

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 March 2007 (08.03.2007)

PCT

(10) International Publication Number
WO 2007/027691 A1

(51) International Patent Classification:
A61B 5/00 (2006.01) A61B 5/05 (2006.01)

(74) Agent: PARKER, Stephen B.; Novak Druce DeLuca & Quigg, 1300 Eye Street, NW, 400 East Tower, Washington, District Of Columbia 20005 (US).

(21) International Application Number:
PCT/US2006/033724

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, 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.

(22) International Filing Date: 29 August 2006 (29.08.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/713,203 31 August 2005 (31.08.2005) US
60/815,191 20 June 2006 (20.06.2006) US

(71) Applicant (for all designated States except US): UNIVERSITY OF VIRGINIA PATENT FOUNDATION [US/US]; UVA Patent Foundation, 250 West Main Street, Suite 300, Charlottesville, Virginia 22902 (US).

(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, 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).

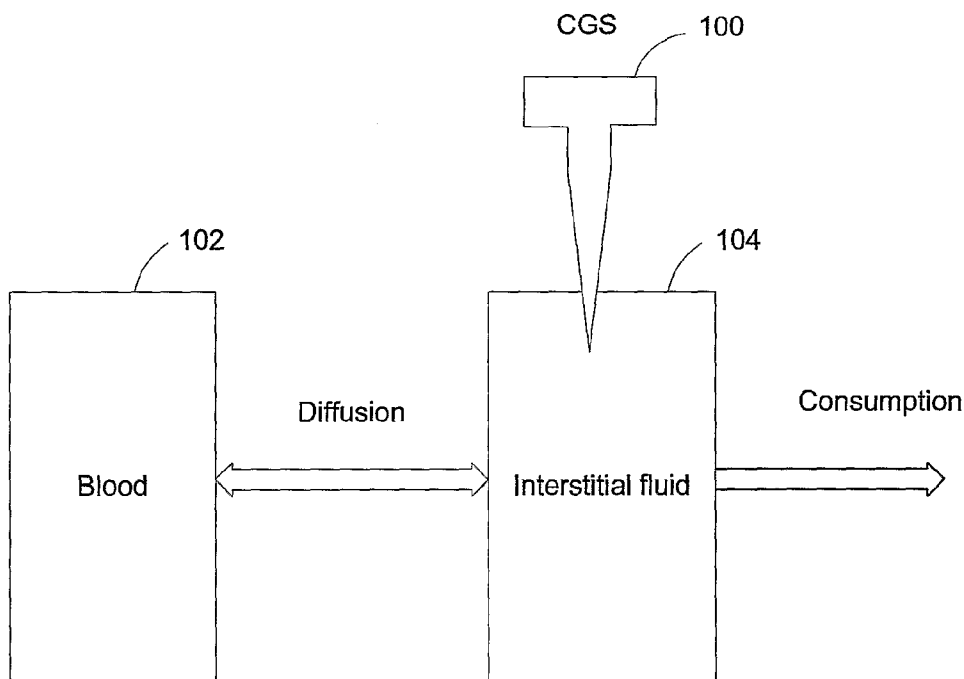
(72) Inventors; and

(75) Inventors/Applicants (for US only): KOVATCHEV, Boris P. [US/US]; Charlottesville, Virginia (US). KING, Christopher Ryan [US/US]; Charlottesville, Virginia (US).

Published:
— with international search report

[Continued on next page]

(54) Title: IMPROVING THE ACCURACY OF CONTINUOUS GLUCOSE SENSORS



(57) Abstract: A method, apparatus, and a kit are capable of improving accuracy of CGS devices using dynamic outputs of continuous glucose sensors.

WO 2007/027691 A1



-
- *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.*

IMPROVING THE ACCURACY OF CONTINUOUS GLUCOSE SENSORS

CROSS-REFERENCE TO RELATED PUBLICATIONS

[0001] This US patent application claims priority under 35 U.S.C. 119(e) from co-pending US provisional applications serial number 60/713,203 filed August 31, 2005, and serial number 60/815,191 filed June 20, 2006, the subject matter of each being incorporated herein by reference in its entirety. The subject matter of each one of the publications and the US provisional application in APPENDIX A attached herewith is incorporated herein by reference in their entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to the art of glucose monitoring, and more particularly to methods and systems for continuous glucose monitoring.

BACKGROUND OF THE INVENTION

[0003] Existing evidence, such as "National Diabetes Fact Sheet" by American Diabetes Association, indicates that currently approximately 18.2 million people in the U.S. have diabetes; and diabetes is the sixth-leading cause of death in the U.S. One in three Americans born in the year 2000 will develop Type 2 diabetes. With the large number of diabetes patients, and with the incidence of diabetes expected to increase, there is a continuously growing need for accurate glucose monitoring systems to monitor glucose levels. Continuous glucose sensors are designed to provide not only real-time glucose levels at a single point in time, but also the trend of a person's glucose levels based on analysis taking place every certain period of time with minimal finger-sticks, leading to improved glycemic / diabetes control.

[0004] Most contemporary continuous glucose sensors (hereafter CGS), however, yield blood glucose (hereafter BG) estimates by sampling interstitial glucose (hereafter IG) in interstitial fluid, rather than BG due to the difficulty in directly measuring BG in artery or blood vessels. A typical glucose (BG) estimation from IG is produced from at least two consecutive approximation steps: 1) Blood-to-interstitial glucose (BG- to-IG) transport; and 2) Derivation of BG values from IG-related electrical current recorded by the sensor. As a result, although CGS technology has made dramatic strides, the development of accurate and reliable CGS devices continues to face numerous challenges in terms of calibration, sensitivity, stability, and

physiological time lag between blood and interstitial glucose concentrations. The difference between BG and CGS readings arises from following major factors: physiology, sensor calibration, noise, and engineering. The physiological time lag and gradients are changing dynamically with time, with BG levels, and across subjects; and the direct frequent in vivo sampling of IG is extremely difficult. Consequently, the evaluation of engineering performance of CGS is left with a central problem: separating the portion of BG/CGS error due to calibration, sensor noise, and BG/IG gradient.

[0005] Therefore, a method and apparatus are desired for improving accuracy and reliability of CGS.

SUMMARY OF THE INVENTION

[0006] Various objects and advantages of the preferred embodiments of the present invention will be appreciated based on this disclosure. According to the preferred embodiments, the present invention improves the accuracy and reliability of CGS by improving the calibration of CGS sensors or remedying errors due to physiological time lag or a combination thereof.

[0007] As an exemplary embodiment of the invention, a method for improving accuracy of a continuous glucose sensor (CGS) is disclosed herein. The method comprises: calibrating the CGS at a first time; and changing the CGS calibration at a second time that is determined based upon a dynamically monitored CGS value, a rate of CGS change, and a predetermined criterion.

[0008] As another exemplary embodiment of the invention, a method for improving accuracy of a continuous glucose sensor (CGS) is disclosed herein. The method comprises: calibrating the CGS using a first blood glucose data and a second blood glucose data different from the first glucose data.

[0009] As yet another exemplary embodiment of the invention, a continuous glucose sensing (CGS) device is disclosed herein. The device comprises: first means for measuring interstitial glucose level so as to obtain a CGS output; and a calibration module accessible to the CGS output for improving accuracy of the CGS, further comprising: a monitoring module accessible to the CGS output for dynamically monitoring the CGS and a time derivative of the CGS; and instructing another calibration event based on the dynamic CGS value, the time derivative of the CGS value, and a predetermined criterion.

[0010] As yet another exemplary embodiment of the invention, a computer-readable medium having computer executable instructions for performing a method for improving accuracy of a continuous glucose sensor is disclosed, wherein the method comprises: retrieving an initial blood glucose value and a CGS value obtained in a measurement for the initial blood glucose value; monitoring the CGS value and a time derivative of the CGS value over time; determining whether to initiate another calibration based on the monitored CGS values and the time derivative of the CGS value; and calibrating the CGS if it is determined to initiate said another calibration.

[0011] As yet another exemplary embodiment of the invention, a computer-readable medium having computer executable instructions for performing a method for improving accuracy of a continuous glucose sensor is disclosed, wherein the method comprises: retrieving a blood glucose value and a CGS value obtained in a measurement for the initial blood glucose value at a first time; and calibrating the CGS at a second time determined by a CGS value at substantially the second time, a time derivative of the CGS, and a predetermined criterion.

[0012] As yet another exemplary embodiment of the invention, a system used for treating a disease associated with blood glucose is disclosed herein. The system comprises: a continuous glucose device of claim 300; means for delivering the CGS values to a disease treating center that is capable of issuing a corresponding treating instruction or taking a corresponding treating action.

[0013] Various objects and/or advantages of some preferred embodiments of the invention can be, in some preferred examples, achieved via the features of the independent claims attached hereto. Additional preferred embodiments are further set forth in the dependent claims. In the claims, only elements denoted by the words "means for" are intended to be interpreted as means plus function claims under 35 U.S.C. §112, the sixth paragraph.

BRIEF DESCRIPTION OF DRAWINGS

[0014] The preferred embodiments of the invention can be best understood from the following detailed description taken in conjunction with the accompanying drawings of which:

[0015] FIG. 1 schematically illustrates a method for measuring blood glucose levels using a continuous glucose sensor according to an example of the invention;

[0016] FIG. 2 is an exploded diagram showing the continuous glucose sensor comprising a calibrator of FIG. 1;

- [0017] FIG. 3 is a gram illustrates functional modules of the calibrator and the time lag corrector according to an example of the invention;
- [0018] FIG. 4a is a block diagram of the calibration module according to an example of the invention;
- [0019] FIG. 4b is a flow chart of a calibration process according to an example of the invention;
- [0020] FIG. 5 illustrates therein the blood glucose differential during calibration and the accuracy of the CGS improved by an exemplary method of the invention;
- [0021] FIG. 6 is a flow chart showing the steps executed for improving the accuracy of the CGS using the time-lag correction method of the invention;
- [0022] FIG. 7 is a flow chart showing the steps executed for calibrating the CGS according to yet another example of the invention;
- [0023] FIG. 8 is a diagram showing the improved CGS measurement using an exemplary method of the invention;
- [0024] FIG. 9 is another diagram showing the improved CGS measurement using an exemplary method of the invention;
- [0025] FIG. 10 is yet another diagram showing the improved CGS measurement using an exemplary method of the invention;
- [0026] FIG. 11 is a flow chart showing the steps executed for improving the accuracy of the CGS according to yet another example of the invention;
- [0027] FIG. 12 is a diagram illustrating a system in which examples of the invention can be implemented; and
- [0028] FIG. 13 is a diagram showing an exemplary computing device having computer-readable instructions in which example of the invention can be implemented.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0029] This invention provides a method and device for improving accuracy of continuous glucose sensors by improving the calibration of the CGS or by remedying errors arising from the physiological time lag between BG and IG, or a combination thereof. In view of many possible variations within the spirit of the invention, the invention will be discussed in the following with reference to specific examples. However, it will be appreciated by those skilled in the art that the following discussion is for demonstration purposes, and should not be

interpreted as a limitation. Other variations without departing from the spirit of the invention are also applicable.

[0030] Inaccuracies of most current CGS devices are mainly attributed to poor CGS calibration, physiology time lag, and random errors. To reduce the inaccuracy of the CGS, an improved calibration procedure is proposed. The reduction of inaccuracy can alternatively be achieved by remedying the error related to physiological time lag, which is also proposed in this invention. In fact, the improved calibration procedure and the time lag remedy procedure can alternatively be combined together so as to achieve a better performance of CGS.

[0031] Referring to FIG. 1, a method of measuring glucose levels *in vivo* according to an example of the invention is schematically illustrated therein. Because of the large difficulty in directly measuring glucose levels in blood vessels or arteries 102, CGS 100 detects blood glucose level by measuring the glucose level in interstitial fluid 104 that interacts with blood vessels or arteries; and associating the output value of the CGS to the blood glucose level (the process is often referred to as calibration). This indirect measurement stands on the proven basis that the blood glucose level co-varies with the glucose level in the interstitial fluid.

[0032] To improve the accuracy of CGS, accuracy improver 106 is provided as shown in FIG. 2. The accuracy improver can improve the accuracy of the CGS by improving the CGS calibration through an optimal calibration recommendation (which will be discussed afterwards), or by remedying the error related to the physiology time lag (which will be discussed afterwards), or by a combination thereof. Even though FIG. 2 shows that the accuracy improver is included in the CGS (100) as a functional member, it is not required to be so. In other examples, the accuracy improver can be a stand-alone module or method that is separate from the CGS. Specifically, the accuracy improver can be implemented in a device in connection to the CGS output for improving the accuracy of the CGS. Moreover, the accuracy module can be implemented in the form of a sequence of computer-executable codes stored in a computer-readable medium; or can be implemented in hardware of the device, which will be detailed afterwards.

[0033] As an example of the invention, FIG. 3 schematically illustrates an exploded view of the accuracy improver (106) in FIG. 2. In this particular example, the accuracy improver (106) comprises CGS calibration module 108 and time lag correction module 110. The CGS calibration module, by performing an optimal calibration recommendation cycle, is designated for improving the calibration of the CGS, thus improving the overall accuracy of the CGS. The time lag correction module (110) is designated for remedying the error from the

physiology time lag between the blood glucose and interstitial glucose levels. Depending upon the specific function of the accuracy improver as discussed above, the accuracy improver may have only one or both of the CGS calibration and time lag correction modules.

