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

(11) **EP 2 494 921 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
14.09.2016 Bulletin 2016/37

(51) Int Cl.:
A61B 5/145 *(2006.01)* ***A61B 5/1495*** *(2006.01)*
A61B 5/1486 *(2006.01)* ***G01N 27/327*** *(2006.01)*

(21) Application number: **12170103.1**

(22) Date of filing: **27.07.2004**

(54) **Processing analyte sensor data**

Verarbeitung von Analytsensordaten

Traitement des données de capteur d'analyte

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

(30) Priority:
01.08.2003 US 632537
01.08.2003 US 633329
01.08.2003 US 633367
01.08.2003 US 633404

(43) Date of publication of application:
05.09.2012 Bulletin 2012/36

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
04779357.5 / 1 648 293

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Description

Field of the Invention

[0001] The present invention relates generally to systems and methods for analyte sensor data processing. Particularly, the present invention relates to retrospectively and/or prospectively initiating a calibration, converting sensor data, updating the calibration, evaluating received reference and sensor data, and evaluating the calibration for the analyte sensor.

Background of the Invention

[0002] Diabetes mellitus is a disorder in which the pancreas cannot create sufficient insulin (Type I or insulin dependent) and/or in which insulin is not effective (Type 2 or non-insulin dependent). In the diabetic state, the victim suffers from high blood sugar, which can cause an array of physiological derangements (e.g., kidney failure, skin ulcers, or bleeding into the vitreous of the eye) associated with the deterioration of small blood vessels. A hypoglycemic reaction (low blood sugar) can be induced by an inadvertent overdose of insulin, or after a normal dose of insulin or glucose-lowering agent accompanied by extraordinary exercise or insufficient food intake.

[0003] Conventionally, a diabetic person carries a self-monitoring blood glucose (SMBG) monitor, which typically comprises uncomfortable finger pricking methods. Due to the lack of comfort and convenience, a diabetic will normally only measure his or her glucose level two to four times per day. Unfortunately, these time intervals are so far spread apart that the diabetic will likely find out too late, sometimes incurring dangerous side effects, of a hyper- or hypo-glycemic condition. In fact, it is not only unlikely that a diabetic will take a timely SMBG value, but the diabetic will not know if their blood glucose value is going up (higher) or down (lower) based on conventional methods, inhibiting their ability to make educated insulin therapy decisions.

[0004] WO 00/49941 discloses a method of calibrating glucose monitor data including collecting the glucose monitor data over a period of time at predetermined intervals. It also includes obtaining at least two reference glucose values from a reference source that temporally correspond with the glucose monitor data obtained at the predetermined intervals. Also included is calculating the calibration characteristics using the reference glucose values and the corresponding glucose monitor data to regress the obtained glucose monitor data. And calibrating the obtained glucose monitor data using the calibration characteristics is included. The reference source is a blood glucose meter and the at least two reference glucose values are obtained from blood tests.; In additional embodiments, the calculation of the calibration characteristics is obtained using linear regression and in particular embodiments, least squares linear regression. Alternatively, the calculation of the calibration characteristics is obtained using non-linear regression

Summary of the Invention

[0005] Systems and methods are needed that accurately provide estimated glucose measurements to a diabetic patient continuously and/or in real time so that they can proactively care for their condition to safely avoid hyper- and hypo-glycemic conditions. Real time and retrospective estimated glucose measurements require reliable data processing in order to provide accurate and useful output to a patient and/or doctor.

[0006] Similarly, systems and methods are needed that accurately provide substantially continuous estimated analyte measurements for a variety of known analytes (e.g., oxygen, salts, protein, and vitamins) to provide prospective and/or retrospective data analysis and output to a user.

[0007] Accordingly, systems and methods are provided for retrospectively and/or prospectively calibrating a sensor, initializing a sensor, converting sensor data into calibrated data, updating and maintaining a calibration over time, evaluating received reference and sensor data for clinical acceptability, and evaluating the calibration statistical acceptability, to ensure accurate and safe data output to a patient and/or doctor.

[0008] In a first aspect, there is provided receiving a sensor data stream, including one or more sensor data points, from a continuous analyte sensor; receiving one or more reference data points; operating a processor module to match reference data points with time-matched sensor data points to form a calibration set including at least one matched data pair; and characterised by: determining the stability of the continuous analyte sensor by evaluating stability by monitoring the frequency content of the sensor data stream over a predetermined amount of time by comparing a template or templates with actual sensor data, wherein a predetermined amount of argument agreement between the template and the actual sensor data is indicative of sensor stability, and wherein the template or templates reflect acceptable levels of glucose physiology.

[0009] In an embodiment of the method of the first aspect, the method additionally includes providing output to the user based on the stability of the sensor on an interface control module.

[0010] In an embodiment of the method of the first aspect, the output from the interface control module includes at least one of a numeric estimated analyte value, an indication of directional trend of analyte concentration, and a graphical representation of an estimated analyte value.

[0011] In an embodiment of the method of the first aspect, the output is displayed on a user interface.

[0012] In an embodiment of the method of the first aspect, the step of receiving a sensor data stream from an analyte sensor includes receiving sensor data from a continuous glucose sensor.

[0013] In an embodiment of the method of the first aspect, the step of receiving a sensor data stream includes receiving sensor data from an implantable glucose sensor.

[0014] In an embodiment of the method of the first aspect, the system of any one of claims 1 to 6, wherein the sensor data points are in the form of a raw data signal directly related to the measured analyte from the analyte sensor, wherein the raw data signal is digital data in counts converted by an analog to digital converter from an analog signal in voltage or amps representative of an analyte concentration.

[0015] In an embodiment of the method of the first aspect, the analyte sensor uses an electrochemical method of analyte sensing.

[0016] In a second aspect, there is provided a system comprising: a sensor data module operatively linked to a continuous analyte sensor and configured to receive a sensor data stream, including one or more sensor data points, from the sensor; a reference input module adapted to obtain one or more reference data points; a processor module associated with the sensor data module and the reference input module and programmed to match reference data points with time-matched sensor data points to form a calibration set including at least one matched data pair; and a stability module associated with the processor module programmed to determine the stability of the continuous analyte sensor, characterised in that the stability module evaluates stability by monitoring the frequency content of the sensor data stream over a predetermined amount of time by comparing a template or templates with actual sensor data, wherein a predetermined amount of agreement between the template or the templates and the actual sensor data is indicative of sensor stability, and wherein the template or templates reflect acceptable levels of glucose physiology.

[0017] In an embodiment of the second aspect, there is provided an interface control module that provides output to the user based on the stability of the sensor.

[0018] In an embodiment of the second aspect, the output from the interface control module includes at least one of a numeric estimated analyte value, an indication of directional trend of analyte concentration, and a graphical representation of an estimated analyte value.

[0019] In an embodiment of the second aspect, the output is displayed on a user interface.

[0020] In an embodiment of the second aspect, the continuous analyte sensor is a continuous glucose sensor and the sensor data module is configured to receive sensor data from the continuous glucose sensor.

[0021] In an embodiment of the second aspect, receiving a sensor data stream includes receiving sensor data from an implantable glucose sensor.

Brief Description of the Drawings

[0022]

Figure 1 is an exploded perspective view of a glucose sensor in one embodiment.
Figure 2 is a block diagram that illustrates the sensor electronics in one embodiment.
Figure 3 is a graph that illustrates data smoothing of a raw data signal in one embodiment.
Figures 4A to 4D are schematic views of a receiver in first, second, third, and fourth embodiments, respectively.
Figure 5 is a block diagram of the receiver electronics in one embodiment.
Figure 6 is a flow chart that illustrates the initial calibration and data output of the sensor data in one embodiment.
Figure 7 is a graph that illustrates a regression performed on a calibration set to obtain a conversion function in one exemplary embodiment.
Figure 8 is a flow chart that illustrates the process of evaluating the clinical acceptability of reference and sensor data in one embodiment.
Figure 9 is a graph of two data pairs on a Clarke Error Grid to illustrate the evaluation of clinical acceptability in one exemplary embodiment.
Figure 10 is a flow chart that illustrates the process of evaluation of calibration data for best calibration based on inclusion criteria of matched data pairs in one embodiment.
Figure 11 is a flow chart that illustrates the process of evaluating the quality of the calibration in one embodiment.
Figure 12A and 12B are graphs that illustrate an evaluation of the quality of calibration based on data association in one exemplary embodiment using a correlation coefficient.

Detailed Description of Certain Embodiments

[0023] The following description and examples illustrate some exemplary embodiments of the disclosed invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a certain exemplary embodiment should not be deemed to limit the scope of the present invention.

Defmitions

[0024] In order to facilitate an understanding of the preferred embodiments, a number of terms are defined below.

[0025] The term "analyte," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, to refer to a substance or chemical constituent in a biological fluid (for example, blood, interstitial fluid, cerebral spinal fluid, lymph fluid or urine) that can be analyzed. Analytes can include naturally occurring substances, artificial substances, metabolites, and/or reaction products. In some embodiments, the analyte for measurement by the sensor heads, devices, and methods is analyte. However, other analytes are contemplated as well, including but not limited to acarboxyprothrombin; acylcamitine; adenine phosphoribosyl transferase; adenosine deaminase; albumin; alpha-fetoprotein; amino acid profiles (arginine (Krebs cycle), histidine/urocanic acid, homocysteine, phenylalanine/tyrosine, tryptophan); andrenostenedione; antipyrine; arabinitol enantiomers; arginase; benzoylecgonine (cocaine); biotinidase; biopterin; c-reactive protein; carnitine; carnosinase; CD4; ceruloplasmin; chenodeoxycholic acid; chloroquine; cholesterol; cholinesterase; conjugated 1-ß hydroxy-cholic acid; cortisol; creatine kinase; creatine kinase MM isoenzyme; cyclosporin A; d-penicillamine; de-ethylchloroquine; dehydroepiandrosterone sulfate; DNA (acetylator polymorphism, alcohol dehydrogenase, alpha 1-antitrypsin, cystic fibrosis, Duchenne/Becker muscular dystrophy, analyte-6-phosphate dehydrogenase, hemoglobin A, hemoglobin S, hemoglobin C, hemoglobin D, hemoglobin E, hemoglobin F, D-Punjab, beta-thalassemia, hepatitis B virus, HCMV, HIV-1, HTLV-1, Leber hereditary optic neuropathy, MCAD, RNA, PKU, Plasmodium vivax, sexual differentiation, 21-deoxycortisol); desbutylhalofantrine; dihydropteridine reductase; diptheria/tetanus antitoxin; erythrocyte arginase; erythrocyte protoporphyrin; esterase D; fatty acids/acylglycines; free ß-human chorionic gonadotropin; free erythrocyte porphyrin; free thyroxine (FT4); free triiodothyronine (FT3); fumarylacetoacetase; galactose/gal-1-phosphate; galactose-1-phosphate uridyltransferase; gentamicin; analyte-6-phosphate dehydrogenase; glutathione; glutathione perioxidase; glycocholic acid; glycosylated hemoglobin; halofantrine; hemoglobin variants; hexosaminidase A; human erythrocyte carbonic anhydrase I; 17-alpha-hydroxyprogesterone; hypoxanthine phosphoribosyl transferase; immunoreactive trypsin; lactate; lead; lipoproteins ((a), B/A-1, ß); lysozyme; mefloquine; netilmicin; phenobarbitone; phenytoin; phytanic/pristanic acid; progesterone; prolactin; prolidase; purine nucleoside phosphorylase; quinine; reverse triiodothyronine (rT3); selenium; serum pancreatic lipase; sissomicin; somatomedin C; specific antibodies (adenovirus, anti-nuclear antibody, anti-zeta antibody, arbovirus, Aujeszky's disease virus, dengue virus, Dracunculus medinensis, Echinococcus granulosus, Entamoeba histolytica, enterovirus, Giardia duodenalisa, Helicobacter pylori, hepatitis B virus, herpes virus, HIV-1, IgE (atopic disease), influenza virus, Leishmania donovani, leptospira, measles/mumps/rubella, Mycobacterium leprae, Mycoplasma pneumoniae, Myoglobin, Onchocerca volvulus, parainfluenza virus, Plasmodium falciparum, poliovirus, Pseudomonas aeruginosa, respiratory syncytial virus, rickettsia (scrub typhus), Schistosoma mansoni, Toxoplasma gondii, Trepenoma pallidium, Trypanosoma cruzi/rangeli, vesicular stomatis virus, Wuchereria bancrofti, yellow fever virus); specific antigens (hepatitis B virus, HIV-1); succinylacetone; sulfadoxine; theophylline; thyrotropin (TSH); thyroxine (T4); thyroxine-binding globulin; trace elements; transferrin; UDP-galactose-4-epimerase; urea; uroporphyrinogen I synthase; vitamin A; white blood cells; and zinc protoporphyrin. Salts, sugar, protein, fat, vitamins and hormones naturally occurring in blood or interstitial fluids can also constitute analytes in certain embodiments. The analyte can be naturally present in the biological fluid, for example, a metabolic product, a hormone, an antigen, an antibody, and the like. Alternatively, the analyte can be introduced into the body, for example, a contrast agent for imaging, a radioisotope, a chemical agent, a fluorocarbon-based synthetic blood, or a drug or pharmaceutical composition, including but not limited to insulin; ethanol; cannabis (marijuana, tetrahydrocannabinol, hashish); inhalants (nitrous oxide, amyl nitrite, butyl nitrite, chlorohydrocarbons, hydrocarbons); cocaine (crack cocaine); stimulants (amphetamines, methamphetamines, Ritalin, Cylert, Preludin, Didrex, PreState, Voranil, Sandrex, Plegine); depressants (barbituates, methaqualone, tranquilizers such as Valium, Librium, Miltown, Serax, Equanil, Tranxene); hallucinogens (phencyclidine, lysergic acid, mescaline, peyote, psilocybin); narcotics (heroin, codeine, morphine, opium, meperidine, Percocet, Percodan, Tussionex, Fentanyl, Darvon, Talwin, Lomotil); designer drugs (analogs of fentanyl, meperidine, amphetamines, methamphetamines, and phencyclidine, for example, Ecstasy); anabolic steroids; and nicotine. The metabolic products of drugs and pharmaceutical compositions are also contemplated analytes. Analytes such as neurochemicals and other chemicals generated within the body can also be analyzed, such as, for example, ascorbic acid, uric acid, dopamine, noradrenaline, 3-methoxytyramine (3MT), 3,4-Dihydroxyphenylacetic acid (DOPAC), Homovanillic acid (HVA), 5-Hydroxytryptamine (5HT), and 5-Hydroxyindoleacetic acid (FHIAA).

[0026] The terms "operably connected" and "operably linked," as used herein, are broad terms and are used in their ordinary sense, including, without limitation, one or more components linked to another component(s) in a manner that allows transmission of signals between the components, e.g., wired or wirelessly. For example, one or more electrodes can be used to detect the amount of analyte in a sample and convert that information into a signal; the signal can then be transmitted to an electronic circuit means. In this case, the electrode is "operably linked" to the electronic circuitry.

[0027] The term "EEPROM," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, electrically erasable programmable read-only memory, which is user-modifiable read-only memory (ROM) that can be erased and reprogrammed (e.g., written to) repeatedly through the application of higher than normal electrical voltage.

[0028] The term "SRAM," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, static random access memory (RAM) that retains data bits in its memory as long as power is being supplied.

[0029] The term "A/D Converter," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, hardware that converts analog signals into digital signals.

[0030] The term "microprocessor," as used herein, is a broad term and is used in its ordinary sense, including, without limitation a computer system or processor designed to perform arithmetic and logic operations using logic circuitry that responds to and processes the basic instructions that drive a computer.

[0031] The term "RF transceiver," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a radio frequency transmitter and/or receiver for transmitting and/or receiving signals.

[0032] The term "jitter" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, uncertainty or variability of waveform timing, which can be cause by ubiquitous noise caused by a circuit and/or environmental effects; jitter can be seen in amplitude, phase timing, or the width of the signal pulse.

[0033] The term "raw data signal," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an analog or digital signal directly related to the measured analyte from the analyte sensor. In one example, the raw data signal is digital data in "counts" converted by an A/D converter from an analog signal (e.g., voltage or amps) representative of an analyte concentration.

[0034] The term "counts," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a unit of measurement of a digital signal. In one example, a raw data signal measured in counts is directly related to a voltage (converted by an A/D converter), which is directly related to current.

[0035] The term "analyte sensor," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, any mechanism (e.g., enzymatic or non-enzymatic) by which analyte can be quantified. For example, some embodiments utilize a membrane that contains glucose oxidase (GOX) that catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate:

$$\text{GOX} + \text{Glucose} + O_2 \rightarrow \text{Gluconate} + H_2O_2 + \text{reduced GOX}$$

[0036] Because for each glucose molecule metabolized, there is a proportional change in the co-reactant O_2 and the product H_2O_2, one can use an electrode to monitor the current change in either the co-reactant or the product to determine glucose concentration.

