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(54) **METHODS AND SYSTEMS FOR OPTIMIZING SENSOR FUNCTION BY THE APPLICATION OF VOLTAGE**

VERFAHREN UND SYSTEME ZUR OPTIMIERUNG DER SENSORFUNKTION DURCH ANLEGEN VON SPANNUNG

PROCÉDÉS ET SYSTÈMES POUR OPTIMISER LE FONCTIONNEMENT D'UN CAPTEUR PAR L'APPLICATION D'UNE TENSION

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Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The invention lies in the field of analyte sensors (e.g. glucose sensors used in the management of diabetes) and methods and materials for making and using such sensors. More particularly, the invention pertains to methods and apparatus for initializing an analyte sensor.

2. Description of Related Art

[0002] Analyte sensors such as biosensors include devices that use biological elements to convert a chemical analyte in a matrix into a detectable signal. There are many types of biosensors used for a wide variety of analytes. The most studied type of biosensor is the amperometric glucose sensor, which is crucial to the successful glucose level control for diabetes.

[0003] A typical glucose sensor works according to the following chemical reactions:

$$\text{GLUCOSE} + O_2 \xrightarrow{\text{GLUCOSE OXIDASE}} \text{GLUCONIC ACID} + H_2O_2 \qquad \text{Equation 1}$$

$$H_2O_2 \longrightarrow O_2 + 2H^+ + 2e^- \qquad \text{Equation 2}$$

The glucose oxidase is used to catalyze the reaction between glucose and oxygen to yield gluconic acid and hydrogen peroxide (equation 1). The H_2O_2 reacts electrochemically as shown in equation 2, and the current can be measured by a potentiostat. These reactions, which occur in a variety of oxidoreductases known in the art, are used in a number of amperometric sensor designs.

[0004] As analyte sensor technology matures and new applications for sensor technology are developed, there is a need for methods and materials that facilitate the use of sensors in new technological applications. For example, hospitals increasingly use continuous glucose sensors to monitor patient physiology, for example in ICU environments. In such hospital environments, situations arise where a sensor must be disconnected from, and reconnected to, sensor electronics, for example, when a patient needs to undergo a magnetic resonance imaging (MRI) procedure. Because processors are incompatible with MRI, the sensor electronics need to be disconnected from the sensor until the MRI is completed.

[0005] In conventional sensor setups, if a sensor is disconnected from and then reconnected to sensor electronics, there is a significant delay before the sensor becomes stabilized enough to start sensing again. The delay can last from several minutes to a couple of hours, thereby complicating care in clinical settings. In addition, in individuals using analyte sensors in non-hospital settings (e.g. diabetics using glucose sensors to manage their disease), relatively long sensor initialization and/or start-up periods following sensor implantation can be problematical due to both the inconvenience to the user as well as the delayed receipt of information relating to user health. Because many diabetics do not have medical training, they may forgo optimal monitoring and modulation of blood glucose levels due to complexities associated with such management, for example, a two hour start-up period which can be an inconvenience in view of a patient's active daily routine.

[0006] For the above-noted reasons, methods and sensor systems that are designed to reduce sensor initialization and/or start-up times are desirable.

SUMMARY OF THE INVENTION

[0007] The invention disclosed herein provides methods and systems for optimizing the initialization and/or performance of analyte sensors that have been (e.g. temporarily) disconnected from the electronic components of their analyte monitoring systems. Aspects of the invention are useful, for example, in situations where an implantable electrochemical glucose sensor is temporarily disconnected from the electronic components of an analyte monitoring systems during a hospital procedure such as a magnetic resonance imaging (MRI) procedure.

[0008] The invention disclosed herein has a number of aspects. The invention includes a method of initializing an analyte sensor, typically an electrochemical analyte sensor, the method comprising determining a disconnection time,

wherein the disconnection time is the amount of time a sensor has been disconnected from sensor electronics, and then selecting an initialization protocol based on the disconnection time. Typically, the initialization protocol is selected from the group comprising or consisting of: (a) a first initialization scheme comprising applying a first series of voltage pulses to the sensor and (b) a second initialization scheme comprising applying a second series of voltage pulses to the sensor, wherein the first initialization scheme is selected if the disconnection time falls within a first time range and the second initialization scheme is selected if the disconnection time falls within a second time range. Conveniently, one can then apply the selected initialization protocol to the sensor.

[0009] The invention also includes apparatus for initializing an analyte sensor, said apparatus comprising: a disconnection timer configured to determine the amount of time that said analyte sensor has been disconnected from sensor electronics, an initialization protocol selector configured to select an initialization protocol based on said disconnection time, the initialization protocol selector being configured to select from the group comprising: (a) a first initialization scheme comprising a first series of voltage pulses, and (b) a second initialization scheme comprising a second series of voltage pulses, wherein the initialization protocol selector is configured to select the first initialization scheme if the disconnection time falls within a first time range and to select the second initialization scheme if the disconnection time falls within a second time range, said apparatus being configured to apply the selected initialization protocol to the analyte sensor.

[0010] The group of initialization protocols may further comprise or consist of (c) a third initialization scheme comprising the application of no voltage to the sensor, wherein the third initialization scheme is selected if the disconnection time is less than the first time range and the second time range.

[0011] It is possible to utilize different disconnection time ranges that, for example, can depend upon the specific context in which a sensor is disconnected from sensor electronics. The first time range can be, for example, greater than 120 minutes (e.g. a range of 120 minutes to at least 24 hours etc.). Similarly, the second time range can be, for example, between 10 and 120 minutes.

[0012] The method can preferably further comprise applying a stabilization voltage to the sensor, after applying the selected initialization voltage, for a first stabilization time. The method may further include determining whether the sensor is stable after applying the first stabilization voltage; and if the sensor is not stable, applying a second stabilization voltage to the sensor for a second stabilization time. Example stabilization time periods include times less than forty minutes, such as 10, 16, 20, and 26 minutes, or 30 minutes. The second stabilization time may be the same or different than the first stabilization time.

[0013] The invention may include calibrating the sensor after the stabilization of the sensor, if the sensor is stable. Calibration may include measuring blood glucose using a blood glucose meter and correlating the value found to the sensor measurements. The calibration of the sensor can preferably be performed only if the disconnection time falls within the first or second time range. Advantageously, if the sensor is not stable after a predetermined maximum stabilization time, the initialization protocol is ended so that a new sensor may be connected to the sensor electronics. The predetermined maximum stabilization period may be 30 minutes or more. Other predetermined maximum stabilization periods are also possible, such as 35 or 40 minutes.

[0014] Conveniently, determining a disconnection time includes measuring the current output of the sensor and comparing the measured output to a disconnection threshold value. One possible threshold value is 0.6 nA. An exemplary range of potential threshold values is 1-10 nA. Preferably, a timer records time of disconnection. The timer is preferably inbuilt in the program. The event of reconnection is detected when the current output is above a reconnection threshold, such as 4 nA.

[0015] The first initialization scheme preferably includes the application of at least two voltages for a first predetermined initialization time. The at least two voltages may be pulsed, stepped or switched voltages. They may be applied in a repetitive sequence or each may be applied only once. Similarly, the second initialization scheme preferably includes the application of at least two voltages for a second predetermined initialization time. The at least two voltages may be pulsed, stepped or switched voltages. They may be applied in a repetitive sequence or each may be applied only once. The predetermined second initialization time may be less than 30 minutes.

[0016] The invention may include a method or an apparatus for detecting hydration of the sensor. Hydration is preferably detected prior to applying the selected initiation protocol, and preferably includes applying a series of hydration pulses to the sensor for a first hydration time; recording the current response of the sensor during application of the series of hydration pulses; and comparing the current response to a predetermined hydration threshold. Application of the series of hydration pulses may be terminated if the current response reaches or exceeds the predetermined hydration threshold. Detecting hydration may further include applying a second series of hydration pulses to the sensor for a second hydration time if the current response does not reach the predetermined hydration threshold during the first predetermined hydration time. The predetermined hydration threshold may be 100 nA or 50 nA, for example. Example hydration pulses may be a series of 0 V and 2 V pulses, for example for 20 seconds or 2 minutes each.

[0017] The analyte sensing system preferably further comprises a monitoring device in communication with the electronics device, wherein the monitoring device includes circuitry to monitor the signals received from the analyte sensor

and to calculate the concentration of the analyte from the signals. The monitoring device may be connected directly to the sensor and/or sensor electronics or may receive data wirelessly. The sensor electronics may be part of the monitor or separate from the monitor.

