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(54) **METHOD, SYSTEM AND COMPUTER PROGRAM PRODUCT FOR REAL-TIME DETECTION OF SENSITIVITY DECLINE IN ANALYTE SENSORS**

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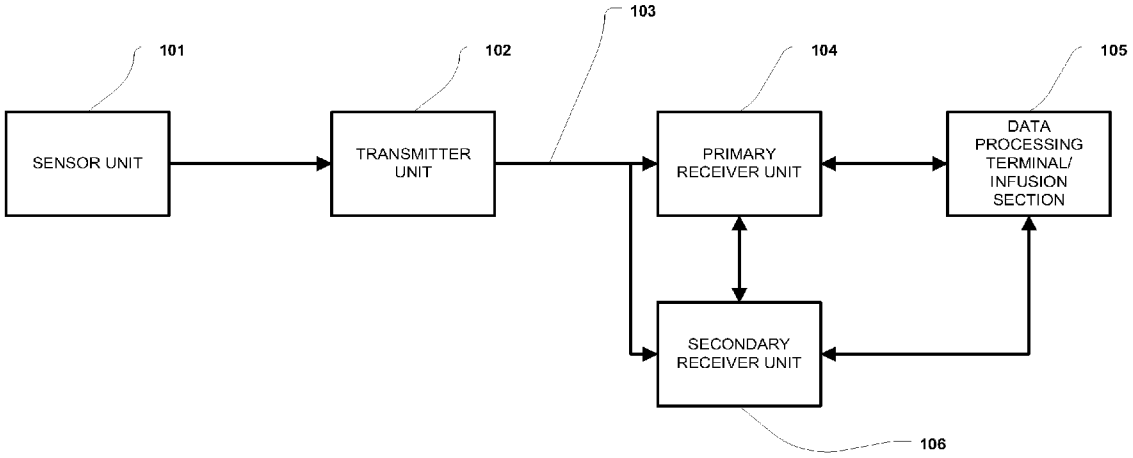
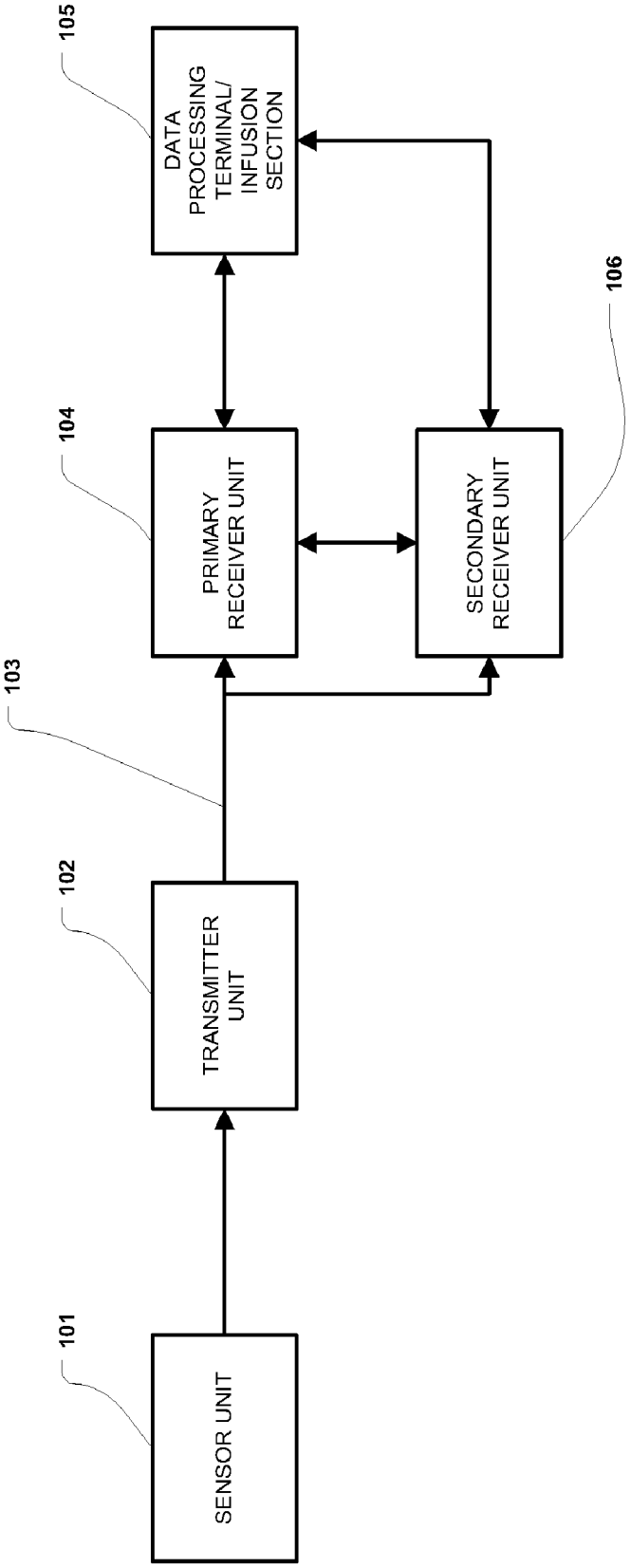
(57) **ABSTRACT**

Method, system and computer program product for providing real time detection of analyte sensor sensitivity decline is continuous glucose monitoring systems are provided.



100


105
DATA PROCESSING TERMINAL/ INFUSION SECTION
104
PRIMARY RECEIVER UNIT
106
SECONDARY RECEIVER UNIT
103
102
TRANSMITTER UNIT
101
SENSOR UNIT

100

FIGURE 1

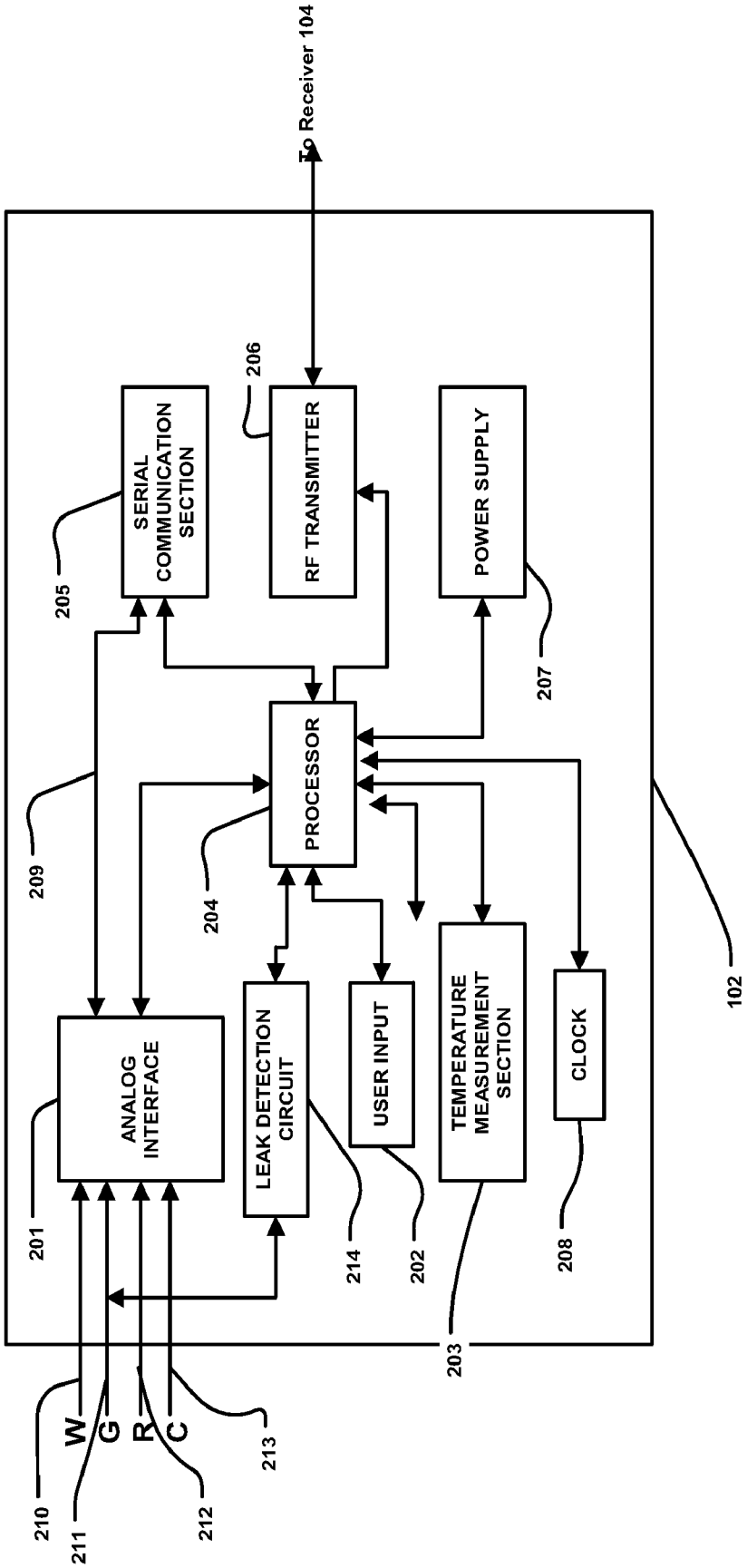

To Receiver 104
SERIAL COMMUNICATION SECTION
RF TRANSMITTER
POWER SUPPLY
PROCESSOR
ANALOG INTERFACE
LEAK DETECTION CIRCUIT
USER INPUT
TEMPERATURE MEASUREMENT SECTION
CLOCK
W
G
R
C
201
202
203
204
205
206
207
208
209
210
211
212
213
214
102

FIGURE 2

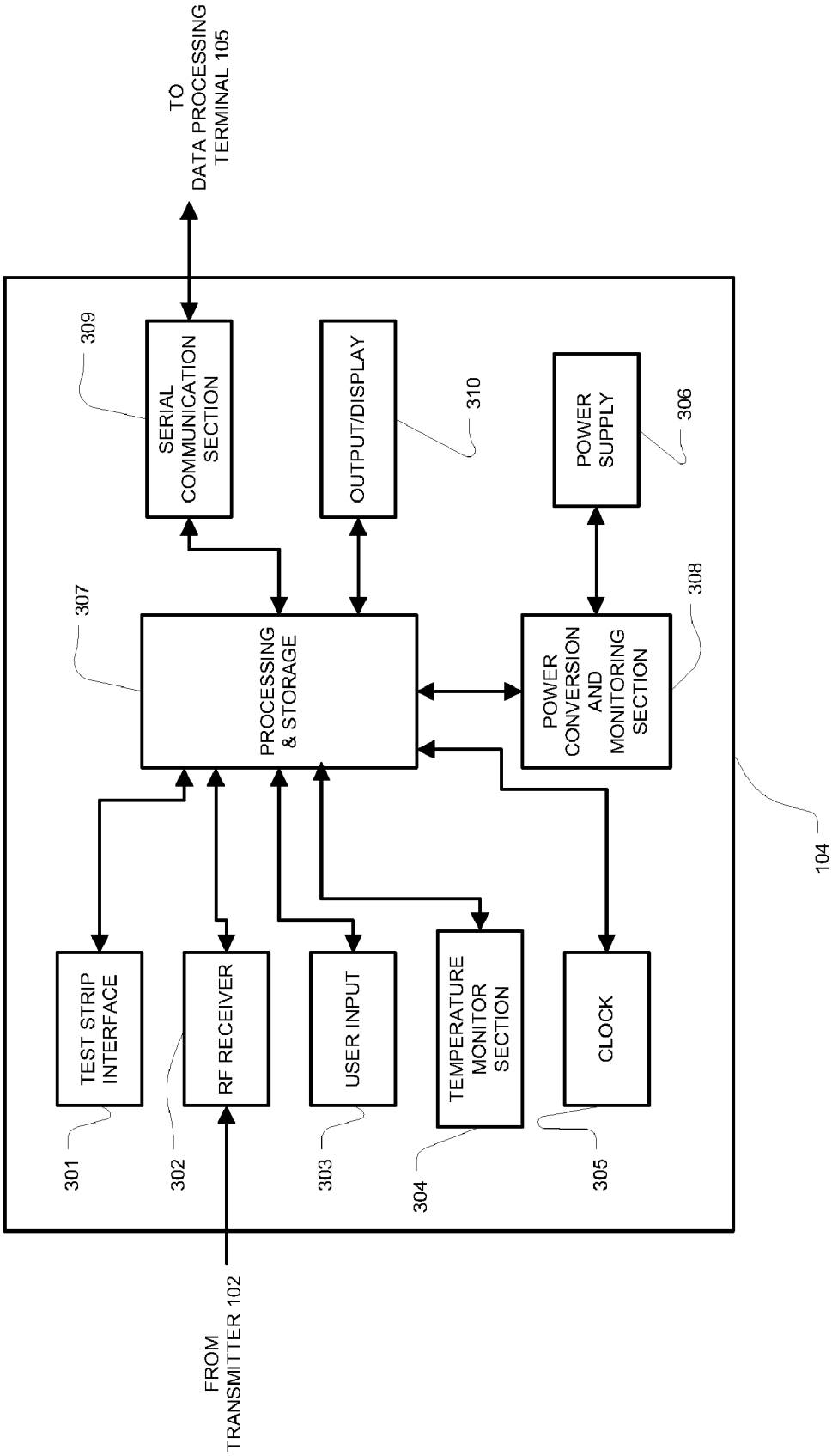

TO
DATA PROCESSING
TERMINAL 105
309
SERIAL
COMMUNICATION
SECTION
OUTPUT/DISPLAY
310
POWER
SUPPLY
306
307
PROCESSING
& STORAGE
POWER
CONVERSION
AND
MONITORING
SECTION
308
104
TEST STRIP
INTERFACE
RF RECEIVER
USER INPUT
TEMPERATURE
MONITOR
SECTION
CLOCK
301
302
303
304
305
FROM
TRANSMITTER 102