[0037] The term "host," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, mammals, particularly humans.

[0038] The term "matched data pairs", as used herein, is a broad term and is used in its ordinary sense, including, without limitation, reference data (e.g., one or more reference analyte data points) matched with substantially time corresponding sensor data (e.g., one or more sensor data points).

[0039] The term "Clarke Error Grid", as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an error grid analysis, which evaluates the clinical significance of the difference between a reference glucose value and a sensor generated glucose value, taking into account 1) the value of the reference glucose measurement, 2) the value of the sensor glucose measurement, 3) the relative difference between the two values, and 4) the clinical significance of this difference. See Clarke et al., "Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose", Diabetes Care, Volume 10, Number 5, September-October 1987, the contents of which are incorporated by reference herein in their entirety.

[0040] The term "Consensus Error Grid", as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an error grid analysis that assigns a specific level of clinical risk to any possible error between two time corresponding glucose measurements. The Consensus Error Grid is divided into zones signifying the degree of risk posed by the deviation. See Parkes et al., "A New Consensus Error Grid to Evaluate the Clinical Significance of Inaccuracies in the Measurement of Blood Glucose", Diabetes Care, Volume 23, Number 8, August 2000, the contents of which are incorporated by reference herein in their entirety.

[0041] The term "clinical acceptability", as used herein, is a broad term and is used in its ordinary sense, including, without limitation, determination of the risk of inaccuracies to a patient. Clinical acceptability considers a deviation between time corresponding glucose measurements (e.g., data from a glucose sensor and data from a reference glucose monitor) and the risk (e.g., to the decision making of a diabetic patient) associated with that deviation based on the glucose value indicated by the sensor and/or reference data. One example of clinical acceptability can be 85% of a given set of measured analyte values within the "A" and "B" region of a standard Clarke Error Grid when the sensor measurements are compared to a standard reference measurement.

[0042] The term "R-value," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, one conventional way of summarizing the correlation of data; that is, a statement of what residuals (e.g., root mean square deviations) are to be expected if the data are fitted to a straight line by the a regression.

[0043] The term "data association" and "data association function," as used herein, are a broad terms and are used in their ordinary sense, including, without limitation, a statistical analysis of data and particularly its correlation to, or deviation from, from a particular curve. A data association function is used to show data association. For example, the data that forms that calibration set as described herein can be analyzed mathematically to determine its correlation to, or deviation from, a curve (e.g., line or set of lines) that defines the conversion function; this correlation or deviation is the data association. A data association function is used to determine data association. Examples of data association functions include, but are not limited to, linear regression, non-linear mapping/regression, rank (e.g., non-parametric) correlation, least mean square fit, mean absolute deviation (MAD), mean absolute relative difference. In one such example, the correlation coefficient of linear regression is indicative of the amount of data association of the calibration set that forms the conversion function, and thus the quality of the calibration.

[0044] The term "quality of calibration" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the statistical association of matched data pairs in the calibration set used to create the conversion function. For example, an R-value can be calculated for a calibration set to determine its statistical data association, wherein an R-value greater than 0.79 determines a statistically acceptable calibration quality, while an R-value less than 0.79 determines statistically unacceptable calibration quality.

[0045] The term "substantially" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, being largely but not necessarily wholly that which is specified.

[0046] The term "congruence" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the quality or state of agreeing, coinciding, or being concordant. In one example, congruence can be determined using rank correlation.

[0047] The term "concordant" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, being in agreement or harmony, and/or free from discord.

[0048] The phrase "continuous (or continual) analyte sensing," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the period in which monitoring of analyte concentration is continuously, continually, and or intermittently (but regularly) performed, for example, about every 5 to 10 minutes.

[0049] The term "sensor head," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the region of a monitoring device responsible for the detection of a particular analyte. In one example, a sensor head comprises a non-conductive body, a working electrode (anode), a reference electrode and a counter electrode (cathode) passing through and secured within the body forming an electrochemically reactive surface at one location on the body and an electronic connective means at another location on the body, and a sensing membrane affixed to the body and covering the electrochemically reactive surface. The counter electrode has a greater electrochemically reactive surface area than the working electrode. During general operation of the sensor a biological sample (e.g., blood or interstitial fluid) or a portion thereof contacts (directly or after passage through one or more membranes or domains) an enzyme (e.g., glucose oxidase); the reaction of the biological sample (or portion thereof) results in the formation of reaction products that allow a determination of the analyte (e.g., glucose) level in the biological sample. In some embodiments, the sensing membrane further comprises an enzyme domain (e.g., and enzyme layer), and an electrolyte phase (e.g., a free-flowing liquid phase comprising an electrolyte-containing fluid described further below).

[0050] The term "electrochemically reactive surface," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the surface of an electrode where an electrochemical reaction takes place. In the case of the working electrode, the hydrogen peroxide produced by the enzyme catalyzed reaction of the analyte being detected creates a measurable electronic current (e.g., detection of analyte utilizing analyte oxidase produces H2O2 peroxide as a by product, H2O2 reacts with the surface of the working electrode producing two protons ($2H^+$), two electrons ($2e^-$) and one molecule of oxygen (02) which produces the electronic current being detected). In the case of the counter electrode, a reducible species, e.g., 02 is reduced at the electrode surface in order to balance the current being generated by the working electrode.

[0051] The term "electronic connection," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, any electronic connection known to those in the art that can be utilized to interface the sensor head electrodes with the electronic circuitry of a device such as mechanical (e.g., pin and socket) or soldered.

[0052] The term "sensing membrane," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a permeable or semi-permeable membrane that can be comprised of two or more domains and constructed of materials of a few microns thickness or more, which are permeable to oxygen and may or may not be permeable to an analyte of interest. In one example, the sensing membrane comprises an immobilized glucose oxidase enzyme, which enables an electrochemical reaction to occur to measure a concentration of glucose.

[0053] The term "biointerface membrane," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a permeable membrane that can be comprised of two or more domains and constructed of materials of a few microns thickness or more, which can be placed over the sensor body to keep host cells (e.g., macrophages) from gaining proximity to, and thereby damaging, the sensing membrane or forming a barrier cell layer and interfering with the transport of analyte across the tissue-device interface.

[0054] In the disclosure which follows, the following abbreviations apply: Eq and Eqs (equivalents); mEq (milliequivalents); M (molar); mM (millimotar) μM (micromolar); N (Normal); mol (moles); mmol (millimoles); μmol (micromoles); nmol (nanomoles); g (grams); mg (milligrams); μg (micrograms); Kg (kilograms); L (liters); mL (milliliters); dL (deciliters); μL (microliters); cm (centimeters); mm (millimeters); μm (micrometers); nm (nanometers); h and hr (hours); min. (minutes); s and sec. (seconds); [deg.]C (degrees Centigrade).

Overview

[0055] The preferred embodiments relate to the use of an analyte sensor that measures a concentration of analyte of interest or a substance indicative of the concentration or presence of the analyte. The sensor is a continuous device, for example a subcutaneous, transdermal, or intravascular device. In some embodiments, the device can analyze a plurality of intermittent blood samples. The analyte sensor can use any method of analyte-sensing, including enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, radiometric, or the like.

[0056] The analyte sensor uses any known method, including invasive, minimally invasive, and non-invasive sensing techniques, to provide an output signal indicative of the concentration of the analyte of interest. The output signal is typically a raw signal that is used to provide a useful value of the analyte of interest to a user, such as a patient or physician, who can be using the device. Accordingly, appropriate smoothing, calibration, and evaluation methods can be applied to the raw signal and/or system as a whole to provide relevant and acceptable estimated analyte data to the user.

Sensor

[0057] The analyte sensor useful with the preferred embodiments can be any device capable of measuring the concentration of an analyte of interest. One exemplary embodiment is described below, which utilizes an implantable glucose sensor. However, it should be understood that the devices and methods described herein can be applied to any device capable of detecting a concentration of analyte of and providing an output signal that represents the concentration of the analyte.

[0058] Figure 1 is an exploded perspective view of a glucose sensor in one embodiment. The implantable glucose sensor (10) utilizes amperometric electrochemical sensor technology to measure glucose. In this exemplary embodiment, a body (12) and a head (14) house electrodes (16) and sensor electronics, which are described in more detail with reference to Fig. 2. Three electrodes (16) are operably connected to the sensor electronics (Fig. 2) and are covered by a sensing membrane (17) and a biointerface membrane (18, which are attached by a clip (19. In alternative embodiments, the number of electrodes can be less than or greater than three.

[0059] The three electrodes (16), which protrude through the head (14), including a platinum working electrode, a platinum counter electrode, and a silver/silver chloride reference electrode. The top ends of the electrodes are in contact with an electrolyte phase (not shown), which is a free-flowing fluid phase disposed between the sensing membrane and the electrodes. The sensing membrane (17) includes an enzyme, e.g., glucose oxidase, which covers the electrolyte phase. In turn, the biointerface membrane (18) covers the sensing membrane (17) and serves, at least in part, to protect the sensor from external forces that can result in environmental stress cracking of the sensing membrane (17).

[0060] In the illustrated embodiment, the counter electrode is provided to balance the current generated by the species being measured at the working electrode. In the case of a glucose oxidase based glucose sensor, the species being measured at the working electrode is H_2O_2. Glucose oxidase catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate according to the following reaction:

$$\text{GOX} + \text{Glucose} + O_2 \rightarrow \text{Gluconate} + H_2O_2 + \text{reduced GOX}$$

[0061] The change in H_2O_2 can be monitored to determine glucose concentration because for each glucose molecule metabolized, there is a proportional change in the product H_2O_2. Oxidation of H_2O_2 by the working electrode is balanced by reduction of ambient oxygen, enzyme generated H_2O_2, or other reducible species at the counter electrode. The H_2O_2 produced from the glucose oxidase reaction further reacts at the surface of working electrode and produces two protons ($2H^+$), two electrons ($2e^+$), and one oxygen molecule (O_2) (See, e.g., Fraser, D.M. "An Introduction to In vivo Biosensing: Progress and problems." In "Biosensors and the Body," D.M. Fraser, ed., 1997, pp. 1-56 John Wiley and Sons, New York.)

[0062] In one embodiment, a potentiostat is used to measure the electrochemical reaction(s) at the electrode(s) (see Fig. 2). The potentiostat applies a constant potential between the working and reference electrodes to produce a current value. The current that is produced at the working electrode (and flows through the circuitry to the counter electrode) is proportional to the diffusional flux of H_2O_2. Accordingly, a raw signal can be produced that is representative of the concentration of glucose in the users body, and therefore can be utilized to estimate a meaningful glucose value, such as described elsewhere herein.

[0063] One problem of enzymatic glucose sensors such as described above is the non-glucose reaction rate-limiting phenomenon. For example, if oxygen is deficient, relative to the amount of glucose, then the enzymatic reaction will be limited by oxygen rather than glucose. Consequently, the output signal will be indicative of the oxygen concentration rather than the glucose concentration.

[0064] Figure 2 is a block diagram that illustrates the sensor electronics in one embodiment. In this embodiment, the potentiostat (20) is shown, which is operatively connected to electrodes (16) (Fig. 1) to obtain a current value, and includes a resistor (not shown) that translates the current into voltage. An A/D converter (21) digitizes the analog signal into counts for processing. Accordingly, the resulting raw data signal in counts is directly related to the current measured by the potentiostat (20).

[0065] A microprocessor (22) is the central control unit that houses EEPROM (23)and SRAM (24), and controls the processing of the sensor electronics. Alternative embodiments utilize a computer system other than a microprocessor to process data as described herein. In some alternative embodiments, an application-specific integrated circuit (ASIC) can be used for some or all the sensor's central processing. The EEPROM (23) provides semi-permanent storage of data, storing data such as sensor ID and necessary programming to process data signals (e.g., programming for data smoothing such as described below). The SRAM (24) is used for the system's cache memory, for example for temporarily storing recent sensor data.

[0066] A battery (25) is operatively connected to the microprocessor (22) and provides the necessary power for the sensor. In one embodiment, the battery is a Lithium Manganese Dioxide battery, however any appropriately sized and powered battery can be used (e.g., AAA, Nickel-cadmium, Zinc-carbon, Alkaline, Lithium, Nickel-metal hydride, Lithium-ion, Zinc-air, Zinc-mercury oxide, Silver-zinc, or hermetically-sealed). In some embodiments, a plurality of batteries can be used to power the system. A quartz crystal (26) is operatively connected to the microprocessor (22) and maintains system time for the computer system as a whole.

[0067] An RF Transceiver (27) is operably connected to the microprocessor (22) and transmits the sensor data from the sensor to a receiver (see Figs. 4 and 5). Although an RF transceiver is shown here, other embodiments include a wired rather than wireless connection to the receiver. In yet other embodiments, the receiver is transcutaneously powered via an inductive coupling, for example. A quartz crystal (28) provides the system time for synchronizing the data transmissions from the RF transceiver. The transceiver (27) can be substituted for a transmitter in one embodiment.

Data Smoothing

[0068] Typically, an analyte sensor produces a raw data signal that is indicative of the analyte concentration of a user, such as described in more detail with reference to Figs. 1 and 2, above. However, it is well known that the above described glucose sensor is only one example of an abundance of analyte sensors that are able to provide a raw data signal output indicative of the concentration of the analyte of interest. Thus, it should be understood that the devices and methods of the preferred embodiments, including data smoothing, calibration, evaluation, and other data processing, can be applied to raw data obtained from any analyte sensor capable of producing a output signal.

[0069] It has been found that raw data signals received from an analyte sensor include signal noise, which degrades the quality of the data. Thus, it has been known to use smoothing algorithms help improve the signal-to-noise ratio in the sensor by reducing signal jitter, for example. One example of a conventional data smoothing algorithms include finite impulse response filter (FIR), which is particularly suited for reducing high-frequency noise (see Steil et al. U.S. Patent No. 6,558,351). Other analyte sensors have utilized heuristic and moving average type algorithms to accomplish data smoothing of signal jitter in data signals, for example.

[0070] It is advantageous to also reduce signal noise by attenuating transient, low frequency, non-analyte related signal fluctuations (e.g., transient ischemia and/or long transient periods of postural effects that interfere with sensor function due to lack of oxygen and/or other physiological effects).

[0071] In one embodiment, this attenuation of transient low frequency non-analyte related signal noise is accomplished using a recursive filter. In contrast to conventional non-recursive (e.g., FIR) filters in which each computation uses new input data sets, a recursive filter is an equation that uses moving averages as inputs; that is, a recursive filter includes previous averages as part of the next filtered output. Recursive filters are advantageous at least in part due to their computational efficiency.

[0072] Figure 3 is a graph that illustrates data smoothing of a raw data signal in one embodiment. In this embodiment, the recursive filter is implemented as a digital infinite impulse response filter (IIR) filter, wherein the output is computed using 6 additions and 7 multiplies as shown in the following equation:

$$y(n) = \frac{a_0 * x(n) + a_1 * x(n-1) + a_2 * x(n-2) + a_3 * x(n-3) - b_1 * y(n-1) - b_2 * y(n-2) - b_3 * y(n-3)}{b_0}$$

This polynomial equation includes coefficients that are dependent on sample rate and frequency behavior of the filter. In this exemplary embodiment, frequency behavior passes low frequencies up to cycle lengths of 40 minutes, and is based on a 30 second sample rate.

[0073] In some embodiments, data smoothing can be implemented in the sensor and the smoothed data transmitted to a receiver for additional processing. In other embodiments, raw data can be sent from the sensor to a receiver for data smoothing and additional processing therein. In yet other embodiments, the sensor is integral with the receiver and therefore no transmission of data is required.

[0074] In one exemplary embodiment, wherein the sensor is an implantable glucose sensor, data smoothing is performed in the sensor to ensure a continuous stream of data. In alternative embodiments, data smoothing can be transmitted from the sensor to the receiver, and the data smoothing performed at the receiver; however, there can be a risk of transmit-loss in the radio transmission from the sensor to the receiver when the transmission is wireless. For example, in embodiments wherein a sensor is implemented in vivo, the raw sensor signal can be more consistent within the sensor (in vivo) than the raw signal transmitted to a source (e.g., receiver) outside the body (e.g., if a patient were to take the receiver off to shower, communication between the sensor and receiver can be lost and data smoothing in the receiver would halt accordingly.) Consequently, a multiple point data loss in the filter can take, for example, anywhere from 25 to 40 minutes for the smoothed data to recover to where it would have been had there been no data loss.

