestens ein heterozyklischer Stickstoffbestandteil des Polymers unabhängig aus Pyridin, Imidazol, Oxazo, Thiazol, Pyrazol und irgendeinem Derivat davon, ausgewählt ist.

Revendications

1. Membrane réticulée comprenant :

un polymère ayant la formule :



dans laquelle la ligne horizontale solide représente un squelette de polymère ;
A est un alkyle substitué avec un constituant hydrosoluble ;
D est choisi parmi un phénylalkyle, un alcoxystyrène, un hydroxyalkyle, un alcoxyalkyle, un alcoxycarbonylalkyle, un constituant contenant un poly(éthylèneglycol), et un constituant contenant un polyhydroxyle ; et
chacun parmi n, l, p et q est indépendamment un nombre positif.

Abbott Ex. 1002 - 785/1438

2. Membrane selon la revendication 1, dans laquelle A est chargé négativement.

3. Membrane selon la revendication 1, dans laquelle A est choisi parmi un sulfonate, un carboxylate et un phosphate.

4. Membrane selon la revendication 1, dans laquelle A est choisi parmi un sulfopropyle, un sulfobutyle, un carboxypropyle et un carboxypentyle.

5. Membrane selon la revendication 1, dans laquelle A est de formule L-G, où L est un lieur alkyle linéaire ou ramifié en C2 à C12 et G est un carboxy ou un sulfonate chargé négativement.

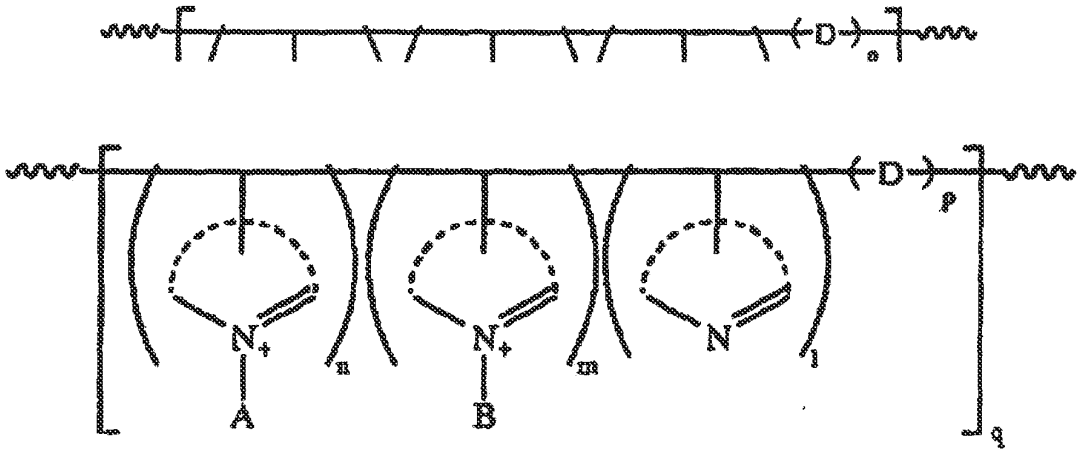
6. Membrane selon la revendication 5, dans laquelle L est substitué avec un aryle, un alcoxy, un alcényle, un alkynyle, --F, --Cl, --OH, un aldéhyde, une cétone, un ester ou un amide.

7. Membrane selon la revendication 1, dans laquelle D est un styrène ou un méthacrylate d'alkyle en C1 à C18.

8. Membrane selon la revendication 1, dans laquelle une masse moléculaire moyenne du polymère est supérieure à 50 000.

9. Membrane selon la revendication 1, dans laquelle une masse moléculaire moyenne du polymère est supérieure à 200 000.

10. Membrane selon la revendication 1, dans laquelle le polymère comprend en outre un copolymère contenant B tel que le polymère a la formule :



dans laquelle B est un modificateur et m est un nombre positif.

11. Membrane selon la revendication 10, dans laquelle B est choisi parmi un agent chélatant, un constituant chargé négativement, un constituant hydrocarboné hydrophobe, un constituant hydroxyle ou polyhydroxy hydrophile ou un polymère de silicone et un poly(éthylène glycol).

12. Membrane selon la revendication 10, dans laquelle B est un poly(éthylène glycol) ayant une masse moléculaire de 100 à 20 000.

13. Membrane selon la revendication 10, dans laquelle B est un poly(éthylène glycol) ayant une masse moléculaire de 200 à 2 000.

14. Membrane selon la revendication 10, dans laquelle [n/(n+m+l+p)]x100 % est de 1 à 25%.

15. Membrane selon la revendication 10, dans laquelle [m/(n+m+l+p)Jx100 % est de 1 à 15%.

Abbott Ex. 1002 - 786/1438

16. Membrane selon la revendication 10, dans laquelle [l/(n+m+l+p)]x100 % est de 20à90%.

17. Membrane selon la revendication 10, dans laquelle [p/(n+m+l+p)]x100 % est de 1 à50%.

18. Membrane selon la revendication 1, dans laquelle au moins un constituant azoté hétérocyclique du polymère est choisi indépendamment parmi une pyridine, un imidazole, un oxazole, un thiazole, un pyrazole et l'un quelconque de leurs dérivés.

Abbott Ex. 1002 - 787/1438

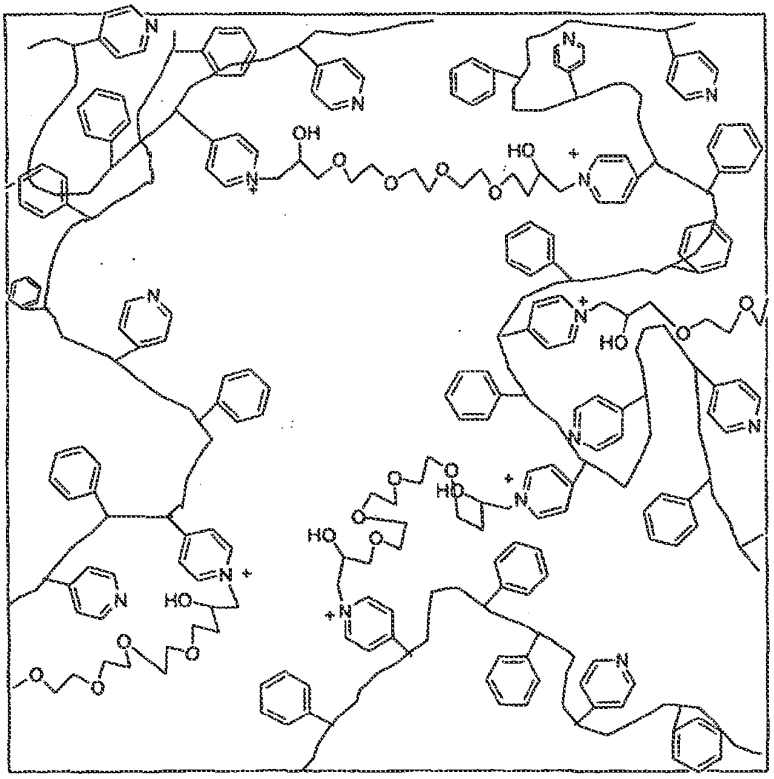


Figure 1

Abbott Ex. 1002 - 788/1438

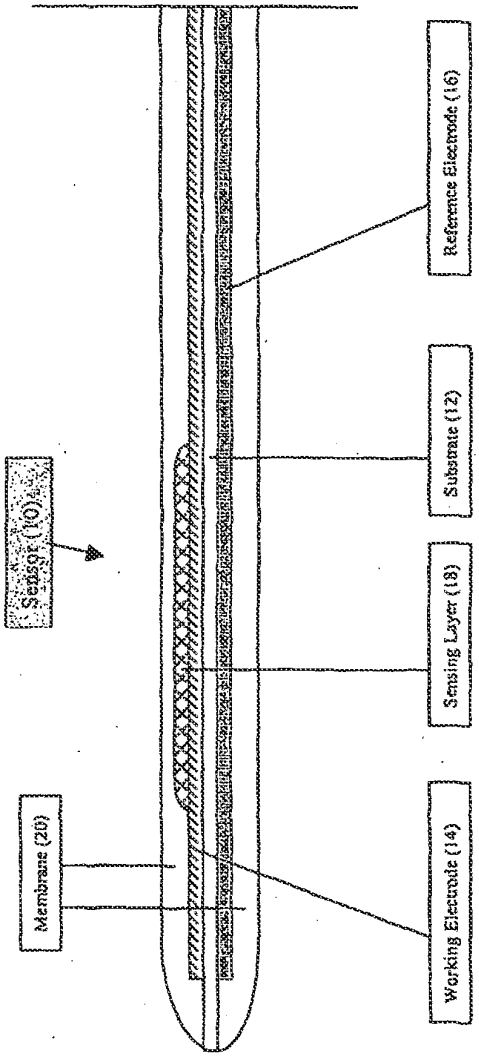


Figure 2A

Abbott Ex. 1002 - 789/1438

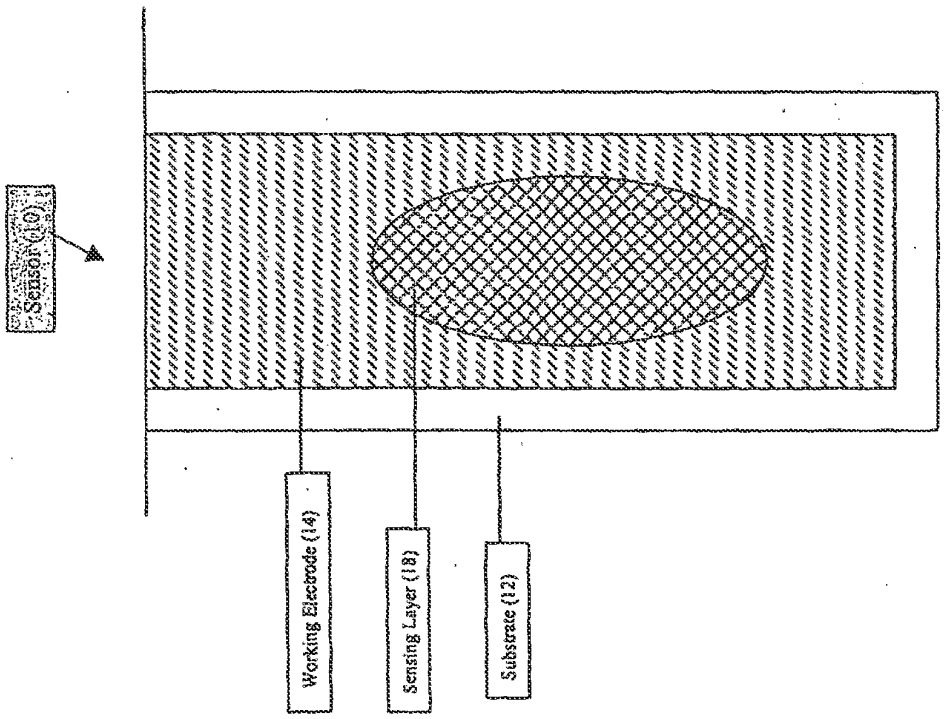


Figure 2B

Abbott Ex. 1002 - 790/1438

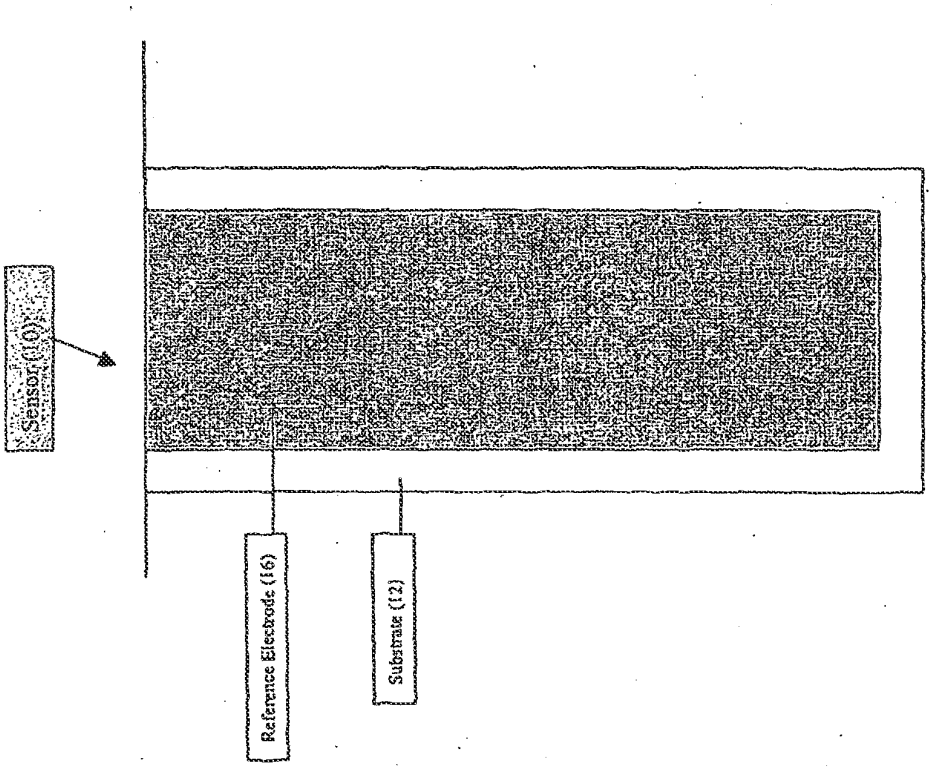


Figure 2C

Abbott Ex. 1002 - 791/1438

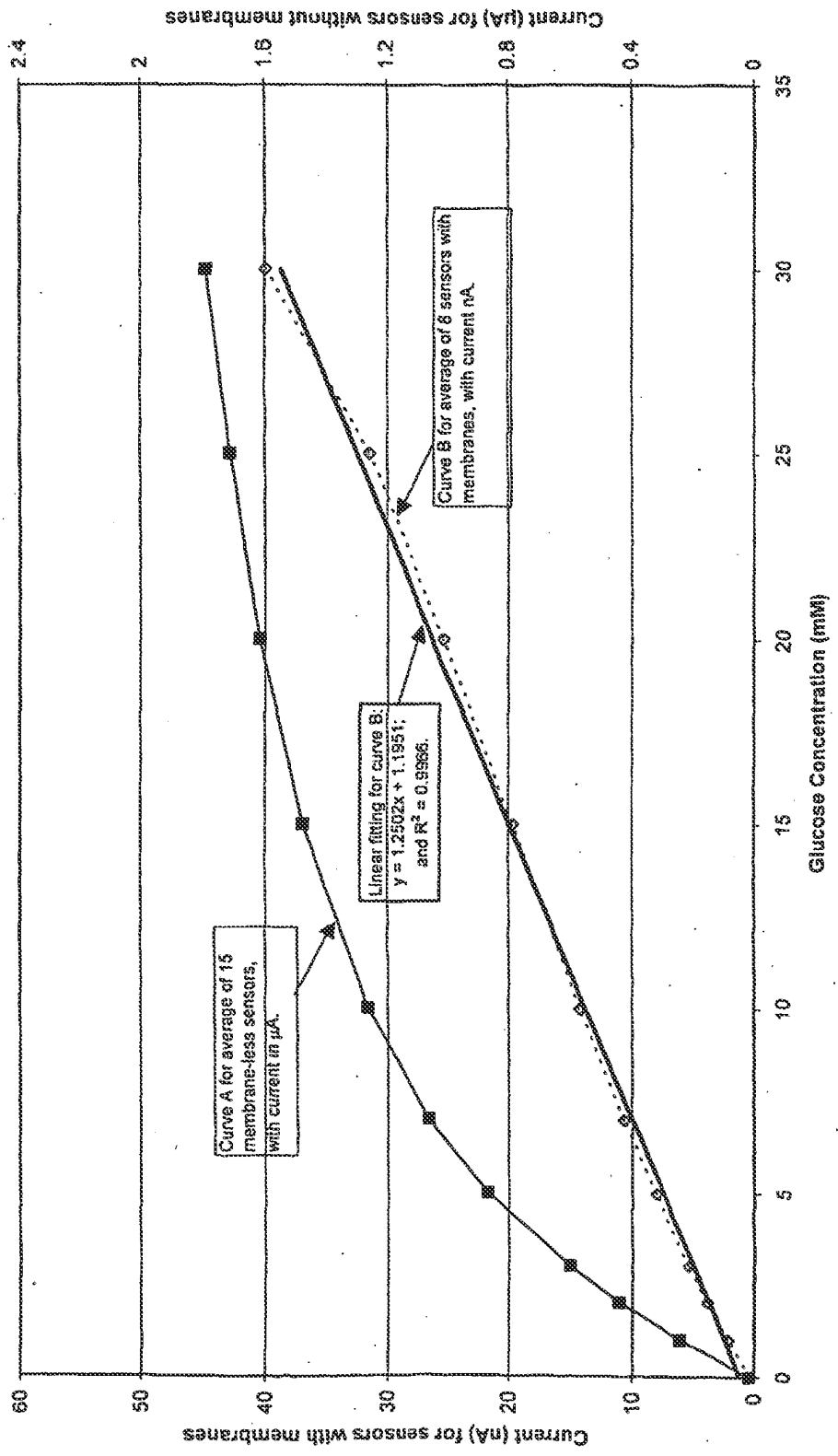


Figure 3. Calibration Curves at 37 °C

Abbott Ex. 1002 - 792/1438

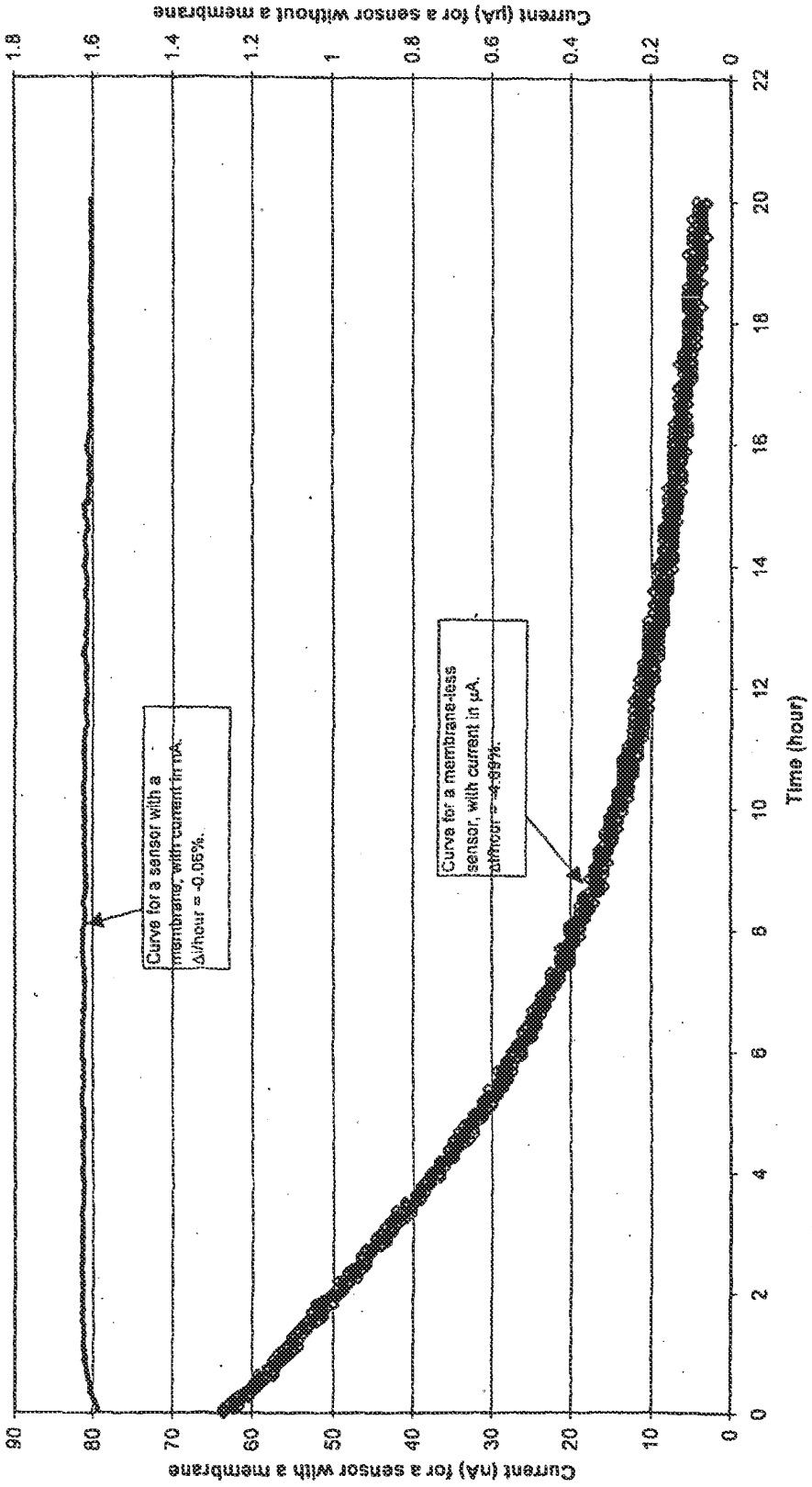
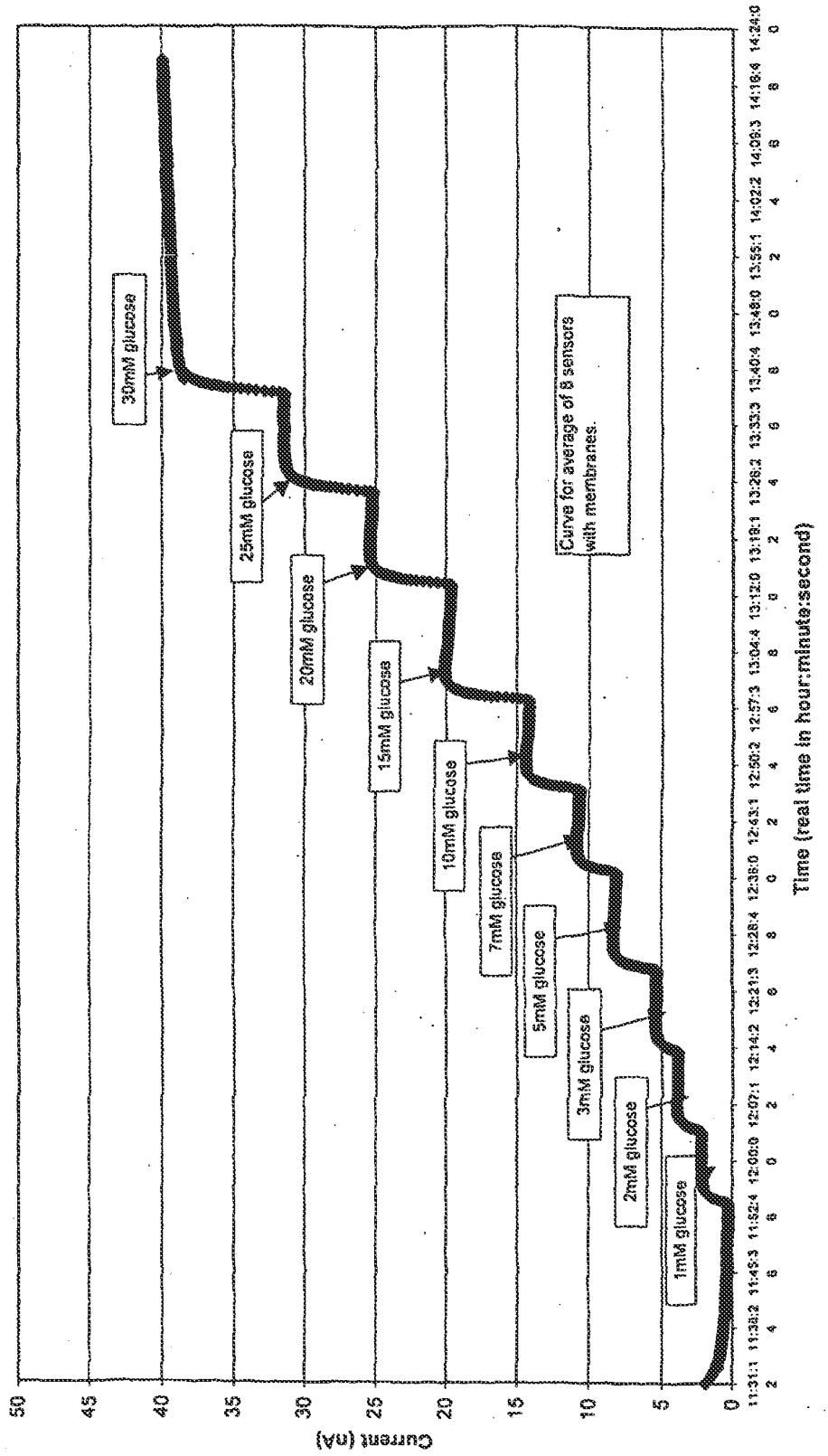


Figure 4. Stability Curves at 37°C

Abbott Ex. 1002 - 793/1438

Figure 5. Responsivity Curve at 37 °C



Abbott Ex. 1002 - 794/1438

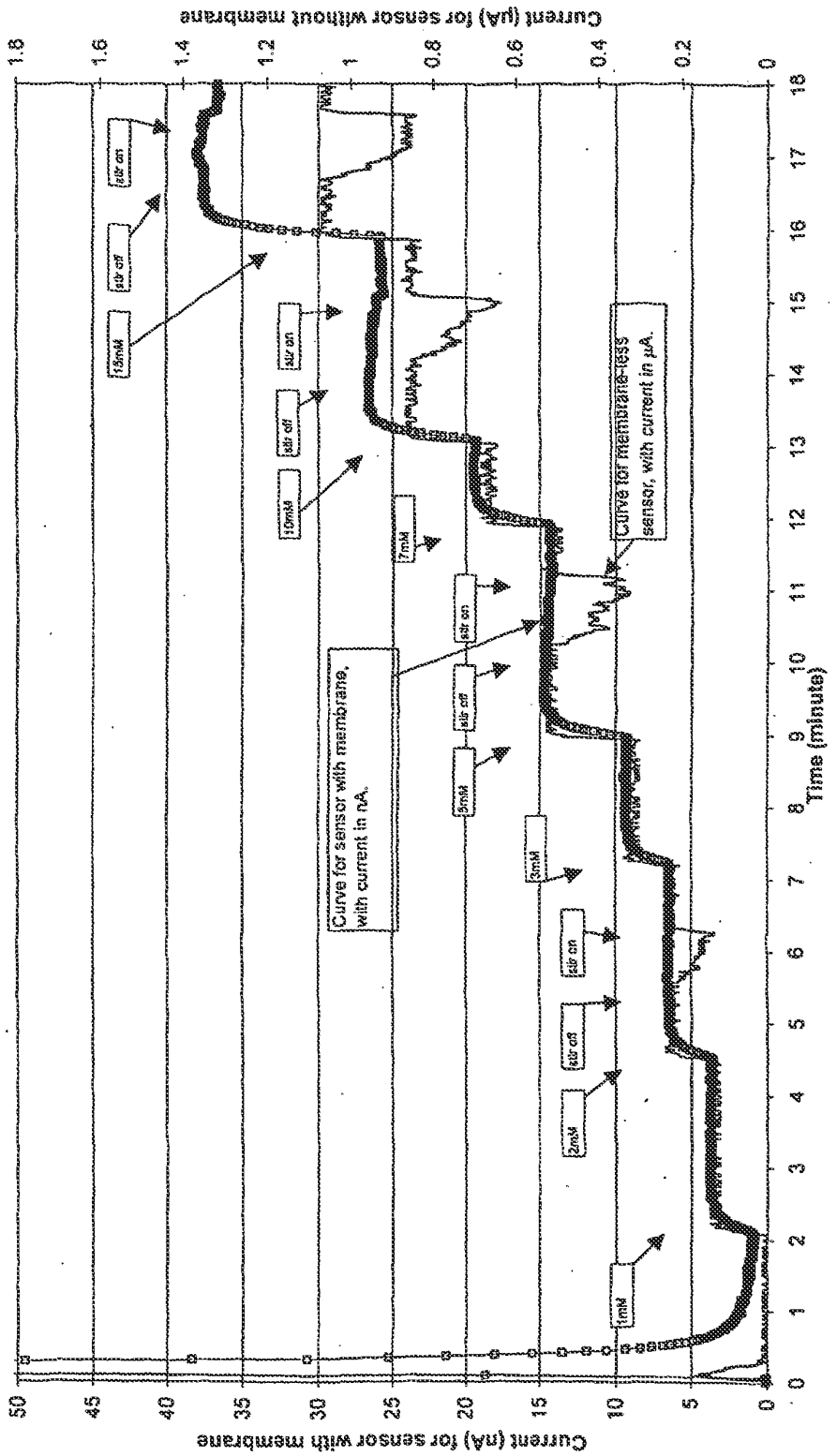


Figure 6. Motion-Sensitivity Curves at 37 °C

Abbott Ex. 1002 - 795/1438

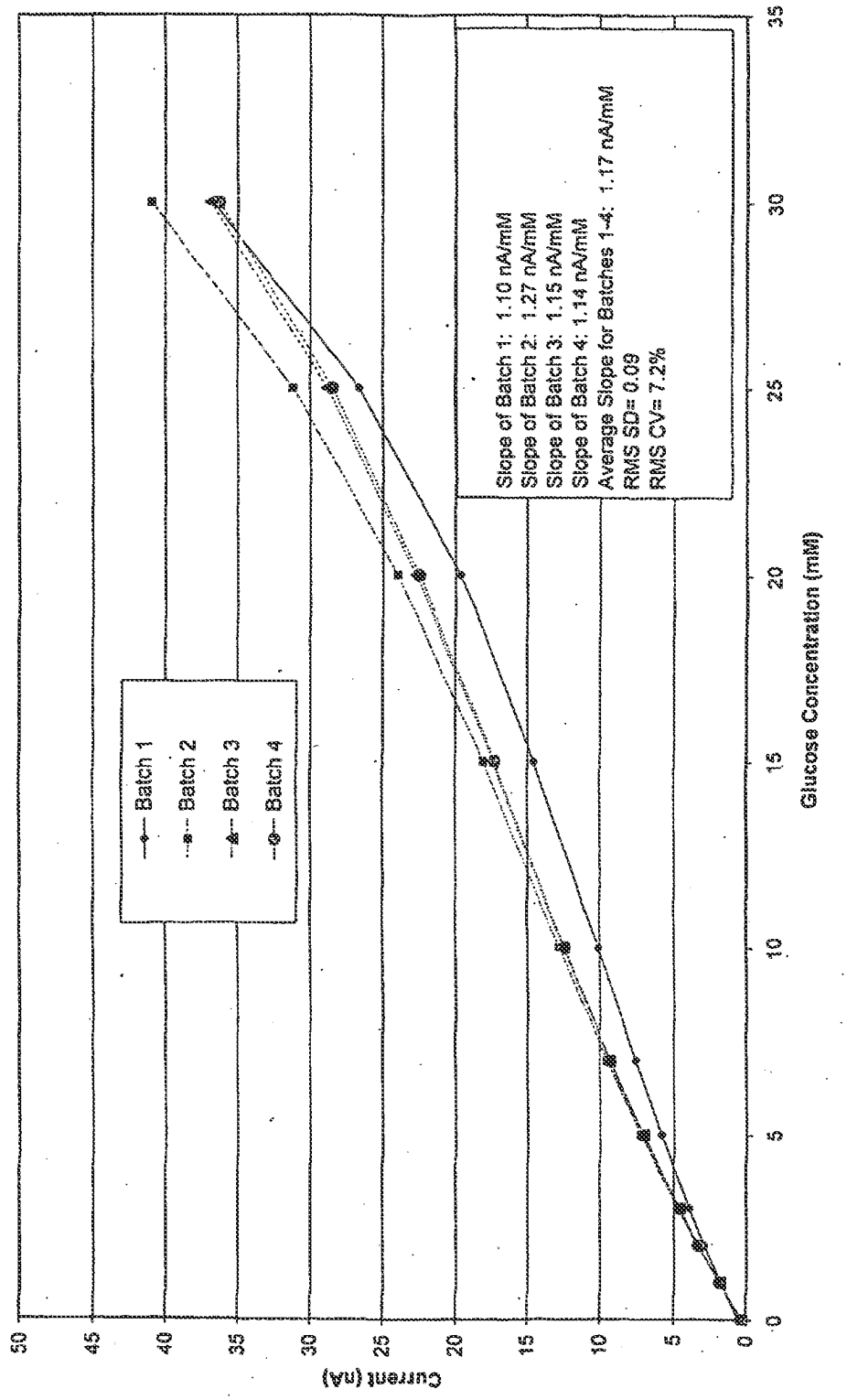


Figure 7A: Calibration Curves for Sensor Batches 1-4 at 37°C

Abbott Ex. 1002 - 796/1438

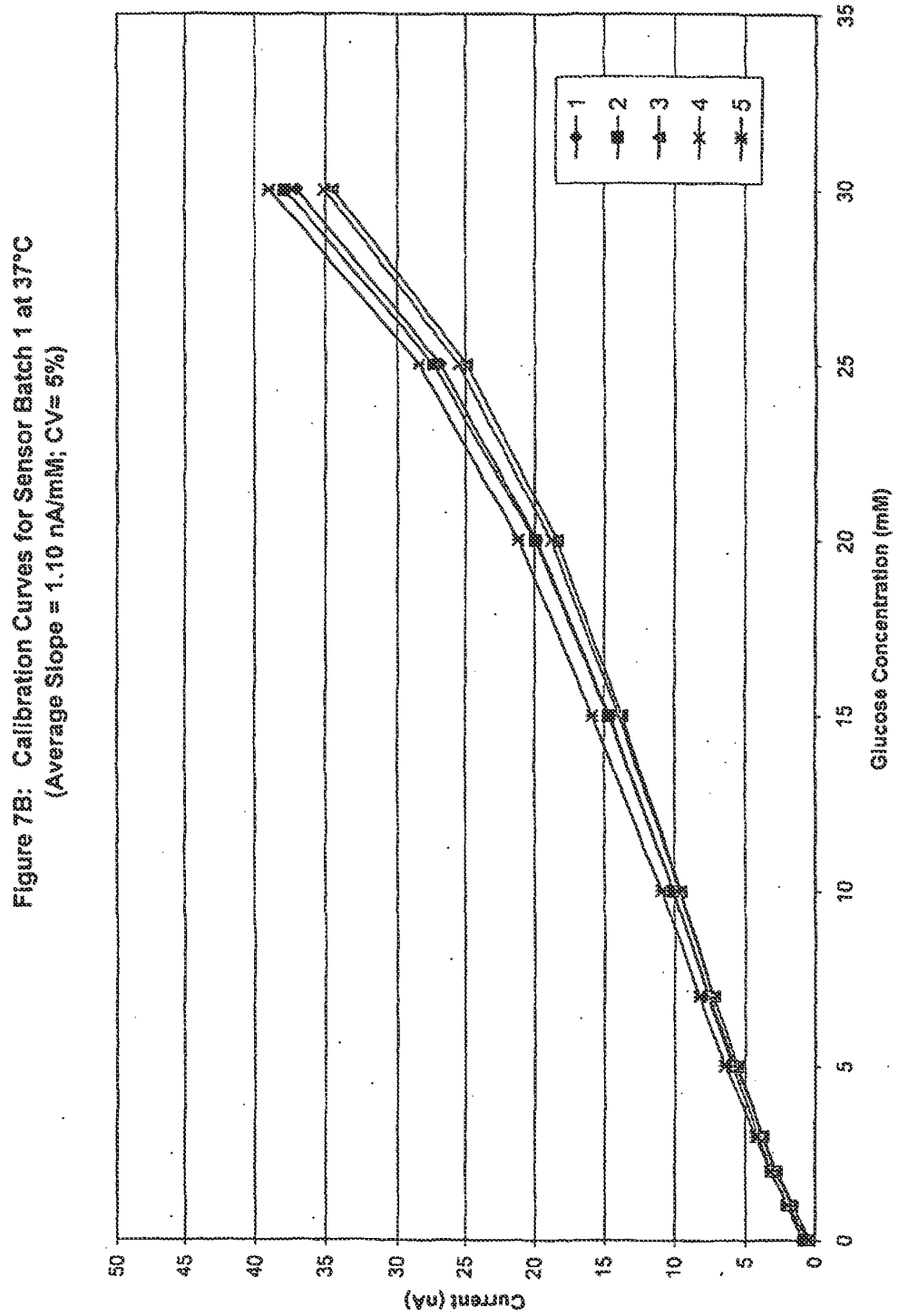


Figure 7B: Calibration Curves for Sensor Batch 1 at 37°C
(Average Slope = 1.10 nA/mM; CV= 5%)

Abbott Ex. 1002 - 797/1438

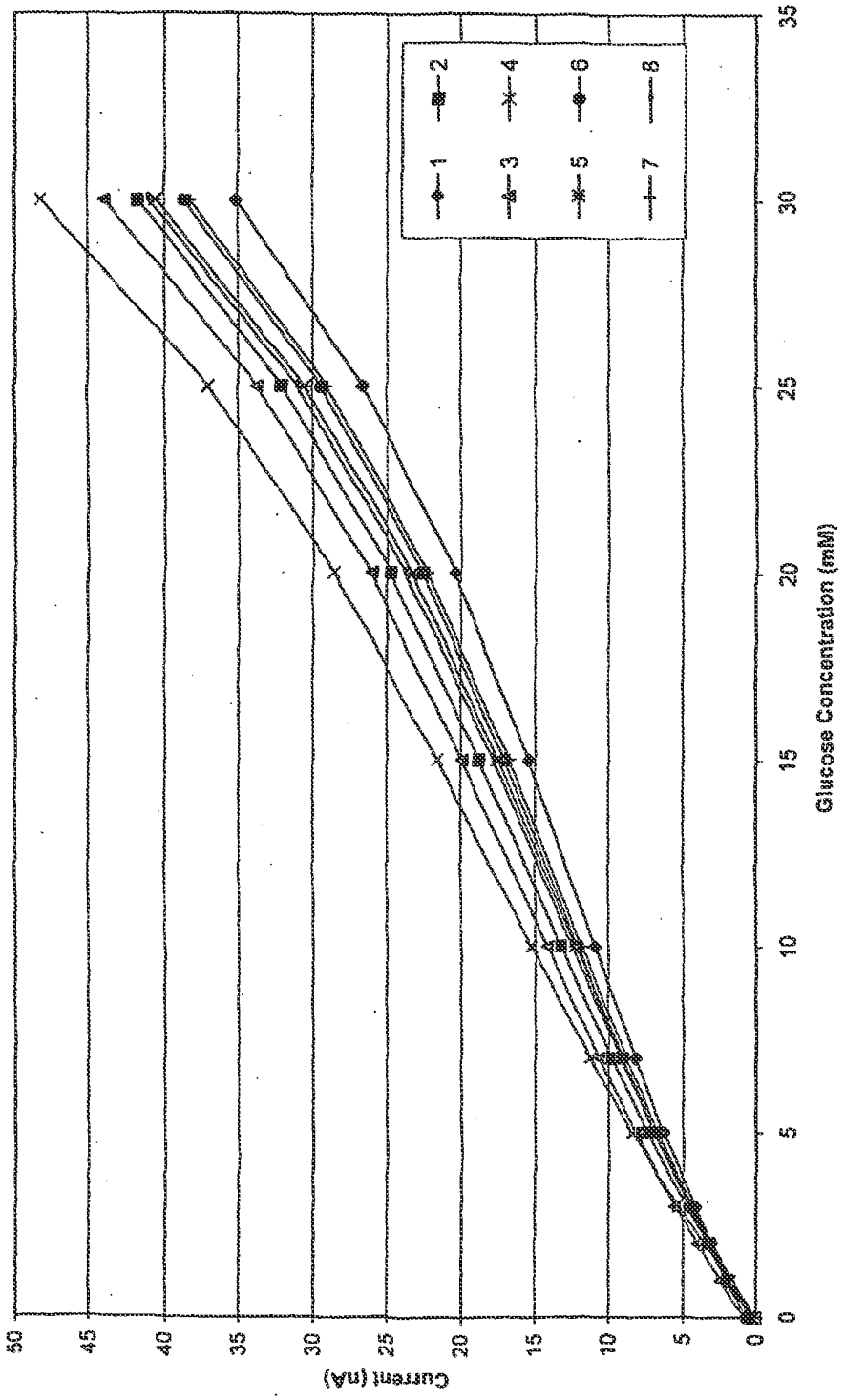


Figure 7C: Calibration Curves for Sensor Batch 2 at 37°C
(Average Slope = 1.27 nA/mM; CV= 10%)

Abbott Ex. 1002 - 798/1438

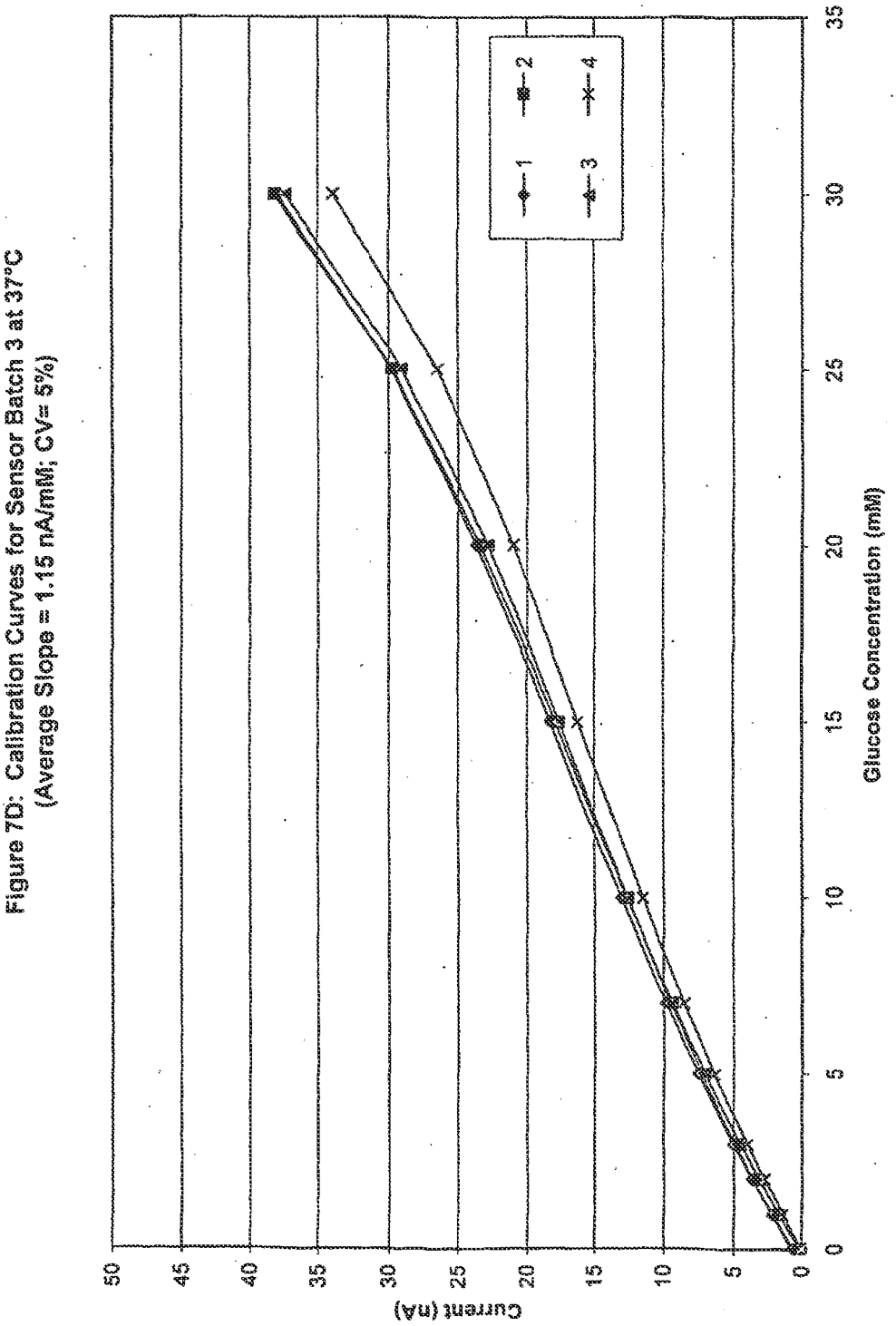


Figure 7D: Calibration Curves for Sensor Batch 3 at 37°C
(Average Slope = 1.15 nA/mM; CV= 5%)