FIGURE 3

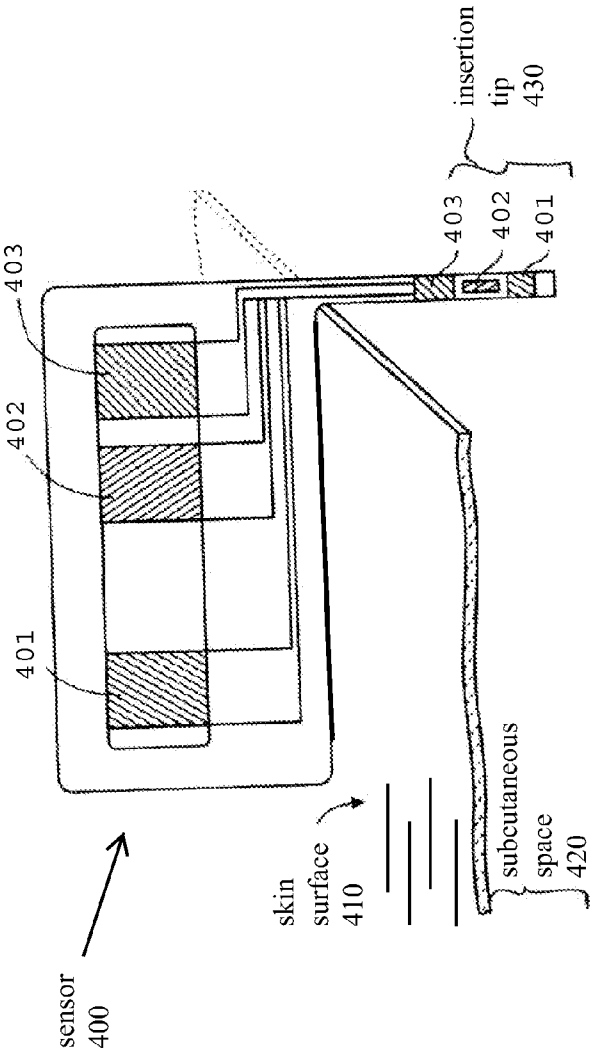


FIGURE 4A

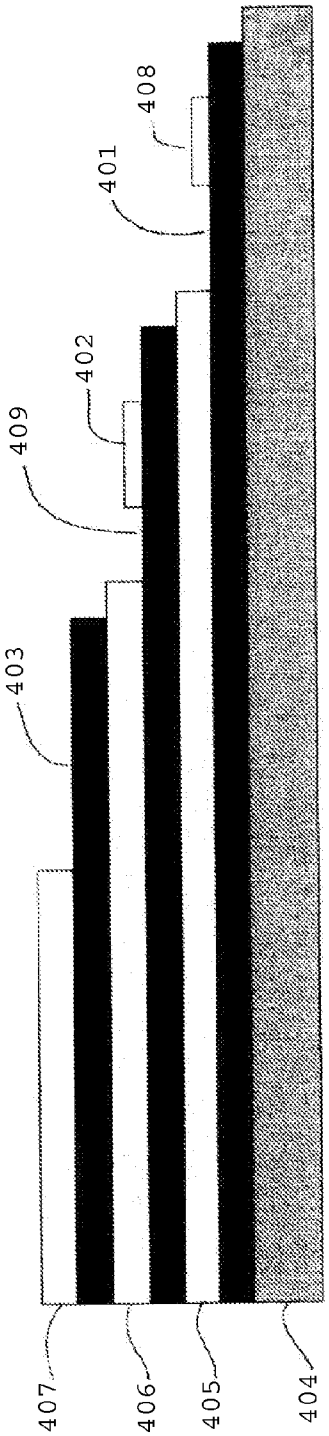
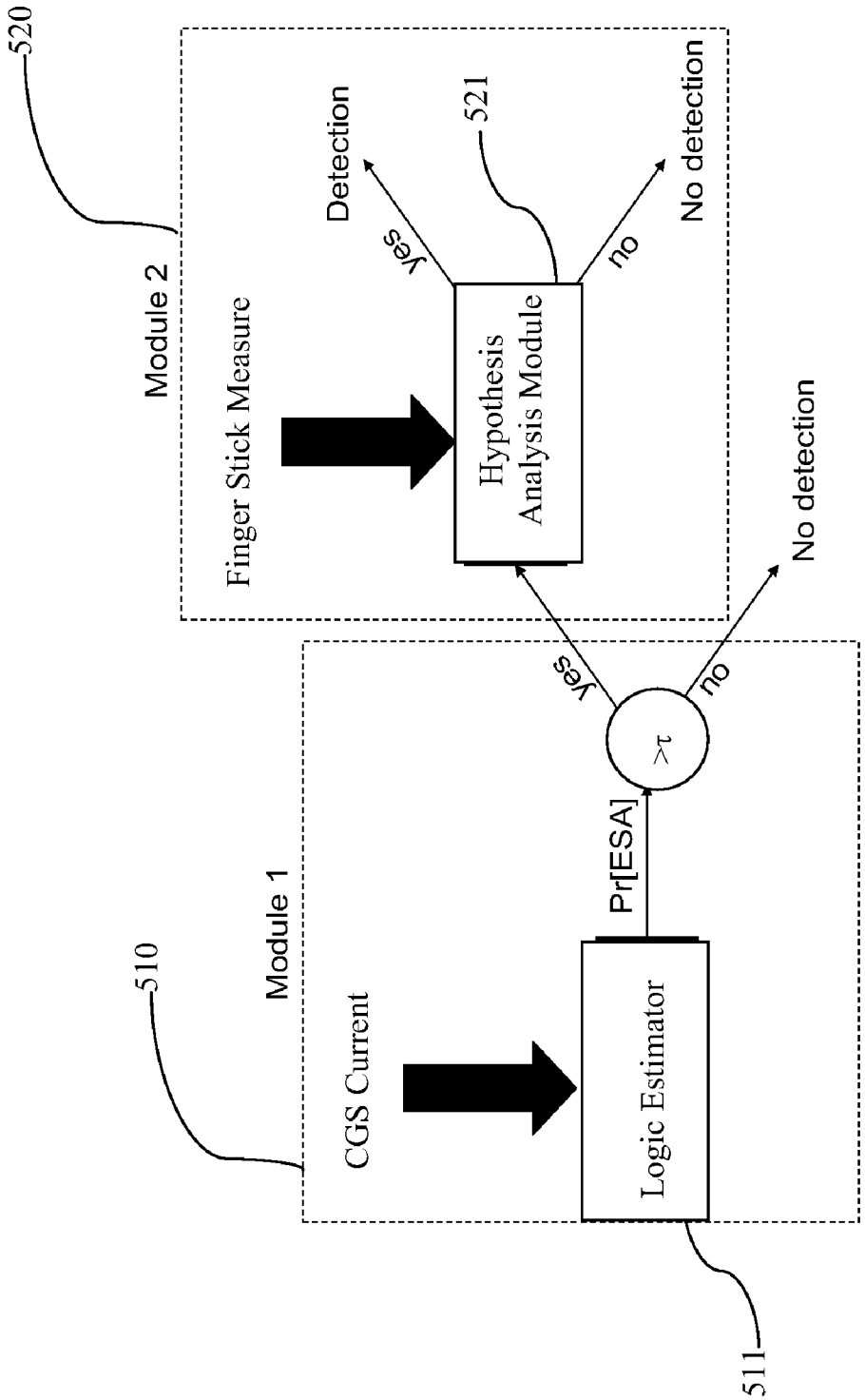


FIGURE 4B


520
Module 2
Finger Stick Measure
Hypothesis
Analysis Module
521
Detection
No detection
yes
no
No detection
510
Module 1
CGS Current
Logic Estimator
Pr[ESA]
$>\tau$
yes
no
511

500

FIGURE 5

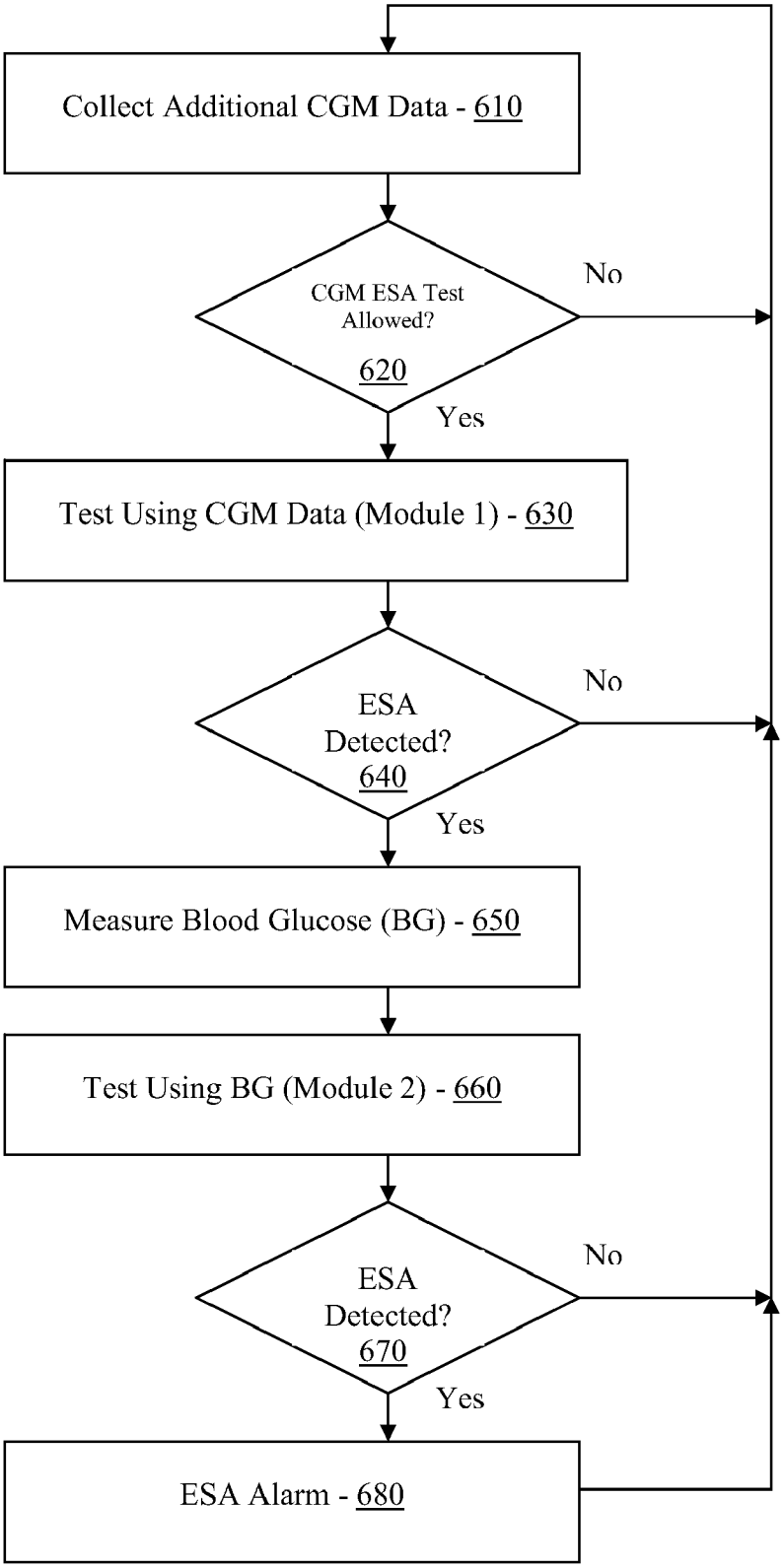

Collect Additional CGM Data - 610
CGM ESA Test Allowed?
620
No
Yes
Test Using CGM Data (Module 1) - 630
ESA Detected?
640
No
Yes
Measure Blood Glucose (BG) - 650
Test Using BG (Module 2) - 660
ESA Detected?
670
No
Yes
ESA Alarm - 680