Receiver

[0075] Figures 4A to 4D are schematic views of a receiver in first, second, third, and fourth embodiments, respectively. A receiver (40) comprises systems necessary to receive, process, and display sensor data from an analyte sensor, such as described elsewhere herein. Particularly, the receiver (40) can be a pager-sized device, for example, and comprise a user interface that has a plurality of buttons (42) and a liquid crystal display (LCD) screen (44), and which can include a backlight. In some embodiments the user interface can also include a keyboard, a speaker, and a vibrator such as described with reference to Fig. 5.

[0076] Fig. 4A illustrates a first embodiment wherein the receiver shows a numeric representation of the estimated analyte value on its user interface, which is described in more detail elsewhere herein.

[0077] Fig. 4B illustrates a second embodiment wherein the receiver shows an estimated glucose value and one hour of historical trend data on its user interface, which is described in more detail elsewhere herein.

[0078] Fig. 4C illustrates a third embodiment wherein the receiver shows an estimated glucose value and three hours of historical trend data on its user interface, which is described in more detail elsewhere herein.

[0079] Fig. 4D illustrates a fourth embodiment wherein the receiver shows an estimated glucose value and nine hours of historical trend data on its user interface, which is described in more detail elsewhere herein.

[0080] In some embodiments a user is able to toggle through some or all of the screens shown in Figs. 4A to 4D using a toggle button on the receiver. In some embodiments, the user is able to interactively select the type of output displayed on their user interface. In some embodiments, the sensor output can have alternative configurations, such as is described with reference to Fig. 6, block (69), for example.

[0081] Figure 5 is a block diagram of the receiver electronics in one embodiment. The receiver can comprise a configuration such as described with reference to Figs. 4A to 4D, above. Alternatively, the receiver can comprise any configuration, including a desktop computer, laptop computer, a personal digital assistant (PDA), a server (local or remote to the receiver), or the like. In some embodiments, a receiver can be adapted to connect (via wired or wireless connection) to a desktop computer, laptop computer, a PDA, a server (local or remote to the receiver), or the like in order to download data from the receiver. In some alternative embodiments, the receiver is housed within or directly connected to the sensor in a manner that allows sensor and receiver electronics to work directly together and/or share data processing resources. Accordingly, the receiver, including its electronics, can be generally described as a "computer system."

[0082] A quartz crystal (50) is operatively connected to an RF transceiver (51) that together function to receive and synchronize data signals (e.g., raw data signals transmitted from the RF transceiver). Once received, the microprocessor (52) processes the signals, such as described below.

[0083] The microprocessor (52) is the central control unit that provides the necessary processing, such as calibration algorithms stored within an EEPROM (53). The EEPROM (53) is operatively connected to the microprocessor (52) and provides semi-permanent storage of data, storing data such as receiver ID and necessary programming to process data signals (e.g., programming for performing calibration and other algorithms described elsewhere herein). In some embodiments, an application-specific integrated circuit (ASIC) can be used for some or all the receiver's central processing.

An SRAM (54) is used for the system's cache memory and is helpful in data processing.

[0084] The microprocessor (52), which is operatively connected to EEPROM (53) and SRAM (54), controls the processing of the receiver electronics including, but not limited to, a sensor data receiving module, a reference data receiving module, a data matching module, a calibration set module, a conversion function module, a sensor data transformation module, a quality evaluation module, a interface control module, and a stability determination module, which are described in more detail below. Any of the above processing can be programmed into and performed in the sensor electronics (Fig. 2) in place of, or in complement with, the receiver electronics (Fig. 5).

[0085] A battery (55) is operatively connected to the microprocessor (52) and provides the necessary power for the receiver. In one embodiment, the battery is a AAA battery, however any appropriately sized and powered battery can be used. In some embodiments, a plurality of batteries can be used to power the system. A quartz crystal (56) is operatively connected to the microprocessor (52) and maintains system time for the computer system as a whole.

[0086] A user interface (57) comprises a keyboard, speaker, vibrator, backlight, LCD, and a plurality of buttons. The components that comprise the user interface (57) provide the necessary controls to interact with the user. A keyboard can allow, for example, input of user information about himself/herself, such as mealtime, exercise, insulin administration, and reference analyte values. A speaker can provide, for example, audible signals or alerts for conditions such as present and/or predicted hyper- and hypoglycemic conditions. A vibrator can provide, for example, tactile signals or alerts for reasons such as described with reference to the speaker, above. A backlight can be provided, for example, to aid the user in reading the LCD in low light conditions. An LCD can be provided, for example, to provide the user with visual data output such as described in more detail with reference to Figs. 4A to 4D and Fig. 6. Buttons can provide toggle, menu selection, option selection, mode selection, and reset, for example.

[0087] Communication ports, including a personal computer (PC) com port (58) and a reference analyte monitor com port (59) can be provided to enable communication with systems that are separate from, or integral with, the receiver. The PC com port (58) comprises means for communicating with another computer system (e.g., PC, PDA, server, or the like). In one exemplary embodiment, the receiver is able to download historic data to a physician's PC for retrospective analysis by the physician. The reference analyte monitor com port (59) comprises means for communicating with a reference analyte monitor so that reference analyte values can be automatically downloaded into the receiver. In one embodiment, the reference analyte monitor is integral with the receiver, and the reference analyte com port (59) allows internal communication between the two integral systems. In another embodiment, the reference analyte monitor com port (59) allows a wireless or wired connection to the reference analyte monitor such as a self-monitoring blood glucose monitor (e.g., for measuring finger stick blood samples).

Algorithms

[0088] Reference is now made to Fig. 6, which is a flow chart that illustrates the initial calibration and data output of the sensor data (60), in one embodiment.

[0089] Calibration of an analyte sensor comprises data processing that converts sensor data signal into an estimated analyte measurement that is meaningful to a user. Accordingly, a reference analyte value is used to calibrate the data signal from the analyte sensor.

[0090] At block (61), a sensor data receiving module, also referred to as the sensor data module, receives sensor data (e.g., a data stream), including one or more time-spaced sensor data points, from a sensor via the receiver, which can be in wired or wireless communication with the sensor. The sensor data point(s) can be smoothed, such as described with reference to Fig. 3, above. During the initialization of the sensor, prior to initial calibration, the receiver (e.g., computer system) receives and stores the sensor data, however it may not display any data to the user until initial calibration and possibly stabilization of the sensor has been determined.

[0091] At block (62), a reference data receiving module, also referred to as the reference input module, receives reference data from a reference analyte monitor, including one or more reference data points. In one embodiment, the reference analyte points can comprise results from a self-monitored blood analyte test (e.g., from a finger stick test). In one such embodiment, the user can administer a self-monitored blood analyte test to obtain an analyte value (e.g., point) using any known analyte sensor, and then enter the numeric analyte value into the computer system. In another such embodiment, a self-monitored blood analyte test comprises a wired or wireless connection to the receiver (e.g. computer system) so that the user simply initiates a connection between the two devices, and the reference analyte data is passed or downloaded between the self-monitored blood analyte test and the receiver. In yet another such embodiment, the self-monitored analyte test is integral with the receiver so that the user simply provides a blood sample to the receiver, and the receiver runs the analyte test to determine a reference analyte value.

[0092] Certain acceptability parameters can be set for reference values received from the user. For example, in one embodiment, the receiver may only accept reference analyte values between about 40 and about 400 mg/dL. Other examples of determining valid reference analyte values are described in more detail with reference to Fig. 8.

[0093] At block (63), a data matching module, also referred to as the processor module, matches reference data (e.g., one or more reference analyte data points) with substantially time corresponding sensor data (e.g., one or more sensor data points) to provide one or more matched data pairs. In one embodiment, one reference data point is matched to one time corresponding sensor data point to form a matched data pair. In another embodiment, a plurality of reference data points are averaged (e.g., equally or non-equally weighted average, mean-value, median, or the like) and matched to one time corresponding sensor data point to form a matched data pair. In another embodiment, one reference data point is matched to a plurality of time corresponding sensor data points averaged to form a matched data pair. In yet another embodiment, a plurality of reference data points are averaged and matched to a plurality of time corresponding sensor data points averaged to form a matched data pair.

[0094] In one embodiment, a time corresponding sensor data comprises one or more sensor data points that occur 15 $\pm$ 5 min after the reference analyte data timestamp (e.g., the time that the reference analyte data is obtained). In this embodiment, the 15 minute time delay has been chosen to account for an approximately 10 minute delay introduced by the filter used in data smoothing and an approximately 5 minute physiological time-lag (e.g., the time necessary for the analyte to diffusion through a membrane(s) of an analyte sensor). In alternative embodiments, the time corresponding sensor value can be more or less than the above-described embodiment, for example $\pm$ 60 minutes. Variability in time correspondence of sensor and reference data can be attributed to, for example a longer or shorter time delay introduced by the data smoothing filter, or if the configuration of the analyte sensor incurs a greater or lesser physiological time lag.

[0095] In some practical implementations of the sensor, the reference analyte data can be obtained at a time that is different from the time that the data is input into the receiver. Accordingly, it should be noted that the "time stamp" of the reference analyte (e.g., the time at which the reference analyte value was obtained) is not the same as the time at which the reference analyte data was obtained by receiver. Therefore, some embodiments include a time stamp requirement that ensures that the receiver stores the accurate time stamp for each reference analyte value, that is, the time at which the reference value was actually obtained from the user.

[0096] In some embodiments, tests are used to evaluate the best matched pair using a reference data point against individual sensor values over a predetermined time period (e.g., about 30 minutes). In one such exemplary embodiment, the reference data point is matched with sensor data points at 5-minute intervals and each matched pair is evaluated. The matched pair with the best correlation can be selected as the matched pair for data processing. In some alternative embodiments, matching a reference data point with an average of a plurality of sensor data points over a predetermined time period can be used to form a matched pair.

[0097] At block (64), a calibration set module, also referred to as the processor module, forms an initial calibration set from a set of one or more matched data pairs, which are used to determine the relationship between the reference analyte data and the sensor analyte data, such as will be described in more detail with reference to block (67), below.

[0098] The matched data pairs, which make up the initial calibration set, can be selected according to predetermined criteria. The criteria for the initial calibration set can be the same as, or different from, the criteria for the update calibration set, which is described in more detail with reference to Fig. 10. In some embodiments, the number (n) of data pair(s) selected for the initial calibration set is one. In other embodiments, n data pairs are selected for the initial calibration set wherein n is a function of the frequency of the received reference data points. In one exemplary embodiment, six data pairs make up the initial calibration set.

[0099] In some embodiments, the data pairs are selected only within a certain analyte value threshold, for example wherein the reference analyte value is between about 40 and about 400 mg/dL. In some embodiments, the data pairs that form the initial calibration set are selected according to their time stamp. In some embodiments, the calibration set is selected such as described with reference to Fig. 10.

[0100] At block (65), a stability determination module, also referred to as the start-up module, determines the stability of the analyte sensor over a period of time. Some analyte sensors can have an initial instability time period during which the analyte sensor is unstable for environmental, physiological, or other reasons. One example of initial sensor instability is an embodiment wherein the analyte sensor is implanted subcutaneously; in this example embodiment, stabilization of the analyte sensor can be dependent upon the maturity of the tissue ingrowth around and within the sensor. Another example of initial sensor instability is in an embodiment wherein the analyte sensor is implemented transdermally; in this example embodiment, stabilization of the analyte sensor can be dependent upon electrode stabilization and/or sweat, for example.

[0101] Accordingly, in some embodiments, determination of sensor stability can include waiting a predetermined time period (e.g., an implantable sensor is known to require a time period for tissue, and a transdermal sensor is known to require time to equilibrate the sensor with the user’s skin); in some embodiments, this predetermined waiting period is between about one minute and about six weeks. In some embodiments, the sensitivity (e.g., sensor signal strength with respect to analyte concentration) can be used to determine the stability of the sensor; for example, amplitude and/or variability of sensor sensitivity can be evaluated to determine the stability of the sensor. In alternative embodiments, detection of pH levels, oxygen, hypochlorite, interfering species (e.g., ascorbate, urea, and acetaminophen), correlation between sensor and reference values (e.g., R-value), baseline drift and/or offset, and the like can be used to determine the stability of the sensor. In one exemplary embodiment, wherein the sensor is a glucose sensor, it is known to provide a signal that is associated with interfering species (e.g., ascorbate, urea, acetaminophen), which can be used to evaluate sensor stability. In another exemplary embodiment, wherein the sensor is a glucose sensor such as described with reference to Figs. 1 and 2, the counter electrode can be monitored for oxygen deprivation, which can be used to evaluate sensor stability or functionality.

[0102] At decision block (66), the system (e.g., microprocessor) determines whether the analyte sensor is sufficiently stable according to certain criteria, such as described above. In one embodiment wherein the sensor is an implantable glucose sensor, the system waits a predetermined time period believed necessary for sufficient tissue ingrowth and evaluates the sensor sensitivity (e.g., between about one minute and six weeks). In another embodiment, the receiver determines sufficient stability based on oxygen concentration near the sensor head. In yet another embodiment, the sensor determines sufficient stability based on a reassessment of baseline drift and/or offset. According to the invention, the system evaluates stability by monitoring the frequency content of the sensor data stream over a predetermined amount of time (e.g., 24 hours); whereby a template (or templates) are provided that reflect acceptable levels of glucose physiology and are compared with the actual sensor data, wherein a predetermined amount of agreement between the template and the actual sensor data is indicative of sensor stability. A few examples of determining sufficient stability are given here, however a variety of known tests and parameters can be used to determine sensor stability without departing from the spirit and scope of the preferred embodiments.

[0103] If the receiver does not assess that the stability of the sensor is sufficient, then the processing returns to block (61), wherein the receiver receives sensor data such as described in more detail above. The above-described steps are repeated until sufficient stability is determined.

[0104] If the receiver does assess that the stability of the sensor is sufficient, then processing continues to block (67) and the calibration set is used to calibrate the sensor.

[0105] At block (67), the conversion function module uses the calibration set to create a conversion function. The conversion function substantially defines the relationship between the reference analyte data and the analyte sensor data.

[0106] A variety of known methods can be used with the preferred embodiments to create the conversion function from the calibration set. In one embodiment, wherein a plurality of matched data points form the initial calibration set, a linear least squares regression is performed on the initial calibration set such as described with reference to Fig. 7.

[0107] Figure 7 is a graph that illustrates a regression performed on a calibration set to create a conversion function in one exemplary embodiment. In this embodiment, a linear least squares regression is performed on the initial calibration set. The x-axis represents reference analyte data; the y-axis represents sensor data. The graph pictorially illustrates regression of the matched pairs (76) in the calibration set. Regression calculates a slope (72) and an offset (74) ($y=mx+b$), which defines the conversion function.

[0108] In alternative embodiments other algorithms could be used to determine the conversion function, for example forms of linear and non-linear regression, for example fuzzy logic, neural networks, piece-wise linear regression, polynomial fit, genetic algorithms, and other pattern recognition and signal estimation techniques.

[0109] In yet other alternative embodiments, the conversion function can comprise two or more different optimal conversions because an optimal conversion at any time is dependent on one or more parameters, such as time of day, calories consumed, exercise, or analyte concentration above or below a set threshold, for example. In one such exemplary embodiment, the conversion function is adapted for the estimated glucose concentration (e.g., high vs. low). For example in an implantable glucose sensor it has been observed that the cells surrounding the implant will consume at least a small amount of glucose as it diffuses toward the glucose sensor. Assuming the cells consume substantially the same amount of glucose whether the glucose concentration is low or high, this phenomenon will have a greater effect on the concentration of glucose during low blood sugar episodes than the effect on the concentration of glucose during relatively higher blood sugar episodes. Accordingly, the conversion function is adapted to compensate for the sensitivity differences in blood sugar level. In one implementation, the conversion function comprises two different regression lines wherein a first regression line is applied when the estimated blood glucose concentration is at or below a certain threshold (e.g., 150 mg/dL) and a second regression line is applied when the estimated blood glucose concentration is at or above a certain threshold (e.g., 150 mg/dL). In one alternative implementation, a predetermined pivot of the regression line that forms the conversion function can be applied when the estimated blood is above or below a set threshold (e.g., 150 mg/dL), wherein the pivot and threshold are determined from a retrospective analysis of the performance of a conversion function and its performance at a range of glucose concentrations. In another implementation, the regression line that forms the conversion function is pivoted about a point in order to comply with clinical acceptability standards (e.g., Clarke Error Grid, Consensus Grid, mean absolute relative difference, or other clinical cost function). Although only a few example implementations are described, the preferred embodiments contemplate numerous implementations wherein the conversion function is adaptively applied based on one or more parameters that can affect the sensitivity of the sensor data over time.