IMPROVED CGS CALIBRATION

[0034] It is known in the art that the accuracy of CGS calibration depends on the rate of blood glucose (hereafter BG) change and the BG value ($BG(t)$) at the time (t) of calibration. The rate of BG change can be mathematically expressed as the time derivative of $BG(t)$: $d(BG(t)) / dt$. Given the fact that calibrations with variant inputs are better than those with single or non-varying inputs, the CGS calibration of the invention uses variant inputs.

[0035] As an example, FIG. 4a is a diagram showing functional modules of an exemplary CGS calibration (118) of FIG. 3. Referring to FIG. 4a, CGS calibrator 118 comprises initial calibration module 111, storing module 113, reassigning module 115, and decision loop module 117 that further comprises monitoring module 119, internal request module 121, self-check initiation module 123, determining module 125, and sensor calibration module 129.

[0036] The initial calibration module performs initial calibration so as to obtain an initial calibration data pair $SG(0)$ and $BG(0)$ from an initial measurement of $BG(0)$. Storing module 113 couples to the output of the initial calibration module 111 and stores the initial calibration data pair $SG(0)$ and $BG(0)$. Monitoring module 119 connects to the output of the storing module and dynamically monitors the CGS output $SG(t)$ and the rate of $SG(t)$ change $SG'(t)=dSG(t) / dt$. Internal request module 121 connects to the output of the monitor module and manages internal requests for calibration. Self-check initiation module 123 is connected to the output of the internal request module and designated for initiating a self-check procedure for optimal calibration timing. In connection with the output of self-check module 123, determining module 125 makes decisions of whether to perform another calibration by sensor calibration module 129 at the particular time. The calibration data from the calibration after the decision are reassigned to the CGS through reassign module 115.

[0037] It is noted that one or more above functional modules can be incorporated into other functional modules in practice. In particular, sensor calibration module 129 can be incorporated into initial sensor calibration module 111 for performing CGS calibration. Any of monitor module 119, internal request module 121, self-check module 123, and determining module 125 can be incorporated into combined functional module(s).

[0038] An exemplary operation of the functional modules in FIG. 4a so as to accomplish the desired optimal calibration recommendation process of the invention is schematically illustrated in FIG. 4b. Referring to FIG. 4b, an initial calibration is performed by measuring the blood glucose level $BG(0)$ at the initial time t so as to obtain an initial CGS output $SG(0)$ (step 112). This step can be performed by initial calibration module 111 in FIG. 4a. The initial pair of data $BG(0)$ and $SG(0)$ is recorded at step 114. This step can be performed by storing module 113 in FIG. 4a. Such initial calibration can be performed at a time recommended by the CGS manufacture, or at a time determined by the user. The calibration procedure then enters to calibration decision making loop 118 that is administrated by decision loop module 117 as shown in FIG. 4a.

[0039] The calibration decision making loop starts from step 120 that monitors sensor values $SG(t)$ and the rate of change $SG'(t)$ over time with $SG'(t)$ being defined as the first order time derivative of $SG(t)$, that is $SG'(t)=dSG(t)/dt$. The dynamic monitoring and derivation of the $SG'(t)$ can be performed by monitor module 119 in FIG. 4a. Upon receiving another calibration request at a specific time t_1 (step 122), a self-check procedure for optimal calibration timing is initiated at step 124. This step triggers the sequence of actions determining whether a calibration should be performed or not performed at this time, e.g. 126 and 128 in Figure 4b. The receiving of the calibration request and delivering such request to initiate the self-check procedure can be accomplished by the internal request module 121 in FIG. 4a; and the self-check initiation can be accomplished by the self-check initiation module 123 in FIG. 4a. It is noted that the internal request for another calibration can be initiated at the time defined by the manufacture, or alternatively, by a time defined by the user, such as a doctor or even proper patients.

[0040] Following the initiation of the self-check procedure at step 124, it is determined whether $|SG'(t_1)| < 1$ at step 126. This determination step can be performed by determination module 125 in FIG. 4a. If $|SG'(t_1)| \geq 1$, the procedure flows back to step 120 to continuously monitoring the $SG(t)$ and $SG'(t)$ values. Otherwise, the procedure makes another determination of whether $|SG(t_1)-SG(t_0)|$ is greater than $d(mg/dl)$, wherein $d(mg/dl)$ is the pre-determined difference threshold between the initial $SG(0)$ and the CGS output at time t_1 $SG(t_1)$. As an example, $d(mg/dl)$ can be 10 mg/dl or higher, such as 15 mg/dl or higher, and more preferably 30 mg/dl or higher. Either one or both of the determinations at steps 126 and 128 can be performed by determination module 125 as shown in FIG. 4a. If $|SG(t_1)-SG(t_0)|$ is equal to or less than $d(mg/dl)$ at step 128, the procedure flows back to step 120. Otherwise,

another calibration is performed at step 130, by for example, sensor calibration module 129 in FIG. 4a. The CGS calibration values are reassigned at step 116 based on the recalibration at step 130, for example, by respectively replacing the calibration values $SG(t_0)$ and $BG(t_0)$ with the recalibrated values $SG(t_1)$ and $BG(t_1)$. The reassigned calibration values are stored at step 114. The above reassignment can be accomplished by reassigning module 115 in FIG. 4a.

[0041] After reassigning and recording, the calibration process re-enters the decision making cycle 118, and repeat the above steps 114, 120, 122, 124, 126, 128, 130, and 116. The number of calibration cycles can be determined by the default number of calibrations suggested by the CGS manufacture, or alternatively, by the user. As an example, a plurality of calibration cycles – e.g. 2 to 10, or more typically 3 to 4 calibration cycles can be performed during the first 24 hours of CGS life.

[0042] The improved accuracy of CGS using the optimal calibration method as discussed above can be validated by the following experimental data and computer-simulations, as shown in FIG. 5.

EXPERIMENTAL DATA

[0043] To test the accuracy of the CGS incorporating the accuracy improvement method as discussed above, a measurement is conducted on thirty-nine (39) subjects with type 1 diabetes mellitus (T1DM). The 39 participants have the following statistics: average age 42.5 years with standard deviation (SD) of 12 (SD=12), average duration of T1DM 21.6 years (SD=94), average HbA1c =7.4% (SD=0.8), 16 males.

[0044] The study was approved by the University of Virginia IRB Subjects. The subjects were admitted to the general clinic research center (GCRC) in the evening prior to the study. The participants' BG levels were controlled overnight within euglycemic range of 100-150 mg/dl (5.5-8.3 mmol/l). A Minimed CGMSTM was attached to each subject and was calibrated during the study in accordance with the manufacturer's instructions. All CGMSTM were inserted in the abdomen. Hyperinsulinemic clamps were performed in the morning. Each clamp used constant insulin infusion rate of 1mU/kg/min and variable glucose infusion rate to achieve and maintain BG levels at approximately 110 mg/dl (around 6mmol/l). Subsequently, the glucose infusion rate was reduced to permit a controlled decline in BG of approximately 1mg/dl/min until BG reached 50mg/dl (around 2.8mmol/l). Glucose infusion was then resumed to allow a recovery to normal glucose levels. The euglycemic portion of the clamp study varied in length from 70 to 210 minutes; and the duration of the BG reduction procedure ranged from

30 to 60 minutes. The recovery ranged from 30 to 60 minutes. Arterialized blood was achieved by warming the hand to 50°C and was sampled every 5 minutes for reference BG levels. To allow for insulin to reach its steady state effect, the first 15 minutes of data after the beginning of infusion were ignored. CGMS™ readings were synchronized with reference BG.

COMPUTER SIMULATION OF SENSOR OPTIMAL CALIBRATION

[0045] A recalibration of the sensor using 2 reference BG values taken during the clamp study described above is computer-simulated, as shown in FIG. 5 that presents the sensor error as a function of the difference between the two BG values. The simulated recalibration uses the standard linear calibration function of the CGMS™. The results from the recalibration are compared to the sensors' own accuracy displayed during the experiment and to a "perfect" calibration using all available reference BG values.

[0046] Referring to FIG. 5, the *X*-axis presents the distance between two simulated calibration points in BG units (*mg/dl*); and the *Y*-axis presents the mean absolute error (MAE) of the sensor output with the two-point calibration. It can be seen in the figure that MAE is high if the two calibration BGs are close by value. MAE decreases rapidly when the difference approaches 20 *mg/dl*, and slowly decreases thereafter. The upper horizontal line in the figure represents the MAE of the sensor's own calibration; and the lower horizontal line represents the MAE resulting from a "perfect" calibration using all available reference points.

[0047] It can also be seen in the figure that the BG calibration difference *d* with value larger than 30 *mg/dl* but lower than 40 *mg/dl* achieves excellent results; whereas the difference *d* with a value larger than 40 *mg/dl* achieves "nearly-perfect" results. It is worthwhile to point that the sensor calibration during the experiment described above was always done in periods of steady BG kept at euglycemia, thus the influence of BG rate of change was minimal.

CORRECTION OF PHYSIOLOGY TIME LAG

[0048] In addition to the calibration of CGS, physiology time lag between BG and IG also causes inaccuracy in the CGS output. This arises from the fact that most of current CGS devices do not directly measure the blood glucose levels, but the IG levels in the interstitial fluids instead. CGS devices then convert the IG readings into estimates of BG. Therefore, an improved conversion method from IG to BG will lead to improved performance of CGS. An object of the invention improves the conversion from IG to BG by including the physiology time lag between the IG and BG levels. Such improvement is accomplished through analyses

and incorporation of the time dependency between IG and BG. Specifically, a mathematical model is established for describing the time dependency among BG and IG or CGS output. Based upon the established model, a mathematical equation is derived to quantitatively express the time dependence of CGS output on BG – that is CGS is a function of BG. This equation is then converted so as to express BG as a function of CGS. The inverted equation can thus be used to predict the BG level for given CGS output values. In application, the inverted equation is applied to the raw CGS data to produce accurate BG estimates.

MATHEMATICAL MODEL

[0049] Given the fact that glucose is a relatively small molecule, it is believed that glucose can diffuse freely through capillary wall, such as blood vessels and adipose tissues. Adipose tissue is highly vascularized; and the interstitial fluid occupies a relatively thin layer between cells. This fact implies that there is no volume element that is very far from a cell surface, nor is it very far from a capillary wall. Therefore, uptake and diffusion of glucose in the interstitial fluid can be assumed to be relatively topologically uniform.

[0050] The transportation behavior of the IG and BG according to the invention is depicted in FIG. 1. Referring again to FIG. 1, the transport behavior of glucose between interstitial fluid and blood vessels (or adipose tissues) can be modeled as diffusion. IG in the interstitial fluid also experiences consumption, which results in amount and/or concentration reduction.

[0051] For deriving a mathematical diffusion equation, it is assumed that the particular local interstitial environment in question does not significantly contribute to the development of the BG/time curve, therefore, the time dependence of BG level, $BG(t)$, evolves independently, and can be treated as an exogenous variable in the system. This assumption is particularly safe especially in hyperinsulinemic clamp situations where the BG level is mostly controlled by the IV infusion of dextrose. It is further assumed that the uptake of glucose follows either an IG independent path, or one described by Michaelis-Menten kinetics, as expressed respectively in equations 1a and 1b:

$$\dot{IG}(t) \Big|_{UU} = \frac{dIG(t)}{dt} \Big|_{UU} = -\alpha(t) \dots \text{Eq. 1a}$$

$$\dot{IG}(t) \Big|_{MM} = \frac{dIG(t)}{dt} \Big|_{MM} = -\alpha(t) \frac{IG(t)}{K_m + IG(t)} \dots \text{Eq. 1b}$$

In the above equations, α is the uptake of glucose per unit time per unit volume.