Abbott Ex. 1002 - 799/1438

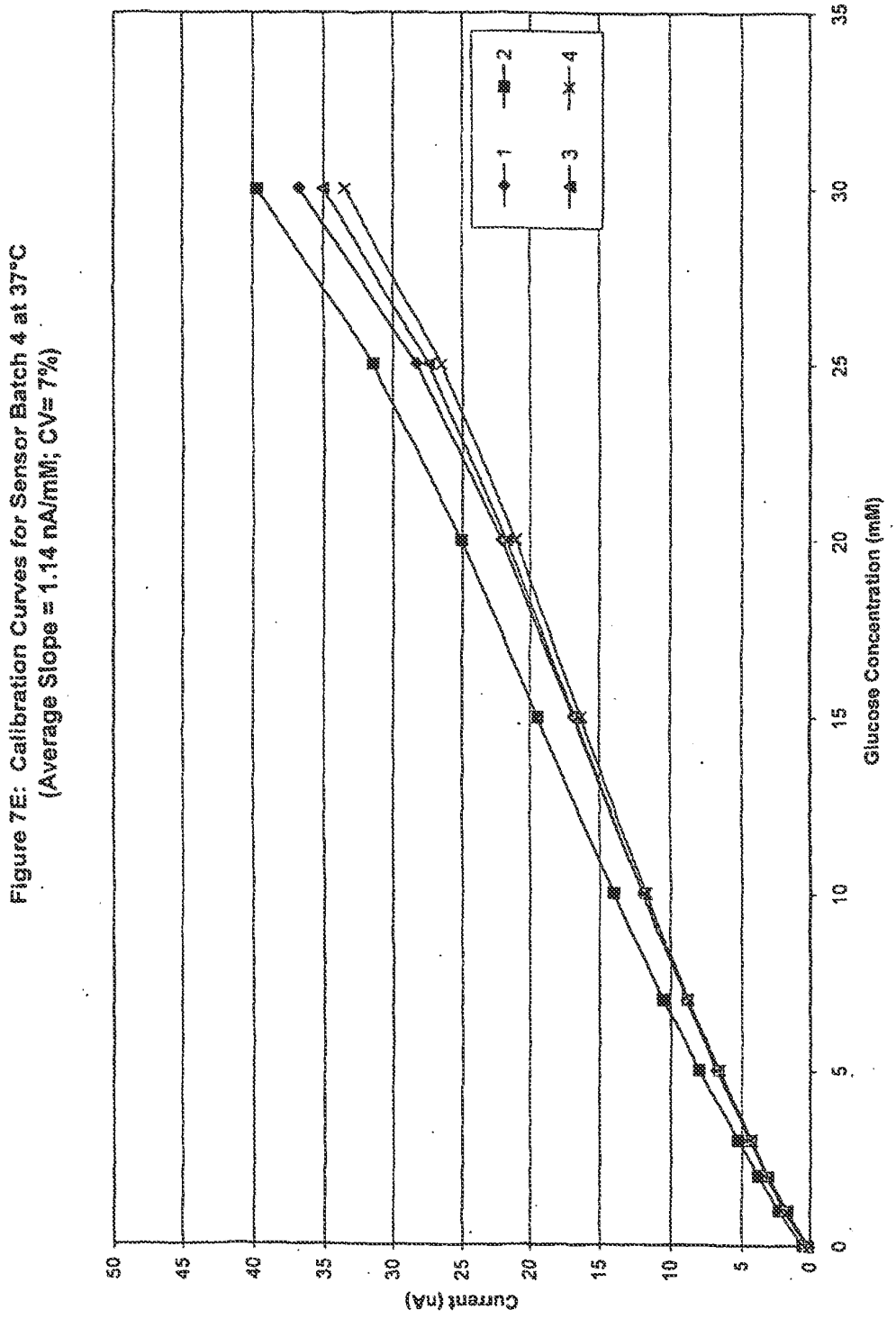


Figure 7E: Calibration Curves for Sensor Batch 4 at 37°C
(Average Slope = 1.14 nA/mM; CV= 7%)

Abbott Ex. 1002 - 800/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 5882494 A **[0003] [0012]**
- US 4759828 A, Young **[0011]**
- US 4484987 A, Gough **[0011]**
- US 5284140 A **[0011]**
- US 5322063 A, Allen **[0011]**
- US 5777060 A, Van Antwerp **[0012]**
- US 5786439 A, Van Antwerp **[0012]**
- WO 0157241 A2 **[0013]**
- US 4929313 A **[0014]**
- US 5543326 A **[0015]**
- US 6011077 A **[0064]**
- US 6134461 A **[0068] [0073]**
- WO 0136660 A2 **[0070] [0073]**

Non-patent literature cited in the description

- **SHAW, G.W. et al.** *Biosensors and Bioelectronics,* 1991, vol. 6, 401 **[0011]**
- **BINDRA, D.S. et al.** *Anal. Chem.,* 1991, vol. 63, 1692 **[0011]**
- **SHICHIRI, M. et al.** *Horm. Metab. Res., Suppl. Ser.,* 1988, vol. 20, 17 **[0011]**
- **BERGSTROM, K. et al.** *J. Biomed. Mat. Res.,* 1992, vol. 26, 779 **[0057]**
- **CHEN, T. et al.** In Situ Assembled Mass-Transport Controlling Micromembranes and Their Application in Implanted Amperometric Glucose Sensors. *Anal. Chem.,* 2000, vol. 72 (16), 3757-3763 **[0086]**

Abbott Ex. 1002 - 801/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 931 253 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
22.02.2012 Bulletin 2012/08

(21) Application number: **06804124.3**

(22) Date of filing: **25.09.2006**

(51) Int Cl.:
A61B 5/05 *(2006.01)*

(86) International application number:
PCT/US2006/037314

(87) International publication number:
WO 2007/041072 (12.04.2007 Gazette 2007/15)

(54) APPARATUS FOR PROVIDING RECHARGEABLE POWER IN DATA MONITORING AND MANAGEMENT SYSTEMS

GERÄT ZUR LIEFERUNG VON WIEDER AUFLADBARER ENERGIE IN DATENÜBERWACHUNGS- UND VERWALTUNGSSYSTEMEN

APPAREIL FOURNISSANT DE L ÉNERGIE RECHARGEABLE À DES SYSTÈMES DE SURVEILLANCE ET DE GESTION DE DONNÉES

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

(30) Priority: **30.09.2005 US 240273**

(43) Date of publication of application:
18.06.2008 Bulletin 2008/25

(73) Proprietor: **Abbott Diabetes Care Inc.**
Alameda, CA 94502 (US)

(72) Inventors:
- **REGGIARDO, Christopher, V.**
Castro Valley, CA 94546 (US)
- **FENNELL, Martin J.**
Concord, California 94521 (US)

(74) Representative: **Horton, Andrew Robert Grant et al**
Bowles Horton
Felden House
Dower Mews
High Street
Berkhamsted, Hertfordshire HP4 2BL (GB)

(56) References cited:
WO-A-01/52727
WO-A-99/22236
US-A1- 2002 193 679
US-A1- 2004 263 354
US-A1- 2006 025 663

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 931 253 B1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] Analayte, e.g., glucose monitoring systems including continuous and discrete monitoring systems generally include a small, lightweight battery powered and microprocessor controlled system which is configured to detect signals proportional to the corresponding measured glucose levels using an electrometer, and RF signals to transmit the collected data. One aspect of certain glucose monitoring systems include a transcutaneous or subcutaneous analyte sensor configuration which is, for example, partially mounted on the skin of a subject whose glucose level is to be monitored. The sensor cell may use a two or three-electrode (work, reference and counter electrodes) configuration driven by a controlled potential (potentiostat) analog circuit connected through a contact system.

[0002] The analyte sensor may be configured so that a portion thereof is placed under the skin of the patient so as to detect the analyte levels of the patient, and another portion of segment of the analyte sensor that is in communication with the transmitter unit. The transmitter unit is configured to transmit the analyte levels detected by the sensor over a wireless communication link such as an RF (radio frequency) communication link. To transmit signals, the transmitter unit requires a power supply such as a battery. Generally, batteries have a limited life span and require periodic replacement. More specifically, depending on the power consumption of the transmitter unit, the power supply in the transmitter unit may require frequent replacement or the transmitter unit may require replacement (e.g, disposable power supply such as disposable battery).

[0003] This may be cumbersome and inconvenient to the patient. Moreover, in continuous glucose monitoring systems, when the transmitter unit fails to transmit the glucose data from the sensor due to power failure, the patient may be approaching a critical physiological state such as hyperglycemia or hypoglycemia with little warning or knowledge. This could potentially be fatal to the patient.

[0004] At the same time, however, it may be undesirable to limit the functions of the transmitter so as to reduce the power consumption in order to prolong the battery life of the transmitter. For example, the transmitter unit may be configured to transmit less periodically or frequently to save battery power - this may in turn potentially result in inaccurate determination of monitored glucose levels as the detected levels are not sufficiently close together to provide a comprehensive result of the continuous monitoring.

[0005] Moreover, increasing the battery size may prolong the operating life of the transmitter unit, but would result in a more physically cumbersome design, and would add extra weight to be carried by the patient which is generally undesirable.

[0006] In view of the foregoing, it would be desirable to have an approach to provide a rechargeable power supply for the transmitter unit in the data monitoring and management system such that the compact, lightweight configuration of the transmitter unit worn by the patient can be maintained. Moreover, in view of the foregoing, it would be desirable to have various options for the power supply and/or a rechargeable power supply for the transmitter unit in the data monitoring and management systems.

[0007] The invention is defined in the independent claim 1, which is partitioned relative to the document US 2004/02103354 A1.

[0008] In view of the foregoing, in accordance with the various embodiments of the present invention, there is provided an apparatus for providing a disposable power supply source integrated into the housing of the transmitter unit mount that is placed on the skin of the patient, and configured to receive or "mate" with the transmitter unit. The transmitter unit mount is configured to be disposable with the analyte sensor, such that with each replacement of the analyte sensor (for example, every three or five days), the power supply providing power to the transmitter unit is also replaced.

[0009] In a further embodiment of the present invention, the transmitter unit may further be configured to include a rechargeable battery such that when the transmitter unit is mounted to the transmitter unit mount (that includes a separate disposable power supply), the power supply unit of the transmitter unit mount is configured to charge the rechargeable power supply of the transmitter unit. In this manner, the transmitter unit may be configured to maintain the communication link with the corresponding receiver unit during the period when the patient is replacing the analyte sensor (along with the transmitter unit mount).

[0010] Yet in a further embodiment of the present invention, the transmitter may be configured to include a series of capacitor combinations (and/or in conjunction with other circuitry including a corresponding series of DC/DC converters) configured to store charge so as to provide power to the transmitter. In one embodiment, the capacitor may include a single large capacitor (supercap) as energy store to provide power to the transmitter in the data monitoring and management system.

[0011] These and other objects, features and advantages of the present invention will become more fully apparent from the following detailed description of the embodiments, the appended claims and the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

FIG. 1 illustrates a block diagram of a data monitoring and management system for practicing one embodiment of the present invention;

FIG. 2 is a block diagram of the transmitter of the data monitoring and management system shown in

Abbott Ex. 1002 - 803/1438

FIG. 1 in accordance with one embodiment of the present invention;

FIG. 3 illustrates a cross sectional view of the transmitter and transmitter mount configuration for providing power to the transmitter in the data monitoring and management system in accordance with one embodiment of the present invention;

FIG. 4 is a circuit diagram of the energy storage approach for providing power to the transmitter in the data monitoring and management system in accordance with one embodiment of the present invention; and

FIG. 5 illustrates another energy storage approach for providing power to the transmitter in the data monitoring and management system in accordance with another embodiment of the present invention.

DETAILED DESCRIPTION

[0013] FIG. 1 illustrates a data monitoring and management system such as, for example, an analyte (e.g., glucose) monitoring system 100 in accordance with one embodiment of the present invention. The subject invention is further described primarily with respect to a glucose monitoring system for convenience and such description is in no way intended to limit the scope of the invention. It is to be understood that the analyte monitoring system may be configured to monitor a variety of analytes, e.g., lactate, and the like.

[0014] Indeed, analytes that may be monitored 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 monitored.

[0015] The glucose monitoring system 100 includes a sensor 101, a transmitter 102 coupled to the sensor 101, and a receiver 104 which is configured to communicate with the transmitter 102 via a communication link 103. The receiver 104 may be further configured to transmit data to a data processing terminal 105 for evaluating the data received by the receiver 104. Moreover, the data processing terminal in one embodiment may be configured to receive data directly from the transmitter 102 via a communication link 106 which may optionally be configured for bi-directional communication.

[0016] Only one sensor 101, transmitter 102, communication link 103, receiver 104, and data processing terminal 105 are shown in the embodiment of the glucose monitoring system 100 illustrated in FIG. 1. However, it will be appreciated by one of ordinary skill in the art that the glucose monitoring system 100 may include one or more sensor 101, transmitter 102, communication link 103, receiver 104, and data processing terminal 105, where each receiver 104 is uniquely synchronized with a respective transmitter 102. Moreover, within the scope of the present invention, the glucose monitoring system 100 may be a continuous monitoring system, or semi-continuous, or a discrete monitoring system.

[0017] In one embodiment of the present invention, the sensor 101 is physically positioned in or on the body of a user whose glucose level is being monitored. The sensor 101 may be configured to continuously sample the glucose level of the user and convert the sampled glucose level into a corresponding data signal for transmission by the transmitter 102. In one embodiment, the transmitter 102 is mounted on the sensor 101 so that both devices are positioned on the user's body. The transmitter 102 performs data processing such as filtering and encoding on data signals, each of which corresponds to a sampled glucose level of the user, for transmission to the receiver 104 via the communication link 103.

[0018] In one embodiment, the glucose monitoring system 100 is configured as a one-way RF communication path from the transmitter 102 to the receiver 104. In such embodiment, the transmitter 102 transmits the sampled data signals received from the sensor 101 without acknowledgement from the receiver 104 that the transmitted sampled data signals have been received. For example, the transmitter 102 may be configured to transmit the encoded sampled data signals at a fixed rate (e.g., at one minute intervals) after the completion of the initial power on procedure. Likewise, the receiver 104 may be configured to detect such transmitted encoded sampled data signals at predetermined time intervals. Alternatively, the glucose monitoring system 100 may be configured with a bi-directional RF (or otherwise) communication between the transmitter 102 and the receiver 104.

[0019] Additionally, in one aspect, the receiver 104 may include two sections. The first section is an analog interface section that is configured to communicate with the transmitter 102 via the communication link 103. In one embodiment, the analog interface section may include an RF receiver and an antenna for receiving and amplifying the data signals from the transmitter 102, which are thereafter, demodulated with a local oscillator and filtered through a band-pass filter. The second section of the receiver 104 is a data processing section which is configured to process the data signals received from the transmitter 102 such as by performing data decoding, error detection and correction, data clock generation, and data bit recovery.

[0020] In operation, upon completing the power-on procedure, the receiver 104 is configured to detect the presence of the transmitter 102 within its range based on, for example, the strength of the detected data signals received from the transmitter 102 or a predetermined transmitter identification information. Upon successful synchronization with the corresponding transmitter 102, the receiver 104 is configured to begin receiving from the transmitter 102 data signals corresponding to the user's

Abbott Ex. 1002 - 804/1438

detected glucose level. More specifically, the receiver 104 in one embodiment is configured to perform synchronized time hopping with the corresponding synchronized transmitter 102 via the communication link 103 to obtain the user's detected glucose level.

[0021] Referring again to FIG. 1, the data processing terminal 105 may include a personal computer, a portable computer such as a laptop or a handheld device (e.g., personal digital assistants (PDAs)), and the like, each of which may be configured for data communication with the receiver via a wired or a wireless connection. Additionally, the data processing terminal 105 may further be connected to a data network (not shown) for storing, retrieving and updating data corresponding to the detected glucose level of the user.

[0022] Within the scope of the present invention, the data processing terminal 105 may include an infusion device such as an insulin infusion pump or the like, which may be configured to administer insulin to patients, and which may be configured to communicate with the receiver unit 104 for receiving, among others, the measured glucose level. Alternatively, the receiver unit 104 may be configured to integrate an infusion device therein so that the receiver unit 104 is configured to administer insulin therapy to patients, for example, for administering and modifying basal profiles, as well as for determining appropriate boluses for administration based on, among others, the detected glucose levels received from the transmitter 102.

[0023] Additionally, the transmitter 102, the receiver 104 and the data processing terminal 105 may each be configured for bi-directional wireless communication such that each of the transmitter 102, the receiver 104 and the data processing terminal 105 may be configured to communicate (that is, transmit data to and receive data from) with each other via the wireless communication link 103. More specifically, the data processing terminal 105 may in one embodiment be configured to receive data directly from the transmitter 102 via the communication link 106, where the communication link 106, as described above, may be configured for bi-directional communication. In this embodiment, the data processing terminal 105 which may include an insulin pump, may be configured to receive the glucose signals from the transmitter 102, and thus, incorporate the functions of the receiver 103 including data processing for managing the patient's insulin therapy and glucose monitoring. In one embodiment, the communication link 103 may include one or more of an RF communication protocol, an infrared communication protocol, a Bluetooth enabled communication protocol, an 802.11x wireless communication protocol, or an equivalent wireless communication protocol which would allow secure, wireless communication of several units (for example, per HIPPA requirements) while avoiding potential data collision and interference.

[0024] FIG. 2 is a block diagram of the transmitter of the data monitoring and detection system shown in FIG. 1 in accordance with one embodiment of the present invention. Referring to the Figure, the transmitter 102 in one embodiment includes an analog interface 201 configured to communicate with the sensor 101 (FIG. 1), a user input 202, and a temperature detection section 203, each of which is operatively coupled to a transmitter processor 204 such as a central processing unit (CPU). As can be seen from FIG. 2, there are provided four contacts, three of which are electrodes - work electrode (W) 210, guard contact (G) 211, reference electrode (R) 212, and counter electrode (C) 213, each operatively coupled to the analog interface 201 of the transmitter 102 for connection to the sensor unit 201 (FIG. 1). In one embodiment, each of the work electrode (W) 210, guard contact (G) 211, reference electrode (R) 212, and counter electrode (C) 213 may be made using a conductive material that is either printed or etched, for example, such as carbon which may be printed, or metal foil (e.g., gold) which may be etched.

[0025] Further shown in FIG. 2 are a transmitter serial communication section 205 and an RF transmitter 206, each of which is also operatively coupled to the transmitter processor 204. Moreover, a power supply 207 such as a battery is also provided in the transmitter 102 to provide the necessary power for the transmitter 102. Additionally, as can be seen from the Figure, clock 208 is provided to, among others, supply real time information to the transmitter processor 204.

[0026] In one embodiment, a unidirectional input path is established from the sensor 101 (FIG. 1) and/or manufacturing and testing equipment to the analog interface 201 of the transmitter 102, while a unidirectional output is established from the output of the RF transmitter 206 of the transmitter 102 for transmission to the receiver 104. In this manner, a data path is shown in FIG. 2 between the aforementioned unidirectional input and output via a dedicated link 209 from the analog interface 201 to serial communication section 205, thereafter to the processor 204, and then to the RF transmitter 206. As such, in one embodiment, via the data path described above, the transmitter 102 is configured to transmit to the receiver 104 (FIG. 1), via the communication link 103 (FIG. 1), processed and encoded data signals received from the sensor 101 (FIG. 1). Additionally, the unidirectional communication data path between the analog interface 201 and the RF transmitter 206 discussed above allows for the configuration of the transmitter 102 for operation upon completion of the manufacturing process as well as for direct communication for diagnostic and testing purposes.

[0027] As discussed above, the transmitter processor 204 is configured to transmit control signals to the various sections of the transmitter 102 during the operation of the transmitter 102. In one embodiment, the transmitter processor 204 also includes a memory (not shown) for storing data such as the identification information for the transmitter 102, as well as the data signals received from the sensor 101. The stored information may be retrieved and processed for transmission to the receiver 104 under

Abbott Ex. 1002 - 805/1438

the control of the transmitter processor 204. Furthermore, the power supply 207 may include a commercially available battery.

[0028] The transmitter 102 is also configured such that the power supply section 207 is capable of providing power to the transmitter for a minimum of about three months of continuous operation after having been stored for about eighteen months in a low-power (non-operating) mode. In one embodiment, this may be achieved by the transmitter processor 204 operating in low power modes in the non-operating state, for example, drawing no more than approximately 1 μA of current. Indeed, in one embodiment, the final step during the manufacturing process of the transmitter 102 may place the transmitter 102 in the lower power, non-operating state (i.e., post-manufacture sleep mode). In this manner, the shelf life of the transmitter 102 may be significantly improved. Moreover, as shown in FIG. 2, while the power supply unit 207 is shown as coupled to the processor 204, and as such, the processor 204 is configured to provide control of the power supply unit 207, it should be noted that within the scope of the present invention, the power supply unit 207 is configured to provide the necessary power to each of the components of the transmitter unit 102 shown in FIG. 2.

[0029] Referring back to FIG. 2, the power supply section 207 of the transmitter 102 in one embodiment may include a rechargeable battery unit that may be recharged by a separate power supply recharging unit so that the transmitter 102 may be powered for a longer period of usage time. Moreover, in one embodiment, the transmitter 102 may be configured without a battery in the power supply section 207, in which case the transmitter 102 may be configured to receive power from an external power supply source (for example, a battery) as discussed in further detail below.

[0030] Referring yet again to FIG. 2, the temperature detection section 203 of the transmitter 102 is configured to monitor the temperature of the skin near the sensor insertion site. The temperature reading is used to adjust the glucose readings obtained from the analog interface 201. The RF transmitter 206 of the transmitter 102 may be configured for operation in the frequency band of 315 MHz to 322 MHz, for example, in the United States. Further, in one embodiment, the RF transmitter 206 is configured to modulate the carrier frequency by performing Frequency Shift Keying and Manchester encoding. In one embodiment, the data transmission rate is 19,200 symbols per second, with a minimum transmission range for communication with the receiver 104.

[0031] Referring yet again to FIG. 2, also shown is a leak detection circuit 214 coupled to the guard electrode (G) 211 and the processor 204 in the transmitter 102 of the data monitoring and management system 100. The leak detection circuit 214 in accordance with one embodiment of the present invention may be configured to detect leakage current in the sensor 101 to determine whether the measured sensor data are corrupt or whether the measured data from the sensor 101 is accurate.

[0032] Additional detailed description of the continuous glucose monitoring system, its various components including the functional descriptions of the transmitter are provided in U.S. Patent No. 6,175,752 issued January 16, 2001 entitled "Analyte Monitoring Device and Methods of Use", and in application No. 10/745,878 filed December 26, 2003 entitled "Continuous Glucose Monitoring System and Methods of Use", each assigned to the Assignee of the present application.

[0033] FIG. 3 illustrates a cross sectional view of the transmitter and transmitter mount configuration for providing power to the transmitter in the data monitoring and management system in accordance with one embodiment of the present invention. Referring to the Figure, there is shown a transmitter unit mount 302 which is placed on the skin 301 of the patient, and configured to receive a portion of the sensor 101, and the other end portion of the sensor is inserted, e.g., subcutaneously, under the patient's skin 301. Referring to FIG. 3, the transmitter unit mount 302 is configured to receive or "mate" with the transmitter 102 so that the transmitter 102 is in electrical contact with the sensor 101 that extends from the patient's skin 301 at the sensor contact 304. In one embodiment and as discussed above, the sensor contact 304 may be configured to operatively couple the analog interface unit 201 of the transmitter 102 with the sensor electrodes and contacts (working electrode 210, guard trace 211, reference electrode 212, and counter electrode 213).

[0034] While not shown in the Figure, the transmitter unit mount 302 in one embodiment is firmly affixable onto the patient's skin 201 by an adhesive layer on the surface of the transmitter unit mount 302 that is in contact with the patient's skin 201. In this manner, the patient's movement of the body does not substantially affect the position of the transmitter unit mount 302, and thus the sensor 101 in contact with the transmitter 102. Referring back to FIG. 3, also shown is a power supply 303 (such as, for example, a battery) mounted to the transmitter unit mount 302. In one embodiment, the power supply 303 is positioned to establish electrical contact with the transmitter 102 at the power supply contact 305, when the transmitter is mounted onto the transmitter unit mount 302.

[0035] More specifically, in this configuration, the internal power supply 207 and/or other components of the transmitter 102 are coupled to the external power supply 303 via the power supply contact 305. In this manner, when the transmitter 102 is mounted to the transmitter unit mount 302, the internal power supply 207 of the transmitter 102 is configured to receive power from the external power supply 303, and thus may be configured to transmit sensor data received from the sensor 101.

[0036] Within the scope of the present invention, the external power supply 303 mounted to the transmitter unit mount 302 may include a disposable battery, or a printed battery which may be printed onto the surface of

Abbott Ex. 1002 - 806/1438

the transmitter unit mount 302 on the surface where the transmitter 102 is configured to physically contact the transmitter unit mount 302.

[0037] In a further embodiment, as discussed above, the internal power supply 207 of the transmitter 102 may include a rechargeable battery which may be configured to receive power to recharge from the external power supply 303 mounted to the transmitter unit mount 302, when the transmitter 102 is mounted to the transmitter unit mount 302. In this manner, the external power supply 303 may be configured to provide power to recharge the internal power supply 207 of the transmitter 102, and further, to provide power to the transmitter 102.

[0038] Within the scope of the present invention, the rechargeable internal power supply 207 in the transmitter 102 and the external power supply 303 mounted on the transmitter unit mount 302 may include one or more of alkaline, nickel metal hydride, lithium, nickel cadmium, lithium hydride, polymer batteries, polymorphic heavy ion salts, bi-metallic interstitial lattice ionic crystals or ferromagnetic materials. Furthermore, in one embodiment, the external power supply 303 may be mounted or coupled to the transmitter unit mount 302 by one of insert molding, welding, casting or printing.

[0039] In the manner described above, in accordance with one embodiment of the present invention, a transmitter unit mount 302 may be configured to integrate a power supply such as a battery 303 that is disposable, so that when the transmitter 102 is mounted, power is provided to the transmitter 102. When the transmitter 102 is dismounted from the transmitter unit mount 302, then the transmitter 102 may be powered off and the transmitter unit mount 302 and the power supply 303 are discarded. The transmitter 102 in one embodiment may also be configured to enter a low power sleep state powered by the remaining charge in the power supply 207.

[0040] In one embodiment, the power supply 303 which includes disposable batteries can be very small since it is a disposable battery which is to be replaced with each sensor 101 replacement, and thus does not require a large capacity (thus allowing the size of the battery to be small). One example of such disposable battery as power supply 303 is a silver oxide battery.

[0041] Within the scope of the present invention, there is also provided an embodiment which includes a second rechargeable battery integrated with the transmitter 102 so that the transmitter 102 may be configured to maintain the RF communication link with the receiver 104 and/or the data processing terminal 105. In this embodiment, as discussed above, when the transmitter 102 is mounted to the transmitter mount unit 302, the internal power supply 207 of the transmitter 102 is configured to recharge from the energy powered by the external power supply 303 of the transmitter unit mount 302.

[0042] FIG. 4 is a circuit diagram of the energy storage approach for providing power to the transmitter in the data monitoring and management system in accordance with one embodiment of the present invention. Referring to the Figure, there is shown the disposable power supply 401 of the transmitter unit mount 302 which is configured to be replaced with the replacement of the sensor 101 (FIG. 1). Also, shown is the transmitter 102 including, among others, the internal power supply 207, which, in one embodiment, includes a plurality of DC/DC converters 403, 404, 405, each operatively coupled to a respective capacitors 406, 407, 408. Also shown in FIG. 4 is a resistor 409 operatively coupled to a rechargeable battery 402 of the transmitter 102. The rechargeable batter 402 of the transmitter 102 shown in FIG. 4 in one embodiment corresponds to the power supply 207 of the transmitter 102 shown in FIG. 2.

[0043] In one embodiment, referring to FIG. 4, when the transmitter 102 is mounted to the transmitter unit mount 302, the power supply 401 of the transmitter unit mount 302 is configured to charge the rechargeable battery 402 of the transmitter 102. The DC/DC converter 403 in one embodiment is configured to boost the voltage signal from power supply 401 (e.g., 1.5 Volts) to the voltage level needed for the processor 204 of the transmitter 102 to operate (for example, to 3 Volts). Indeed, as shown in FIG. 4, the voltage level at the Analog Front End (AFE) of the transmitter 102 can be derived from the node 410 shown in the Figure.

[0044] Referring back to FIG. 4, in one embodiment, the energy from capacitor 406 and/or from the rechargeable battery 402 of the transmitter 102 may be used to charge the capacitor 407 to a predetermined value (e.g., between a 5 Volt to 35 Volt range) by the DC/DC converter 404 boosting the voltage level to the predetermined range from the 3 Volts at node 410. In one embodiment, both the rechargeable battery 402 and the capacitor 406, or alternatively, the rechargeable battery 402 or the capacitor 406, may be used to charge the capacitor 407, depending upon the various system requirements and the design trade-offs. One example of the capacitor 407 is a Tantalum type capacitor.

[0045] Indeed, increasing the voltage from 3 Volts to 30 Volts, for example, provides approximately 100 times the energy storage (since the energy stored in a capacitor is equal to one half of the product of the capacitance multiplied with the capacitor voltage squared i.e., $\frac{1}{2}CV^2$). Then, referring again to FIG. 4, the stored energy in capacitor 407 is converted by the DC/DC converter 405 and filtered by capacitor 408 to a functional voltage level which the processor 204 of the transmitter 102 may be configured to utilize for the RF transmission operation (e.g., 3.3 Volts or 5 Volts).

[0046] As pulsed (or peak) current is drawn by the processor 204 in the transmitter 102, during the RF transmission operations, the voltage across the capacitor 407 drops from a high value towards the minimum value for DC/DC converter operation. In other words, in one embodiment, the capacitor 407 is "trickle charged" at a low current during periods when the pulse current is not active, and when the large peak load occurs, the capacitor 407 is configured to draw charge from the capacitor and

Abbott Ex. 1002 - 807/1438

not the source.

[0047] In this manner, in one embodiment of the present invention, the DC/DC converters 404 and 405 and the corresponding capacitors 407 and 408, are configured to draw a small current from the energy store (e.g., capacitor 406 or the rechargeable battery 402), and to store energy on capacitor 407 that provides a large peak (pulsed) current capability to the processor 204 and RF transmitter 206. This allows low current drive power sources, such as a printed battery or a low current coin-cell battery to power the transmitter 107 in normal operations. For test and configuration purposes, a more robust power source such as a bench power supply may be used to support continuous operation.

[0048] FIG. 5 illustrates another energy storage approach for providing power to the transmitter in the data monitoring and management system in accordance with another embodiment of the present invention. Referring to the Figure, in one embodiment of the present invention, a single large capacitor (supercap) 501 is used for energy store in the transmitter 102, as opposed to, for example, the capacitor 406 shown in the embodiment in FIG. 4. Moreover, it can be seen that the power supply 502 (e.g., battery) of the transmitter 102 shown in FIG. 5 is similar to the power-supply 402 shown in FIG. 4. Further, the boost circuit 503 shown in FIG. 5 in one embodiment corresponds to the DC/DC converter 403 of the embodiment shown in FIG. 4.

[0049] Referring back to FIG. 5, the use of the single supercap 501 in parallel with the power supply 502 for energy storage has advantages in terms of size and cost. Moreover, it should be noted that the equivalent series resistance (ESR) of the capacitor is an important design consideration. Indeed, in general, supercaps have a higher ESR which tends to limit the efficiency and effectiveness of the supercap design, especially in cases where the working voltage is greater than 2.5 volts. Moreover, within the scope of the present invention, the battery 502 may need to have relatively high current capacity (for example, compared to the rechargeable battery 402 shown in FIG. 4), due to ESR of the supercap 501.

[0050] In one embodiment, the supercap 501 may be configured to provide a low internal resistance energy source that allows a large current to be delivered to the transmitter unit 102. It is difficult to achieve this directly from a battery. Small batteries generally cannot deliver a high current, so for a relatively small and compact size design such as for the design of the transmitter unit 102, this provides a significant advantage. Also, while at low temperatures the internal resistance of batteries increase, this may be mitigated by using a supercap or other type of storage capacitor connected in parallel with the battery.

[0051] In the manner described above, an apparatus including a data transmission unit in one embodiment includes a sensor, a transmitter base including a first power supply, and a transmitter unit coupled to the transmitter base, the transmitter unit including a second power supply, the transmitter unit further configured to establish electrical contact with the sensor, and further, where the transmitter unit is configured to draw power from one or more of the first power supply and the second power supply.

[0052] The sensor may in one embodiment include an analyte sensor transcutaneously positioned in a patient such that at least a portion of the analyte sensor is in fluid contact with a biological fluid of the patient.

[0053] Moreover, the first power supply may include a disposable battery, such as, for example, a silver oxide battery, and where the second power supply may include a rechargeable battery configured to selectively draw power from the first power supply.

[0054] In a further embodiment, each of the first power supply and the second power supply may include one of a disposable battery or a rechargeable battery.

[0055] The transmitter unit in one embodiment may be configured to transmit one or more signals, where the one or more signals correspond to a respective one or more signals received from the sensor, and where the transmitter unit may be configured for wireless communication or may include a physical connection. Additionally, the one or more signal received from the sensor corresponds to one or more analyte levels (for example, glucose levels) of a patient detected by the sensor.

[0056] An apparatus in a further embodiment of the present invention includes a sensor transcutaneously positioned in a patient, a transmitter base including a transmitter base power supply, a transmitter unit coupled to the transmitter base power supply of the transmitter base, the transmitter base power supply of the transmitter base configured to provide power to the transmitter unit, the transmitter unit further configured to establish electrical contact with the sensor.

[0057] In one embodiment, the sensor may include an analyte sensor where least a portion of the analyte sensor is in fluid contact with a biological fluid of the patient, where the biological fluid includes one of interstitial fluid, lactate or oxygen.

[0058] Moreover, the apparatus in one embodiment may also include a receiver unit configured to receive the one or more signals from the transmitter unit.

[0059] In still a further embodiment, the transmitter base power supply may include a disposable battery such as for example, a silver oxide battery.

[0060] Also, the transmitter unit may further include a transmitter unit power supply disposed substantially within the housing of the transmitter unit, where the transmitter unit power supply may in one embodiment include a rechargeable battery, and also, where the rechargeable battery may be configured to substantially draw power from the transmitter base power supply.

[0061] An apparatus in still a further embodiment includes a rechargeable battery, and a transmitter unit coupled to the rechargeable battery configured to draw power from the rechargeable battery.

Abbott Ex. 1002 - 808/1438

Claims

1. An apparatus for the transmission of data obtained from a transcutaneous sensor, comprising:

   a sensor (101) including an electrical contact portion and an insertion portion, wherein the insertion portion is adapted for transcutaneous positioning under a skin surface of a patient and for contacting biological fluid under the skin surface;
   a mount unit (302) which is configured to receive a portion of the sensor and includes an adhesive layer provided on a mount surface of the mount unit, which is configured to be positioned on the skin surface of the patient such that the adhesive layer is in contact with the skin surface and retains the mount surface of the mount unit in a substantially fixed position on the skin surface; and
   a data transmitter unit (102);

   characterised in that the mount unit (302) includes an electrical power supply (303), the data transmitter unit (102) is adapted for mounting on the mount unit and is further configured to establish electrical contact with the electrical contact portion of the sensor (101) when mounted on the mount unit; and the data transmitter unit (102) includes a electrical energy store (207) and is configured to be able to draw power from both the power supply (303) in the mount unit and the electrical energy store.

2. Apparatus according to claim 1 wherein the power supply (303) of the mount unit comprises a disposable battery.

3. Apparatus according to claim 2 wherein the electrical energy store (207) of the transmitter unit includes a rechargeable battery, and further wherein the rechargeable battery is configured to substantially draw power from the disposable battery.

4. Apparatus according to any forgoing claim wherein the data transmitter unit (102) is configured to transmit one or more signals, where the one or more signals correspond to a respective one or more signals received from the sensor.

5. Apparatus according to claim 4 wherein the one or more signals received from the sensor (101) correspond to one or more analyte levels detected by the sensor (101).

6. Apparatus according to claim 4 or 5 wherein the data transmitter unit (102) is configured to wirelessly transmit the one or more signals.

Patentansprüche

1. Vorrichtung für die Übertragung von Daten, die von einem transkutanen Sensor erhalten werden, die aufweist:

   einen Sensor (101) mit einem elektrischen Kontaktabschnitt und einem Einführabschnitt, wobei der Einführabschnitt zur transkutanen Positionierung unter einer Hautoberfläche eines Patienten und zum Kontakt mit einem biologischen Fluid unter der Hautoberfläche ausgelegt ist;
   eine Halterungseinheit (302), die dazu ausgelegt ist, einen Abschnitt des Sensors aufzunehmen, und eine Klebeschicht umfasst, die an einer Halterungsoberfläche der Halterungseinheit vorgesehen ist, die so ausgelegt ist, dass sie auf der Hautoberfläche des Patienten derart positioniert wird, dass die Klebeschicht mit der Hautoberfläche in Kontakt steht und die Halterungsoberfläche der Halterungseinheit in einer im Wesentlichen festen Position auf der Hautoberfläche festhält; und
   eine Datensendeeinheit (102);

   dadurch gekennzeichnet, dass die Halterungseinheit (302) eine elektrische Leistungsversorgung (303) umfasst, die Datensendeeinheit (102) zum Anbringen an der Halterungseinheit ausgelegt ist und ferner dazu ausgelegt ist, einen elektrischen Kontakt mit dem elektrischen Kontaktabschnitt des Sensors (101) herzustellen, wenn sie an der Halterungseinheit angebracht ist; und die Datensendeeinheit (102) einen Speicher (207) für elektrische Energie umfasst und so ausgelegt ist, dass sie Leistung von sowohl der Leistungsversorgung (303) in der Halterungseinheit als auch vom Speicher für elektrische Energie beziehen kann.

2. Vorrichtung nach Anspruch 1, wobei die Leistungsversorgung (303) der Halterungseinheit eine wegwerfbare Batterie aufweist.

3. Vorrichtung nach Anspruch 2, wobei der Speicher (207) für elektrische Energie der Sendeeinheit eine wiederaufladbare Batterie umfasst, und wobei ferner die wiederaufladbare Batterie so ausgelegt ist, dass sie im Wesentlichen Leistung von der wegwerfbaren Batterie bezieht.

4. Vorrichtung nach irgendeinem vorhergehenden Anspruch, wobei die Datensendeeinheit (102) dazu ausgelegt ist, ein oder mehrere Signale zu übertragen, wobei das eine oder die mehreren Signale einem jeweiligen oder jeweiligen mehreren Signalen, die vom Sensor empfangen werden, entsprechen.

5. Vorrichtung nach Anspruch 4, wobei das eine oder

Abbott Ex. 1002 - 809/1438

die mehreren Signale, die vom Sensor (101) empfangen werden, einem oder mehreren Analytenspiegeln entsprechen, die durch den Sensor (101) erfasst werden.

6. Vorrichtung nach Anspruch 4 oder 5, wobei die Datensendeeinheit (102) dazu ausgelegt ist, das eine oder die mehreren Signale drahtlos zu übertragen.

Revendications

1. Appareil pour la transmission de données obtenues à partir d'un capteur transcutané, comprenant :

   un capteur (101) comprenant une partie de contact électrique et une partie d'insertion, où la partie d'insertion est adaptée pour le positionnement transcutané sous une surface de la peau d'un patient et pour entrer en contact avec un fluide biologique sous la surface de la peau ;
   une unité de montage (302) qui est configurée pour recevoir une partie du capteur et comprend une couche adhésive prévue sur une surface de montage de l'unité de montage, qui est configurée pour être positionnée sur la surface de la peau du patient de sorte que la couche adhésive soit en contact avec la surface de la peau et maintienne la surface de montage de l'unité de montage dans une position sensiblement fixe sur la surface de la peau ; et
   une unité de transmission de données (102) ;

   caractérisé en ce que l'unité de montage (302) comprend une alimentation en énergie électrique (303), l'unité de transmission de données (102) est adaptée pour le montage sur l'unité de montage et est en outre configurée pour établir un contact électrique avec la partie de contact électrique du capteur (101) lorsqu'elle est montée sur l'unité de montage ; et l'unité de transmission de données (102) comprend une réserve d'énergie électrique (207) et est configurée pour être capable de prélever de l'énergie à la fois à partir de l'alimentation en énergie (303) dans l'unité de montage et de la réserve d'énergie électrique.

2. Appareil selon la revendication 1, dans lequel l'alimentation en énergie (303) de l'unité de montage comprend une batterie non rechargeable.

3. Appareil selon la revendication 2, dans lequel la réserve d'énergie électrique (207) de l'unité de transmission comprend une batterie rechargeable, et en outre dans lequel la batterie rechargeable est configurée pour prélever sensiblement de l'énergie à partir de la batterie non rechargeable.

4. Appareil selon l'une quelconque des revendications précédentes, dans lequel l'unité de transmission de données (102) est configurée pour transmettre un ou plusieurs signaux, lesquels un ou plusieurs signaux correspondent à un ou plusieurs signaux respectifs reçus à partir du capteur.

5. Appareil selon la revendication 4, dans lequel l'un ou plusieurs signaux reçus à partir du capteur (101) correspondent à un ou plusieurs niveaux d'analytes détectés par le capteur (101).

6. Appareil selon la revendication 4 ou 5, dans lequel l'unité de transmission de données (102) est configurée pour transmettre sans fil l'un ou plusieurs signaux.