[0110] Referring again to Fig. 6, at block (68), a sensor data transformation module uses the conversion function to transform sensor data into substantially real-time analyte value estimates, also referred to as calibrated data, as sensor data is continuously (or intermittently) received from the sensor. For example, in the embodiment of Fig. 7, the sensor data, which can be provided to the receiver in "counts", is translated in to estimate analyte value(s) in mg/dL. In other words, the offset value at any given point in time can be subtracted from the raw value (e.g., in counts) and divided by the slope to obtain the estimate analyte value:

$$mg / dL = \frac{(rawvalue - offset)}{slope}$$

[0111] In some alternative embodiments, the sensor and/or reference analyte values are stored in a database for retrospective analysis.

[0112] At block (69), an output module provides output to the user via the user interface. The output is representative of the estimated analyte value, which is determined by converting the sensor data into a meaningful analyte value such as described in more detail with reference to block (68), above. User output can be in the form of a numeric estimated analyte value, an indication of directional trend of analyte concentration, and/or a graphical representation of the estimated analyte data over a period of time, for example. Other representations of the estimated analyte values are also possible, for example audio and tactile.

[0113] In one exemplary embodiment, such as shown in Fig. 4A, the estimated analyte value is represented by a numeric value. In other exemplary embodiments, such as shown in Figs. 4B to 4D, the user interface graphically represents the estimated analyte data trend over predetermined a time period (e.g., one, three, and nine hours, respectively). In alternative embodiments, other time periods can be represented.

[0114] In some embodiments, the user interface begins displaying data to the user after the sensor's stability has been affirmed. In some alternative embodiments however, the user interface displays data that is somewhat unstable (e.g., does not have sufficient stability at block (66); in these embodiments, the receiver can also include an indication of instability of the sensor data (e.g., flashing, faded, or another indication of sensor instability displayed on the user interface). In some embodiments, the user interface informs the user of the status of the stability of the sensor data.

[0115] Accordingly, after initial calibration of the sensor, and possibly determination of stability of the sensor data, real-time continuous analyte information can be displayed on the user interface so that the user can regularly and proactively care for his/her diabetic condition within the bounds set by his/her physician.

[0116] In alternative embodiments, the conversion function is used to predict analyte values at future points in time. These predicted values can be used to alert the user of upcoming hypoglycemic or hyperglycemic events. Additionally, predicted values can be used to compensate for the time lag (e.g., 15 minute time lag such as described elsewhere herein), so that an estimate analyte value displayed to the user represents the instant time, rather than a time delayed estimated value.

[0117] In some embodiments, the substantially real time estimated analyte value, a predicted future estimate analyte value, a rate of change, and/or a directional trend of the analyte concentration is used to control the administration of a constituent to the user, including an appropriate amount and time, in order to control an aspect of the user's biological system. One such example is a closed loop glucose sensor and insulin pump, wherein the analyte data (e.g., estimated glucose value, rate of change, and/or directional trend) from the glucose sensor is used to determine the amount of insulin, and time of administration, that can be given to a diabetic user to evade hyper- and hypoglycemic conditions.

[0118] Reference is now made to Fig. 8, which is a flow chart that illustrates the process of evaluating the clinical acceptability of reference and sensor data (80), in one embodiment. Although some clinical acceptability tests are disclosed here, any known clinical standards and methodologies can be applied to evaluate the clinical acceptability of reference and analyte data herein.

[0119] The conventional analyte meters (e.g., self-monitored blood analyte tests) are known to have a +-20% error in analyte values. For example, gross errors in analyte readings are known to occur due to patient error in self-administration of the blood analyte test. In one such example, if the user has traces of sugar on his/her finger while obtaining a blood sample for a glucose concentration test, then the measured glucose value will likely be much higher than the actual glucose value in the blood. Additionally, it is known that self-monitored analyte tests (e.g., test strips) are occasionally subject to manufacturing error.

[0120] Another cause for error includes infrequency and time delay that can occur if a user does not self-test regularly, or if a user self-tests regularly but does not enter the reference value at the appropriate time or with the appropriate time stamp. Therefore, it can be advantageous to validate the acceptability of reference analyte values prior to accepting them as valid entries. Accordingly, the receiver evaluates the clinical acceptability of received reference analyte data prior to their acceptance as a valid reference value.

[0121] In one embodiment, the reference analyte data (and/or sensor analyte data) is evaluated with respect to substantially time corresponding sensor data (and/or substantially time corresponding reference analyte data) to determine the clinical acceptability of the reference analyte and/or sensor analyte data. Clinical acceptability considers a deviation between time corresponding glucose measurements (e.g., data from a glucose sensor and data from a reference glucose monitor) and the risk (e.g., to the decision making of a diabetic patient) associated with that deviation based on the glucose value indicated by the sensor and/or reference data. Evaluating the clinical acceptability of reference and sensor analyte data, and controlling the user interface dependent thereon, can minimize clinical risk.

[0122] In one embodiment, the receiver evaluates clinical acceptability each time reference data is obtained. In another embodiment, the receiver evaluates clinical acceptability after the initial calibration and stabilization of the sensor, such as described with reference to Fig. 6, above. In some embodiments, the receiver evaluates clinical acceptability as an initial pre-screen of reference analyte data, for example after determining if the reference glucose measurement is between about 40 and 400 mg/dL. In other embodiments, other methods of pre-screening data can be used, for example by determining if a reference analyte data value is physiologically feasible based on previous reference analyte data values (e.g., below a maximum rate of change).

[0123] After initial calibration such as described in more detail with reference to Fig. 6, the sensor data receiving module (61) receives substantially continuous sensor data (e.g., a data stream) via a receiver and converts that data into estimated analyte values. As used herein, "substantially continuous" is broad enough to include a data stream of individual measurements taken at time intervals (e.g., time-spaced) ranging from fractions of a second up to, e.g., 1, 2, or 5 minutes. As sensor data is continuously converted, it can be occasionally recalibrated such as described in more detail with reference Fig. 10. Initial calibration and re-calibration of the sensor requires a reference analyte value. Accordingly, the receiver can receive reference analyte data at any time for appropriate processing. These reference analyte values can be evaluated for clinical acceptability such as described below as a fail-safe against reference analyte test errors.

[0124] At block (81), the reference data receiving module, also referred to as the reference input module, receives reference analyte data from a reference analyte monitor. In one embodiment, the reference data comprises one analyte value obtained from a reference monitor. In some alternative embodiments however, the reference data includes a set of analyte values entered by a user into the interface and averaged by known methods such as described elsewhere herein.

[0125] In some embodiments, the reference data is pre-screened according to environmental and physiological issues, such as time of day, oxygen concentration, postural effects, and patient-entered environmental data. In one example embodiment, wherein the sensor comprises an implantable glucose sensor, an oxygen sensor within the glucose sensor is used to determine if sufficient oxygen is being provided to successfully complete the necessary enzyme and electrochemical reactions for glucose sensing. In another example embodiment wherein the sensor comprises an implantable glucose sensor, the counter electrode could be monitored for a "rail-effect", that is, when insufficient oxygen is provided at the counter electrode causing the counter electrode to reach operational (e.g., circuitry) limits. In yet another example embodiment, the patient is prompted to enter data into the user interface, such as meal times and/or amount of exercise, which could be used to determine likelihood of acceptable reference data.

[0126] Evaluation data, such as described in the paragraph above, can be used to evaluate an optimum time for reference analyte measurement. Correspondingly, the user interface can then prompt the user to provide a reference data point for calibration within a given time period. Consequently, because the receiver proactively prompts the user during optimum calibration times, the likelihood of error due to environmental and physiological limitations can decrease and consistency and acceptability of the calibration can increase.

[0127] At block (82), the clinical acceptability evaluation module, also referred to as clinical module, evaluates the clinical acceptability of newly received reference data and/or time corresponding sensor data. In some embodiments of evaluating clinical acceptability, the rate of change of the reference data as compared to previous data is assessed for clinical acceptability. That is, the rate of change and acceleration (or deceleration) of many analytes has certain physiological limits within the body. Accordingly, a limit can be set to determine if the new matched pair is within a physiologically feasible range, indicated by a rate of change from the previous data that is within known physiological and/or statistical limits. Similarly, in some embodiments any algorithm that predicts a future value of an analyte can be used to predict and then compare an actual value to a time corresponding predicted value to determine if the actual value falls within a clinically acceptable range based on the predictive algorithm, for example.

[0128] In one exemplary embodiment, the clinical acceptability evaluation module (82) matches the reference data with a substantially time corresponding converted sensor value such as described with reference to Fig. 6 above, and plots the matched data on a Clarke Error Grid such as described in more detail with reference to Fig. 9.

[0129] Figure 9 is a graph of two data pairs on a Clarke Error Grid to illustrate the evaluation of clinical acceptability in one exemplary embodiment. The Clarke Error Grid can be used by the clinical acceptability evaluation module to evaluate the clinical acceptability of the disparity between a reference glucose value and a sensor glucose (e.g., estimated glucose) value, if any, in an embodiment wherein the sensor is a glucose sensor. The x-axis represents glucose reference glucose data and the y-axis represents estimated glucose sensor data. Matched data pairs are plotted accordingly to their reference and sensor values, respectively. In this embodiment, matched pairs that fall within the A and B regions of the Clarke Error Grid are considered clinically acceptable, while matched pairs that fall within the C, D, and E regions of the Clarke Error Grid are not considered clinically acceptable. Particularly, Fig. 9 shows a first matched pair (92) is shown which falls within the A region of the Clarke Error Grid, therefore is it considered clinically acceptable. A second matched pair (94) is shown which falls within the C region of the Clarke Error Grid, therefore it is not considered clinically acceptable.

[0130] A variety of other known methods of evaluation of clinical acceptability can be utilized. In one alternative embodiment, the Consensus Grid is used to evaluate the clinical acceptability of reference and sensor data. In another alternative embodiment, a mean absolute difference calculation can be used to evaluate the clinical acceptability of the reference data. In another alternative embodiment, the clinical acceptability can be evaluated using any relevant clinical acceptability test, such as a known grid (e.g., Clarke Error or Consensus), and including additional parameters such as time of day and/or the increase or decreasing trend of the analyte concentration. In another alternative embodiment, a rate of change calculation can be used to evaluate clinical acceptability. In yet another alternative embodiment, wherein the received reference data is in substantially real time, the conversion function could be used to predict an estimated glucose value at a time corresponding to the time stamp of the reference analyte value (this can be required due to a time lag of the sensor data such as described elsewhere herein). Accordingly, a threshold can be set for the predicted estimated glucose value and the reference analyte value disparity, if any.

[0131] Referring again to Fig. 8, the results of the clinical acceptability evaluation are assessed. If clinical acceptability is determined with the received reference data, then processing continues to block (84) to optionally recalculate the conversion function using the received reference data in the calibration set. If, however, clinical acceptability is not determined, then the processing progresses to block (86) to control the user interface, such as will be described with reference to block (86) below.

[0132] At block (84), the conversion function module optionally recreates the conversion function using the received reference data. In one embodiment, the conversion function module adds the newly received reference data (e.g., including the matched sensor data) into the calibration set, displaces the oldest, and/or least concordant matched data pair from the calibration set, and recalculates the conversion function accordingly. In another embodiment, the conversion function module evaluates the calibration set for best calibration based on inclusion criteria, such as described in more detail with reference to Fig. 10.

[0133] At (85), the sensor data transformation module uses the conversion function to continually (or intermittently) convert sensor data into estimated analyte values, also referred to as calibrated data, such as described in more detail with reference to Fig. 6, block (68).

[0134] At block (86), the interface control module, also referred to as the fail-safe module, controls the user interface based upon the clinical acceptability of the reference data received. If the evaluation (block (82)) deems clinical acceptability, then the user interface can function as normal; that is, providing output for the user such as described in more detail with reference to Fig. 6, block (69).

[0135] If however the reference data is not considered clinically acceptable, then the fail-safe module begins the initial stages of fail-safe mode. In some embodiments, the initial stages of fail-safe mode include altering the user interface so that estimated sensor data is not displayed to the user. In some embodiments, the initial stages of fail-safe mode include prompting the user to repeat the reference analyte test and provide another reference analyte value. The repeated analyte value is then evaluated for clinical acceptability such as described with reference to blocks (81) to (83), above.

[0136] If the results of the repeated analyte test are determined to be clinically unacceptable, then fail-safe module can alter the user interface to reflect full fail-safe mode. In one embodiment, full fail-safe mode includes discontinuing sensor analyte display output on the user interface. In other embodiments, color-coded information, trend information, directional information (e.g., arrows or angled lines), gauges, and/or fail-safe information can be displayed, for example.

[0137] If the results of the repeated analyte test are determined to be clinically acceptable, then the first analyte value is discarded, and the repeated analyte value is accepted. The process returns to block (84) to optionally recalculate the conversion function, such as described in more detail with reference to block (84), above.

[0138] Reference is now made to Fig. 10, which is a flow chart that illustrates the process of evaluation of calibration data for best calibration based on inclusion criteria of matched data pairs (100), in one embodiment.

[0139] Calibration of analyte sensors can be variable over time; that is, the conversion function suitable for one point in time may not be suitable for another point in time (e.g., hours, days, weeks, or months later). For example, in an embodiment wherein the analyte sensor is subcutaneously implantable, the maturation of tissue ingrowth over time can cause variability in the calibration of the analyte sensor. As another example, physiological changes in the user (e.g., metabolism, interfering blood constituents, lifestyle changes) can cause variability in the calibration of the sensor. Accordingly, a continuously updating calibration algorithm is disclosed that includes reforming the calibration set, and thus recalculating the conversion function, over time according to a set of inclusion criteria.

[0140] At block (101), the reference data receiving module, also referred to as the reference input module, receives a new reference analyte value (e.g., data point) from the reference analyte monitor. In some embodiments, the reference analyte value can be pre-screened according to criteria such as described in more detail with reference to Fig. 6, block (62). In some embodiments, the reference analyte value can be evaluated for clinical acceptability such as described in more detail with reference to Fig. 8.

[0141] At block (102), the data matching module, also referred to as the processor module, forms one or more updated matched data pairs by matching new reference data to substantially time corresponding sensor data, such as described in more detail with reference to Fig. 6, block (63).

[0142] At block (103), a calibration evaluation module evaluates the new matched pair(s) inclusion into the calibration set. In some embodiments, the receiver simply adds the updated matched data pair into the calibration set, displaces the oldest and/or least concordant matched pair from the calibration set, and proceeds to recalculate the conversion function accordingly (block (105)).

[0143] In some embodiments, the calibration evaluation includes evaluating only the new matched data pair. In some embodiments, the calibration evaluation includes evaluating all of the matched data pairs in the existing calibration set and including the new matched data pair; in such embodiments not only is the new matched data pair evaluated for inclusion (or exclusion), but additionally each of the data pairs in the calibration set are individually evaluated for inclusion (or exclusion). In some alternative embodiments, the calibration evaluation includes evaluating all possible combinations of matched data pairs from the existing calibration set and including the new matched data pair to determine which combination best meets the inclusion criteria. In some additional alternative embodiments, the calibration evaluation includes a combination of at least two of the above-described embodiments.

[0144] Inclusion criteria comprise one or more criteria that define a set of matched data pairs that form a substantially optimal calibration set. One inclusion criterion comprises ensuring the time stamp of the matched data pairs (that make up the calibration set) span at least a set time period (e.g., three hours). Another inclusion criterion comprises ensuring that the time stamps of the matched data pairs are not more than a set age (e.g., one week old). Another inclusion criterion ensures that the matched pairs of the calibration set have a substantially distributed amount of high and low raw sensor data, estimated sensor analyte values, and/or reference analyte values. Another criterion comprises ensuring all raw sensor data, estimated sensor analyte values, and/or reference analyte values are within a predetermined range (e.g., 40 to 400 mg/dL for glucose values). Another criterion comprises evaluating the rate of change of the analyte concentration (e.g., from sensor data) during the time stamp of the matched pair(s). For example, sensor and reference data obtained during the time when the analyte concentration is undergoing a slow rate of change can be less susceptible inaccuracies caused by time lag and other physiological and non-physiological effects. Another criterion comprises evaluating the congruence of respective sensor and reference data in each matched data pair; the matched pairs with the most congruence can be chosen. Another criterion comprises evaluating physiological changes (e.g., low oxygen due to a user's posture that can effect the function of a subcutaneously implantable analyte sensor, or other effects such as described with reference to Fig. 6) to ascertain a likelihood of error in the sensor value. Evaluation of calibration set criteria can comprise evaluating one, some, or all of the above described inclusion criteria. It is contemplated that additional embodiments can comprise additional inclusion criteria not explicitly described herein.

[0145] At block (104), the evaluation of the calibration set determines whether to maintain the previously established calibration set, or if the calibration set should be updated (e.g., modified) with the new matched data pair. In some embodiments, the oldest matched data pair is simply displaced when a new matched data pair is included. A new calibration set can include not only the determination to include the new matched data pair, but in some embodiments, can also determine which of the previously matched data pairs should be displaced from the calibration set.