FIGURE 6

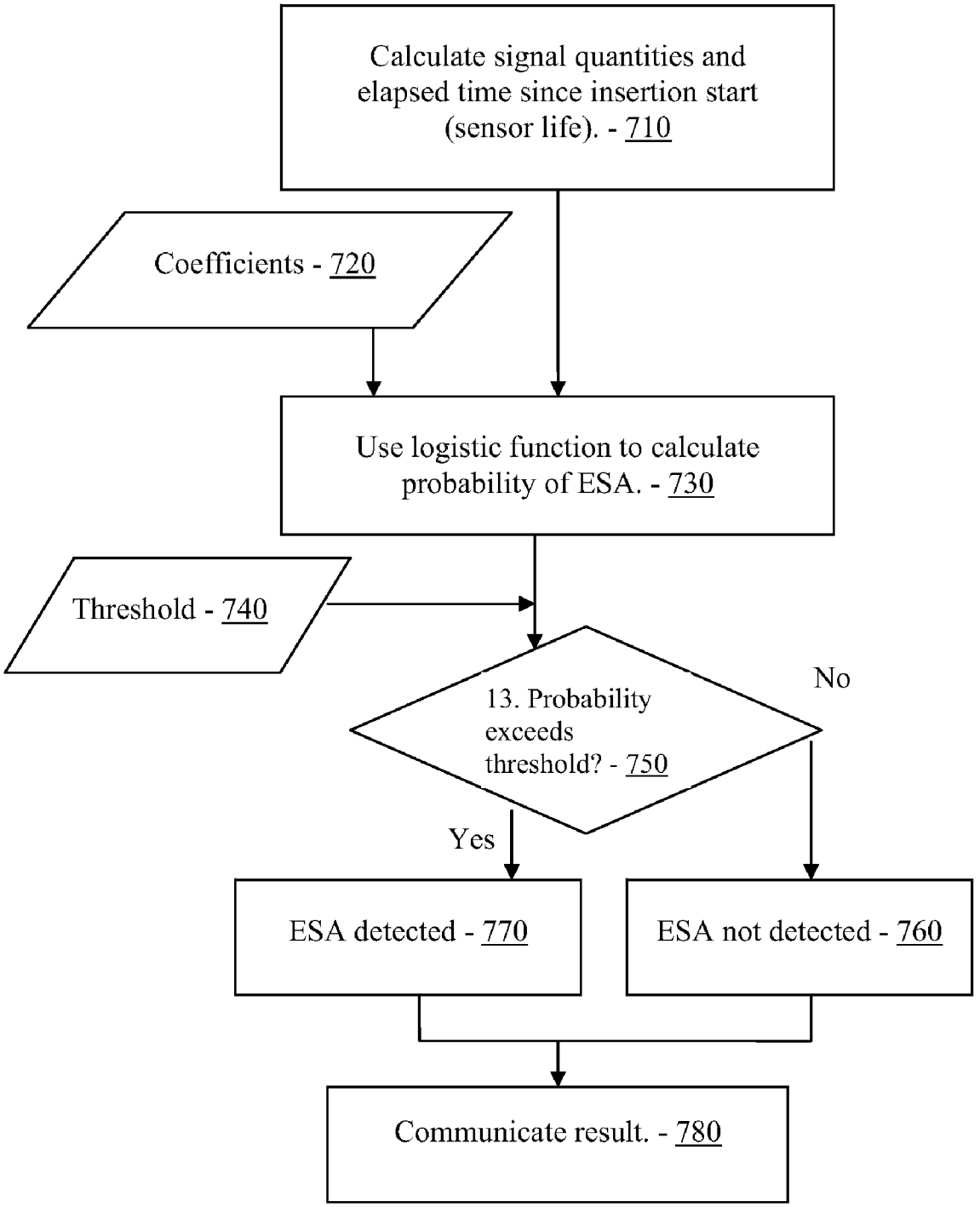

Calculate signal quantities and elapsed time since insertion start (sensor life). - 710
Coefficients - 720
Use logistic function to calculate probability of ESA. - 730
Threshold - 740
13. Probability exceeds threshold? - 750
No
Yes
ESA detected - 770
ESA not detected - 760
Communicate result. - 780

FIGURE 7

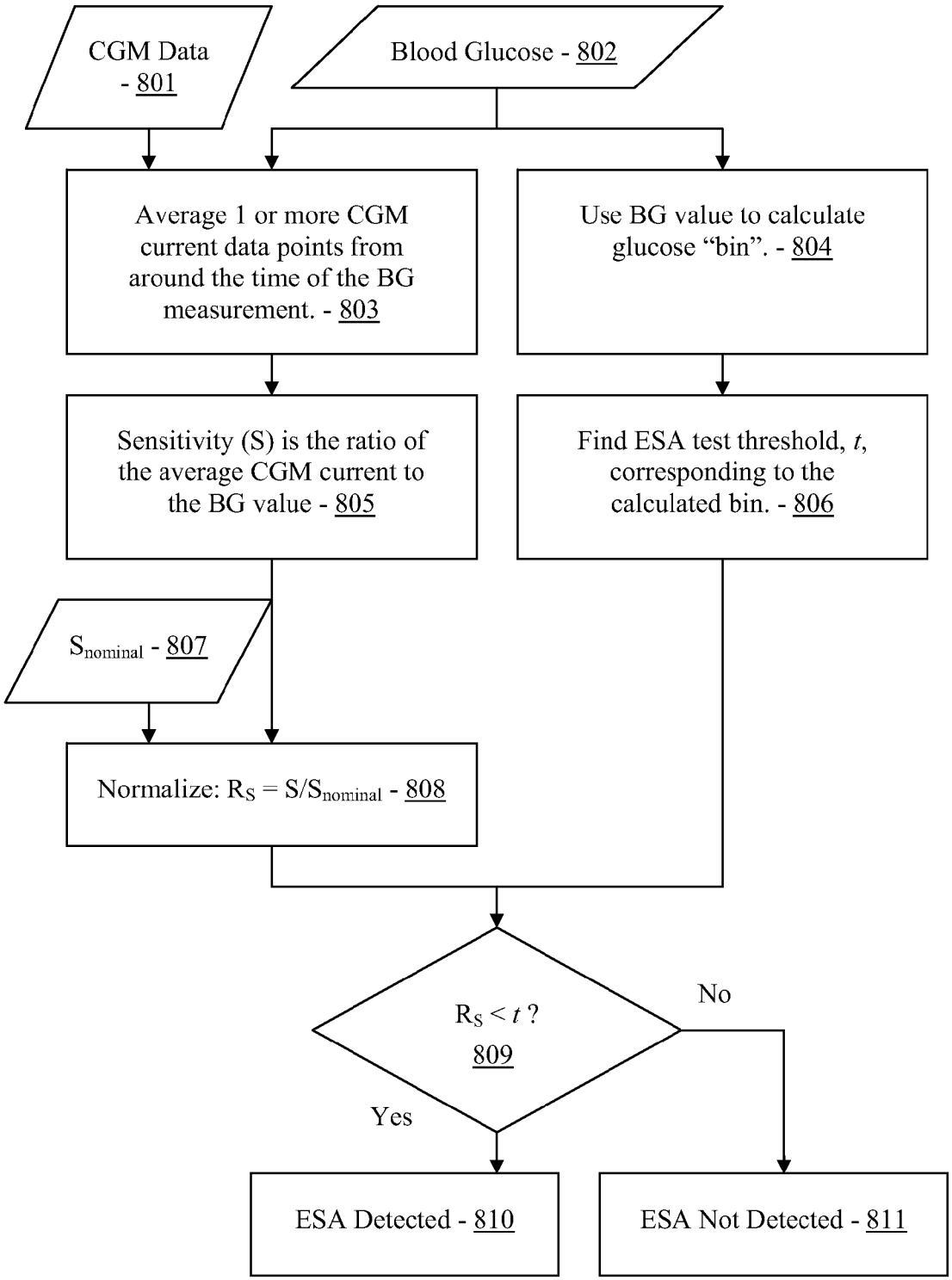

CGM Data - 801
Blood Glucose - 802
Average 1 or more CGM current data points from around the time of the BG measurement. - 803
Use BG value to calculate glucose "bin". - 804
Sensitivity (S) is the ratio of the average CGM current to the BG value - 805
Find ESA test threshold, t, corresponding to the calculated bin. - 806
$S_{nominal}$ - 807
Normalize: $R_S = S/S_{nominal}$ - 808
$R_S < t$?
809
No
Yes
ESA Detected - 810
ESA Not Detected - 811

FIGURE 8

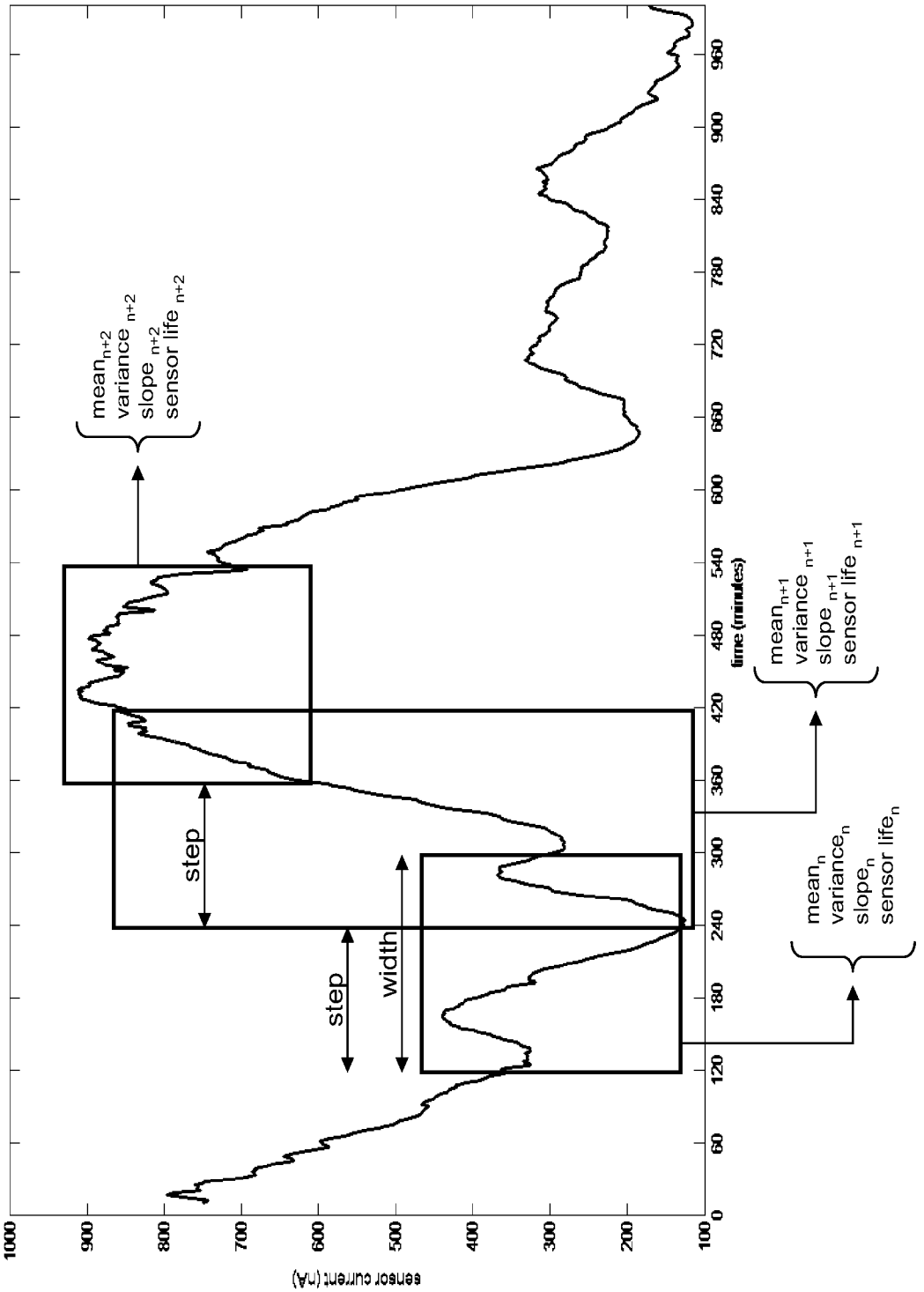

sensor current (nA)
time (minutes)
step
step
width
mean$_{n+2}$
variance$_{n+2}$
slope$_{n+2}$
sensor life$_{n+2}$
mean$_{n+1}$
variance$_{n+1}$
slope$_{n+1}$
sensor life$_{n+1}$
mean$_n$
variance$_n$
slope$_n$
sensor life$_n$