BRIEF DESCRIPTION OF THE FIGURES

[0018] The invention will now be further described, by way of non-limitative example, with reference to the accompanying drawings, in which:

FIG. 1 provides a schematic of the well-known reaction between glucose and glucose oxidase. As shown in a stepwise manner, this reaction involves glucose oxidase (GOx), glucose and oxygen in water. In the reductive half of the reaction, two protons and electrons are transferred from 1-D-glucose to the enzyme yielding d-gluconolactone. In the oxidative half of the reaction, the enzyme is oxidized by molecular oxygen yielding hydrogen peroxide. The d-gluconolactone then reacts with water to hydrolyze the lactone ring and produce gluconic acid. In certain electrochemical sensors of the invention, the hydrogen peroxide produced by this reaction is oxidized at the working electrode ($H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$);
FIG. 2 provides a diagrammatic view of a typical layered analyte sensor configuration of the current invention;
FIG. 3 provides a perspective view illustrating a subcutaneous sensor insertion set, a telemetered characteristic monitor transmitter device, and a data receiving device exemplifying features of the invention;
FIG. 4 provides a flow chart illustrating selection of an initialization scheme according to an example of the invention;
FIG. 5 provides a flow chart illustrating an initialization scheme according to an example of the invention;
FIG. 6 provides a flow chart illustrating an initialization scheme according to an example of the invention;
FIG. 7 provides a flow chart illustrating an initialization scheme according to an example of the invention;
FIG. 8A provides a graph showing the potential (V) versus time (s) according to one example of the present invention;
FIG. 8B provides a graph showing the potential (V) versus time (s) according to one example of the present invention;
FIG. 9A provides a graph showing the signal response (iSig) when a sensor is reconnected to a processor after 2 hours of disconnection;
FIG. 9B provides a graph showing the signal response (iSig) when a sensor is reconnected to a processor after 2 hours of disconnection and initialized according to an example of the present invention;
FIG. 10 provides a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 11 provides a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 12 provides a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 13 is a graphical illustration of a hydration scheme according to an example of the invention;
FIG. 14 is a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 15 is a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 16 is a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 17 is a graphical illustration of an initialization scheme according to an example of the invention;
FIG. 18 is a graph showing a boxplot of recovery time for certain initialization schemes according to the present invention;
FIG. 19 is a graph showing a boxplot of recovery time based on the amount of time in an initialization scheme of the present invention;
FIG. 20 shows a schematic of a potentiostat that may be used to measure current according to the present invention. As shown in FIG. 20, a potentiostat 300 may include an op amp 310 that is connected in an electrical circuit so as to have two inputs: Vset and Vmeasured. As shown, Vmeasured is the measured value of the voltage between a reference electrode and a working electrode. Vset, on the other hand, is the optimally desired voltage across the working and reference electrodes. The current between the counter and reference electrode is measured, creating a current measurement (isig) that is output from the potentiostat.

DETAILED DESCRIPTION

[0019] Unless otherwise defined, all terms of art, notations and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. Many of the techniques and procedures described or referenced herein are well understood and commonly employed using conventional methodology by those skilled in the art. As appropriate, procedures involving the use of commercially available kits and reagents are generally carried out in accordance with manufacturer defined protocols and/or parameters unless otherwise noted. A number of terms are defined below.

[0020] It is to be understood that these examples are not limited to the particular methodology, protocol, apparatus and reagent described as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular examples only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0021] It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an oxidoreductase" includes a plurality of such oxidoreductases and equivalents thereof known to those skilled in the art, and so forth. All numbers recited in the specification and associated claims that refer to values that can be numerically characterized with a value other than a whole number (e.g. the concentration of a compound in a solution) are understood to be modified by the term "about".

[0022] 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 fluid such as 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 cases, the analyte for measurement by the sensing regions, devices, and methods is glucose. However, other analytes are contemplated as well, including but not limited to, lactate. Salts, sugars, proteins fats, vitamins and hormones naturally occurring in blood or interstitial fluids can constitute analytes in certain examples. The analyte can be naturally present in the biological fluid (i.e. endogenous) for example, a metabolic product, a hormone, an antigen, an antibody, and the like. Alternatively, the analyte can be introduced into the body (i.e. exogenous), 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. The metabolic products of drugs and pharmaceutical compositions are also contemplated analytes.

[0023] The term "sensor," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the portion or portions of an analyte-monitoring device that detects an analyte. The sensor typically includes an electrochemical cell that has a working electrode, a reference electrode, and optionally a counter electrode passing through and secured within the sensor body forming an electrochemically reactive surface at one location on the body, an electronic connection at another location on the body, and a membrane system affixed to the body and covering the electrochemically reactive surface. During general operation of the sensor, a biological sample (for example, blood or interstitial fluid), or a portion thereof, contacts (directly or after passage through one or more membranes or domains) an enzyme (for example, 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 level in the biological sample.

[0024] The terms "electrical potential" and "potential" as used herein, are broad terms and are used in their ordinary sense, including, without limitation, the electrical potential difference between two points in a circuit which is the cause of the flow of a current. The term "system noise," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, unwanted electronic or diffusion-related noise which can include Gaussian, motion-related, flicker, kinetic, or other white noise, for example.

[0025] As discussed in detail below, the invention includes the use of an electrochemical sensor that measures a concentration of an analyte of interest or a substance indicative of the concentration or presence of the analyte in fluid. The sensor can optionally be a continuous device, for example a subcutaneous, transdermal, or intravascular device. The device can optionally analyze a plurality of intermittent blood samples. The sensors disclosed herein can use 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. Typically, the sensor is of the type that senses a product or reactant of an enzymatic reaction between an analyte and an enzyme in the presence of oxygen as a measure of the analyte in vivo or in vitro. Such sensors typically comprise a membrane surrounding the enzyme through which an analyte migrates. The product can then be measured using electrochemical methods and thus the output of an electrode system functions as a measure of the analyte.

[0026] The invention disclosed herein includes sensors of the type used, for example, in subcutaneous or transcutaneous monitoring of blood glucose levels in a diabetic patient. A variety of implantable, electrochemical biosensors have been developed for the treatment of diabetes and other life-threatening diseases. Many existing sensor designs use some form of immobilized enzyme to achieve their bio-specificity. The invention described herein can be adapted and implemented with a wide variety of known electrochemical sensors, including for example, U.S. Patent Application No. 20050115832, U.S. Pat. Nos. 6,001,067, 6,702,857, 6,212,416, 6,119,028, 6,400,974, 6,595,919, 6,141,573, 6,122,536, 6,512,939 5,605,152, 4,431,004, 4,703,756, 6,514,718, 5,985,129, 5,390,691, 5,391, 250, 5,482,473, 5,299,571, 5,568,806, 5,494,562, 6,120,676, 6,542,765, 7,033,336 as well as PCT International Publication Numbers WO 01/58348, WO 04/021877, WO 03/034902, WO 03/035117, WO 03/035891, WO 03/023388, WO 03/022128, WO 03/022352, WO 03/023708, WO 03/036255, WO03/036310 WO 08/042,625, and WO 03/074107, and European Patent Application EP 1153571.

[0027] While the invention can include glucose and/or lactate sensors, the methods and apparatus disclosed herein can be adapted for use with any one of the wide variety of sensors known in the art. The analyte sensor elements,

architectures and methods for making and using these elements that are disclosed herein can be used to establish a variety of layered sensor structures. Such sensors of the invention can exhibit a surprising degree of flexibility and versatility, characteristics which allow a wide variety of sensor configurations to be designed to examine a wide variety of analyte species.

[0028] Typically according to the present invention, the transduction of the analyte concentration into a processable signal is by electrochemical means. These transducers may include any of a wide variety of amperometric, potentiometric, or conductimetric base sensors known in the art. Moreover, the microfabrication sensor techniques and materials of the instant invention may be applied to other types of transducers (e.g., acoustic wave sensing devices, thermistors, gas-sensing electrodes, field-effect transistors, optical and evanescent field wave guides, and the like) fabricated in a substantially nonplanar, or alternatively, a substantially planar manner. A useful discussion and tabulation of transducers which may be exploited in a biosensor as well as the kinds of analytical applications in which each type of transducer or biosensor, in general, may be utilized, is found in an article by Christopher R. Lowe in Trends in Biotech. 1984, 2(3), 59-65.

[0029] Specific aspects of the invention are discussed in detail in the following sections.

I. Typical Elements, Configurations and Analyte Sensor Examples of the Invention

A. Typical Architectures Found in Examples of the Invention

[0030] FIG. 2 illustrates a cross-section of a typical sensor example **100** of the present invention. This sensor example is formed from a plurality of components that are typically in the form of layers of various conductive and nonconductive constituents disposed on each other according to art accepted methods and/or the specific methods of the invention disclosed herein. The components of the sensor are typically characterized herein as layers because, for example, it allows for a facile characterization of the sensor structure shown in FIG. 2. Artisans will understand however that the sensor constituents can be combined such that multiple constituents form one or more heterogeneous layers. In this context, those of skill in the art will understand that the ordering of the layered constituents can be altered.