[0146] At block (105), the conversion function module recreates the conversion function using the modified calibration set. The calculation of the conversion function is described in more detail with reference to Fig. 6.

[0147] At block (106), the sensor data transformation module converts sensor data to calibrated data using the updated conversion function. Conversion of raw sensor data into estimated analyte values is described in more detail with reference to Fig. 6.

[0148] Reference is now made to Fig. 11, which is a flow chart that illustrates the process of evaluating the quality of the calibration (110), in one embodiment. The calibration quality can be evaluated by determining the statistical association of data that forms the calibration set, which determines the confidence associated with the conversion function used in calibration and conversion of raw sensor data into estimated analyte values.

[0149] In one embodiment calibration quality can be evaluated after initial or updated calculation of the conversion function such as described elsewhere herein. However, calibration quality can be performed at any time during the data processing.

[0150] At block (111), a sensor data receiving module, also referred to as the sensor data module, receives the sensor data from the sensor such as described in more detail with reference to Fig. 6.

[0151] At block (112), a reference data receiving module, also referred to as the reference input module, receives reference data from a reference analyte monitor, such as described in more detail with reference to Fig. 6.

[0152] At block (113), the data matching module, also referred to as the processor module, matches received reference data with substantially time corresponding sensor data to provide one or more matched data pairs, such as described in more detail with reference to Fig. 6.

[0153] At block (114), the calibration set module, also referred to as the processor module, forms a calibration set from one or more matched data pairs such as described in more detail with reference to Figs. 6, 8, and 10.

[0154] At block (115), the conversion function module calculates a conversion function using the calibration set, such as described in more detail with reference to Figs. 6, 8, and 10.

[0155] At block (116), the sensor data transformation module continuously (or intermittently) converts received sensor data into estimated analyte values, also referred to as calibrated data, such as described in more detail with reference to Figs. 6, 8, and 10.

[0156] At block (117), a quality evaluation module evaluates the quality of the calibration. In one embodiment, the quality of the calibration is based on the association of the calibration set data using statistical analysis. Statistical analysis can comprise any known cost function such as linear regression, non-linear mapping/regression, rank (e.g., non-parametric) correlation, least mean square fit, mean absolute deviation (MAD), mean absolute relative difference, and the like. The result of the statistical analysis provides a measure of the association of data used in calibrating the system. A threshold of data association can be set to determine if sufficient quality is exhibited in a calibration set.

[0157] In another embodiment, the quality of the calibration is determined by evaluating the calibration set for clinical acceptability, such as described with reference to blocks (82) and (83) (e.g., Clarke Error Grid, Consensus Grid, or clinical acceptability test). As an example, the matched data pairs that form the calibration set can be plotted on a Clarke Error Grid, such that when all matched data pairs fall within the A and B regions of the Clarke Error Grid, then the calibration is determined to be clinically acceptable.

[0158] In yet another alternative embodiment, the quality of the calibration is determined based initially on the association of the calibration set data using statistical analysis, and then by evaluating the calibration set for clinical acceptability. If the calibration set fails the statistical and/or the clinical test, the processing returns to block (115) to recalculate the conversion function with a new (e.g., optimized) set of matched data pairs. In this embodiment, the processing loop (block (115) to block (117)) iterates until the quality evaluation module 1) determines clinical acceptability, 2) determines sufficient statistical data association, 3) determines both clinical acceptability and sufficient statistical data association, or 4) surpasses a threshold of iterations; after which the processing continues to block (118).

[0159] Figs. 12A and 12B illustrate one exemplary embodiment wherein the accuracy of the conversion function is determined by evaluating the correlation coefficient from linear regression of the calibration set that formed the conversion function. In this exemplary embodiment, a threshold (e.g., 0.79) is set for the R-value obtained from the correlation coefficient.

[0160] Figure 12A and 12B are graphs that illustrate an evaluation of the quality of calibration based on data association in one exemplary embodiment using a correlation coefficient. Particularly, Figs. 12A and 12B pictorially illustrate the results of the linear least squares regression performed on a first and a second calibration set (Figs. 12A and 12B, respectively). The x-axis represents reference analyte data; the y-axis represents sensor data. The graph pictorially illustrates regression that determines the conversion function.

[0161] The regression line (and thus the conversion function) formed by the regression of the first calibration set of Fig. 12A is the same as the regression line (and thus the conversion function) formed by the regression of the second calibration set of Fig. 12B. However, the correlation of the data in the calibration set to the regression line in Fig. 12A is significantly different than the correlation of the data in the calibration set to the regression line in Fig. 12A. In other words, there is a noticeably greater deviation of the data from the regression line in Fig. 12B than the deviation of the data from the regression line in Fig. 12A.

[0162] In order to quantify this difference in correlation, an R-value can be used to summarize the residuals (e.g., root mean square deviations) of the data when fitted to a straight line via least squares method, in this exemplary embodiment. R-value can be calculated according to the following equation:

$$R = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - x)^2}\sqrt{\sum_i y_i - y)^2}}$$

In the above equation: *i* is an index (1 to n), x is a reference analyte value, *y* is a sensor analyte value, $\bar{x}$ is an average of l/*n* reference analyte values, and $\bar{y}$ is an average of l/*n* sensor analyte values.

[0163] In the exemplary calibration set shown in Fig. 12A, the calculated R-value is about 0.99, which can also be expressed as the correlation coefficient of regression. Accordingly, the calibration exhibits sufficient data association (and thus insufficient quality) because it falls above the 0.79 threshold set in this exemplary embodiment.

[0164] In the exemplary calibration set shown in Fig. 12B, the calculated R-value is about 0.77, which can also be expressed as the correlation coefficient of regression. Accordingly, the calibration exhibits insufficient data association (and thus insufficient quality) because it falls below the 0.79 threshold set in this exemplary embodiment.

[0165] Reference is again made to Fig. 11, at block (118), the interface control module, also referred to as the fail-safe module, controls the user interface based upon the quality of the calibration. If the calibration is exhibits sufficient quality, then the user interface can function as normal; that is providing output for the user such as described in more detail with reference to Fig. 6.

[0166] If however the calibration is not deemed sufficient in quality, then fail-safe module (118 begins the initial stages of fail-safe mode, which are described in more detail with reference to Fig. 8. In some embodiments, the initial stages of fail-safe mode include altering the user interface so that estimated sensor data is not displayed to the user. In some embodiments, the initial stages of fail-safe mode also include prompting the user to provide an updated reference analyte value. The updated analyte value is then processed as described above and the updated conversion function that results from the repeated reference analyte test, if any, is evaluated for statistical accuracy.

[0167] If the results of the updated evaluation again exhibit insufficient quality, then the fail-safe module alters user interface to reflect full fail-safe mode, which is described in more detail with reference to Fig. 8. If however the results of the updated evaluation exhibit sufficient quality, then the first reference analyte value is discarded, and the repeated reference analyte value is accepted and the process continues as described herein.

[0168] The initial stages of fail-safe mode and full fail safe mode can be similar to that described with reference to Fig. 8, including user interface control for example. Additionally, it is contemplated herein that a variety of difference modes between initial and full fail-safe mode can be provided depending on the relative quality of the calibration. In other words, the confidence level of the calibration quality can control a plurality of different user interface screens providing error bars, ± values, and the like. Similar screens can be implements in the clinical acceptability embodiments described with reference to Fig. 8.

[0169] All references cited herein are incorporated herein by reference in their entirety. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0170] The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

[0171] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0172] The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope of the invention as embodied in the attached claims.

Claims

1. A system for initializing a continuous analyte sensor (10), comprising:

a sensor data module operatively linked to a continuous analyte sensor (10) and configured to receive a sensor data stream, including one or more sensor data points, from the sensor;
a reference input module adapted to obtain one or more reference data points;
a processor module associated with the sensor data module and the reference input module and programmed to match reference data points with time-matched sensor data points to form a calibration set including at least one matched data pair; and
a stability module associated with the processor module programmed to determine the stability of the continuous analyte sensor, **characterised in that** the stability module evaluates stability by monitoring the frequency content of the sensor data stream over a predetermined amount of time by comparing a template or templates with actual sensor data, wherein a predetermined amount of agreement between the template or the templates and the actual sensor data is indicative of sensor stability, and wherein the template or templates reflect acceptable levels of glucose physiology.

2. The system of Claim 1, wherein the system additionally includes an interface control module that provides output to the user based on the stability of the sensor.

3. The system of Claim 2, wherein the output from the interface control module includes at least one of a numeric estimated analyte value, an indication of directional trend of analyte concentration, and a graphical representation of an estimated analyte value.

4. The system of Claim 2 or 3, wherein the output is displayed on a user interface.

5. The system of any one of Claims 1 to 4, wherein the continuous analyte sensor is a continuous glucose sensor and the sensor data module is configured to receive sensor data from the continuous glucose sensor.

6. The system of Claim 5, wherein receiving a sensor data stream includes receiving sensor data from an implantable glucose sensor.

7. A method for initializing a continuous analyte sensor (10), comprising the steps of:

receiving a sensor data stream, including one or more sensor data points, from a continuous analyte sensor (10);
receiving one or more reference data points;
operating a processor module to match reference data points with time-matched sensor data points to form a calibration set including at least one matched data pair; and
characterised by:

determining the stability of the continuous analyte sensor by evaluating stability by monitoring the frequency content of the sensor data stream over a predetermined amount of time by comparing a template or templates with actual sensor data, wherein a predetermined amount of agreement between the template and the actual sensor data is indicative of sensor stability, and wherein the template or templates reflect acceptable levels of glucose physiology.

8. The method of Claim 7 additionally including providing output to the user based on the stability of the sensor on an interface control module.

9. The method of Claim 7 or 8, wherein the output from the interface control module includes at least one of a numeric estimated analyte value, an indication of directional trend of analyte concentration, and a graphical representation of an estimated analyte value.

10. The method of Claim 8 or 9, wherein the output is displayed on a user interface.

11. The method of any one of Claims 8 to 10, wherein the step of receiving a sensor data stream from an analyte sensor (10) includes receiving sensor data from a continuous glucose sensor.

12. The method of Claim 11, wherein the step of receiving a sensor data stream includes receiving sensor data from an implantable glucose sensor.

13. The method of any one of claims 7 to 12, or the system of any one of claims 1 to 6, wherein the sensor data points are in the form of a raw data signal directly related to the measured analyte from the analyte sensor, wherein the raw data signal is digital data in counts converted by an analog to digital converter from an analog signal in voltage or amps representative of an analyte concentration.

14. The method of any one of claims 7 to 12 or 13 or the system of any one of claims 1 to 6 or 13, wherein the analyte sensor uses an electrochemical method of analyte sensing.

Patentansprüche

1. System zum Initialisieren eines Dauer-Analyt-Sensors (10), umfassend:

eine Sensordatenmodul, das betrieblich mit einem Dauer-Analyt-Sensor (10) verbunden und konfiguriert ist, einen Sensordatenstrom, der einen oder mehrere Sensordatenpunkte enthält, aus dem Sensor zu empfangen;
ein Referenzeingangsmodul, das ausgelegt ist, einen oder mehrere Referenzdatenpunkte zu ermitteln;
ein Prozessormodul, das mit dem Sensordatenmodul und dem Referenzeingangsmodul assoziiert ist, und programmiert ist, Referenzdatenpunkte mit Zeit-abgeglichenen Sensordatenpunkten abzugleichen, um einen

Kalibrierungssatz zu bilden, der zumindest ein abgeglichenes Datenpaar enthält; und
ein Stabilitätsmodul, das mit dem Prozessormodul assoziiert ist, programmiert, die Stabilität des Dauer-Analyt-Sensors zu bestimmen, **dadurch gekennzeichnet,**
dass das Stabilitätsmodul die Stabilität durch Überwachen des Frequenzinhalts des Sensordatenstroms eine vorbestimmte Zeit lang evaluiert, durch Vergleichen einer Vorlage oder von Vorlagen mit tatsächlichen Sensordaten, wobei ein vorbestimmter Übereinstimmungsbetrag zwischen der Vorlage oder den Vorlagen und den tatsächlichen Sensordaten für eine Sensorstabilität indikativ ist, und wobei die Vorlage oder die Vorlagen akzeptable Glukose-Physiologiespiegel widerspiegeln.

2. System nach Anspruch 1, wobei das System zusätzlich ein Schnittstellensteuermodul beinhaltet, das eine Ausgabe an den Anwender bereitstellt, basierend auf der Stabilität des Sensors.

3. System nach Anspruch 2, wobei die Ausgabe aus dem Schnittstellensteuermodul einen numerisch geschätzten Analytwert, eine Indikation eines Richtungstrends von Analytkonzentration, oder/und eine graphische Repräsentation eines geschätzten Analytwerts enthält.

4. System nach Anspruch 2 oder 3, wobei die Ausgabe auf einer Anwenderschnittstelle angezeigt ist.

5. System nach einem der Ansprüche 1 bis 4, wobei der Dauer-Analyt-Sensor ein Dauerglukosesensor ist und das Sensordatenmodul konfiguriert ist, Sensordaten aus dem Dauerglukosesensor zu empfangen.

6. System nach Anspruch 5, wobei das Empfangen eines Sensordatenstroms das Empfangen von Sensordaten aus einem implantierbaren Glukosesensor beinhaltet.

7. Verfahren zum Initialisieren eines Dauer-Analyt-Sensors (10), umfassend die Schritte:

Empfangen eines Sensordatenstroms, der einen oder mehrere Sensordatenpunkte enthält, aus einem Dauer-Analyt-Sensor (10);
Betreiben eines Prozessormoduls, um Referenzdatenpunkte mit Zeit-abgeglichenen Sensordatenpunkten abzugleichen, um einen Kalibrierungssatz zu bilden, der zumindest ein abgeglichenes Datenpaar enthält; und
gekennzeichnet durch:

Bestimmen der Stabilität des Dauer-Analyt-Sensors **durch** Evaluieren der Stabilität **durch** Überwachen des Frequenzinhalts des Sensordatenstroms eine vorbestimmte Zeit lang, **durch** Vergleichen einer Vorlage oder von Vorlagen mit tatsächlichen Sensordaten, wobei ein vorbestimmter Übereinstimmungsbetrag zwischen der Vorlage und den tatsächlichen Sensordaten für eine Sensorstabilität indikativ ist, und wobei die Vorlage oder die Vorlagen akzeptable Glukose-Physiologiespiegel widerspiegeln.

8. Verfahren nach Anspruch 7, zusätzlich beinhaltend Bereitstellen einer Ausgabe an den Anwender, basierend auf der Stabilität des Sensors, auf einem Schnittstellensteuermodul.

9. Verfahren nach Anspruch 7 oder 8, wobei die Ausgabe aus dem Schnittstellensteuermodul einen numerisch geschätzten Analytwert, eine Indikation eines Richtungstrends von Analytkonzentration, oder/und eine graphische Repräsentation eines geschätzten Analytwerts enthält.

10. Verfahren nach Anspruch 8 oder 9, wobei die Ausgabe auf einer Anwenderschnittstelle angezeigt wird.

11. Verfahren nach einem der Ansprüche 8 bis 10, wobei der Schritt des Empfangens eines Sensordatenstroms aus einem Analyt-Sensor (10) das Empfangen von Sensordaten aus einem Dauerglukosesensor beinhaltet.

12. Verfahren nach Anspruch 11, wobei der Schritt des Empfangens eines Sensordatenstroms das Empfangen von Sensordaten aus einem implantierbaren Glukosesensor beinhaltet.

13. Verfahren nach einem der Ansprüche 7 bis 12, oder System nach einem der Ansprüche 1 bis 6, wobei die Sensordatenpunkte in Form eines sich direkt auf den gemessene Analyten beziehenden Rohdatensignals aus dem Analytsensor vorliegen, wobei das Rohdatensignal Digitaldaten in Zahlenwerten ist, die durch einen Analog-Digital-Wandler aus einem Analogsignal in Volt oder Ampere, die für eine Analytkonzentration repräsentativ sind, umgewandelt sind.

14. Verfahren nach einem der Ansprüche 7 bis 12 oder 13, oder System nach einem der Ansprüche 1 bis 6 oder 13, wobei der Analytsensor ein elektrochemisches Verfahren des Analyte-Erfassens einsetzt.

Revendications

1. Système pour initialiser un capteur d'analyte continu (10), comprenant :

un module de données de capteur fonctionnellement lié à un capteur d'analyte continu (10) et configuré pour recevoir un flux de données de capteur, comprenant un ou plusieurs points de données de capteur, du capteur ;
un module d'entrée de référence adapté pour obtenir un ou plusieurs points de données de référence ;
un module de processeur associé au module de données de capteur et au module d'entrée de référence et programmé pour assortir des points de données de référence à des points de données de capteur synchronisés pour former un jeu d'étalonnage comprenant au moins une paire de données assorties ; et
un module de stabilité associé au module de processeur programmé pour déterminer la stabilité du capteur d'analyte continu, **caractérisé en ce que** le module de stabilité évalue la stabilité en surveillant le contenu de fréquence du flux de données de capteur durant une période de temps prédéterminée en comparant un ou des modèles à des données de capteur réelles,
dans lequel la quantité prédéterminée de correspondance entre le ou les modèles et les données de capteur réelles est indicative de stabilité du capteur et dans lequel le ou les modèles reflètent des niveaux acceptables de physiologie du glucose.