Abbott Ex. 1002 - 810/1438

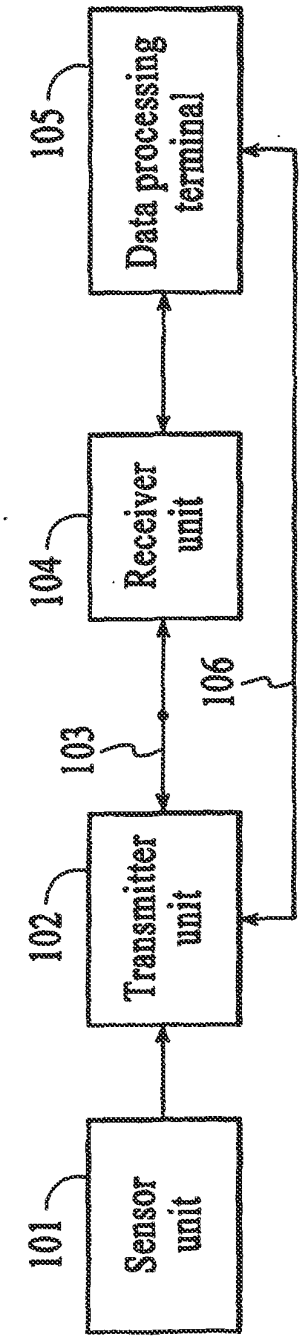


FIG.1

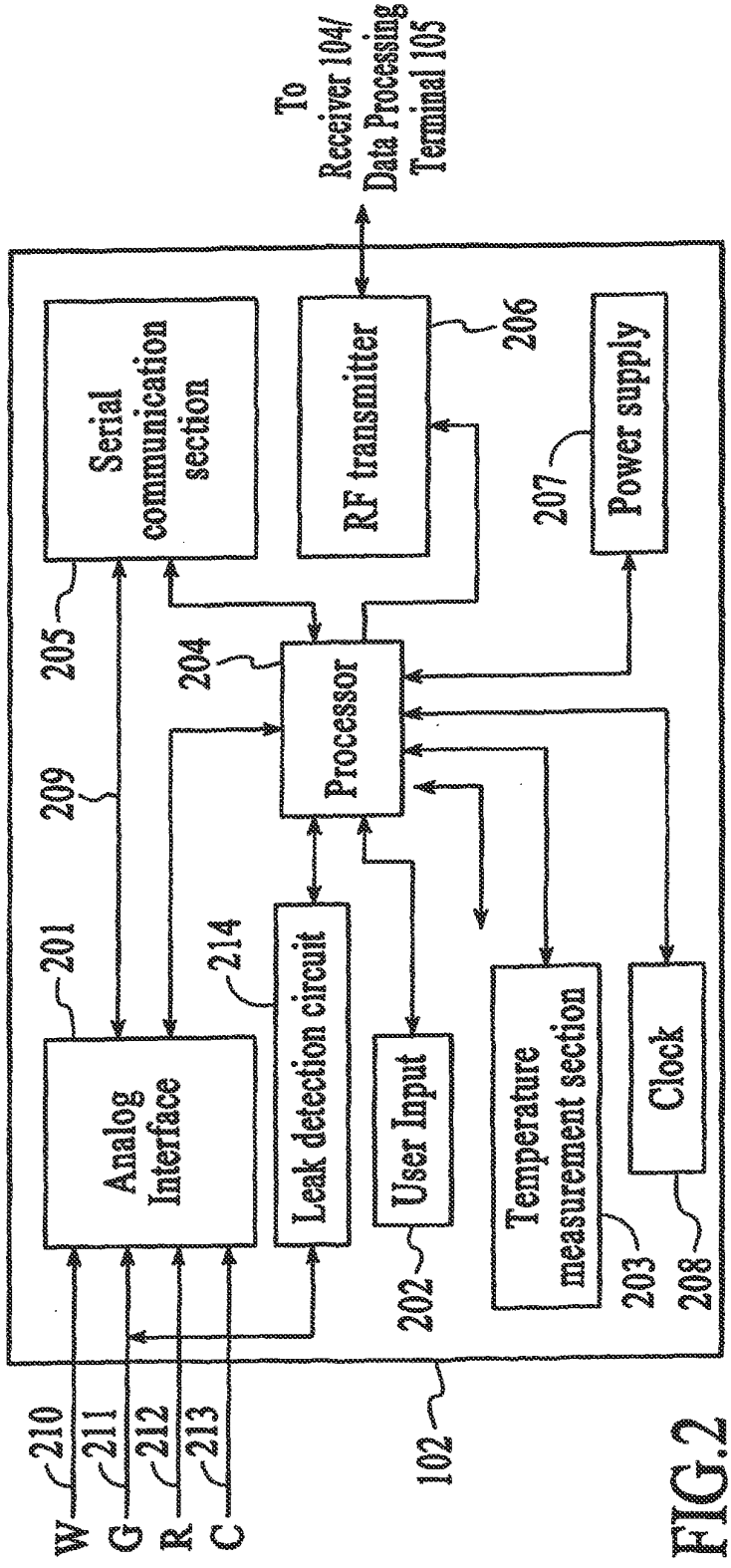


FIG.2

Abbott Ex. 1002 - 811/1438

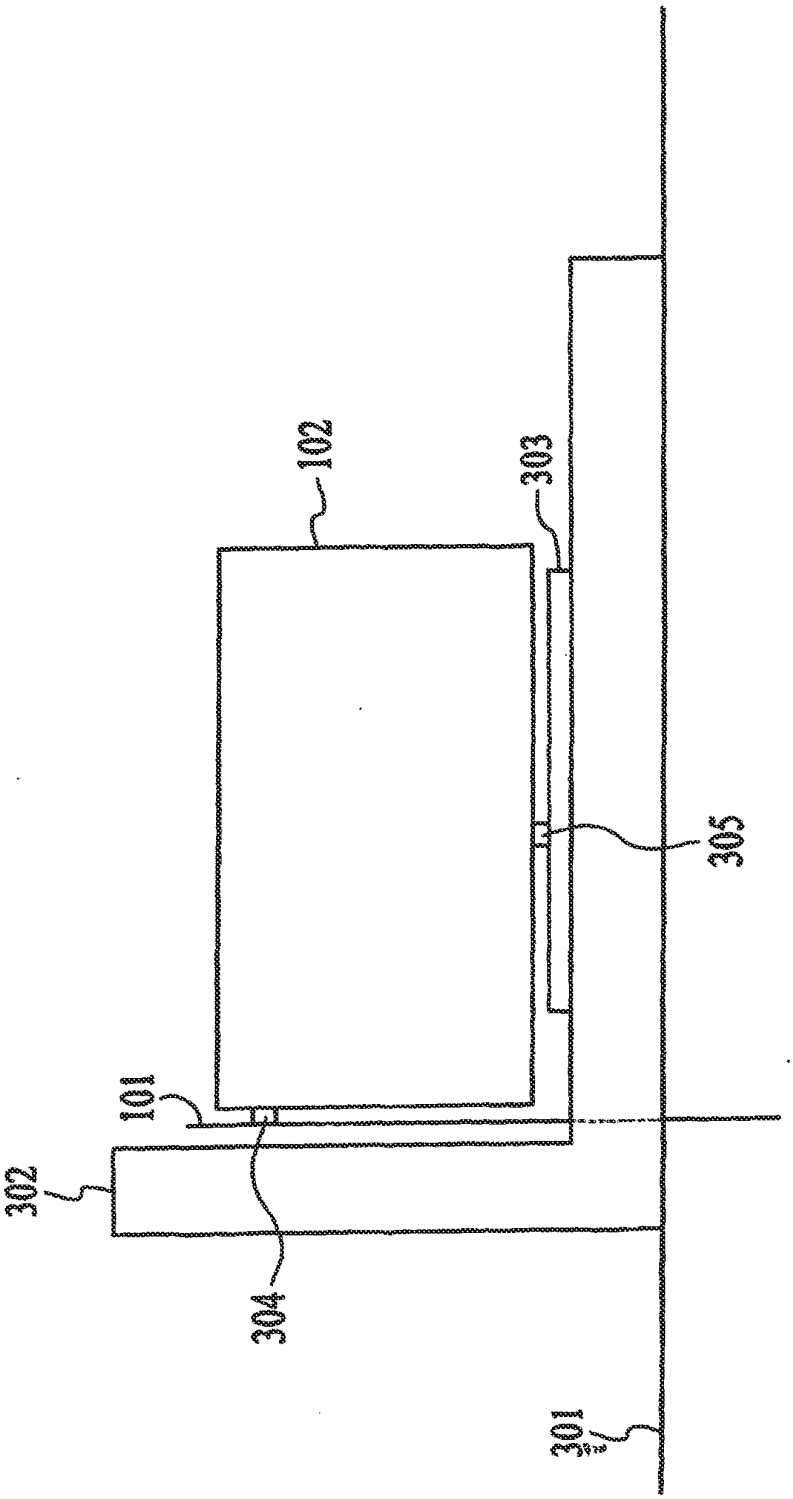


FIG.3

Abbott Ex. 1002 - 812/1438

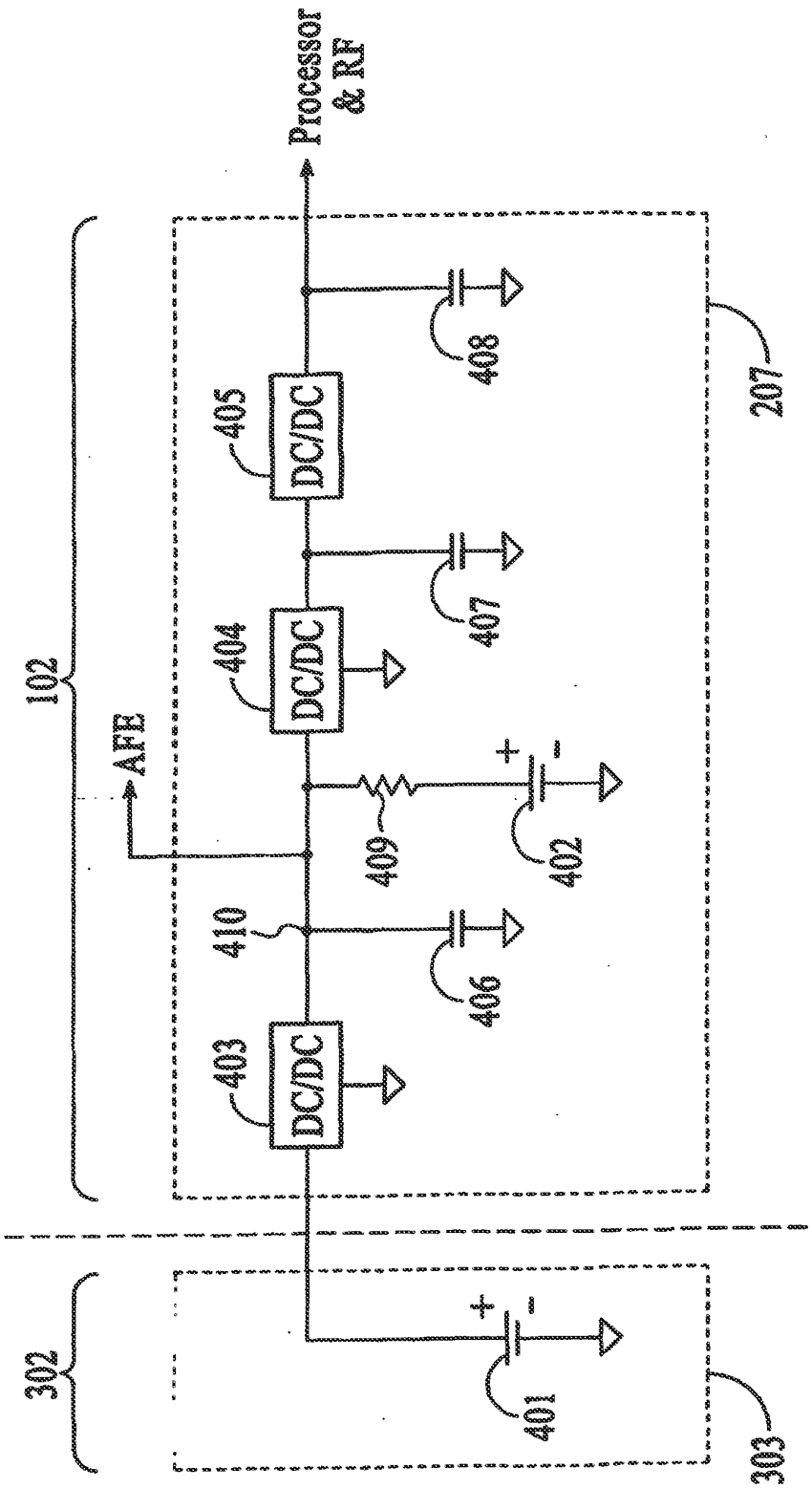


FIG.4

Abbott Ex. 1002 - 813/1438

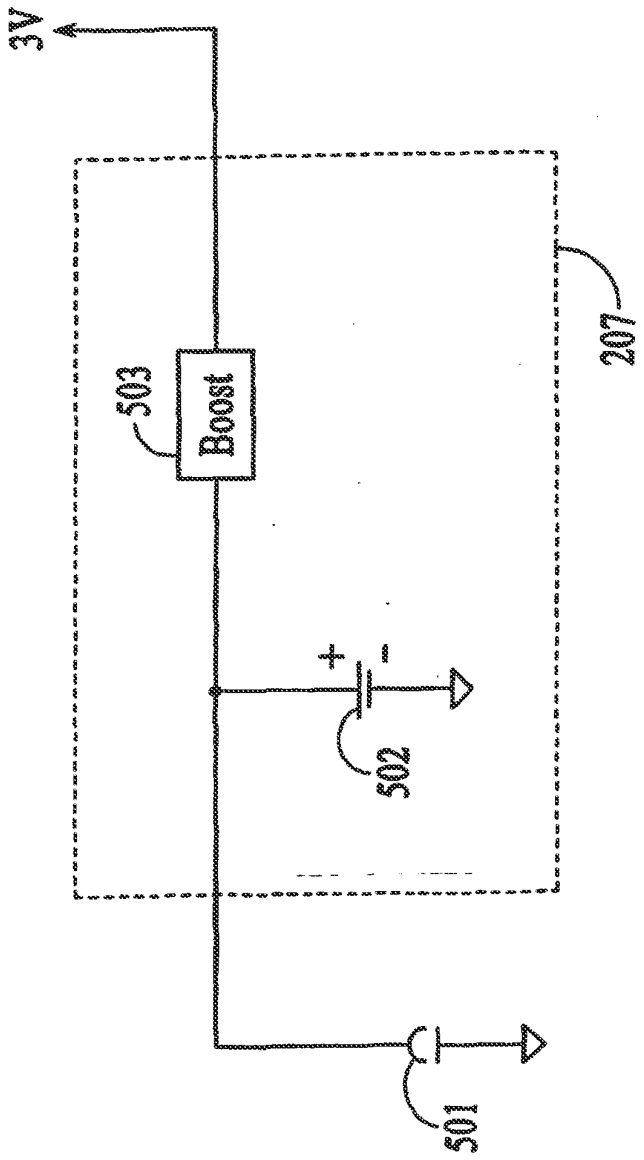


FIG.5

Abbott Ex. 1002 - 814/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 200402103354 A1 **[0007]**
- US 6175752 B **[0032]**
- US 10745878 B **[0032]**

Abbott Ex. 1002 - 815/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 051 620 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
28.04.2010 Bulletin 2010/17

(21) Application number: **07825964.5**

(22) Date of filing: **26.07.2007**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/IB2007/052971

(87) International publication number:
WO 2008/017981 (14.02.2008 Gazette 2008/07)

(54) METHOD AND DEVICE FOR MONITORING A PHYSIOLOGICAL PARAMETER

VERFAHREN UND VORRICHTUNG ZUR ÜBERWACHUNG EINES PHYSIOLOGISCHEN PARAMETERS

PROCÉDÉ ET DISPOSITIF POUR SURVEILLER UN PARAMÈTRE PHYSIOLOGIQUE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR

(30) Priority: **08.08.2006 EP 06118605**

(43) Date of publication of application:
29.04.2009 Bulletin 2009/18

(73) Proprietor: **Koninklijke Philips Electronics N.V.**
5621 BA Eindhoven (NL)

(72) Inventors:
- **VERBITSKY, Evgeny**
  NL-5656 AE Eindhoven (NL)
- **DE BOKX, Pieter, K.**
  NL-5656 AE Eindhoven (NL)
- **DENTENEER, Theodorus, J., J.**
  NL-5656 AE Eindhoven (NL)
- **VON BASUM, Golo**
  NL-5656 AE Eindhoven (NL)
- **OTAL, Begonya**
  NL-5656 AE Eindhoven (NL)
- **MURESAN, Adrian, S.**
  NL-5656 AE Eindhoven (NL)
- **GORIS, Annelies**
  NL-5656 AE Eindhoven (NL)
- **VAN HERK, Johannes, J.**
  NL-5656 AE Eindhoven (NL)

(74) Representative: **Van Velzen, Maaike Mathilde**
Philips
Intellectual Property & Standards
P.O. Box 220
5600 AE Eindhoven (NL)

(56) References cited:
EP-A- 1 078 258
WO-A-97/28737
US-A1- 2005 240 356
US-B1- 6 923 763

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Printed by Jouve, 75001 PARIS (FR)

EP 2 051 620 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a method and device for monitoring a physiological parameter.

BACKGROUND OF THE INVENTION

[0002] About two hundred million people suffer from diabetes mellitus. Diabetes is a chronic condition in which the body does not properly regulate or utilize the insulin, which results in abnormal (too high/too low) levels of glucose in the blood. A tight glycemic monitoring is desirable for these patients. Presently, methods for observing the glucose levels require, for example, the finger-stick blood sample, which is further processed by a glucose meter. But observation alone is not sufficient for glycemic control. Any diabetic decision support system should be able to predict future values of the blood glucose with a time horizon of 30 to 60 minutes as accurately as possible. Within the predicted time the patient can then take the appropriate actions, as for example food intake or insulin injection, so that theses actions can become effective in time.

[0003] There are several problems which must be resolved by a prediction method. First of all, the dynamics of glucose - insulin interaction is rather complicated. Even continuous measurement of the blood glucose provides only part of the actual information about the state of the system. Secondly, fluctuations in blood glucose levels are intrinsically non-stationary and depend on external factors like food and insulin injections. Thirdly, even for the same patient, given the same food intake and insulin injections , the glucose dynamics can be different due to variation in a large number of parameters, as for example body temperature or physical activity, which are known to affect the glucose metabolic rates.

[0004] For example, in US 6 923 763 B1 a prediction method is proposed based on a complex dynamic model that includes measured glucose values, heart rate and heart rate variability to try to estimate the blood glucose level in the future and estimate the risk of hypoglycemia. The approach is based on dynamic modeling of the glucose-regulation. One drawback of the prediction by dynamical models for glucose evolution is that the models are non-linear, complex and contain a large number of physiological parameters which cannot be measured.

SUMMARY OF THE INVENTION

[0005] It is therefor an object of the present invention to provide a method for monitoring a physiological parameter with a more reliable prediction of the evolution of the physiological parameter.

[0006] The above objective is accomplished by a method for monitoring a physiological parameter, in particular for monitoring a blood glucose level, comprising

- logging the physiological parameter by repeated measurements and predicting the evolution of the physiological parameter,

wherein the evolution of the physiological parameter over an interval of autonomous evolution is predictable by a parametric model.

[0007] The logging comprises preferably a non-invasive, continuous method of measuring the physiological parameter, e.g. for glucose measurements. Continuous in this sense means, that, if required, the measurements are performed about every 5 to 10 minutes, preferably automatically.

[0008] An interval of autonomous evolution in the sense of this invention is meant to be a time interval with a relatively simple evolution of the physiological parameter, e.g. the blood glucose level. Such intervals are primarily characterized by the absence of drastic external influences like food intake, insulin injections, physical exercises, etc. Within an interval of autonomous evolution one is able to use a parametric model for the physiological parameter, like glucose concentration. The person skilled in the art understands that the parametric model can be derived from statistical analysis of continuous traces of the evolution of the physiological parameter, which can be described well approximated over a limited time interval. An advantage of the inventive method is, that a limited number of parameters and models of reduced complexity can be used, despite the complexity of underlying processes.

[0009] Within an autonomous interval, the evolution of the physiological parameter is predictable by the following parametric model:

$$G(t) = Q(t; p_1, \ldots, p_k),$$

Abbott Ex. 1002 - 817/1438

where G(t) is the level of the physiological parameter at time t, which is predicted by the value Q at time t and with the parameters p_1, ..., p_k. The parametric model is used to extrapolate, i.e., predict the future values of the physiological parameter, especially the blood glucose concentration.

[0010] For the interval of autonomous evolution, which comprises a plurality of previous measurements (at times t_{k-i}, for i=1...m), an optimal set of parameters or parameter vector $\vec{p}_{k-1}$, according to the parametric model is preferably determined by the Least Squares Method:

$$\vec{p}_{k-1} = \underset{\vec{p}}{\operatorname{argmin}} \sum_{i=1}^{m} \left| G(t_{k-i}) - Q(t_{k-i}; \vec{p}) \right|^2$$

[0011] The prediction according to the inventive method comprises the steps of

- adding a new measurement of the physiological parameter to the previous measurements of the interval of autonomous evolution,
- conducting a test, whether the new measurement together with the previous measurements still form an interval of autonomous evolution, and depending upon this test,
- adapting the interval of autonomous evolution and preferably adapting the parametric model,
- predicting the evolution of the physiological parameter, using the parametric model for the adapted interval of autonomous evolution and
- associating a likelihood value to the predicted evolution of the physiological parameter, the prediction of the evolution of the physiological parameter being discarded (23) if the likelihood value is below a certain threshold value.

[0012] A new measurement $(t_k, G(t_k))$ and a multitude of previous measurements of the interval of autonomous evolution $\{(t_{k-i}, G(t_{k-i}))\}$, with i running from 1 to m, together form a new interval upon which the test is conducted. The person skilled in the art understands, that in this test, the new measurement is compared to the previously predicted evolution of the physiological parameter. The interval of autonomous evolution is then adapted accordingly. For example the interval of autonomous evolution is narrowed such that the parametric model is able to predict the evolution of the physiological parameter, i.e. to predict the new measurement. The person skilled in the art also understands that the modified interval of autonomous evolution comprises at least the new measurement. When the interval of autonomous evolution is adapted, the parametric model is preferably adapted as well. The adapted parametric model is then used for the prediction of the future evolution of the physiological parameter.

[0013] The future evolution, using the optimal set of parameters, is predicted by the parametric model:

$$\tilde{G}(t_k + \Delta t) = Q(t_k + \Delta t; \vec{p}_k),$$

where Δt is the desired time horizon of 30 to 60 minutes.

[0014] Advantageously, the inventive parametric model, in principle, is not physical, i.e. the parametric model is primarily selected on the basis of adequate description of glucose traces, and not necessarily using complex models describing the full glucose regulatory system. Nevertheless, incorporation of at least parts of physical models is not excluded by the present invention. It is beneficial to use non-physical models, because they are simpler and contain fewer or no unknown parameters. For a complex non-linear dynamical system, which does not admit an analytic solution, proper estimation of the unknown parameters is much more difficult, if not infeasible. This can be done for type 1 diabetes, which is easier to model than type 2 or type 3 diabetes. The inventive method is advantageously applicable to glucose monitoring and prediction in general, and does not assume a particular type of diabetes.

[0015] Advantageously, a likelihood value is associated to the predicted evolution of the physiological parameter, the prediction of the evolution of the physiological parameter being discuded if the likelihood value is below a certain, predefined threshold value. The likelihood value advantageously reflects the trust in the accuracy of the prediction. For example it the interval of autonomous evolution used for the prediction of glucose concentration is too small (too short), or, the interval was just adapted, this reduces the likelihood value. On the other hand, if the interval of autonomous evolution is relatively long and the set of optimal parameters has not changed drastically in a few last iterations, the likelihood value is higher. An advantage of the embodiment is to avoid prediction at all if the likelihood value is too small. The primary goal of the inventive monitoring and prediction of, for example, glucose concentrations is to prevent hypoglycemic and hyperglycemic events, is events where glucose levels become dangerously low or dangerously high.

Abbott Ex. 1002 - 818/1438

These events typically occur at the end of long intervals of autonomous evolution. Hence, according to the present invention such predictions will have high likelihood values. Advantageously, extremely low or high glucose predictions cause an alarm for the patient and call for an appropriate action and a large number of false alarms is prevented.

[0016] The interval of autonomous evolution is preferably adapted by removing at least one measurement of the plurality of measurements of the interval of autonomous evolution. The person skilled in the art understands, that the oldest measurements of the interval of autonomous evolution are preferably removed first. The advantage of this method is, that an interval of autonomous evolution is not terminated, once the test is negative, but prediction is continued with a modified, smaller interval of autonomous evolution.

[0017] In a preferred embodiment of the present invention the test is conducted again, now testing whether the new measurement together with the measurements of the adapted interval form an interval of autonomous evolution. Furthermore preferred, the steps of removing at least one measurement and conducting the test is repeated until the adapted interval is an interval of autonomous evolution.

[0018] A preferred way of obtaining a new interval of autonomous evolution is, to repeatedly remove only the oldest measurement and then conduct the test, so that the longest possible, new interval of autonomous evolution can be determined. If, however, the plurality of measurements fails the test until only the new measurement is left, no interval of autonomous evolution can be determined. According to the inventive method, a new interval of autonomous evolution can be determined earliest after the next measurement.

[0019] A number of quantitative characteristics can be used to evaluate the quality of the new interval of autonomous evolution. Preferably, in the test an error is calculated by comparing the physiological parameter of the new measurement to a predicted physiological parameter of a preceding iteration:

$$e_k = \left| G(t_k) - Q(t_k; \vec{p}_{k-1}) \right|$$

[0020] If the error does not exceed a predefined threshold, the interval of autonomous evolution is extended by adding a new observation value.

[0021] In another preferred embodiment, a new set of parameters for the parametric model is determined, wherein the parametric model with the new set of parameters optimally describes the evolution of the physiological parameter over the interval of autonomous evolution including the new measurement.

[0022] The new set of parameters is preferably determined after the Least Squares Method:

$$\vec{p}_k = \underset{\vec{p}}{\operatorname{argmin}} \sum_{i=0}^{m} \left| G(t_{k-i}) - Q(t_{k-i}; \vec{p}) \right|^2$$

[0023] Then, a distance between a new vector, defined by the new set of parameters and a former vector, defined by the set of parameters of the preceding iteration is calculated:

$$\left\| \vec{p}_k - \vec{p}_{k-1} \right\|^2 = \sum_{i=1}^{m} \left| p_{k,i} - p_{k-1,i} \right|^2$$

[0024] Again, if the distance does not exceed a predefined threshold value, the new measurement is added and the current interval of autonomous evolution is extended.

[0025] If the measurement is rejected in the test, the current interval of autonomous evolution is adapted. Most advantageously the new measurement can be added to the plurality of measurements forming the interval of autonomous evolution on the right, and the oldest measurements can be removed from the left until a smaller plurality of measurements meets the criterion of autonomous evolution.

[0026] In a preferred embodiment of the inventive method, a step of alarming a patient in case the predicted evolution of the physiological parameter is below or above a dangerous level. Advantageously, a patient suffering from diabetes can be alarmed early enough to prevent hypoglycemia or hyperglycemia.

[0027] Alternatively or additionally, an advice for the patient is provided, suggesting an agent or an amount of an agent to be administered, in particular an amount of insulin. The inventive system advantageously provides a decision support to the patient.

Abbott Ex. 1002 - 819/1438

[0028] An important aspect of the prediction is the stability of the results. Variations in the predicted evolution, which are faster than typical variations of glucose concentrations, should be avoided. In a preferred embodiment of the invention, the step of predicting the evolution of the physiological parameter is conducted using a multitude of parametric models for the adapted interval of autonomous evolution and obtaining the prediction as a weighted sum of the predictions of the multitude of parametric models:

$$\text{Prediction}(t+\Delta t) = \sum_{j=1}^{M} w_j \text{Prod.Model}_j(t+\Delta t)$$

wherein the weights w_j of the parametric models are selected adaptively, preferably depending on a quality of the prediction of each parametric model in the previous iterations and/or depending on the number of iterations each parametric model has been used. For example, the weight w_j for the j-th parametric model reflects the quality of the prediction of the j-th model demonstrated so far and/or the time period the model during which the model has been used. If the weight of a particular parametric model drops below a certain predefined threshold value the parametric model is preferably discarded (or its weight is set to zero) and a substitute parametric model is added to the multitude of parametric models. One of the advantages of this embodiment is to increase the stability of the prediction. Machine Learning theory provides methods for collecting predictions from several models ("experts") in one super-model ("super-expert"), which can outperform each of the individual "experts".

[0029] Preferably a number of threshold values, particularly the threshold value for the weight of the parametric models and/or the threshold for the likelihood value are adapted. Advantageously, the variability between different individuals is met by this embodiment. Again, Machine Learning techniques may advantageously be used, to adapt the threshold values.

[0030] In a further preferred embodiment the inventive method comprises the step of adapting the interval of autonomous evolution and/or the parametric model depending on external parameters known to be affecting the physiological parameter. The external parameters are preferably associated to ingestion, administration of insulin, physical activity and/or emotional stress of the patient. These major factors, which influence the intervals of autonomous evolution in glucose dynamics, are preferably detected and the parametric model is adapted appropriately. This advantageously enhances the accuracy of the predicted evolution, as the intervals of autonomous evolution can be updated earlier, for example.

[0031] In a still further preferred embodiment, the external parameters are manually inputted by a patient or by an auxiliary. For example, a device can be equipped with "food", "insulin", "exercise" buttons, which will advantageously provide information on forthcoming changes in the interval of autonomous evolution. Alternatively calorie input forms, food lists and/or databases can be used.

[0032] According to another preferred embodiment at least one of the external parameters is detected by at least one sensor. Sensors could be heart rate sensors, heart rate variability sensors, insulin pump sensors or food intake sensors. The reliability of the prediction is advantageously enhanced, as it does not depend on the accurateness of the input of the patient, who may forget to give or give wrong input on food intake, exercise or amounts of injected insulin.

[0033] In a preferred embodiment the physical activity is determined by an accelerometer, more preferably by an accelerometer summarizing the acceleration in three directions in space. In a further preferred embodiment the physical activity is determined by analyzing a heart rate of a patient by a heart rate sensor. With relation to exercise, these embodiments advantageously provide relatively accurate readings for a parameter which is difficult to quantify for a patient.

[0034] Another aspect of the present invention is a monitoring device for monitoring a physiological parameter of a patient, in particular for monitoring a blood glucose level, comprising a physiological parameter measuring means and a computing means, the computing means having a data storage for storing measurements and a processor unit for calculating a prediction of the evolution of the physiological parameter, using the method according to the present invention. The monitoring device advantageously provides reliable prediction of the evolution of the physiological parameter.

[0035] The monitoring device preferably comprises input means for inputting external parameters which are known to affect the physiological parameter, such as ingestion, administration of insulin, physical activity and/or emotional stress of the patient. The input means preferably comprises at least a button for manual input of each external parameter. In this embodiment the quality of the predicted evolution is enhanced, as information on forthcoming changes in the interval of autonomous evolution is provided by the patient.

[0036] Preferably the monitoring device comprises output means for outputting alarm messages and/or advice messages to the patient. The inventive monitoring device thus provides a (diabetic) decision support system with the ability

Abbott Ex. 1002 - 820/1438

to predict future evolution of the physiological parameter, especially the blood glucose level, with a time horizon of 30 to 60 minutes.

[0037] Preferably the monitoring device being connected to a detector for detecting a physical activity of the patient, preferably a three-axial accelerometer.

[0038] It is known that food intake, insulin uptake and exercise influence the blood glucose level most. The reliability of the prediction of the monitoring device usually depends on the accurateness of the input of the user. If he or she forgets to give or gives wrong input on food intake, exercise or amounts of injected insulin the model/device will give false predictions. With relation to exercise it is difficult anyhow to quantify the input. The monitoring device according to the present invention overcomes the abovementioned disadvantages by providing a monitoring device that comprises an detector for detecting a physical activity of the patient. This activity sensor senses the motions of a body and therewith provides a continuous input with relation to the physical activity of a person suffering from diabetes. In this way the input with regard to the exercise level is advantageously reliable.

[0039] The detector is preferably wearable by the patient, more preferably the detector is arranged in or at a belt, a watch or a mobile phone. This makes it easy to wear the detector all day long, which advantageously provides objective and detailed information on the duration and intensity of the activity of the patient (sleep, rest, sitting, exercise etc).

[0040] Preferably, the monitoring device in combination with the detector is initialized once to learn the specific reaction of a patient's activity on his or her blood glucose level, also in relation to prior food- and insulin-intake. Preferably, a first time usage requires an individual initialization of the model. For example, the user wears the detector together with the monitoring device and performs a set of standardized activities of different intensities. The prediction of the evolution of the physiological parameter is adapted during this initialization phase on an individual basis of the response of the different activity levels on the physiological parameter, in particular the blood glucose level. This information is used to update the parameter prediction model. An existing blood glucose level prediction device can be extended with the detector to improve the reliability of the blood glucose level evolution prediction.

BRIEF DESCRIPTION OF THE INVENTION

[0041] These and other characteristics, features and advantages of the present invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the principles of the invention. The description is given for the sake of example only, without limiting the scope of the invention. The reference figures quoted below refer to the attached drawings.

Fig. 1 depicts exemplarily a blood glucose evolution over an interval of time.

Fig. 2 illustrates schematically a method according to the present invention.

Fig. 3 illustrates schematically the method and embodiments of the monitoring device according to the present invention.

Fig. 4 depicts exemplarily a diagram of physical activity over an interval of time.

Fig. 5 illustrates an idealized pattern of insulin secretion over an interval of time.

DETAILED DESCRIPTION OF THE EMBODIMENT

[0042] The present invention will be described with respect to particular embodiments and with reference to certain drawings but the invention is not limited thereto but only by the claims. The drawings described are only schematic and are non-limiting. In the drawings, the size of some of the elements may be exaggerated and not drawn on scale for illustrative purposes.

[0043] Where an indefinite or definite article is used when referring to a singular noun, e.g. "a", "an", "the", this includes a plural of that noun unless something else is specifically stated.

[0044] Furthermore, the terms first, second, third and the like in the description and in the claims are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described of illustrated herein.

[0045] Moreover, the terms top, bottom, over, under and the like in the description and the claims are used for descriptive purposes and not necessarily for describing relative positions. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other orientations than described or illustrated herein.

[0046] It is to be noticed that the term "comprising", used in the present description and claims, should not be interpreted as being restricted to the means listed thereafter; it does not exclude other elements or steps. Thus, the scope of the expression "a device comprising means A and B" should not be limited to devices consisting only of components A and B. It means that with respect to the present invention, the only relevant components of the device are A and B.

Abbott Ex. 1002 - 821/1438

[0047] Fundamental work on glucoregulatory systems demonstrate without a doubt a great variation of possible dynamic evolutions of the blood glucose level 1, one of which is exemplarily depicted in Figure 1. The abscissa 11 shows an interval oftime in minutes and the axis of ordinates 12 the blood glucose concentration in milligrams per deciliter. Statistical analysis of continuous glucose traces 1 allows, that despite the complexity of underlying processes, glucose traces 1, limited in time, can be described and well approximated, using a limited number of parameters and models of reduced complexity. By inspecting glucose trace 1, it is possible to identify time intervals 2 with a relatively simple glucose evolution. Such time intervals 2 are referred to in here as intervals of autonomous evolution 2. Such intervals are primarily characterized by an absence of drastic external influences like food intake, insulin injections, physical exercise. Within an interval of autonomous evolution 2 it is possible to use a relatively simple parametric model for the glucose concentration.

[0048] In Figure 2 the method according to the invention is depicted schematically. By analyzing a multitude of measurements, a parametric model 3 is created, which is able give a predicted evolution 7 for the physiological parameter with sufficient accuracy over an interval of autonomous evolution 2. Besides a new measurement 4 and stored previous measurements 20, no physical parameters are necessary for the inventive method. In order to enhance the prediction 7, the parametric model can incorporate external parameters 5, which arc known to influence the physiological parameter. For example ingestion, insulin administration, physical activity or mental stress radically influence the blood glucose level. An external parameter 5 can be inputted manually or automatically by a sensor or detector 6, as for example a detector for the physical activity, such as a heart rate sensor or an accelerometer.

[0049] In Figure 3 an embodiment of the inventive method is schematically depicted, further showing the appropriate parts of the inventive monitoring device. A measurement device 40 is used to take the new measurement 4, which is added to a plurality of former measurements, stored on a data storage 31. The plurality of former measurements represent the former interval of autonomous evolution 2 at the time of a previous measurement. The new measurement 4 and the plurality of former measurements form together a new plurality of measurements 20. A test 21 is conducted, whether the new plurality of measurements 20 forms an interval of autonomous evolution. For the test 21, the former prediction of the future evolution by the parametric model 3 is compared to the new measurement 4, which is shown by feedback line 23. If the criterion of an interval of autonomous evolution is not met, at least one, preferably the oldest measurement 22 of the plurality of measurements 20 is removed and the test 21 is repeated. If the criterion of an interval of autonomous evolution is met, the parametric model 3 is adapted if necessary and a prediction 7 for the future evolution of the physiological parameter is calculated. A likelihood value 23, representing the reliability of the predicted evolution 7, is also calculated. If the likelihood value 23 is below a predefined threshold, the prediction 7 is discarded 24. Otherwise the predicted evolution 7 is outputted by an output means 70. The process starts again upon the next new measurement. All mentioned calculations are performed by a processor unit 32, which is, like data storage 31, part of a computing means 30.

[0050] According to an embodiment of the invention, the parametric model 3 is additionally adapted depending upon external parameters 5, which are derived from an input means 50 and/or from a detector 6. The input means 50 is preferably equipped with buttons 51, 52, 53, which are pressed by a patient upon certain activities in order to provide information on forthcoming changes in the interval of autonomous evolution to the monitoring device. For example button 51 is used for ingestion, button 52 for insulin administration and button 53 for physical exercises. Detector 6 preferably detects physical activity of the patient automatically, for example by way of a three-axial accelerometer worn by the patient.

[0051] Figure 4 shows a diagram of a detected activity pattern 8 for a person who wore the detector 6 for 24 hours. The time is shown on the abscissa 11. For example a tri-axial accelerometer gives every minute the sum of accelerations in three directions. These accelerations are shown on the axis of ordinates. They can be converted into a calorific value, but the arbitrary units can as well be directly used by the parametric model.

[0052] Figure 5 shows an idealized pattern of insulin secretion for a healthy individual who has consumed three standard meals, breakfast B, lunch L and dinner D. Again on the abscissa 11 the time is shown. On the ordinate the insulin effect is qualitatively shown. HS marks the bedtime. People with diabetes can use two types of insulin; the long acting insulin or basal insulin 9 and the short acting insulin 10 (bolus). The bolus type of insulin 9 is mostly injected before the onset of a meal. The effects of the long acting insulin 10 can be predicted more accurately by the inventive method and monitoring device. A day of less activity or of higher activity than normal, influences the insulin level, which may result in hyperglycemia or hypoglycemia. The detector for detecting physical activity measures and summarizes the acceleration, compares it to a day of normal activity and the monitoring system can warn the patient that he/she is more/less active and should adapt his insulin profile.

[0053] The present invention is related to a method and device for monitoring a physiological parameter, like the blood glucose level, using prediction of future evolution of the physiological parameter based on continuous traces. The present method and device can be employed as a decision support system for diabetic patients.

Abbott Ex. 1002 - 822/1438

Claims

1. Method for monitoring a physiological parameter (1), in particular for monitoring a blood glucose level, comprising

   - logging the physiological parameter (1) by repeated measurements (4) and
   - predicting the evolution of the physiological parameter (1),

   wherein the evolution of the physiological parameter over an interval of autonomous evolution (2) is predictable by a parametric model (3), the prediction comprising the steps of

   - adding a new measurement (4) of the physiological parameter to the previous measurements (20) of the interval of autonomous evolution (2),
   - conducting a test (21), whether the new measurement together with the previous measurements still form an interval of autonomous evolution and, depending upon this test,
   - adapting the interval of autonomous evolution and preferably adapting the parametric model (3),
   - predicting (7) the evolution of the physiological parameter, using the parametric model (3) for the adapted interval of autonomous evolution and

   associating a likelihood value to the predicted evolution of the physiological parameter, the prediction of the evolution of the physiological parameter being discarded (23) if the likelihood value is below a certain threshold value.

2. Method according to claim 1, wherein the interval of autonomous evolution (2) is adapted by removing at least one measurement (22) of a plurality of measurements of the interval of autonomous evolution.

3. Method according to claim 2, wherein the test is conducted, whether the new measurement together with the measurements of the adapted interval form an interval of autonomous evolution.

4. Method according to claim 3, wherein the steps of removing at least one measurement (22) and conducting the test is repeated until the adapted interval is an interval of autonomous evolution.

5. Method according to one of claims 1 or 3, wherein the step of conducting the test comprises

   - calculation of an error by comparing the physiological parameter of the new measurement to a predicted physiological parameter of a preceding iteration, or
   - determination of a new set of parameters for the parametric model, wherein the parametric model with the new set of parameters optimally describes the evolution of the physiological parameter over the interval of autonomous evolution including the new measurement and calculation of a distance between a new vector, defined by the new set of parameters and a former vector, defined by a set of parameters of a preceding iteration.

6. Method according to claim 1, further comprising

   - the step of alarming a patient in case the predicted evolution (7) of the physiological parameter (1) is below or above a dangerous level and/or
   - the step of outputting an advice, in particular suggesting an agent or an amount of an agent to be administered, in particular an amount of insulin.

7. Method according to claim 1, the step of predicting the evolution of the physiological parameter is conducted using a multitude of parametric models for the adapted interval of autonomous evolution and obtaining the prediction as a weighted sum of the predictions of the multitude of parametric models, wherein the weights of the parametric models are defined adaptively, preferably depending upon a quality of the prediction of each parametric model in the previous iterations and/or depending upon the number of iterations each parametric model has been used.

8. Method according to claim 7, wherein each parametric model is discarded when its weight drops below a threshold value and a substitute parametric model is added to the multitude of parametric models.

9. Method according to one of claims 7 or 8, wherein a number of threshold values, particularly the threshold value for the weight of the parametric models and/or the threshold for the likelihood value are adapted.

Abbott Ex. 1002 - 823/1438

10. Method according to claim 1, further comprising the step of adapting the interval of autonomous evolution (2) and/or the parametric model (3) depending on external parameters (5) known to be affecting the physiological parameter (1).

11. Method according to claim 10, wherein the external parameters (5) are associated to ingestion, administration of insulin, physical activity and/or emotional stress of the patient.

12. Monitoring device for monitoring a physiological parameter (1) of a patient, in particular for monitoring a blood glucose level, comprising a physiological parameter measuring means (40) and a computing means (30), the computing means having a data storage (31) for storing measurements (4) and a processor unit (32) for calculating a prediction of the evolution of the physiological parameter, according to the method of claim 1.

13. Monitoring device according to claim 12, further comprising input means (50) for inputting external parameters (5) which are known to affect the physiological parameter (1), such as ingestion, administration of insulin, physical activity and/or emotional stress of the patient.

14. Monitoring device according to claim 13, wherein the input means comprises at least one button (51, 52, 53) for manual input of each external parameter.

15. Monitoring device according to claim 14, further comprising output means (70) for outputting alarm messages and/or advice messages to the patient.

16. Monitoring device according to claim 12, wherein the monitoring device being connected to a detector (6) for detecting a physical activity of the patient, preferably a three-axial accelerometer.

Patentansprüche

1. Verfahren zur Überwachung eines physiologischen Parameters (1), insbesondere zur Überwachung eines Blutzukkerspiegels, wobei das Verfahren Folgendes umfasst:

   - Protokollieren des physiologischen Parameters (1) durch wiederholte Messungen (4) und
   - Vorhersagen der Evolution des physiologischen Parameters (1),

   wobei die Evolution des physiologischen Parameters über ein Intervall autonomer Evolution (2) durch ein parametrisches Modell (3) vorhersagbar ist, wobei die Vorhersage die Folgenden Schritte umfasst:

   - Hinzufügen einer neuen Messung (4) des physiologischen Parameters zu den vorhergehenden Messungen (20) des Intervalls autonomer Evolution (2),
   - Durchführen eines Tests (21), ob die neue Messung zusammen mit den vorhergehenden Messungen immer noch ein Intervall autonomer Evolution bildet, und abhängig von diesem Test
   - Anpassen des Intervalls autonomer Evolution und vorzugsweise Anpassen des parametrischen Modells (3),
   - Vorhersagen (7) der Evolution des physiologischen Parameters anhand des parametrischen Modells (3) für das angepasste Intervall autonomer Evolution und
   - Zuordnen eines Likelihood-Wertes zu der vorhergesagten Evolution des physiologischen Parameters, wobei die Vorhersage der Evolution des physiologischen Parameters ausgesondert (23) wird, wenn der Likelihood-Wert unter einem bestimmten Schwellenwert liegt.

2. Verfahren nach Anspruch 1, wobei das Intervall autonomer Evolution (2) angepasst wird, indem mindestens eine Messung (22) der Vielzahl von Messungen des Intervalls autonomer Evolution entfernt wird.

3. Verfahren nach Anspruch 2, wobei der Test durchgeführt wird, ob die neue Messung zusammen mit den Messungen des angepassten Intervalls ein Intervall autonomer Evolution bildet.

4. Verfahren nach Anspruch 3, wobei die Schritte des Entfernens mindestens einer Messung (22) und des Durchführens des Tests wiederholt werden, bis das angepasste Intervall ein Intervall autonomer Evolution ist.

5. Verfahren nach einem der Ansprüche 1 oder 3, wobei der Schritt des Durchführens des Tests Folgendes umfasst.

Abbott Ex. 1002 - 824/1438

- Berechnen eines Fehlers durch Vergleichen des physiologischen Parameters der neuen Messung mit einem vorhergesagten physiologischen Parameter einer vorhergehenden Iteration, oder
- Ermitteln eines neuen Parametersatzes für das parametrische Modell, wobei das parametrische Modell mit dem neuen Parametersatz die Evolution des physiologischen Parameters über das Intervall autonomer Evolution einschließlich der neuen Messung optimal beschreibt, und Berechnen eines Abstands zwischen einem neuen Vektor, der durch den neuen Parametersatz definiert wird, und einem früheren Vektor, der durch einen Parametersatz einer vorhergehenden Iteration definiert wird.

6. Verfahren nach Anspruch 1, das weiterhin Folgendes umfasst:

- den Schritt des Alarmierens eines Patienten, falls die vorhergesagte Evolution (7) des physiologischen Parameters (1) unter oder über einem gefährlichen Niveau liegt und/oder
- den Schritt des Ausgebens einer Empfehlung, insbesondere des Vorschlagens eines zu verabreichenden Wirkstoffs oder einer zu verabreichenden Wirkstoffmenge, insbesondere einer Insulinmenge.