[0052] It is noted that equations 1a and 1b describe the explicit time dependence. Other variables, such as insulin levels, exercise, and the like, which may directly effect the glucose uptake BG and IG , are not excluded from the equations. Km is a constant in equation 1b; and it does not introduce additional fitable parameters. In practice, Km can take those published values for the activity of GLUT-4, asset forth in “*Whole body glucose metabolism*” by Zierler K, in *Am J Physiol.* 276:E409-E426, 1999, the subject matter of which is incorporated herein by reference in entirety. By referring to Fick's Law, the change in $IG(t)$ due to diffusion from the blood can be described by equation 2:

$$\dot{IG}(t) \Big|_{diffusion} = \beta \times [BG(t) - IG(t)] \dots \text{Eq. 2}$$

where β is the permeability of the capillary wall to glucose. Since there are no other clear sources or sinks of glucose in the interstitial fluid, the net change of glucose can be derived by adding equations 1a and 1b, which can be expressed as the following equations 3a and 3b, wherein equation 3a corresponds to the uniform uptake diffusion model, and equation 3b corresponds to the Michaelis-Menten kinetic model.

$$\dot{IG}(t) \Big|_{net-UU} = \frac{dIG(t)}{dt} \Big|_{net-UU} = \beta \times [BG(t) - IG(t)] - \alpha(t) \dots \text{Eq. 3a}$$

$$\dot{IG}(t) \Big|_{net-MM} = \frac{dIG(t)}{dt} \Big|_{net-MM} = \beta \times [BG(t) - IG(t)] - \alpha(t) \frac{IG(t)}{Km + IG(t)} \dots \text{Eq. 3b}$$

MATHEMATICAL SOLUTIONS FOR EAUTIONS 3a AND 3b

Equation 3a is an ordinary differential equation that has analytical solutions; while equation 3b is a non-linear differential equation of the second type *Abel* equation that requires numerical simulation. The analytical solution for equation 3a is expressed in the following equation 4:

$$IG(t) \Big|_{net-UU} = e^{-\beta t} \times \left[\int [\beta \times BG(s) - \alpha \times IG(ts)] e^{st} ds \right] \dots \text{Eq. 4}$$

By assuming that α and β are constant over time, equation 4 can be reduced to the following equation 6 using the Delta-tau notation as presented in the following equation 5:

$$\Delta^\tau (f(t)) \equiv f(t) - e^{-\beta(t-\tau)} f(\tau) \dots \text{Eq. 5}$$

$$IG(t) = IG(\tau) e^{-\beta(t-\tau)} + \sum_{l=0}^{\infty} \left(\frac{-1}{\beta} \right)^l \Delta^\tau (BG^l - \alpha / \beta) \dots \text{Eq. 6}$$

[0053] By removing the higher order derivative terms of $BG(t)$ in equation 6, equation 6 can then be reduced to a form to which a Kalman recursion analysis based on Kalman filtering/smoothing technique are applicable. An exemplary of such technique is set forth in “*Optimal Control and Estimation*” New York: Dover Publications, 1994 37, the subject matter of which is incorporated herein by reference in entirety, wherein a “state-space model” and recursion process are used. The recursion process is attached herein in Appendix B. Using the “state-space model” and with the assumption that CGS readings are uniformly spaced by a small time ξ , a state-space model for dependence of CGS output and IG can be described in the following equation 9.

$$CGS(t_i) = calibration \times IG(t_i) + R \times w_0 \dots \text{Eq. 9, wherein}$$

$$IG(t_i) = e^{-\beta \tau} \times IG(t_{i-\xi}) + f(t_i) + Q \times w_s; \text{ and wherein}$$

$$f(t_i) = \sum_{j=0}^{\infty} \left(\frac{-1}{\beta} \right)^j \Delta^j (BG(t)^j - \alpha / \beta).$$

[0054] A state-space model for CGS output including the BG evolution can be expressed as the following equation 10.

$$\begin{bmatrix} BG_{i+1} \\ \dot{BG}_{i+1} \\ \ddot{BG}_{i+1} \\ BG_i \\ \dot{BG}_i \\ \ddot{BG}_i \\ IG_i \\ \alpha \end{bmatrix} = \begin{bmatrix} 1 & \varepsilon & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & \varepsilon & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -\frac{1}{\beta} & \frac{1}{\beta^2} & -e^{-\beta \varepsilon} & \frac{e^{-\beta \varepsilon}}{\beta} & \frac{e^{-\beta \varepsilon}}{\beta^2} & e^{-\beta \varepsilon} & -\frac{1}{\beta} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} BG_i \\ \dot{BG}_i \\ \ddot{BG}_i \\ BG_{i-1} \\ \dot{BG}_{i-1} \\ \ddot{BG}_{i-1} \\ IG_{i-1} \\ \alpha \end{bmatrix} + Q \times w_s \begin{bmatrix} 0 \\ 0 \\ \varepsilon \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Equation 10

[0055] A state-space model for CGS output including the BG evolution and linear projection can be expressed as the following equation 11.

$$\begin{bmatrix} BG_{i+1} \\ \dot{BG}_{i+1} \\ \ddot{BG}_{i+1} \\ IG_{i+1} \\ \alpha \end{bmatrix} = \begin{bmatrix} 1 & \varepsilon & 0 & 0 & 0 \\ 0 & 1 & \varepsilon & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ \beta\varepsilon & 0 & 0 & 1-\beta\varepsilon & -\varepsilon \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} BG_i \\ \dot{BG}_i \\ \ddot{BG}_i \\ IG_i \\ \alpha \end{bmatrix} + Q \times w_s \begin{bmatrix} 0 \\ 0 \\ \varepsilon \\ 0 \\ 0 \end{bmatrix} \dots \text{Eq. 11}$$

[0056] Inversion of equations 3a and 3b can be similarly performed given the estimates of consumption, permeability, IG , and the rate of change of IG . The inversed equations of 3a and 3b are respectively presented as the following equations 12a and 12b:

$$BG(t) = \frac{IG(t) + \alpha(t)}{\beta} + IG(t) \dots \text{Eq. 12a}$$

$$BG(t) = \frac{IG(t)}{\beta} + IG(t) \times \left[1 + \frac{\alpha / \beta}{Km + IG(t)} \right] \dots \text{Eq. 12b}$$

[0057] Equations 12a and 12b indicate that the use of CGS becomes important to provide accurate estimates of the rate of change of IG . Presentations of the inversed equations 12a and 12b are also possible, which are expressed as following equations 13 and 14.

$$\begin{bmatrix} IG(t_i) \\ IG(t_{i-1}) \\ CGS(t_{i+1}) \end{bmatrix} = \begin{bmatrix} 0 & 0 & \text{calib} \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \times \begin{bmatrix} IG(t_{i-1}) \\ IG(t_{i-2}) \\ CGS(t_i) \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ CGS(t_{i+1}) \end{bmatrix} + Q \times w_s \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \dots \text{Eq. 13}$$

$$f(t_i) = \begin{bmatrix} 1 & -e^{-\beta\varepsilon} & 0 \end{bmatrix} \times \begin{bmatrix} IG(t_i) \\ IG(t_{i-1}) \\ CGS(t_{i+1}) \end{bmatrix} + R \times w_0 \dots \text{Eq. 14}$$

[0058] It is noted that the observation in the above described model is the function of $BG(t)$ that defined in equation 7. If one accepts a polynomial smoothing/interpolation formula to describe the course of $BG(t)$, then it, too can be linearly inverted, as shown in the attached Appendix C.

ALGORITHMIC IMPLEMENTATION

[0059] The above described mathematical model and equations can then be applied to the CGS readings for remedying the physiology time lag between $IG(t)$ and $BG(t)$ by predicting BG levels using CGS outputs. An exemplary procedure of the invention is presented in the flow chart of FIG. 6.

[0060] Referring to FIG. 6, the mathematical model as discussed above is developed at step 132. The model describes the dynamics among $BG(t)$, $IG(t)$, and CGS output $SG(t)$. Based upon the model developed at step 132, the first mathematical equation is reduced so as to find out $SG(t)$ as a function of $BG(t)$. This first equation is preferably developed using Fick's law of diffusion and Michaelis-Menten consumption. The first equation is then inversed so as to estimate the dynamics of $BG(t)$ as a function of CGS output $SG(t)$ at step 136. The inversed equation can then be applied to the CGS raw data to improve the accuracy of the CGS readings at step 138. An exemplary application of the inversed equation to the raw CGS data at step 138 is illustrated in FIG. 7.

[0061] Referring to FIG. 7, sets of raw data are obtained at step 140. The data sets comprise CGS outputs $SG(t_i)$, sample time $Tm(t_i)$, and parameters $Par(\alpha, \beta, calib)$, wherein parameter $calib$ is a parameter presented in equation 9 as *calibration*. The raw CGS data are preferably preprocessed (though not required) at step 142. Specifically, the CGS raw data are processed by initial regression and/or filtering to smooth CGS raw data. This step is important in that the investigation showed that the raw CGS data current suffer from noise and random spikes that need to be filtered out in order to improve the accuracy of the inverted model equation. There are many ways to regress and/ or filter the CGS data. For example, the raw CGS data can be filtered based upon clinically observed BG rate-of-change in combination with a Bayesian estimation technique. In another example, the raw CGS output can be processed with a Kalman filter based methods of equations 10 and 11 that produce optimal estimation with the assumption that the evolution of BG meets its limitations.

[0062] Given the pre-processed CGS data (or directly the raw CGS data without the above pre-processing), the rate of change (time derivative) of CGS output is calculated at step 144. A unique feature of the CGS output is the ability to estimate the derivative of their outputs. However, because of the observation and systematic noise and wandering sensor sensitivity, it is observed that such instant raw estimates are rarely optimal. Instead, a short-interval polynomial smoothing technique using exponential weights can produce better results, as indicated by experiments. Then the IG proportionality coefficients are applied to CGS at step 146, followed by application of the inverted model as described above to estimate the BG level at step 148.

SOFTWARE IMPLEMENTATION

[0063] The process as described with reference to FIG. 7 can be implemented in many ways, one of which is in software. As an example, the above process can be implemented in a real-time version, which can be of particular usage for the application directly into CGS outputs so as to convert the raw CGS outputs into BG estimates, and produce real-time results. A set of real-time implementation program codes is attached herein as appendix D. Alternatively, the process can be implemented as a retrospective version that is of particular usage for performing retrospective improvement of CGS accuracy; and is applicable to CGS that do not display real-time data. A set of program codes for the retrospective implementation is attached herein as appendix E. It is noted that for ease of reference, the beginning of each line numbers is removed. A linearized version of the parameters is employed in favor of the computation speed. It will be appreciated by those skilled in the art that the program codes presented in appendices D and E are based on for demonstration purposes, and should not be interpreted as a limitation. Many other variations without departing from the spirit of the invention are also applicable.

TESTING OF THE METHOD

[0064] The above described process for remedying the physiology time lag between BG and CGS output has been evaluated on data acquired during a study performed at the University of Virginia General Clinical Research Center (GCRC), which was an "add-on" project to ongoing NIH research grant (RO1 DK 51562, Principal Investigator Boris Kovatchev). The add-on study was sponsored by Abbott Diabetes Care (P.I. William Clarke) to perform a direct comparison between two CGS: Abbott NavigatorTM and Minimed CGMS. The development and testing of the model were among the objectives of the add-on study.

Subjects for the study

[0065] Sixteen subjects with T1DM (11 *male*, 5 *female*, age 42 with standard deviation (SD) of 3 years, duration of diabetes 20 year with SD of 3 years. Informed consent was obtained from each. Subjects were admitted to the General Clinical Research Center in the evening prior to the study following a physical examination. A CGS system, the Freestyle NavigatorTM was applied to each subject for approximately 12 hours prior to the initiation of the data recording, in accordance with the manufacturer's instructions and calibrated as recommended. All systems were inserted in the abdomen. No BG reference *vs.* CGS comparisons was made

until the next morning. Study Protocol is defined as that identical hyperinsulinemic clamps were performed on two consecutive days:

[0066] On each day the hyperinsulinemic clamp used constant insulin infusion rate of $40mU/kg/min$ and variable glucose infusion rate to achieve and maintain BG levels at approximately $110\ mg/dl$. Subsequently, the glucose infusion rate was reduced to permit a controlled decline in BG levels of approximately $1mg/dl/min$ until the BG level reached $40mg/dl$. The euglycemic clamp portion of the study varied in length from 70 to 210 minutes, while the duration of the BG reduction procedure ranged from 30 to 60 minutes. Arterialized blood was sampled every 5 minutes and reference BG levels were determined using a Beckman Glucose Analyzer (Beckman Instruments, Inc, Fullerton, CA). Freestyle Navigator™ glucose readings were recorded each minute and were synchronized with reference BG with a precision of 30 seconds. Reference and Navigator™ rates and direction of BG change were calculated at five-minute intervals. This procedure resulted in 29 clamp data sets for the 16 participants in the study.

SOFTWARE USED FOR ANALYSIS

[0067] Numerical analysis was conducted using R 2.1.1, which is an open-source free programming language and suite for statistic analysis (<http://www.r-project.org>). Beyond the base packages, the "odesolve," "fields," and "dsel" packages and their dependencies from CRAN repositories were used Microsoft Excel was used to produce graphs.

RESULTS

[0068] Equation 12a was applied to the unfiltered Navigator™ raw data with parameters found via nonlinear least squares. Each data run begins at the start of descent into hypoglycemia. Table 1 presents a summary of the results for all 29 clamp events. It can be seen that the average RMS error of the Navigator™ was reduced more than 3-folds; and the % RMS error was reduced more that 5-folds. In addition, the correlation between reference and sensor BG was improved by the model:

TABLE 1

	BG prediction using a method of the invention	Navigator™
RMS error (<i>mg/dl</i>)	8.1	27.3

RMS % error	10.6	55.1
Pearson Correlation	0.995	0.940

[0069] FIG. 8 to FIG. 10 depicts the results. Specifically, FIG. 8 shows the average of the 29 events matched at the nadir with five-minute data intervals. The solid diamond symbols are reference BG recorded by the Beckman analyzer. The solid squares are the data of the NavigatorTM. The open squares are the navigatorTM corrected by a method of the invention. It can be seen in the figure that the model-corrected data are much closer to reference BG than the original navigatorTM outputs. FIG. 9 and FIG. 10 show two individual patients with one-minute data interval. In both cases, a correction of the NavigatorTM data by a method of the invention (open squares) results in improved tracing of reference BG.

A COMBINED ACCURACY IMPROVEMENT METHOD AND DEVICE

[0070] As discussed above, the accuracy of the CGS output can be improved by an example of the invention through an improved calibration method. Alternatively, CGS accuracy can also be improved by remedying the physiology time lag between the BG and IG. In another example of the invention, the above two correction methods can be combined so as to further improve the CGS accuracy. FIG. 11 illustrates a flow chart for performing a combined accuracy improving process in accordance with another example of the invention.

[0071] Referring to FIG. 11, the combined process starts from calibrating the CGS using the method as described above with reference to FIG. 4. System errors can be eliminated or reduced. The CGS outputs from the calibrated CGS are preprocessed at step 152 by filtering and/or smoothing the calibrated CGS output. This step can be performed using the same or different method as described at step 142 in FIG. 7. It is noted that this step, though preferred, is not required. From the pre-process, sensor noise and/or minor random fluctuations in the CGS outputs and the first order time derivative can be removed or reduced. The first order time derivations of CGS outputs $SG(t_i)$ are calculated at step 144. The IG proportionality coefficient are then applied to the CGS outputs followed by the application of the inverted model equations to estimate the BG level, as described with reference to FIG. 6, which will not be repeated herein.