FIGURE 9

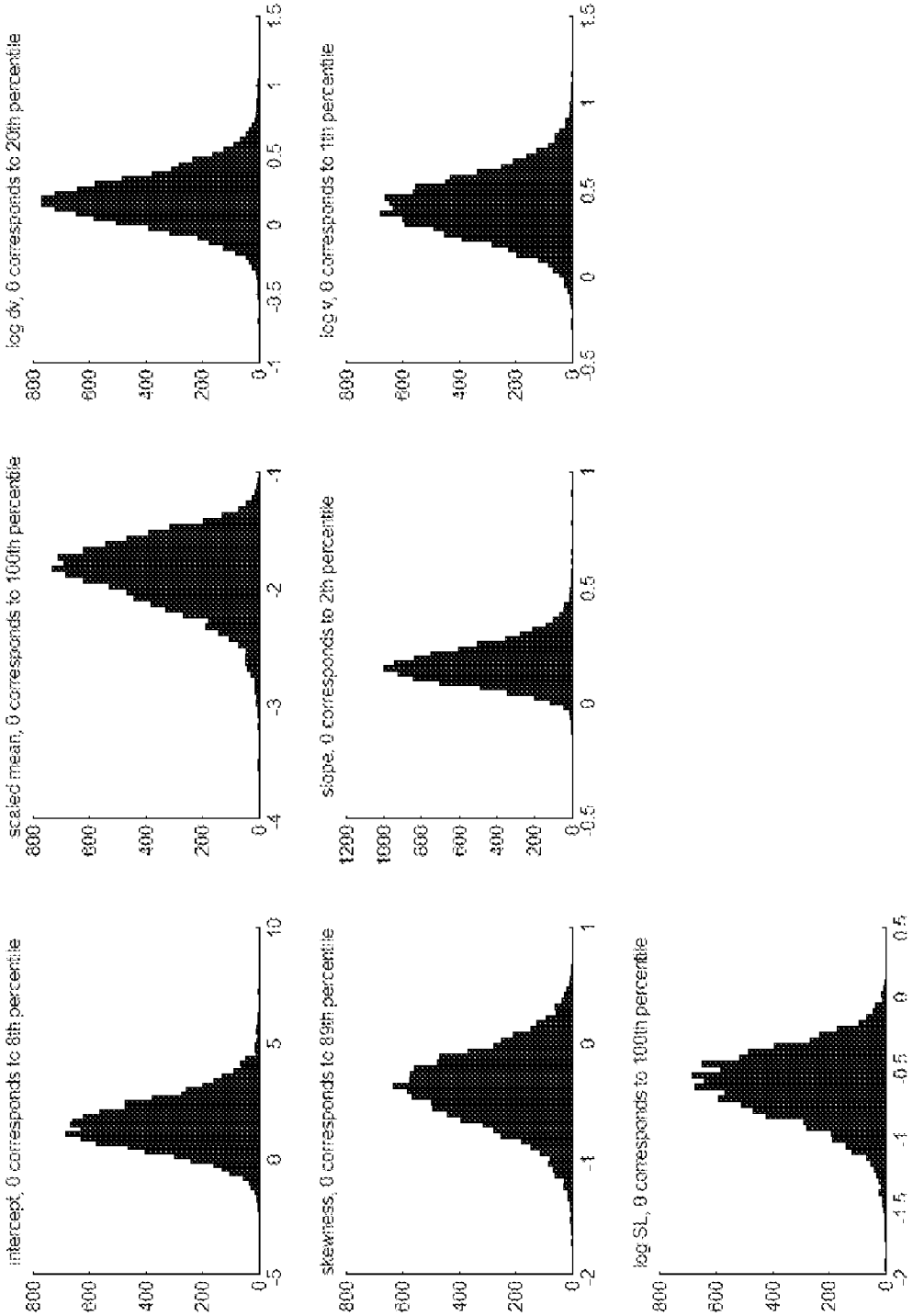

intercept, 0 corresponds to 8th percentile
scaled mean, 0 corresponds to 100th percentile
log dv, 0 corresponds to 20th percentile
skewness, 0 corresponds to 89th percentile
slope, 0 corresponds to 2th percentile
log v, 0 corresponds to 1th percentile
log SL, 0 corresponds to 100th percentile

FIGURE 10

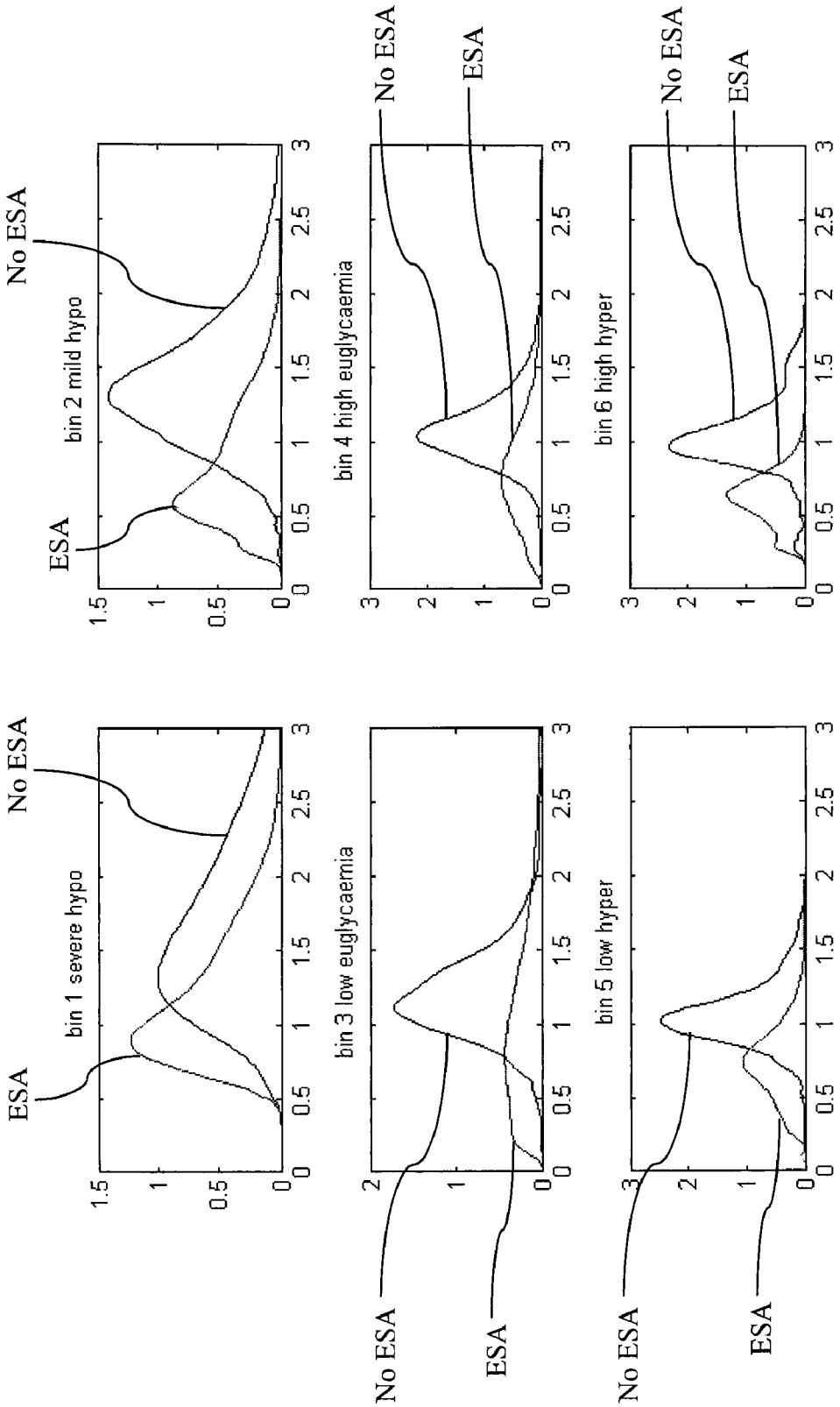

bin 1 severe hypo
bin 2 mild hypo
bin 3 low euglycaemia
bin 4 high euglycaemia
bin 5 low hyper
bin 6 high hyper
ESA
No ESA

FIGURE 11

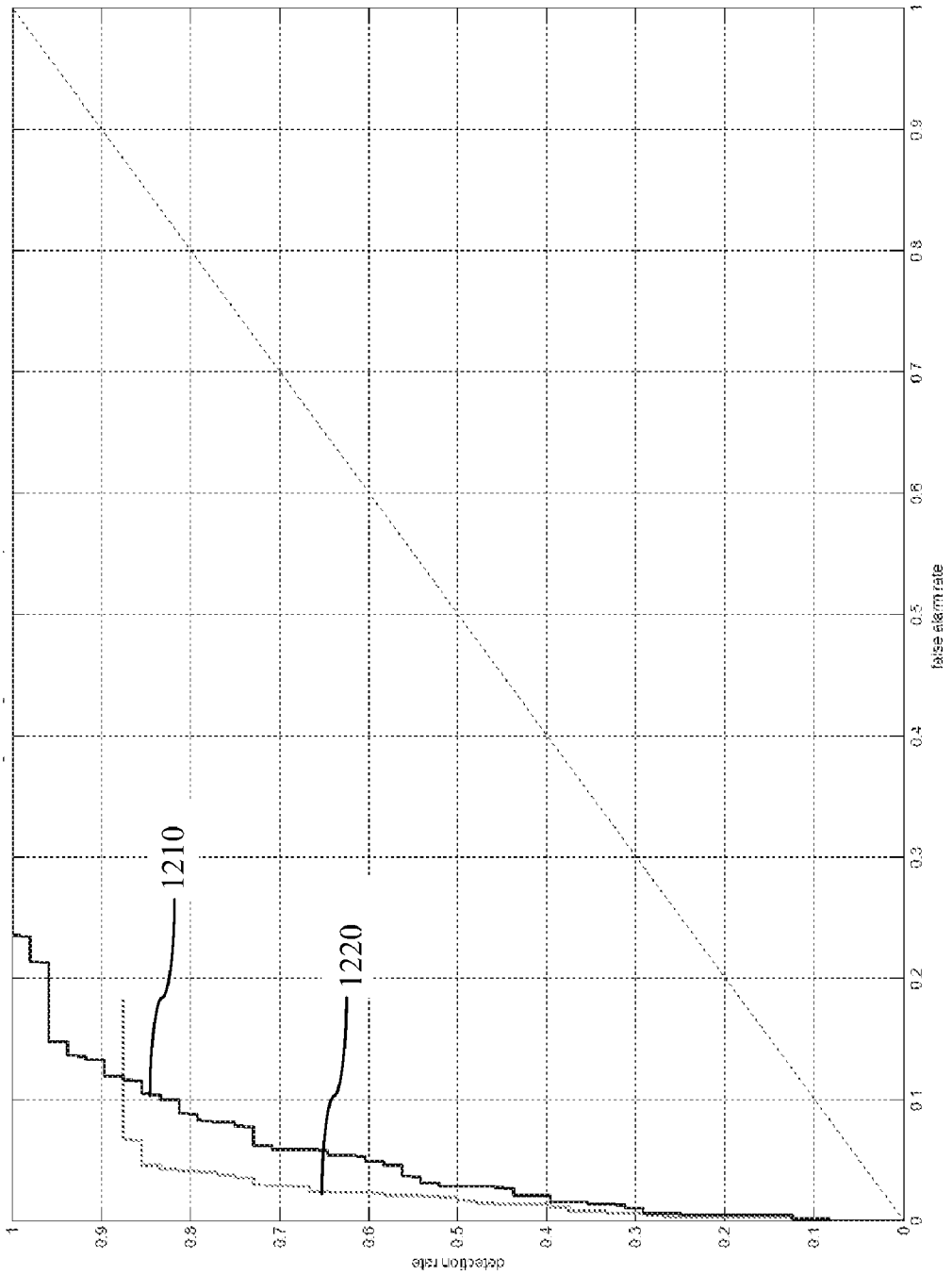

1210
1220
detection rate
false alarm rate
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

FIGURE 12

METHOD, SYSTEM AND COMPUTER PROGRAM PRODUCT FOR REAL-TIME DETECTION OF SENSITIVITY DECLINE IN ANALYTE SENSORS

RELATED APPLICATION

[0001] This application claims priority under 35 USC §119 to U.S. Provisional Application No. 60/854,566 entitled "Method, System and computer program product for real-time detection of sensitivity decline in continuous glucose sensors (CGS)" filed on Oct. 26, 2006, the disclosure of which is incorporated herein by reference for all purposes.

BACKGROUND

[0002] Analyte, 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 analyte monitoring systems include a transcutaneous or subcutaneous analyte sensor configuration which is, for example, partially mounted on the skin of a subject whose analyte 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.

[0003] 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 a receiver/monitor unit. The receiver/monitor unit performs data analysis, among others on the received analyte levels to generate information pertaining to the monitored analyte levels.

[0004] In view of the foregoing, it would be desirable to have an accurate assessment of the glucose level fluctuations, and in particular, the detection of analyte sensor signal drop outs of sensor sensitivity referred to as Early Signal Attenuation (ESA).

SUMMARY OF THE DISCLOSURE

[0005] In one embodiment, method, system and computer program product for receiving a plurality of analyte sensor related signals, determining a probability of signal attenuation associated with the received plurality of analyte sensor related signals, verifying the presence of signal attenuation when the determined probability exceeds a predetermined threshold level, and generating a first output signal associated with the verification of the presence of signal attenuation, are disclosed.