7. Verfahren nach Anspruch 1, wobei der Schritt des Vorhersagens der Evolution des physiologischen Parameters durch Verwenden einer Vielzahl von parametrischen Modellen für das angepasste Intervall autonomer Evolution und Erlangen der Vorhersage als eine gewichtete Summe der Vorhersagen der Vielzahl parametrischer Modelle durchgeführt wird, wobei die Gewichte der parametrischen Modelle adaptiv definiert werden, vorzugsweise abhängig von einer Qualität der Vorhersage jedes parametrischen Modells in den vorhergehenden Iterationen und/oder abhängig von der Anzahl Iterationen, die jedes parametrische Modell verwendet hat.

8. Verfahren nach Anspruch 7, wobei jedes parametrische Modell ausgesondert wird, wenn sein Gewicht unter einen Schwellenwert fällt, und ein parametrisches Ersatzmodell zu der Vielzahl parametrischer Modelle hinzugefügt wird.

9. Verfahren nach einem der Ansprüche 7 oder 8, wobei eine Anzahl von Schwellenwerten, insbesondere der Schwellenwert für das Gewicht der parametrischen Modelle und/oder der Schwellenwert für den Likelihood-Wert, angepasst werden.

10. Verfahren nach Anspruch 1, das weiterhin den Schritt des Anpassens des Intervalls autonomer Evolution (2) und/oder des parametrischen Modells (3) abhängig von externen Parametern (5) umfasst, die bekanntlich den physiologischen Parameter (1) beeinflussen.

11. Verfahren nach Anspruch 10, wobei die externen Parameter (5) der Nahrungsaufnahme, der Verabreichung von Insulin, der körperlichen Aktivität und/oder dem emotionalen Stress des Patienten zugehörig sind.

12. Überwachungsvorrichtung zur Überwachung eines physiologischen Paramters (1) eines Patienten, insbesondere zur Überwachung eines Blutzuckerspiegels, mit einem Mittel (40) zum Messen des physiologischen Parameters und einem Berechnungsmittel (30), wobei das Berechnungsmittel einen Datenspeicher (31) zum Speichern von Messungen (4) und eine Prozessoreinheit (32) zum Berechnen einer Vorhersage der Evolution des physiologischen Parameters entsprechend dem Verfahren nach Anspruch 1 umfasst.

13. Überwachungsvorrichtung nach Anspruch 12, weiterhin mit Eingabemitteln (50) zum Eingeben externer Parameter (5), die bekanntermaßen den physiologischen Parameter (1) beeinflussen, wie die Nahrungsaufnahme, die Verabreichung von Insulin, körperliche Aktivität und/oder emotionaler Stress des Patienten.

14. Überwachungsvorrichtung nach Anspruch 13, wobei das Eingabemittel mindestens eine Taste (51, 52, 53) für die manuelle Eingabe jedes externen Parameters umfasst.

15. Überwachungsvorrichtung nach Anspruch 14, weiterhin mit Ausgabemitteln (70) zum Ausgeben von Alarmmeldungen und/oder Empfehlungsmeldungen an den Patienten.

16. Überwachungsvorrichtung nach Anspruch 12, wobei die Überwachungsvorrichtung mit einem Detektor (6) zum Detektieren einer körperlichen Aktivität des Patienten, vorzugsweise einem dreiachsigen Beschleunigungsaufnehmer, verbunden ist

Abbott Ex. 1002 - 825/1438

Revendications

1. Procédé pour surveiller un paramètre physiologique (1), en particulier pour surveiller un niveau de glucose dans le sang, consistant à

    - enregistrer le paramètre physiologique (1) grâce à des mesures répétées (4) et
    - prédire l'évolution du paramètre physiologique (1),

    dans lequel l'évolution du paramètre physiologique sur un intervalle d'évolution autonome (2) est prévisible grâce à un modèle paramétrique (3), la prédiction comprenant les étapes consistant à

    - ajouter une nouvelle mesure (4) du paramètre physiologique aux mesures précédentes (20) de l'intervalle d'évolution autonome (2),
    - effectuer un essai (21), pour savoir si la nouvelle mesure conjointement avec les mesures précédentes forment toujours un intervalle d'évolution autonome et, en fonction de cet essai,
    - adapter l'intervalle d'évolution autonome et adapter de préférence le modèle paramétrique (3),
    - prédire (7) l'évolution du paramètre physiologique, au moyen du modèle paramétrique (3), pour l'intervalle adapté d'évolution autonome et

    associer une valeur de vraisemblance à l'évolution prédite du paramètre physiologique, la prédiction de l'évolution du paramètre physiologique étant écartée (23) si la valeur de vraisemblance se trouve en dessous d'une certaine valeur de seuil.

2. Procédé selon la revendication 1, dans lequel l'intervalle d'évolution autonome (2) est adapté en supprimant au moins une mesure (22) d'une pluralité de mesures de l'intervalle d'évolution autonome.

3. Procédé selon la revendication 2, dans lequel l'essai est effectué si la nouvelle mesure conjointement avec les mesures de l'intervalle adapté forment un intervalle d'évolution autonome.

4. Procédé selon la revendication 3, dans lequel les étapes de suppression d'au moins une mesure (22) et de réalisation de l'essai sont répétées jusqu'à ce que l'intervalle adapté soit un intervalle d'évolution autonome.

5. Procédé selon l'une quelconque des revendications 1 ou 3, dans lequel l'étape de réalisation de l'essai consiste à

    - calculer une erreur en comparant le paramètre physiologique de la nouvelle mesure à un paramètre physiologique prédit d'une itération précédente, ou
    - déterminer un nouvel ensemble de paramètres pour le modèle paramétrique,

    dans lequel le modèle paramétrique avec le nouvel ensemble de paramètres décrit de manière optimale l'évolution du paramètre physiologique par rapport à l'intervalle d'évolution autonome comprenant la nouvelle mesure et le nouveau calcul d'une distance entre un nouveau vecteur, défini par le nouvel ensemble de paramètres et un ancien vecteur, défini par un ensemble de paramètres d'une itération précédente.

6. Procédé selon la revendication 1, comprenant en outre

    - l'étape consistant à avertir un patient dans le cas où l'évolution prédite (7) du paramètre physiologique (1) est en dessous ou au-dessus d'un niveau dangereux et/ou
    - l'étape consistant à produire un conseil, en particulier, à suggérer un agent ou une quantité d'un agent à administrer, en particulier, une quantité d'insuline.

7. Procédé selon la revendication 1, l'étape de prédiction de l'évolution du paramètre physiologique étant effectuée au moyen d'une multitude de modèles paramétriques pour l'intervalle adapté de l'évolution autonome et en obtenant la prédiction sous forme d'une somme pondérée des prédictions de la multitude des modèles paramétriques, dans lequel les poids des modèles paramétriques sont définis de manière adaptative, de préférence en fonction d'une qualité de la prédiction de chaque modèle paramétrique dans les itérations précédentes et/ou en fonction du nombre d'itérations que chaque modèle paramétrique a utilisé.

8. Procédé selon la revendication 7, dans lequel chaque modèle paramétrique est écarté lorsque son poids tombe en

Abbott Ex. 1002 - 826/1438

dessous d'une valeur de seuil et un modèle paramétrique de remplacement est ajouté à la multitude de modèles paramétriques.

9. Procédé selon l'une quelconque des revendications 7 ou 8, dans lequel un nombre des valeurs de seuil, en particulier, la valeur de seuil pour le poids des modèles paramétriques et/ou le seuil pour la valeur de vraisemblance sont adaptés.

10. Procédé selon la revendication 1, comprenant en outre l'étape consistant à adapter l'intervalle d'évolution autonome (2) et/ou le modèle paramétrique (3) en fonction des paramètres externes (5) connus pour affecter le paramètre physiologique (1).

11. Procédé selon la revendication 10,dans lequel les paramètres externes (5) sont associés à l'ingestion, l'administration d'insuline, l'activité physique et/ou la tension émotionnelle du patient.

12. Dispositif de surveillance pour surveiller un paramètre physiologique (1) d'un patient, en particulier, pour surveiller un niveau de glucose dans le sang, comprenant des moyens de mesure de paramètre physiologique (40) et des moyens de calcul (30), les moyens de calcul ayant une mémoire de données (31) destinée à stocker des mesures (4) et une unité de traitement (32) destinée à calculer une prédiction de l'évolution du paramètre physiologique, selon le procédé de la revendication 1.

13. Dispositif de surveillance selon la revendication 12, comprenant en outre des moyens d'entrée (50) destinés à entrer les paramètres externes (5) qui sont connus pour affecter le paramètre physiologique (1), tels que l'ingestion, l'administration d'insuline, l'activité physique et/ou la tension émotionnelle du patient.

14. Dispositif de surveillance selon la revendication 13, dans lequel les moyens d'entrée comprennent au moins un bouton (51, 52, 53) pour entrer manuellement chaque paramètre externe.

15. Dispositif de surveillance selon la revendication 14, comprenant en outre des moyens de sortie (70) pour produire des messages d'alarme et/ou des messages de conseil au patient.

16. Dispositif de surveillance selon la revendication 12, dans lequel le dispositif de surveillance est connecté à un détecteur (6) pour détecter une activité physique du patient, de préférence un accéléromètre tri-axial.

Abbott Ex. 1002 - 827/1438

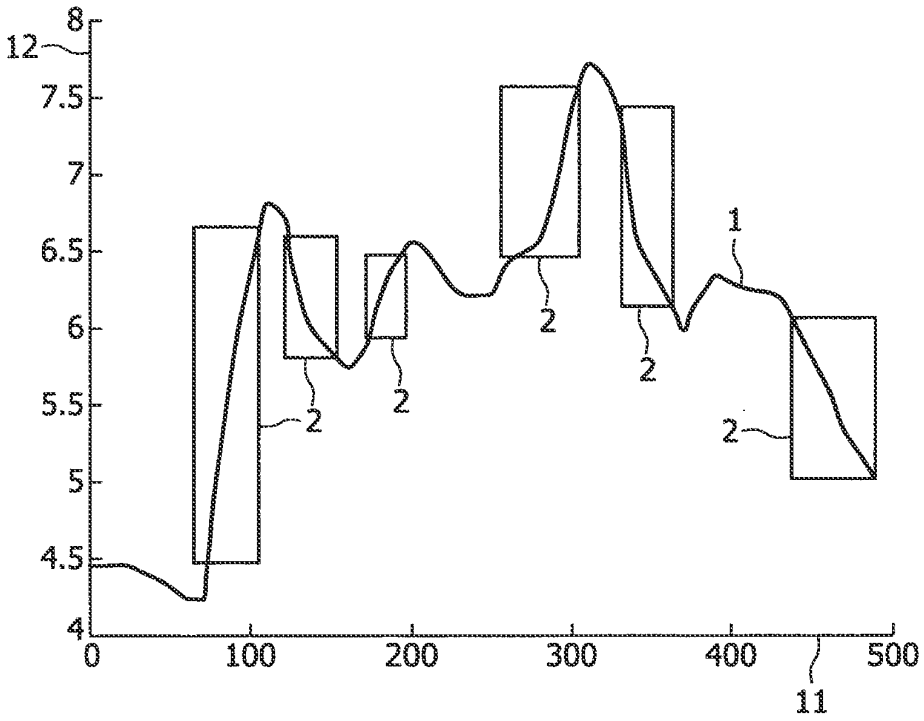


FIG. 1

Abbott Ex. 1002 - 828/1438

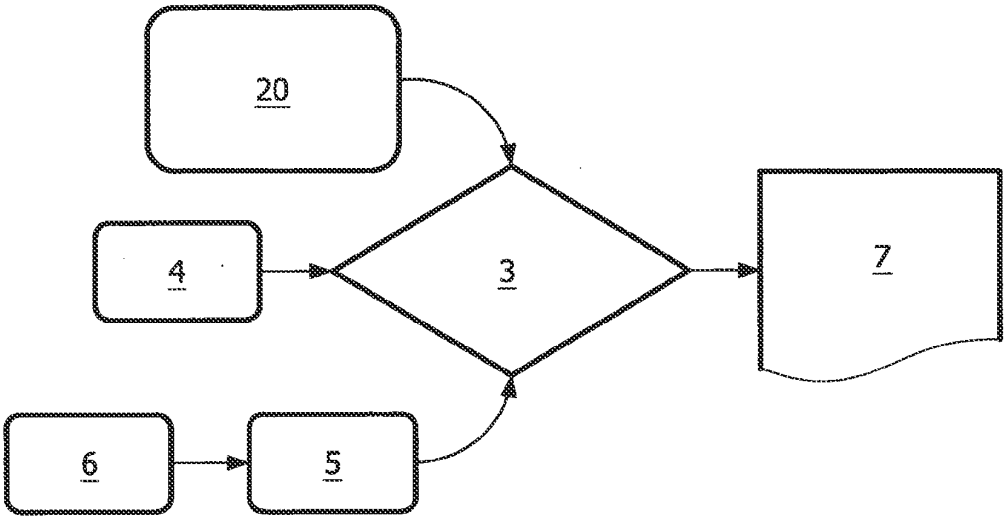


FIG. 2

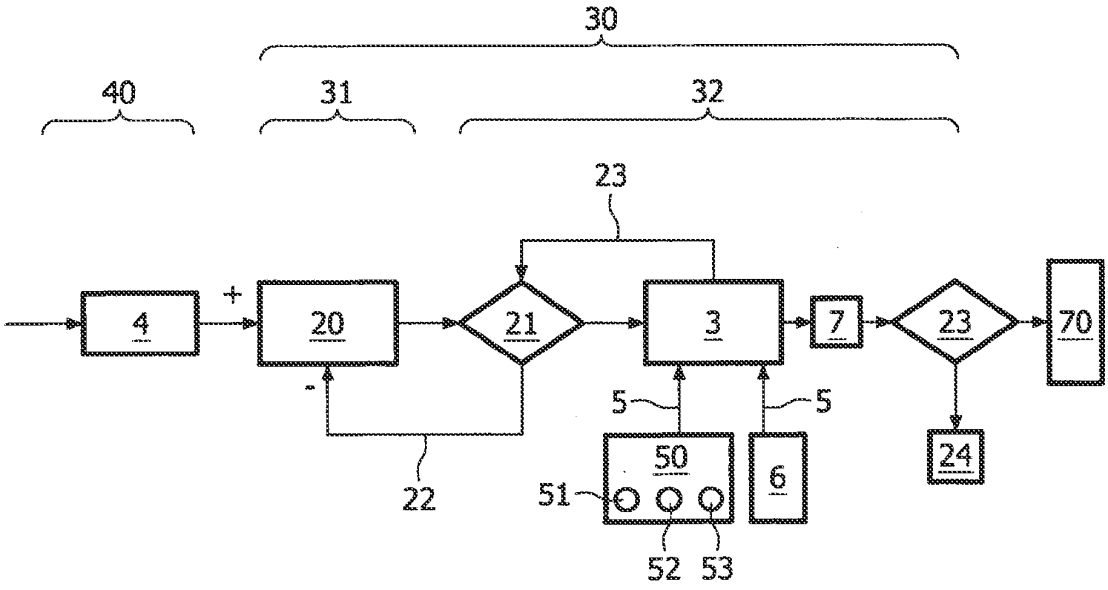


FIG. 3

Abbott Ex. 1002 - 829/1438

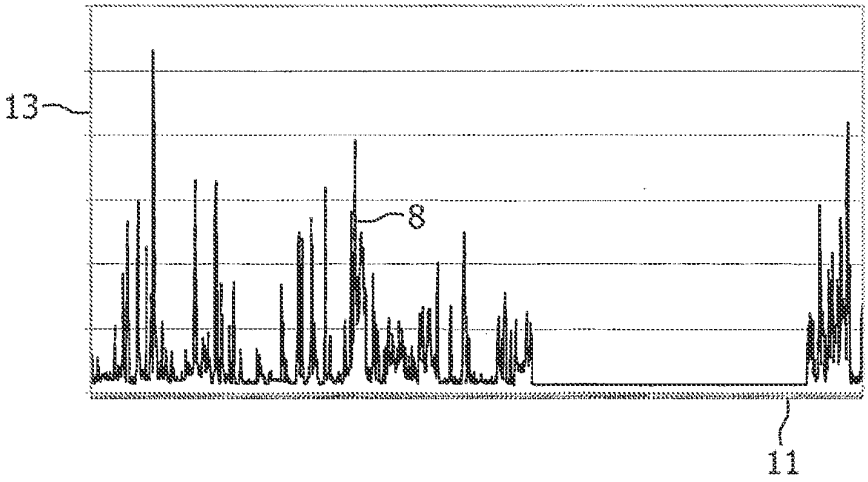


FIG. 4

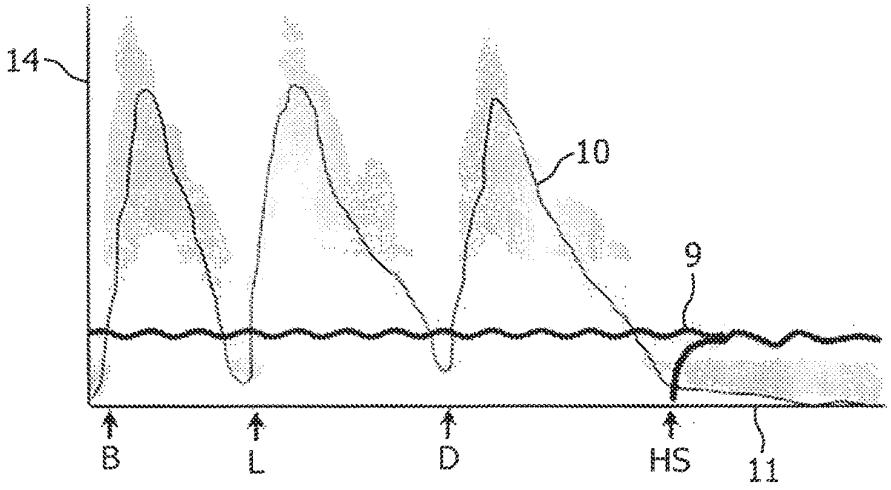


FIG. 5

Abbott Ex. 1002 - 830/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 6923763 B1 **[0004]**

Abbott Ex. 1002 - 831/1438

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 069 771 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
02.11.2011 Bulletin 2011/44

(21) Application number: **07836189.6**

(22) Date of filing: **23.07.2007**

(51) Int Cl.:
G01N 27/327 *(2006.01)*

(86) International application number:
PCT/US2007/016554

(87) International publication number:
WO 2008/016501 (07.02.2008 Gazette 2008/06)

(54) ANALYTE SENSORS AND METHODS

ANALYTSENSOREN UND ENTSPRECHENDE VERFAHREN

DÉTECTEURS D'ANALYTE ET PROCÉDÉS ASSOCIÉS

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR

(30) Priority: **01.08.2006 US 461725**

(43) Date of publication of application:
17.06.2009 Bulletin 2009/25

(60) Divisional application:
11182024.7

(73) Proprietor: **Abbott Diabetes Care Inc.**
Alameda, CA 94502 (US)

(72) Inventors:
- **WANG, Yi**
  San Ramon, CA 94582 (US)
- **FELDMAN, Benjamin, J.**
  Oakland, CA 94618 (US)

(74) Representative: **Tollett, Ian et al**
Williams Powell
Staple Court
11 Staple Inn Buildings
London, WC1V 7QH (GB)

(56) References cited:
WO-A-2006/042304
DE-A1- 10 343 477
US-A- 5 762 770
US-A1- 2006 144 704

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 069 771 B1

Printed by Jouve, 75001 PARIS (FR)

Description

FIELD OF THE INVENTION

[0001] This invention relates to analytical sensors for the detection of analytes in a sample, and methods of making and using the sensors.

BACKGROUND

[0002] Biosensors, also referred to as analytical sensors or merely sensors, are commonly used to determine the presence and concentration of a biological analyte in a sample. Such biosensors are used, for example, to monitor blood glucose levels in diabetic patients.

[0003] As sensors continue to be used, there continues to be an interest in sensors that are easy to manufacture and easy for a patient to use.

[0004] US 2006/144704A1 and WO 2006/042304 disclose known systems relating to analyte concentration measurement.

SUMMARY

[0005] In the present invention, at least one pre-sensor or test sensor is made and tested for its slope and y-intercept. Subsequent sensors would be adjusted accordingly to have the desired, pre-determined slope and y-intercept; the adjustment would be based on the slope and y-intercept from the pre-sensor or test sensor. In some embodiments, a number of test sensors (e.g., 10 or 100) may be made, their slope and y-intercept averaged, and that average is used to adjust the shape and/or size of a batch of sensors (e:g., 1,000 sensors, 50,000 sensors, or 1,000,000 sensors).

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] Referring now to the drawings, wherein like reference numerals and letters indicate corresponding structure throughout the several views:

FIG. 1 is a schematic view of a sensor strip ;
FIG. 2 is an exploded view of the sensor strip shown in FIG. 1, the layers illustrated individually with the electrodes in a first configuration;
FIG. 3 is an enlarged top plan view of a portion of the sensor strip of FIG. 1;
FIG. 4 is an enlarged top plan view of an alternate sensor strip, similar to FIG. 3;
FIG. 5 is a schematic view of a third example of a sensor strip ; and
FIG. 6 is an exploded view of the sensor strip shown in FIG. 5, the layers illustrated individually with the electrodes in a first configuration.

DETAILED DESCRIPTION

[0007] In some currently available systems, a value indicative of the calibration code of a sensor is manually entered into the meter or other equipment, for example, by the user. Based on the calibration code, the meter uses one of several programs or parameters stored within the meter. In other currently available systems, the sensor calibration code is directly read by the meter or other equipment, thus not requiring input or other interaction by the user. These sensors, however, still have a calibration code associated with them, which includes slope and y-intercept values. The slope and y-intercept values are used to determine the analyte concentration based on the measured signal. The calibration code, whether inputted manually or automatically, is needed to standardize the analysis results received from non- standardized sensors. In other words, different sensors vary, e.g., from lot to lot, a sufficient amount that, if no compensation were made, the results would differ from sensor to sensor and the results could be clinically inaccurate.

[0008] The sensors of this disclosure are calibration-adjusted to a pre-determined calibration (slope and y-intercept), during the manufacturing process, to avoid the need for the user to input or otherwise set a calibration code for the sensor or perform other calibration procedure(s) before using the sensor. The sensors of this disclosure are also calibration-adjusted to avoid the need for the meter to read a calibration code.

[0009] It has been determined that the measured signal (e.g., charge due to electrooxidation or electroreduction) from the analyte in a sample is proportional to a physical element of the sensor. For example, when coulometry is used to obtain a signal proportionate to the analyte concentration, the signal obtained is proportional to the volume of sample being assayed. For amperometry or other kinematical electrolysis, the signal is proportion to the area of the electrode

Abbott Ex. 1002 - 833/1438

(s), e.g., the at least one working electrode, in the sample chamber. By physically altering the sensor's sample chamber volume or electrode area within the sample chamber during the manufacturing process, e.g., after the assembly of multiple layers, the slope and y-intercept of the sensor lot can be controlled, e.g., shifted, to provide a sensor with a pre-determined calibration. The relationship between the sample chamber volume and the measured signal may be linear. Additionally or alternatively, the relationship between the electrode area and the measured signal may be linear.

[0010] This disclosure also provides methods for making sensors that avoid the need for the user to input or otherwise set a calibration code for the sensor, or perform other calibration procedure(s) before using the sensor.

[0011] Referring to the Drawings in general and FIGS. 1 and 2 in particular, a first example of a sensor 10 is schematically illustrated, herein shown in the shape of a strip. It is to be understood that the sensor may be any suitable shape. Sensor strip 10 has a first substrate 12, a second substrate 14, and a spacer 15 positioned therebetween.

[0012] Sensor strip 10 includes at least one working electrode 22 and at least one counter electrode 24. Sensor strip 10 also includes an optional insertion monitor 30. Sensor strip 10 has a first, distal end 10A and an opposite, proximal end 10B. At distal end 10A, sample to be analyzed is applied to sensor 10. Distal end 10A could be referred as 'the fill end', 'sample receiving end', or similar. Proximal end 10B of sensor 10 is configured for operable, and usually releasable, connecting to a device such as a meter.

[0013] Sensor strip 10 is a layered construction, in certain embodiments having a generally rectangular shape, i.e., its length is longer than its width, although other shapes 10 are possible as well, as noted above. The length of sensor strip 10 is from end 10A to end 10B.

[0014] The dimensions of a sensor may vary. The overall length of sensor strip 10 may be no less than about 10 mm and no greater than about 50 mm. For example, the length may be between about 30 and 45 mm; e.g., about 30 to 40 mm. It is understood, however that shorter and longer sensor strips 10 could be made. The overall width of sensor strip 10 may be no less than about 3 mm and no greater than about 15 mm. For example, the width may be between about 4 and 10 mm, about 5 to 8 mm, or about 5 to 6 mm. In one particular example, sensor strip 10 has a length of about 32 mm and a width of about 6 mm. In another particular example, sensor strip 10 has a length of about 40 mm and a width of about 5 mm. In yet another particular example, sensor strip 10 has a length of about 34 mm and a width of about 5 mm.

[0015] Briefly referring to FIGS. 3 and 4, two different configurations of a portion of sensors are illustrated. FIG. 3 shows a portion of sensor strip 10 that includes first end 10A and sample chamber 20. FIG. 4 shows a portion of a sensor strip 10 that includes a sensor first end 10A' and a sample chamber 20'. The shape of sensors 10, 10' is the result of physically altering the sensor's measurement zone during the manufacturing process to provide sensor strips 10, 10' with pre-determined calibration. Additional details are provided below.

Substrates and Spacer

[0016] As provided above, sensor strip 10 has first and second substrates 12, 14, non-conducting, inert substrates which form the overall shape and size of sensor strip 10. Substrates 12, 14 may be substantially rigid or substantially flexible. In certain
embodiments, substrates 12, 14 are flexible or deformable. Examples of suitable materials for substrates 12, 14 include, but are not limited, to polyester, polyethylene, polycarbonate, polypropylene, nylon, and other "plastics" or polymers.

[0017] The substrate material may be "Melinex" polyester. Other non-conducting materials may also be used.

[0018] Substrate 12 includes first or distal end 12A and second or proximal end 12B, and substrate 14 includes first or distal end 14A and second or proximal end 14B.

[0019] As indicated above, positioned between substrate 12 and substrate 14 may be spacer 15 to separate first substrate 12 from second substrate 14. Spacer 15 may extend from end 10A to end 10B of sensor strip 10, or extends short of one or both ends. Spacer 15 is an inert non-conducting substrate, typically at least as flexible and deformable (or as rigid) as substrates 12, 14. Spacer 15 may be an adhesive layer or double-sided adhesive tape or film that is continuous and contiguous. Any adhesive selected for spacer 15 should be selected to not diffuse or release material which may interfere with accurate analyte measurement.

[0020] The thickness of spacer 15 may be constant throughout, and may be at least about 0.01 mm (10 μm) and no greater than about 1 mm or about 0.5 mm. For example, the thickness may be between about 0.02 mm (20 μm) and about 0.2 mm (200 μm). In one certain example, the thickness is about 0.05 mm (50 μm), and about 0.1 mm (100 μm) in another example.

Sample Chamber

[0021] The sensor includes a sample chamber for receiving a volume of sample to be analyzed; in the example illustrated, particularly in FIG. 1, sensor strip 10 includes sample chamber 20 having an inlet 21 for access to sample chamber 20. In the example illustrated, sensor strip 10 is a side-fill sensor strip, having inlet 21 present on a side edge of strip 10. Tip-fill sensors, having an inlet at, for example, end 10A, are also within the scope of this disclosure, as well

Abbott Ex. 1002 - 834/1438

as corner and top filling sensors. Sample chamber 20 is configured so that when a sample is provided in chamber 20, the sample is in electrolytic contact with both a working electrode and a counter electrode, which allows electrical current to flow between the electrodes to effect the electrolysis (electrooxidation or electroreduction) of the analyte.

[0022] Sample chamber 20 is defined by substrate 12, substrate 14 and spacer 15; or sample chamber 20 exists between substrate 12 and substrate 14 where spacer 15 is not present. Typically, a portion of spacer 15 is removed to provide a volume between substrates 12, 14 without spacer 15; this volume of removed spacer is sample chamber 20. If spacer 15 is included between substrates 12, 14, the thickness of sample chamber 20 is generally the thickness of spacer 15.

[0023] Sample chamber 20 has a volume sufficient to receive a sample of biological fluid therein. If sensor strip 10 is a small volume sensor, sample chamber 20 has a volume that is typically no more than about 1 μL, for example no more than about 0.5 μL, and also for example, no more than about 0.25 μL. A volume of no more than about 0.1 μL is also suitable for sample chamber 20, as are volumes of no more than about 0.05 μL and about 0.03 μL.

[0024] A measurement zone is contained within sample chamber 20 and is the region of the sample chamber that contains only that portion of the sample that is interrogated during the analyte assay. In some designs, the measurement zone has a volume that is approximately equal to the volume of sample chamber 20.

[0025] The measurement zone may includes 80%, 90% or about 100% of the sample chamber.

[0026] As provided above, the thickness of sample chamber 20 corresponds typically to the thickness of spacer 15. Particularly for facing electrode configurations, as in the sensor illustrated in FIG. 2, 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 20 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, which may be about 5 seconds or less.

Electrodes

[0027] As provided above, the sensor includes a working electrode and at least one counter electrode. The counter electrode may be a counter/reference electrode. If multiple counter electrodes are present, one of the counter electrodes will be a counter electrode and one or more may be reference electrodes.

[0028] For sensor 10, at least one working electrode is positioned on one of first substrate 12 and second substrate 14 in the measurement zone and/or sample chamber. In FIG. 2, working electrode 22 is illustrated on substrate 12. Working electrode 22 extends from the sample chamber 20, proximate distal end 10A, to the other end of the sensor 10, end 10B, as an electrode extension called a "trace". The trace provides a contact pad 23 for providing electrical connection to a meter or other device to allow for data and measurement collection, as will be described later. Contact pad 23 may be positioned on a tab 26 that extends from the substrate on which working electrode 22 is positioned, such as substrate 12. A tab has more than one contact pad positioned thereon, or a single contact pad is used to provide a connection to one or more electrodes; that is, multiple electrodes are coupled together and are connected via one contact pad.

[0029] Working electrode 22 may be a layer of conductive material such as gold, carbon, platinum, ruthenium dioxide, palladium, or other non-corroding, conducting material. Working electrode 22 may be a combination of two or more conductive materials. An example of a suitable conductive epoxy is ECCOCOAT CT5079-3 Carbon-Filled Conductive Epoxy Coating (available from W.R. Grace Company, Woburn, MA). The material of working electrode 22 typically has relatively low electrical resistance and is typically electrochemically inert over the potential range of the sensor during operation.

[0030] Working electrode 22 may be applied on substrate 12 by any of various methods, 30 including by being deposited, such as by vapor deposition or vacuum deposition or otherwise sputtered, printed on a flat surface or in an embossed or otherwise recessed surface, transferred from a separate carrier or liner, etched, or molded. Suitable methods of printing include screen-printing, piezoelectric printing, ink jet printing, laser printing, photolithography, and painting.

[0031] As provided above, at least a portion of working electrode 22 is provided in sample chamber 20 for the analysis of analyte, in conjunction with the counter electrode.

[0032] The sensor includes at least one counter electrode positioned within the measurement zone and/or sample chamber. In FIG. 2, counter electrode 24 is illustrated on substrate 14. In alternate embodiments, a counter electrode is present on a different surface or substrate, such as substrate 12. Counter electrode 24 extends from the sample chamber 20, proximate first end 10A, to the other end of the sensor 10, end 10B, as an electrode extension called a "trace". The trace provides a contact pad 25 for providing electrical connection to a meter or other device to allow for data and measurement collection, as will be described later. Contact pad 25 may be positioned on a tab 27 that extends from the substrate on which counter electrode 24 is positioned, such as substrate 12 or 14. A tab has more than one contact pad positioned thereon, or a single contact pad is used to provide a connection to one or more electrodes; that is, multiple electrodes are coupled together and are connected via one contact pad.

Abbott Ex. 1002 - 835/1438

[0033] Counter electrode 24 may be constructed in a manner similar to working electrode 22. Suitable materials for the counter/reference or reference electrode include Ag/AgCl or Ag/AgBr on a non-conducting base material or silver chloride on a silver metal base. The same materials and methods may be used for counter electrode 24 as are available for working electrode 22, although different materials and methods may also be used. Counter electrode 24 may include a mix of multiple conducting materials, such as Ag/AgCl and carbon.

[0034] Working electrode 22 and counter electrode 24 may be disposed opposite to and facing each other to form facing electrodes. See for example, FIG. 2, which has working electrode 22 on substrate 12 and counter electrode 24 on substrate 14, forming facing electrodes: In this configuration, the sample chamber is typically present between the two electrodes 22, 24. Working electrode 22 and counter electrode 24 may alternately be positioned generally planar to one another, such as on the same substrate, to form co-planar or planar electrodes.

[0035] In some instances, it is desirable to be able to determine when the sample chamber of the sensor is sufficiently filled with sample. Sensor strip 10 may be indicated as filled, or substantially filled, by observing a signal between an optional indicator electrode and one or both of working electrode 22 or counter electrode 24 as sample chamber 20 fills with fluid. When fluid reaches the indicator electrode, the signal from that electrode will change. Suitable signals for observing include, for example, voltage, current, resistance, impedance, or capacitance between the indicator electrode and, for example, working electrode 22. 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.

[0036] Typically, the indicator electrode is further downstream from a sample inlet, such as inlet 21, than working electrode 22 and/or counter electrode 24.

[0037] For side-fill sensors, such as sensor 10 of FIGS. 1 and 2, an indicator electrode may be present on each side of the 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 may also have a single indicator electrode and may include some indication as to which side should be placed in contact with the sample fluid.

[0038] The indicator electrode may also be used to improve the precision of the analyte measurements. The indicator electrode may operate as a working electrode or as a counter electrode or counter/reference electrode. Measurements from the indicator electrode/working electrode may be combined (e.g., added or averaged) with those from the first counter/reference electrode/working electrode to obtain more accurate measurements.

[0039] The sensor or equipment that the sensor connected is with (e.g., a meter) may include a signal (e.g., a visual sign or auditory tone) that is activated in response to activation of the indicator electrode to alert the user that the desired zone has been filled. The sensor or equipment 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 may 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.

Sensing Chemistry

[0040] In addition to working electrode 22, sensing chemistry material(s) are preferably provided in sample chamber 20 for the analysis of the analyte. Sensing chemistry material facilitates the transfer of electrons between working electrode 22 and the analyte in the sample. Any sensing chemistry may be used in sensor strip 10; the sensing chemistry may include one or more materials.

[0041] The sensing chemistry may be diffusible or leachable, or non-diffusible or non-leachable. For purposes of discussion herein, the term "diffusible" will be used to represent "diffusible or leachable" and the term "non-diffusible" will be used to represent "non-diffusible or non-leachable" and variations thereof. Placement of sensing chemistry components may depend on whether they are diffusible or not. For example, both non- diffusible and/or diffusible component (s) may form a sensing layer on working electrode 22. Alternatively, one or more diffusible components may be present on any surface in sample chamber 20 prior to the introduction of the sample to be analyzed: As another example, one or more diffusible component(s) may be placed in the sample prior to introduction of the sample into sample chamber 20.

[0042] The sensing chemistry generally includes an electron transfer agent that facilitates the transfer of electrons to or from the analyte. The electron transfer agent may be diffusible or non-diffusible, and may be present on working electrode 22 as a layer. One example of a suitable 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. Other enzymes may be used for other analytes.

[0043] The electron transfer agent, whether it is diffusible or not, facilitates a current between working electrode 22 and the analyte and enables the electrochemical analysis of molecules. The agent facilitates the transfer electrons between the electrode and the analyte.

[0044] This sensing chemistry may, additionally to or alternatively to the electron transfer agent, include a redox

Abbott Ex. 1002 - 836/1438

mediator, such as 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, which are typically mono-, di-, tri-, or tetradentate. The redox mediator may be a polymeric redox mediator or a redox polymer (i.e., a polymer having one or more redox species). Examples of suitable redox mediators and redox polymers are disclosed in U.S. Patent No. 6,338,790, for example, and in U.S. Patent Nos. 6,605,200 and 6,605,201.

[0045] If the redox mediator is non-diffusible, then the redox mediator may be present on working electrode 22 as a layer. When having a redox mediator and an electron transfer agent, if the redox mediator and electron transfer agent are both non-leachable, then both components are on working electrode 22 as individual layers, or combined and applied as a single layer.

[0046] The redox mediator, whether diffusible or not, mediates a current between 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 agent to transfer electrons between the electrode and the analyte.

Insertion Monitor

[0047] The sensor may include an indicator to notify when proper insertion of the sensor into receiving equipment, such as a meter, has occurred. As seen in FIGS. 1 and 2, sensor strip 10 includes insertion monitor 30 on an exterior surface of one of substrates 12, 14, in the illustrated sensor, sensor 10. Insertion monitor 30 is configured and arranged to close an electrical circuit when sensor 10 is properly inserted into the meter connector.

[0048] Insertion monitor 30 may be a stripe extending across an exterior surface of sensor 10, for example, from side edge to side edge, with one contact pad for connection to a meter. It is understood that alternatively the stripe need not extend to both side edges, and the insertion monitor may be two or more contact pads for connection to a meter. The two or more contact pads could electrically connected to each other by a material, such as a conductive ink.

[0049] Insertion monitor 30 can be used to encode information regarding sensor strip 10. The encoded information may be, for example, the test time needed for accurate analyte concentration analysis, the expiration date of sensor strip 10, various correction factors, such as for environmental temperature and/or pressure, selection of the analyte to be analyzed (e.g., glucose, ketone, lactate), and the like. Additionally, insertion monitor 30 can be used to encode calibration information for the sensor, e.g., for the manufacturing lot or that specific sensor strip. However, in accordance with this disclosure, the sensor requires no calibration code; rather, the sensor is configured with a pre-determined calibration, based on the volume of the measurement zone.

[0050] Additional details regarding insertion monitors, and their use for encoding information, are described, for example, in U.S. Patent application publication no. 2006/0091006 Al. Additionally, U.S. Patent application publication no. 2006/0091006 Al provides various details regarding connection of sensors with insertion monitors with meters and connectors.

[0051] Referring to FIGS. 5 and 6 in particular, an alternate example of a sensor is illustrated as sensor strip 110. Similar to sensor strip 10, sensor strip 110 has a first substrate 112, a second substrate 114, and a spacer 115 positioned therebetween. Sensor strip 1 10 includes at least one working electrode 122 and at least one counter electrode 124.

[0052] Sensor strip 110 has a first, distal end 110A and an opposite, proximal end 110B. At distal end 110A, sample to be analyzed is applied to sensor 110. Distal end 110A 30 could be referred as 'the fill end', 'sample receiving end', or similar. Proximal end 110B of sensor 110 is configured for operable, and preferably releasable, connecting to a device such as a meter. Similar to sensor strip 10, sensor strip 110 is a layered construction, having a generally rectangular shape, which is formed by first and second substrates 112, 114. Substrate 112 includes first or distal end 112A and second or proximal end 112B, and substrate 114 includes first or distal end 114A and second or proximal end 114B. The discussion above about substrates 12, 14 and spacer 15 applies to substrates 112, 114 and spacer 15.

[0053] Sensor strip 110 includes sample chamber 120 having an inlet 121 for access to sample chamber 120. Sensor strip 110 is a tip-fill sensor, having inlet 121 at end 110A.

[0054] Similar to sample chamber 20 of sensor strip 10, sample chamber 120 is defined by substrate 112, substrate 114 and spacer 115. Generally opposite to inlet 121, through substrate 112 is a vent 130 from sample chamber 120. The discussion above about sample chamber 20 and its measurement zone applies to sample chamber 120.

[0055] For sensor 110, at least one working electrode 122 is illustrated on substrate 114. Working electrode 122 extends from end 114A into sample chamber 120 to end 114B and 110B. Sensor 110 also includes at least one counter electrode 124, in this embodiment on substrate 114. Counter electrode 124 extends from sample chamber 120, proximate first end 110A, to end 110B, as an electrode extension called a "trace". Working electrode 122 and counter electrode 124 are present on the same substrate e.g., as planar or co-planar electrodes. The electrodes 122, 124 may include sensing chemistry material(s) thereon.

Abbott Ex. 1002 - 837/1438

General Method for Manufacturing Sensors

[0056] Sensor strips 10, 110 discussed above, are sandwiched or layered constructions having substrates 12, 14, 112, 114 spaced apart, such as by spacer 15, 115. Such a construction may be made by laminating the various layers together, in any suitable manner. An alternate method for making sensor strips 10, 110, and other sensors, is to mold the sensors.

[0057] Molding may include positioning at least two spaced apart electrically 30 conductive electrodes (e.g., wires) in a mold, and molding a body of insulative material around the electrodes, with one end having therein means for receiving a fluid sample. More specifically, molding could include positioning at least two spaced apart electrically conductive electrodes (e.g., wires) in a mold, before or after molding, treating at least one of the electrodes with one or more chemicals to change the electrical properties of the treated electrode upon contact with a fluid sample, and molding a body of insulative material around the electrodes with one end having therein means for receiving a fluid sample. The body may be molded in multiple pieces, e.g., two pieces, with a body and end cap for attaching to one another after the molding is completed, or in a single piece.

[0058] A sensor may be made by positioning electrodes on one or more substrates, the substrates including a first substrate, optionally contacting at least a portion of at least one electrode with sensing material(s), and configuring the sensor by positioning a spacer between the two substrates to maintain the substrates in a fixed, layered orientation relative to each other.

Calibration of Sensors

[0059] Whether the sensors are laminated, molded, or made by some other process, after or during forming the sensor, a portion of the sensor can be physically modified (e.g., removed, re-shaped, reacted, etc.) to provide the sensor with a pre-determined slope and y-intercept. Typically, the physically modified portion of the sensor includes the sample chamber and/or measurement zone. The sample chamber shape and/or size can be altered to provide the sensor with the desired pre-determined slope and y-intercept. Additionally or alternately, the electrode area within the sample chamber and/or measurement zone is altered, sometimes without altering the sample chamber shape and/or size.

[0060] Referring again to FIGS. 3 and 4, two different configurations of sensors are 30 illustrated. FIG. 3 shows a portion of sensor strip 10 that includes first end 10A and FIG. 4 shows a portion of a sensor strip 10' that includes a sensor first end 10A'. Sensor strip 10 includes first edge 102 (which in this embodiment is also sensor end 10A), second edge 104 and third edge 106, each of which is a straight, linear edge. The corners formed by the meeting of edges 104, 106 with edge 102 are angular, having an internal angle of about 108 degrees. Sample chamber 20 extends across sensor strip 10 from edge 104 to edge 106. Sensor strip 10' includes first edge 102' (which in this embodiment is also sensor end 10A'), second edge 104' and third edge 106'. Edges 104' and 106' are arcuate edges. Additionally, the corners formed by the meeting of edges 104', 106' with edge 102' are rounded or radiused. Also A sample chamber 20' extends across sensor 10' from edge 104' to edge 106'. The volume of sample chamber 20, 20' is defined by side edges 104, 104' and 106, 106' and the thickness of the sample chamber.

[0061] To clarify understanding, the following discussion will use the term "pre-sensor" when referring to the sensor prior to any physical alteration of the sensor.

[0062] Sensors 10, 10' are the result of physically altering the sample chamber and/or measurement zone after the manufacturing process of the pre-sensor to provide sensors that have a pre-determined slope and y-intercept. "Physically altering" can include removing a portion of the sample chamber and/or measurement zone of the pre-sensor. FIG. 3 illustrates a first phantom portion 104° (i.e., 104 superscript naught), which corresponds to the portion of the pre-sensor removed to form edge 104, and a second phantom portion 106° (i.e., 106 superscript naught), which corresponds to the portion of the pre-sensor removed to form edge 106. By removing phantom portions 104°, 106°, a portion of the sample chamber, i.e., that present in portions 104°, 106°, is also removed, thus physically altering the pre-sensor. For sensors 10, 10' of FIGS. 3 and 4, the calibration code is proportional to the volume of the measurement zone and/or the sample chamber of the sensor.