2. Système selon la revendication 1, dans lequel le système comprend en outre un module de commande d'interface qui fournit une sortie à l'utilisateur en fonction de la stabilité du capteur.

3. Système selon la revendication 2, dans lequel la sortie du module de commande d'interface comprend au moins l'une ou l'autre d'une valeur d'analyte numérique estimée, d'une indication de tendance directionnelle de concentration d'analyte et d'une représentation graphique d'une valeur d'analyte estimée.

4. Système selon la revendication 2 ou la revendication 3, dans lequel la sortie est affichée sur une interface utilisateur.

5. Système selon l'une quelconque des revendications 1 à 4, dans lequel le capteur d'analyte continu est un capteur de glucose continu et le module de données de capteur est configuré pour recevoir des données du capteur de glucose continu.

6. Système selon la revendication 5, dans lequel la réception d'un flux de données du capteur comprend la réception de données d'un capteur de glucose implantable.

7. Procédé pour initialiser un capteur d'analyte continu (10), comprenant les étapes consistant à :

recevoir un flux de données de capteur comprenant un ou plusieurs points de données d'un capteur d'analyte continu (10) ;
recevoir un ou plusieurs points de données de référence ;
le fonctionnement d'un module de processeur pour assortir des points de données de référence à des points de données de capteur synchronisés pour former un jeu d'étalonnage comprenant au moins une paire de données assorties ; et
caractérisé par :

la détermination de la stabilité du capteur d'analyte continu en évaluant la stabilité en surveillant le contenu de fréquence du flux de données du capteur durant une période prédéterminée en comparant un ou des modèles à des données de capteur réelles, dans lequel la quantité prédéterminée de correspondance entre le modèle et les données de capteur réelles est indicative d'une stabilité du capteur et dans lequel le ou les modèles reflètent des niveaux acceptables de physiologie du glucose.

8. Procédé selon la revendication 7, comprenant en outre la fourniture d'une sortie à l'utilisateur en fonction de la stabilité du capteur sur un module de commande d'interface.

9. Procédé selon la revendication 7 ou la revendication 8, dans lequel la sortie du module de commande d'interface comprend au moins l'une ou l'autre d'une valeur d'analyte numérique estimée, d'une indication de tendance directionnelle de concentration d'analyte et d'une représentation graphique d'une valeur d'analyte estimée.

10. Procédé selon la revendication 8 ou la revendication 9, dans lequel la sortie est affichée sur une interface utilisateur.

11. Procédé selon l'une quelconque des revendications 8 à 10, dans lequel l'étape de réception d'un flux de données d'un capteur d'analyse (10) comprend la réception de données d'un capteur de glucose continu.

12. Procédé selon la revendication 11, dans lequel l'étape de réception d'un flux de données du capteur comprend la réception de données d'un capteur de glucose implantable.

13. Procédé selon l'une quelconque des revendications 7 à 12 ou système selon l'une quelconque des revendications 1 à 6, dans lequel les points de données du capteur se présentent sous forme d'un signal de données brutes directement connexe à l'analyte mesuré du capteur d'analyte, dans lequel le signal de données brutes est formé de données numériques en comptes convertis par un convertisseur analogique-numérique à partir d'un signal analogique en tension ou en ampères représentatif d'une concentration d'analyte.

14. Procédé selon l'une quelconque des revendications 7 à 12 ou 13 ou système selon l'une quelconque des revendications 1 à 6 ou 13, dans lequel le capteur d'analyte utilise un procédé électrochimique de détection d'analyte.

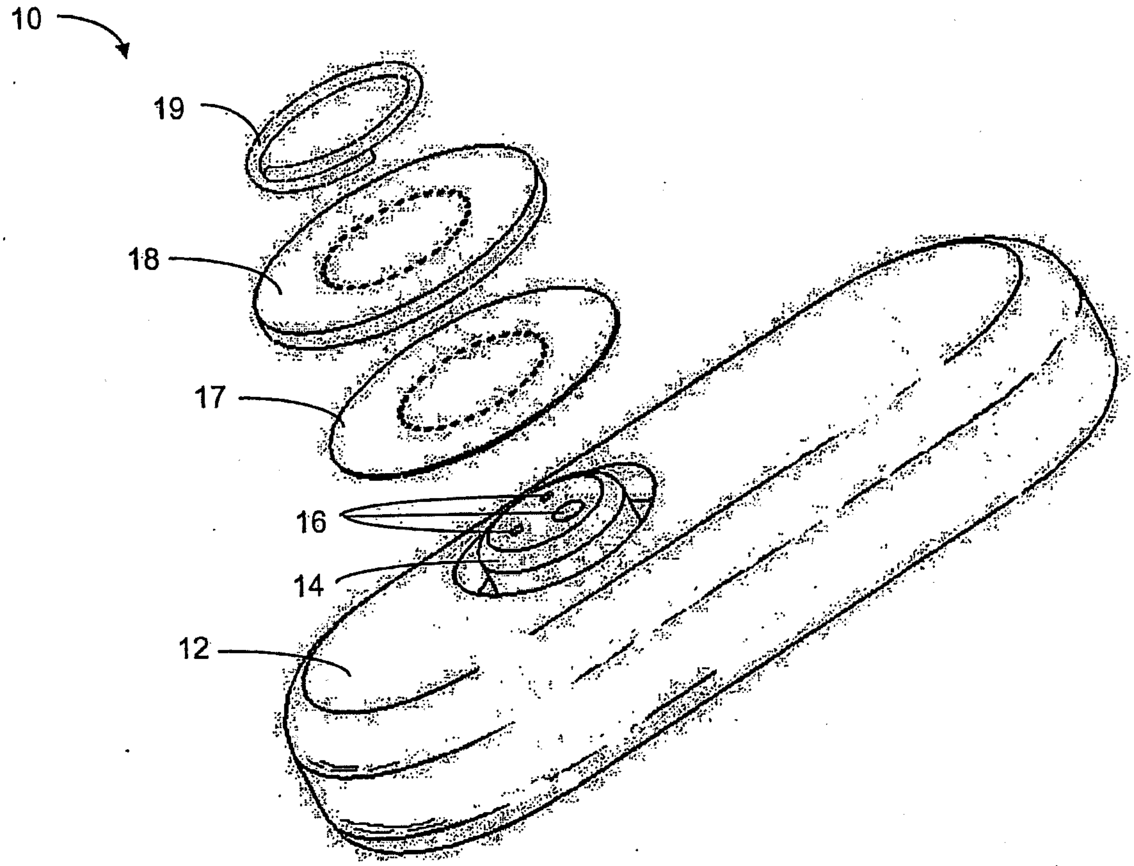

FIG. 1

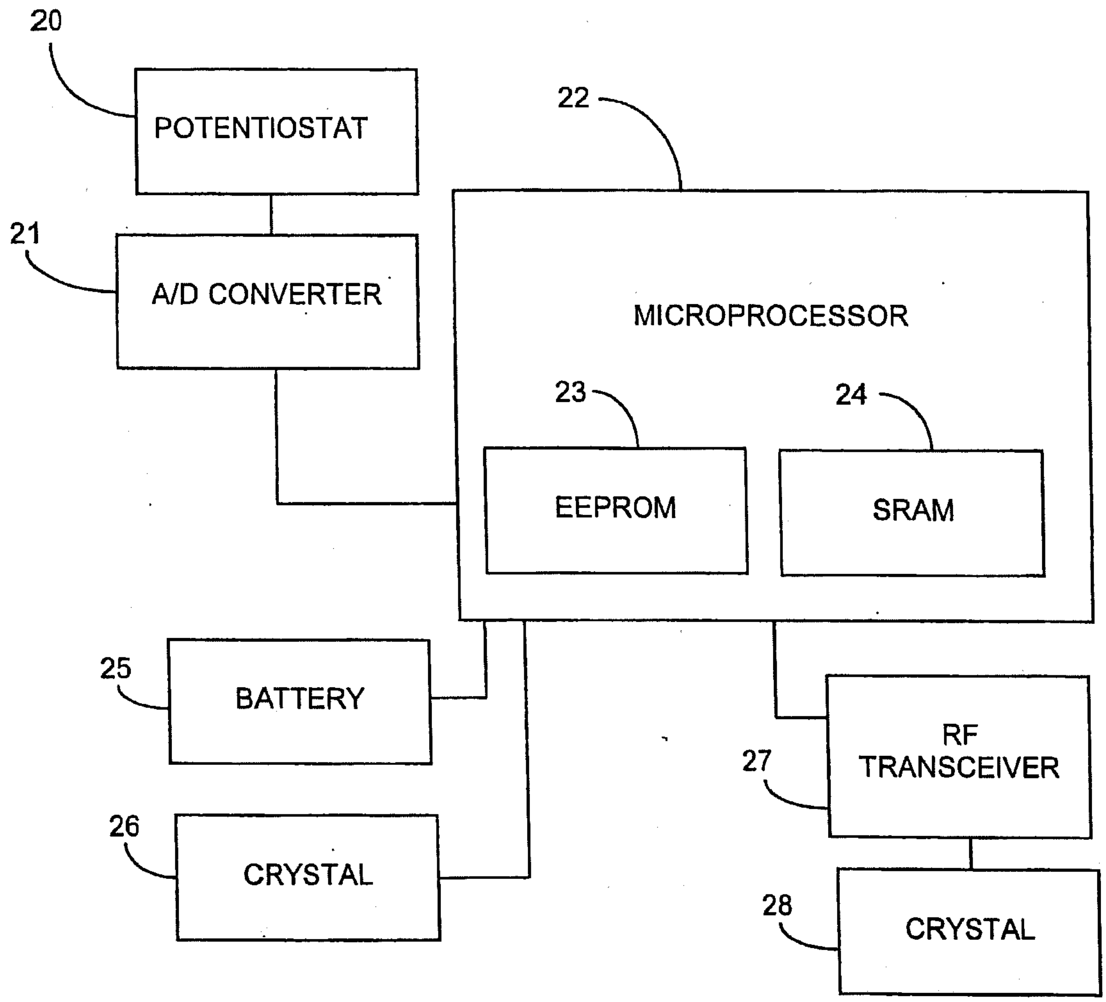
20
POTENTIOSTAT
21
A/D CONVERTER
22
MICROPROCESSOR
23
EEPROM
24
SRAM
25
BATTERY
26
CRYSTAL
27
RF
TRANSCEIVER
28
CRYSTAL

FIG. 2

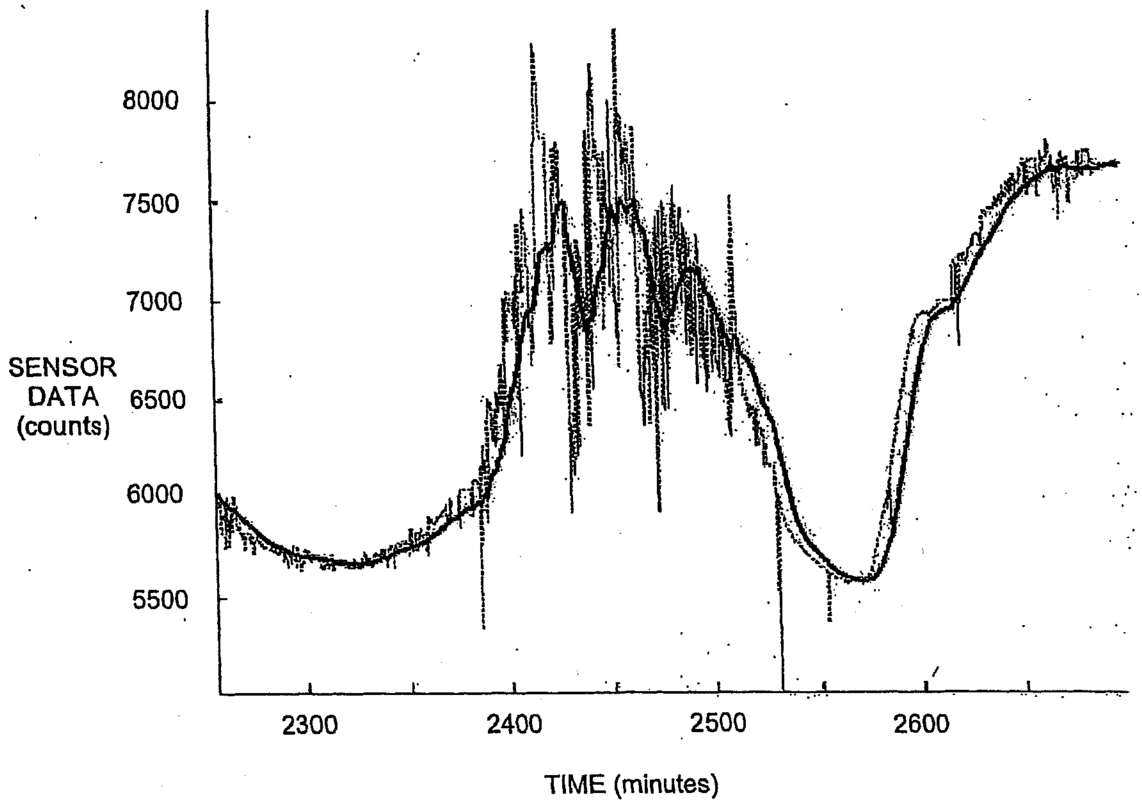
8000
7500
7000
SENSOR
DATA
(counts)
6500
6000
5500
2300
2400
2500
2600
TIME (minutes)