[0006] These and other objects, features and advantages of the present disclosure 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

[0007] FIG. **1** illustrates a block diagram of a data monitoring and management system for practicing one or more embodiments of the present disclosure;

[0008] FIG. **2** is a block diagram of the transmitter unit of the data monitoring and management system shown in FIG. **1** in accordance with one embodiment of the present disclosure;

[0009] FIG. **3** is a block diagram of the receiver/monitor unit of the data monitoring and management system shown in FIG. **1** in accordance with one embodiment of the present disclosure;

[0010] FIGS. **4**A-**4**B illustrate a perspective view and a cross sectional view, respectively of an analyte sensor in accordance with one embodiment of the present disclosure;

[0011] FIG. **5** is a block diagram illustrating real time early signal attenuation (ESA) in one embodiment of the present disclosure;

[0012] FIG. **6** is a flowchart illustrating an overall ESA detection routine in accordance with one embodiment of the present disclosure;

[0013] FIG. **7** is a flowchart illustrating real-time detection of sensor current abnormalities described in conjunction with module **1** of FIG. **5** in accordance with one embodiment of the present disclosure;

[0014] FIG. **8** is a flowchart illustrating verification routine of module **2** in FIG. **5** to confirm or reject the output of module **1** in accordance with one embodiment of the present disclosure;

[0015] FIG. **9** illustrates a real time current signal characteristics evaluation approach based on a sliding window process of module **1** in FIG. **5** in accordance with one embodiment of the present disclosure;

[0016] FIG. **10** illustrates bootstrap estimation of coefficients for module **1** of FIG. **5** in accordance with one embodiment of the present disclosure;

[0017] FIG. **11** illustrates Gaussian kernel estimation of the normalized sensitivity density of module **2** of FIG. **5** in accordance with one embodiment of the present disclosure; and

[0018] FIG. **12** illustrates output curve of the first module compared with the output curve of the combined first and second modules of FIG. **5**, based on a predetermined test data set and detection threshold of FIG. **7** in accordance with embodiment of the present disclosure.

DETAILED DESCRIPTION

[0019] As described in further detail below, in accordance with the various embodiments of the present disclosure, there is provided method, system and computer program product for real time detection of analyte sensor sensitivity decline in data processing and control systems including, for example, analyte monitoring systems. In particular, within the scope of the present disclosure, there are provided method, system and computer program product for the detection of episodes of low sensor sensitivity that may cause clinically significant sensor related errors, including, for example, early sensor attenuation (ESA) represented by sensor sensitivity (defined as the ratio between the analyte sensor current level and the blood glucose level) decline which may exist during the initial 12-24 hours of the sensor life, or during night time use of the analyte sensor ("night time drop outs").

[0020] FIG. **1** illustrates a data monitoring and management system such as, for example, analyte (e.g., glucose) monitoring system **100** in accordance with one embodiment of the present disclosure. The subject disclosure 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 disclosure. 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.

[0021] 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.

[0022] The analyte monitoring system **100** includes a sensor **101**, a transmitter unit **102** coupled to the sensor **101**, and a primary receiver unit **104** which is configured to communicate with the transmitter unit **102** via a communication link **103**. The primary receiver unit **104** may be further configured to transmit data to a data processing terminal **105** for evaluating the data received by the primary receiver unit **104**. Moreover, the data processing terminal in one embodiment may be configured to receive data directly from the transmitter unit **102** via a communication link which may optionally be configured for bi-directional communication.

[0023] Also shown in FIG. **1** is a secondary receiver unit **106** which is operatively coupled to the communication link **103** and configured to receive data transmitted from the transmitter unit **102**. Moreover, as shown in the Figure, the secondary receiver unit **106** is configured to communicate with the primary receiver unit **104** as well as the data processing terminal **105**. Indeed, the secondary receiver unit **106** may be configured for bi-directional wireless communication with each of the primary receiver unit **104** and the data processing terminal **105**. As discussed in further detail below, in one embodiment of the present disclosure, the secondary receiver unit **106** may be configured to include a limited number of functions and features as compared with the primary receiver unit **104**. As such, the secondary receiver unit **106** may be configured substantially in a smaller compact housing or embodied in a device such as a wrist watch, for example. Alternatively, the secondary receiver unit **106** may be configured with the same or substantially similar functionality as the primary receiver unit **104**, and may be configured to be used in conjunction with a docking cradle unit for placement by bedside, for night time monitoring, and/or bi-directional communication device.

[0024] Only one sensor **101**, transmitter unit **102**, communication link **103**, and data processing terminal **105** are shown in the embodiment of the analyte monitoring system **100** illustrated in FIG. **1**. However, it will be appreciated by one of ordinary skill in the art that the analyte monitoring system **100** may include one or more sensor **101**, transmitter unit **102**, communication link **103**, and data processing terminal **105**. Moreover, within the scope of the present disclosure, the analyte monitoring system **100** may be a continuous monitoring system, or semi-continuous, or a discrete monitoring system. In a multi-component environment, each device is configured to be uniquely identified by each of the other devices in the system so that communication conflict is readily resolved between the various components within the analyte monitoring system **100**.

[0025] In one embodiment of the present disclosure, the sensor **101** is physically positioned in or on the body of a user whose analyte level is being monitored. The sensor **101** may be configured to continuously sample the analyte level of the user and convert the sampled analyte level into a corresponding data signal for transmission by the transmitter unit **102**. In one embodiment, the transmitter unit **102** is coupled to the sensor **101** so that both devices are positioned on the user's body, with at least a portion of the analyte sensor **101** positioned transcutaneously under the skin layer of the user. The transmitter unit **102** performs data processing such as filtering and encoding on data signals, each of which corresponds to a sampled analyte level of the user, for transmission to the primary receiver unit **104** via the communication link **103**.

[0026] In one embodiment, the analyte monitoring system **100** is configured as a one-way RF communication path from the transmitter unit **102** to the primary receiver unit **104**. In such embodiment, the transmitter unit **102** transmits the sampled data signals received from the sensor **101** without acknowledgement from the primary receiver unit **104** that the transmitted sampled data signals have been received. For example, the transmitter unit **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 primary receiver unit **104** may be configured to detect such transmitted encoded sampled data signals at predetermined time intervals. Alternatively, the analyte monitoring system **100** may be configured with a bi-directional RF (or otherwise) communication between the transmitter unit **102** and the primary receiver unit **104**.

[0027] Additionally, in one aspect, the primary receiver unit **104** may include two sections. The first section is an analog interface section that is configured to communicate with the transmitter unit **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 unit **102**, which are thereafter, demodulated with a local oscillator and filtered through a band-pass filter. The second section of the primary receiver unit **104** is a data processing section which is configured to process the data signals received from the transmitter unit **102** such as by performing data decoding, error detection and correction, data clock generation, and data bit recovery.

[0028] In operation, upon completing the power-on procedure, the primary receiver unit **104** is configured to detect the presence of the transmitter unit **102** within its range based on, for example, the strength of the detected data signals received from the transmitter unit **102** or predetermined transmitter identification information. Upon successful synchronization with the corresponding transmitter unit **102**, the primary receiver unit **104** is configured to begin receiving from the transmitter unit **102** data signals corresponding to the user's detected analyte level. More specifically, the primary receiver unit **104** in one embodiment is configured to perform synchronized time hopping with the corresponding synchronized transmitter unit **102** via the communication link **103** to obtain the user's detected analyte level.

[0029] 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 analyte level of the user.

[0030] Within the scope of the present disclosure, 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 analyte 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 analyte levels received from the transmitter unit **102**.

[0031] Additionally, the transmitter unit **102**, the primary receiver unit **104** and the data processing terminal **105** may each be configured for bi-directional wireless communication such that each of the transmitter unit **102**, the primary receiver unit **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 unit **102** via the communication link **106**, where the communication link **106**, as described above, may be configured for bi-directional communication.

[0032] In this embodiment, the data processing terminal **105** which may include an insulin pump, may be configured to receive the analyte signals from the transmitter unit **102**, and thus, incorporate the functions of the receiver **103** including data processing for managing the patient's insulin therapy and analyte 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.

[0033] 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 disclosure. Referring to the Figure, the transmitter unit **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 measurement section **203**, each of which is operatively coupled to a transmitter processor **204** such as a central processing unit (CPU).

[0034] 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 unit **102** to provide the necessary power for the transmitter unit **102**. Additionally, as can be seen from the Figure, a clock **208** is provided to, among others, supply real time information to the transmitter processor **204**.

[0035] As can be seen from FIG. **2**, the sensor unit **101** (FIG. **1**) is 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 unit **102**. 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, or alternatively provided on a substrate material using laser or photolithography.

[0036] 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 unit **102**, while a unidirectional output is established from the output of the RF transmitter **206** of the transmitter unit **102** for transmission to the primary receiver unit **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 unit **102** is configured to transmit to the primary receiver unit **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 unit **102** for operation upon completion of the manufacturing process as well as for direct communication for diagnostic and testing purposes.

[0037] As discussed above, the transmitter processor **204** is configured to transmit control signals to the various sections of the transmitter unit **102** during the operation of the transmitter unit **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 unit **102**, as well as the data signals received from the sensor **101**. The stored information may be retrieved and processed for transmission to the primary receiver unit **104** under the control of the transmitter processor **204**. Furthermore, the power supply **207** may include a commercially available battery.

[0038] The transmitter unit **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 unit **102** may place the transmitter unit **102** in the lower power, non-operating state (i.e., post-manufacture sleep mode). In this manner, the shelf life of the transmitter unit **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 disclosure, 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**.

[0039] Referring back to FIG. **2**, the power supply section **207** of the transmitter unit **102** in one embodiment may include a rechargeable battery unit that may be recharged by a separate power supply recharging unit (for example, provided in the receiver unit **104**) so that the transmitter unit **102** may be powered for a longer period of usage time. Moreover, in one embodiment, the transmitter unit **102** may be configured without a battery in the power supply section **207**, in which case the transmitter unit **102** may be configured to receive power from an external power supply source (for example, a battery) as discussed in further detail below.

[0040] Referring yet again to FIG. **2**, the temperature detection section **203** of the transmitter unit **102** is configured to monitor the temperature of the skin near the sensor insertion site. The temperature reading is used to adjust the analyte readings obtained from the analog interface **201**. The RF transmitter **206** of the transmitter unit **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 primary receiver unit **104**.

[0041] 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 unit **102** of the data monitoring and management system **100**. The leak detection circuit **214** in accordance with one embodiment of the present disclosure 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.

[0042] FIG. **3** is a block diagram of the receiver/monitor unit of the data monitoring and management system shown in FIG. **1** in accordance with one embodiment of the present disclosure. Referring to FIG. **3**, the primary receiver unit **104** includes a blood glucose test strip interface **301**, an RF receiver **302**, an input **303**, a temperature detection section **304**, and a clock **305**, each of which is operatively coupled to a receiver processor **307**. As can be further seen from the Figure, the primary receiver unit **104** also includes a power supply **306** operatively coupled to a power conversion and monitoring section **308**. Further, the power conversion and monitoring section **308** is also coupled to the receiver processor **307**. Moreover, also shown are a receiver serial communication section **309**, and an output **310**, each operatively coupled to the receiver processor **307**.

[0043] In one embodiment, the test strip interface **301** includes a glucose level testing portion to receive a manual insertion of a glucose test strip, and thereby determine and display the glucose level of the test strip on the output **310** of the primary receiver unit **104**. This manual testing of glucose can be used to calibrate sensor **101**. The RF receiver **302** is configured to communicate, via the communication link **103** (FIG. **1**) with the RF transmitter **206** of the transmitter unit **102**, to receive encoded data signals from the transmitter unit **102** for, among others, signal mixing, demodulation, and other data processing. The input **303** of the primary receiver unit **104** is configured to allow the user to enter information into the primary receiver unit **104** as needed. In one aspect, the input **303** may include one or more keys of a keypad, a touch-sensitive screen, or a voice-activated input command unit. The temperature detection section **304** is configured to provide temperature information of the primary receiver unit **104** to the receiver processor **307**, while the clock **305** provides, among others, real time information to the receiver processor **307**.

[0044] Each of the various components of the primary receiver unit **104** shown in FIG. **3** is powered by the power supply **306** which, in one embodiment, includes a battery. Furthermore, the power conversion and monitoring section **308** is configured to monitor the power usage by the various components in the primary receiver unit **104** for effective power management and to alert the user, for example, in the event of power usage which renders the primary receiver unit **104** in sub-optimal operating conditions. An example of such sub-optimal operating condition may include, for example, operating the vibration output mode (as discussed below) for a period of time thus substantially draining the power supply **306** while the processor **307** (thus, the primary receiver unit **104**) is turned on. Moreover, the power conversion and monitoring section **308** may additionally be configured to include a reverse polarity protection circuit such as a field effect transistor (FET) configured as a battery activated switch.

[0045] The serial communication section **309** in the primary receiver unit **104** is configured to provide a bi-directional communication path from the testing and/or manufacturing equipment for, among others, initialization, testing, and configuration of the primary receiver unit **104**. Serial communication section **104** can also be used to upload data to a computer, such as time-stamped blood glucose data. The communication link with an external device (not shown) can be made, for example, by cable, infrared (IR) or RF link. The output **310** of the primary receiver unit **104** is configured to provide, among others, a graphical user interface (GUI) such as a liquid crystal display (LCD) for displaying information. Additionally, the output **310** may also include an integrated speaker for outputting audible signals as well as to provide vibration output as commonly found in handheld electronic devices, such as mobile telephones presently available. In a further embodiment, the primary receiver unit **104** also includes an electro-luminescent lamp configured to provide backlighting to the output **310** for output visual display in dark ambient surroundings.