[0063] Referring to FIG. 5, sensor 110 is the result of physically altering the electrode area and the sample chamber and/or measurement zone after the manufacturing process of the pre-sensor to provide sensors that have a pre-determined slope and y-intercept. FIG. 5 illustrates phantom portion 110° (i.e., 110 superscript naught), which corresponds to the portion of the pre-sensor removed to form edge 110A. By removing phantom portion 110°, a portion of the working electrode 122, i.e., that present on substrate 114 within phantom portion 110°, is also removed, thus physically altering the pre-sensor. For sensor 110 above, the calibration slope and y-intercept are proportional to the area of the electrode (s), e.g., working electrode 122, in the sample chamber of the sensor. The the volume of the sample chamber is reduced, due to the removal of phantom portion 110°. It is noted that alternatively the sample chamber volume and/or measurement zone volume may remain the same although the area of the electrodes is modified. One exemplary method for modifying the electrode area, e.g., removing area, is by the use of non-invasive procedures, such as a single or multiple energy

Abbott Ex. 1002 - 838/1438

beams (e.g., lasers, UV light, electron beam, etc.) that pass through the inert substrates but physically alter the electrodes. In this process, areas of electrode(s) may be removed or otherwise rendered inactive.

[0064] To provide a plurality of sensors, such as sensor strips 10, 10', 110 with the same pre-determined calibration from a plurality of pre-sensors, each of the pre-sensors may be physically altered, as needed, to obtain the desired pre-determined physical characteristics and the desired sensor. It is understood that this discussion also applies to a batch or lot of sensors in addition to a single sensor. For example, a first pre-sensor may have a response that is too high compared to the desired level and a second pre-sensor may have a response that is within the desired level. In such a situation, a portion of the first pre-sensor may be removed to provide a sensor having a measurement zone, sample chamber, or electrode area that is comparable to that of the second pre-sensor and is within the desired level.

[0065] In some situations, however, a pre-sensor, e.g., a third sensor strip, may have a response that is too low compared to the desired level. Because mostly it would be difficult or impractical to increase the measurement zone, sample chamber, and/or electrode area of the pre-sensor after it has been assembled, in some manufacturing operations the desired response level may be artificially lowered in order to pre-calibrate the sensor. With such an artificially lowered desired level, for a pre-sensor that has a response within that desired artificially low level, a pre-determined portion of the pre-sensor's active area may be removed to obtain a sensor with the actual desired level; for a pre-sensor that has a response above the desired artificially low, a larger portion than the pre-determined portion of the pre-sensor's active area may be removed to obtain a sensor with the actual desired level; and for a pre-sensor that has a response below the desired artificially low level, a smaller portion than the pre-determined portion of the pre-sensor's active area is removed in order to obtain a sensor with the actual desired level. In other words, using such a methodology, all the pre-sensors would be physically altered to obtain sensors with the same desired pre-determined calibration.

[0066] The pre-sensor is modified in order to obtain the desired pre-determined calibration, either by altering the volume of the sample chamber and/or measurement zone or by the electrode area in the sample chamber. Referring to FIGS. 3 and 4, the volume of the sample chamber and/or measurement zone is modified by removing phantom portions 104°, 106°, and the electrode area is modified in FIG. 5 by removing phantom portion 110°.

[0067] According to the present invention, no actual pre-sensor is subsequently modified to form the sensor, but rather, a pre-sensor is used as a template for one or more sensors (e.g., batch or lot of sensors, e.g., at least 100 sensors, at least 1,000 sensors, or even at least 50,000 sensors). Multiple sensors are obtained from a large sheet construction having working electrodes, counter electrodes and sample chambers. See for example, U.S. Patent No. 6,338,790, particularly FIGS. 31A and 31B and the description associated therewith, which describes methods of making a plurality of sensors from a large sandwiched sheet construction. From this sheet, one (or more) test sensors could be removed (e.g., punched) using a standard template (e.g., shape and size), and these test sensors could be tested for their difference from the desired slope and y-intercept, and the results typically averaged. Subsequently removed sensors would be modified from the test sensor, as needed, by removing (e.g., punching) an appropriately shaped and sized sensor, which may differ from the test sensors, to obtain the desired slope and y-intercept. In this method, the test sensors provide a guide for the modification needed, so that each sensor is not individually tested.

[0068] It is understood that other configurations of phantom portions would be suitable. For example, sensor 10 of FIG. 3 has edge 102 and edges 104, 106 forming an angle of about 108 degrees. This corner angle could be about 90 degrees or be a high as 180 degrees; in most embodiments, however, this corner angle is in the range of about 90 to about 145 degrees. Angles less than 90 degrees could be used for a concave edge 102, 102'. The corners could be sharp, as in FIG. 3, or rounded, as in FIG. 4. Any or all of edges 102, 104, 106 may be straight or curved, with concave, convex, or a combination of shapes. Both sensor strips 10, 10' have edge 102, 102' forming end 10A, 10A'; or the sensor end could be defined by the meeting of edges 104, 106 (i.e., the side edges meet at a point with no end edge), or the sensor could be asymmetrical, e.g., having only one portion removed from the sensor. Other shapes for sensors would be suitable. FIGS. 5 and 6 illustrate sensor strip 110 with a blunt end 110A, having 90 degree corners. After providing any of sensors 10, 10', 110, the proximal ends, e.g., 10B, 110B could be adjusted so that all sensors in the lot have the same final size.

Application of the Sensor

[0069] A common use for a sensor made by methods according to the present invention, such as sensor strip 10, 10' 110, is for the determination of analyte concentration in a biological fluid, such as glucose concentration in blood, interstitial fluid, and the like, in a patient or other user. Additional analytes that may be determined include but are not limited to, for example, acetyl choiine, 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.

[0070] Sensors may be available at pharmacies, hospitals, clinics, from doctors, and other sources of medical devices.

Abbott Ex. 1002 - 839/1438

Multiple sensors may be packaged together and sold as a single unit; e.g., a package of about 25, about 50, or about 100 sensors, or any other suitable number. A kit may include one or more sensors, and additional components such as control solutions and/or lancing device and/or meter, etc.

[0071] Sensors may be used for an electrochemical assay, or, for a photometric test. Sensors are generally configured for use with an electrical meter, which may be connectable to various electronics. A meter may be available at generally the same locations as the sensors, and sometimes may be packaged together with the sensors, e.g., as a kit.

[0072] Examples of suitable electronics connectable to the meter include a data processing terminal, such as a personal computer (PC), a portable computer such as a laptop or a handheld device (e.g., personal digital assistants (PDAs)), and the like. The electronics are configured for data communication with the receiver via a wired or a wireless connection. Additionally, the electronics may further be connected to a data network (not shown) for storing, retrieving and updating data corresponding to the detected glucose level of the user.

[0073] The various devices connected to the meter may wirelessly communicate with a server device, e.g., using a common standard such as 802.11 or Bluetooth RF protocol, or an IrDA infrared protocol. The server device could be another portable device, such as a Personal Digital Assistant (PDA) or notebook computer, or a larger device such as a desktop computer, appliance, etc. In some arrangements, the server device has a display, such as a liquid crystal display (LCD), as well as an input device, such as buttons, a keyboard, mouse or touchscreen. With such an arrangement, the user can control the meter indirectly by interacting with the user interface(s) of the server device, which in turn interacts with the meter across a wireless link.

[0074] The server device may also communicate with another device, such as for sending data from the meter and/or the service device to a data storage or computer. For example, the service device could send and/or receive instructions (e.g., an insulin pump protocol) from a health care provider computer. Examples of such communications include a PDA synching data with a personal computer (PC), a mobile phone communicating over a cellular network with a computer at the other end, or a household appliance communicating with a computer system at a physician's office.

[0075] A lancing device or other mechanism to obtain a sample of biological fluid, e.g., blood, from the patient or user may also be available at generally the same locations as the sensors and the meter, and sometimes may be packaged together with the sensor and/or meter, e.g., as a kit.

[0076] The sensors are particularly suited for inclusion in an integrated device, i.e., a device which has the sensor and a second element, such as a meter or a lancing device, in the device. The integrated device may be based on providing an electrochemical assay or a photometric assay. Sensors may be integrated with both a meter and a lancing device. Having multiple elements together in one device reduces the number of devices needed to obtain an analyte level and facilitates the sampling process. For example, a housing may include one or more of the sensor strips, a skin piercing element

[0077] and a processor for determining the concentration of an analyte in a sample applied to the strip. A plurality of sensors may be retained in a cassette in the housing interior and, upon actuation by a user, a single sensor may be dispensed from the cassette so that at least a portion extends out of the housing for use.

Operation of the Sensor Strip

[0078] In use, a sample of biological fluid is provided into the sample chamber of the sensor, where the level of analyte is determined. The analysis may be based on providing an electrochemical assay, wherein it is the level of glucose in blood that is determined, and the source of the biological fluid is a drop of blood drawn from a patient, e.g., after piercing the patient's skin with a lancing device, which could be present in an integrated device, together with the sensor strip.

[0079] Prior to providing the sample to the sensor, or even after providing the sample to the sensor, there is no need for the user to input a calibration code or other information regarding the operation and/or interaction of the sensor with the meter or other equipment. The sensor is configured so that the results received from the analysis are clinically accurate, without the user having to adjust the sensor or the meter. The sensor is physically configured to provide accurate results that are repeatable by a batch of sensors.

[0080] After receipt of the sample in the sensor, the analyte in the sample is, e.g., electrooxidized or electroreduced, at the working electrode and the level of current obtained at the counter electrode is correlated as analyte concentration. The sensor may be operated with or without applying a potential to the electrodes, wherein the electrochemical reaction occurs spontaneously and a potential need not be applied between the working electrode and the counter electrode, or a potential is applied between the working electrode and the counter electrode.

[0081] The invention has been described with reference to various specific and preferred embodiments and techniques. However, it will be apparent to one of ordinarily skill in the art that many variations and modifications may be made while remaining within the scope of the invention.

Abbott Ex. 1002 - 840/1438

Experimental

[0082] Five sensor strips, each having a distal end similar to that illustrated in FIG. 4, were punched from a laminated sheet composed of two substrates and a spacer layer therebetween, with at least one working electrode and at least one counter electrode in facing configuration. Each of the sensor strips had arcuate edges, similar to edges 104', 106' in FIG. 4. The table below provides parameters for the five sensor strips. The "tip distance" was the distance between the distal most end of the sensor strip (e.g., end 10A' in FIG. 4) and the sample chamber (e.g., sample chamber 20' in FIG. 4). The punch that formed the distal end and the arcuate edges was the same punch for each of the sensor strips. Thus, as the distance between the tip and the sample chamber increased, the length of the sample chamber (between the arcuate edges) increased, thus increasing the sample chamber volume.

Tip distance (0.001 inch)	Sample chamber volume (nanoliter)	Charge (microcoulombs)
10	97	98.7
20	103	107.7
30	109	115.9
40	114	123.4
50	120	127.9

[0083] This data shows a linear relationship between the sample chamber volume and the measured charge; the linear equation is y=1.3x - 26.4. Also, the data shows a linear relationship between the tip distance and the measured charge; the linear equation is y=0-.74x + 92.5. With this knowledge, the punch position to achieve the desired sensor response for this batch of sensors can be calculated.

Claims

1. A method of making a plurality of calibration-adjusted sensors (10, 10', 110) comprising:

   providing a sheet construction comprising a plurality of working electrodes (22, 122), a plurality of counter electrodes (24, 124), and a plurality of sample chambers (20, 20', 120), each sample chamber having at least a working electrode and at least a counter electrode therein;
   separating a first sensor (10, 10', 110) from the sheet construction, wherein the first sensor (10, 10', 110) has a calibration code with a slope and y-intercept, and comparing the slope and y-intercept to a desired slope and y- intercept; and
   separating a second sensor (10, 10', 110) from the sheet construction subsequent to the first sensor, the second sensor having a calibration code with the desired slope and y-intercept, wherein a shape and/or size of the sample chamber (20, 20', 120) of the second sensor and/or an electrode area of the second sensor is guided by the comparison of the slope and y-intercept of the calibration code of the first sensor to the desired slope and y-intercept.

2. A method as claimed in claim 1, wherein the second sensor (10, 10', 110) is physically different than the first sensor.

3. A method as claimed in claim 1, further comprising:

   separating a third sensor (10, 10', 110) subsequent to the first sensor, the third sensor (10, 10', 110) having a calibration code with the desired slope and y-intercept.

4. A method as claimed in claim 3, wherein the third sensor (10, 10', 110) is physically different than the first sensor.

5. A method as claimed in claim 1 or claim 3, further comprising:

   separating at least 100 sensors (10, 10', 110) subsequent to the first sensor, the at least 100 sensors (10, 10', 110) having a calibration code with the desired slope and y-intercept.

Abbott Ex. 1002 - 841/1438

6. A method as claimed in claim 1, further comprising:

providing a first substrate and providing the plurality of working electrodes thereon;
providing a spacer layer over the first substrate; and
overlaying the spacer layer with a second substrate.

7. A method as claimed in any of the preceding claims, wherein each sensor is a tip-fill sensor, a side-fill sensor, comer-fill sensor, or a top-fill sensor.

8. A method as claimed in any of the preceding claims, wherein the second sensor (10, 10', 110) is different than the first sensor (10, 10', 110) by a volume of the sample chamber.

9. A method as claimed in any of the preceding claims, wherein the second sensor (10, 10', 110) is different than the first sensor (10, 10', 110) by an electrode area in the sample chamber.

10. A method as claimed in any of the preceding claims, wherein the slope and y-intercept of the calibration code of the first sensor (10, 10', 110) is different than the desired slope and y-intercept.

11. A method as claimed in any of the preceding claims, wherein the separating of the sensors (10, 10', 110) from the construction sheet comprises punching.

Patentansprüche

1. Verfahren zur Herstellung einer Vielzahl von kalibrierungs-angepassten Sensoren (10, 10', 110), das folgendes aufweist:

Bereitstellung einer Blattkonstruktion, die eine Vielzahl von aktiven Elektroden (22,122), eine Vielzahl von Gegenelektroden (24, 124) und eine Vielzahl von Probekammern (20,20', 120) aufweist, wobei jede Probekammer mindestens eine aktive Elektrode und mindestens eine Gegenelektrode enthält;
Abtrennen eines ersten Sensors (10, 10', 110) von der Blattkonstruktion, wobei der erste Sensor (10, 10', 110) einen Kalibrierungs-Code mit Steigungs- und y-Achsenabschnittswerten aufweist, und Vergleichen der Steigungs- und y-Achsenabschnittswerte mit gewünschten Steigungs- und y-Achsenabschnittswerten; und
Abtrennen eines zweiten Sensors (10, 10', 110) von der Blattkonstruktion, nach dem ersten Sensor, wobei der zweite Sensor einen Kalibrierungs-Code mit den gewünschten Steigungs- und y-Achsen -abschnittswerten aufweist, wobei eine Form und/oder eine Größe der Probenkammer (20, 20', 120) des zweiten Sensors und/oder einer Elektrodenfläche des zweiten Sensors geführt wird durch den Vergleich der Steigungs- und y-Achsenabschnittswerte des Kalibrierungs-Codes des ersten Sensors mit den gewünschten Steigungs- und y-Achsenabschnittswerten.

2. Ein Verfahren nach Anspruch 1, bei dem der zweite Sensor (10, 10', 110) sich physikalisch von dem ersten Sensor unterscheidet.

3. Ein Verfahren nach Anspruch 1, das ferner aufweist:

Abtrennen eines dritten Sensors (10, 10', 110) nach dem ersten Sensor, wobei der dritte Sensors (10, 10', 110) einen Kalibrierungs-Code mit den gewünschten Steigungs- und y-Achsenabschnittswerte aufweist.

4. Ein Verfahren nach Anspruch 3, bei dem der dritte Sensor (10, 10', 110) sich physikalisch von dem ersten Sensor unterscheidet.

5. Ein Verfahren nach Anspruch 1 oder 3, das ferner aufweist:

Abtrennen von mindestens 100 Sensoren (10, 10', 110) nach dem ersten Sensor, wobei die mindestens 100 Sensoren (10, 10', 110) einen Kalibrierungs-Code mit den gewünschten Steigungs- und y-Achsenabschnittswerten aufweist.

6. Ein Verfahren nach Anspruch 1, das ferner aufweist:

Abbott Ex. 1002 - 842/1438

Bereitstellen eines ersten Substrats und Bereitstellen der Vielzahl der aktiven Elektroden auf diesem;
Bereitstellen einer Abstandslage über dem ersten Substrat; und
Überdecken der Abstandslage mit einem zweiten Substrat.

7. Ein Verfahren nach einem der vorhergehenden Ansprüche, bei dem jeder Sensor ein Spitzenfüllsensor, ein Seitenfüllsensor, ein Eckfüllsensor oder ein Kopffüllsensor ist.

8. Ein Verfahren nach einem der vorhergehenden Ansprüche, bei dem der zweite Sensor (10, 10', 110) sich von dem ersten Sensor (10, 10', 110) durch ein Volumen der Probenkammer unterscheidet.

9. Ein Verfahren nach einem der vorhergehenden Ansprüche, bei dem der zweite Sensor (10, 10', 110) sich von dem ersten Sensor (10, 10', 110) durch eine Elektrodenfläche in der Probenkammer unterscheidet.

10. Ein Verfahren nach einem der vorhergehenden Ansprüche, bei dem die Steigungs- und y-Achsenabschnittswerte des Kalibrierungscodes des ersten Sensors (10, 10', 110) sich unterscheiden von den gewünschten Steigungs- und y-Achsenabschnittswerten.

11. Ein Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Abtrennen der Sensoren (10, 10', 110) von der Blattkonstruktion einen Stanzvorgang umfasst.

Revendications

1. Procédé de fabrication d'une pluralité de détecteurs étalonnés (10, 10', 110) comprenant :

fournir une construction en feuille comprenant une pluralité d'électrodes de travail (22, 122), une pluralité de contre-électrodes (24, 124), et une pluralité de chambres (20, 20', 120) à échantillon, chaque chambre à échantillon comportant au moins une électrode de travail et au moins une contre-électrode à l'intérieur de celle-ci ;
séparer un premier détecteur (10, 10', 110) d'avec la construction en feuille, dans lequel le premier détecteur (10, 10', 110) a un code d'étalonnage avec une inclinaison et une intersection avec l'axe Y, et comparer l'inclinaison et l'intersection avec l'axe Y à une inclinaison et une intersection avec l'axe Y souhaitées ; et
séparer un deuxième détecteur (10, 10', 110) d'avec la construction en feuille ultérieur au premier détecteur, le deuxième détecteur ayant un code d'étalonnage avec l'inclinaison et l'intersection avec l'axe Y souhaitées, dans lequel une forme et/ou une taille de la chambre (20, 20', 120) à échantillon du deuxième détecteur et/ou une zone d'électrode du deuxième détecteur est guidée par une comparaison de l'inclinaison et de l'intersection avec l'axe Y du code d'étalonnage du premier détecteur avec l'inclinaison et l'intersection avec l'axe Y souhaitées.

2. Procédé selon la revendication 1, dans lequel le deuxième détecteur (10, 10', 110) est physiquement différent du premier détecteur.

3. Procédé selon la revendication 1, comprenant en outre :

séparer un troisième détecteur (10, 10', 110) ultérieur au premier détecteur, le troisième détecteur (10, 10', 110) ayant un code d'étalonnage avec l'inclinaison et l'intersection avec l'axe Y souhaitées.

4. Procédé selon la revendication 3, dans lequel le troisième détecteur (10, 10', 110) est physiquement différent du premier détecteur.

5. Procédé selon la revendication 1 ou la revendication 3, comprenant en outre :

séparer au moins 100 détecteurs (10, 10', 110) ultérieur au premier détecteur, les au moins 100 détecteurs (10, 10', 110) ayant un code d'étalonnage avec l'inclinaison et l'intersection avec l'axe Y souhaitées.

6. Procédé selon la revendication 1, comprenant en outre :

fournir un premier substrat et fournir la pluralité d'électrodes de travail sur celui-ci ;
fournir une couche d'espacement sur le premier substrat ; et

Abbott Ex. 1002 - 843/1438

recouvrir la couche d'espacement d'un deuxième substrat.

7. Procédé selon l'une des revendications précédentes, dans lequel chaque détecteur est un détecteur à remplissage par un bout, un détecteur à remplissage par un côté, un détecteur à remplissage par un coin, ou un détecteur à remplissage par le dessus.

8. Procédé selon l'une des revendications précédentes, dans lequel le deuxième détecteur (10, 10', 110) est différent du premier détecteur (10, 10', 110) de par un volume de la chambre à échantillon.

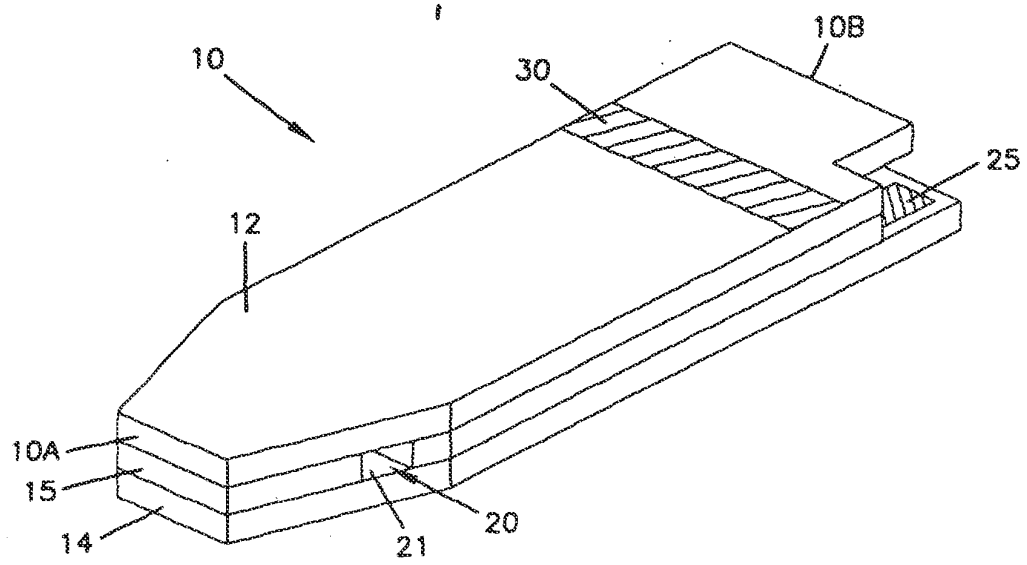
9. Procédé selon l'une des revendications précédentes, dans lequel le deuxième détecteur (10, 10', 110) est différent du premier détecteur (10, 10', 110) de par une zone d'électrode dans la chambre à échantillon.

10. Procédé selon l'une des revendications précédentes, dans lequel l'inclinaison et l'intersection avec l'axe Y du premier détecteur (10, 10', 110) sont différentes de l'inclinaison et l'intersection avec l'axe Y souhaitées.

11. Procédé selon l'une des revendications précédentes, dans lequel la séparation des détecteurs (10, 10', 110) d'avec la feuille de construction comprend un poinçonnage.

Abbott Ex. 1002 - 844/1438

FIG. 1



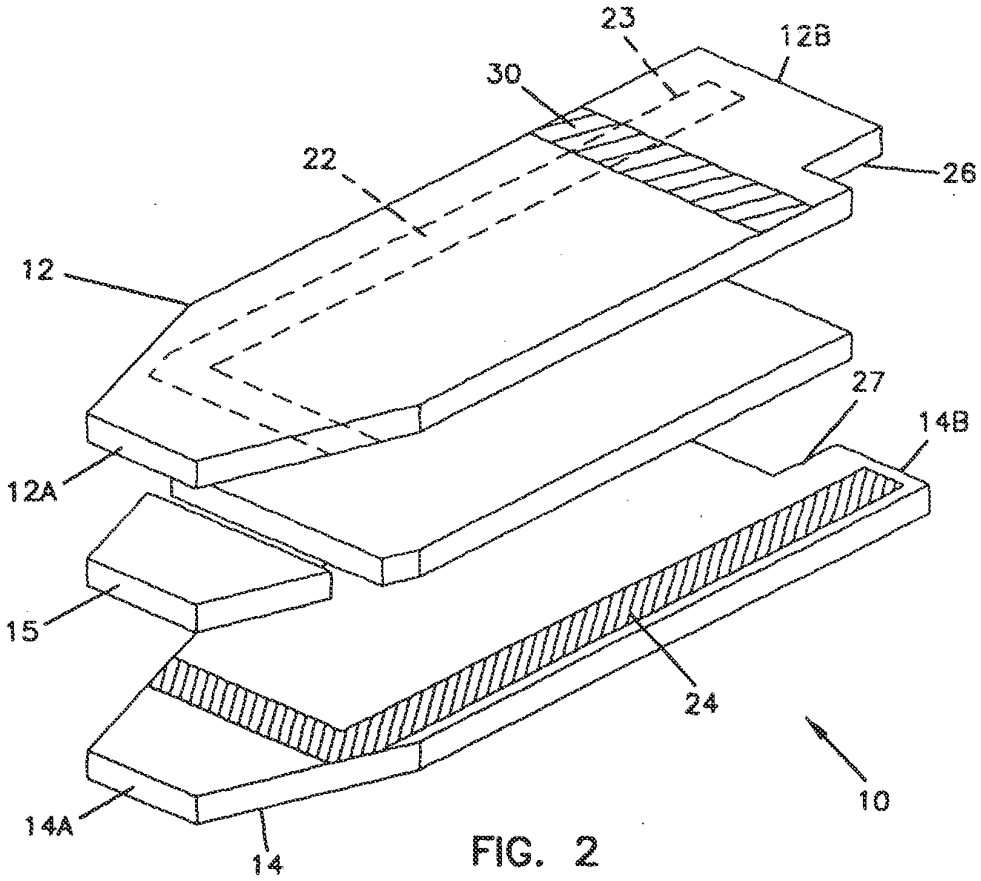


FIG. 2

Abbott Ex. 1002 - 845/1438

FIG. 3

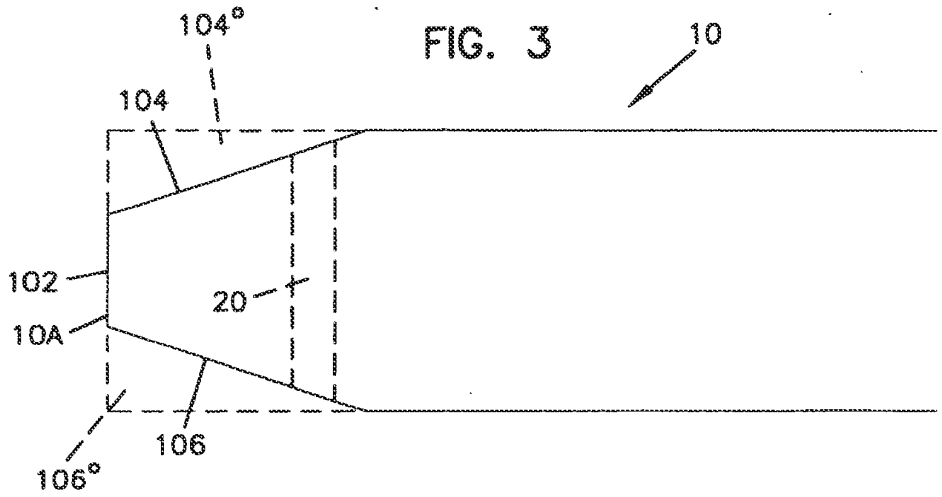
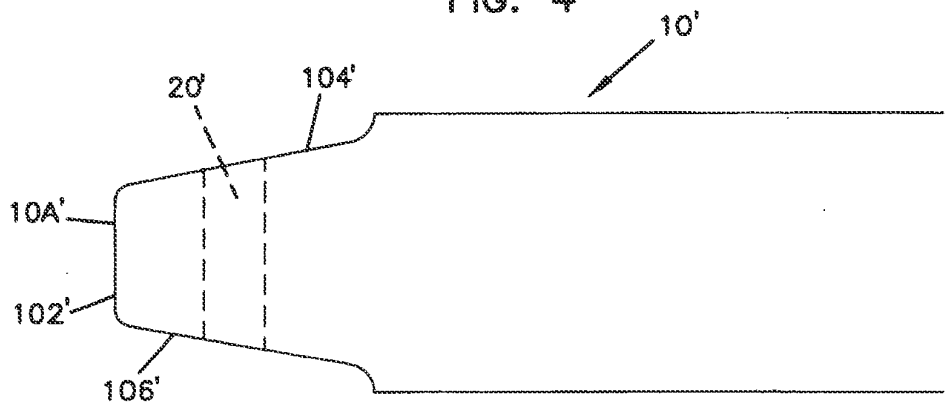


FIG. 4



Abbott Ex. 1002 - 846/1438

FIG. 5

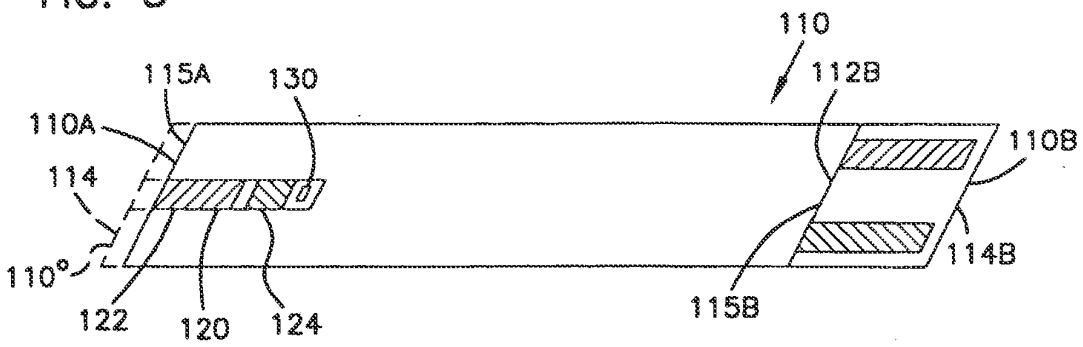
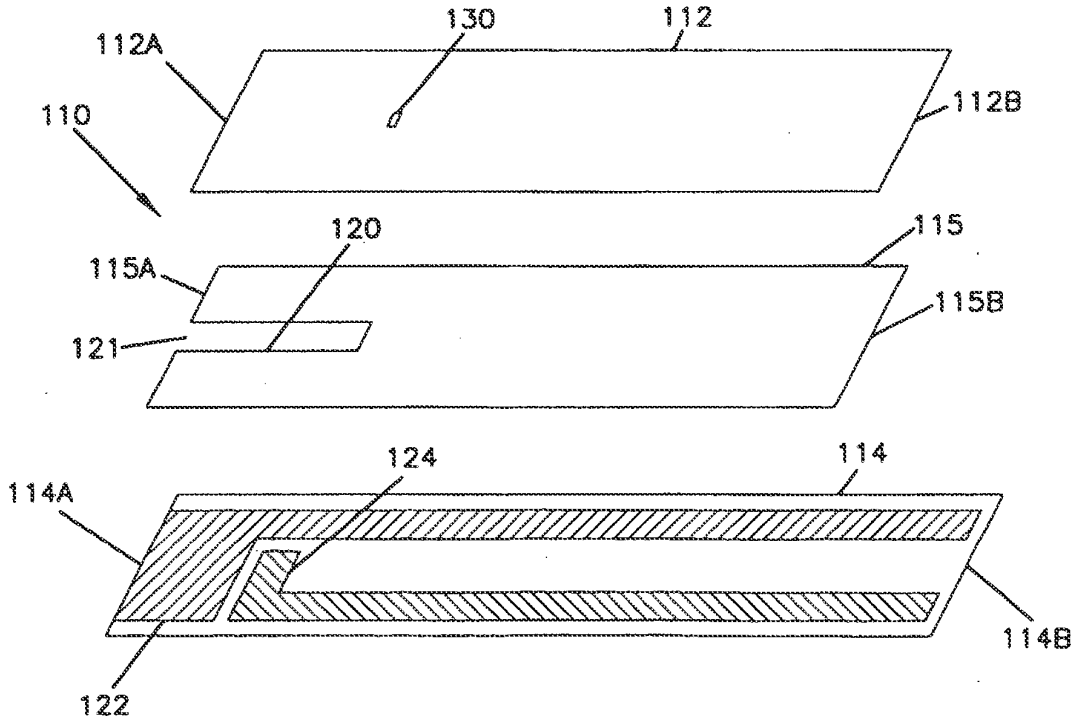


FIG. 6



Abbott Ex. 1002 - 847/1438

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 2006144704 A1 **[0004]**
- WO 2006042304 A **[0004]**
- US 6338790 B **[0044] [0067]**
- US 6605200 B **[0044]**
- US 6605201 B **[0044]**
- US 20060091006 A1 **[0050]**

Abbott Ex. 1002 - 848/1438

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/00 | A1

(11) International Publication Number: **WO 99/58051**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/US99/10380

(22) International Filing Date: 11 May 1999 (11.05.99)

(30) Priority Data:
60/085,373 13 May 1998 (13.05.98) US

(71) Applicant: CYGNUS, INC. [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US).

(72) Inventors: BERNER, Bret; 239 El Granada Boulevard, El Granada, CA 94018 (US). CHIANG, Chia-Ming; 380 Shad Court, Foster City, CA 94404 (US). GARRISON, Michael, D.; 4747 30th Avenue N.E., K-175, Seattle, WA 98198 (US). JONA, Jana; 3 Yosemite Drive, Bear, DE 19701 (US). POTTS, Russell, O.; 76 Uranus Terrace, San Francisco, CA 94114 (US). TAMADA, Janet; 505 Cypress Point Drive #271, Mountain View, CA 94043 (US). TIERNEY, Michael, J.; 368 N. Sixth Street, San Jose, CA 95112 (US).

(74) Agents: MCCLUNG, Barbara; Cygnus, Inc., 400 Penobscot Drive, Redwood City, CA 94063 (US) et al.

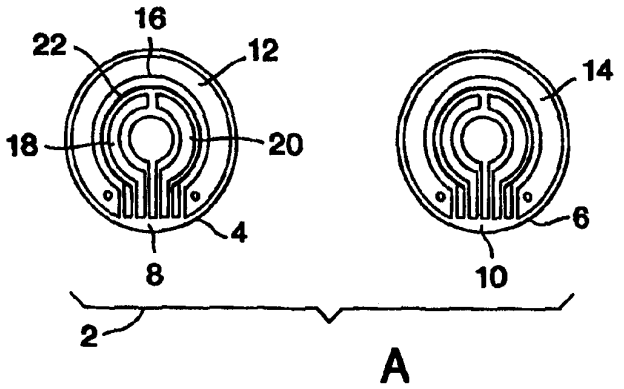
(81) Designated States: CA, JP, KR, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

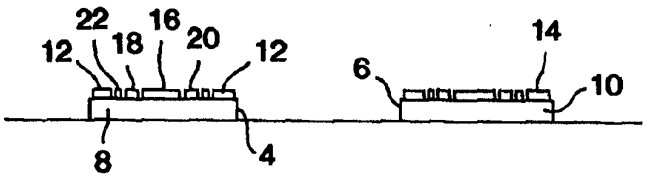
(54) Title: MONITORING OF PHYSIOLOGICAL ANALYTES

(57) Abstract

Methods and devices are provided for measuring the concentration of target chemical analytes present in a biological system. Device configuration and/or measurement techniques are employed in order to reduce the effect of interfering species on sensor sensitivity. One important application of the invention involves a method and device for monitoring blood glucose values.



A



B

Abbott Ex. 1002 - 849/1438

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

MONITORING OF PHYSIOLOGICAL ANALYTES

Field of the Invention

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

Background of the Invention

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.

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

Abbott Ex. 1002 - 851/1438

several long-term effects of diabetes, such as heart disease, atherosclerosis, blindness, stroke, hypertension and kidney failure.

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.

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.

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

Abbott Ex. 1002 - 852/1438

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.

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.

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

Abbott Ex. 1002 - 853/1438

in the reservoir.

Summary of the Invention

The present invention provides methods and sampling systems for measuring the concentration of an analyte present in a biological system. The methods of the invention generally entail 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.

Analyte sampling is carried out using a transdermal sampling system that is placed in operative contact with 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.

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,

Abbott Ex. 1002 - 854/1438

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.

Accordingly, it is an object of the invention to provide 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.

In one aspect of the invention, a method is provided 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

Abbott Ex. 1002 - 855/1438

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).

In another aspect of the invention, a method is provided 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

Abbott Ex. 1002 - 856/1438

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.

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.

Abbott Ex. 1002 - 857/1438

In yet another aspect of the invention, a method is provided 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 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.

In one aspect of the methods and devices of the present invention, a charge segregation step can be used to reduce the presence of interfering species at the

Abbott Ex. 1002 - 858/1438

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.

In a related aspect of the invention, a method is provided 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.

In a still further related aspect of the invention, a method is provided for measuring the concentration of an analyte present in a biological system. The method

Abbott Ex. 1002 - 859/1438

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.

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

Abbott Ex. 1002 - 860/1438

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.

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

Abbott Ex. 1002 - 861/1438

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.

In a further aspect, the methods and 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.

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.

Brief Description of the Drawings

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

Abbott Ex. 1002 - 862/1438

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**.

Abbott Ex. 1002 - 863/1438

Detailed Description of the Preferred Embodiments

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.

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.

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.

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

Definitions

The terms "analyte" and "target analyte" are used herein to denote any physiological analyte of interest

Abbott Ex. 1002 - 864/1438

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.

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,

Abbott Ex. 1002 - 865/1438

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.

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,

Abbott Ex. 1002 - 866/1438

cannulas, and miniaturized etched, ablated or molded flow paths.

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.

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.

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.

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.

As used herein, the term "continual measurement"

Abbott Ex. 1002 - 867/1438

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.

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.

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.

The term "iontophoresis" intends a method for transporting substances across tissue by way of an

Abbott Ex. 1002 - 868/1438

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).

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.

"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.

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

Abbott Ex. 1002 - 869/1438

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.).

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).

The "sensor element" can include components in addition to a biosensor electrode, for example, it can

Abbott Ex. 1002 - 870/1438

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.

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").

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,

Abbott Ex. 1002 - 871/1438

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.

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.

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

Abbott Ex. 1002 - 872/1438

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.

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.

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.

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

Abbott Ex. 1002 - 873/1438

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.

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.

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.

"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.

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

Abbott Ex. 1002 - 874/1438

effect substantially uniform deposition of a material onto a substrate, e.g., Gravure-type printing, extrusion coating, screen coating, spraying, painting, or the like.

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.

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.

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

The present invention relates to the use of a device for transdermally extracting and measuring the concentration of a target analyte present in a

Abbott Ex. 1002 - 875/1438

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.

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

Abbott Ex. 1002 - 876/1438

action, for example a drug or pharmacological agent.

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.

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

Abbott Ex. 1002 - 877/1438

uric acid with urate oxidase system, urea with a urease system, cholesterol with a cholesterol oxidase system, and theophylline with a xanthine oxidase system.

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).

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

Abbott Ex. 1002 - 878/1438

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.

Accordingly, in one embodiment of the invention, a method is provided 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

Abbott Ex. 1002 - 879/1438

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).

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.

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

Abbott Ex. 1002 - 880/1438

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

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

Abbott Ex. 1002 - 881/1438

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.

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.

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 one preferred embodiment, the transdermal sampling device is maintained in contact

Abbott Ex. 1002 - 882/1438

with the biological system in order to provide for continual or continuous monitoring of the analyte concentration.

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 the subject method in order to improve the signal-to-noise ratio in detected signals.

Although all of the methods 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.

Accordingly, in another embodiment of the invention, an automatic sampling system is used to

Abbott Ex. 1002 - 883/1438

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.

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.

In certain embodiments of the invention, one or more additional collection reservoirs are used in the

Abbott Ex. 1002 - 884/1438

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.

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 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.

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.

In order to facilitate detection of the analyte, an

Abbott Ex. 1002 - 885/1438

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.

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

Abbott Ex. 1002 - 886/1438

xanthine oxidase system.

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.

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.

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

Abbott Ex. 1002 - 887/1438

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.

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.

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

Abbott Ex. 1002 - 888/1438

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.

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.

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

Abbott Ex. 1002 - 889/1438

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**.

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

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.

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.

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

Abbott Ex. 1002 - 890/1438

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.

After a suitable iontophoretic extraction period,

Abbott Ex. 1002 - 891/1438

one or both of the sensor electrode sets can be activated in order to detect extracted substances including the analyte of interest.

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.

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.

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

Abbott Ex. 1002 - 892/1438

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.

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.

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

Abbott Ex. 1002 - 893/1438

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.

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.

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.

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 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

Abbott Ex. 1002 - 894/1438

connected to the adjacent bimodal electrode which acts as a counter electrode at which electrons generated at the sensing electrode are consumed.

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.

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.

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

Abbott Ex. 1002 - 895/1438

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.

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

Abbott Ex. 1002 - 896/1438

cycles in a 24 hour period.

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.

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

Abbott Ex. 1002 - 897/1438

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).

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

Abbott Ex. 1002 - 898/1438

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.

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 a 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

Abbott Ex. 1002 - 899/1438

provided for continually monitoring the sampling system to ensure proper operations.

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.

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

Abbott Ex. 1002 - 900/1438

wait for the sampling system to warm-up before calibrating it.

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 response. 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.

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

Abbott Ex. 1002 - 901/1438

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.

In another embodiment 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.

The benefits provided by this selective extraction technique can be enhanced using any one, or a

Abbott Ex. 1002 - 902/1438

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).

In a preferred embodiment of the above method, 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

Abbott Ex. 1002 - 903/1438

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.

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,

Abbott Ex. 1002 - 904/1438

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).

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 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.

In a related embodiment which uses the above

Abbott Ex. 1002 - 905/1438

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.

In one preferred embodiment of the method, 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

Abbott Ex. 1002 - 906/1438

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.

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 embodiment, 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 of the invention 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.

In another related embodiment 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

Abbott Ex. 1002 - 907/1438

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.

In yet a further embodiment, 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

Abbott Ex. 1002 - 908/1438

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.

Accordingly, in the present embodiment, 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 method, the potential is reduced to about 0.42V in order to substantially eliminate the signal component due to the tryptophan and tyrosine interfering species.

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, in yet another embodiment of the invention, a method for measuring the concentration of an analyte present in a biological system is provided which entails 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

Abbott Ex. 1002 - 909/1438

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.

In a related embodiment, 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

Abbott Ex. 1002 - 910/1438

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.

In a still further embodiment, 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

Abbott Ex. 1002 - 911/1438

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.

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

Abbott Ex. 1002 - 912/1438

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 of the invention (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.

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

Abbott Ex. 1002 - 913/1438

concentration at preprogrammed intervals. Other modifications and additions to the above embodiments will be apparent to those skilled in the art upon reading the present enabling disclosure.

Examples

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 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

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

Abbott Ex. 1002 - 914/1438

electrode.

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.

Abbott Ex. 1002 - 915/1438

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.

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

Abbott Ex. 1002 - 916/1438

neutral species.

Example 2

Reduced Sensitivity to Interfering Species at Lower Biosensor Operating Potentials

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

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.

Abbott Ex. 1002 - 917/1438

What is claimed is:

1. A method for measuring the concentration of an analyte present in a biological system, said method comprising

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 said biological system, and

a sensing step in which the extracted sample is contacted with sensor means to obtain a measurement signal that is related to analyte concentration,

wherein said measurement cycle further comprises a process for selectively favoring 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 purge step which is performed after the sensing step, (e) a charge segregation step, and (f) any combination thereof.

2. The method of claim 1, wherein the differential signal process comprises:

(a) dividing the extracted sample into first and second sample portions;

Abbott Ex. 1002 - 918/1438

(b) contacting the first sample portion with said sensor means to obtain a first signal which predominantly comprises signal components due to interfering species and background variations;

(c) contacting the second sample portion with said sensor means to obtain the measurement signal which comprises analyte-specific signal components; and

(d) subtracting the first signal from the measurement signal to obtain a signal which is specifically related to the analyte.

3. The method of claim 2, wherein step (c) entails contacting the second sample portion with an enzyme which reacts with the extracted analyte to provide an analyte-specific signal.

4. The method of claim 3, wherein the enzyme is glucose oxidase and the analyte is blood glucose.

5. The method of claim 1, wherein the differential signal process comprises:

(a) extracting first and second samples in the extraction step, wherein at least the second sample contains extracted analyte;

(b) contacting the first sample with said sensor means to obtain a first signal which predominantly comprises signal components due to interfering species and background variations;

(c) contacting the second sample with said sensor means to obtain the measurement signal which comprises

Abbott Ex. 1002 - 919/1438

analyte-specific signal components; and

(d) subtracting the first signal from the measurement signal to obtain a signal which is specifically related to the analyte.