[0031] The example shown in FIG. 2 includes a base layer **102** to support the sensor **100.** The base layer **102** can be made of a material such as a metal and/or a ceramic and/or a polymeric substrate, which may be self-supporting or further supported by another material as is known in the art. The invention may include a conductive layer **104** which is disposed on and/or combined with the base layer **102.** Typically the conductive layer **104** comprises one or more electrodes. An operating sensor **100** typically includes a plurality of electrodes such as a working electrode, a counter electrode and a reference electrode. The invention may also include a plurality of working and/or counter and/or reference electrodes and/or one or more electrodes that performs multiple functions, for example one that functions as both as a reference and a counter electrode.

[0032] As discussed in detail below, the base layer **102** and/or conductive layer **104** can be generated using many known techniques and materials. Preferably, the electrical circuit of the sensor is defined by etching the disposed conductive layer **104** into a desired pattern of conductive paths. A typical electrical circuit for the sensor **100** comprises two or more adjacent conductive paths with regions at a proximal end to form contact pads and regions at a distal end to form sensor electrodes. An electrically insulating cover layer **106** such as a polymer coating can be disposed on portions of the sensor **100.** Acceptable polymer coatings for use as the insulating protective cover layer **106** can include, but are not limited to, non-toxic biocompatible polymers such as silicone compounds, polyimides, biocompatible solder masks, epoxy acrylate copolymers, or the like. In the sensors of the present invention, one or more exposed regions or apertures **108** can be made through the cover layer **106** to open the conductive layer **104** to the external environment and to, for example, allow an analyte such as glucose to permeate the layers of the sensor and be sensed by the sensing elements. Apertures **108** can be formed by a number of techniques, including laser ablation, tape masking, chemical milling or etching or photolithographic development or the like. During manufacture, a secondary photoresist can also be applied to the protective layer **106** to define the regions of the protective layer to be removed to form the aperture(s) **108.** The exposed electrodes and/or contact pads can also undergo secondary processing (e.g. through the apertures **108**), such as additional plating processing, to prepare the surfaces and/or strengthen the conductive regions.

[0033] In the sensor configuration shown in FIG. 2, an analyte sensing layer **110** (which is typically a sensor chemistry layer, meaning that materials in this layer undergo a chemical reaction to produce a signal that can be sensed by the conductive layer) is disposed on one or more of the exposed electrodes of the conductive layer **104.** Typically, the analyte sensing layer **110** is an enzyme layer. Most typically, the analyte sensing layer **110** comprises an enzyme capable of producing and/or utilizing oxygen and/or hydrogen peroxide, for example the enzyme glucose oxidase. Optionally the enzyme in the analyte sensing layer is combined with a second carrier protein such as human serum albumin, bovine serum albumin or the like. Preferably, an oxidoreductase enzyme such as glucose oxidase in the analyte sensing layer **110** reacts with glucose to produce hydrogen peroxide, a compound which then modulates a current at an electrode. As this modulation of current depends on the concentration of hydrogen peroxide, and the concentration of hydrogen

peroxide correlates to the concentration of glucose, the concentration of glucose can be determined by monitoring this modulation in the current. The hydrogen peroxide is preferably oxidized at a working electrode which is an anode (also termed herein the anodic working electrode), with the resulting current being proportional to the hydrogen peroxide concentration. Such modulations in the current caused by changing hydrogen peroxide concentrations can by monitored by any one of a variety of sensor detector apparatuses such as a universal sensor amperometric biosensor detector or one of the other variety of similar devices known in the art such as glucose monitoring devices produced by Medtronic Diabetes.

[0034] The analyte sensing layer **110** can be applied over portions of the conductive layer or over the entire region of the conductive layer. Typically the analyte sensing layer **110** is disposed on the working electrode which can be the anode or the cathode. Optionally, the analyte sensing layer **110** is also disposed on a counter and/or reference electrode. While the analyte sensing layer **110** can be up to about 1000 microns (μm) in thickness, typically the analyte sensing layer is relatively thin as compared to those found in sensors previously described in the art, and is for example, typically less than 1, 0.5, 0.25 or 0.1 microns in thickness. As discussed in detail below, some methods for generating a thin analyte sensing layer **110** include brushing the layer onto a substrate (e.g. the reactive surface of a platinum black electrode), as well as spin coating processes, dip and dry processes, low shear spraying processes, ink-jet printing processes, silk screen processes and the like. Brushing may be used to: (1) allow for a precise localization of the layer; and (2) push the layer deep into the architecture of the reactive surface of an electrode (e.g. platinum black produced by an electrodeposition process).

[0035] Typically, the analyte sensing layer **110** is coated and or disposed next to one or more additional layers. Optionally, the one or more additional layers includes a protein layer **116** disposed upon the analyte sensing layer **110.** Typically, the protein layer **116** comprises a protein such as human serum albumin, bovine serum albumin or the like. Typically, the protein layer **116** comprises human serum albumin. An additional layer may preferably include an analyte modulating layer **112** that is disposed above the analyte sensing layer **110** to regulate analyte contact with the analyte sensing layer **110.** For example, the analyte modulating membrane layer **112** can comprise a glucose limiting membrane, which regulates the amount of glucose that contacts an enzyme such as glucose oxidase that is present in the analyte sensing layer. Such glucose limiting membranes can be made from a wide variety of materials known to be suitable for such purposes, e.g., silicone compounds such as polydimethyl siloxanes, polyurethanes, polyurea cellulose acetates, Nafion, polyester sulfonic acids (e.g. Kodak AQ), hydrogels or any other suitable hydrophilic membranes known to those skilled in the art.

[0036] The architecture or thickness of a sensor layer can conveniently be used to optimize a property of the sensor. For example, the elongated base layer can be comprised of a dielectric or polyimide ceramic material that is at least 100 microns thick. The analyte modulating layer may be at least 6, 7, 8, 9, 10, 15, 20, 25 or 30 microns thick. The invention may use a thick layer (e.g. 25 or 30 microns) of an analyte modulating layer because this thick layer is observed to optimize the linearity of an analyte signal over a range of signals (e.g. glucose concentration). Such thick layers have further properties that are desirable, for example a longer analyte modulating layer lifetime (e.g. due to the extra material), a property that makes them particularly suited for long term sensors.

[0037] An adhesion promoter layer **114** may be disposed between the analyte modulating layer **112** and the analyte sensing layer **110** as shown in FIG. 2 in order to facilitate their contact and/or adhesion. An adhesion promoter layer **114** may be disposed between the analyte modulating layer **112** and the protein layer **116** as shown in FIG. 2 in order to facilitate their contact and/or adhesion. The adhesion promoter layer **114** can be made from any one of a wide variety of materials known in the art to facilitate the bonding between such layers. Typically, the adhesion promoter layer **114** comprises a silane compound. Alternatively, protein or like molecules in the analyte sensing layer **110** can be sufficiently crosslinked or otherwise prepared to allow the analyte modulating membrane layer **112** to be disposed in direct contact with the analyte sensing layer **110** in the absence of an adhesion promoter layer **114.**

[0038] The sensor can be designed to include additional layers such as an interference rejection layer discussed below.

B. Typical Analyte Sensor Constituents Used in Examples of the Invention

[0039] The following disclosure provides examples of typical elements/constituents used in sensor examples of the invention. While these elements can be described as discrete units (e.g. layers), those of skill in the art understand that sensors can be designed to contain elements having a combination of some or all of the material properties and/or functions of the elements/constituents discussed below (e.g. an element that serves both as a supporting base constituent and/or a conductive constituent and/or a matrix for the analyte sensing constituent and which further functions as an electrode in the sensor). Those in the art understand that these thin film analyte sensors can be adapted for use in a number of sensor systems such as those described below.

Base Constituent

[0040] Sensors of the invention typically include a base constituent (see, e.g. element 102 in FIG. 2). The term "base constituent" is used herein according to art accepted terminology and refers to the constituent in the apparatus that typically provides a supporting matrix for the plurality of constituents that are stacked on top of one another and comprise the functioning sensor. In one form, the base constituent comprises a thin film sheet of insulative (e.g. electrically insulative and/or water impermeable) material. This base constituent can be made of a wide variety of materials having desirable qualities such as dielectric properties, water impermeability and hermeticity. Some materials include metallic, and/or ceramic and/or polymeric substrates or the like.

[0041] The base constituent may be self-supporting or further supported by another material as is known in the art. In the sensor configuration shown in FIG. 2, the base constituent **102** may comprise a ceramic. Alternatively, the base constituent may comprise a polymeric material such as a polyimide. The ceramic base may comprise a composition that is predominantly Al_2O_3 (e.g. 96%). The use of alumina as an insulating base constituent for use with implantable devices is disclosed in U.S. Pat. Nos. 4,940,858, 4,678,868 and 6,472,122. The base constituents of the invention can further include other elements known in the art, for example hermetical vias (see, e.g. WO 03/023388). Depending upon the specific sensor design, the base constituent can be relatively thick constituent (e.g. thicker than 50, 100, 200, 300, 400, 500 or 1000 microns). Alternatively, one can utilize a nonconductive ceramic, such as alumina, in thin constituents, e.g., less than about 30 microns.