[0046] Referring back to FIG. **3**, the primary receiver unit **104** in one embodiment may also include a storage section such as a programmable, non-volatile memory device as part of the processor **307**, or provided separately in the primary receiver unit **104**, operatively coupled to the processor **307**. The processor **307** is further configured to perform Manchester decoding as well as error detection and correction upon the encoded data signals received from the transmitter unit **102** via the communication link **103**.

[0047] In a further embodiment, the one or more of the transmitter unit **102**, the primary receiver unit **104**, secondary receiver unit **105**, or the data processing terminal/infusion section **105** may be configured to receive the blood glucose value wirelessly over a communication link from, for example, a glucose meter. In still a further embodiment, the user or patient manipulating or using the analyte monitoring system **100** (FIG. **1**) may manually input the blood glucose value using, for example, a user interface (for example, a keyboard, keypad, and the like) incorporated in the one or

more of the transmitter unit **102**, the primary receiver unit **104**, secondary receiver unit **105**, or the data processing terminal/infusion section **105**.

[0048] Additional detailed description of the continuous analyte monitoring system, its various components including the functional descriptions of the transmitter are provided in U.S. Pat. No. 6,175,752 issued Jan. 16, 2001 entitled "Analyte Monitoring Device and Methods of Use", and in application Ser. No. 10/745,878 filed Dec. 26, 2003 entitled "Continuous Glucose Monitoring System and Methods of Use", each assigned to Abbott Diabetes Care, Inc., of Alameda, Calif.

[0049] FIGS. **4**A-**4**B illustrate a perspective view and a cross sectional view, respectively of an analyte sensor in accordance with one embodiment of the present disclosure. Referring to FIG. **4**A, a perspective view of a sensor **400**, the major portion of which is above the surface of the skin **410**, with an insertion tip **430** penetrating through the skin and into the subcutaneous space **420** in contact with the user's biofluid such as interstitial fluid. Contact portions of a working electrode **401**, a reference electrode **402**, and a counter electrode **403** can be seen on the portion of the sensor **400** situated above the skin surface **410**. Working electrode **401**, a reference electrode **402**, and a counter electrode **403** can be seen at the end of the insertion tip **403**.

[0050] Referring now to FIG. **4**B, a cross sectional view of the sensor **400** in one embodiment is shown. In particular, it can be seen that the various electrodes of the sensor **400** as well as the substrate and the dielectric layers are provided in a stacked or layered configuration or construction. For example, as shown in FIG. **4**B, in one aspect, the sensor **400** (such as the sensor unit **101** FIG. **1**), includes a substrate layer **404**, and a first conducting layer **401** such as a carbon trace disposed on at least a portion of the substrate layer **404**, and which may comprise the working electrode. Also shown disposed on at least a portion of the first conducting layer **401** is a sensing layer **408**.

[0051] Referring back to FIG. **4**B, a first insulation layer such as a first dielectric layer **405** is disposed or stacked on at least a portion of the first conducting layer **401**, and further, a second conducting layer **409** such as another carbon trace may be disposed or stacked on top of at least a portion of the first insulation layer (or dielectric layer) **405**. As shown in FIG. **4**B, the second conducting layer **409** may comprise the reference electrode **402**, and in one aspect, may include a layer of silver/silver chloride (Ag/AgCl).

[0052] Referring still again to FIG. **4**B, a second insulation layer **406** such as a dielectric layer in one embodiment may be disposed or stacked on at least a portion of the second conducting layer **409**. Further, a third conducting layer **403** which may include carbon trace and that may comprise the counter electrode **403** may in one embodiment be disposed on at least a portion of the second insulation layer **406**. Finally, a third insulation layer **407** is disposed or stacked on at least a portion of the third conducting layer **403**. In this manner, the sensor **400** may be configured in a stacked or layered construction or configuration such that at least a portion of each of the conducting layers is separated by a respective insulation layer (for example, a dielectric layer).

[0053] Additionally, within the scope of the present disclosure, some or all of the electrodes **401**, **402**, **403** may be provided on the same side of the substrate **404** in a stacked construction as described above, or alternatively, may be provided in a co-planar manner such that each electrode is disposed on the same plane on the substrate **404**, however, with a dielectric material or insulation material disposed between the conducting layers/electrodes. Furthermore, in still another aspect of the present disclosure, the one or more conducting layers such as the electrodes **401**, **402**, **403** may be disposed on opposing sides of the substrate **404**.

[0054] FIG. **5** is a block diagram illustrating real time early signal attenuation (ESA) in one embodiment of the present disclosure. Referring to FIG. **5**, in one embodiment, the overall sensitivity decline detector **500** includes a first module **510** configured to perform an estimation of the probability of sensitivity decline based on a window of analyte sensor measurements to determine whether a finger stick measurement of blood glucose level is necessary. Based on the estimated probability of the sensitivity decline performed by the first module **510**, when it is determined that the finger stick measurement of the blood glucose level is necessary, as shown in FIG. **5**, in one aspect of the present disclosure, the second module **520** uses the measured blood glucose value to verify or otherwise confirm or reject the estimated probability of the sensitivity decline performed by the first module **510**. In one aspect, the second module **520** may be configured to confirm or reject the results of the first module **510** (e.g., the estimated probability of sensitivity decline) based upon a statistical determination.

[0055] That is, in one aspect, the first module **510** of the sensitivity decline detector **500** of FIG. **5** may be configured to estimate the probability of the analyte sensor sensitivity decline based on an analysis of a window of sensor values (for example, current signals from the analyte sensor for a predetermined time period). More specifically, the first module **510** may be configured to estimate the probability of the sensor sensitivity decline based on a sliding window extractor of sensor current signal characteristics, a model based estimation of the probability of sensitivity decline based on the determined or retrieved sensor current signal characteristics, and/or a comparison of the estimated probability to a predetermined threshold value τ.

[0056] Referring back to FIG. **5**, the logistic estimator **511** of the first module **510** may be configured in one embodiment to retrieve or extract a sliding window of sensor current signal characteristics, and to perform the estimation of the probability of the sensitivity decline based on the sensor current signal characteristics, and to compare the estimated probability of the sensitivity decline to a predetermined threshold τ to determine, whether verification of the estimated sensitivity decline is desired, or whether it can be confirmed that ESA or night time drop outs is not detected based on the estimated probability of the sensitivity decline.

[0057] Referring again to FIG. **5**, as shown, when it is determined that confirmation or verification of the estimated probability of the sensitivity decline is desired (based on, for example, when the estimated probability exceeds the predetermined threshold value τ determined in the first module **510**, hypothesis analysis module **521** of the second module **520** in the sensitivity decline detector **500** in one embodiment receives the capillary blood measurement from a blood glucose measurement device such as a blood glucose meter including FreesStyle® Lite, Freestyle Flash®, FreeStyle Freedom®, or Precision Xtra™ blood glucose meters commercially available from Abbott Diabetes Care, Inc., of Alameda, Calif. In one aspect, based on the received capillary blood glucose measurement and the analyte sensor current characteristics or values, the estimated probability of the sensor sensitivity decline may be confirmed or rejected, thus

confirming the presence of ESA or night time drop out (in the event the corresponding data point is associated with night time sensor current value), or alternatively, confirming that the ESA or night time drop out is not present.

[0058] In the manner described, in one aspect of the present disclosure, there is provided a real time detection routine based on sensor current signal characteristics, where the detector **500** (FIG. **5**) includes a first module **510** configured in one embodiment to perform the detection and estimation of the probability of the sensor sensitivity decline, and a second module **520** configured in one aspect to verify the presence or absence of ESA or night time drop outs based on the probability estimations determined by the first module **510**. Accordingly, in one aspect of the present disclosure, ESA episodes or night time declines or drop outs maybe accurately detected while minimizing the potential for false alarms or false negatives.

[0059] Referring again to FIG. **5**, a sliding window process is used in the first module **510** of the sensor sensitivity estimator **500** in one embodiment to mitigate between the desire for a real time decision process and the necessity of redundancy for sensor current characteristics estimation. An example of the sliding window process is illustrated in accordance with one embodiment of the present disclosure in FIG. **9**.

[0060] For instance, in one aspect, during the processing performed by the first module **510**, at each iteration of the decision process, a time window is selected, and based on the sensor current signals determined during the selected time window, one or more predetermined sensor characteristics are determined. By way of nonlimiting examples, the one or more predetermined sensor characteristics may include the mean current signal level, the current signal variance, the average slope of the current signal, and the average sensor life (or the time elapsed since the insertion or transcutaneous positioning of the analyte sensor).

[0061] Thereafter, the selected time window is then slid by a fixed number of minutes for the next iteration. In one aspect, the width or duration of the time window and the incremental step size may be predetermined or established to 60 minutes, thus generating non-overlapping time window to minimize potential correlation between decisions. Within the scope of the present disclosure, other approaches may be contemplated, for example, where the sliding time windows may include time duration of approximately 30 minutes with an incremental one minute step.

[0062] In one aspect, the following expressions may be used to determine the sensor characteristic estimations discussed above such as, for example, the sensor signal mean, the average slope and the variance values:

$$\begin{bmatrix} \text{mean} \\ \text{slope} \end{bmatrix} = (X'X)^{-1}X'Y$$

Where X is a matrix with a column of 1s and a column of data index and Y is a column vector of current values

$$\text{variance} = \frac{1}{n-1}\sum_{i=0}^{width}(current_{t+i} - \text{mean})^2$$

where t is the index of the first available data point in the time window

[0063] Referring back to FIG. **5**, after estimating or determining the sensor characteristics described above, a four-dimensional feature vector corresponding to a time window of sensor current signal is generated. In one aspect, the generated feature vector and logistic regression approach may be used to estimate the probability that the sensor is undergoing or experiencing early signal attenuation (ESA) during each of the predetermined time window. In one aspect, the logistic regression approach for determination or estimation of the probability of ESA presence Pr[ESA] may be expressed as follows:

$$Pr[ESA \mid x_n] = \frac{\exp^{\langle \beta, x_n \rangle}}{1 + \exp^{\langle \beta, x_n \rangle}}$$

$$x_n = \begin{bmatrix} 1 \\ \log(mean_n) \\ \log(variance_n) \\ slope_n \\ \log(sensorlife_n) \end{bmatrix}$$

[0064] In one aspect, the coefficient vector β plays a significant role in the efficiency of the sensor signal attenuation estimation. That is, in one embodiment, a predetermined number of sensor insertions may be used to empirically determine or estimate the model coefficients. More specifically, in one aspect, a bootstrap estimation procedure may be performed to add robustness to the model coefficients. For example, a generalized linear model fit approach may be applied to a predetermined time period to determine the coefficient vector β. Based on a predefined number of iterations, an empirical probability distribution function of each coefficient may be determined, for example, as shown in FIG. **10**, where each selected coefficient corresponds to the mode of the associated distribution.

[0065] After the determination of the one or more sensor current characteristics or parameters, and the determination of the corresponding coefficients, the probability of ESA presence Pr[ESA] is estimated based on, in one embodiment, the following expression:

$$Pr[ESA \mid x_n] = \frac{\exp^{1.511 - 1.813\times\log(mean) + 0.158\times slope + 0.399\times\log(variance) - 0.576\times\log(SensorLife)}}{1 + \exp^{1.511 - 1.813\times\log(mean) + 0.158\times slope + 0.399\times\log(variance) - 0.576\times\log(SensorLife)}} \quad (2)$$

[0066] It is to be noted that within the scope of the present disclosure, the estimation of the probability of the ESA presence Pr[ESA] as described by the function shown above may be modified depending upon the design or the associated underlying parameters, such as, for example, the time of day information, or the detrended variance of the sensor current signal, among others.

[0067] Referring yet again to FIG. **5**, after the determination of the probability of ESA presence based on the estimation described above, in one aspect, the estimated probability is compared to a preselected threshold level, and based on the comparison, a request for capillary blood glucose measurement may be prompted. In one aspect, the predetermined threshold level may include 0.416 for comparison with the estimated probability of ESA presence. Alternatively, within the scope of the present disclosure, the predetermined threshold level may vary within the range of approximately 0.3 to 0.6.

[0068] As described above, in one aspect of the present disclosure, the first module **510** of the sensor sensitivity estimator **500** (FIG. **5**) is configured to perform estimation of the probability of ESA presence based on the characteristics or parameters associated with the analyte sensor and the sensor current signals. In one embodiment, the second module **520** of the sensor sensitivity estimator **500** (FIG. **5**) may be configured to perform additional processing based on capillary blood glucose measurement to provide substantially real time estimation of the early sensor attenuation (ESA) of the analyte sensors. That is, since ESA is defined by a drop or decrease of sensitivity (that is, the current signal of the sensor over the blood glucose ratio), the distribution of the sensitivity during ESA occurrence is generally lower than the distribution during normal functioning conditions. Additionally, based on the non linear relation ship between the sensor current level and blood glucose measurements, the ESA presence probability estimation using capillary blood measurements may be determined using a bin (e.g., category) construction approach, as well as the estimation of the empirical distribution functions of the nominal sensitivity ratio.