6. The method of claim 5, wherein step (c) entails contacting the second sample with an enzyme which reacts with the extracted analyte to provide an analyte-specific signal.

7. The method of claim 6, wherein the enzyme is glucose oxidase and the analyte is blood glucose.

8. The method of claim 1, wherein the selective electrochemical detection process comprises contacting the extracted sample with an electrochemical biosensor electrode which is maintained at a lowered potential in order to selectively detect analyte-specific signal components over signal components due to interfering species.

9. The method of claim 8, wherein the biosensor electrode is maintained at a potential of about 0.5V or less.

10. The method of claim 1, wherein the sample is extracted into a collection reservoir which is in operative contact with the sampling system.

11. The method of claim 10, wherein the sensor

Abbott Ex. 1002 - 920/1438

means comprises an electrochemical biosensor electrode which is in contact with the collection reservoir.

12. The method of claim 11, wherein the extraction and sensing steps are repeated while the sampling system is maintained in contact with the biological system to provide for continual or continuous measurement of the analyte.

13. The method of claim 12, wherein the purge step comprises operating the biosensor electrode for a sufficient period of time to substantially remove residual signal components from the collection reservoir after a sensing step has been carried out.

14. The method of claim 13, wherein the biosensor electrode is operated at a potential of about 0.6V or greater during the purge step.

15. The method of claim 1, wherein the analyte is transdermally extracted from the biological system using iontophoresis.

16. The method of claim 1, wherein the analyte is blood glucose.

17. The method of claim 1, wherein the extraction step comprises a charge segregation step wherein certain interfering species are preferentially collected at the anode.

Abbott Ex. 1002 - 921/1438

18. The method of claim 1, wherein said biological system includes skin, and said extracting of analyte from the biological system further comprises enhancement of skin permeability by pricking the skin with micro-needles.

19. A method for measuring the concentration of an analyte present in a biological system, said method comprising

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 said 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, wherein:

(a) the sampling system comprises (i) 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 said first sampling means and said first sensor element are in operative contact with the first collection reservoir; and (ii) 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 said second

Abbott Ex. 1002 - 922/1438

sampling means and said second sensor element are in operative contact with the second collection reservoir; and

(b) the measurement cycle comprises (i) operating the first iontophoretic sampling means as an iontophoretic cathode during a first phase of the extraction step, (ii) 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, (iii) purging residual signal from the sampling system in a purging step, (iv) operating the second iontophoretic sampling means as an iontophoretic cathode during a second phase of the extraction step, and (v) 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, wherein at least one of said first and second signals comprises an analyte-specific signal component.

20. The method of claim 19, wherein the first and second sensor elements are respectively first and second electrochemical biosensor electrodes.

21. The method of claim 20, wherein the second collection reservoir contains an enzyme which reacts with extracted analyte to provide an analyte-specific electrochemical signal component in the second signal.

22. The method of claim 20, wherein the second biosensor electrode is operated at a potential of about

Abbott Ex. 1002 - 923/1438

0.5V or less during the second phase of the sensing step.

23. The method of claim 19, wherein the purge step comprises operating the second biosensor electrode for a sufficient period of time to substantially remove signal components from the second collection reservoir.

24. The method of claim 23, wherein the second biosensor electrode is operated at a potential of about 0.6V or greater during the purge step.

25. The method of claim 19, wherein the measurement cycle further comprises a delay step between the second phase of the extraction step and second phase of the sensing step.

26. The method of claim 21, wherein the first collection reservoir does not contain the enzyme, the first signal predominantly contains signal components due to interfering species and background variations, and the first signal is subtracted from the second signal to obtain a signal which is specifically related to the analyte.

27. The method of claim 20, wherein the first and second collection reservoirs contain an enzyme which reacts with extracted analyte to respectively provide an analyte-specific electrochemical signal component in the first and second signals.

Abbott Ex. 1002 - 924/1438

28. The method of claim 19, wherein the measurement cycle is repeated at least once while the sampling system is maintained in contact with the biological system to provide for continual or continuous measurement of the analyte.

29. The method of claim 28 further comprising a second purging step for purging residual signal from the sampling system after step (e).

30. The method of claim 21, wherein the analyte is blood glucose and the enzyme is glucose oxidase.

31. The method of claim 27, wherein the analyte is blood glucose and the enzyme is glucose oxidase.

32. The method of claim 19, wherein the measurement cycle comprises a charge segregation step wherein certain interfering species preferentially collect at the anode.

33. The method of claim 19, wherein said biological system includes skin, and said extracting of analyte from the biological system further comprises enhancement of skin permeability by pricking the skin with micro-needles.

34. A method for measuring the concentration of an analyte present in a biological system, said method comprising:

(a) transdermally extracting the analyte from the

Abbott Ex. 1002 - 925/1438

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 said biological system, wherein 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;

(b) 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;

(c) contacting the analyte extracted into the first collection reservoir with sensing means in a sensing step to obtain an active signal;

(d) contacting the substances collected into the third collection reservoir with sensing means in the sensing step to obtain a blank signal; and

(e) subtracting the blank signal from the active signal to provide an analyte-specific signal.

35. A method for measuring the concentration of an analyte present in a biological system, said method comprising:

(a) transdermally extracting the analyte from the biological system in an extraction step using an

Abbott Ex. 1002 - 926/1438

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 said biological system, wherein said 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;

(b) contacting the analyte extracted into the first collection reservoir with sensing means in a sensing step to obtain an active signal;

(c) contacting the substances extracted into the second collection reservoir with sensing means in the sensing step to obtain a blank signal; and

(d) subtracting the blank signal from the active signal to provide an analyte-specific signal.

36. The method of claim 35, wherein the first collection reservoir contains an enzyme which reacts with extracted analyte to provide an analyte-specific signal.

37. A method for measuring the concentration of an analyte present in a biological system, said method comprising:

(a) transdermally extracting the analyte from the biological system in an extraction step using an

Abbott Ex. 1002 - 927/1438

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 said biological system, wherein said 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; and

(b) contacting the analyte extracted into the first and second collection reservoirs with sensing means in a sensing step to obtain multiple analyte-specific signals.

38. The method of claim 37, wherein the first and second collection reservoirs contain an enzyme which reacts with extracted analyte to provide an analyte-specific signal.

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

(a) iontophoretic sampling means for transdermally extracting the analyte from the biological system across a skin or mucosal surface of said biological system;

(b) sensing means in operative contact with the analyte extracted by the sampling means, wherein said sensing means obtains a detectable signal from the

Abbott Ex. 1002 - 928/1438

extracted analyte and said signal is specifically related to the analyte; and

(c) microprocessor means in operative communication with the sampling means and the sensing means, wherein said microprocessor means controls said sampling and sensing means to provide a measurement cycle in which analyte-specific signal components are detected in the substantial absence of signal components due to interfering species.

40. The sampling system of claim 39, wherein:

(a) said sampling system comprises (i) 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 said first sampling means and said first sensor element are in operative contact with the first collection reservoir; and (ii) 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 said second sampling means and said second sensor element are in operative contact with the second collection reservoir; and

(b) the microprocessor controls a measurement cycle which entails (i) operating the first iontophoretic sampling means as an iontophoretic cathode

Abbott Ex. 1002 - 929/1438

during a first phase of the extraction step, (ii) 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, (iii) purging residual signal from the sampling system in a purging step, (iv) operating the second iontophoretic sampling means as an iontophoretic cathode during a second phase of the extraction step, and (v) 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, wherein at least one of said first and second signals comprises an analyte-specific signal component.

41. The sampling system of claim 40, wherein the first and second sensor elements are respectively first and second electrochemical biosensor electrodes.

42. The sampling system of claim 41, wherein the second collection reservoir contains an enzyme which reacts with extracted analyte to provide an analyte-specific electrochemical signal component in the second signal.

43. The sampling system of claim 42, wherein the analyte is blood glucose and the enzyme is glucose oxidase.

44. The sampling system of claim 41, wherein the first and second collection reservoirs contain an enzyme

Abbott Ex. 1002 - 930/1438

which reacts with extracted analyte to respectively provide an analyte-specific electrochemical signal component in the first and second signals.

45. The sampling system of claim 44, wherein the analyte is blood glucose and the enzyme is glucose oxidase.

46. The sampling system of claim 39, 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.

47. Use of the sampling system of claim 40 to continually or continuously measure an analyte present in a biological system.

Abbott Ex. 1002 - 931/1438

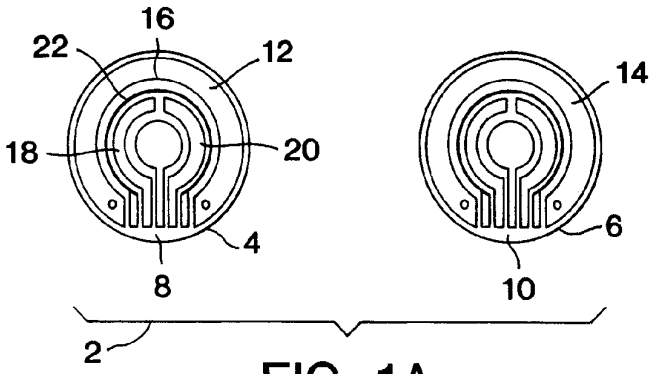


FIG. 1A

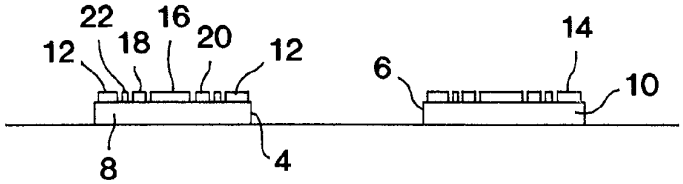


FIG. 1B

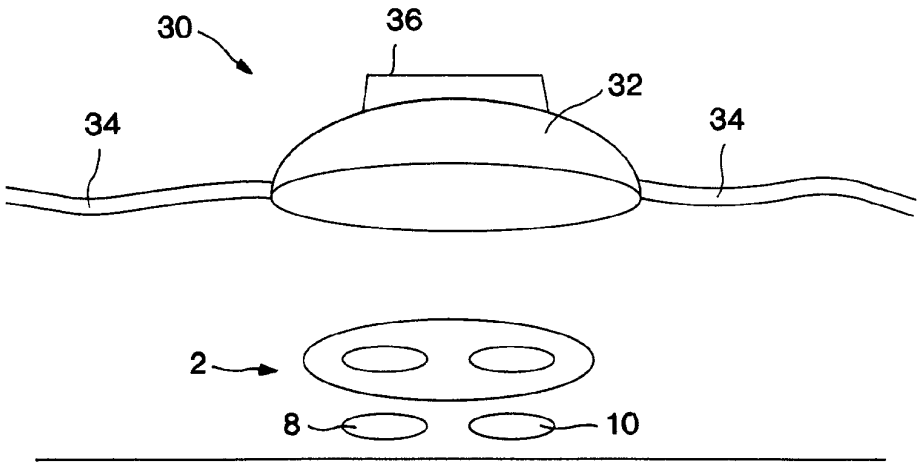


FIG. 2

Abbott Ex. 1002 - 932/1438

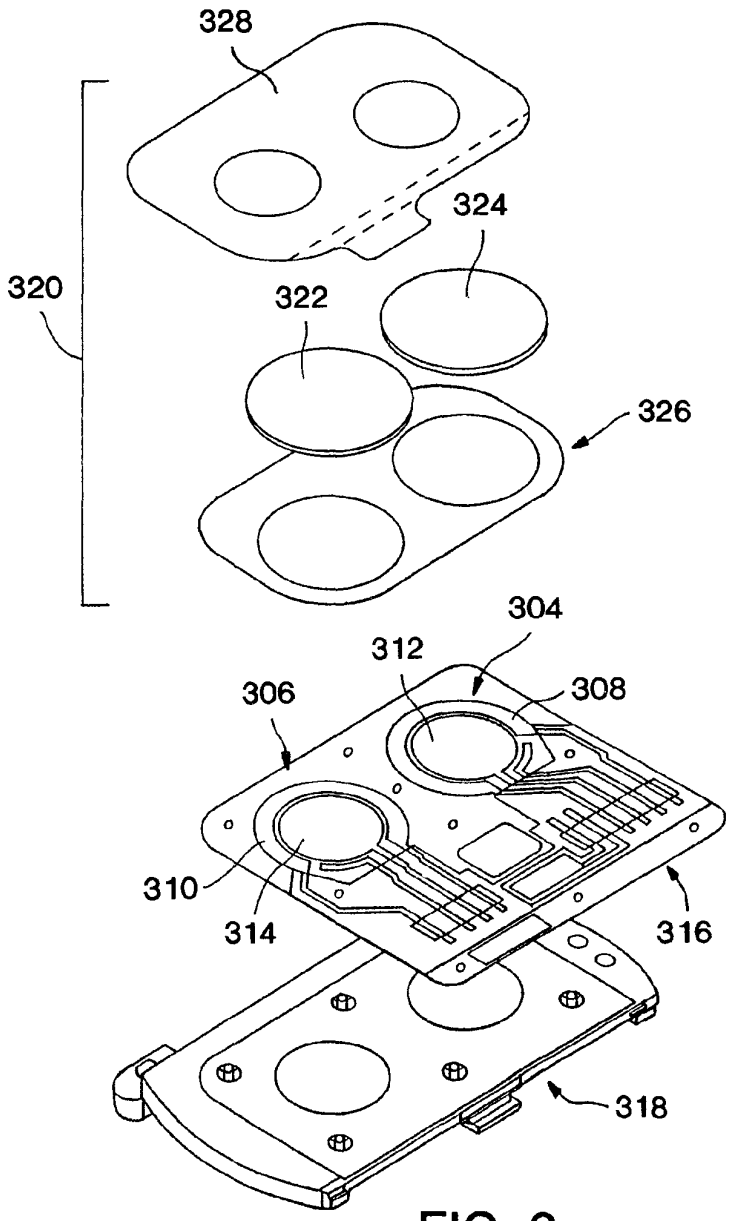


FIG. 3

Abbott Ex. 1002 - 933/1438

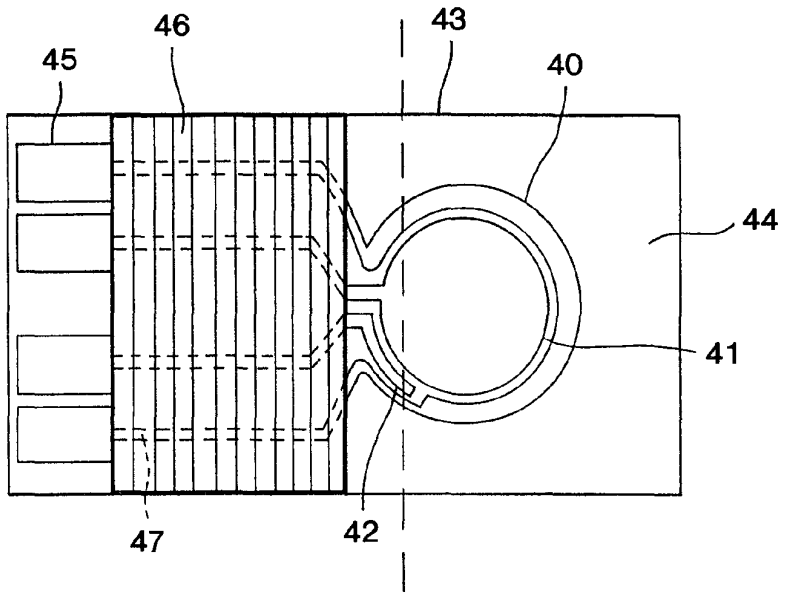


FIG. 4

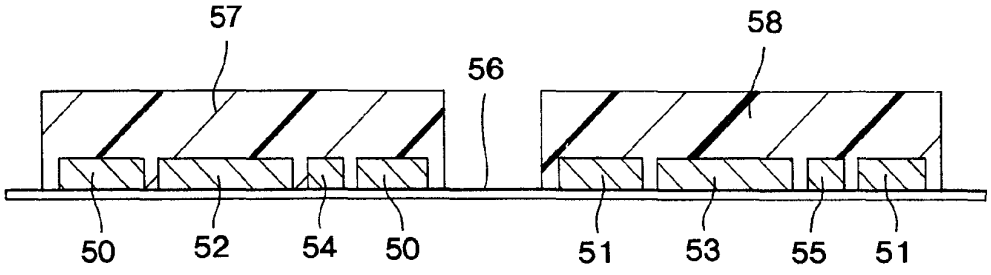


FIG. 5

Abbott Ex. 1002 - 934/1438

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 99/10380

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 00110 A (CYGNUS) 4 January 1996 (1996-01-04)	1,8, 10-12, 15,16, 39-47
A	the whole document	2-7, 18-21, 25,27, 28,30-38

A	WO 98 00194 A (SONTRA MEDICAL) 8 January 1998 (1998-01-08) page 18, line 11 - line 21	18,33

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 1999	06/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lemercier, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

Abbott Ex. 1002 - 935/1438

INTERNATIONAL SEARCH REPORT

formation on patent family members

Inter nal Application No
PCT/US 99/10380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600110 A	04-01-1996	AU 2944995 A	19-01-1996
		CA 2193885 A	04-01-1996
		EP 0766578 A	09-04-1997
		JP 10506293 T	23-06-1998
WO 9800194 A	08-01-1998	EP 0925088 A	30-06-1999

Abbott Ex. 1002 - 936/1438

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 October 2002 (24.10.2002)

PCT

(10) International Publication Number
WO 02/082989 A1

(51) International Patent Classification[7]: A61B 5/00

(21) International Application Number: PCT/US02/06831

(22) International Filing Date: 7 March 2002 (07.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/834,440 13 April 2001 (13.04.2001) US

(71) Applicant: **ABBOTT LABORATORIES** [US/US]; D-377 AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: **KHALIL, Omar, S.**; 1506 Portwine Ct, Libertyville, IL 60048 (US). **YEH, Shu-Jen**; 920 Stratford Ct, Grayslake, IL 60030 (US). **KANTOR, Stanislaw**; 485 Satinwood Terr, Buffalo Grove, IL 60089 (US). **HANNA, Charles, F.**; 410 W Lincoln, Libertyville, IL 60048 (US). **SHAIN, Eric, B.**; 459 Grove Street, Glencoe, IL 60022 (US).

(74) Agents: **WEINSTEIN, David, L.** et al.; D-377 AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

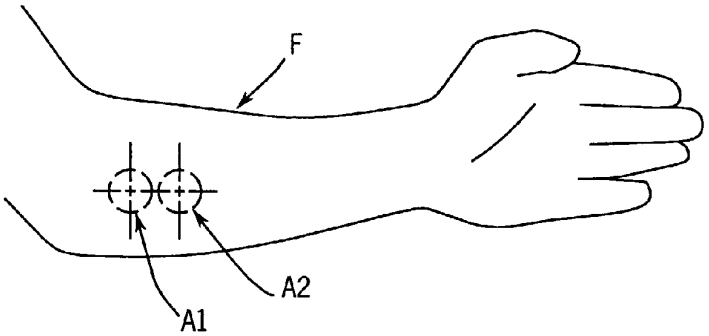
(81) Designated States *(national)*: CA, JP.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR OPTICAL MEASUREMENTS OF TISSUE TO DETERMINE DISEASE STATE OR CONCENTRATION OF AN ANALYTE



(57) Abstract: A method for collecting optical data at two morphologically similar, substantially non-overlapping, and preferably adjacent, areas on the surface of a tissue, while the temperature in each area is being maintained or modulated according to a temperature program. The optical data obtained are inserted into a mathematical relationship, e.g., an algorithm, that can be used to predict a disease state (such as the diabetes mellitus disease state) or the concentration of an analyte for indicating a physical condition (such as blood glucose level). This invention can be used to differentiate between disease status, such as, for example, diabetic and non-diabetic. The method involves the generation of a calibration (or training) set that utilizes the relationship between optical signals emanating from the skin under different thermal stimuli and disease status, e.g., diabetic status, established clinically. This calibration set can be used to predict the disease state of other subjects. Structural changes, as well as circulatory changes, due to a disease state are determined at two morphologically similar, but substantially non-overlapping areas on the surface of human tissue, e.g., the skin of a forearm, with each area being subjected to different temperature modulation programs. In addition to determination of a disease state, this invention can also be used to determine the concentration of an analyte in the tissues. This invention also provides an apparatus for the determination of a disease state, such as diabetes, or concentration of an analyte, such as blood glucose level, by the method of this invention.

WO 02/082989 A1

METHOD FOR OPTICAL MEASUREMENTS OF TISSUE TO DETERMINE DISEASE STATE OR CONCENTRATION OF AN ANALYTE

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to an apparatus and method for the non-invasive diagnosis of a disease state or the non-invasive determination of concentrations of analytes *in vivo*.

2. Discussion of the Art

Diabetes mellitus is a chronic systemic disease in which the body either fails to produce or fails to respond to the hormone insulin, which regulates the metabolism of glucose. It is estimated that there are 16 million diabetics in the United States and 100 million diabetics worldwide. The growth rate in the number of diabetics is estimated at 11.5% annually. The number of diabetics is estimated to be as high as 154 million worldwide by the year 2000 (H. King, R. E. Aubert, and W. H. Herman, "Global burden of diabetes, 1995 – 2025 prevalence, numerical estimates and projections" Diabetes Care 1998;21:1414), and to exceed 200 million worldwide by the year 2010. A large number of diabetics remain undiagnosed. A method for screening for diabetes would be beneficial for early diagnosis and for starting treatment and management well before the onset of complications.

Diabetes is frequently associated with microangiopathy. Microangiopathy results from the effect of diabetes on microcirculation, which involves the small blood vessels such as capillaries, venules, arterioles, and shunts. Microangiopathy can lead to micro-vessel complications such as neuropathy (nerve damage), retinopathy (eye damage), and nephropathy (kidney failure). The expression "diabetic angiopathy" deals with effect of diabetes on the arterial as well as the other elements of the vascular system such as venules, veins, and lymph subsystem. The relationship between diabetes and impaired circulation has been known in the medical art for the past two decades. Laser Doppler flowmetry has been used to diagnose peripheral vascular disease and vascular complications in diabetic patients. Impaired circulation is manifested by a decrease in

Abbott Ex. 1002 - 938/1438

cutaneous blood flow and a decrease in response to temperature changes, i.e., cooling or warming of the skin.

There is growing evidence that microcirculatory defects can be detected well before detection of fasting hyperglycemia, i.e. high blood glucose level for a fasting subject (N. Wiernsperger, Diabetologia 2000; 43; 1439-1449). Laser Doppler flowmetry and capillary microscopy studies have indicated microcirculation disturbances due to diabetes and have shown differences in cutaneous blood flow between diabetics and non-diabetics (S. B. Wilson, "Detection of microvascular impairment in type 1 diabetes by laser Doppler flowmetry, Clinical Physiology, 1992; 12; 195). In diabetic subjects, heating of a body part, or contralateral cooling of a body part, resulted in impaired blood flow, as measured by laser Doppler flowmetry (M. Rendell et al, "Microvascular blood flow, volume and velocity measurements by laser Doppler techniques in IDDM" Diabetes; 1989: 819-824). However, these studies of capillary blood flow and laser Doppler flowmetry were reported for advanced stages of diabetes (M Rendell et al, "Diabetic cutaneous microangiopathy" American Journal of Medicine 1992; 93: 611). Additionally, X-ray crystallographic studies showed differences in structure of tissues of diabetic subjects, due to cross-linking of collagen fibers resulting from glycation (V. J. James et al., "Use of X-ray Diffraction in Study of Human Diabetic and Aging Collagen", Diabetes, Vol. 40 (1991) 391-394).

Diabetes and certain other diseases cause structural changes to the skin that can affect the optical properties thereof, the response of these optical properties to changes in concentration of glucose or other analytes, and the response of these optical properties to cutaneous temperature changes. R. G. Sibbald et al., "Skin and Diabetes", Endocrinology and Metabolism Clinics of North America, Vol. 25, No. 2 (1996) 463-472, summarize a set of structural effects of the skin that are associated with diabetes. Included among these effects is thickened skin, which may relate pathophysiologically to accelerated collagen aging, with elastic fiber fraying and increased crosslinking, resulting from glycosylation of collagen fibers. Another effect of diabetes is "yellow skin", which also results from glycosylation of dermal collagen. Change in dermal collagen structure in diabetic patients has been also reported by V. M. Monnier et al., "Skin Collagen Glycation, Glycoxidation, and Crosslinking Are Lower in Subjects With Long-Term Intensive Versus Conventional Therapy of Type 1 Diabetes", Diabetes, Vol. 48 (1999) 870-880. Further, V. J. James et al., "Use of X-ray Diffraction in Study of Human Diabetic and Aging Collagen", Diabetes, Vol. 40 (1991) 391-394, shows that collagen skin fiber undergoes a structural change as a result of diabetes. The net effect of these

Abbott Ex. 1002 - 939/1438

findings is that there are structural differences, i.e., size, level of crosslinking, and distribution of collagen fibers, in the skin of diabetic subjects as compared with the skin of non-diabetic subjects. These differences result in a difference in the scattering characteristics of the skin of diabetic subjects.

In order to understand the effect of the structural differences between the skin of diabetics and that of non-diabetics on the measured optical signals, it is useful to examine the scattering of light in human tissue.

The scattering of light by human tissue can be approximated by an equation that expresses the reduced scattering coefficient μ'_s for a tissue or a turbid medium as:

$$\mu'_s = 3.28\pi a^2 \rho (2\pi a n_{medium}/\lambda)^{0.37} (m-1)^{2.09} \qquad (1)$$

where "a" represents the average cell diameter, ρ represents the number concentration of cells, "n_{medium}" represents the refractive index of interstitial fluid, λ represents the wavelength, and m represents the ratio of the refractive index of the cells to that of the interstitial fluid ($m = n_{cells}/n_{medium}$). The scattering coefficient changes as cell size "a" or refractive index "n_{medium}" change. Temperature can affect the scattering coefficient by a change in cell diameter "a", a change in the number concentration of cells ρ, or a change in the refractive index mismatch "m". Because the diabetic status is independent of glucose concentration, i.e., a diabetic patient can have high or low blood glucose level, it is possible to assume that the diabetic status is independent of "m". However, differences in crosslinking of collagen for diabetics may lead to a different range for the dimensional parameter "a" between the diabetic and the non-diabetic groups. Differences in the variable "a" will lead to a difference in the scattering characteristics of the skin of diabetic subjects, because the scattering characteristics affect the term "a" in Equation (1). Thus, the response of the scattering coefficient to changes in glucose concentration, or other concentrations of analytes, and the response of the scattering coefficient to cutaneous temperature changes are expected to be different for diabetic subjects as compared to those responses of the same parameters determined for non-diabetic subjects.

Scattering properties of tissue can vary with temperature as a result of one or more of the following changes:

(a) an increase in temperature can decrease the refractive index of interstitial fluid and increase the scattering coefficient of tissue;

Abbott Ex. 1002 - 940/1438

(b) an increase in temperature can change the refractive index of cell membranes;

(c) an increase in temperature can increase cell size, and hence, can increase the scattering coefficient.

In the case of (a) or (b), an increase in the refractive index mismatch "m" in Equation (1), which increases as the temperature increases, can also increase the scattering coefficient.

Methods of diagnosing diabetes typically require a large number of laboratory tests, such as, for example, successive blood glucose level measurements while the patient is in a fasting state, determination of serum glycated hemoglobin HbA1c, and oral glucose tolerance (or meal tolerance) tests. These tests are usually performed after clinical symptoms of diabetes are observed. These symptoms include thirst, fatigue, and frequent urination (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Diabetes Care 1997; 20:117-135). The use of a glycated hemoglobin test has been equivocal in diagnosing diabetes, even though it is time-consuming and requires drawing of blood. See C. L. Rohlfing et al., "Use of HbA1c in screening for undiagnosed diabetes in US population", Diabetes Care 2000; 23: 187-191.

A non-invasive test for screening diabetics will save a great number of laboratory tests and will allow screening larger populations, even if clinical symptoms of diabetes are not evident. A non-invasive test will also allow early diagnosis and subsequent control of diabetes, which in turn will delay the onset of complications from diabetes. If uncontrolled, diabetes can result in a variety of adverse clinical manifestations, including retinopathy, atherosclerosis, microangiopathy, nephropathy, and neuropathy. In its advanced stages, diabetes can cause blindness, coma, and ultimately death.

Non-invasive determination of glucose has been the subject of several patents. U. S. Patent Nos. 5, 082,787; 5,068,536; 5,077,476; 5,086,229; 5,204,532; 5,237,178; 5,362,966 describe transmission measurements through the finger. U. S. Patent Nos. 5,321,265; and, US 5,434,412 describe Kromoscopic methods for the determination of glucose. U. S. Patent Nos. 5,492,118 and 5,551,422 describe measurements based on light scattering. United States Patent Nos. 4,655,225; 4,882,492; 5,460,177; 4,975,581 describe methods for the detection of glucose with light of long wavelength (> 1100 nm) where glucose does, presumably, have stronger absorption bands. United States Patent Nos. 5,009,230; 4,975,581; 5,379,764; 4,655,225; 5,893,364; 5,497,769; 5,209,231; and

Abbott Ex. 1002 - 941/1438

5,348,003 describe a variety of optical methods for the non-invasive determination of blood glucose level in the human body.

U. S. Patent No. 5,362,966 describes measurement of finger temperature away from the optical measurement area. WO 95/04924 describes a near infrared non-invasive measurement instrument, where light is introduced and measured at an extremity, such as a finger tip, while the temperature of the same extremity is measured at another location remote from the location of the optical measurement area. The temperature value measured is used in the calculation algorithm together with the optical data to determine the concentration of an analyte. The temperature at the measurement site is not controlled or varied according to a preset program. U. S. Patent No. 5,551,422 describes a glucose sensor that is brought to a specified temperature, preferably somewhat above the body normal temperature, with a thermostatically controlled heating system. U. S. Patent No. 5,666,956 describes a method for the determination of glucose from the infrared emission of the tympanic membrane. U. S. Patent No. 5,978,691 describes a method of measuring changes in molecular behavior, induced by a change in thermal energy, to facilitate the measurement of physiological parameters in blood.

U. S. Patent No. 5,844,239 describes a fiber-optics-based optical device for determination of the optical properties at a shallow depth in a tissue. The sensor comprises several unit fiber bundles. Each unit fiber bundle has a light introduction fiber and several light collection fibers arranged in concentric rings. Signals from each group of fibers at the same distance are detected to enhance the signal to noise ratio. Further, signals from the plurality of unit bundles are added up, or averaged, to further improve the signal to noise ratio. The temperature is not controlled at the positions where the unit bundles contact the skin. The temperature is not varied according to a preset program.

U. S. Application Serial No. 09/080,470, filed May 18, 1998, assigned to the assignee of this application, describes a sensor employing a temperature control for non-invasive determination of blood glucose level. U. S. Application Serial No. 09/098,049, filed November 23, 1998, assigned to the assignee of this application, describes methods for determining optical properties of tissue having a plurality of layers non-invasively. Both applications disclose the use of a temperature controllable optical element that contacts the skin.

Cutaneous microcirculation occurs at depths of 1 to 2 mm below the epidermal surface of the skin (I. M. Braverman, "The Cutaneous Microcirculation: Ultrastructure and

Abbott Ex. 1002 - 942/1438

Microanatomical Organization", Microcirculation (1997) Vol. 4, No. 3, 329-340). Thus, measurement of optical properties of skin close to the surface thereof can provide useful information on the effect of blood circulation on the concentration of metabolites in tissues that are close to the surface of the skin. Also, studies of blood circulation close to the surface of the skin by means of laser Doppler flowmetry (referred to as LDF herein) have shown that laser Doppler flowmetry is a good tool for diagnosing peripheral circulatory disease. Laser Doppler flowmetry (LDF) measurements are restricted to the top-most layer of the skin (≈ 200 microns) because the beam loses its coherence due to scattering. Temperature dependence of laser Doppler flowmetry studies does not incorporate structural changes in the skin due to diabetes. Thus, a deficiency in the LDF prior art is the lack of inclusion of temperature dependence of scattering in the classification and diagnosis of diabetes complications.

Although a variety of detection techniques have been disclosed in the art, there is still no commercially available device that provides reliable non-invasive measurements of blood glucose level. As a result, current approaches to non-invasive metabolite testing, such as glucose monitoring, have not achieved wide acceptance.

SUMMARY OF THE INVENTION

This invention provides a method for collecting optical data at two morphologically similar, substantially non-overlapping, and preferably adjacent, areas on the surface of a human tissue, while the temperature in each area is being maintained or modulated according to a temperature program. The optical data obtained are inserted into a mathematical relationship, e.g., an algorithm, that can be used to predict a disease state (such as the diabetes mellitus disease state) or the concentration of an analyte for indicating a physical condition (such as blood glucose level).

This invention can be used to differentiate between disease status, such as, for example, diabetic and non-diabetic. The discovery underlying the method of this invention is that certain optical properties of human tissue change in response to changes in temperature of the tissue. The method involves the generation of a calibration (or training) set that utilizes the relationship between optical signals emanating from the skin under different thermal stimuli and disease status, e.g., diabetic status, established clinically. This calibration set can be used to predict the disease state of other subjects. Because thermal stimuli affect microcirculatory action within the

Abbott Ex. 1002 - 943/1438

capillary loops, the method depends upon measuring the optical properties of the tissue at different areas on the surface of the tissue, to a depth of up to two millimeters, as a function of thermal stimuli. Structural changes, as well as circulatory changes, due to a disease state are determined at two morphologically similar, but substantially non-overlapping areas on the surface of human tissue, e.g., the skin of a forearm, with each area being subjected to different temperature modulation programs. In addition to determination of a disease state, this invention can also be used to determine the concentration of an analyte in a human tissue. This invention also provides an apparatus for the determination of a disease state, such as diabetes, or concentration of an analyte in a human tissue, such as blood glucose level, by the method of this invention.

In one aspect, this invention provides a method for determining a disease state of a subject. The method comprises the steps of:

(a) measuring at least one optical property at a first area on a human tissue to obtain a first set of data, the first area being subjected to a first temperature program;

(b) measuring at least one optical property at a second area on the human tissue to obtain a second set of data, the second area being subjected to a second temperature program, the second temperature program being different from the first temperature program, the second area being morphologically similar to but not substantially overlapping with the first area;

(c) inserting the first set of data and the second set of data into a mathematical relationship to calculate a mathematical output; and

(d) comparing the mathematical output to a category selector to determine the disease state of the human.

The mathematical relationship is typically established by correlating the parameter with the disease state, which is determined by invasive methods. As used herein, the expression "disease state" means the status of a subject having an abnormal cardiovascular condition, a neoplasmic condition, or other disease that affects the tissues. A representative example of a disease state is diabetes. The thus-established mathematical relationship can be used to determine the disease state of a subject.

In another aspect, this invention provides a method for determining the concentration of an analyte in a tissue of a subject. The method comprises the steps of:

Abbott Ex. 1002 - 944/1438

(a) measuring at least one optical property at a first area on the tissue to obtain a first set of data, the first area being subjected to a first temperature program;

(b) measuring at least one optical property at a second area on the tissue to obtain a second set of data, the second area being subjected to a second temperature program, the second temperature program being different from the first temperature program, the second area being morphologically similar to but not substantially overlapping with the first area; and

(c) inserting the first set of data and the second set of data into a mathematical relationship to calculate the concentration of the analyte.

The mathematical relationship is typically established by correlating the parameter with the concentration of the analyte, which is determined by invasive methods. The thus-established mathematical relationship can be used to determine the concentration of the analyte in the tissue of a subject.

In another aspect, this invention provides an apparatus for carrying out the method of this invention. The apparatus comprises:

(a) means for illuminating at least two areas of tissue with light;

(b) means for collecting light re-emitted from the at least two areas of tissue;

(c) means for measuring the intensity of the re-emitted light collected at the two areas of tissue; and

(d) means for controlling the temperature of the at least two areas of the tissue simultaneously by means of temperature programs.

One embodiment of this invention involves a method for non-invasive diagnosis of a disease state, such as, for example, diabetes, or the concentration of an analyte, such as, for example, blood glucose level.

The measurements at the first area and at the second area can be made simultaneously. Alternatively, the measurements at the first area and at the second area can be made sequentially.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 Illustrates measurement areas on a human forearm.

Abbott Ex. 1002 - 945/1438

FIG. 2 is a schematic diagram illustrating a device suitable for use in this invention. The device employs one optical head and is suitable for sequential measurements. The portion of the device that contacts a body part is shown as a cross-section.

FIG. 3 is a schematic diagram illustrating a device suitable for use in this invention. The device employs two optical heads and is suitable for simultaneous measurements. The portion of the device that contacts a body part is shown as a cross-section.

FIG. 4 is a schematic diagram illustrating a device suitable for use in this invention. The device employs one optical head and is suitable for sequential measurements. The portion of the device that contacts a body part is shown as a cross-section. The device of FIG. 4 is a variation of the device shown in FIG. 2.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the expression "optical properties" refers to the absorption, scattering, emission, reflectance, and depolarization properties of biological tissues. The expression "optical parameter" refers to a parameter that describes and defines an optical property of a medium and its components. Examples of optical parameters include, but are not limited to, absorption coefficient, scattering coefficient, and extinction coefficient of analytes. The expression "scattering media" refers to media that both scatter light and absorb light. The expression "absorption coefficient" (i.e. μ_a) refers to the probability of light absorption per unit path length, which is equal to 2.303 εC in cm^{-1}, where, ε is molar extinction coefficient and C is the molar concentration. The expression "reduced scattering coefficient" (i.e. μ_s') refers to the probability of equivalently isotropic (uniform in all directions) scattering per unit path length, which is equal to $\sigma\rho$ in cm^{-1}, where, σ is scattering cross section and ρ is the number density of scattering centers. The expression "light penetration depth" (i.e. δ) refers to the rate of decay of intensity of light in scattering media with respect to the path traveled by the light in the same direction as the incident light. Light penetration depth represents the depth at which light intensity in the tissue is attenuated to 1/e of its original value and is related to the absorption and scattering coefficients as $\delta = 1/\sqrt{(3\,\mu_a(\mu_a + \mu_s'))}$.

Abbott Ex. 1002 - 946/1438

The expression "diffuse reflectance" (reflectance therein unless specified otherwise) refers to measurement of light that is re-emitted from a sample at all angles different from the direction of the incident light, and over an area wider than the area where the incident light is introduced into the sample. The expressions "spatially resolved scattering" or "spatially resolved diffuse reflectance" and "localized reflection" refer to a measurement of light that is re-emitted from a sample and collected at several light collection sites at specific distances from a light introduction site. Alternatively, these expressions can refer to the light collected at a given light collection site on the sample boundary as a result of introducing light at discrete light introduction sites located on the same boundary at a set of defined distances from the light collection site. In both instances, μ_a and μ'_s are calculated from the intensity distribution of the re-emitted light with respect to distances, i.e., the re-emitted light intensity at a multiplicity of sampling distances. The expressions "re-emitted light" and "reflected light" are used synonymously herein, as are the expressions "reflectance" and the "intensity of re-emitted light", unless otherwise indicated.

The expression "light introduction site" means a location on the surface of a sample, e.g., a body part, tissue, or the like, at which light is injected or introduced into the sample, by means of, for example, an optical fiber. The source of the light can be located at the light introduction site or can be located remote from the light introduction site. If the source of light is located remote from the light introduction site, the light must be transmitted to the light introduction site by light transmitting means, such as, for example, optical fibers. The expression "light collection site" means a location on the surface of a sample, e.g., a body part, tissue, or the like, at which light that is re-emitted from the sample is collected for measurement. The detector, which determines the intensity of the re-emitted light, can be located at the light collection site or can be located remote from the light collection site. If the detector is located remote from the light collection site, the light must be transmitted to the detector by light transmitting means, such as, for example, optical fibers. The distance between a light introduction site and a light collection site, as measured along the surface of a sample, is defined as the "sampling distance". For a given sample, the sampling distance determines the mean distance from the surface of the sample into the interior of the sample at which the scattering and absorption events contribute to the measured re-emitted light. Such mean distance is hereinafter referred to as the "sampling depth", which is a function of the sampling distance. In this invention an "area on the surface of the tissue" may have

Abbott Ex. 1002 - 947/1438

multiple light introduction sites, multiple light collection sites, at least one sampling distance and at least one sampling depth and its optical properties are affected an independently-run temperature program. The expression "temperature program" refers to a sequence of temperature levels as a function of time. Examples of temperature programs include, but are not limited to, (1) maintaining a constant temperature over a period of time; (2) decreasing temperature over a period of time; (3) increasing temperature over a period of time; and (4) combinations of (1), (2), and (3). The expression "not substantially overlapping" means that the areas subjected to temperature programs can overlap slightly so long as the temperature programs to which the areas are subjected are distinguishable. However, it is preferred that the areas that are subjected to the temperature programs not overlap.

The expression "blood flow" means the velocity of red blood cells in blood vessels. Blood flow is usually measured by laser Doppler flowmetry. The term "vasodilatation" refers to the increase in diameter of a blood or lymph vessel by the action of a nerve. A chemical agent such as insulin or increasing tissue temperature can induce vasodilatation. The term "microcirculation" refers to the movement of blood in capillaries, arterioles, and venules as a result of constriction and relaxation of vessel walls. The term "artery" means a blood vessel that conducts blood from the heart to tissues and organs. Arteries are lined up with smooth flat cells (endothelium) and are surrounded by thick muscular elastic walls containing fibrous tissue. Arteries branch repeatedly until their diameter is less than 300 microns; these small-branched arteries are called "arterioles." Walls of arterioles are formed from smooth muscle. The function of arterioles is to control blood supply to the capillaries. The term "capillary" refers to a minute hair-like tube (5-20 microns in diameter) having a wall consisting of a single layer of flattened cells (endothelium). Capillary walls are permeable to water, oxygen, glucose, amino acids, carbon dioxide and inorganic ions. The capillaries form a network in all tissues. They are supplied by oxygenated blood by the arterioles and pass deoxygenated blood to the venules.

A "vein" is a blood vessel that conducts blood from the tissues and organs back to the heart; the vein is lined with smooth flat cells (endothelium) and is surrounded by muscular and fibrous tissue. Walls of veins are thin and the diameter of veins is large compared with the diameter of arteries. The vein contains valves that allow unidirectional flow of blood to the heart. A "venule" is a small vein that collects blood from capillaries and joins other venules to form a vein. A venule has more connective tissue than a capillary, but has similar small molecules permeability as a capillary.

Abbott Ex. 1002 - 948/1438

Arterioles and venules are connected through the capillary loop or through shunts. The term "shunt" refers to a passage or a connection (anastomosis) between two blood vessels. An arteriovenous shunt is a passage of blood from an artery (or arteriole) to a vein (or venule) that does not go through the capillary loop. The term "plexus" refers to a braid of blood vessels. In the skin, the "upper plexus" or the "superficial plexus" refers to the braid of arterioles and venules found at the top layer of the dermis. The "lower plexus" or deep plexus" refers to the braid of arterioles and venules that found at the lower layer of the dermis. Each of the braids is referred to as a "vascular plexus" and both are interconnected. Arterioles, venules, capillary loops, the upper plexus and the lower plexus comprise the microvasulature system and are responsible for controlling skin temperature and the flow of blood and nutrients to the skin and disposal of metabolic products from the skin.

FIG. 1 shows a human forearm "F", on which are marked of two morphologically similar, substantially non-overlapping areas "A1" and "A2" on the surface of the tissue. The two areas are selected to have similar morphology (such as the presence of hair, bone, appearance of veins). While not required, it is preferred that the areas be adjacent. Each area is subjected to a temperature program to induce optical changes, which result from changes in absorption and scattering properties of the tissue. The temperature programs are not identical. Changes in absorption properties of the tissue can be induced by changes in microcirculation, while changes in scattering properties of the tissue can be induced by changes in the refractive index mismatch between the scattering centers in the tissue and the fluid medium surrounding these centers. This mismatch is caused by changes in temperature.