[0072] Table 2 shows the accuracy improvement using the methods according to example of the invention by comparing the CGS outputs obtained from the methods of the invention and the CGS outputs in a typical CGS in the art without employing the methods of the invention.

The CGS outputs obtained from the typical CGS in the art are referenced in "Evaluating the accuracy of continuous glucose monitoring sensors: continuous glucose error grid analysis illustrated by theasense freestyle navigator data," by B Kovatchev, L Gonder Frederick, D Cox, and W Clarke, *Diabetes Care*, vol. 27, pp 1922-1928,2004.

TABLE 2

Zone	CG_EGA Accuracy Results			MAE <i>mg/dl</i>	MAPE %	N
	Accuracy %	Benign %	Error %			
Panel A: Original calibration						
Hypoglycemia	50	0	50	27.9	50.1	376
Euglycemia	96.4	0.2	3.4	20.4	22.6	532
Panel B: <i>d=30 mg/dl</i> calibration						
Hypoglycemia	86.7	4.8	8.5	10.9	19.8	376
Euglycemia	93.4	2.6	3.9	13.6	14.9	532
Panel C: BG and SG (CGS output) compensation						
Hypoglycemia	100	0	0	4.9	8.4	376
Euglycemia	99.4	0.6	0	7.9	8.4	532

[0073] Panel A of Table 2 presents the continuous glucose error-grid analysis (CG-EGA) of the accuracy of Minimed CGMS™ during the clamp study described above, stratified by hypoglycemia and euglycemia. The clinically accurate sensor readings were 50.0% during hypoglycemia and 96.4% during euglycemia. The large difference between these percentages is primarily due to the more demanding clinical accuracy standards. For hypoglycemia events: while for steady euglycemic state there is a large clinical tolerance for sensor errors. During clinically dangerous and rapidly developing conditions, such as hypoglycemia, the sensor is desired to meet higher standards in order to provide accurate feedback for appropriate and timely treatment decision. The CG-EGA reflects this distinction. Further, the MAE and the mean absolute percent error (MAPE) are included in Table 1 and stratified by BG range as well.

[0074] The panel B in Table 2 presents the CG-EGA, MAE and MAPE of a sensor re-calibrated by two reference BGs that are 30 *mg/dl* apart (e.g. differential *d* is 30 *mg/dl*), which is a clinically reasonable differential in the studied BG range. It can be seen that the percent of CG-EGA accurate readings increases from 50% to 86.7%, while MAE is reduced from 27.9 to 10.9 *mg/dl* during hypoglycemia. Improvement in MAE and MAPE is observed during euglycemia as well.

[0075] The panel C of Table 2 presents the CG-EGA, MAE and MAPE of the SIG vs. BG estimated after sensor re-calibration. It can be seen that the "accuracy" of SIG following BG fluctuation is high – nearly 100%, which signifies an excellent theoretical limit for potential sensor accuracy.

[0076] Examples of the invention can be implemented in many ways. For example, it can be implemented as a functional member of a continuous glucose sensor, or can be implemented as a standalone module associated with the continuous glucose sensor. In either instance, examples of the invention can be implemented as a set of program codes of software installed in a computing device, or a set of computer-executable codes of a hardware device coupled to the continuous glucose sensor. Regardless the implementation media, example of the invention can be associated with individual continuous glucose sensors for improving the accuracy of the individual glucose sensors. Alternatively, examples of the invention can be implemented in such a way that the real-time CGS data, along with related errors and error correction parameters and data, can be transmitted to an error processing center. The transmission may or may not be with the glucose data. In this way, a generalized continuous glucose sensing system can be established.

[0077] FIG. 12 diagrammatically illustrates an exemplary system in which examples of the invention can be implemented. Referring to FIG. 12, clinic setup 158 provides a place for doctors (e.g. 164) to diagnose patients (e.g. 160) with diseases related with glucose. Continuous glucose sensor (or sensing device incorporating glucose testing function) 162 can be used to monitor and/or test the glucose levels of the patient. Such monitor and/or test can be short term (e.g. clinical visit) or long term (e.g. clinical stay or family). The continuous glucose sensor incorporates therein an example of the accuracy improvement methods as discussed above. The CGS outputs with improved accuracy can be used by the doctor for appropriate actions, such as insulin injection or food feeding for the patient, or other appropriate actions. Alternatively, the CGS output with improved accuracy can be delivered to computer terminal 168 for instant or future analyses. The delivery can be through cable or wireless or any other

suitable medium. The CGS output with improved accuracy from the patient can also be delivered to a portable device, such as PDA 166. The CGS outputs with improved accuracy can be delivered to a glucose monitoring center 172 for processing and/or analyzing. Such delivery can be made accomplished through many ways, such as network connection 170, which can be wired or wireless.

[0078] In addition to the CGS outputs with improved accuracy, errors, parameters for accuracy improvements, and any accuracy related information can be delivered, such as to computer 168, and / or data processing center 172 for performing error analyses. This can provide a centralized accuracy monitoring and/or accuracy enhancement for glucose centers, due to the importance of the glucose sensors.\

[0079] As discussed earlier, examples of the invention can also be implemented in a standalone computing device associated with the target continuous glucose sensors. An exemplary computing device in which examples of the invention can be implemented is schematically illustrated in FIG. 13. Although such devices are well known to those of skill in the art, a brief explanation will be provided herein for the convenience of other readers.

[0080] Referring to FIG. 13, in its most basic configuration, computing device 174 typically includes at least one processing unit 180 and memory 176. Depending on the exact configuration and type of computing device, memory 176 can be volatile (such as RAM), non-volatile (such as ROM, flash memory, *etc.*) or some combination of the two.

[0081] Additionally, device 174 may also have other features and/or functionality. For example, the device could also include additional removable and/or non-removable storage including, but not limited to, magnetic or optical disks or tape, as well as writable electrical storage media. Such additional storage is the figure by removable storage 182 and non-removable storage 178. Computer storage media includes volatile and nonvolatile, removable and non-removable media implemented in any method or technology for storage of information such as computer readable instructions, data structures, program modules or other data. The memory, the removable storage and the non-removable storage are all examples of computer storage media. Computer storage media includes, but is not limited to, RAM, ROM, EEPROM, flash memory or other memory technology, CDROM, digital versatile disks (DVD) or other optical storage, magnetic cassettes, magnetic tape, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to store the desired information and which can accessed by the device. Any such computer storage media may be part of, or used in conjunction with, the device.

[0082] The device may also contain one or more communications connections 184 that allow the device to communicate with other devices (e.g. other computing devices). The communications connections carry information in a communication media. Communication media typically embodies computer readable instructions, data structures, program modules or other data in a modulated data signal such as a carrier wave or other transport mechanism and includes any information delivery media. The term "modulated data signal" means a signal that has one or more of its characteristics set or changed in such a manner as to encode information in the signal. By way of example, and not limitation, communication media includes wired media such as a wired network or direct-wired connection, and wireless media such as acoustic, RF, infrared and other wireless media. As discussed above, the term computer readable media as used herein includes both storage media and communication media.

[0083] It will be appreciated by those of skill in the art that a new and useful method for improving accuracy of continuous glucose sensing devices and system using the same have been discussed herein. In view of the many possible embodiments to which the principles of this invention may be applied, however, it should be recognized that the embodiments described herein with respect to the drawing figures are meant to be illustrative only and should not be taken as limiting the scope of invention. Those of skill in the art will recognize that the illustrated embodiments can be modified in arrangement and detail without departing from the spirit of the invention. Therefore, the invention as described herein contemplates all such embodiments as may come within the scope of the following claims and equivalents thereof.

APPENDIX A

Subject matter of the following publications and US provisional application are incorporated herein by reference in entirety

1. Santiago JV: Lessons from the Diabetes Control and Complications Trial. *Diabetes* 1993, 42 1549-1554.
2. B. Feldman, R B~azgS, Schwartz, and R. Weinstein, "A continuous glucose sensor based on wired enzyme technology and results from a 3day trial in patients with type 1 diabetes," *Diabetes Technol Ther*, vol 5, pp 769-778,2003,
3. D Klonoff, "Continuous glucose monitoring: Roadmap for 21st century diabetes therapy," *Diabetes Care*, vol28, pp 1231-1239,2005.
4. E Cheyne, D. Cavan, and D. Kerr, "Performance of continuous glucose monitoring system during controlled hypoglycemia in healthy volunteers," *Diabetes Technol Ther* , vol4, pp 607-613,2002
5. M Boyne, D Silver, J . Kaplan, and C. Saudek, "Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor;" *Diabetes*, vol 52, pp 2790-2794,2003,
6. P T Stout, J R. Racchini, and M. E Hilgers, "A novel approach to mitigating the physiological lag between blood and interstitial fluid glucose measurements," *Diabetes Technol Ther*, vol. 6, pp. 635-644,2004
7. E. Kulcu, J. Tamada, G. Reach, R Potts, and M. Lesho, "Physiological differences between interstitial glucose and blood glucose measured in human subjects," *Diabetes Care*, vol 26, pp 2405-2409,2003,
8. A Schoonen and K Wientjes, "A model for transport of glucose in adipose tissue to a microdialysis probe," *Diabetes Technol Ther*, vol. 5, pp. 589-598,2003
9. G. M Steil, K Rebrin, F Hariri, S Jinagonda, S Tadros, C Darwin, and M F Saad, "Interstitial fluid glucose dynamics during insulin induced hypoglycaemia," *Diabetologia*, vol 48, pp. 1833-1840,2005,
10. K Rebrin and G Steil, "Can interstitial glucose assessment replace blood glucose measurements?" *Diabetes Technol Ther*, vol. 2, pp. 461472,2000,,
11. Kovatchev, L Gonder Frederick, D Cox, and W Clarke, "Evaluating the accuracy of continuous glucose monitoring sensors: continuous glucose error grid analysis illustrated by the sense freestyle navigator data," *Diabetes Care*, vol. 27, pp 1922-1928,2004
12. W Clarke, D. Cox, L Gonder Frederick, W Carter, and S Pohl, "Evaluating clinical accuracy of systems for self-monitoring of blood glucose," *Diabetes Care*, vol. 10, pp 622-

628.1987,

13. Hanefeld M: Postprandial hyperglycemia: noxious effects on the vessel wall *International Journal of Clinical Practice*, 2002, Supplement 129: 45-50
14. Esposito K, Giugliano D, Nappo F, Martella K, for the Campanian Postprandial Hyperglycemia Study Group. *Circulation*, 2004,110: 214-219
15. Quaglim L, Piconi L, Assalone R, Martinelli L, Motz E, Ceriello A: Intermittent I-High Glucose Enhances Apoptosis Related to Oxidative Stress in Human Umbilical Vein Endothelial Cells: The Role of protein Kinase C and NAD(P)H-Oxidase Activation *Diabetes*, 2003,a: 2795-2804.
16. Van der Does FE, De Neeling JN, Snoek F J, Kostense PI, Grootenhuys PA, Bouter LM, and RJ Heine: Symptoms and well-being in relation to glycemic control in type II diabetes *Diabetes Care*, 1996,u: 204-210
17. De Sonnaville JJ, Snoek F J Colly LP, Deville W, Wijkel D Heine RJ: Well-being and symptoms in relation to insulin therapy in type 2 diabetes. *Diabetes Care*, 1998, a:919- 24,
18. Cox DJ, Gonder-Frederick LA, McCall A, et al The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes *International Journal of Clinical Practice*, 2002, Supplement 129: 20-26
19. Hirsh IB, Brownlee M: Should minimal blood glucose variability become the gold standard of glycemic control? *Jof Diabete~ and Its Complications* ,2005,D: 178-1 81
20. Reichard P, Phil M Mortality and treatment side effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention study *Diabetes* 43: 313-317, 1994
21. The Diabetes Control and Complications Trial Research Group The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus *N Engl J Med* 329: 978-986, 1993
22. Gross TM, Bode BW, Einhorn D, Kayne DM, Reed IH, White NH, Masttototaro JJ: Performance evaluation of the MiMed continuous glucose monitoring system during patient home use *Diabetes Technol Ther* 2000;2:49-56
23. Tav~iDs R, Shoaibi A: The public health impact of the MiniMed Continuous Glucose Monitoring System (CGMSO): an assessment of the literature *Diabetes Technol Ther* 2004;6:5 18-522
24. Chico A, Vidal-Rios P, Subiia M, Novials A: The continuous glucose monitoring system is usehl for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than fiequent capillary glucose measurements for improving metabolic control *Diabetes Care* 26:1153-,1157,2003