Conductive Constituent

[0042] The electrochemical sensors of the invention typically include a conductive constituent disposed upon the base constituent that includes at least one electrode for contacting an analyte or its byproduct (e.g. oxygen and/or hydrogen peroxide) to be assayed (see, e.g. element **104** in FIG. 2). The term "conductive constituent" is used herein according to art accepted terminology and refers to electrically conductive sensor elements such as electrodes which are capable of measuring a detectable signal and conducting this to a detection apparatus. An illustrative example of this is a conductive constituent that can measure an increase or decrease in current in response to exposure to a stimuli such as the change in the concentration of an analyte or its byproduct as compared to a reference electrode that does not experience the change in the concentration of the analyte, a coreactant (e.g. oxygen) used when the analyte interacts with a composition (e.g. the enzyme glucose oxidase) present in analyte sensing constituent **110** or a reaction product of this interaction (e.g. hydrogen peroxide). Illustrative examples of such elements include electrodes which are capable of producing variable detectable signals in the presence of variable concentrations of molecules such as hydrogen peroxide or oxygen. Typically one of these electrodes in the conductive constituent is a working electrode, which can be made from non-corroding metal or carbon. A carbon working electrode may be vitreous or graphitic and can be made from a solid or a paste. A metallic working electrode may be made from platinum group metals, including palladium or gold, or a non-corroding metallically conducting oxide, such as ruthenium dioxide. Alternatively the electrode may comprise a silver/silver chloride electrode composition. The working electrode may be a wire or a thin conducting film applied to a substrate, for example, by coating or printing. Typically, only a portion of the surface of the metallic or carbon conductor is in electrolytic contact with the analyte-containing solution. This portion is called the working surface of the electrode. The remaining surface of the electrode is typically isolated from the solution by an electrically insulating cover constituent **106.** Examples of useful materials for generating this protective cover constituent **106** include polymers such as polyimides, polytetrafluoroethylene, polyhexafluoropropylene and silicones such as polysiloxanes.

[0043] In addition to the working electrode, the analyte sensors of the invention typically include a reference electrode or a combined reference and counter electrode (also termed a quasi-reference electrode or a counter/reference electrode). If the sensor does not have a counter/reference electrode then it may include a separate counter electrode, which may be made from the same or different materials as the working electrode. Typical sensors of the present invention have one or more working electrodes and one or more counter, reference, and/or counter/reference electrodes. The sensor of the present invention may have two, three or four or more working electrodes. These working electrodes in the sensor may be integrally connected or they may be kept separate. Optionally, the electrodes can be disposed on a single surface or side of the sensor structure. Alternatively, the electrodes can be disposed on a multiple surfaces or sides of the sensor structure (and can for example be connected by vias through the sensor material(s) to the surfaces on which the electrodes are disposed). The reactive surfaces of the electrodes can be of different relative areas/sizes, for example a 1X reference electrode, a 2.6X working electrode and a 3.6X counter electrode.

[0044] Typically for in vivo use, sensors of the present invention are implanted subcutaneously in the skin of a mammal, such as a person, for direct contact with the body fluids of the mammal, such as blood. Alternatively the sensors can be implanted into other regions within the body of a mammal such as in the intraperotineal space. When multiple working electrodes are used, they may be implanted together or at different positions in the body. The counter, reference, and/or counter/reference electrodes may also be implanted either proximate to the working electrode(s) or at other positions

within the body of the mammal.

[0045] The invention includes sensors comprising electrodes constructed from nanostructured materials. As used herein, a "nanostructured material" is an object manufactured to have at least one dimension smaller than 100 nm. Examples include, but are not limited to, single-walled nanotubes, double-walled nanotubes, multi-walled nanotubes, bundles of nanotubes, fullerenes, cocoons, nanowires, nanofibres, onions and the like.

Interference Rejection Constituent

[0046] The electrochemical sensors of the invention optionally include an interference rejection constituent disposed between the surface of the electrode and the environment to be assayed. In particular, the sensor may rely on the oxidation and/or reduction of hydrogen peroxide generated by enzymatic reactions on the surface of a working electrode at a constant potential applied. Because amperometric detection based on direct oxidation of hydrogen peroxide requires a relatively high oxidation potential, sensors employing this detection scheme may suffer interference from oxidizable species that are present in biological fluids such as ascorbic acid, uric acid and acetaminophen. In this context, the term "interference rejection constituent" is used herein according to art accepted terminology and refers to a coating or membrane in the sensor that functions to inhibit spurious signals generated by such oxidizable species which interfere with the detection of the signal generated by the analyte to be sensed. Certain interference rejection constituents function via size exclusion (e.g. by excluding interfering species of a specific size). Examples of interference rejection constituents include one or more layers or coatings of compounds such as hydrophilic polyurethanes, cellulose acetate (including cellulose acetate incorporating agents such as poly(ethylene glycol), polyethersulfones, polytetra-fluoroethylenes, the perfluoronated ionomer Nafion™, polyphenylenediamine, epoxy and the like. The interference rejection constituents can be comprised of a NAFION (a sulfonated tetrafluorethylene copolymer having the molecular formula C7HF13O5S. C2F4, CAS number [31175-20-9]) and/or a cellulose acetate composition. Illustrative discussions of such interference rejection constituents are found for example in Ward et al., Biosensors and Bioelectronics 17 (2002) 181-189 and Choi et al., Analytical Chimica Acta 461 (2002) 251-260. Other interference rejection constituents include for example those observed to limit the movement of compounds based upon a molecular weight range, for example cellulose acetate as disclosed for example in U.S. Pat. No. 5,755,939.

[0047] An interference rejection membrane (IRM) may comprise NAFION and its effectiveness at inhibiting interfering signals that can be generated by acetominophenol in an amperometric sensor. Typically, an IRM is disposed under an analyte sensing layer (e.g. one comprising glucose oxidase). The IRM can be disposed between the reactive surface of an electrode and an analyte sensing layer. Relatedly, the invention includes methods for inhibiting one or more signals generated by an interfering compound (e.g. by using an interference rejection layer).

Analyte Sensing Constituent

[0048] The electrochemical sensors of the invention include an analyte sensing constituent disposed on the electrodes of the sensor (see, e.g. element **110** in FIG. 2). The term "analyte sensing constituent" is used herein according to art accepted terminology and refers to a constituent comprising a material that is capable of recognizing or reacting with an analyte whose presence is to be detected by the analyte sensor apparatus. Typically this material in the analyte sensing constituent produces a detectable signal after interacting with the analyte to be sensed, typically via the electrodes of the conductive constituent. In this regard the analyte sensing constituent and the electrodes of the conductive constituent work in combination to produce the electrical signal that is read by an apparatus associated with the analyte sensor. Typically, the analyte sensing constituent comprises an oxidoreductase enzyme capable of reacting with and/or producing a molecule whose change in concentration can be measured by measuring the change in the current at an electrode of the conductive constituent (e.g. oxygen and/or hydrogen peroxide), for example the enzyme glucose oxidase. An enzyme capable of producing a molecule such as hydrogen peroxide can be disposed on the electrodes according to a number of processes known in the art. The analyte sensing constituent can coat all or a portion of the various electrodes of the sensor. In this context, the analyte sensing constituent may coat the electrodes to an equivalent degree. Alternatively the analyte sensing constituent may coat different electrodes to different degrees, with for example the coated surface of the working electrode being larger than the coated surface of the counter and/or reference electrode.

[0049] Typically, sensors of the invention utilize an enzyme (e.g. glucose oxidase) that has been combined with a second protein (e.g. albumin) in a fixed ratio (e.g. one that is typically optimized for glucose oxidase stabilizing properties) and then applied on the surface of an electrode to form a thin enzyme constituent. Typically, the analyte sensing constituent comprises a GOx and HSA mixture. When the analyte sensing constituent has GOx, the GOx reacts with glucose present in the sensing environment (e.g. the body of a mammal) and generates hydrogen peroxide according to the reaction shown in FIG. 1, wherein the hydrogen peroxide so generated is anodically detected at the working electrode in the conductive constituent.

[0050] As noted above, the enzyme and the second protein (e.g. an albumin) are typically treated to form a crosslinked

matrix (e.g. by adding a cross-linking agent to the protein mixture). As is known in the art, crosslinking conditions may be manipulated to modulate factors such as the retained biological activity of the enzyme, its mechanical and/or operational stability. Illustrative crosslinking procedures are described in U.S. patent application Ser. No. 10/335,506 and PCT publication WO 03/035891. For example, an amine cross-linking reagent, such as, but not limited to, glutaraldehyde, can be added to the protein mixture. The addition of a cross-linking reagent to the protein mixture creates a protein paste. The concentration of the cross-linking reagent to be added may vary according to the concentration of the protein mixture. While glutaraldehyde is an illustrative crosslinking reagent, other cross-linking reagents may also be used or may be used in place of glutaraldehyde. Other suitable cross-linkers also may be used, as will be evident to those skilled in the art.