FIG. 2 illustrates an embodiment of a device suitable for use in this invention. This device can be used to subject two morphologically similar, non-overlapping areas on the surface of human skin to different temperature programs while optical measurements are made at these two morphologically similar, non-overlapping area on the surface of human skin. The device is similar to that described in WO 99/59464, which is incorporated herein by reference. As shown schematically in FIG. 2, the device 10 comprises a light source module 12, a human interface module 14, and a signal detection module 16. The human interface module 14 has a single optical head. As will be described later, different embodiments may have a plurality of optical heads. These three modules are interconnected through a branched optical fiber bundle 18. The light source module 12 comprises four light emitting diodes (LED's) 20, 22, 24, and 26, by means of which the output of light can be modulated. The LED's are mounted in a

Abbott Ex. 1002 - 949/1438

circular holder 28 and the light from the LED's is collected and then transferred onto an end 30 of an illuminating element 32 by means of a lens assembly 34, e.g., a 28 mm focal length RKE precision eyepiece (Edmund Scientific part No 30787). Each LED is modulated at a different frequency. A portion of the light is diverted by a beam splitter 36 and focused onto a silicon photodiode 38 (Model S-2386-44K 6C, Hamamatsu, Hamamatsu City, Japan) and a pre-amplifier 40 to generate a reference signal, which is used to correct for fluctuations in intensity of the source of light. The remainder of the light beam continues onto the end 30 of the illuminating element 32 housed at the source tip 42 of a fiber bundle 44.

An end 45 of the illuminating element 32 and the ends of the light collecting elements 46, 48, 50, and 52 are mounted in a common tip 54, which is situated at the center of a temperature-controlled disc 56 (2-cm diameter). The common tip 54 and the temperature-controlled disc 56 are parts of the human interface module 14. All of the elements 32, 46, 48, 50, and 52 are fibers made of low OH silica, and each has a diameter of 400 μm (Fiberguide Industries, Stirling, NJ). The light re-emitted from the skin is collected by the light collecting elements 46, 48, 50, and 52 and transmitted to the signal detection module 16. A detector 60, e.g., a quadrant silicon photodiode detector (Advanced Photonics, P/N SD225-2321-040), located in the signal detection module 16 measures the intensity of light transmitted from the four light collecting elements 46, 48, 50, and 52. The distal end of each light collecting element is located in a detection tip 62.

The body interface module 14 of the device 10 can be mounted on a cradle (not shown) that is, in turn, mounted on an arm of a standard clinical reclining chair (not shown). The subject sits in the chair so that the forearm of the subject rests on the cradle. The optical head of the device, which is located in the body interface module 14, is pressed against the dorsal side of the subject's forearm at a constant force of, for example, 160 grams (approximately 45 grams per cm^2). Other means of placing the forearm of the subject in contact with the optical head of the device can also be used. A thermoelectric cooling/heating element 64 (Model SP1507-01AC, Marlow Industries, Dallas, TX) and a controller/power supply unit 66 (Marlow Industries, SE5000-02) controls the temperature of the disc 56, which is placed in contact with the skin of the forearm. A thermocouple (or thermistor) 68 has the function of sensing the temperature in the aluminum disc 56 and providing a feedback to the temperature controller 66. A personal computer employing LabView™ (version 5.1, National Instruments, Austin, TX)

Abbott Ex. 1002 - 950/1438

software program sets the temperature of the disc 56 by means of the controller 66. The personal computer and its accompanying software also manage the acquisition of data.

Light from the illuminating element 32 enters the skin through a body interface module 58 attached on the arm of the reclining clinical chair. The signals from four of the light collecting elements 46, 48, 50, and 52 are transmitted to the detector 60 (Advanced Photonics, P/N SD225-2321-040), one signal to each quadrant of the detector 60. The signal from each quadrant of the detector 60 is amplified separately by an amplifier 70 and measured by means of a multimeter (Model No. 3458A, Hewlett-Packard, Palo Alto, CA). The optical signals are collected and integrated every 30 seconds, because of the limitations of the data transfer rate between the multimeter and the personal computer.

A calibration algorithm is used to correct for fluctuation in the intensity and spectral output of the LED's, spectral response of the detector, relative light throughput of the illuminating element and each light collecting element, and dark current of the detection system (i.e., the current of the detection system when the light source is turned off). Accordingly, the magnitude of the reflectance signal thus obtained differs from its true value only by a common multiplicative factor that is unique for each set of elements, detector, and type of lamp.

The device in FIG. 2 has a single optical head; the device is capable of providing a defined temperature program while optical measurements are being made. In order to carry out the method of this invention, the optical head of the device is brought in contact with the tissue (e.g., human skin) at a first area thereof. A first defined temperature program is run while optical measurements are being made. The arm is moved to allow the device to contact the second area of the tissue, whereat a second defined temperature program is run while optical measurements are being made. In other words, the two areas are contacted sequentially, and the two optical measurements are made sequentially.

FIG. 3 illustrates a device having two optical heads, each optical head capable of providing a defined temperature program while optical measurements are being made. The two optical heads of the device are mounted on a common bracket (not shown). The two optical heads are applied to the skin of the forearm of the subject in the same way as is the device having the single optical head described previously. A constant force spring is used to maintain the optical heads in contact with the forearm. The spring force applied is typically about 200 grams, although the precise amount of force is not critical to the operation of the invention.

Abbott Ex. 1002 - 951/1438

Referring now to FIG. 3, a device 100 can be brought into contact with a body part 102 at two test areas 104, 106 on the body part 102. The device comprises two optical heads, which in turn comprise aluminum discs 108, 110, the temperatures of which can be controlled, and thermoelectric cooling/heating elements 112, 114. The temperature of each disc 108, 110 at each head is controlled by thermoelectric cooling/heating elements 112, 114. The thermoelectric cooling/heating elements 112, 114 (Model SP1507-01AC, Marlow Industries, Dallas, TX) and controller/power supply units 116, 118 (Marlow Industries, SE5000-02) control the temperature of the discs 108, 110, which are placed in contact with the skin, through power inputs from temperature controllers 116, 118. A thermocouple (or thermistor) 120, 122 has the function of sensing the temperature in each aluminum disc 108, 110 and providing a feedback to the temperature controller associated with the particular disc.

The optical heads also include illuminating fibers 124, 126. Light emitted from the skin is collected by fiber groups 128, 130 and fed into detector 132, which also contains electronics to amplify the signal collected from the first area, and detector 134, which also contains electronics to amplify the signal collected from the second area . Light source electronics 140 provide power to operate the light sources of the optical head that is in contact with the first area. In the same manner, light source electronics 142 provide power to operate the light sources of the optical head that is in contact with the second area. A microprocessor/computer 150 controls the temperature controllers 116, 118, light source electronics 140, 142, and signal amplification electronics 132, 134 through cables/connectors 152, 154, 156, 158, 160, and 162. When this device is brought in contact with the tissue, the two optical heads contact the tissue at the two areas simultaneously. The two temperature programs and the measurements accompanying them can be run simultaneously.

Thus, the method of this invention can be characterized as a method in which optical signals are collected at two morphologically similar, non-overlapping, preferably adjacent, areas as the temperature in each area is being maintained or modulated according to a temperature program. The measured values derived from the optical signals obtained are inserted into an algorithm that can be used for predicting a disease state (such as the diabetes mellitus disease state) or into an algorithm that can be used for determining the concentration of a substance in the body, such as blood glucose level.

Abbott Ex. 1002 - 952/1438

When the optical measuring device is brought in contact with the skin or another tissue, several phenomena are observed with respect to the optical signal. In the case of skin, we have discovered that when light is introduced into the skin by an optical measuring device in contact with the skin and the intensity of light transmitted or reflected from the skin is measured, the optical signal measured follows a definite course over time. First, a sharp change in signal is observed over a time period of from about 1 to about 30 seconds. This change is manifested as a decrease in reflectance as a function of time. This decrease is the largest component of the signal change. The magnitude of the decrease varies with the geometry of the optical measuring device, the pressure imparted on the skin, and the nature of the skin of the individual. The change in optical signal as a function of time can be attributed to conformance of the skin, especially the stratum corneum, to the shape of the measuring device.

Second, a decrease in the intensity of reflected light or scattered light appears as a function of time. This decrease takes place over a longer time period, extending over minutes, and exhibits a more gradual slope than does the initial decrease. An increase in glucose concentration in the skin leads to a decrease in the reflected signal in a scattering measurement. An increase in glucose concentration also leads to a decrease in the scattering coefficient of skin. The change in the scattering coefficient is estimated to be $1x10^{-4}$ per mM of glucose. The change in optical signal due to the initial interaction of the device or the mechanical compression of tissue is in the same direction as the effect of increasing glucose concentration, but is at least ten times greater than the increase that can be attributed to a change in glucose concentration.

Third, the difference between the temperature of the measuring device and the temperature of the skin causes a drift in the optical signal over time. If the measuring device is at a temperature higher than that of the skin, heat will flow from the device to the skin, thereby leading to an increase in temperature of the skin and, hence, an increase in scattering coefficient and the intensity of reflected light, as described in U. S. Serial No. 09/419,461, filed October 15, 1999. On the other hand, if the measuring device is at a temperature lower than that of the skin, heat will flow from the skin to the device. This flow of heat will lead to a temporary decrease in the temperature of the skin, a decrease in the scattering coefficient, and a concomitant decrease in intensity of reflected light.

Finally, changes in the surface and subsurface structure of the tissue as a function of time will also affect the optical signal. Thus, opening and closing of arterio-

Abbott Ex. 1002 - 953/1438

venous shunts, movement of interstitial fluid, etc., will lead to a slow change in the measured optical signal.

The method of this invention provides optical measurements along with controlled temperature changes of the cutaneous vascular bed, thereby allowing tracking of microvascular defects and cutaneous structural differences. This tracking is achieved without inconvenience to the subject, such as may be encountered in contralateral cooling of the arm or heating to 44 °C, as in capillary video microscopy. The method of this invention can also eliminate the need for physical movement, such as sitting and standing, during the measurement.

The two-area measurement accompanied by temperature programming corrects for the spontaneous change in optical signal (drift) resulting from the interaction between the probe and skin, during the measurement.

The optical measurements required in this invention can be measurements of diffuse reflectance or spatially resolved diffuse reflectance. Transmission measurements can be used with the method of this invention, when the optical device is applied to a thin body part where temperature can be controlled and varied over the volume interrogated by the light beam. The ear lobe or the webs between the fingers are potential sites for transmission measurements.

One aspect of this invention is the determination of the disease state , e.g., diabetic status, of a subject. A mathematical function can be derived from optical signals at two areas of the tissue (e.g., skin), wherein the temperature is controlled at each area by means of temperature programs. A temperature program can specify a constant temperature value, a set of decreasing temperature values, a set of increasing temperature values, or a set of temperature values that increase and decrease over the given period of time. One such function is expressed by Equation (2) as:

$$f(R_{A1T1}, R_{A1T2}, R_{A2T3}, R_{A2T4}) = [\mathrm{Ln}\ (R_{A1T1}/R_{A1T2})] - [\mathrm{Ln}\ (R_{A2T3}R_{A2T4})] \qquad (2)$$

where

R_{A1T1} represents the measured light intensity at temperature T_1 at the first area of skin,

R_{A1T2} represents the measured light intensity at temperature T_2 at the same first area of the skin,

R_{A2T3} represents the measured light intensity at temperature T_3 at a second area of the skin, and

Abbott Ex. 1002 - 954/1438

R_{A2T4} represents the measured light intensity at temperature T_4 at the same second area of the skin.

T_1 and T_2 represent the limits of the first temperature program. T_3 and T_4 represent the limits of the second temperature program. The temperature program in the first area should differ from the temperature program in the second area. Otherwise, the measurements are merely repetitive.

The derived function(s) $f(R_{A1T1}, R_{A1T2}, R_{A2T3}, R_{A2T4})$, determined at a plurality of sampling distances and at a plurality of wavelengths, and the known disease states, e.g., diabetic or non-diabetic, of each of a set of subjects (i.e., the calibration set) can be processed to generate a discriminant function D. Discriminant functions are used in the art of pattern recognition. See for example Duda and Hart, Pattern Classification and Scene Analysis, John Wiley & Sons (1973), pages 17 to 20, and pages 130 to 138, which pages are incorporated herein by reference. The discriminant function is a decision rule for categorizing objects, in this case placing diabetic subjects and non-diabetic subjects in their respective categories. A subject is classified as diabetic if $D > 0$, and non-diabetic if $D < 0$. As used herein, the decision rule for categorizing objects has been referred to as a "category selector."

The true disease state must, of course, be known in order to utilize optical measurements for the calibration set. D is typically a quadratic expression comprising a plurality of the functions of the type $f(R_{A1T1}, R_{A1T2}, R_{A2T3}, R_{A2T4})$.

An example of a discriminant function is a quadratic expression of the form

$$D = \sum_i \sum_j a_{ij} (\delta_i f_i)(\delta_j f_j) + \sum_i a_i \delta_i f_i + a_o \qquad (3)$$

where

$$\delta_i = 1 \text{ or } 0; \quad \text{and} \sum_i \delta_i = K \qquad (4a)$$

$$\delta_j = 1 \text{ or } 0; \quad \text{and} \sum_j \delta_j = K \qquad (4b)$$

a_{ij}, a_i, and a_0 are constants determined from the calibration set, and subscripts *i* or *j* are indices to specific combinations of wavelength and sampling distance. The number *K* limits the total number of individual wavelength-sampling distance combinations used in the discriminant function. Those skilled in the art can derive and use discriminant functions of other forms, or use neural networks

Abbott Ex. 1002 - 955/1438

to achieve similar classifications. Those skilled in the art will recognize that the two-category classification mentioned above is merely a special case of a multi-category classification and that discriminant functions for multi-category situations can be generated.

The diabetic status of a subject is represented by S_i where

$S_i = +1$ for a diabetic subject

$S_i = -1$ for a non-diabetic subject

The value of the function D can be calculated for each subject i and expressed as D_i. If D_i and S_i have the same sign, the subject is categorized as concordant (i.e., the subject is classified properly). If D_i and S_i have different signs, the subject is categorized as discordant (i.e., the subject is classified improperly). The number of subjects in each category (concordant or discordant) is determined.

The coefficients of the quadratic function D of the calibration (training) set are used to calculate the value of the function D_i for the prediction set. If the calculated value of D_i for a given subject in the prediction set is positive ($D_i > 0$), the subject is classified as diabetic. If the calculated value of D_i for a given subject in the prediction set is negative ($D_i < 0$), the subject is classified as non-diabetic. A 2x2 prediction matrix of the type shown in Table 1 is then established for each experimental condition examined (e.g., initial temperature, final temperature, and cooling rate) at each area. The number of true diabetic subjects identified as diabetic is designated "a", the number of true non-diabetic subjects identified as non-diabetic is designated "d", the number of diabetic subjects identified as non-diabetic (false negative) is designated "c", and the number of non-diabetic designated as diabetic (false positive classification) is designated "b". The number of concordant subjects (a and d) are placed along a diagonal that represents the concordant diabetics and non-diabetics. The numbers of discordant subjects (b and c) are placed on the other diagonal, as indicated in Table 1. The above-described classification method can be used for screening for diabetes in human subjects.

Table 1

Optical Test Result	True Status	
	Diabetic	Non-diabetic
Diabetic	a	b
Non-diabetic	c	d

Abbott Ex. 1002 - 956/1438

The quality of the differentiation between diabetic and non-diabetic subjects is judged by sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV). The term "sensitivity" refers to the ability of a test to identify individuals who are truly positive. The measure of sensitivity is ratio of the number of subjects identified as positive by the test method divided by the total number of truly positive samples as determined by the reference method (i.e., the true status). The term "specificity" refers to the ability of a test to identify individuals who are truly negative. The measure of specificity is the ratio of the number of subjects identified as negative by the test method divided by the total number of truly negative subjects as determined by the reference method . The expression "positive predictive value" or "PPV" is the probability of being truly positive given a positive test result. It is the ratio of the number of truly positive subjects identified as positive by the test method divided by the total number of positive subjects as determined by the test method (in this invention, an optical method). The expression "negative predictive value" or "NPV" is the probability of being truly negative given a negative test result. It is the ratio of the number of truly negative subjects identified by the test method divided by the total number of negative subjects as determined by the test method. The expression "p value" is a parameter that refers to the ability to separate two partially overlapping populations using the χ^2 test. The smaller the value of p, the better is the separation between the two populations.

The performance parameters of the method, namely, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are calculated from the population number a, b, c, and d, where

Sensitivity = a/(a+c),
Specificity = d/(d+b),
Positive predictive value (PPV) = a/(a+b), and
Negative predictive value (NPV) = d/(c+d).

Another suitable application for the method of this invention is a method for the non-invasive determination of the concentration of an analyte, e.g., glucose, in human tissue. The method involves contacting the skin with an optical head at two areas, the areas being morphologically similar but non-overlapping, the areas being subject to different temperature programs.

Abbott Ex. 1002 - 957/1438

A linear regression relationship utilizing, for example, differences of optical measurements at the two areas can be derived for each subject to generate a calibration relationship that relates the concentration of glucose in tissue and the optical signals observed at the first and second areas while these areas are subject to different temperature programs. The concentration of an analyte, e.g., glucose, can be determined from an equation such as the following:

$$[G] = b_0 + \sum_i \sum_j c_{ij}[\ln(R(\lambda_i, r_j, t_1, A_1)) - \ln(R(\lambda_i, r_j, t_1, A_2))] + \sum_i \sum_j d_{ij}[\ln(R(\lambda_i, r_j, t_2, A_1)) - \ln(R(\lambda_i, r_j, t_2, A_2))] \quad (5)$$

where [G] represents the concentration of analyte (e.g., glucose); $R(\lambda_i, r_j, t_1, A_1)$ represents the quantity of reflected light at λ_i, r_j, t_1, A_1; $R(\lambda_i, r_j, t_1, A_2)$ represents the quantity of reflected light at λ_i, r_j, t_1, A_2; $R(\lambda_i, r_j, t_2, A_1)$ represents the quantity of reflected light at λ_i, r_j, t_2, A_1; $R(\lambda_i, r_j, t_2, A_2)$ represents the quantity of reflected light at λ_i, r_j, t_2, A_2; λ_i represents the wavelength of light; r_j represents the sampling distance; t_1 represents a first point in time from the time of contact of the optical device with the tissue, e.g., skin; t_2 represents a second point in time from the time of contact of the optical device with the tissue, e.g., skin; A_1 refers to the first area; and A_2 refers to the second area. The quantities b_0, c_{ij}, d_{ij} are constant coefficients that are determined by means of calibration.

Because the temperature program and the time elapsing between applying the optical head to the tissue determines the subcutaneous temperature, Equation (5) is actually an expression of the value of concentration of the analyte as a function of temperature at each measurement area as shown by equation (6):

$$[G] = b_0 + \sum_i \sum_j c_{ij}[\ln(R(\lambda_i, r_j, T_1, A_1)) - \ln(R(\lambda_i, r_j, T_2, A_2))] + \sum_i \sum_j d_{ij}[\ln(R(\lambda_i, r_j, T_3, A_1)) - \ln(R(\lambda_i, r_j, T_4, A_2))] \quad (6)$$

where [G] represents the concentration of analyte (e.g., glucose); $R(\lambda_i, r_j, T_1, A_1)$ represents the quantity of reflected light at λ_i, r_j, T_1, A_1; $R(\lambda_i, r_j, T_2, A_2)$ represents the quantity of reflected light at λ_i, r_j, T_2, A_2; $R(\lambda_i, r_j, T_3, A_1)$ represents the quantity of reflected light at λ_i, r_j, T_3, A_1; $R(\lambda_i, r_j, T_4, A_2)$ represents the quantity of reflected light at λ_i, r_j, T_4, A_2; λ_i represents the wavelength of light; r_j represents the sampling distance; T_1 represents the temperature at the first area at time t_1, T_2 represents the temperature in

Abbott Ex. 1002 - 958/1438

the first area at time t_2, T_3 represents the temperature in the second area at time t_1, and T_4 represents the temperature in the second area at time t_2. Other examples of temperature programs can be developed by those skilled in the art and equations similar to equations (5) and (6) can be developed to express the concentration of an analyte without deviating from the scope and spirit of this invention. The temperature program applied to the first area must be different from the temperature program applied to the second area. The quantities b_0, c_{ij}, *and* d_{ij} are constant coefficients that are determined by means of calibration.

The method of this invention can be used over a temperature range of from about 0 °C to about 45 °C. A preferred temperature range is from about 10 °C to about 42 °C, and a more preferred temperature range is from about 20 °C to about 40 °C. Generally, the temperature range should be sufficient to provide a detectable change in light penetration depth in tissue without any temperature related injury to the tissue or any significant discomfort to the subject.

One of the embodiments of this invention includes both the temperature dependence of cutaneous circulation and the temperature dependence of structural parameters of the skin in the diagnosis of diabetes and diabetes complications. The measurement of optical properties of human skin across a boundary of the skin is adversely affected by the non-homogeneity of the different layers of the skin. Hormones, drugs, and metabolites in the blood in capillaries contribute to changes in the optical signals measured. The interaction of the optical measuring device and the skin may have different optical effects depending on the state of perfusion of the skin. Thus, highly perfused skin, with high blood content in the capillaries, will be affected by the interaction of the device with the skin and the temperature equilibration between the device and the skin in a different manner than will be a lightly perfused skin, with low blood content in the capillaries. These effects were not mentioned in the prior art. The various embodiments of this invention address these effects and compensate for their contribution to the optical signals. Such compensation will lead to better assessment of the diabetic status and determination of concentration of analytes, such as glucose, in human tissue, such as, for example, human skin.

Non-invasive optical measurements disclosed in the prior art involve illumination and collection of light at a single area on the surface of a body part. Several attempts at spatial averaging of signal over more than one measurement area are used for LDF and applied for the determination of bilirubin. In the case of spatial averaging, the measurement is repeated at several areas on the surface of the body part, the optical

Abbott Ex. 1002 - 959/1438

parameter is determined at each area, and an average value of the optical parameter is calculated. Alternatively, the signal can be measured at several areas on the surface of the body part, averaged, and the concentration of the analyte calculated from the mean of the individually measured signals. The use of a plurality of areas in effect averages out tissue heterogeneity and analyte distribution in tissue. However, in measurements in a plurality of areas, either the temperature is not controlled or the temperature is not varied according to a temperature program. An example of a device in the art that uses spatial averaging of the signal is the bilirubin measurement device having the trademark BiliCheck® and manufactured by SpectRx Inc, (Norcross, Georgia). Another commercially available device that uses spatial averaging is the Peri Flux 4041 measurement device, manufactured by Perimid AB (Jarfalla,Sweden). None of the devices in the prior art discloses the use of measurements of optical parameters under conditions of defined temperature programs at a plurality of detection areas.

The prior art is silent as to the effect of the interaction between the optical measuring device and the skin. The prior art is also silent as to the effect of the interaction between the test fixture or the body part holder and the body part on the measured optical signal, and hence on the value of concentration determined for the analyte.

This invention provides methods and devices for non-invasively measuring at least one clinical diagnostic parameter of a biological sample, such as, for example, a body part. The parameter can be selected, for example, from those such as the presence of a disease condition, progression of a disease state.

This invention addresses the deficiency in the prior art by providing a method to compensate for or alleviate the following effects:

(a) effect of the interaction between the optical measuring device and the tissue;

(b) effect of the interaction between the body part and the body part holder on the measured optical signal, i.e. mechanical compression of the tissue;

(c) effect of thermal equilibration between the body part and the measuring device on light propagation in skin and the measured optical signal; and

(d) effect of surface and subsurface structural differences of the tissue on the measured optical signal.

U. S. Patent Nos. 5,057,695; 5,551,422; 5,676,143; 5,492,118; 5,419,321; 5,632,273; 5,513,642; and 5,935,062 are silent as to measuring optical signals at more than one area on the skin, wherein temperature is varied independently at each area.

Abbott Ex. 1002 - 960/1438

Other methods known in the art operate on large body masses, such as the skull, thigh, or large arm muscles. The cutaneous volumes sampled in the methods in the prior art are too large to allow effective temperature control or effective temperature modulation over these large masses.

The method of this invention offers an advantage over laser Doppler flow measurements alone, because laser Doppler flow measurements deal with cutaneous blood flow in the upper 200 micrometers of the skin. Laser Doppler flow measurements do not account for any structural parameters or spectral effects, because laser Doppler flow measurements only measure the Doppler shift at a single wavelength.

Disease states that can be diagnosed using the method of this invention include, but are not limited to, diabetic status, peripheral vascular disease, a dermal disease state, or a neoplasmic disease state.

The method of this invention can be used on the surface of any tissue wherein light can be introduced into a tissue boundary and intensity of re-emitted light can be measured across the same or another tissue boundary, while at the same time temperature can be modulated to affect a change in light penetration depth in tissue. Accordingly, a temperature-controlled endoscopic probe can be used to diagnose lesions ulcers on the surface of the esophagus or the surface of the cervix.

EXAMPLES

The following non-limiting examples further illustrate the present invention.

EXAMPLE 1

A device of the type shown in FIG. 2 was constructed. The device was capable of performing optical measurements at a single area on the surface of the skin at a given time. Thus, the device was required to be applied twice to the surface of the skin at two morphologically similar, adjacent, substantially non-overlapping areas on the skin.

The wavelengths of the LED's and the frequency at which each one was modulated are shown in Table 2.

Abbott Ex. 1002 - 961/1438

Table 2

LED Number	Wavelength (nm)	Modulation frequency (Hz)	Half band width (nm)
1	660	1024	15
2	590	819	15
3	935	585	25
4	890	455	25

The distance from the center of each light collecting element 46, 48, 50, and 52 to the center of the illuminating element 32 defined the sampling distances r_1, r_3, r_4, and r_6 of this device, which are set forth in Table 3.

Table 3

Element	r_1	r_3	r_4	r_6
Sampling distance (mm)	0.44	0.92	1.21	1.84

EXAMPLE 2

The device described in Example 1 was used in this example. Programmed temperature changes and the optical measurements were carried out at each of the two areas on the surface of the forearm as illustrated in FIG 1. The body interface module 14 of the device 10 was mounted on a cradle (not shown) that was, in turn, mounted on the left arm of a standard clinical reclining chair (not shown). The subject sat in the chair so that the forearm of the subject rested on the cradle. The head of the optical device, which is located in the body interface module 14, was pressed against the dorsal side of the subject's forearm and the data were collected from the time the head of the optical device contacted the skin. Data were collected at the two area sequentially while each area was subjected to a different temperature program. Data from the two areas were used to create a calibration relationship. At one area of the skin, the temperature was maintained at 34 °C for 30 seconds. The temperature was then lowered to 22 °C at the rate of 4 °C per minute. Optical readings were collected every five seconds for four

Abbott Ex. 1002 - 962/1438

minutes. A second area on the surface of the forearm was maintained at 34 °C for 4 ½ minutes. Optical readings were collected every five seconds for four minutes.

The optical data was divided into two classes - the class of diabetics and the class of non-diabetics. A 2x2 table that related the subject's disease status to the optical signal was constructed. The subject's disease status was determined by a reference method wherein the subject had previously been diagnosed as either diabetic or non-diabetic. Four diabetics and four non-diabetics were tested six times to generate 48 data points that were used to generate a calibration relationship. This calibration relationship was used to predict the diabetic status of subjects who were part of a new group, the prediction group. This group included six diabetics and six non-diabetics; each member of the prediction group was tested two times. Prediction of the diabetic status in 120 seconds is shown in Table 4.

Table 4

Optical Test Result	True Status	
	Diabetic	Non-diabetic
Diabetic	11	3
Non-diabetic	1	9

The quality of the differentiation between diabetic and non-diabetic subjects as judged by sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV) at different combinations of temperatures is shown in Table 5.

Table 5

Time (sec)	Temperature (°C)		p	Sensitivity	Specificity	PPV	NPV
	Area 1	Area 2					
120	34	28	0.0038	92	75	79	90
150	34	26	0.0011	92	83	85	91
180	34	24	0.0007	100	75	80	100
210	34	22	0.0011	83	92	91	85

Abbott Ex. 1002 - 963/1438

The temperature programs exemplified in Table 5 could be used to predict the diabetics with a sensitivity of 85% to 100% and specificity between 75% and 92% depending on the temperature differential between the two areas. The PPV was higher than 80% and the NPV was higher than 85%.

EXAMPLE 3

The procedure described in Example 2 was repeated in this example. In this example, one area on the surface of the forearm was maintained at a temperature of 38 °C for 30 seconds. The temperature of this area was then lowered to a temperature of 22 °C at the rate of 5.33 °C per minute. Optical readings were collected every five seconds for four minutes. A second area on the surface of the forearm was maintained at a temperature of 22 °C for 30 seconds. The temperature of this area was then raised to 38 °C at the rate of 5.33 °C per minute. Optical readings were collected every five seconds for four minutes.

The optical data was divided into two classes - the class of diabetics and the class of non-diabetics. A 2x2 table that related the subject's disease status to the optical signal was constructed. The subject's disease status was determined by a reference method wherein the subject had previously been diagnosed as either diabetic or non-diabetic. Four diabetics and four non-diabetics were tested six times to generate 48 data points that were used to generate a calibration relationship. This calibration relationship was used to predict the diabetic status of subjects who were part of a new group, the prediction group. This group included six diabetics and six non-diabetics; each member of the prediction group was tested two times. Prediction of the diabetic status in 120 seconds is shown in Table 6.

Table 6

Optical Test Result	True Status	
	Diabetic*	Non-diabetic*
Diabetic	11	1
Non-diabetic	0	9

*Total number did not equal 12 because subjects displaying outlying signals were rejected.

Abbott Ex. 1002 - 964/1438

Again, the quality of the differentiation between diabetic and non-diabetic subjects as judged by sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV) was estimated at different combinations of temperatures at the two areas is shown in Table 7.

Table 7

Time (sec)	Temperature (°C)		p	Sensitivity	Specificity	PPV	NPV
	Area 1	Area 2					
120	30	30	0.0001	92	90	92	100
150	27.3	32.7	0.0016	73	100	100	77
180	24.7	35.3	0.0004	90	90	90	90
210	22	38	0.0004	82	92	100	83

The temperature programs in Table 7 could be used to predict the diabetics with a sensitivity of 73% to 92% and specificity between 90% and 100%, depending on the temperature differential between the two areas. The PPV was higher than 90% and the NPV was higher than 77%.

EXAMPLE 4

The procedure described in Example 2 was repeated in this example. In this example, one area on the surface of the forearm was maintained at a temperature of 30 °C for 30 seconds. The temperature of this area was then lowered to 22 °C at the rate of 2.67 °C per minute. Optical readings were collected every five seconds for up to 4 minutes. A second area on the surface of the forearm was maintained at a temperature of 30 °C for 30 seconds. The temperature of this area was then raised to 38 °C at the rate of 2.67 °C per minute. Optical readings were collected every five seconds for up to 4 minutes.

The optical data was divided into two classes - the class of diabetics and the class of non-diabetics. A 2x2 table that related the subject's disease status to the optical signal was constructed. The subject's disease status was determined by a reference

Abbott Ex. 1002 - 965/1438

method wherein the subject had previously been diagnosed as either diabetic or non-diabetic. Four diabetics and four non-diabetics were tested six times to generate 48 data points that were used to generate a calibration relationship. This calibration relationship was used to predict the diabetic status of subjects who were part of a new group, the prediction group. This group included six diabetics and six non-diabetics; each member of the prediction group was tested two times. Prediction of the diabetic status in 120 seconds is shown in Table 8.

Table 8

Optical Test Result	True Status	
	Diabetic	Non-diabetic
Diabetic	10	0
Non-diabetic	2	12

The quality of the differentiation between diabetic and non-diabetic subjects as judged by sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV) was estimated at different combinations of temperatures at the two areas. The results are shown in Table 9.

Table 9

Time (sec)	Temperature (°C)		p	Sensitivity	Specificity	PPV	NPV
	Area 1	Area 2					
120	26	34	0.0002	83	100	100	86
150	24.7	35.3	0.0011	92	83	85	91
180	23.3	36.7	0.0007	75	100	100	80
210	22	38	0.0002	100	83	86	100

The temperature programs in Table 9 could be used to predict the diabetics with a sensitivity of 75% to 100%, and specificity between 83% and 100% depending on the temperature differential between the two areas. The PPV was higher than 85% and the NPV was higher than 80%.

Abbott Ex. 1002 - 966/1438

EXAMPLE 5

A device similar to that described in Example 1 was used. This device is illustrated in FIG. 4. The device shown in FIG. 4 is similar to the device shown in FIG. 2, except for the following modifications. The lens assembly 34 (see FIG. 2) was replaced by a four-in-one fiber bundle 200 manufactured by Fiberguide Industries. The fiber bundle 200 contained four fibers designated by the reference numerals 202, 204, 206, 208. Each of the four fibers 202, 204, 206, 208 had a diameter of 400 micrometers and were made of the same material as the illuminating element 32 and the light collecting elements 46, 48, 50, and 52 described previously. Light from each of the LED's 20, 22, 24, and 26 was fed into each of four fibers 202, 204, 206, 208, respectively, the ends of which fibers were bundled in a ferrule (not shown), and focused at the beam splitter 36 leading to the illuminating element 32 by means of a group of lenses 210. Instead of a quadrant detector 60 (see FIG. 2), four individual photodiodes 212, 214, 216, and 218 were used to detect the light from the four fibers 46, 48, 50, and 52, respectively. The electronics and optics were packaged in an aluminum brief case, and the fiber bundle 44 was routed to the body interface module 14. In the device shown in FIG. 4, the reference numerals that matched those of FIG. 2 denote components that are identical or substantially identical to those components of FIG. 2 that employ the same reference numerals. The body interface module 14 was placed on a table (not shown). The subject sat in a chair in front of the body interface module 14 and the arm of the subject was placed on a cradle (not shown) that had been placed on the table. The subject sat in the chair so that the forearm of the subject rested on the cradle. The head of the optical device, which is located in the body interface module 14, was pressed against the dorsal side of the subject's forearm and the data were collected from the time the head of the optical device contacted the skin. The temperature program was the same as used in Example 4 (from 30 °C to 22 °C at the first area, and from 30 °C to 38 °C at the second area). Data were collected at the two areas sequentially for three minutes.

The test was run at a local hospital; a protocol approved by the hospital's Institutional Review Board was used. Subjects were admitted to the hospital the night before the test and were confined for two days. On each day, 10 non-invasive tests and 10 finger stick measurements, taken at the same time as the non-invasive measurements, were conducted. Subjects were fed a standard diet and used diabetes medications as prescribed by their physicians. Data from the two areas were used to

Abbott Ex. 1002 - 967/1438

create a calibration relationship. A leave-one-out cross validation method was used to estimate the standard error of prediction and the correlation coefficient.

A linear regression relationship utilizing differentials of optical measurements can be derived for each subject by means of Equations (5) and (6). In this example, the values of the measurements used were taken at 30 seconds and 180 seconds after the optical head initially contacted an area of the skin.

A summary of the data is shown in Table 10. In this table, the standard error of prediction, which is the root means square calculated prediction error using leave-one-out cross validation method, is "SEP". The leave-one-out cross validation method is described in Wu et al., "Noninvasive Determination of Hemoglobin and Hematocrit Using a Temperature-Controlled Localized Reflectance Tissue Photometer", Analytical Biochemistry, 2000;287:284-293, incorporated herein by reference. The cross validation prediction correlation coefficient is "r", and the standard deviation of the 20 invasively-determined glucose values over the two days is "SDP". The figure of merit is defined as the ratio of the correlation coefficient "r" to the value of (SEP/SDP). The higher the figure of merit, the better the correlation.

The value of (SEP/SDP) is a measure of the spread of the predicted blood glucose level relative to one standard deviation of the blood glucose level in the calibration set. A successful cross-validation requires that the ratio (SEP/SDP) be less than 1.0. In this example, the cut-off value for a successful cross-validation prediction of blood glucose level was set at a SEP/SDP ratio of 0.9. The values of SEP, r, and SEP/SDP are tabulated in Table 10. The underlined SEP/SDP values represent the successful predictions of blood glucose level.

Abbott Ex. 1002 - 968/1438

Table 10

Subject	SEP (mg/dL)	Correlation coefficient r	SDP (mg/dL)	SEP/SDP	Figure of merit
1	78.0	0.63	99.2	0.79	0.80
2	57.3	0.53	66.6	0.86	0.62
3	44.5	0.66	59.6	0.75	0.88
4	52.6	0.25	53.6	0.98	0.25
5	39.7	0.62	50.6	0.78	0.79
6	50.6	0.65	66.1	0.77	0.85
7	41.7	0.74	63.0	0.66	1.12
8	31.0	0.71	44.3	0.70	1.01
9	38.5	0.80	64.4	0.60	1.33
10	51.7	0.38	54.3	0.95	0.40
11	38.8	0.49	44.0	0.88	0.55
12	40.5	0.83	74.2	0.55	1.52
13	63.7	0.52	71.5	0.89	0.59
14	109	0.40	117	0.93	0.43
15	42.0	0.50	48.6	0.86	0.58
16	62.9	0.51	72.5	0.87	0.59
17	76.5	0.62	96.2	0.80	0.78
18	46.1	0.45	50.9	0.91	0.50
19	47.0	0.52	53.6	0.88	0.59
20	45.7	0.45	50.3	0.91	0.49

The value of "r" can be included in the determination of the success rate by calculating the figure of merit, wherein the figure of merit is equal to r /(SEP/SDP). A successful prediction was arbitrarily fixed at a figure of merit cut-off value of 0.70. This figure of merit cut-off value is equivalent to the limit when (SEP/SDP) equals 0.90 and r equals 0.63. The underlined figure of merit values represent a more rigorous prediction of blood glucose level in the twenty diabetic subjects studied. Nine of twenty subjects showed successful prediction of blood glucose levels when this more rigorous figure of merit cut-off value was used. Thus, the sequential method, wherein a single optical head

Abbott Ex. 1002 - 969/1438

and the temperature programs described in this example were used, led to successful predictions of blood glucose levels.

EXAMPLE 6

The device described in FIG. 3 was used in this example. The programmed temperature changes and the optical measurements were carried out at each of the two areas on the surface of the forearm as illustrated in FIG. 1. The body interface module 14 was placed on a table (not shown). The subject sat in front of the body interface module and the arm of the subject was placed on a cradle (not shown) that had been placed on the table. The two heads of the optical device were retracted by the subject's other hand. The two heads of optical device were then allowed to contact the skin and the data were collected from the time the heads contacted the skin. Data were collected at the two areas simultaneously; each area was subjected to a separate temperature program. Data from the two areas were used to derive a calibration relationship. The temperature program at the first area (the area closest to the elbow) was started at 30 °C and held at that temperature for 30 seconds; the temperature was then lowered to 22 °C at a rate of 2.67 °C per minute. The temperature program at the second area (the area farthest from the elbow) was started at 30 °C and held at that temperature for 30 seconds; the temperature was then raised to 38 °C at a rate of 2.67 °C per minute. Data (reflectance at four wavelengths and four distances) were collected for 210 seconds. The natural logarithm of each reflectance value at the two areas was determined. The values of Ln $R(\lambda_i, r_j, t)$ were fitted to the capillary blood glucose level values, as determined by a finger stick procedure, to generate a calibration relationship for each subject. The values used for the line fitting were measured at 30 seconds and 210 seconds after the two optical heads contacted the two areas of the skin. A four term linear model was calculated for each subject. A summary of the data is shown in Table 11. Nineteen of the twenty subjects tested in this example were different from the twenty subjects whose data are shown in Table 10. Subject No. 40 in Table 11 is the same as Subject No. 1 in Table 10. In Table 11, the standard error of prediction, which is the root means square calculated prediction error using leave-one-out cross validation method, is "SEP". The leave-one-out cross validation method is described in Wu et al., "Noninvasive Determination of Hemoglobin and Hematocrit Using a Temperature-Controlled Localized Reflectance Tissue Photometer", Analytical Biochemistry,

Abbott Ex. 1002 - 970/1438

2000;287:284-293, incorporated herein by reference. The cross validation prediction correlation coefficient is "r", and the standard deviation of the 20 invasively-determined glucose values over the two days is "SDP". As defined in Example 5, the figure of merit is equal to r/(SEP/SDP).

Table 11

Subject	SEP (mg/dL)	Correlation coefficient r	SDP (mg/dL)	SEP/SDP	Figure of merit
21	54.4	0.60	67.9	0.80	0.75
22	76.50	0.55	92.1	0.83	0.67
23	60.4	0.66	80.6	0.75	0.89
24	52.0	0.75	78.3	0.66	1.13
25	21.6	0.72	31.8	0.68	1.06
26	76.50	0.76	118.7	0.64	1.17
27	59.1	0.58	72.1	0.82	0.71
28	36.6	0.65	47.3	0.77	0.84
29	60.1	0.66	78.9	0.76	0.86
30	70.3	0.68	96.4	0.73	0.93
31	64.8	0.53	75.3	0.86	0.61
32	40.3	0.55	47.8	0.84	0.65
33	43.3	0.38	46.4	0.93	0.41
34	26.7	0.80	44.5	0.60	1.33
35	29.9	0.58	35.9	0.83	0.70
36	21.9	0.47	24.2	0.91	0.52
37	42.3	0.69	57.9	0.73	0.94
38	62.0	0.63	78.6	0.79	0.80
39	52.4	0.72	76.4	0.69	1.06
40	56.7	0.48	61.7	0.92	0.52

It is possible to use the same criteria as for the determination of the success rate in the non-invasive measurement as was used in Example 5. The use of a (SEP/SDP) ratio of 0.9 yielded seventeen successful predictions of blood glucose levels out of twenty subjects. The successful predictions are designated by underlining. The use of the more rigorous figure of merit cut-off value, i.e., the figure of merit cut-off value being

Abbott Ex. 1002 - 971/1438

0.7, achieved thirteen successful predictions of blood glucose levels out of twenty subjects.

Various modifications and alterations of this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention, and it should be understood that this invention is not to be unduly limited to the illustrative embodiments set forth herein.

Abbott Ex. 1002 - 972/1438

What is claimed is:

1. A method for the determination of a disease state in a tissue of a human, said method comprising the steps of:

(a) measuring at least one optical property at a first area on said tissue to obtain a first set of data, said first area being subjected to a first temperature program;

(b) measuring at least one optical property at a second area on said tissue to obtain a second set of data, said second area being subjected to a second temperature program, said second temperature program being different from the first temperature program, said second area being morphologically similar to but not substantially overlapping with said first area; and

(c) inserting said first set of data and said second set of data into a mathematical relationship to calculate a mathematical output; and

(d) comparing said mathematical output to a category selector to determine said disease state of said human.

2. The method of claim 1, wherein said optical properties are measured with light having a wavelength ranging from about 400 nm to about 2000 nm.

3. The method of claim 1, wherein said optical properties are measured by a diffuse reflectance technique.

4. The method of claim 1, wherein measuring steps (a) and (b) are performed simultaneously.

5. The method of claim 1, wherein measuring steps (a) and (b) are performed sequentially.

6. The method of claim 1, wherein said temperature programs employ temperatures ranging from about 10 °C to about 45 °C.

7. The method of claim 1, wherein said disease state is selected from the group consisting of diabetic state, dermal disease state, neoplasmic disease state, and vascular disease state.

Abbott Ex. 1002 - 973/1438

8. The method of claim 1, wherein said mathematical relationship of step (c) is derived by a method comprising the steps of:

(a) providing a population comprising a sufficient number of human subjects to establish a category selector;

(b) for each of said number of human subjects in said population:

(1) measuring at least one optical property at a first area on said tissue to obtain a first set of data, said first area being subjected to a first temperature program;

(2) measuring at least one optical property at a second area on said tissue to obtain a second set of data, said second area being subjected to a second temperature program, said second temperature program being different from the first temperature program, said second area being morphologically similar to but not substantially overlapping with said first area; and

(c) establishing a mathematical relationship between (i) said optical properties of said first set of data and said second set of data and (ii) said disease state.

9. A method for determining the concentration of an analyte in human tissue, said method comprising the steps of:

(a) measuring at least one optical property at a first area on said tissue to obtain a first set of data, said first area being subjected to a first temperature program;

(b) measuring at least one optical property at a second area on said tissue to obtain a second set of data, said second area being subjected to a second temperature program, said second temperature program being different from the first temperature program, said second area being morphologically similar to but not substantially overlapping with said first area; and

(c) inserting said first set of data and said second set of data into a mathematical relationship to calculate said concentration of said analyte.

10. The method of claim 9, wherein said optical properties are measured with light having a wavelength ranging from about 400 nm to about 2000 nm.