25. Masbototaro J: The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 12:751-758, 1999
26. Feldman B, Brazg R, Schwartz S, Weinstein R : A continuous glucose sensor based on wired enzyme technology -- results from a 3 -day trial in patients with type 1 diabetes *Diabetes Technol Ther* 2003;5(5):769-79
27. Pickup J: Sensitive glucose sensing in diabetes *Lancet* 355:426-427,2000
28. Gerzitsen M, Jansen JA, Lutterman JA: Performance of subcutaneously implanted glucose sensors for continuous monitoring *Neth J Med* 54:167- 179, 1999
29. Boyne, Silver, Kaplan, & Saudek: Timing of Changes in Interstitial and Venous Blood Glucose Measured With a Continuous Subcutaneous Glucose Sensor *Diabetes* 52: 2790-2794,2003
30. Philip J Stout, Joel R Racchini, Michael E Hilgers: A Novel Approach to Mitigating the Physiological Lag Between Blood and Interstitial Fluid Glucose Measurements *Diabetes Technol Ther* 2004 6:5,635-644
31. Schoonen & Wientjes: A Model for Transport of Glucose in Adipose Tissue to a Microdialysis Probe *Diabetes Technol Ther* 2003 5:4,589-59%
32. A S Popel Analysis of capillary-tissue diffusion in multicapillary systems *Mathematical Biosciences*, 39: 18 7-2 11, 1978,
33. G. M. Steil , K. Rebrin, F Hariri, S Jinagonda, S Tadros, C Darwin and M F Saad,, Interstitial fluid glucose dynamics during insulin- induced hypoglycaemia *Diabetologia* 48:7, published online. DOI: 10.1007/s00125-,005-1852-x
34. Zierler K: Whole body glucose metabolism *Am J Physiol* 276:E409-E426, 1999
35. Palfreyman RW, Clark AE, Denton RM, Holman GD, Kozka IS: Kinetic resolution of the separate GLUT 1 and GLUT4 glucose transport activities in 3T3-L1 cells *Biochem J* . 284:275-,282, 1992.
36. Stengel RF : *Optimal Control and Estimation* New York: Dover Publications, 1994
37. Knobbe EJ, Buckingham B: The extended Kalman filter for continuous glucose monitoring *Diabetes Technol Ther* 2005;7:15-27,,
38. Palerm Cesx C., Willis John P., Desemone James, Bequette B Wayne: Hypoglycemia Prediction and Detection Using Optimal Estimation *Diabetes Technol Ther* 2005;7:3-14,
39. "G M. Steil , K Rebrin, F Hariri, S Jinagonda, S Tadros, C Darwin and M F. Saad. Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia *Diabetologia* 48:7,

published online. DOI: 101007/s00125-005-1852-x"

40. International Patent Application Serial No. PCT/US20051013792, entitled "Method, System and Computer Program Product for Evaluating the Accuracy of Blood Glucose Monitoring Sensors/Devices," filed April 21, 2005,

41. US provisional application serial number 60/815,191 to Kovatchev *et al.* filed June 20, 2006;

APPENDIX B – Kalman Recursion

01265-01

Appendix A: Kalman Recursions

If we assume that our data follows a system of the form of A1.1, where x is a hidden system state vector, y is an observation vector, w_s is system noise with covariance matrix Q , w_o is observation noise with covariance matrix R , and the F , G , H matrices define system transitions, then the system is said to be a state space model.

$$\text{A1.1)} \quad \begin{aligned} x_{i+1} &= Fx_i + Gz_i + w_s \\ y_i &= Hx_i + w_o \end{aligned}$$

The Kalman filter is a two step process. First, one-step-ahead predictions are made. Second, a correction to that prediction is made based upon new measurements. Let us introduce to notation of $\hat{x}_{i|j}$ meaning “the estimate of x at i given the measurements up to and including j .” Assuming that we have current estimates of x and the error covariance of that estimate, P , we can write the first step as A1.2. In order to correct the estimates, we then calculate the Kalman gain in A1.3, and update the estimates in A1.4 using the new measurement, y .

$$\text{A1.2)} \quad \begin{aligned} \hat{x}_{i|i-1} &= F\hat{x}_{i-1|i-1} + G\hat{z}_{i-1} \\ \hat{P}_i &= F\hat{P}_{i-1}F^T + Q \end{aligned}$$

$$\text{A1.3)} \quad K_i = \hat{P}_i H^T (H\hat{P}_i H^T + R)^{-1}$$

$$\text{A1.4)} \quad \begin{aligned} \hat{x}_{i|i} &= \hat{x}_{i|i-1} + K_i(y_i - H\hat{x}_{i|i-1}) \\ \hat{P}_i &= (I - K_i H)\hat{P}_i \end{aligned}$$

APPENDIX C – recursion process

01265-01

$$A2.7) \quad X\check{I} = [BG_{i,interp}]$$

$$A2.8) \quad diagonal(\check{X}\check{I}) = \overset{k}{B}\overset{k}{G}$$

The diagonal operator can be written as in A2.9, which reduces A2.8 to A2.10. Furthermore, by again concatenating the first q+1 column vectors we can form the desired matrix A2.1 in A 2.11.

$$A2.9) \quad C_j = \{ C\{ij\}=1, \text{ else } C\{ij\}=0 \}, \quad diagonal(A) = \sum_{i=1}^n C_i A e_i^T$$

$$A2.10) \quad \overset{k}{B}\overset{k}{G} = \{ \sum_{i=1}^n C_i X (X^T W_i X)^{-1} X^T W_i \} \mathbf{B}\mathbf{G}, \quad \{ \dots \} \equiv M_k$$

$$A2.11) \quad \check{B}\check{G} = \sum_{k=0}^q M_k \mathbf{B}\mathbf{G} e_k$$

Finally, by inserting A2.11 into A2.3 we arrive at A 2.12, a linear system which can be solved by methods such as QR decomposition.

$$A2.12) \quad f(t) + \alpha/\beta = \{ (I - \delta B_\delta) \sum_{k=0}^q M_k (-1/\beta)^k \} \mathbf{B}\mathbf{G}$$

APPENDIX D – program codes of real-time implementationVersion 1: Real-time application:

```

1 GetNewBGPreds <- function(Nav,times,par) {
#needs times in minutes to make the parameters work right

#remove missing values

2 times[!is.na(Nav)]->times;Nav[!is.na(Nav)]->Nav;

#second apply the calibration parameter

3 Navipar [ [ 31 ] ->Nav;

#third, create arrays to hold estimates of IG, and dot IG

4 rep(O., times=length(Nav))->Idot; Nav->IG;

#fourth, create estimates of dot IG in the time before much data has been collected

5 (IG[2]-IG[1])/(times [2]-times [1]) ->Idot [2] ;

6 #linear interpolation

7 data frame(y=IG[1:3] ,x=times[1: 31 ]->td;

8 lm(y~x,data=td)->tx;t x$coefficients [2]->tx;attr (tx," names")<-NULL; tx->Idot [3] ;

9 data frame (y=IG[1:4] ,x=times [1:4]) ->td;

10 lm(y~x,data=td) ->tx;tx$coefficients [2]->tx;attr (tx, "namesw")<-NULL; tx->Idot [4] ;
#fifth, create estimates using splines over the CGS data

11 for (i in 5:length(Nav)) (

12 times [ (i-4) : (i) ] ->tt;Nav[ (i-4) : (i) ] ->td;

13 smooth spline(x=tt,y=td,df=1)->temp;

14 predict (temp,t times [i] ,deriv=1)$ y-2Idot [i];

15 predict (temp, times [i]) Sy->IG[i] ;

16 }

#sixth, apply the main formula
17 IG+Idotkpar [ [ 2 ] ]+par [ [ 1 ] ] ->NewBG; #seventh, return the result

18 NewBG)

```

APPENDIX E – program codes of retrospective implementationVersion 2: Retrospective correction:

In addition to the real-time implementation, one can introduce an artificial delay by extending the time over which each spline is interpolated in line 12 from "(i-4):(i)" to "(i-4):(i+4)." In purely retrospective analysis, one can use the more simple form given next.

```

19 GetOldBGPreds <- function(Nav,times,par) {
#eliminate missing values

20 times [ !is.na (Nav)] ->times;

21 Nav [ !is.na (Nav) 1 ->Nav;
#apply calibration parameter

22 par [ [3] 1 *Nav->Nav;
#create a smoothing spline regression over all the data

23 sreg (times, Nav) ->Navfit ;
#use it to predict IG

24 predict (Navfit,times)->IG;
#use it to predict dot IG

25 predict(Navfit,times,deriv=1)->Idot;
#apply main formula

26 (Idot) *par [ [2] ] +par [ [1] 1 +IG->BGpreds;
#return predictions

27 BGpreds)

```

Finally, if the full Michaelis-Menton form of the equation 3 is desired, then one can simply replace "par [[1]]" with "p a r [[1]] * I G / (126.+IG)" in lines 17 and 27. R contains many other smoothing and interpolation facilities, and the use of *sreg*, *smooth spline*, and *lm* can be substituted with many of them, although the input/output format is frequently different.

CLAIMS

I Claim:

1. A method for improving accuracy of a continuous glucose sensor (CGS), comprising:
calibrating the CGS at a first time; and
calibrating the CGS at a second time that is determined based upon at least one of a dynamically monitored CGS value and a rate of CGS change.
2. The method of claim 1, wherein the dynamically monitored CGS value differs by at least 15 mg/dl before the second calibration takes place.
3. The method of claim 1, wherein the dynamically monitored CGS value differs by at least 20 mg/dl before the second calibration takes place.
4. The method of claim 1, wherein the dynamically monitored CGS value differs by at least 30 mg/dl before the second calibration takes place.
5. The method of claim 1, further comprising:
dynamically monitoring the CGS value and the rate of CGS change over time.
6. The method of claim 5, further comprising:
calculating the first order time derivative of the monitored CGS value;
determining whether the absolute value of the first time derivative of the CGS value is substantially less than 1; and
maintaining the calibration of the CGS at the first time when the absolute value of the first time derivative of the CGS value is substantially less than 1.
7. The method of claim 6, further comprising:
determining the absolute change between the CGS at the second time and the CGS at the first time calibration is greater than a pre-determined value when the absolute value of the first time derivative of the CGS value is substantially less than 1; and

maintaining the calibration of the CGS at the first time when the absolute change between the CGS at the second time and the CGS at the first time calibration is greater than a pre-determined value.

8. The method of claim 7, wherein the predetermined value is 30 *mg/dl*.
9. The method of claim 7, wherein the predetermined value is 40 *mg/dl*.
10. The method of claim 7, further comprising:
recalibrating the CGS when it is determined that the absolute change between the CGS at the second time and the CGS at the first time calibration is greater than a pre-determined value.
11. The method of claim 1, further comprising:
improving the accuracy of the CGS output by remedying a physiology time lag between the blood glucose level and a glucose level in an interstitial fluid that interacts with the blood glucose.
12. The method of claim 11, wherein the step of improving the accuracy further comprises:
deriving a mathematical equation describing a time dependence of CGS output on the blood glucose level;
deriving the time dependence blood glucose level as a function of the CGS output; and
applying the derived time dependence blood glucose level function to a set of CGS raw outputs so as to predict the blood glucose level at a later time or correcting the CGS output.
13. The method of claim 12, wherein the mathematical equation is derived based on a model that includes a description of a diffusion interaction between the blood glucose and glucose in the interstitial fluid.
14. The method of claim 12, wherein the mathematical equation is derived based on a model that includes a description of an assumption of the glucose in the interstitial fluid.

15. The method of claim 1, wherein the second time that is determined based upon both of the dynamically monitored CGS value and the rate of CGS change.
16. A method for improving the accuracy of a continuous glucose sensor, comprising:
 - calibrating the continuous glucose sensor using first blood glucose value and second blood glucose value;
 - measuring the first blood glucose value when the continuous glucose sensor measures a corresponding first interstitial glucose value; and
 - measuring the second blood glucose value when the continuous glucose sensor measures a corresponding second interstitial glucose value that is different from the first interstitial glucose value by a predetermined amount.
17. The method of claim 16, wherein the predetermined amount is at least 15 mg/dl.
18. The method of claim 16, wherein the predetermined amount is at least 20 mg/dl.
19. The method of claim 17, wherein the first and second glucose data are obtained at different times.
20. The method of claim 17, wherein the second glucose data is obtained through a decision making loop that comprises a determination of a rate of CGS change based on a pre-determined criterion.
21. The method of claim 20, wherein the pre-determined criterion states that if the rate of CGS change is equal to or greater than a pre-determined value, maintaining the CGS calibration with the first glucose data.
22. The method of claim 21, wherein the pre-determined value is 1.
23. The method of claim 22, wherein the pre-determined criterion further states that if the rate of CGS change is less than 1, performing another decision based on another pre-determined value.

24. The method of claim 23, wherein said another pre-determined criterion states that if the absolute difference between the CGS and the calibrated CGS with the first blood glucose data is equal to or less than a pre-determined difference value, maintaining the CGS calibration with the first glucose data.
25. The method of claim 24, wherein said another pre-determined criterion further states that if the absolute difference between the CGS and the calibrated CGS with the first blood glucose data is greater than the pre-determined difference value, performing another calibration with the second blood glucose data.
26. The method of claim 17, further comprising:
improving the accuracy of the CGS output by remedying a physiology time lag between the blood glucose level and a glucose level in an interstitial fluid that interacts with the blood glucose.
27. The method of claim 26, wherein the step of improving the accuracy further comprises:
deriving a mathematical equation describing a time dependence of CGS output on the blood glucose level;
deriving the time dependence blood glucose level as a function of the CGS output; and
applying the derived time dependence blood glucose level function to a set of CGS raw outputs so as to correct the CGS output for inherent time lags.
28. The method of claim 27, wherein the mathematical equation is derived based on a model that includes a description of a diffusion interaction between the blood glucose and glucose in the interstitial fluid.
29. The method of claim 27, wherein the mathematical equation is derived based on a model that includes a description of an assumption of the glucose in the interstitial fluid.
30. The method of claim 27, wherein the time dependence blood glucose level as a function of the CGS output is an inversed function of the mathematical equation that describes the time dependence of the CGS output on the blood glucose level.