[0069] More particularly, in one aspect of the present disclosure, the instantaneous sensitivity (IS) may be defined as the ratio of the actual current value of the analyte sensor and the actual blood glucose value at a given point in time (defined, for example, by the expression (a) below. However, due to noise in the signals, for example, particularly in the case of a stand alone measurement such as a single blood glucose measurement, the instantaneous sensitivity (IS) may be approximated by determining the average sensor current signal levels around the time of the fingerstick blood glucose determination, determines, for example, by the expression (b) shown below.

$$a.\ DS_t = \frac{current_t}{BG_t} \tag{3}$$

$$b.\ IS_t = \frac{\frac{1}{11}\sum_{i=-5}^{5} current_{t+i}}{BG_t}$$

[0070] Given that each analyte sensor has a different sensitivity, and thus the instantaneous sensitivity (IS) is highly sensor dependent, the absolute value of the instantaneous sensitivity (IS) may not provide reliable indication of ESA presence. On the other hand, during manufacturing, each analyte sensor is associated with a nominal sensitivity value. Accordingly, the ratio of the instantaneous sensitivity over the sensor nominal sensitivity will result in a more sensor independent, reliable ESA detection mechanism. Accordingly, the sensitivity ratio $R_s(t)$ at time t may be defined in one aspect as follows:

$$R_{S(t)} = \frac{IS(t)}{S_{nominal}} = \frac{1}{11}\frac{\sum_{i=-5}^{5} current_{t+i}}{S_{nominal} \times BG_t} \tag{4}$$

[0071] Referring to the discussion above, the blood glucose bin/category construction approach in one embodiment may include defining a transformation of the blood glucose measurement scale which rectifies a discrepancy between the measured and estimated blood glucose values. That is, in one aspect, the defined transformation approach corresponds to or is associated with a typical distribution of blood glucose levels. For example, the transformation approach defining the various bins/categories may be determined based on the following expression:

$$r = 1.509 \times e^{1.084 \times log(log(BG) - 5.381)} \text{ where BG is in mg/dl} \tag{5}$$

[0072] where the following scaled glucose bins may be defined:

[0073] 1. r<−2, severe hypoglycemia

[0074] 2. −2<=r<−1, mild hypoglycemia

[0075] 3. −1<=r<0, low euglycemia

[0076] 4. 0<=r<1, high euglycemia

[0077] 5. 1<=r<2, mild hyperglycemia

[0078] 6. 2<=r, severe hyperglycemia

[0079] Upon determination of the bin/category for use with the estimation of the probability of ESA presence, in one aspect, kernel density estimation (using Gaussian kernel, **24**, for example) may be used to estimate the distribution of the sensitivity ratio Rs in each bin/category described above. In one aspect, this estimation of the distribution in sensitivity ratio Rs is shown in FIG. **11**, where for each bin/category (including, for example, severe hypoglycemia (bin**1**), mild hypoglycemia (bin**2**), low euglycaemia (bin**3**), high euglycaemia (bin**4**), low hyperglycemia (bin**5**), and high hyperglycemia (bin**6**)), each chart illustrates the associated distribution where ESA presence is detected.

[0080] Referring again to the discussions above, based on the estimation of the probability density functions of the estimated distribution of the sensitivity ratio Rs in each bin/category, in one aspect, a non-parametric hypothesis testing approach based on Bayes' law may be implemented. For example, in one aspect of the present disclosure, from Bayes' law, the estimated probability of ESA presence knowing the sensitivities ratio and the blood glucose bin/category may be decomposed based on the following expression:

$$\hat{\Pr}\ [ESA \mid R_S = \rho\ \&\ r \in bin_i] = \frac{\pi_{ESA}\hat{f}_i(\rho)}{\pi_{ESA}\hat{f}_{ESA,i}(\rho) + \pi_{\overline{FSA}}\hat{f}_{\overline{FSA},i}(\rho)} \tag{6}$$

[0081] where π_a is the proportion of events in class a and $\hat{f}_{a,i}$ is the previously estimated probability density function of R_S in bin/category i for class a.

[0082] In addition, to minimize the overall probability of error the following decision rule may be applied:

$$\text{sensor is } ESA \text{ if } \frac{\Pr\ [ESA \mid R_S = \rho \ \&\ r \in bin_i]}{\Pr\ [\overline{ESA} \mid R_S = \rho \ \&\ r \in bin_i]} > 1 \tag{7}$$

$$\Rightarrow \frac{\hat{f}_{ESA,i}(\rho)}{\hat{f}_{\overline{ESA},i}(\rho)} > \frac{\pi_{\overline{ESA}}}{\pi_{ESA}}$$

$$\text{assuming } \pi_{\overline{ESA}} = \pi_{ESA} = 0.5$$

$$\Rightarrow \frac{\hat{f}_{ESA,i}(\rho)}{\hat{f}_{\overline{ESA},i}(\rho)} > 1 \Rightarrow \hat{f}_{ESA,i}(\rho) > \hat{f}_{\overline{ESA},i}(\rho)$$

[0083] Accordingly, based on the above, the hypothesis analysis module (**521**) of the second module **520** shown in FIG. **5** in one embodiment may be configured to verify/confirm the presence of ESA for a given analyte sensor based on the capillary blood glucose level measurement reading, when the capillary blood glucose measurement is in bin/category i, when the sensitivity ratio Rs is less than the corresponding defined threshold level t_i. For example, given the six blood glucose bins/categories (bin**1** to bin**6**) described above, the respective threshold level t_i is: t_1=1.138, t_2=0.853, t_3=0.783, t_4=0.784, t_5=0.829, and t_6=0.797.

[0084] In this manner, in one aspect of the present disclosure, the method, system and computer program product provides for, but not limited to, early detection of sensitivity drops in continuous glucose monitoring systems. Sensitivity drops can be found in the first 24 hours, for example, of the sensor life, and while the potential adverse impacts may be minimized by frequent calibration or sensor masking, such sensitivity drops have clinically significant effects on the accuracy of the sensor data, and in turn, potential danger to the patient using the sensor. Accordingly, in one aspect, there is provided method, system, and computer program product for estimating or determining the probability of the presence of ESA based on the sensor current signal characteristics, and thereafter, performing a confirmation or verification routine to determine whether the sensitivity drop probability estimated based on the sensor current signal characteristics corresponds to a real time occurrence of a corresponding sensitivity drop in the sensor.

[0085] Accordingly, sensor accuracy, and in particular in the critical hypoglycemic ranges may be improved, multiple calibrations and/or sensor masking may be avoided during the early stages of the sensor life, and further, sensor calibration during sensitivity drop occurrence which may result in undetected hypoglycemic events, may be avoided.

[0086] FIG. **6** is a flowchart illustrating an overall ESA detection routine in accordance with one embodiment of the present disclosure. Referring to FIG. **6**, in one embodiment of the present disclosure, a predetermined number of sensor data is retrieved or collected (**610**), and thereafter, it is determined whether the probability estimation for the sensitivity decline determination is appropriate (**620**). In one aspect, one or more of the following parameters may be used to determine whether the determination of the probability estimation of the sensitivity decline is appropriate: presence or collection of sufficient data points associated with the analyte sensor, timing of the probability estimation relative to when the analyte sensor was inserted or subcutaneously positioned, time period since the most recent determination of the probability estimation for the sensitivity decline, among others.

[0087] If is determined that the probability estimation for the sensitivity decline determination is not appropriate (**620**), then the routine shown in FIG. **6** returns to collecting additional sensor data points. On the other hand, if it is determined that the probability estimation for the sensitivity decline determination is appropriate, then the probability estimation for the sensitivity decline determination is performed (**630**). Thereafter, based upon the determined probability estimation for the sensitivity decline, it is determined whether ESA is present or not (**640**).

[0088] That is, based on the analysis performed, for example, by the first module **520** of the sensitivity decline detector **500** (FIG. **5**), if ESA is not detected, then the routine returns to collection and/or retrieval of additional sensor current data (**640**). On the other hand, if based on the analysis described above ESA is detected (**640**), then a capillary blood measurement is requested (for example, by prompting the user to perform a fingerstick blood glucose test and input the blood glucose value) (**650**). Thereafter, the routine shown in FIG. **6** performs the routine for confirming the presence or absence of ESA by, for example, the hypothesis analysis module **521** (FIG. **5**).

[0089] Referring again to FIG. **6**, if based on the analysis using the capillary blood measurement determines that ESA is not present, the routine again returns to the data collection/retrieval mode (**610**). On the other hand, if ESA presence is determined, in one aspect, an alarm or notification may be generated and provided to the user (**680**) to alert the user.

[0090] FIG. **7** is a flowchart illustrating real-time detection of sensor current abnormalities described in conjunction with module **1** of FIG. **5** in accordance with one embodiment of the present disclosure. Referring to FIG. **7**, in one embodiment, analyte sensor data for a defined time period is retrieved or selected. With the analyte sensor data, one or more data processing is performed to determine sensor signal characteristics, including, for example, the mean current signal, the least squares slope, a standard deviation, an average elapsed time since the analyte sensor insertion/positioning (or average sensor life), a variance about the least squares slope (**710**).

[0091] Referring to FIG. **7**, predetermined coefficients based on the analyte sensor data may be retrieved (**720**), and applied to the analyte sensor signals to determine or estimate the probability of ESA presence (**730**). Additionally, further shown in FIG. **7** is a predetermined threshold (**740**) which in one embodiment may be compared to the determined estimated probability of ESA presence (**750**). In one aspect, the predetermined threshold may be determined as the minimum probability of ESA presence for declaring such condition, and may be a tradeoff between false alarms (false positives, where the threshold may be easy to exceed) versus missed detections (false negatives, where the threshold is difficult to exceed).

[0092] Referring still again to FIG. **7**, if it is determined that the estimated probability of ESA presence does not exceed the predetermined threshold (**750**), then it is determined that ESA is not present—that is, sensor current signal attenuation is not detected (**760**). On the other hand, if it is determined that estimated probability of ESA presence exceeds the predetermined threshold, it is determined that ESA is present—that is, sensor current signal attenuation is detected (**770**). In either case, where the ESA presence is determined to be

present or not present, such determination is communicated or provided to the subsequent stage in the analysis (**780**) for further processing.

[0093] FIG. **8** is a flowchart illustrating verification routine of module **2** in FIG. **5** to confirm or reject the output of module **1** in accordance with one embodiment of the present disclosure. Referring to FIG. **8**, with the continuous glucose data (**801**) and the capillary blood glucose measurement (**802**), an average function of one or more continuous glucose sensor current data point at around the same time or approximately contemporaneously with the blood glucose measurement is performed (**803**). In the case where the sensor current data point is a single value, average function will result in the value itself—therefore averaging routine is unnecessary.

[0094] Alternatively, in the case where the sensor data includes more than one data point, for example, 11 data points centered around the time of the blood glucose data point, the average function is performed resulting in an average value associated with the plurality of data points. Thereafter, as shown in FIG. **8**, a sensitivity value (S) is determined based on the calculated average value of the sensor data points as described above and the capillary blood glucose measurement (**805**). For example, the sensitivity value (S) associated with the sensor may be determined as the ratio of the determined average sensor data point value to the blood glucose value.

[0095] Referring still to FIG. **8**, a nominal sensor sensitivity typically determined at the time of sensor manufacturing (**807**) is retrieved and applied to the determined sensor sensitivity value (S) to attain a normalized sensitivity ratio Rs (**808**).

[0096] Referring back to FIG. **8**, based on the measured or received capillary blood glucose measurement (**802**), a corresponding glucose bin described above is determined or calculated (**804**), for example, in one aspect, by applying the function described in equation (5) above. Thereafter, a corresponding ESA test threshold t is determined (**806**) based on the calculated or determined glucose bin. For example, as described above, each glucose bin (bin**1** to bin**6**), is associated with a respective threshold level t which may, in one aspect, be determined by prior analysis or training.

[0097] Referring still again to FIG. **8**, with the normalized sensitivity ratio (**808**) and the calculated bin (**806**), a comparison is made between the normalized sensitivity ratio and the determined or calculated bin (**809**). For example, in the case where the comparison establishes the normalized sensitivity ratio (S) exceeds the calculated bin t, it is determined that early signal attenuation (ESA) is not present (**811**). On the other hand, when the normalized sensitivity ratio (S) is determined to be less than the calculated bin t, then it is determined that ESA in the sensor signals is present.

[0098] FIG. **9** illustrates a real time current signal characteristics evaluation approach based on a sliding window process of module **1** in FIG. **5** in accordance with one embodiment of the present disclosure.

[0099] FIG. **10** illustrates bootstrap estimation of coefficients for module **1** of FIG. **5** in accordance with one embodiment of the present disclosure. Referring to the Figures, the bootstrap estimation procedure performed to add robustness to the model coefficients may include, in one aspect, a generalized linear model fit applied to a predetermined time period to determine the coefficient vector β. Based on a predefined number of iterations, an empirical probability distribution function of each coefficient may be determined, for example, as shown in FIG. **10**, where each selected coefficient corresponds to the mode of the associated distribution.