[0051] The GOx and/or carrier protein concentration may vary. For example, the GOx concentration may be within the range of approximately 50 mg/ml (approximately 10,000 U/ml) to approximately 700 mg/ml (approximately 150,000 U/ml). Typically the GOx concentration is about 115 mg/ml (approximately 22,000 U/ml). The HSA concentration may vary between about 0.5%-30% (w/v), preferably depending on the GOx concentration. Typically the HSA concentration is about 1-10% w/v, and most typically is about 5% w/v. Collagen or BSA or other structural proteins used in these contexts can be used instead of or in addition to HSA. Although GOx is discussed as an illustrative enzyme in the analyte sensing constituent, other proteins and/or enzymes may also be used or may be used in place of GOx, including, but not limited to glucose dehydrogenase or hexokinase, hexose oxidase, lactate oxidase, and the like. Other proteins and/or enzymes may also be used, as will be evident to those skilled in the art. Moreover, although HSA is employed in the example, other structural proteins, such as BSA, collagens or the like, could be used instead of or in addition to HSA.

[0052] As noted above, the analyte sensing constituent may include a composition (e.g. glucose oxidase) capable of producing a signal (e.g. a change in oxygen and/or hydrogen peroxide concentrations) that can be sensed by the electrically conductive elements (e.g. electrodes which sense changes in oxygen and/or hydrogen peroxide concentrations). However, other useful analyte sensing constituents can be formed from any composition that is capable of producing a detectable signal that can be sensed by the electrically conductive elements after interacting with a target analyte whose presence is to be detected. The composition may comprise an enzyme that modulates hydrogen peroxide concentrations upon reaction with an analyte to be sensed. Alternatively, the composition may comprise an enzyme that modulates oxygen concentrations upon reaction with an analyte to be sensed. In this context, a wide variety of enzymes that either use or produce hydrogen peroxide and/or oxygen in a reaction with a physiological analyte are known in the art and these enzymes can be readily incorporated into the analyte sensing constituent composition. A variety of other enzymes known in the art can produce and/or utilize compounds whose modulation can be detected by electrically conductive elements such as the electrodes that are incorporated into the sensor designs described herein. Such enzymes include for example, enzymes specifically described in Table 1, pages 15-29 and/or Table 18, pages 111-112 of Protein Immobilization: Fundamentals and Applications (Bioprocess Technology, Vol 14) by Richard F. Taylor (Editor) Publisher: Marcel Dekker; Jan. 7, 1991).

[0053] Other useful analyte sensing constituents can be formed to include antibodies whose interaction with a target analyte is capable of producing a detectable signal that can be sensed by the electrically conductive elements after interacting with the target analyte whose presence is to be detected. Examples of anti-body-based apparatuses are found in U.S. Pat. Nos. 5,427,912, 5,149,630, 6,410,251, and 4,402,819, which are incorporated herein by reference. For related disclosures, see also U.S. Pat. Nos. 6,703,210, 5,981,203, 5,705,399 and 4,894,253.

[0054] In addition to enzymes and antibodies, other exemplary materials for use in the analyte sensing constituents of the sensors disclosed herein include polymers that bind specific types of cells or cell components (e.g. polypeptides, carbohydrates and the like); single-strand DNA; antigens and the like. The detectable signal can be, for example, an optically detectable change, such as a color change or a visible accumulation of the desired analyte (e.g., cells). Sensing elements can also be formed from materials that are essentially non-reactive (i.e., controls). The foregoing alternative sensor elements are beneficially included, for example, in sensors for use in cell-sorting assays and assays for the presence of pathogenic organisms, such as viruses (HIV, hepatitis-C, etc.), bacteria, protozoa and the like.

[0055] Also contemplated are analyte sensors that measure an analyte that is present in the external environment and that can in itself produce a measurable change in current at an electrode. In sensors measuring such analytes, the analyte sensing constituent can be optional.

Protein Constituent

[0056] The electrochemical sensors of the invention optionally include a protein constituent disposed between the analyte sensing constituent and the analyte modulating constituent (see, e.g. element **116** in FIG. 2). The term "protein constituent" is used herein according to art accepted terminology and refers to constituent containing a carrier protein or the like that is selected for compatibility with the analyte sensing constituent and/or the analyte modulating constituent. Typically, the protein constituent comprises an albumin such as human serum albumin. The HSA concentration may vary between about 0.5%-30% (w/v). Typically the HSA concentration is about 1-10% w/v, and most typically is about

5% w/v. Collagen or BSA or other structural proteins used in these contexts can be used instead of or in addition to HSA. This constituent is typically crosslinked on the analyte sensing constituent according to art accepted protocols.

Adhesion Promoting Constituent

[0057] The electrochemical sensors of the invention can include one or more adhesion promoting (AP) constituents (see, e.g. element **114** in FIG. 2). The term "adhesion promoting constituent" is used herein according to art accepted terminology and refers to a constituent that includes materials selected for their ability to promote adhesion between adjoining constituents in the sensor. Typically, the adhesion promoting constituent is disposed between the analyte sensing constituent and the analyte modulating constituent. Typically, the adhesion promoting constituent is disposed between the optional protein constituent and the analyte modulating constituent. The adhesion promoter constituent can be made from any one of a wide variety of materials known in the art to facilitate the bonding between such constituents and can be applied by any one of a wide variety of methods known in the art. Typically, the adhesion promoter constituent comprises a silane compound such as γ-aminopropyltrimethoxysilane.

[0058] The use of silane coupling reagents, especially those of the formula $R'Si(OR)_3$ in which R' is typically an aliphatic group with a terminal amine and R is a lower alkyl group, to promote adhesion is known in the art (see, e.g. U.S. Pat. No. 5,212,050). For example, chemically modified electrodes in which a silane such as γ-aminopropyltriethoxysilane and glutaraldehyde were used in a step-wise process to attach and to co-crosslink bovine serum albumin (BSA) and glucose oxidase (GOx) to the electrode surface are well known in the art (see, e.g. Yao, T. Analytica Chim. Acta 1983, 148, 27-33).

[0059] The adhesion promoting constituent further may comprise one or more compounds that can also be present in an adjacent constituent such as the polydimethyl siloxane (PDMS) compounds that serves to limit the diffusion of analytes such as glucose through the analyte modulating constituent. The formulation may comprise 0.5-20% PDMS, typically 5-15% PDMS, and most typically 10% PDMS. The adhesion promoting constituent is preferably crosslinked within the layered sensor system and correspondingly includes an agent selected for its ability to crosslink a moiety present in a proximal constituent such as the analyte modulating constituent. The adhesion promoting constituent preferably includes an agent selected for its ability to crosslink an amine or carboxyl moiety of a protein present in a proximal constituent such a the analyte sensing constituent and/or the protein constituent and or a siloxane moiety present in a compound disposed in a proximal layer such as the analyte modulating layer. Optionally, a first compound in the adhesion promoting layer is crosslinked to a second compound in the analyte sensing layer.

Analyte Modulating Constituent

[0060] The electrochemical sensors of the invention include an analyte modulating constituent disposed on the sensor (see, e.g. element **112** in FIG. 2). The term "analyte modulating constituent" is used herein according to art accepted terminology and refers to a constituent that typically forms a membrane on the sensor that operates to modulate the diffusion of one or more analytes, such as glucose, through the constituent. The analyte modulating constituent is preferably an analyte-limiting membrane which operates to prevent or restrict the diffusion of one or more analytes, such as glucose, through the constituents. The analyte-modulating constituent may operate to facilitate the diffusion of one or more analytes, through the constituents. Optionally such analyte modulating constituents can be formed to prevent or restrict the diffusion of one type of molecule through the constituent (e.g. glucose), while at the same time allowing or even facilitating the diffusion of other types of molecules through the constituent (e.g. O_2).

[0061] With respect to glucose sensors, in known enzyme electrodes, glucose and oxygen from blood, as well as some interferants, such as ascorbic acid and uric acid, diffuse through a primary membrane of the sensor. As the glucose, oxygen and interferants reach the analyte sensing constituent, an enzyme, such as glucose oxidase, catalyzes the conversion of glucose to hydrogen peroxide and gluconolactone. The hydrogen peroxide may diffuse back through the analyte modulating constituent, or it may diffuse to an electrode where it can be reacted to form oxygen and a proton to produce a current that is proportional to the glucose concentration. The sensor membrane assembly serves several functions, including selectively allowing the passage of glucose therethrough. In this context, an illustrative analyte modulating constituent is a semi-permeable membrane which permits passage of water, oxygen and at least one selective analyte and which has the ability to absorb water, the membrane having a water soluble, hydrophilic polymer.