31. A system for improving an accuracy of a continuous glucose sensor, comprising:
an accuracy improving module accessible to an output of the continuous glucose sensor,
further comprising:
a decision making mechanism capable of determining a calibration at a time
based upon at least one of a dynamically monitored output of the continuous
glucose sensor.
32. The system of claim 31, wherein the decision making mechanism is capable of
determining the calibration at the time that is based upon the output of the continuous glucose
sensor and a rate of change of the output of the continuous glucose sensor.
33. The system of claim 31, wherein the accuracy improving module further comprises:
an initial request module capable of initiating a calibration at a predetermined time
sequence.
34. The system of claim 33, wherein the decision making mechanism further comprises:
a monitoring module capable of dynamically monitoring the output from the
continuous glucose sensor.
35. The system of claim 34, wherein the decision making mechanism further comprises:
a determination instruction stating that the dynamically monitored output from the
continuous glucose sensor differs by at least 15 mg/dl before the second calibration takes place.
36. The system of claim 34, wherein the decision making mechanism further comprises:
a determination instruction stating that the dynamically monitored output from the
continuous glucose sensor differs by at least 20 mg/dl before the second calibration takes place.
37. The system of claim 34, wherein the decision making mechanism further comprises:
a determination instruction stating that the absolute rate of change is substantially equal
to or greater than 1 before the second calibration takes place.
38. The system of claim 34, further comprising:

a time lag correction module capable of improving the accuracy of the CGS output by remedying a physiology time lag between the blood glucose level and a glucose level in an interstitial fluid that interacts with the blood glucose.

39. A kit, comprising
 - a continuous glucose sensor;
 - a calibration unit in a data communication with to the continuous glucose sensor for calibrating the continuous glucose sensor; and
 - a set of instructions including instructions for instruction monitoring monitored output from the continuous glucose sensor, and performing first and second calibrations at first and second continuous glucose sensor output values that differ by at least 15 mg/dl.
40. The kit of claim 39, wherein the calibration unit is connectable to the continuous glucose sensor.
41. The kit of claim 39, wherein the calibration unit is an integral member of the continuous glucose sensor.
42. The kit of claim 39, wherein the instruction further states that the dynamically monitored output of the continuous glucose sensor differs by at least 20 mg/dl before the second calibration takes place.
43. The kit of claim 39, wherein the instruction further states that an absolute rate of change of the output of the continuous glucose sensor is less than 1 before the second calibration takes place.
44. The kit of claim 39, wherein the accuracy improving mechanism further comprises:
 - a time lag correction module accessible to the output of the continuous glucose sensor and capable of remedying a physiology time lag.
45. A method for improving an accuracy of a continuous glucose sensor, comprising:
 - calibrating the CGS using a first blood glucose level and a second blood glucose level different by a predetermined amount from the first glucose data.

46. The method of claim 45, wherein the predetermined amount is at least 15 mg/dl.
47. The method of claim 46, wherein the predetermined amount is at least 20 mg/dl.
48. The method of claim 47, wherein the second glucose data is obtained through a decision making loop that comprises a determination of a rate of CGS change based on a pre-determined criterion.
49. The method of claim 48, wherein the pre-determined criterion states that if the rate of CGS change is equal to or greater than 1, maintaining the CGS calibration with the first glucose data.
50. A computer-readable medium having computer executable instructions for performing the method set forth in claim 1.
51. A computer-readable medium having computer executable instructions for performing the method set forth in claim 16.
52. A computer-readable medium having computer executable instructions for performing the method set forth in claim 45.
53. A kit, comprising:
a calibration unit for calibrating a continuous glucose, the calibration unit comprising a blood glucose sensor; and
a set of instructions including instructions for monitoring output from a continuous glucose sensor, and performing first and second calibrations at first and second continuous glucose sensor output values that differ by at least 15 mg/dl, where the first and second calibrations comprise respectively first and second determinations of blood glucose with the blood glucose sensor.