FIG. 3

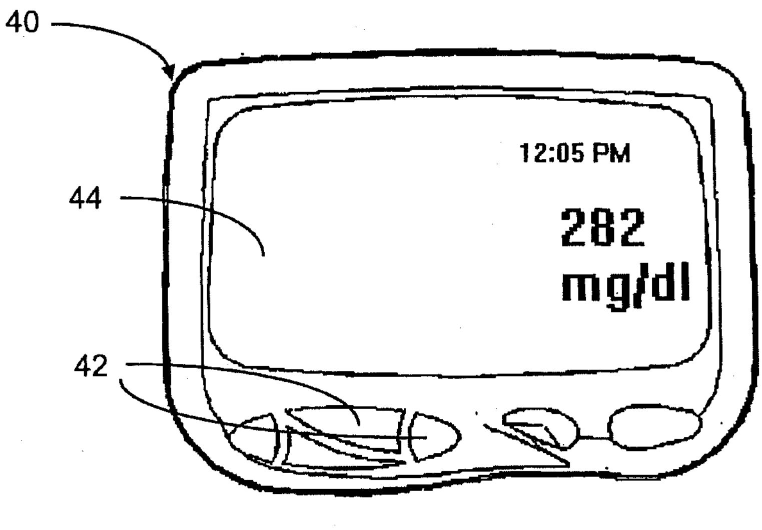

FIG. 4A

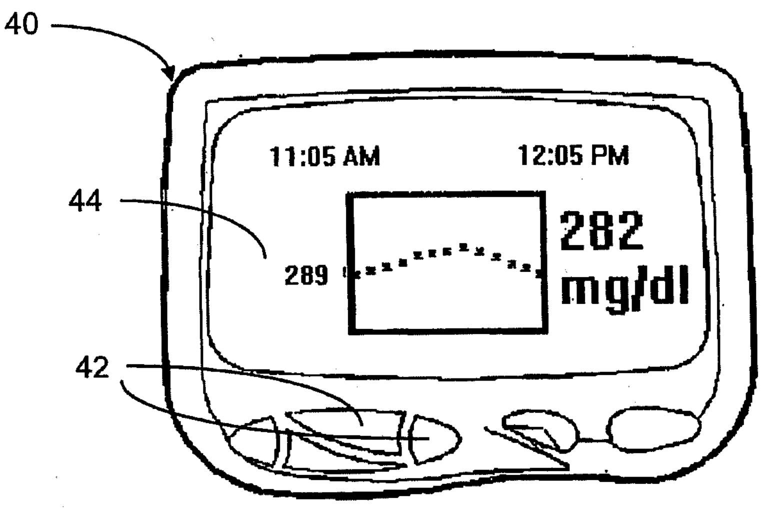

FIG. 4B

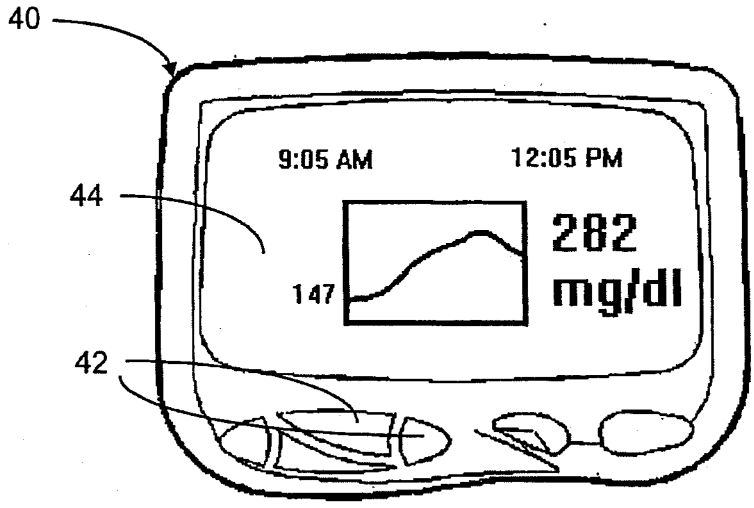
40
44
42
9:05 AM
12:05 PM
147
282
mg/dl

FIG. 4C

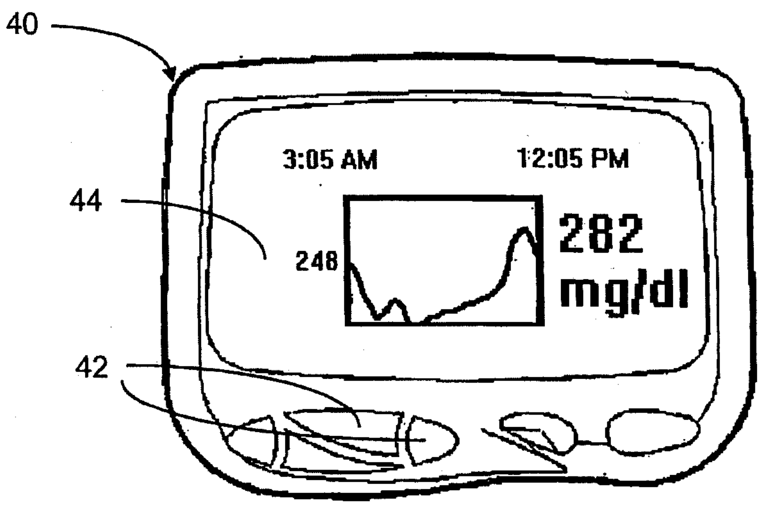
40
44
42
3:05 AM
12:05 PM
248
282
mg/dl

FIG. 4D

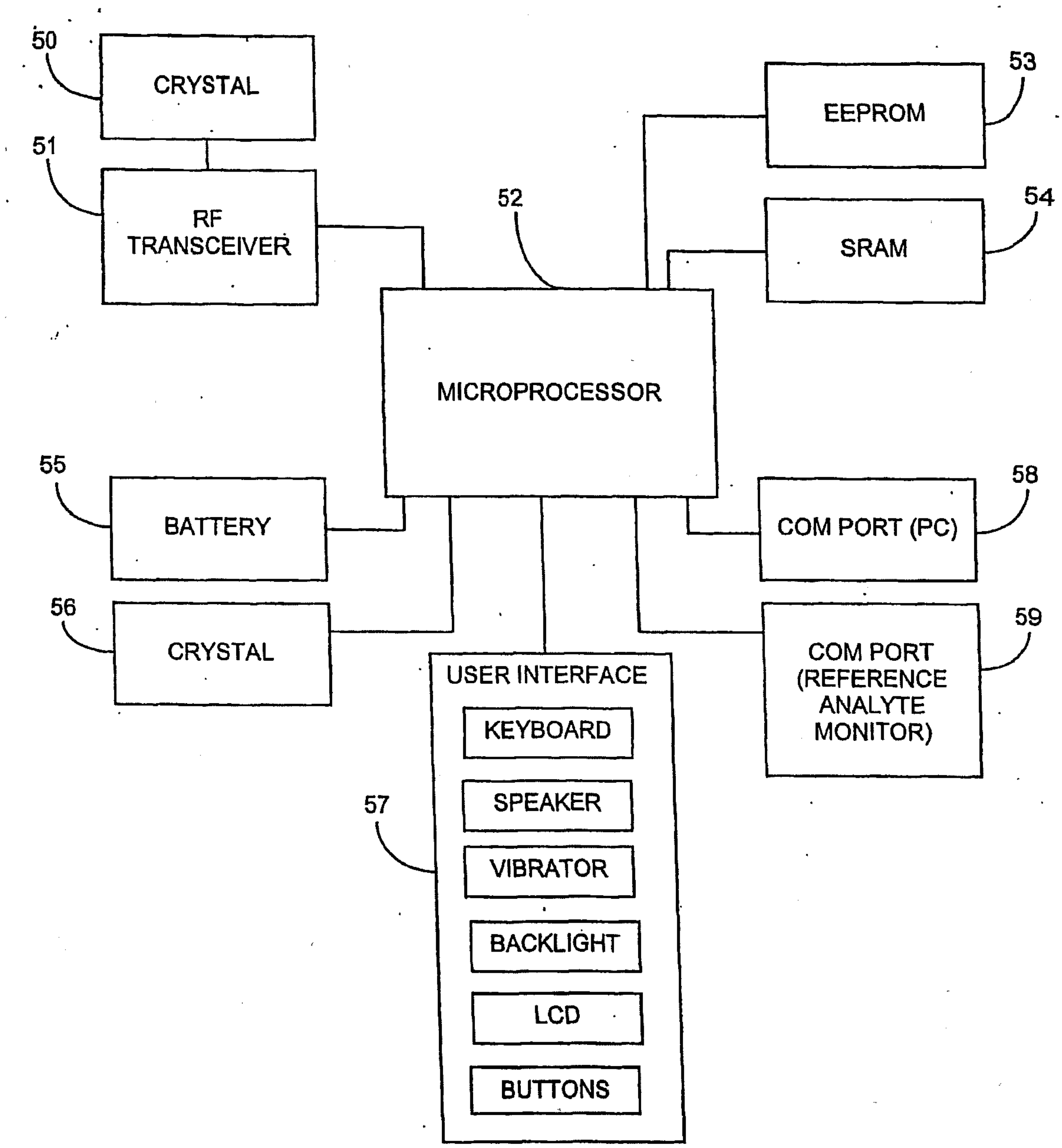
50
CRYSTAL
51
RF
TRANSCEIVER
52
MICROPROCESSOR
53
EEPROM
54
SRAM
55
BATTERY
56
CRYSTAL
57
USER INTERFACE
KEYBOARD
SPEAKER
VIBRATOR
BACKLIGHT
LCD
BUTTONS
58
COM PORT (PC)
59
COM PORT
(REFERENCE
ANALYTE
MONITOR)

FIG. 5

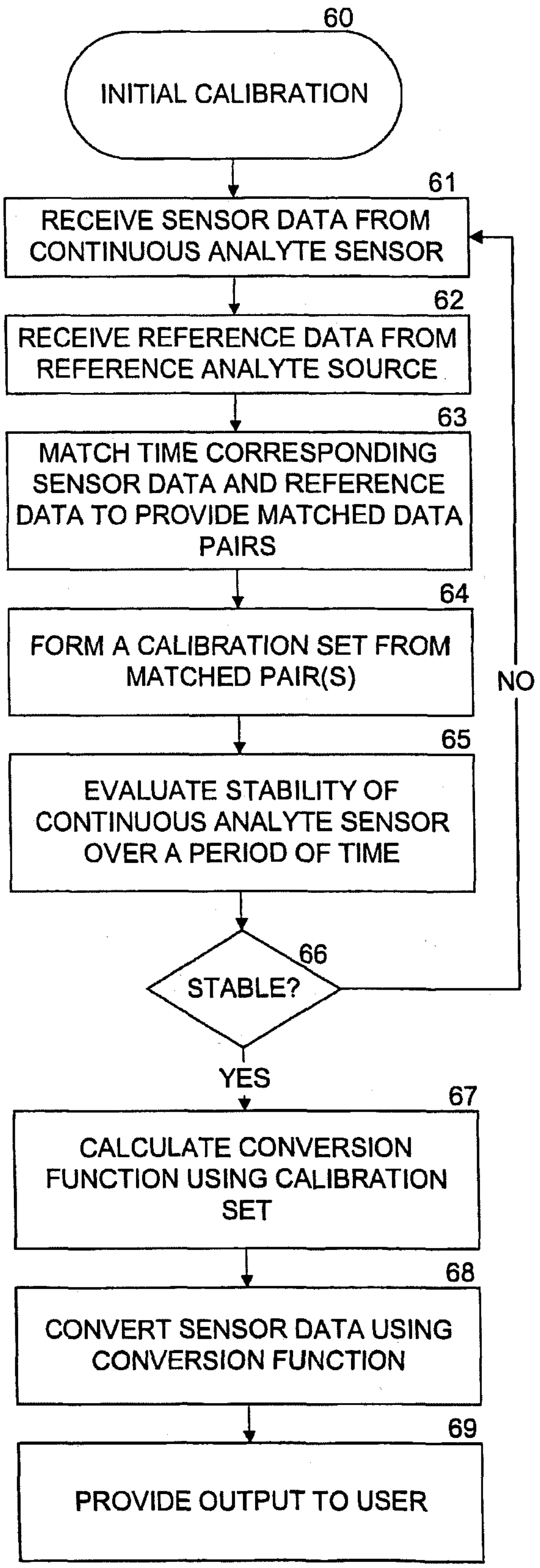
60
INITIAL CALIBRATION
61
RECEIVE SENSOR DATA FROM CONTINUOUS ANALYTE SENSOR
62
RECEIVE REFERENCE DATA FROM REFERENCE ANALYTE SOURCE
63
MATCH TIME CORRESPONDING SENSOR DATA AND REFERENCE DATA TO PROVIDE MATCHED DATA PAIRS
64
FORM A CALIBRATION SET FROM MATCHED PAIR(S)
NO
65
EVALUATE STABILITY OF CONTINUOUS ANALYTE SENSOR OVER A PERIOD OF TIME
66
STABLE?
YES
67
CALCULATE CONVERSION FUNCTION USING CALIBRATION SET
68
CONVERT SENSOR DATA USING CONVERSION FUNCTION
69
PROVIDE OUTPUT TO USER

FIG. 6

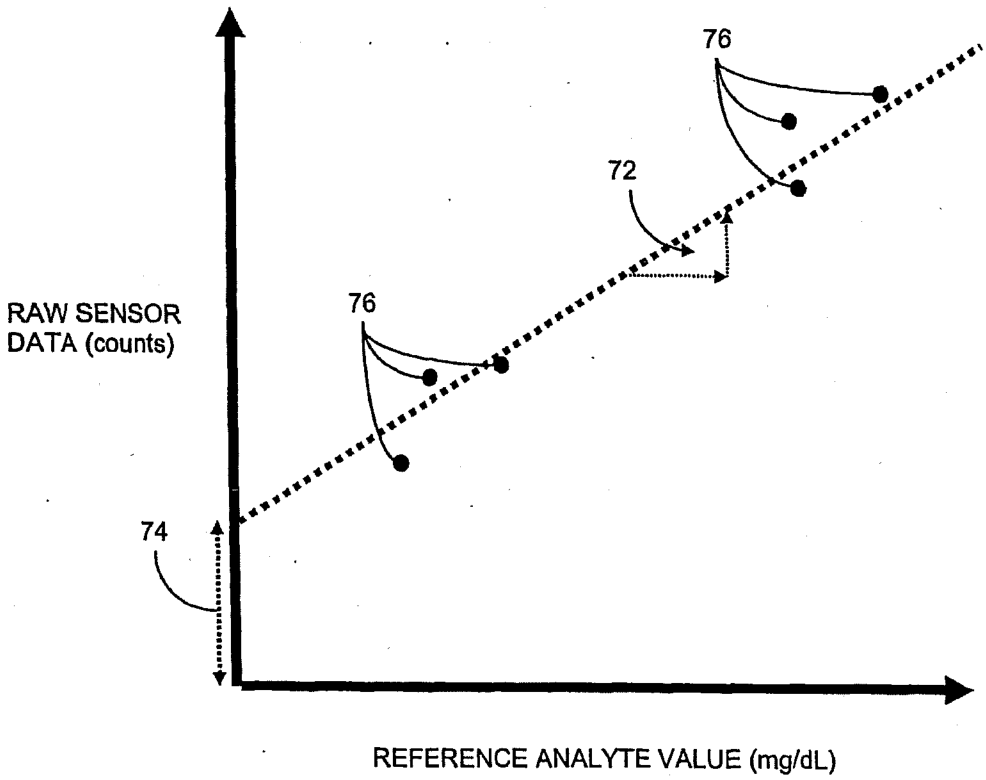
76
76
72
RAW SENSOR
DATA (counts)
74
REFERENCE ANALYTE VALUE (mg/dL)

FIG. 7

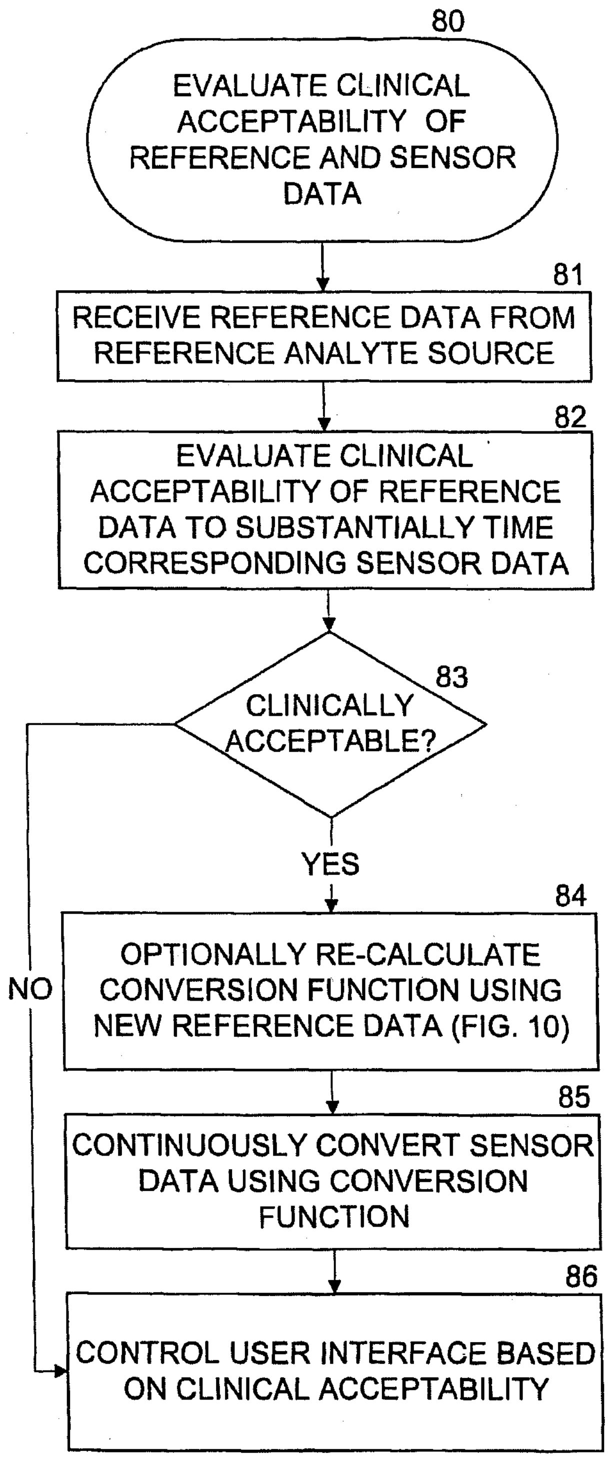
80
EVALUATE CLINICAL ACCEPTABILITY OF REFERENCE AND SENSOR DATA
81
RECEIVE REFERENCE DATA FROM REFERENCE ANALYTE SOURCE
82
EVALUATE CLINICAL ACCEPTABILITY OF REFERENCE DATA TO SUBSTANTIALLY TIME CORRESPONDING SENSOR DATA
83
CLINICALLY ACCEPTABLE?
YES
NO
84
OPTIONALLY RE-CALCULATE CONVERSION FUNCTION USING NEW REFERENCE DATA (FIG. 10)
85
CONTINUOUSLY CONVERT SENSOR DATA USING CONVERSION FUNCTION
86
CONTROL USER INTERFACE BASED ON CLINICAL ACCEPTABILITY