[0062] A variety of illustrative analyte modulating compositions are known in the art and are described for example in U.S. Pat. Nos. 6,319,540, 5,882,494, 5,786,439 5,777,060, 5,771,868 and 5,391,250. The hydrogels described therein are particularly useful with a variety of implantable devices for which it is advantageous to provide a surrounding water constituent. The analyte modulating composition preferably includes PDMS. The analyte modulating constituent may include an agent selected for its ability to crosslink a siloxane moiety present in a proximal constituent. Relatedly, the adhesion promoting constituent may include an agent selected for its ability to crosslink an amine or carboxyl moiety of a protein present in a proximal constituent.

[0063] A hydrophilic analyte modulating layer is preferably coated over at least 50, 75% or 100% of the reactive surface of an electrode (e.g. an electrically conductive wire).

Cover Constituent

[0064] The electrochemical sensors of the invention may include one or more cover constituents which are typically electrically insulating protective constituents (see, e.g. element **106** in FIG. 2). Typically, such cover constituents can be in the form of a coating, sheath or tube and are disposed on at least a portion of the analyte modulating constituent. Acceptable polymer coatings for use as the insulating protective cover constituent can include, but are not limited to, non-toxic biocompatible polymers such as silicone compounds, polyimides, biocompatible solder masks, epoxy acrylate copolymers, or the like. Further, these coatings can be photo-imageable to facilitate photolithographic forming of apertures through to the conductive constituent. A typical cover constituent comprises spun on silicone. As is known in the art, this constituent can be a commercially available RTV (room temperature vulcanized) silicone composition. A typical chemistry in this context is polydimethyl siloxane (acetoxy based).

C. Typical Analyte Sensor System Examples of the Invention

[0065] The sensor elements and sensors can be operatively coupled to a variety of other systems elements typically used with analyte sensors (e.g. structural elements such as piercing members, insertion sets and the like as well as electronic components such as processors, monitors, medication infusion pumps and the like), for example to adapt them for use in various contexts (e.g. implantation within a mammal). The invention includes a method of monitoring a physiological characteristic of a user that includes an input element capable of receiving a signal from a sensor that is based on a sensed physiological characteristic value of the user, and a processor for analyzing the received signal. Typically, the processor determines a dynamic behavior of the physiological characteristic value and provides an observable indicator based upon the dynamic behavior of the physiological characteristic value so determined. The physiological characteristic value can be a measure of the concentration of blood glucose in the user. The process of analyzing the received signal and determining a dynamic behavior may include repeatedly measuring the physiological characteristic value to obtain a series of physiological characteristic values in order to, for example, incorporate comparative redundancies into a sensor apparatus in a manner designed to provide confirmatory information on sensor function, analyte concentration measurements, the presence of interferences and the like.

[0066] The invention includes devices which display data from measurements of a sensed physiological characteristic (e.g. blood glucose concentrations) in a manner and format tailored to allow a user of the device to easily monitor and, if necessary, modulate the physiological status of that characteristic (e.g. modulation of blood glucose concentrations via insulin administration). The invention includes a device comprising a sensor input capable of receiving a signal from a sensor, the signal being based on a sensed physiological characteristic value of a user; a memory for storing a plurality of measurements of the sensed physiological characteristic value of the user from the received signal from the sensor; and a display for presenting a text and/or graphical representation of the plurality of measurements of the sensed physiological characteristic value (e.g. text, a line graph or the like, a bar graph or the like, a grid pattern or the like or a combination thereof). Typically, the graphical representation displays real time measurements of the sensed physiological characteristic value. Such devices can be used in a variety of contexts, for example in combination with other medical apparatuses. The device can be used in combination with at least one other medical device (e.g. a glucose sensor).

[0067] The invention may provide a glucose sensor, a transmitter and pump receiver and a glucose meter. In this system, radio signals from the transmitter can be sent to the pump receiver every 5 minutes to provide providing real-time sensor glucose (SG) values. Values/graphs are displayed on a monitor of the pump receiver so that a user can self monitor blood glucose and deliver insulin using their own insulin pump. Typically the device disclosed herein communicates with a second medical device via a wired or wireless connection. Wireless communication can include for example the reception of emitted radiation signals as occurs with the transmission of signals via RF telemetry, infrared transmissions, optical transmission, sonic and ultrasonic transmissions and the like. Optionally, the device is an integral part of a medication infusion pump (e.g. an insulin pump). Typically in such devices, the physiological characteristic values include a plurality of measurements of blood glucose.

[0068] FIG. 3 provides a perspective view of one generalized example of subcutaneous sensor insertion system and a block diagram of a sensor electronics device according to one illustrative example of the invention. Additional elements typically used with such sensor system examples are disclosed for example in U.S. Patent Application No. 20070163894. FIG. 3 provides a perspective view of a telemetered characteristic monitor system **1,** including a subcutaneous sensor set **10** provided for subcutaneous placement of an active portion of a flexible sensor **12,** or the like, at a selected site in the body of a user. The subcutaneous or percutaneous portion of the sensor set **10** includes a hollow, slotted insertion needle **14** having a sharpened tip **44,** and a cannula **16.** Inside the cannula **16** is a sensing portion **18** of the sensor **12**

to expose one or more sensor electrodes **20** to the user's bodily fluids through a window **22** formed in the cannula **16.** The sensing portion **18** is joined to a connection portion **24** that terminates in conductive contact pads, or the like, which are also exposed through one of the insulative layers. The connection portion **24** and the contact pads are generally adapted for a direct wired electrical connection to a suitable monitor **200** coupled to a display **214** for monitoring a user's condition in response to signals derived from the sensor electrodes **20.** The connection portion **24** may be conveniently connected electrically to the monitor **200** or a characteristic monitor transmitter **100** by a connector block **28** (or the like) as shown and described in U.S. Pat. No. 5,482,473, entitled FLEX CIRCUIT CONNECTOR. Typically, a contact pad and an electrode are at least, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 millimeters apart.

[0069] As shown in FIG. 3, subcutaneous sensor set **10** may be configured or formed to work with either a wired or a wireless characteristic monitor system. The proximal part of the sensor **12** is mounted in a mounting base **30** adapted for placement onto the skin of a user. The mounting base **30** can be a pad having an underside surface coated with a suitable pressure sensitive adhesive layer **32,** with a peel-off paper strip **34** normally provided to cover and protect the adhesive layer **32,** until the sensor set **10** is ready for use. The mounting base **30** may include upper and lower layers **36** and **38,** with the connection portion **24** of the flexible sensor **12** being sandwiched between the layers **36** and **38.** The connection portion **24** may have a forward section joined to the active sensing portion **18** of the sensor **12,** which is folded angularly to extend downwardly through a bore **40** formed in the lower base layer **38.** Optionally, the adhesive layer **32** (or another portion of the apparatus in contact with in vivo tissue) includes an anti-inflammatory agent to reduce an inflammatory response and/or anti-bacterial agent to reduce the chance of infection. The insertion needle **14** is preferably adapted for slide-fit reception through a needle port **42** formed in the upper base layer **36** and through the lower bore **40** in the lower base layer **38.** After insertion, the insertion needle **14** can be withdrawn to leave the cannula **16** with the sensing portion **18** and the sensor electrodes **20** in place at the selected insertion site. The telemetered characteristic monitor transmitter **100** is preferably coupled to a sensor set **10** by a cable **102** through a connector **104** that is electrically coupled to the connector block **28** of the connector portion **24** of the sensor set **10.**

[0070] In the example shown in FIG. 3, the telemetered characteristic monitor **100** includes a housing **106** that supports a printed circuit board **108,** batteries **110,** antenna **112,** and the cable **102** with the connector **104.** The housing **106** is preferably formed from an upper case **114** and a lower case **116** that are sealed with an ultrasonic weld to form a waterproof (or resistant) seal to permit cleaning by immersion (or swabbing) with water, cleaners, alcohol or the like. The upper and lower case **114** and **116** can be formed from a medical grade plastic. However, alternatively, the upper case **114** and lower case **116** may be connected together by other methods, such as snap fits, sealing rings, RTV (silicone sealant) and bonded together, or the like, or formed from other materials, such as metal, composites, ceramics, or the like. The separate case can optionally be eliminated and the assembly can be simply potted in epoxy or other moldable materials that is compatible with the electronics and reasonably moisture resistant. As shown, the lower case **116** may have an underside surface coated with a suitable pressure sensitive adhesive layer **118,** with a peel-off paper strip **120** normally provided to cover and protect the adhesive layer **118,** until the sensor set telemetered characteristic monitor transmitter **100** is ready for use.