Abbott Ex. 1002 - 974/1438

11. The method of claim 9, wherein said optical properties are measured by a diffuse reflectance technique.

12. The method of claim 9, wherein measuring steps (a) and (b) are performed simultaneously.

13. The method of claim 9, wherein measuring steps (a) and (b) are performed sequentially.

14. The method of claim 9, wherein said temperature programs employ temperatures ranging from about 10 °C to about 45 °C.

15. The method of claim 9, wherein said mathematical relationship of step (c) is derived by a method comprising the steps of:

(a) providing a population comprising a sufficient number of human subjects to establish a statistically meaningful mathematical relationship;

(b) for each of said number of human subjects in said population:

(1) measuring at least one optical property at a first area on said tissue to obtain a first set of data, said first area being subjected to a first temperature program;

(2) measuring at least one optical property at a second area on said tissue to obtain a second set of data, said second area being subjected to a second temperature program, said second temperature program being different from the first temperature program, said second area being morphologically similar to but not substantially overlapping with said first area; and

(c) establishing a mathematical relationship between (i) said optical properties of said first set of data and said second set of data and (ii) said concentration of analyte.

16. The method of claim 9, wherein said analyte is selected from the group consisting of glucose, hemoglobin, hematocrit value, tissue water content, urea, and billirubin.

Abbott Ex. 1002 - 975/1438

17. An apparatus for determining a disease state of a human subject or the concentration of an analyte in the tissue of a human, said apparatus comprising:

(a) means for illuminating at least two areas of tissue with light;

(b) means for collecting light re-emitted from said at least two areas of tissue;

(c) means for measuring the intensity of said re-emitted light collected at said two areas of tissue; and

(d) means for controlling the temperature of said at least two areas of said tissue simultaneously by means of temperature programs.

18. The apparatus of claim 17, further including (e) means for correlating the intensity of the re-emitted light collected at said at least two areas of said tissue with said concentration of an analyte or said disease state, provided that said at least two areas are morphologically similar and are substantially non-overlapping.

Abbott Ex. 1002 - 976/1438

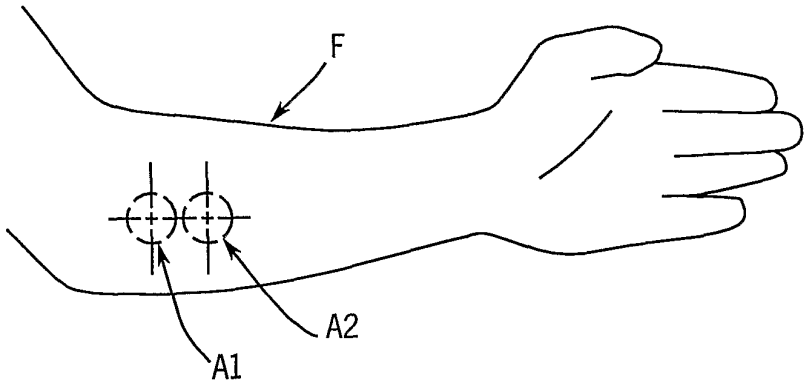


FIG. 1

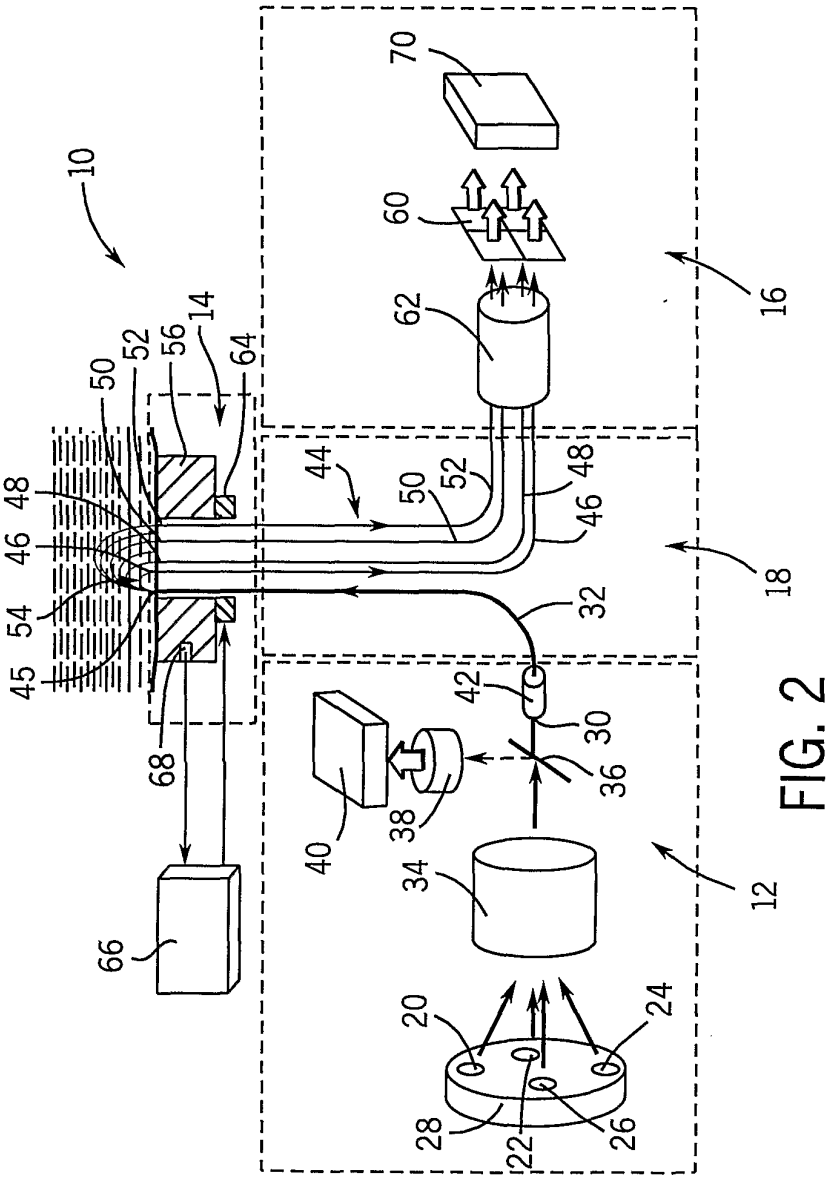

10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
45
46
48
50
52
54
56
60
62
64
66
68
70

FIG. 2

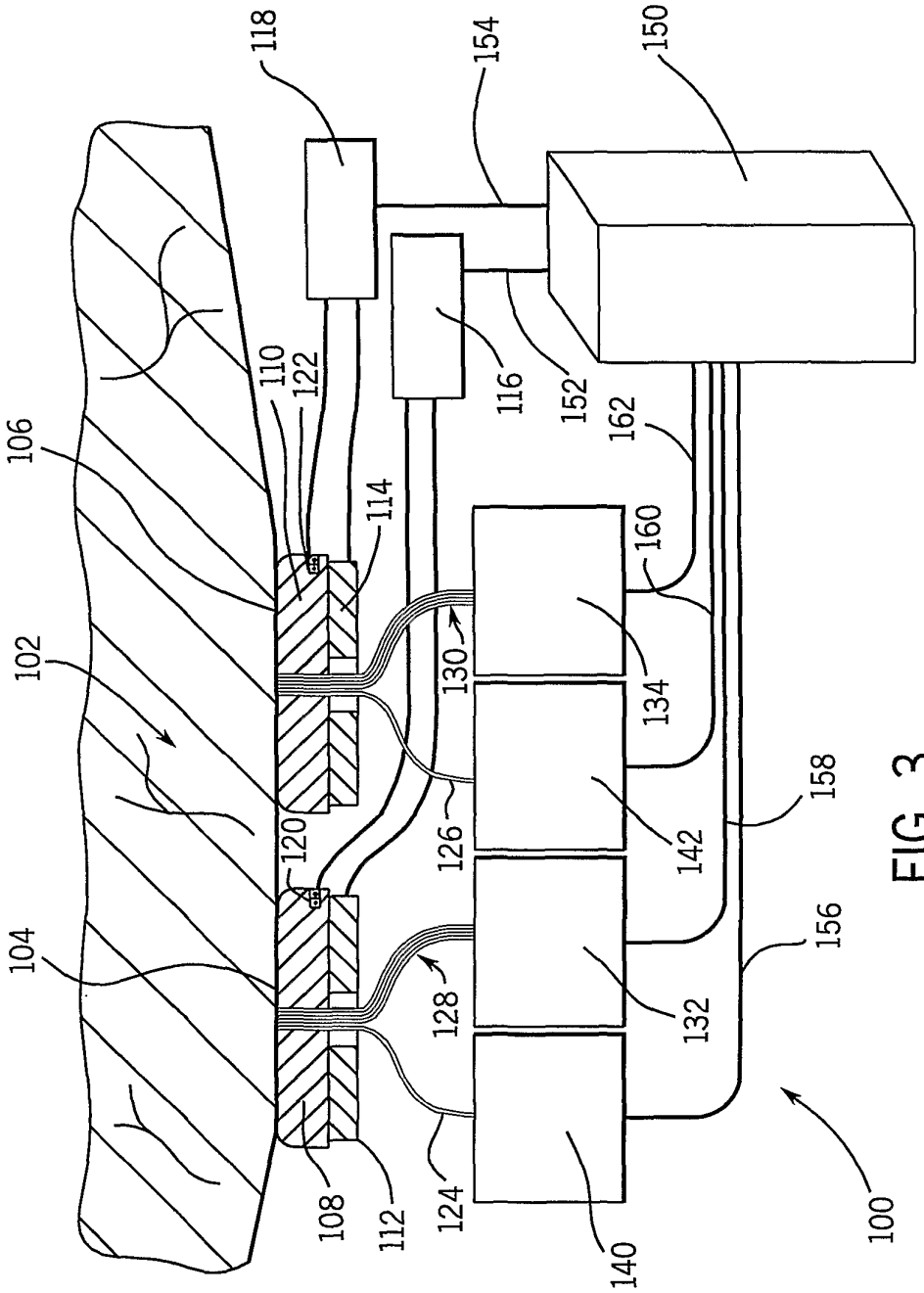

118
154
150
110
122
116
152
162
106
114
160
102
130
134
158
126
142
120
104
128
132
156
108
112
124
140
100

FIG. 3

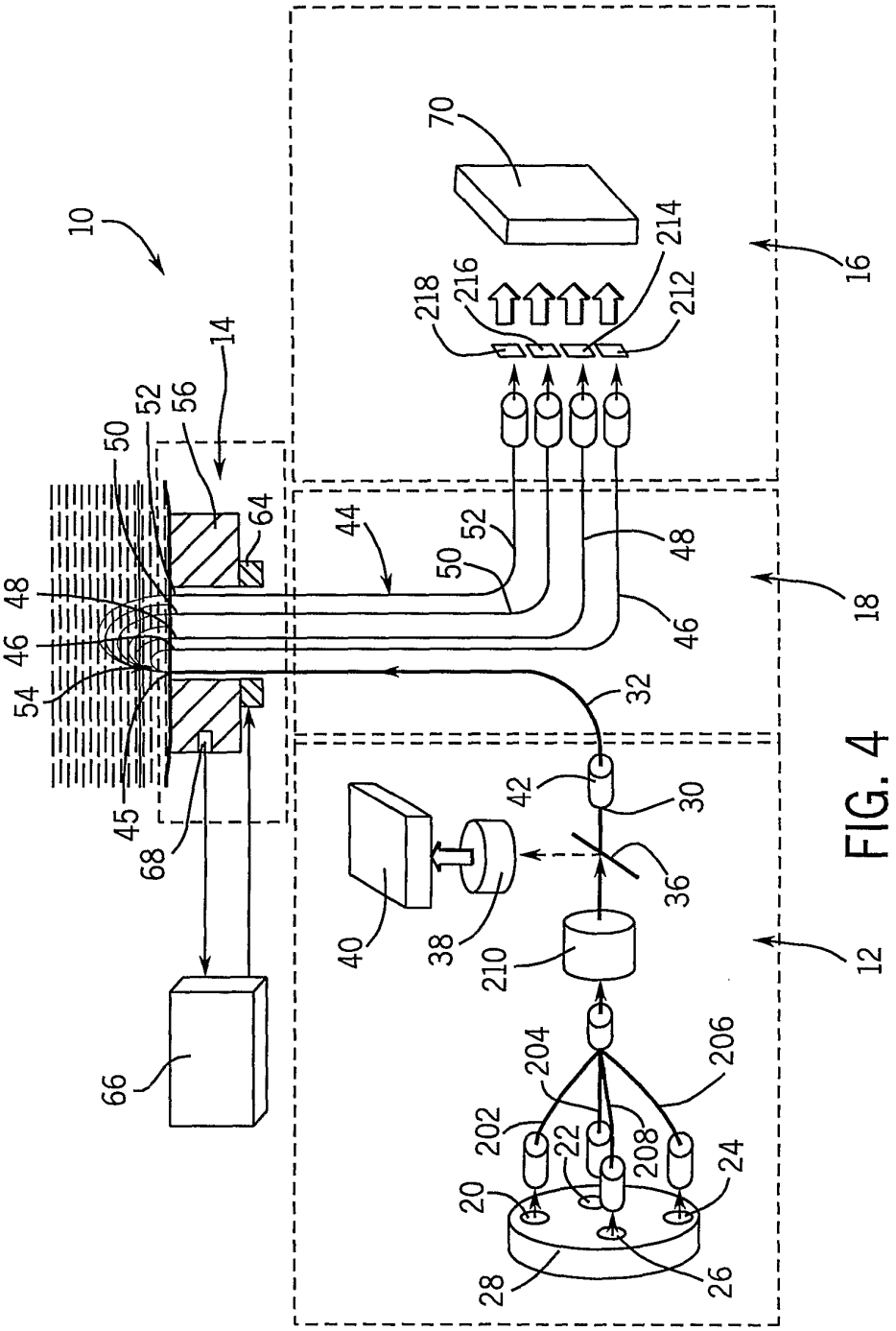

10
12
14
16
18
20
22
24
26
28
30
32
36
38
40
42
44
45
46
48
50
52
54
56
64
66
68
70
202
204
206
208
210
212
214
216
218

FIG. 4

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 02/06831

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 978 691 A (MILLS) 2 November 1999 (1999-11-02) cited in the application column 5, line 62 - line 65 column 7, line 11 -column 9, line 53 column 12, line 7 - line 49	1,4-9, 12-18
A	US 5 348 003 A (CARO) 20 September 1994 (1994-09-20) cited in the application column 5, line 5 - line 50 column 8, line 35 - line 48	1,2, 8-10, 15-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 2002	26/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lemercier, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

Abbott Ex. 1002 - 981/1438

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/US 02/06831

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5978691 A	02-11-1999	AU 3721997 A	10-02-1998
		EP 0944347 A2	29-09-1999
		WO 9803847 A2	29-01-1998
US 5348003 A	20-09-1994	NONE	

Abbott Ex. 1002 - 982/1438

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 April 2008 (10.04.2008)

PCT

(10) International Publication Number
WO 2008/042918 A2

(51) International Patent Classification:
C12Q 1/00 (2006.01) *A61B 5/1486* (2006.01)

(21) International Application Number:
PCT/US2007/080228

(22) International Filing Date: 2 October 2007 (02.10.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

11/543,707	4 October 2006 (04.10.2006)	US
11/543,539	4 October 2006 (04.10.2006)	US
11/543,683	4 October 2006 (04.10.2006)	US
11/543,734	4 October 2006 (04.10.2006)	US
11/692,154	27 March 2007 (27.03.2007)	US
11/865,572	1 October 2007 (01.10.2007)	US

(71) Applicant *(for all designated States except US)*: **DEXCOM, INC.** [US/US]; 5555 Oberlin Drive, San Diego, CA 92121 (US).

(72) Inventors: **SIMPSON, Peter**; 227 N. Vulcan Avenue, Encinitas, California 92024 (US). **BRISTER, Mark**; 1055 Valley Side Lane, Encinitas, California 92024 (US). **WIGHTLIN, Matthew**; 8637 Jenny Avenue, San Diego, CA 92123 (US). **PRYOR, Jack**; 15590 Paseo Jenghiz, San Diego, California 92129 (US).

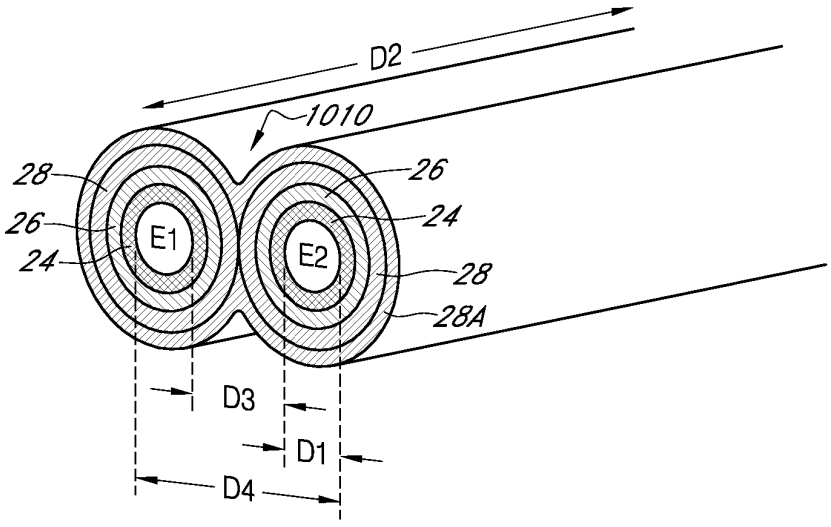
(74) Agent: **MALLON, Joseph, J.**; Knobbe Martens Olson & Bear LLP, 2040 Main Street 14th Floor, Irvine, CA 92614 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) **Title:** DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR



(57) **Abstract:** Disclosed herein are systems and methods for a continuous analyte sensor, such as a continuous glucose sensor. One such system utilizes first and second working electrodes working electrodes E1, E2 including a membrane having an electrode domain 24, an enzyme domain 26 and a resistance domain 28 to measure additional analyte or non-analyte related signal. Such measurements may provide a background and/or sensitivity measurement(s) for use in processing sensor data and may be used to trigger events such as digital filtering of data or suspending display of data.

WO 2008/042918 A2

DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR

FIELD OF THE INVENTION

[0001] The present invention relates generally to systems and methods for measuring an analyte concentration in a host.

BACKGROUND OF THE INVENTION

[0002] 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 may cause an array of physiological derangements (for example, kidney failure, skin ulcers, or bleeding into the vitreous of the eye) associated with the deterioration of small blood vessels. A hypoglycemic reaction (low blood sugar) may 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.

[0003] Conventionally, a diabetic person carries a self-monitoring blood glucose (SMBG) monitor, which typically comprises uncomfortable finger pricking methods. Due to the lack of comfort and convenience, a diabetic will normally only measure his or her glucose level two to four times per day. Unfortunately, these time intervals are so far spread apart that the diabetic will likely find out too late, sometimes incurring dangerous side effects, of a hyper- or hypo-glycemic condition. In fact, it is not only unlikely that a diabetic will take a timely SMBG value, but the diabetic will not know if their blood glucose value is going up (higher) or down (lower) based on conventional methods, inhibiting their ability to make educated insulin therapy decisions.

SUMMARY OF THE INVENTION

[0004] A variety of continuous glucose sensors have been developed for detecting and/or quantifying glucose concentration in a host. These sensors have typically required one or more blood glucose measurements, or the like, from which to calibrate the continuous glucose sensor to calculate the relationship between the current output of the sensor and blood glucose measurements, to provide meaningful values to a patient or doctor. Unfortunately, continuous glucose sensors are conventionally also sensitive to non-glucose related changes in the baseline

Abbott Ex. 1002 - 984/1438

current and sensitivity over time, for example, due to changes in a host's metabolism, maturation of the tissue at the biointerface of the sensor, interfering species which cause a measurable increase or decrease in the signal, or the like. Therefore, in addition to initial calibration, continuous glucose sensors should be responsive to baseline and/or sensitivity changes over time, which requires recalibration of the sensor. Consequently, users of continuous glucose sensors have typically been required to obtain numerous blood glucose measurements daily and/or weekly in order to maintain calibration of the sensor over time.

[0005] In a first aspect, a continuous glucose sensor is provided, the sensor comprising a first working electrode comprising a first electroactive surface disposed beneath an active enzymatic portion of a sensor membrane, wherein the first working electrode is configured to generate a first signal having a first noise component related to a noise-causing species; and a second working electrode comprising a second electroactive surface disposed beneath an inactive-enzymatic or a non-enzymatic portion of the sensor membrane, wherein the second working electrode is configured to generate a second signal having a second noise component related to the noise-causing species; wherein the first electroactive surface and the second electroactive surface are each dimensioned to integrate at least one signal generated by a plurality of local point sources that produce the noise-causing species, such that the first noise component and the second noise component are substantially equivalent.

[0006] In an embodiment of the first aspect, at least one dimension of each of the first electroactive surface and second electroactive surface is greater than a sum of diameters of about 10 average human cells.

[0007] In an embodiment of the first aspect, at least one dimension of each of the first electroactive surface and second electroactive surface is greater than about 500μm.

[0008] In an embodiment of the first aspect, each of the first electroactive surface and second electroactive surface is configured and arranged to integrate noise detected about a circumference of the sensor.

[0009] In an embodiment of the first aspect, the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having

Abbott Ex. 1002 - 985/1438

electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

[0010] In an embodiment of the first aspect, the noise-causing species is non-constant.

[0011] In an embodiment of the first aspect, the first electroactive surface and second electroactive surface are spaced at a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first electroactive surface and the second electroactive surface.

[0012] In an embodiment of the first aspect, the first electroactive surface and second electroactive surface are spaced at a distance less than a crosstalk diffusion distance of a measured species.

[0013] In an embodiment of the first aspect, the measured species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

[0014] In an embodiment of the first aspect, the sensor further comprises a physical diffusion barrier configured and arranged to physically block crosstalk from the active enzymatic portion of the sensor membrane to the second electroactive surface by at least 50%.

[0015] In an embodiment of the first aspect, the physical diffusion barrier is configured and arranged to physically block an amount of the measured species diffusing from the active enzymatic portion of the membrane to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

[0016] In an embodiment of the first aspect, the sensor further comprises a physical diffusion barrier comprising a discontinuous portion of a membrane disposed between the first electroactive surface and the second electroactive surface.

[0017] In an embodiment of the first aspect, the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein the first barrier layer and the second barrier layer are each independently formed.

[0018] In an embodiment of the first aspect, the physical diffusion barrier comprises a first resistance domain formed on the first working electrode and a second resistance domain

Abbott Ex. 1002 - 986/1438

formed on the second working electrode, and the sensor membrane further comprises a third resistance domain disposed continuously over the first and second resistance domains, wherein the first resistance domain and the second resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the sensor to the second electroactive surface by at least 2-fold, and the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

[0019] In an embodiment of the first aspect, the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measured species by at least 10-fold.

[0020] In an embodiment of the first aspect, the sensitivities of the first signal and the second signals are within 20% of each other.

[0021] In a second aspect, a continuous glucose sensor configured for insertion into a host and for detecting glucose in the host is provided, the sensor comprising a first working electrode comprising a first electroactive surface disposed beneath an active enzymatic portion of a sensor membrane, wherein the first working electrode is configured to generate a first signal having a first noise component related to a noise-causing species; a second working electrode comprising a second electroactive surface disposed beneath an inactive-enzymatic or a non-enzymatic portion of the sensor membrane, wherein the second working electrode is configured to generate a second signal having a second noise component related to the noise-causing species; and a physical diffusion barrier; wherein the first electroactive surface and the second electroactive surface are spaced at a distance that allows noise caused by a local point source that produces noise-causing species to be measured substantially equivalently at the first electroactive surface and the second electroactive surface.

[0022] In an embodiment of the second aspect, the sensor membrane has a thickness, and wherein the distance between the first electroactive surface and the second electroactive surface is less than about twice the thickness of the sensor membrane.

[0023] In an embodiment of the second aspect, the thickness of the sensor membrane is less than about 80 microns.

[0024] In an embodiment of the second aspect, the distance between the first electroactive surface and the second electroactive surface is less than or equal to about a crosstalk diffusion distance of a measurable species.

Abbott Ex. 1002 - 987/1438

[0025] In an embodiment of the second aspect, the measurable species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

[0026] In an embodiment of the second aspect, the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

[0027] In an embodiment of the second aspect, the active enzymatic portion of the membrane is configured to produce a measurable species, and wherein the physical diffusion barrier is configured and arranged to physically block at least some diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface.

[0028] In an embodiment of the second aspect, the physical diffusion barrier is configured and arranged to physically block at least 50% of the measurable species diffusing from the active enzymatic portion of the membrane to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

[0029] In an embodiment of the second aspect, the measurable species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

[0030] In an embodiment of the second aspect, the physical diffusion barrier comprises a discontinuous portion of the membrane disposed between the first electroactive surface and the second electroactive surface.

[0031] In an embodiment of the second aspect, the physical diffusion barrier comprises a first barrier layer formed on the first electrode and a second barrier layer formed on the second electrode, wherein each of the first barrier layer and the second barrier layer is independently formed.

[0032] In an embodiment of the second aspect, the physical diffusion barrier comprises a first resistance domain formed on the first electrode and a second resistance domain formed on the second electrode, and wherein the first resistance domain and the second

Abbott Ex. 1002 - 988/1438

resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface by at least 2-fold.

[0033] In an embodiment of the second aspect, the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measurable species by at least 10-fold.

[0034] In an embodiment of the second aspect, the sensor membrane further comprises a third resistance domain disposed continuously over the first electroactive surface and the second electroactive surface, wherein the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

[0035] In an embodiment of the second aspect, the sensor further comprises an insulator configured to insulate the first working electrode from the second working electrode, wherein the sensor membrane is the insulator.

[0036] In an embodiment of the second aspect, the first electroactive surface and the second electroactive surface are each dimensioned to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

[0037] In an embodiment of the second aspect, the first electroactive surface and the second electroactive surface are each sized in at least one dimension such that each of the first noise component and second noise component can be integrated across the dimension.

[0038] In an embodiment of the second aspect, the dimension is greater than a sum of diameters of about 10 average human cells.

[0039] In an embodiment of the second aspect, each of the first electroactive surface and the second electroactive surface is dimensioned such that each of the first noise component and the second noise component is substantially equivalent.

[0040] In a third aspect, a sensor configured and arranged for insertion into a host and for continuously detecting glucose in the host is provided, the sensor comprising a first working electrode configured to generate a first signal having a first noise component related to a noise-causing species, the first working electrode having a first electroactive surface having a first surface area; and a second working electrode configured to generate a second signal having a second noise component related to the noise-causing species, the second working electrode having a second electroactive surface having a second surface area; wherein the first working

Abbott Ex. 1002 - 989/1438

electrode and the second working electrode are configured and arranged to integrate the first noise component and the second noise component about a circumference of the sensor.

[0041] In an embodiment of the third aspect, the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

[0042] In an embodiment of the third aspect, the noise-causing species is non-constant.

[0043] In an embodiment of the third aspect, the first surface area and the second surface area are each dimensioned to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

[0044] In an embodiment of the third aspect, the first surface area and the second surface area are each sized in at least one dimension such that each of the first noise component and the second noise component can be integrated across the dimension.

[0045] In an embodiment of the third aspect, the dimension is greater than a sum of diameters of about 10 average human cells.

[0046] In an embodiment of the third aspect, the dimension is greater than about 500μm.

[0047] In an embodiment of the third aspect, the first surface area and the second surface area are each dimensioned such that each of the first noise component and the second noise component is substantially equivalent.

[0048] In an embodiment of the third aspect, the first surface area and the second surface area are each dimensioned such that each of the first noise component and the second noise component is equivalent to ±10%.

[0049] In an embodiment of the third aspect, the first electroactive surface and the second electroactive surface are spaced a distance that allows noise caused by a local point

Abbott Ex. 1002 - 990/1438

source that produces noise-causing species to be measured equivalently at the first electroactive surface and the second electroactive surface.

[0050] In an embodiment of the third aspect, the first electroactive surface is disposed beneath an active enzymatic portion of a sensor membrane and the second electroactive surface is disposed beneath at least one of an inactive enzymatic or a non-enzymatic portion of the sensor membrane, and wherein the first electroactive surface and the second electroactive surface are spaced a distance less than about a crosstalk distance of a measurable species produced in the active enzymatic portion of the sensor membrane.

[0051] In an embodiment of the third aspect, the measurable species comprises H_2O_2.

[0052] In an embodiment of the third aspect, the crosstalk distance comprises a maximum distance the measurable species can diffuse from the active enzymatic portion of the sensor membrane to the second electroactive surface, and thereby cause a measurable signal on the second working electrode.

[0053] In an embodiment of the third aspect, the sensor further comprises a physical diffusion barrier.

[0054] In an embodiment of the third aspect, the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein each of the first barrier layer and the second barrier layer is independently formed.

[0055] In an embodiment of the third aspect, the physical diffusion barrier comprises a first resistance domain formed on the first working electrode and a second resistance domain formed on the second working electrode, and wherein the first resistance domain and the second resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface by at least 2-fold.

[0056] In an embodiment of the third aspect, the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measurable species by at least 10-fold.

[0057] In an embodiment of the third aspect, the sensor membrane further comprises a third resistance domain disposed continuously over the first resistance domain and the second

Abbott Ex. 1002 - 991/1438

resistance domain, wherein the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

[0058] In an embodiment of the third aspect, the sensor further comprises an insulator configured to insulate the first working electrode from the second working electrode, wherein the sensor membrane is the insulator.

[0059] In a fourth aspect, a continuous glucose sensor configured and arranged for insertion into a host and for detecting glucose in the host is provided, the sensor comprising a first working electrode comprising a first electroactive surface disposed beneath an active enzymatic portion of a sensor membrane, wherein the first electroactive surface is configured to measure a measurable species; a second working electrode comprising a second electroactive surface disposed beneath at least one of an inactive enzymatic portion of the sensor membrane and a non-enzymatic portion of the sensor membrane, wherein the second electroactive surface is configured to measure said measurable species, and wherein the first electroactive surface and the second electroactive surface are spaced within a crosstalk distance of the measurable species; and a physical diffusion barrier disposed between the first working electrode and the second working electrode, wherein the physical diffusion barrier is configured and arranged such that there is substantially no signal associated with crosstalk.

[0060] In an embodiment of the fourth aspect, the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

[0061] In an embodiment of the fourth aspect, the noise-causing species is non-constant.

[0062] In an embodiment of the fourth aspect, the measurable species is H_2O_2 produced in an active enzymatic portion of a sensor membrane.

Abbott Ex. 1002 - 992/1438

[0063] In an embodiment of the fourth aspect, the crosstalk distance is a maximum distance the measurable species can diffuse between the active enzymatic portion of the membrane and the second working electrode, and be detected as crosstalk.

[0064] In an embodiment of the fourth aspect, the first electroactive surface has a first area and the second electroactive surface has a second area; wherein the first area and the second area are dimensioned such that the first noise component and the second noise component are substantially equivalent.

[0065] In an embodiment of the fourth aspect, at least one dimension of each of the first area and the second area is greater than a sum of diameters of about 10 average human cells.

[0066] In an embodiment of the fourth aspect, at least one dimension of each of the first area and the second area is greater than about 500μm.

[0067] In an embodiment of the fourth aspect, the first area and the second area are each configured and arranged to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

[0068] In an embodiment of the fourth aspect, the first area and the second area are each configured and arranged to integrate noise detected about a circumference of the sensor.

[0069] In an embodiment of the fourth aspect, the physical diffusion barrier comprises a discontinuous portion of the membrane disposed between the first electroactive surface and the second electroactive surface.

[0070] In an embodiment of the fourth aspect, the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein the first barrier layer and the second barrier layer are independently formed.

[0071] In an embodiment of the fourth aspect, the physical diffusion barrier comprises a first resistance domain formed on the first working electrode and a second resistance domain formed on the second working electrode, and wherein the first resistance domain and the second resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface by at least 2-fold.

Abbott Ex. 1002 - 993/1438

[0072] In an embodiment of the fourth aspect, the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measurable species by at least 10-fold.

[0073] In an embodiment of the fourth aspect, the sensor membrane further comprises a third resistance domain disposed continuously over the first resistance domain and the second resistance domain, wherein the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

[0074] In an embodiment of the fourth aspect, the sensor further comprises an insulator configured to insulate the first working electrode from the second working electrode, wherein the sensor membrane is the insulator.

[0075] In an embodiment of the fourth aspect, the first electroactive surface and the second electroactive surface are spaced a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first electroactive surface and the second electroactive surface.

[0076] In a fifth aspect, a continuous glucose sensor configured and arranged for insertion into a host for and detecting glucose in the host is provided, the sensor comprising a first working electrode comprising a first resistance domain, wherein the first working electrode is configured to generate a first signal having a first noise component related to a noise-causing species; a second working electrode comprising a second resistance domain, wherein the second working electrode is configured to generate a second signal having a second noise component related to the noise-causing species; and a third resistance domain disposed continuously over the first resistance domain and the second resistance domain.

[0077] In an embodiment of the fifth aspect, the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

[0078] In an embodiment of the fifth aspect, the noise-causing species is non-constant.

Abbott Ex. 1002 - 994/1438

[0079] In an embodiment of the fifth aspect, the first signal comprises a first sensitivity and the second signal comprises a second sensitivity, and wherein the third resistance domain is configured such that the first sensitivity and the second sensitivity are substantially equivalent.

[0080] In an embodiment of the fifth aspect, the first sensitivity and the second sensitivity are equivalent to ±10%.

[0081] In an embodiment of the fifth aspect, each of the first resistance domain and the second resistance domain is independently formed on the first working electrode and the second working electrode, respectively.

[0082] In an embodiment of the fifth aspect, the first working electrode comprises a first electroactive surface and a first membrane portion disposed thereon, the first membrane portion comprising an active enzymatic enzyme domain and the first resistance domain, and wherein the second working electrode comprises a second electroactive surface and a second membrane portion disposed thereon, the second membrane portion comprising at least one of an inactive enzymatic portion or a non-enzymatic portion and the second resistance domain.

[0083] In an embodiment of the fifth aspect, the active enzymatic enzyme domain is configured to generate a measurable species.

[0084] In an embodiment of the fifth aspect, the measurable species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

[0085] In an embodiment of the fifth aspect, the sensor further comprises a physical diffusion barrier, wherein physical diffusion barrier comprises the first resistance domain and the second resistance domain.

[0086] In an embodiment of the fifth aspect, the physical diffusion barrier is configured and arranged to attenuate diffusion of the measurable species from the active enzymatic enzyme domain to the second electroactive surface by at least 2-fold.

[0087] In an embodiment of the fifth aspect, the diffusion is attenuated by at least 10-fold.

[0088] In an embodiment of the fifth aspect, the physical diffusion barrier is configured and arranged to physically block some crosstalk from the active enzymatic enzyme domain to the second electroactive surface.

Abbott Ex. 1002 - 995/1438

[0089] In an embodiment of the fifth aspect, the physical diffusion barrier is configured and arranged to physically block an amount of a measurable species diffusing from the active enzymatic enzyme domain to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

[0090] In an embodiment of the fifth aspect, the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein each of the first barrier layer and the second barrier layer is independently formed.

[0091] In an embodiment of the fifth aspect, the first electroactive surface and the second electroactive surface are spaced closer together than a crosstalk distance.

[0092] In an embodiment of the fifth aspect, the crosstalk distance comprises a distance less than a maximum distance the measurable species can diffuse, and generate a signal associated with crosstalk.

[0093] In an embodiment of the fifth aspect, the first electroactive surface and the second electroactive surface are spaced a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first and second electroactive surfaces.

[0094] In an embodiment of the fifth aspect, each of the first electroactive surface and the second electroactive surface is configured and arranged to integrate the signal caused by a plurality of local point sources that produce noise-causing species *in vivo*, such that the first noise component and the second noise component are substantially equivalent.

[0095] In an embodiment of the fifth aspect, the first electroactive surface and the second electroactive surface are configured and arranged to integrate signals detected about a circumference of the sensor.

[0096] In an embodiment of the fifth aspect, the first electroactive surface and the second electroactive surface are each sized in at least one dimension such that the first noise component and the second noise component can be integrated across the dimension.

[0097] In an embodiment of the fifth aspect, the dimension of each of the first electroactive surface and the second electroactive surface is greater than a sum of diameters of about 10 average human cells.

Abbott Ex. 1002 - 996/1438

[0098] In an embodiment of the fifth aspect, the dimension of each of the first electroactive surface and the second electroactive surface is greater than about 500μm.

BRIEF DESCRIPTION OF THE DRAWINGS

[0099] Fig. 1A is a perspective view of a continuous analyte sensor, including an implantable body with a membrane system disposed thereon

[0100] Fig. 1B is an expanded view of an alternative embodiment of a continuous analyte sensor, illustrating the *in vivo* portion of the sensor.

[0101] Fig. 2A is a schematic view of a membrane system in one embodiment, configured for deposition over the electroactive surfaces of the analyte sensor of Fig. 1A.

[0102] Fig. 2B is a schematic view of a membrane system in an alternative embodiment, configured for deposition over the electroactive surfaces of the analyte sensor of Fig. 1B.

[0103] Fig. 3A which is a cross-sectional exploded schematic view of a sensing region of a continuous glucose sensor in one embodiment wherein an active enzyme of an enzyme domain is positioned only over the glucose-measuring working electrode.

[0104] Fig. 3B is a cross-sectional exploded schematic view of a sensing region of a continuous glucose sensor in another embodiment, wherein an active portion of the enzyme within the enzyme domain positioned over the auxiliary working electrode has been deactivated.

[0105] Fig. 4 is a block diagram that illustrates continuous glucose sensor electronics in one embodiment.

[0106] Fig. 5 is a drawing of a receiver for the continuous glucose sensor in one embodiment.

[0107] Fig. 6 is a block diagram of the receiver electronics in one embodiment.

[0108] Fig. 7A1 is a schematic of one embodiment of a coaxial sensor having axis A-A.

[0109] Fig. 7A2 is a cross-section of the sensor shown in Fig. 7A1.

[0110] Fig. 7B is a schematic of another embodiment of a coaxial sensor.

[0111] Fig. 7C is a schematic of one embodiment of a sensor having three electrodes.

[0112] Fig. 7D is a schematic of one embodiment of a sensor having seven electrodes.

Abbott Ex. 1002 - 997/1438

[0113] Fig. 7E is a schematic of one embodiment of a sensor having two pairs of electrodes and insulating material.

[0114] Fig. 7F is a schematic of one embodiment of a sensor having two electrodes separated by a reference electrode or insulating material.

[0115] Fig. 7G is a schematic of another embodiment of a sensor having two electrodes separated by a reference electrode or insulating material.

[0116] Fig. 7H is a schematic of another embodiment of a sensor having two electrodes separated by a reference electrode or insulating material.

[0117] Fig. 7I is a schematic of another embodiment of a sensor having two electrodes separated by reference electrodes or insulating material.

[0118] Fig. 7J is a schematic of one embodiment of a sensor having two electrodes separated by a substantially X-shaped reference electrode or insulating material.

[0119] Fig 7K is a schematic of one embodiment of a sensor having two electrodes coated with insulating material, wherein one electrode has a space for enzyme, the electrodes are separated by a distance ***D*** and covered by a membrane system.

[0120] Fig. 7L is a schematic of one embodiment of a sensor having two electrodes embedded in an insulating material.

[0121] Fig. 7M is a schematic of one embodiment of a sensor having multiple working electrodes and multiple reference electrodes.

[0122] Fig. 7N is a schematic of one step of the manufacture of one embodiment of a sensor having, embedded in insulating material, two working electrodes separated by a reference electrode, wherein the sensor is trimmed to a final size and/or shape.

[0123] Fig. 8A is a schematic on one embodiment of a sensor having two working electrodes coated with insulating material, and separated by a reference electrode.

[0124] Fig. 8B is a schematic of the second end (e.g., *ex vivo* terminus) of the sensor of Fig 8A having a stepped connection to the sensor electronics.

[0125] Fig. 9A is a schematic of one embodiment of a sensor having two working electrodes and a substantially cylindrical reference electrode there around, wherein the second end (the end connected to the sensor electronics) of the sensor is stepped.

Abbott Ex. 1002 - 998/1438

[0126] Fig. 9B is a schematic of one embodiment of a sensor having two working electrodes and an electrode coiled there around, wherein the second end (the end connected to the sensor electronics) of the sensor is stepped.

[0127] Fig. 10 is a schematic illustrating metabolism of glucose by Glucose Oxidase (GOx) and one embodiment of a diffusion barrier ***D*** that substantially prevents the diffusion of H_2O_2 produced on a first side of the sensor (e.g., from a first electrode that has active GOx) to a second side of the sensor (e.g., to the second electrode that lacks active GOx).

[0128] Fig. 11 is a schematic illustrating one embodiment of a triple helical coaxial sensor having a stepped second terminus for engaging the sensor electronics.

[0129] Fig. 12 is a graph that illustrates *in vitro* signal (raw counts) detected from a sensor having three bundled wire electrodes with staggered working electrodes. Plus GOx (thick line) = the electrode with active GOx. No GOx (thin line) = the electrode with inactive or no GOx.

[0130] Fig. 13 is a graph that illustrates *in vitro* signal (counts) detected from a sensor having the configuration of the embodiment shown in Fig. 7J (silver/silver chloride X-wire reference electrode separating two platinum wire working electrodes). Plus GOx (thick line) = the electrode with active GOx. No GOx (thin line) = the electrode with inactive or no GOx.

[0131] Fig. 14 is a graph that illustrates an *in vitro* signal (counts) detected from a dual-electrode sensor with a bundled configuration similar to that shown in **Fig. 7C** (two platinum working electrodes and one silver/silver chloride reference electrode, not twisted).

[0132] Fig. 15 is a graph that illustrates an *in vivo* signal (counts) detected from a dual-electrode sensor with a bundled configuration similar to that shown in **Fig. 7C** (two platinum working electrodes, not twisted, and one remotely disposed silver/silver chloride reference electrode).

[0133] Fig. 16 is a two-dimensional schematic of a dual-electrode sensor in one embodiment, illustrating the sensor's first and second electroactive surfaces (of the first and second working electrodes, respectively) beneath a sensor membrane, wherein noise-causing species produced by a plurality of point sources can impinge upon an electroactive surface.

[0134] Fig. 17 is a two-dimensional schematic of a dual-electrode sensor in one embodiment, illustrating the sensor's first and second electroactive surfaces (of the first and

Abbott Ex. 1002 - 999/1438

second working electrodes, respectively) beneath a sensor membrane, wherein noise from a single point source (e.g., a cell) can impinge upon both electroactive surfaces.

[0135] Fig. 18 is a cross-sectional schematic illustrating a dual electrode sensor, in one embodiment, including a physical diffusion barrier.

[0136] Fig. 19A is a graph that illustrates an *in vivo* signal (counts) detected from a dual-electrode sensor, in one embodiment, implanted in a non-diabetic human host.

[0137] Fig. 19B is a graph that illustrates an *in vivo* signal (counts) detected from a dual-electrode, in another embodiment, implanted in a non-diabetic human host.

[0138] Fig. 20A is a graph that illustrates an *in vivo* signal (counts) detected from a dual-electrode, in one embodiment, implanted in a non-diabetic human host.

[0139] Fig. 20B is a graph that illustrates an *in vivo* signal (counts) detected from a dual-electrode, in another embodiment, implanted in a non-diabetic human host.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0140] The following description and examples illustrate some exemplary embodiments of the disclosed invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a certain exemplary embodiment should not be deemed to limit the scope of the present invention.

Definitions

[0141] In order to facilitate an understanding of the disclosed invention, a number of terms are defined below.

[0142] The term "analyte" 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 it is not to be limited to a special or customized meaning), and refers without limitation to a substance or chemical constituent in a biological fluid (for example, blood, interstitial fluid, cerebral spinal fluid, lymph fluid or urine) that can be analyzed. Analytes may include naturally occurring substances, artificial substances, metabolites, and/or reaction products. In some embodiments, the analyte for measurement by the sensor heads, devices, and methods disclosed herein is glucose. However, other analytes are contemplated as well, including but not limited to acarboxyprothrombin; acylcarnitine; adenine phosphoribosyl transferase; adenosine deaminase; albumin; alpha-

Abbott Ex. 1002 - 1000/1438