FIG. 8

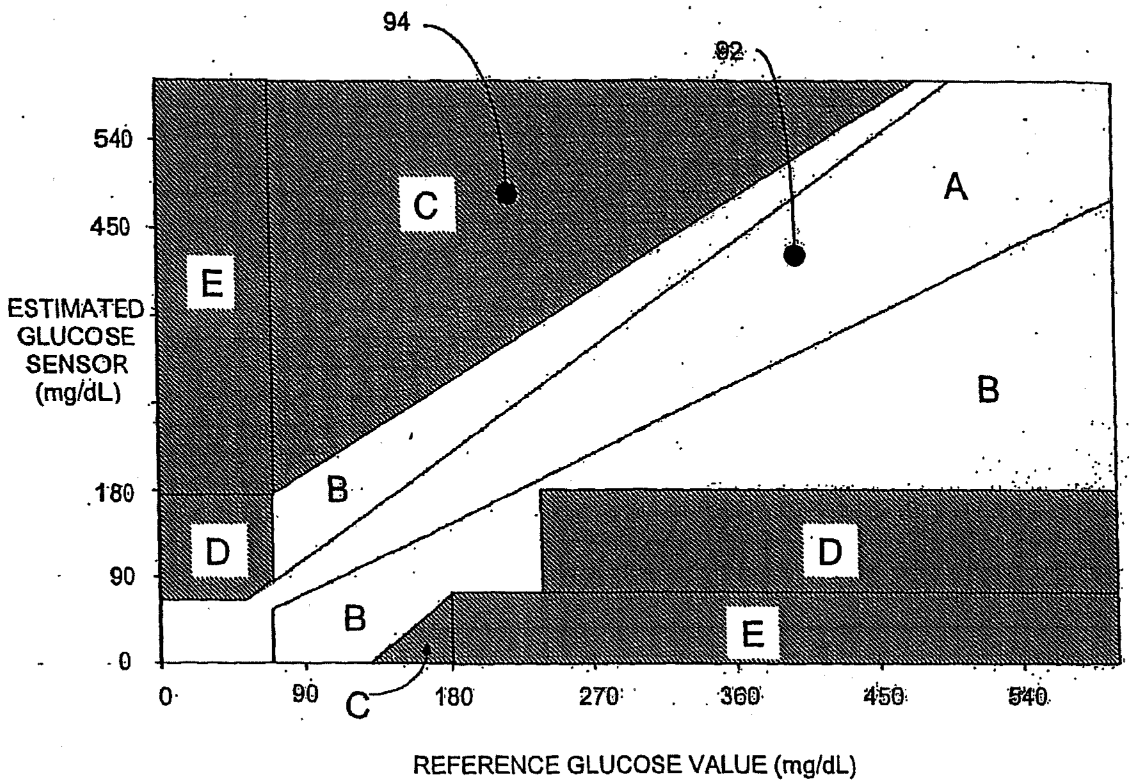
94
92
540
450
ESTIMATED GLUCOSE SENSOR (mg/dL)
180
90
0
C
A
E
B
B
D
D
B
E
C
0
90
180
270
360
450
540
REFERENCE GLUCOSE VALUE (mg/dL)

FIG. 9

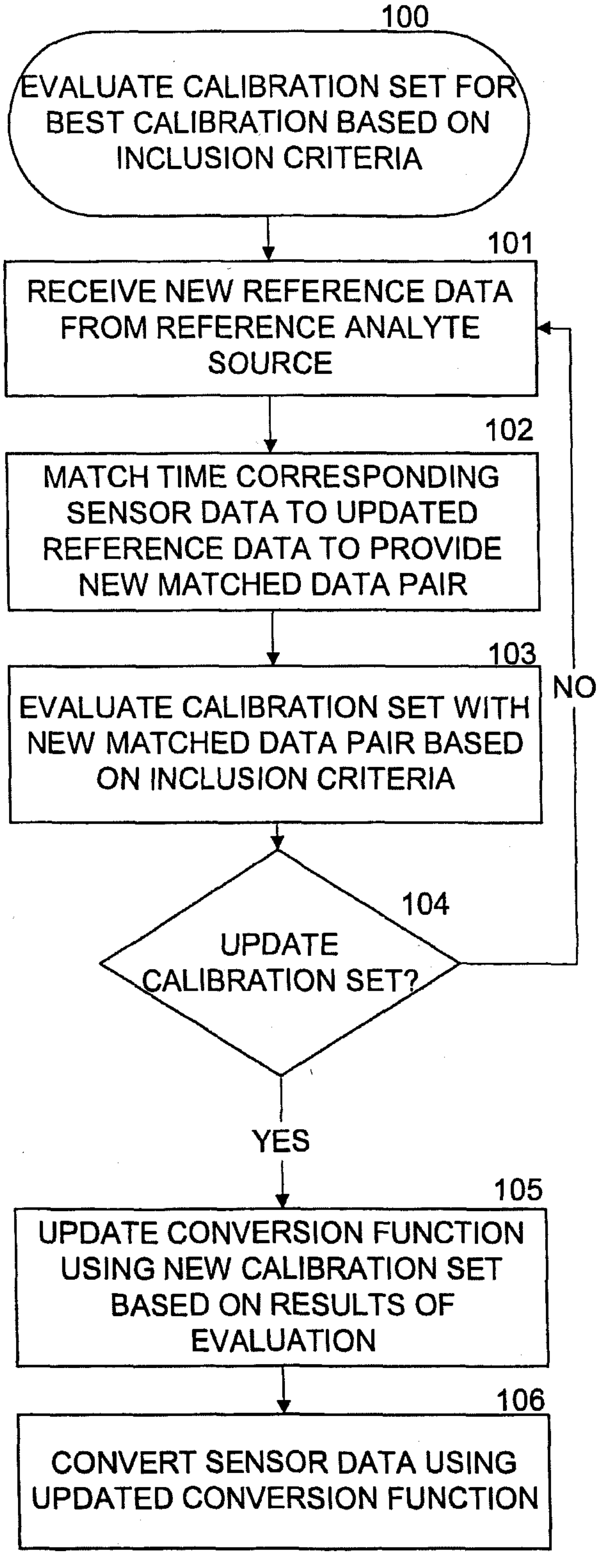
100
EVALUATE CALIBRATION SET FOR BEST CALIBRATION BASED ON INCLUSION CRITERIA
101
RECEIVE NEW REFERENCE DATA FROM REFERENCE ANALYTE SOURCE
102
MATCH TIME CORRESPONDING SENSOR DATA TO UPDATED REFERENCE DATA TO PROVIDE NEW MATCHED DATA PAIR
103
EVALUATE CALIBRATION SET WITH NEW MATCHED DATA PAIR BASED ON INCLUSION CRITERIA
NO
104
UPDATE CALIBRATION SET?
YES
105
UPDATE CONVERSION FUNCTION USING NEW CALIBRATION SET BASED ON RESULTS OF EVALUATION
106
CONVERT SENSOR DATA USING UPDATED CONVERSION FUNCTION

FIG. 10

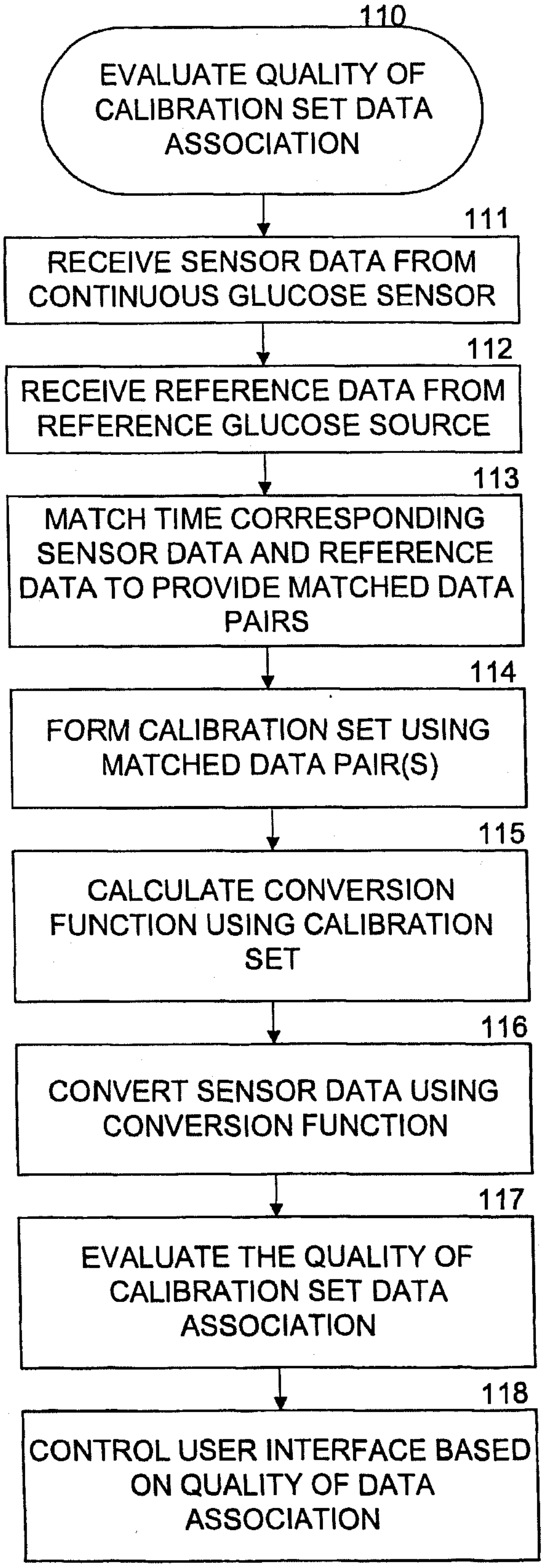
110
EVALUATE QUALITY OF CALIBRATION SET DATA ASSOCIATION
111
RECEIVE SENSOR DATA FROM CONTINUOUS GLUCOSE SENSOR
112
RECEIVE REFERENCE DATA FROM REFERENCE GLUCOSE SOURCE
113
MATCH TIME CORRESPONDING SENSOR DATA AND REFERENCE DATA TO PROVIDE MATCHED DATA PAIRS
114
FORM CALIBRATION SET USING MATCHED DATA PAIR(S)
115
CALCULATE CONVERSION FUNCTION USING CALIBRATION SET
116
CONVERT SENSOR DATA USING CONVERSION FUNCTION
117
EVALUATE THE QUALITY OF CALIBRATION SET DATA ASSOCIATION
118
CONTROL USER INTERFACE BASED ON QUALITY OF DATA ASSOCIATION

FIG. 11

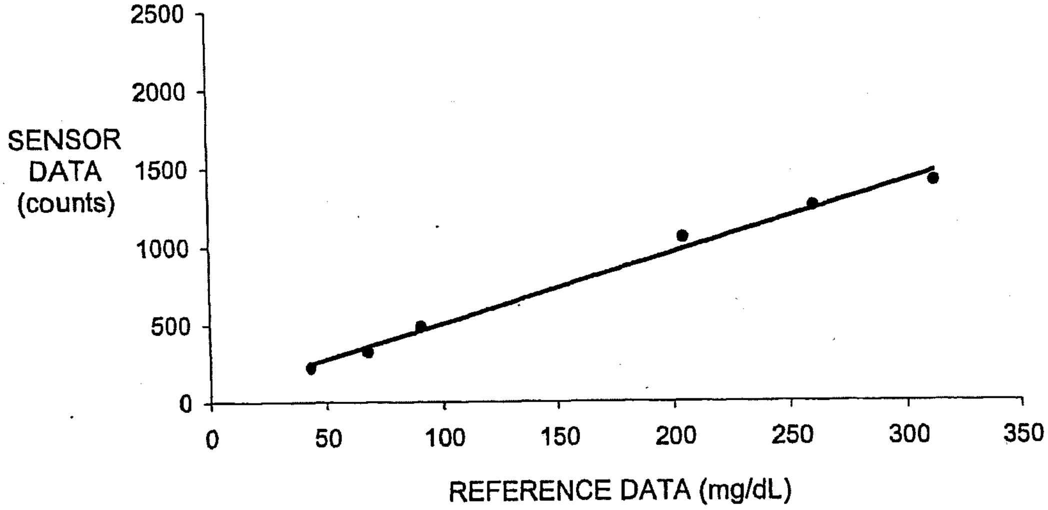

FIG. 12A

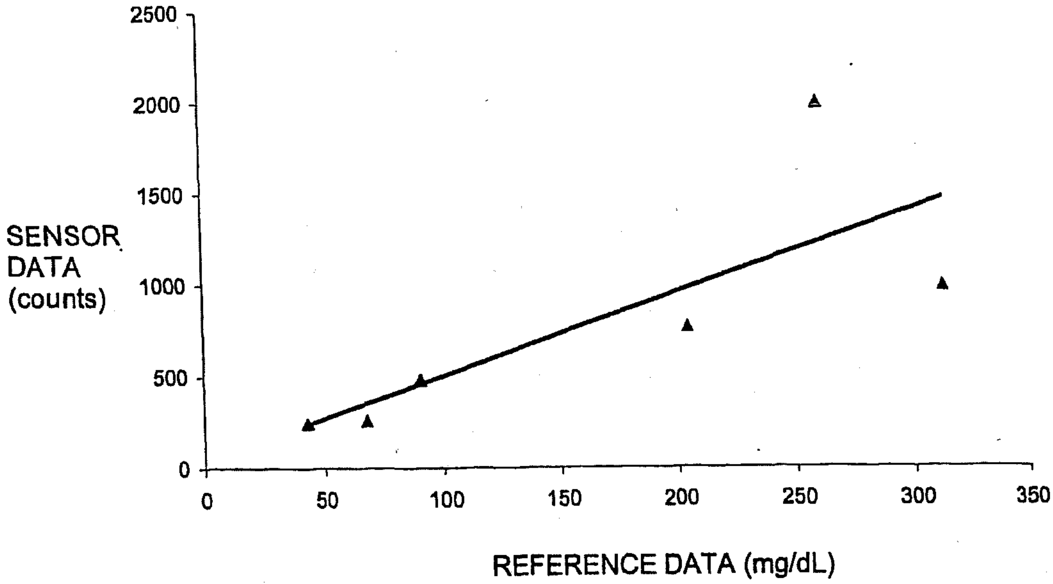

FIG. 12B

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 0049941 A **[0004]**
- US 6558351 B, Steil **[0069]**

Non-patent literature cited in the description

- **CLARKE et al.** Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose. *Diabetes Care,* September 1987, vol. 10 (5 **[0039]**
- **PARKES et al.** A New Consensus Error Grid to Evaluate the Clinical Significance of Inaccuracies in the Measurement of Blood Glucose. *Diabetes Care,* August 2000, vol. 23 (8 **[0040]**
- An Introduction to In vivo Biosensing: Progress and problems. **FRASER, D.M.** Biosensors and the Body. John Wiley and Sons, 1997, 1-56 **[0061]**

专利名称(译)	处理分析物传感器数据		
公开(公告)号	EP2494921B1	公开(公告)日	2016-09-14
申请号	EP2012170103	申请日	2004-07-27
[标]申请(专利权)人(译)	德克斯康公司		
申请(专利权)人(译)	DEXCOM INC.		
当前申请(专利权)人(译)	DEXCOM INC.		
[标]发明人	GOODE PAUL V JR BRAUKER JAMES H KAMATH APURV U CARR BRENDEL VICTORIA		
发明人	GOODE, PAUL V JR BRAUKER, JAMES H KAMATH, APURV U CARR-BRENDEL, VICTORIA THROWER, JAMES P		
IPC分类号	A61B5/145 A61B5/1495 A61B5/1486 G01N27/327 A61B5/00 G01D18/00 G01N31/00 G01N33/487		
CPC分类号	A61B5/0031 A61B5/1433 A61B5/14532 A61B5/14546 A61B5/14865 A61B5/1495 A61B5/150022 A61B5/4839 A61B5/743 A61B2560/0223 A61B2560/04 A61B2562/085 G01N33/48707 Y02A90/22 Y02A90/26 A61B5/1468 A61B5/1473		
优先权	10/632537 2003-08-01 US 10/633329 2003-08-01 US 10/633367 2003-08-01 US 10/633404 2003-08-01 US		
其他公开文献	EP2494921A2 EP2494921A3		
外部链接	Espacenet		

摘要(译)

用于处理传感器分析物数据的系统和方法，包括启动校准（60），更新校准（100），评估参考和传感器分析物数据（80）的临床可接受性，以及评估传感器校准的质量（110）。在初始校准期间，在一段时间内评估分析物传感器数据以确定传感器的稳定性。可以使用一个或多个匹配的传感器和参考分析物数据对的校准集来校准传感器（10）。在根据新接收的参考分析物数据的入选标准评估校准集以进行最佳校准之后，可以更新校准。基于参考和分析物数据的临床可接受性和传感器校准的质量提供故障安全机制。算法提供对来自分析物传感器（10）的估计血液分析物数据的优化前瞻性和回顾性分析。