[0071] As shown in FIG. 3, the subcutaneous sensor set **10** facilitates accurate placement of a flexible thin film electrochemical sensor **12** of the type used for monitoring specific blood parameters representative of a user's condition. The sensor **12** monitors glucose levels in the body, and may be used in conjunction with automated or semi-automated medication infusion pumps of the external or implantable type as described in U.S. Pat. No. 4,562,751; 4,678,408; 4,685,903 or 4,573,994, to control delivery of insulin to a diabetic patient.

[0072] As shown in FIG. 3, the sensor electrodes **10** may be used in a variety of sensing applications and may be configured in a variety of ways. For example, the sensor electrodes **10** may be used in physiological parameter sensing applications in which some type of biomolecule is used as a catalytic agent. For example, the sensor electrodes **10** may be used in a glucose and oxygen sensor having a glucose oxidase enzyme catalyzing a reaction with the sensor electrodes **20.** The sensor electrodes **10,** along with a biomolecule or some other catalytic agent, may be placed in a human body in a vascular or non-vascular environment. For example, the sensor electrodes **20** and biomolecule may be placed in a vein and be subjected to a blood stream, or may be placed in a subcutaneous or peritoneal region of the human body.

[0073] As shown in FIG. 3, the monitor of sensor signals **200** may also be referred to as a sensor electronics device **200.** The monitor **200** may include a power source, a sensor interface, processing electronics (i.e. a processor), and data formatting electronics. The monitor **200** may be coupled to the sensor set **10** by a cable **102** through a connector that is electrically coupled to the connector block **28** of the connection portion **24.** In an alternative example the cable may be omitted. The monitor **200** may include an appropriate connector for direct connection to the connection portion **104** of the sensor set **10.** The sensor set **10** may be modified to have the connector portion **104** positioned at a different location, e.g., on top of the sensor set to facilitate placement of the monitor **200** over the sensor set.

D. Examples of the Invention and Associated Characteristics

[0074] The invention disclosed herein focuses on (preferably implantable) analyte sensors and sensor systems that

are designed to include elements and/or configurations of elements that facilitate sensor initialization and/or start-up times (preferably in vivo), for example, the time that it takes for a sensor to settle into its environment (e.g. become appropriately hydrated), and/or begin to sense analyte concentrations and/or start transmitting meaningful information to a user. As discussed further herein, it is known in the art that the amount time required for sensor initialization and/or start-up prior to its use can be relatively long (e.g. in amperometric glucose sensors, the sensor start-up initialization times can range from 2 to 10 hours), a factor which can hinder the use of such sensors in the administration of medical care. For example, in hospital settings, a relatively long sensor initialization and/or start-up period can delay the receipt of important information relating to patient health (e.g. hyperglycemia or hypoglycemia in a diabetic patient), thereby delaying treatments predicated on the receipt of such information (e.g. the administration of insulin).

[0075] In addition, a relatively long sensor initialization and/or start-up period in hospital settings can require repeated monitoring by hospital staff, a factor which contributes to the costs of patient care. Moreover, these long initialization times can also be a problem if a sensor needs to be removed from sensor electronics and then connected again, for example for an MRI procedure where the sensor electronics are not compatible. In this context, electronic processing and/or telemetering is typically employed with the amperometric sensors, which are, for example, useful for buffering the electrical signals produced by the sensors, processing the sensor signals for transmission, and communicating the buffered, processing signals via a link to a monitoring unit etc.

[0076] Sensors having reduced initialization and/or start-up times in vivo in hospital settings and sensors and sensor systems that are designed to include elements and/or configurations of elements that diminish long sensor initialization and/or start-up times are highly desirable. With glucose sensors for example, even a 15-30 minute reduction of sensor initialization and/or start-up time is highly desirable because, for example, such shorter initialization times can: (1) reduce the need for patient monitoring by hospital personnel, a factor which contributes to the cost-effectiveness of such medical devices; and (2) reduce delays in the receipt of important information relating to patient health. It is further desirable to reduce the initialization time even further for sensors that are already in the body of a patient but have been disconnected from sensor electronics for a short amount of time, such as less than 2 hours.

[0077] In individuals using analyte sensors in non-hospital settings (e.g. diabetics using glucose sensors to manage their disease), relatively long sensor initialization and/or start-up periods are also problematical due to both the inconvenience to the user as well as the delayed receipt of information relating to user health. Because many diabetics do not have medical training, they may forgo optimal monitoring and modulation of blood glucose levels due to complexities associated with such management, for example, a two hour start-up period which can be an inconvenience in view of a patient's active daily routine. For these reasons, sensors and sensor systems that are designed to include elements and/or configurations of elements can reduce sensor initialization and/or start-up times in are highly desirable in situations where such sensors are operated by a diabetic patient without medical training because they facilitate the patient's convenient management of their disease, behavior which is shown to decrease the well known morbidity and mortality issues observed in individuals suffering from chronic diabetes.

[0078] While the analyte sensor and sensor systems disclosed herein are typically designed to be implantable within the body of a mammal, the inventions disclosed herein are not limited to any particular environment and can instead be used in a wide variety of contexts, for example for the analysis of most in vivo and in vitro liquid samples including biological fluids such as interstitial fluids, whole-blood, lymph, plasma, serum, saliva, urine, stool, perspiration, mucus, tears, cerebrospinal fluid, nasal secretion, cervical or vaginal secretion, semen, pleural fluid, amniotic fluid, peritoneal fluid, middle ear fluid, joint fluid, gastric aspirate or the like. In addition, solid or desiccated samples may be dissolved in an appropriate solvent to provide a liquid mixture suitable for analysis.

[0079] Distributed electrode configurations can be used in methods designed to overcome problems with sensors and sensor systems that occur due to lack of hydration (e.g. slow start-up initialization times), fluid stagnation, a patient's immune response, or the like. For example, systems with such distributed electrode configurations are shown in U.S. Patent No. 6,770,729.

[0080] The distributed electrodes, if present, are preferably organized/disposed within a flex-circuit assembly (i.e. a circuitry assembly that utilizes flexible rather than rigid materials). Such a flex-circuit assembly provides an interconnected assembly of elements (e.g. electrodes, electrical conduits, contact pads and the like) configured to facilitate wearer comfort (for example by reducing pad stiffness and wearer discomfort) as well as parameter measurement performance and are disclosed in more detail in U.S. Patent Application Serial Nos. 12/184,046 (filed July 31, 2008).

[0081] Typically, the electrodes in a sensor are of a rectangular shape, i.e. have a longer side and a shorter side (including those of a rectangular shape, yet having rounded edges). The electrode configuration can be such that a longer side of at least one of the electrodes in a distributed electrode pattern is parallel to a longer side of at least one of the other electrodes in the distributed electrode pattern (and optionally all of the electrodes in the distributed electrode pattern). Example sensors are shown in U.S. Patent Application Serial No. 12/184,046 (filed July 31, 2008).

[0082] An aperture is typically positioned on the cover layer so that a fluid comprising the analyte contacts the reference electrode, the working electrode and the counter electrode in a sequential manner so as to facilitate sensor hydration and/or sensor start-up or initialization. The aperture can be fully open, i.e. opens the electrodes to the external environment

by having aperture edges that line up with or are below the electrodes in the sensor. An optimized profile is shown in U.S. Patent Application Serial No. 12/184,046 (filed July 31, 2008), incorporated herein by reference.

[0083] Sensor systems that comprise wire electrodes may be used in methods designed to overcome problems that can occur with implantable sensors and sensor systems due to lack of hydration (e.g. slow start-up initialization times) and/or fluid stagnation by enhancing the flexing and movement of the implanted components in a manner that enhances fluid flow and inhibit a gas bubble or a stagnating pool of fluid from remaining on top of or close to an electrode in a manner that compromises sensor function. In addition, sensors comprising a wire electrodes can be combined with certain complementary elements disclosed herein so as to further overcome problems that result from a lack of hydration, fluid stagnation, a patient's immune response, or the like (e.g. distributed electrode configurations, flex sensor assemblies, multiple electrode sensors, voltage pulsing methods etc.).

[0084] As discussed herein, the sensor may be directly connected to sensor electronics, which may be part of or separately connected (wirelessly or via or other direct connection) to a monitoring device that monitors the signals received from the sensor. Depending on the construction of the sensor device and/or monitor (whether separate or together with the sensor device), one or both of the sensor electronics and monitor may make calculations based on the signals sensed at the sensor to convert the signals to actual analyte measurements and to determine various characteristics of the data received. As discussed herein, a number of different characteristics may be used to help get a more accurate picture of the actual level of analyte in the patient. These characteristics can include current values at different time intervals, such as during relaxation of the curve, change in currents, change in total charge, and/or calculated relaxation parameters.