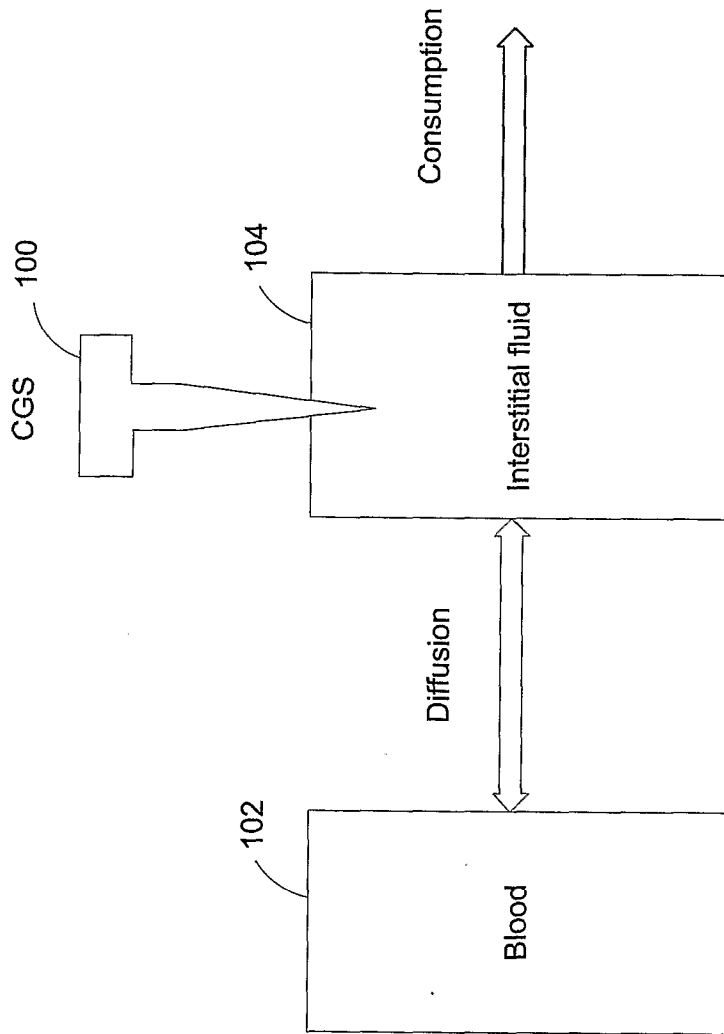


FIG. 1

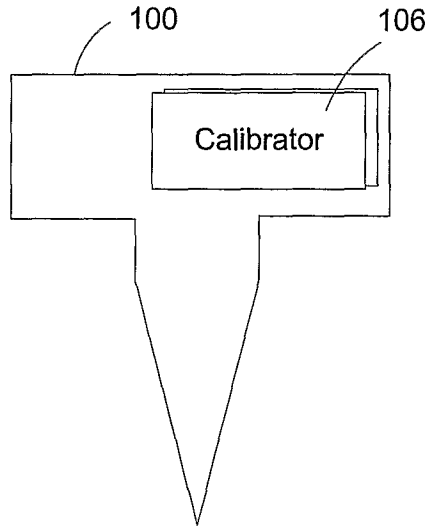


FIG. 2

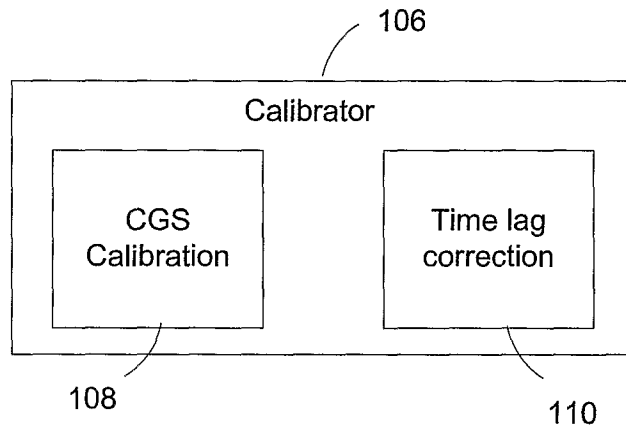


FIG. 3

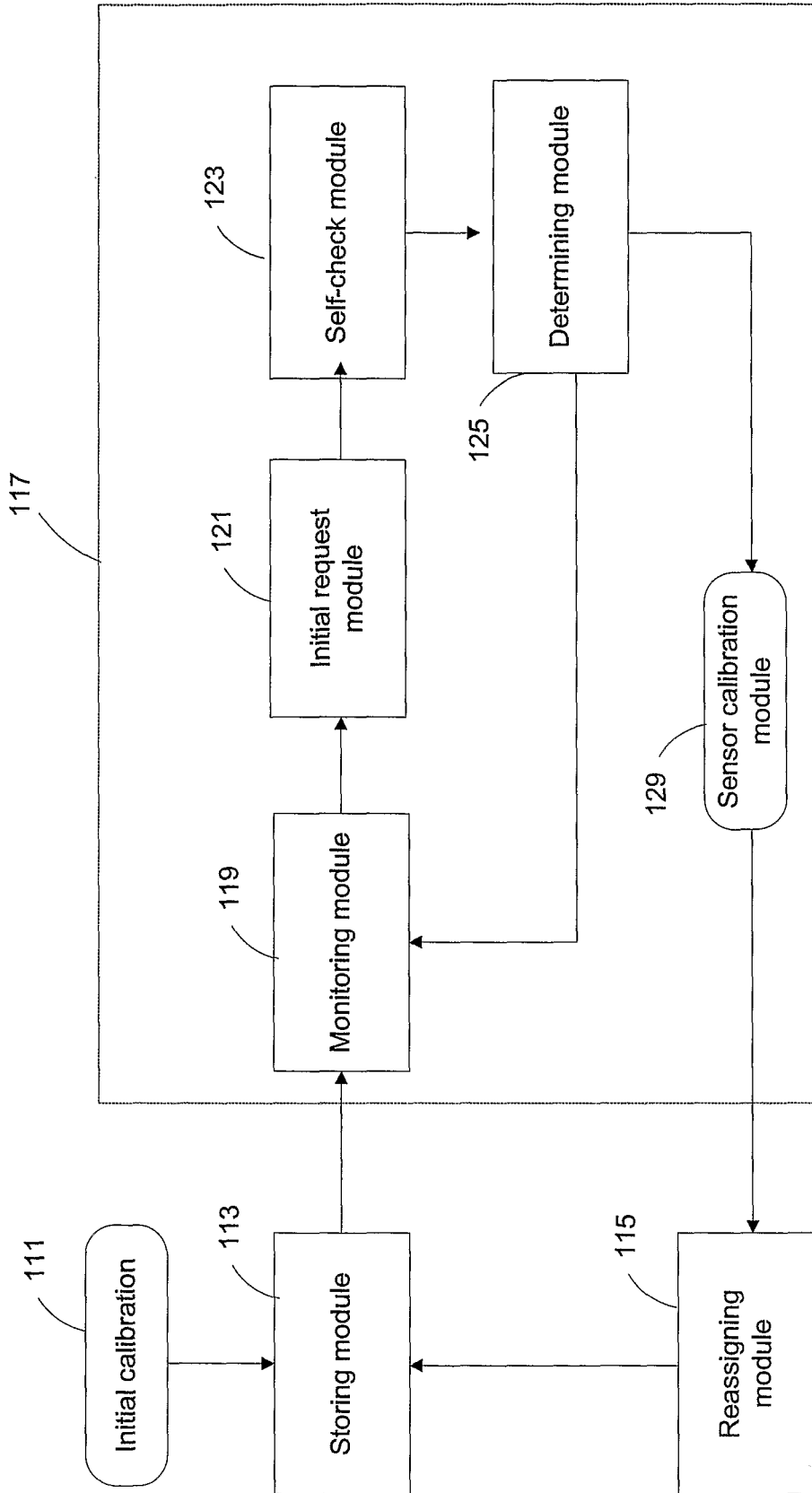


FIG. 4a

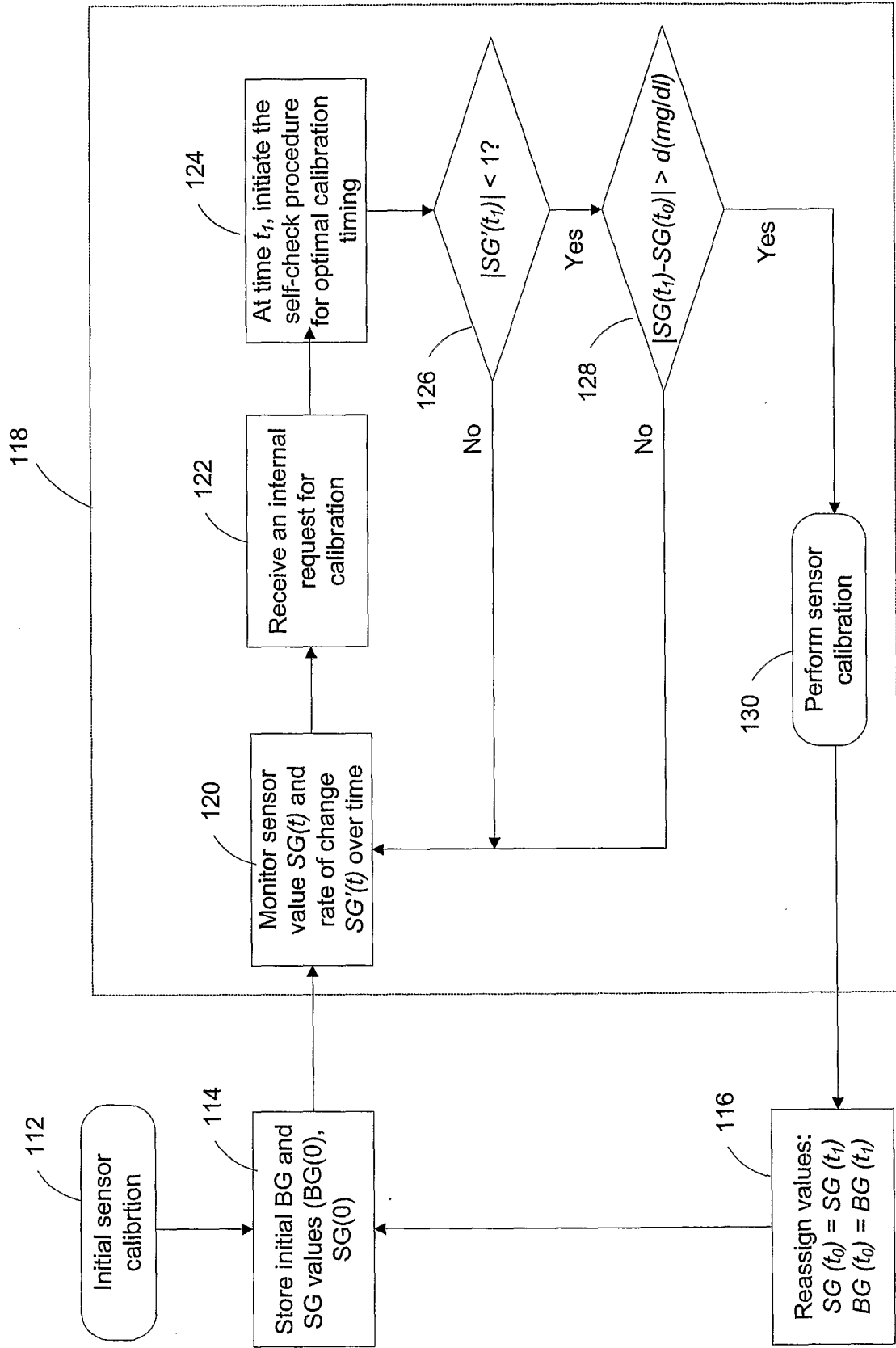


FIG. 4b

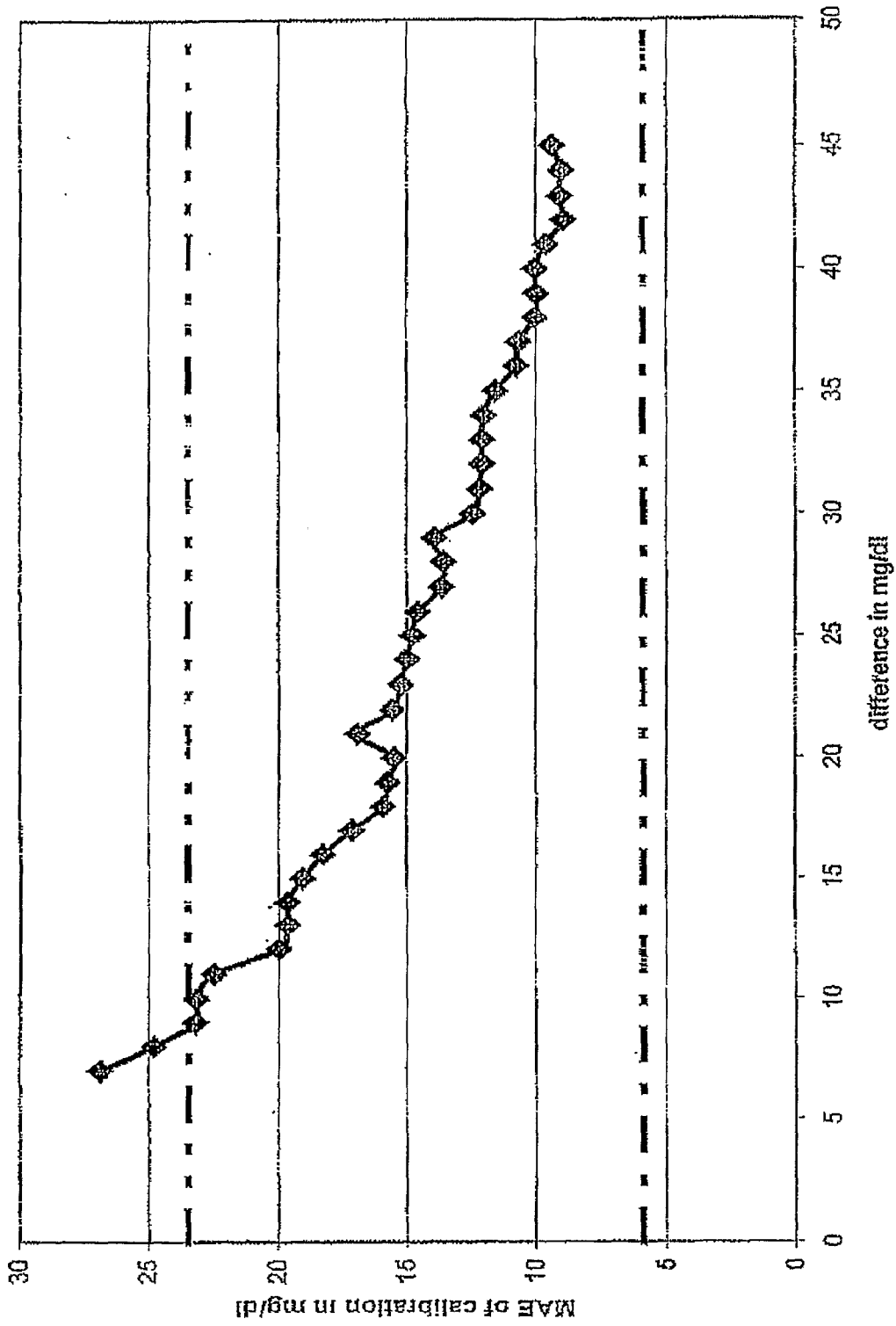


FIG. 5

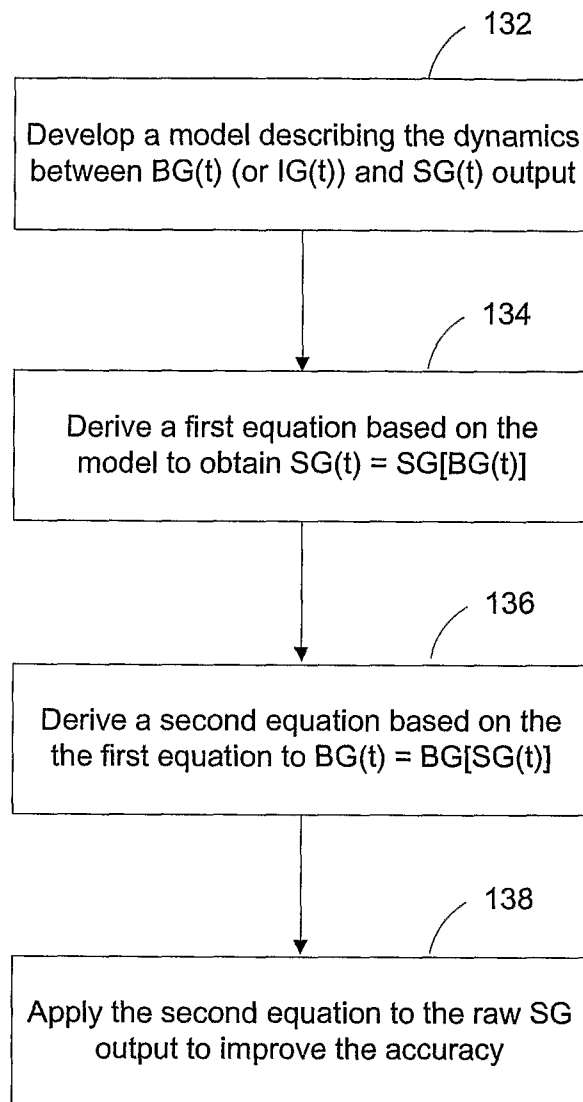


FIG. 6

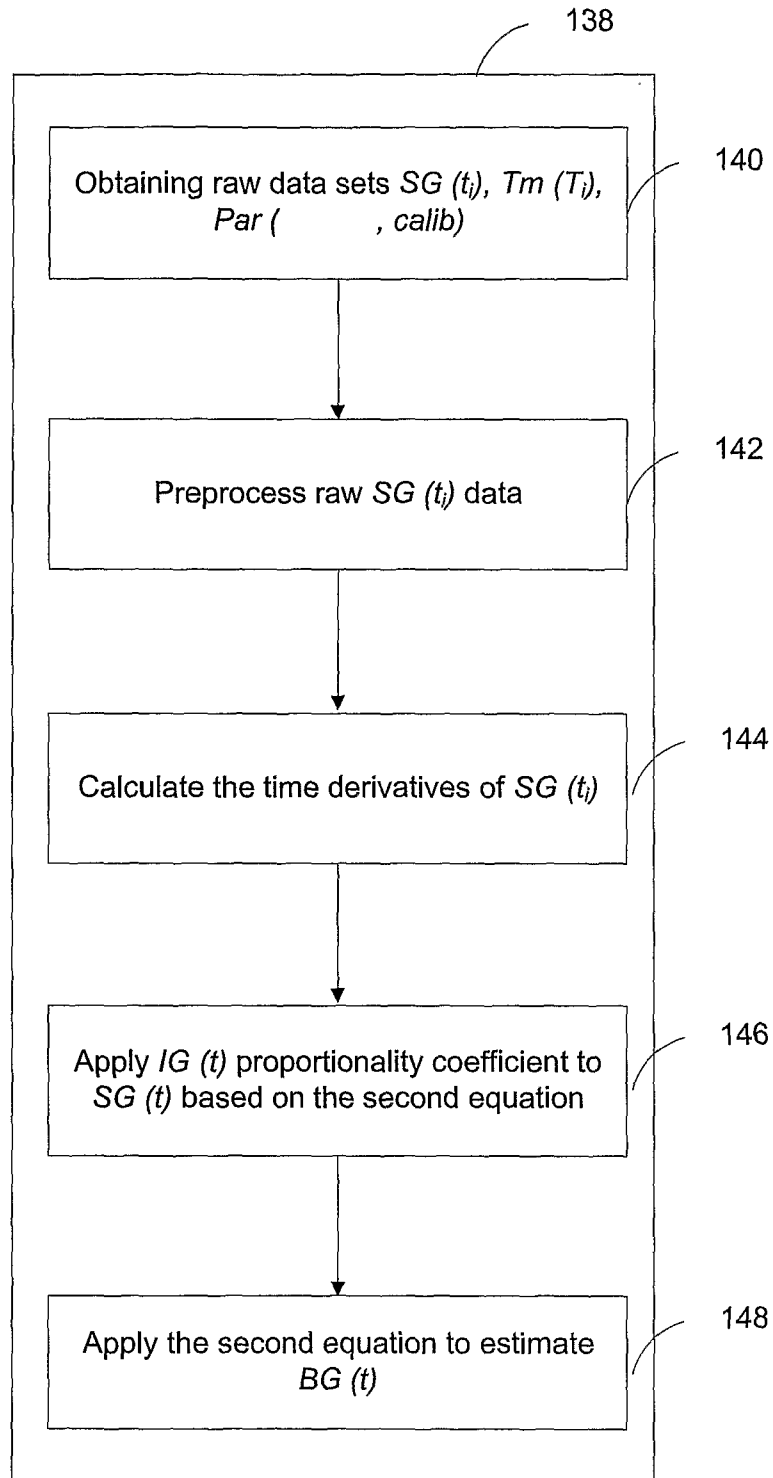


FIG. 7

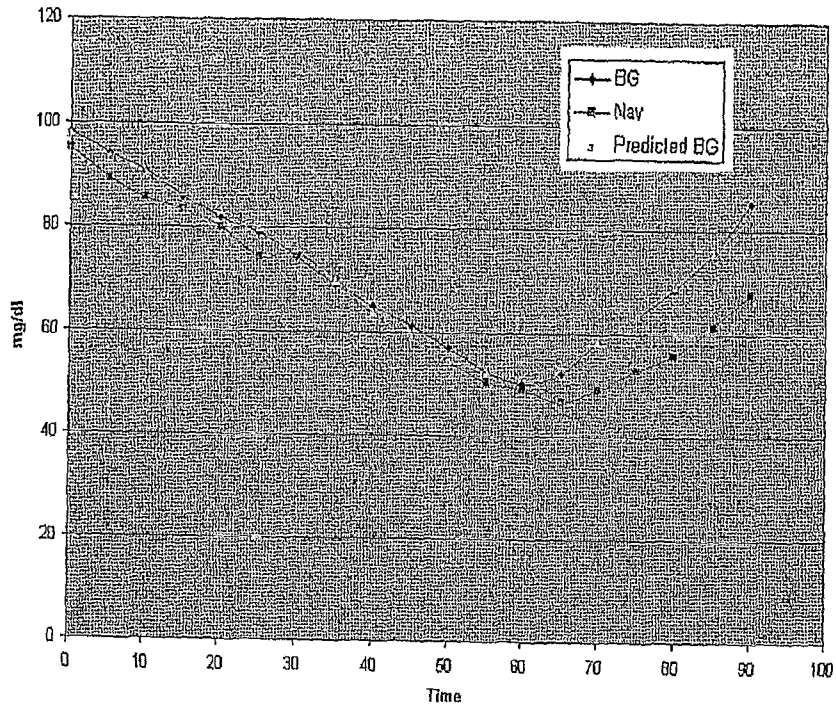


FIG. 8

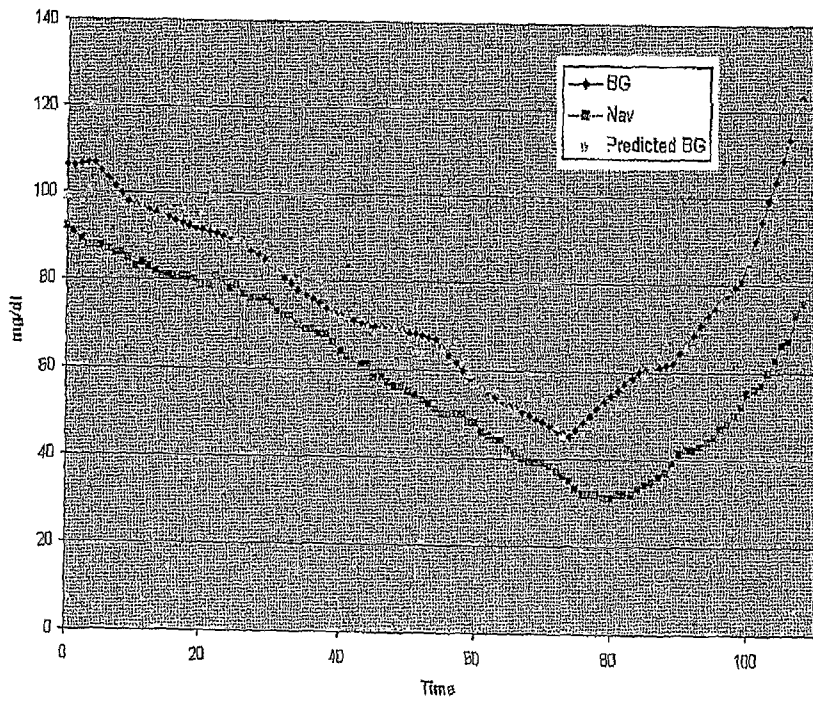


FIG. 9

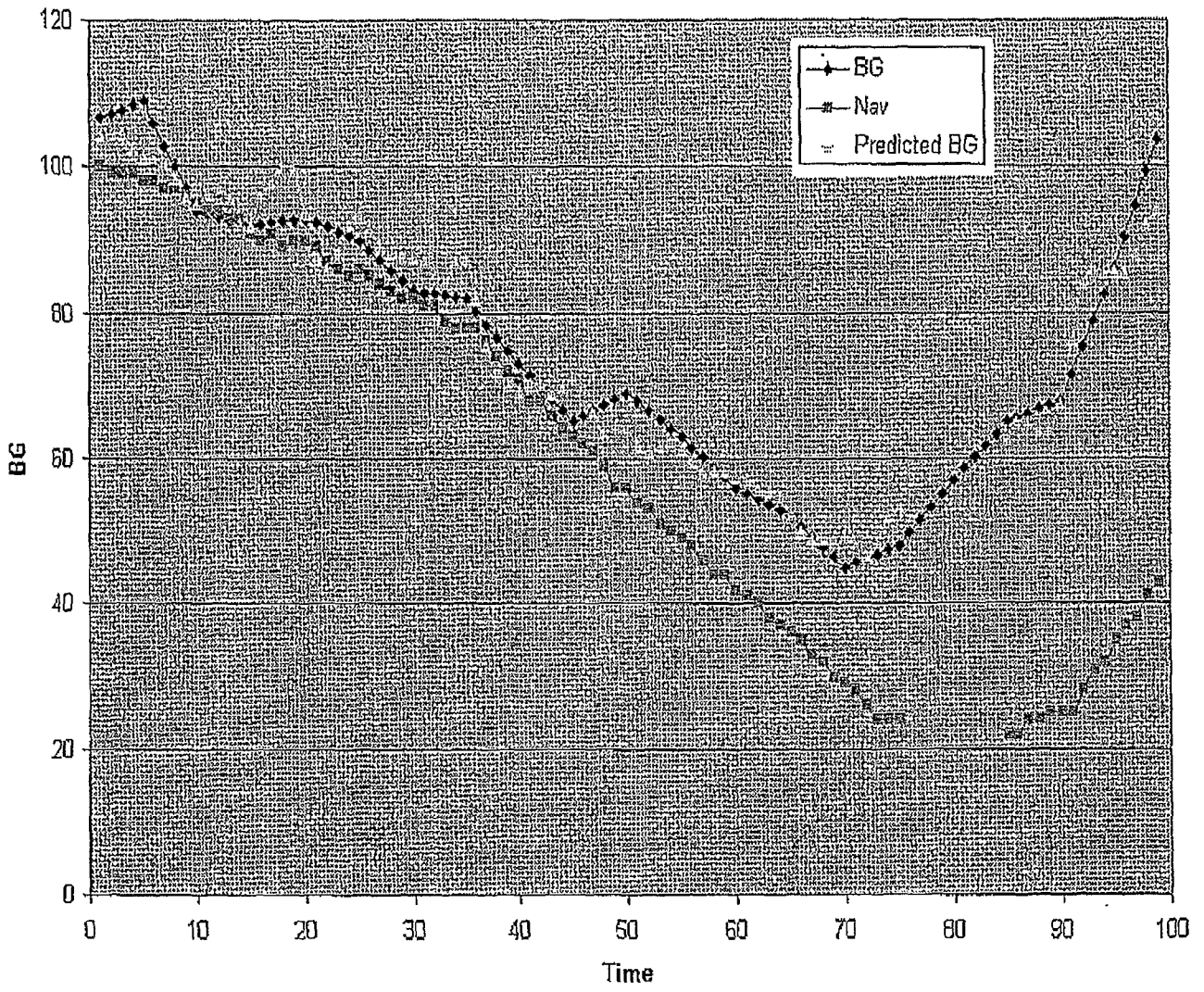


FIG. 10

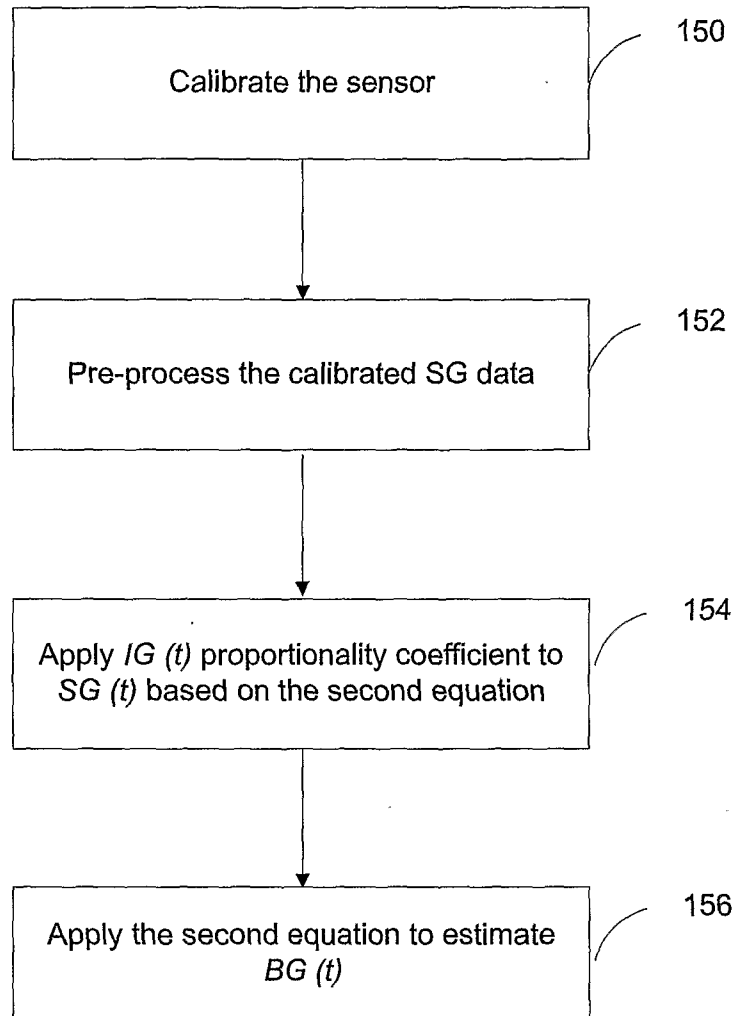


FIG. 11

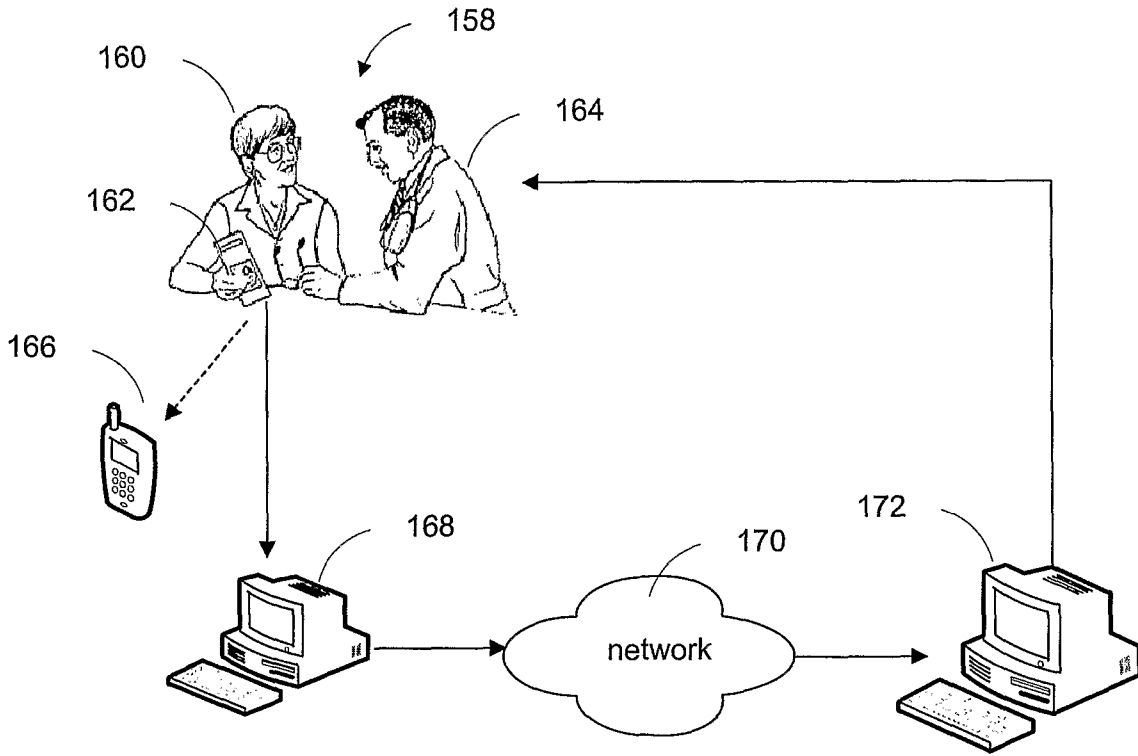


FIG. 12

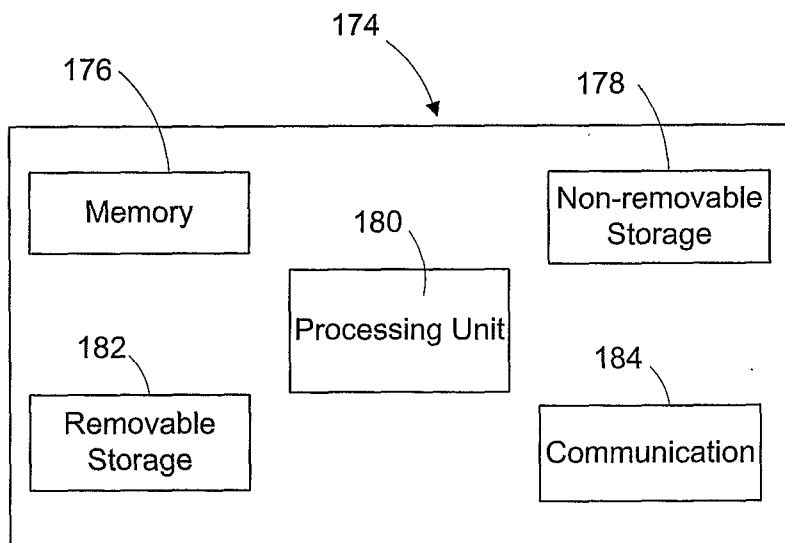


FIG. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/33724

A. CLASSIFICATION OF SUBJECT MATTER
 IPC: **A61B 5/00**(2007.01)
 A61B 5/05(2007.01)

 USPC: 600/365
 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)
 U.S. : 600/309,345,347,365

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 practicable, 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 --- A	US 6,558,351 B1 (STEIL et al.) 06 May 2003 (06.05.2003). fig. 32: col. 8, line 57-col. 9, line 50; col. 11, lines 30-51; col. 17, lines 1-18; col. 21, line 15-col. 24, line 16; col. 25, lines 6-29; col. 26, lines 12-39; col. 16, line 65-col. 27, line 60; col. 32, line 54-col. 33, line 65.	1,11,31,38, 50 ----- 2-10,12-30,32-37,39-49,51-53
X --- A	US 5,660,163 A (SCHULMAN et al.) 26 August 1997 (26.08.1997), abstract; col.2, line 28-col. 3, line 43;	1,5,31,33,34,45,50,52 ----- 2-4,6-30,32,35-44,46-49,51,53

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 27 November 2006 (27.11.2006)	Date of mailing of the international search report 22 JAN 2007
--	--

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Charles Marmor, II <i>Sharon D. Greene Jr</i> Telephone No. (571) 272-3000
---	---