[0100] FIG. **11** illustrates Gaussian kernel estimation of the normalized sensitivity density of module **2** of FIG. **5** in accordance with one embodiment of the present disclosure. Referring to FIG. **11**, as described above in conjunction with FIG. **5**, in one aspect, kernel density estimation (using Gaussian kernel, **24**, for example) may be used to estimate the distribution of the sensitivity ratio Rs in each bin/category described above. The estimation of the distribution in sensitivity ratio Rs in one aspect is shown in FIG. **11**, where for each bin/category (including, for example, severe hypoglycemia (bin**1**), mild hypoglycemia (bin**2**), low euglycaemia (bin**3**), high euglycaemia (bin**4**), low hyperglycemia (bin**5**), and high hyperglycemia (bin**6**)), the corresponding chart illustrates the associated distribution where ESA presence is detected as compared to the distribution where no ESA presence is detected.

[0101] FIG. **12** illustrates a comparison of rate of false alarms (false positives) and sensitivity decline detection rate in accordance with embodiment of the present disclosure. That is, FIG. **12** represents the relation between ESA detection rate and false alarm rate. In one aspect, curve **1210** illustrates the output results of the first module **510** in the sensitivity decline detector **500** (FIG. **5**) based on the logistic regression classifier, while curve **1220** illustrates the combined output of the first module **510** and the second module **520** of the sensitivity decline detector **500** (FIG. **5**) based, for example, on a logistic rule classifier prompting a blood glucose measurement in the case of ESA presence probability exceeding a predetermined threshold level. In one embodiment, based on a threshold level of 0.416 determining the ESA presence probability, the rate of ESA detection is approximately 87.5% and a false alarm rate is approximately 6.5%.

[0102] In the manner described above, in accordance with the various embodiments of the present disclosure, real time detection of ESA or night time drop outs of analyte sensor sensitivities are provided. For example, an analyte sensor with lower than normal sensitivity may report blood glucose values lower than the actual values, thus potentially underestimating hyperglycemia, and triggering false hypoglycemia alarms. Moreover, since the relationship between the sensor current level and the blood glucose level is estimated using a reference blood glucose value (for example, calibration points), if such calibration is performed during a low sensitivity period, once the period comes to an end, all glucose measurements will be positively biased, thus potentially masking hypoglycemia episodes. Accordingly, the occurrence of errors in the relation between the current signal output of the analyte sensor and the corresponding blood glucose level may be monitored and detected in real time such that the patients may be provided with the ability to take corrective actions.

[0103] Indeed, real time detection of variations in the glucose levels in patients using monitoring devices such as analyte monitoring devices provide temporal dimension of glucose level fluctuations provide the ability to tightly control glycemic variation to control diabetic conditions. More specifically, in accordance with the various embodiments of the present disclosure, the analyte monitoring systems may be configured to provide warnings about low glucose levels in real time in particular, when the patient may not be suspecting hypoglycemia or impending hypoglycemia, and thus provide

the ability to help patients avoid life-threatening situations and self-treat during hypoglycemic attacks.

[0104] Accordingly, in one aspect of the present disclosure, the detection of episodes of low sensor sensitivity includes a first module which may be configured to execute a real-time detection algorithm based on analyte sensor current signal characteristics, and further, a second module which may be configured to perform a statistical analysis based on a single blood glucose measurement to confirm or reject the initial detection of the sensor sensitivity decline performed by the first module. In this manner, in one aspect of the present disclosure, accurate detection of ESA episodes or night time drop outs or declines in sensor current signal levels may be provided with minimal false alarms.

[0105] Accordingly, a computer implemented method in one aspect includes receiving a plurality of analyte sensor related signals, determining a probability of signal attenuation associated with the received plurality of analyte sensor related signals, verifying the presence of signal attenuation when the determined probability exceeds a predetermined threshold level, and generating a first output signal associated with the verification of the presence of signal attenuation.

[0106] Further, determining the probability of signal attenuation may include determining one or more characteristics associated with the received plurality of analyte sensor related signals, and applying a predetermined coefficient to the plurality of analyte sensor related signals.

[0107] In another aspect, the determined one or more characteristics may include one or more mean value associated with the analyte sensor related signals, the least square slope associated with the analyte sensor related signals, a standard deviation associated with the analyte sensor related signals, an average elapsed time from positioning the analyte sensor, or a variance about a least squares slope associated with the analyte sensor related signals.

[0108] Also, in still another aspect, the predetermined threshold level may be user defined or defined by a system expert.

[0109] In still another aspect, when the determined probability does not exceed the predetermined threshold level, the method may further include generating a second output signal associated with absence of signal attenuation condition.

[0110] Additionally, in yet a further aspect, verifying the presence of signal attenuation may include selecting a signal attenuation threshold level, determining a sensitivity level associated with the analyte related sensor signals, and confirming the presence of signal attenuation based at least in part on a comparison of the determined sensitivity level and the selected signal attenuation threshold level, where the signal attenuation threshold level may be associated with a blood glucose measurement.

[0111] Also, the blood glucose measurement may in another aspect include a capillary blood glucose sampling.

[0112] In yet still another aspect, the sensitivity level associated with the analyte related sensor may include a ratio of nominal sensitivity associated with the analyte related sensor signals and the sensitivity value associated with the analyte related sensor signals, where the sensitivity value may be determined as a ratio of the average of the analyte related sensor signals and a blood glucose measurement.

[0113] Moreover, confirming the presence of signal attenuation in another aspect may include determining that the sensitivity level is less than the selected signal attenuation threshold level, which in one aspect, may be determined by a system expert.

[0114] An apparatus in accordance with another aspect of the present disclosure includes a data storage unit, and a processing unit operatively coupled to the data storage unit configured to receive a plurality of analyte sensor related signals, determine a probability of signal attenuation associated with the received plurality of analyte sensor related signals, verify the presence of signal attenuation when the determined probability exceeds a predetermined threshold level, and generate a first output signal associated with the verification of the presence of signal attenuation.

[0115] The processing unit may be configured to determine the probability of signal attenuation is configured to determine one or more characteristics associated with the received plurality of analyte sensor related signals, and to apply a predetermined coefficient to the plurality of analyte sensor related signals.

[0116] The determined one or more characteristics may include one or more mean value associated with the analyte sensor related signals, the least square slope associated with the analyte sensor related signals, a standard deviation associated with the analyte sensor related signals, an average elapsed time from positioning the analyte sensor, or a variance about a least squares slope associated with the analyte sensor related signals, where the predetermined threshold level may be user defined, or defined by a system expert.

[0117] When the determined probability does not exceed the predetermined threshold level, the processing unit may be further configured to generate a second output signal associated with absence of signal attenuation condition.

[0118] In still another aspect, the processing unit may be further configured to select a signal attenuation threshold level, determine a sensitivity level associated with the analyte related sensor signals, and confirm the presence of signal attenuation based at least in part on a comparison of the determined sensitivity level and the selected signal attenuation threshold level.

[0119] The signal attenuation threshold level may be associated with a blood glucose measurement.

[0120] The blood glucose measurement may include a capillary blood glucose sampling.

[0121] The sensitivity level associated with the analyte related sensor may include a ratio of nominal sensitivity associated with the analyte related sensor signals and the sensitivity value associated with the analyte related sensor signals, where the sensitivity value may be determined as a ratio of the average of the analyte related sensor signals and a blood glucose measurement.

[0122] The processing unit may be further configured to determine that the sensitivity level is less than the selected signal attenuation threshold level, which may be, in one aspect determined by a system expert.

[0123] In still another aspect, the apparatus may include a user output unit operatively coupled to the processing unit to display the first output signal.

[0124] A system for detecting signal attenuation in a glucose sensor in still another aspect of the present disclosure includes an analyte sensor for transcutaneous positioning through a skin layer of a subject, a data processing device operatively coupled to the analyte sensor to periodically receive a signal associated with the analyte sensor, the data processing device configured to determine a probability of the

early signal attenuation (ESA), and to verify the presence of early signal attenuation based on one or more predetermined criteria.

[0125] The data processing device may include a user interface to output one or more signals associated with the presence or absence of early signal attenuation associated with the analyte sensor.

[0126] Various other modifications and alterations in the structure and method of operation of this disclosure will be apparent to those skilled in the art without departing from the scope and spirit of the disclosure. Although the disclosure has been described in connection with specific preferred embodiments, it should be understood that the disclosure as claimed should not be unduly limited to such specific embodiments. It is intended that the following claims define the scope of the present disclosure and that structures and methods within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A computer implemented method, comprising:

receiving a plurality of analyte sensor related signals;

determining a probability of signal attenuation associated with the received plurality of analyte sensor related signals;

verifying the presence of signal attenuation when the determined probability exceeds a predetermined threshold level; and

generating a first output signal associated with the verification of the presence of signal attenuation.

2. The method of claim **1** wherein determining the probability of signal attenuation includes:

determining one or more characteristics associated with the received plurality of analyte sensor related signals; and

applying a predetermined coefficient to the plurality of analyte sensor related signals.

3. The method of claim **2** wherein the determined one or more characteristics includes one or more mean value associated with the analyte sensor related signals, the least square slope associated with the analyte sensor related signals, a standard deviation associated with the analyte sensor related signals, an average elapsed time from positioning the analyte sensor, or a variance about a least squares slope associated with the analyte sensor related signals.

4. The method of claim **1** wherein the predetermined threshold level is user defined.

5. The method of claim **1** wherein when the determined probability does not exceed the predetermined threshold level, generating a second output signal associated with absence of signal attenuation condition.

6. The method of claim **1** wherein verifying the presence of signal attenuation includes:

selecting a signal attenuation threshold level;

determining a sensitivity level associated with the analyte related sensor signals; and

confirming the presence of signal attenuation based at least in part on a comparison of the determined sensitivity level and the selected signal attenuation threshold level.

7. The method of claim **6** wherein the signal attenuation threshold level is associated with a blood glucose measurement.

8. The method of claim **7** wherein the blood glucose measurement include a capillary blood glucose sampling.

9. The method of claim **6** wherein the sensitivity level associated with the analyte related sensor includes a ratio of nominal sensitivity associated with the analyte related sensor signals and the sensitivity value associated with the analyte related sensor signals.

10. The method of claim **9** wherein the sensitivity value is determined as a ratio of the average of the analyte related sensor signals and a blood glucose measurement.

11. The method of claim **6** wherein confirming the presence of signal attenuation includes determining that the sensitivity level is less than the selected signal attenuation threshold level.

12. An apparatus, comprising:

a data storage unit; and

a processing unit operatively coupled to the data storage unit configured to receive a plurality of analyte sensor related signals, determine a probability of signal attenuation associated with the received plurality of analyte sensor related signals, verify the presence of signal attenuation when the determined probability exceeds a predetermined threshold level, and generate a first output signal associated with the verification of the presence of signal attenuation.

13. The apparatus of claim **12** wherein the processing unit configured to determine the probability of signal attenuation is configured to determine one or more characteristics associated with the received plurality of analyte sensor related signals, and to apply a predetermined coefficient to the plurality of analyte sensor related signals.

14. The apparatus of claim **13** wherein the determined one or more characteristics includes one or more mean value associated with the analyte sensor related signals, the least square slope associated with the analyte sensor related signals, a standard deviation associated with the analyte sensor related signals, an average elapsed time from positioning the analyte sensor, or a variance about a least squares slope associated with the analyte sensor related signals.

15. The apparatus of claim **12** wherein the predetermined threshold level is user defined.

16. The apparatus of claim **12** wherein when the determined probability does not exceed the predetermined threshold level, the processing unit is further configured to generate a second output signal associated with absence of signal attenuation condition.

17. The apparatus of claim **12** wherein the processing unit is further configured to select a signal attenuation threshold level, determine a sensitivity level associated with the analyte related sensor signals, and confirm the presence of signal attenuation based at least in part on a comparison of the determined sensitivity level and the selected signal attenuation threshold level.

18. The apparatus of claim **17** wherein the signal attenuation threshold level is associated with a blood glucose measurement.

19. The apparatus of claim **18** wherein the blood glucose measurement include a capillary blood glucose sampling.

20. The apparatus of claim **17** wherein the sensitivity level associated with the analyte related sensor includes a ratio of nominal sensitivity associated with the analyte related sensor signals and the sensitivity value associated with the analyte related sensor signals.

21. The apparatus of claim **20** wherein the sensitivity value is determined as a ratio of the average of the analyte related sensor signals and a blood glucose measurement.

22. The apparatus of claim **17** wherein the processing unit is further configured to determine that the sensitivity level is less than the selected signal attenuation threshold level.

23. The apparatus of claim **12** including a user output unit operatively coupled to the processing unit to display the first output signal.

24. A system for detecting signal attenuation in an analyte sensor, comprising:

an analyte sensor for transcutaneous positioning through a skin layer of a subject; and

a data processing device operatively coupled to the analyte sensor to periodically receive a signal associated with the analyte sensor, the data processing device configured to determine a probability of the early signal attenuation (ESA), and to verify the presence of early signal attenuation based on one or more predetermined criteria.

25. The system of claim **24** wherein the data processing device includes a user interface to output one or more signals associated with the presence or absence of early signal attenuation associated with the analyte sensor.

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