[0085] The invention includes sensors and sensor systems having configurations of elements and/or architectures that optimize aspects of sensor function. For example, the invention may be constructed to include multiple and/or redundant elements such as multiple sets of sensors and/or sensor system elements such as multiple piercing members (e.g. needles) and/or a cannulas organized on an insertion apparatus for use at a patient's in vivo insertion site. For example, sensor sets may include dual piercing members as disclosed in U.S. Patent Application Serial No. 13/008,723, filed January 18, 2011.

[0086] The first and second electrochemical sensors are preferably operatively coupled to a sensor input capable of receiving signals from the first and second electrochemical sensors; and a processor coupled to the sensor input, wherein the processor is capable of characterizing one or more signals received from the first and second electrochemical sensors. Optionally, a pulsed voltage is used to obtain a signal from an electrode. The processor can be capable of comparing a first signal received from a working electrode in response to a first working potential with a second signal received from a working electrode in response to a second working potential.

[0087] While the invention can comprise one or two piercing members, optionally such sensor apparatuses can include 3 or 4 or 5 or more piercing members that are coupled to and extend from a base element and are operatively coupled to 3 or 4 or 5 or more electrochemical sensors (e.g. microneedle arrays, examples of which are disclosed for example in U.S. Pat. Nos. 7,291,497 and 7,027,478, and U.S. patent Application No. 20080015494). In addition, while the invention may typically include a base element that positions and supports the implanted sensors, in alternative configurations of the invention, the plurality of sensors are not coupled to a base element.

[0088] As noted above, the invention can use voltage switching as part of the sensing process. The invention can use voltage switching not only in the detection of interfering species and/or specific analyte concentrations but also to facilitate the hydration and/or initialization of the sensor. In particular, the time for initialization ("run-in") differs for different sensors and can take hours. The invention can include a sensor initialization scheme involving high frequency initialization (switching of voltage potentials). In one illustrative example, a triple initialization profile is used where the voltage of the sensor is switched between a first potential such as 0, 280, 535, 635 or 1.070 millivolts and a second potential such as 0, 280, 535, 635 or 1.070 millivolts over a period of 5, 10, 20, 30 or 45 seconds or 1, 5, 10 or 15 minutes. Certain voltage switching profiles further use voltage pulsing in the detection of analyte signals. The number of pulses used is typically at least 2 and can be 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or more. Pulses can be for a predetermined period of time, for example 1, 3, 5, 7, 10, 15, 30, 45, 60, 90 or 120 seconds. One illustrative example of this comprises 6 pulses, each a few seconds long. By using such voltage switching, the sensor run-in is greatly accelerated, a factor which optimizes a user's introduction and activation of the sensor. Certain of these methods can be adapted for use with similar methods known in the art (see, e.g. U.S. Pat. Nos. 5,320,725; 6,251,260 and U.S. Patent Application No. 2005/0161346).

[0089] A pulsed (e.g. produced or transmitted or modulated in short bursts or pulses) voltage may be used to obtain a signal from one or more electrodes of the sensor. Relatedly, a pulsed current or the like is used. Such pulsing for example can be used to reduce/compensate for background current readings. Pulsing allows sensors to detect lower concentrations of glucose more efficiently, that there is a linear response to glucose switching, and that pulsing can be used to both decrease the background current and reduce the effect of interferants. A variety of different voltage pulsed and/or voltage switched sensors are contemplated. In this context, sensor systems can include a processor in or separate from sensor electronics, where the processor includes software algorithms that control factors such as voltage output and/or working potential and/or pulsing and or switching and/or the time periods of such factors. Sensor systems can

also include various hardware features designed to facilitate voltage pulsing, for example discharge circuit elements. In particular, high frequency switching can sometimes require a discharge circuit element so that layers discharge held charge (wherein the sensor layers analogous to a capacitor). One illustrative example is a sensor having two specific potential dedicated electrodes (e.g. at 280 mv and 535 mv) that is designed to obtain readings of both electrodes as the sensor switches between them. In this context, it is known in the art to take a sensor reading at a wide range of potentials (see, e.g. U.S. Pat. Nos. 5,320,725, 6,251,260, 7,081,195 and Patent Application No. 2005/0161346). A processor can be used to observe signals obtained from one of two working electrodes in a sensor via a pulsed voltage and to compare it to the signal obtained from the second working electrode, wherein this second working electrode is not exposed to a pulsed voltage.

[0090] Sensor systems that utilize voltage pulsing and/or switching as disclosed herein are preferably used in methods designed to overcome problems that can occur with implantable sensors and sensor systems due to lack of hydration (e.g. slow start-up initialization times) and/or fluid stagnation by enhancing the ability of a fluid to flow around the implanted components in a manner that inhibits the likelihood of a gas bubble or a stagnating pool of fluid from forming and/or remaining on top of or close to an electrode in a manner that compromises sensor function. In addition, voltage pulsing and/or switching can be combined with certain complementary elements disclosed herein so as to further overcome problems that result from a lack of hydration, fluid stagnation, a patient's immune response, or the like (e.g. distributed electrode configurations, multiple electrode sensors, multiple sensor apparatuses having multiple implantation sites, etc.).

[0091] Varied voltage is preferably used, for example applying repeated cycles of step electrode potentials. The varied voltage results in a continuous mode of glucose sensing providing much more information during chronological glucose monitoring. Using a varying voltage scheme such as a stepped voltage scheme has many advantages. For example, its inherent self-correlation is quite large compared to a constant potential approach.

[0092] When step electrode potentials are used, for example, each waveform cycle of signal relaxation response that is obtained contains a number of characteristic electrode current readings (Isigs). These readings change and relaxation times will directly correlate with glucose concentrations. Continuous repetition of such cycles results in a robust continuous glucose monitoring system. The characteristic signal responses, by correlating to glucose, also correlate with each other under normal conditions throughout any glucose changes. Thus, this method provides higher system reliability as compared to a fixed potential sensing mode, which only returns one characteristic electrode current reading during sensing. Changes in system self-correlation based on multiple electrode potentials can also be useful in identifying the presence of substances that may interfere with glucose response and tracking such as interferants. Multiple electrode potentials can be used, for example, stepped electrode potentials.

[0093] As discussed herein, methods such as voltage switching may be used to initialize the sensor prior to the time at which sensing data will be used to determine analyte readings. As such, there may be an initialization period prior to the sensor duration time period. In addition or alternatively, also as discussed herein, there may be a hydration period prior to the sensor duration time period.

[0094] In some cases, the sensor needs to be disconnected from the sensor electronics for a period and then reconnected. For example, in hospitals, a sensor may need to be disconnected during certain operations or procedures. One such procedure is magnetic resonance imaging (MRI), which is not compatible with processors or sensor electronics. In such cases, the sensor is disconnected for a certain amount of time and then reconnected to the sensor electronics. Unfortunately, the prior art processes of initialization can take up to a couple of hours. During normal operation, the sensor usually operates in an amperometric detection mode at a steady operation potential (e.g., 0.535 V) to provide a steady-state faradaic current response that corresponds to the glucose concentrations. In an event when the sensor needs to be disconnected and reconnected for a brief period of time, the sensor undergoes transient current response which is non-faradaic and does not truly correspond to actual glucose values. The typical response curve is shown in FIG. 9A, which shows the current response (iSig) in nA over a period of time. For an implanted sensor, this transient response can cause delayed start-up after reconnecting. The transient current response could last from several minutes to a couple of hours before the sensor is stabilized. The length of time for this transient current also depends on how long the sensor was disconnected.

[0095] To minimize the delayed start-up upon reconnection of the sensor, the present invention may use a soft initialization method. In this soft initialization method, voltage steps or other variations are applied in sequences that will minimize the time to reach steady state current. The typical response curve after soft initialization is shown in FIG. 9B. As can be seen, and as discussed further herein, the time for the response to normalize is much less than without the soft initialization method.

[0096] A method is preferably provided for detecting disconnection and reconnection of the sensor electronics processor to the sensor. Current output to the sensor electronics processor is preferably measured. When the current output is below a disconnection threshold, an event of disconnection is determined. The threshold may be, for example, 0.6 nA. After a disconnection event, the current output level to the sensor electronics continues to be measured. When it rises above a reconnection threshold, an event of reconnection is determined. The threshold may be the same as the disconnection level or it may be smaller, for example, 0.4 nA. In examples of the invention, the threshold disconnection

level may be any level up to about 1.0 μA.

[0097] When the events of disconnection and reconnection are measured, the amount of time of disconnection may also be measured. If this disconnection time falls within certain ranges, the system of the present invention may select a type of initialization. For example, there may be two or three disconnection time ranges. It is possible that there could me more disconnection time ranges if fourth, fifth, or more types of initializations are desired.

[0098] Typically, the invention comprises a method of initializing a sensor (typically an analyte sensor, such as a glucose sensor) by determining a disconnection time, wherein the disconnection time is the amount of time a sensor has been disconnected from sensor electronics. An initialization protocol can then be selected based on the disconnection time. The disconnection time can be characterized by determining if it falls within a selected time range. The time range can comprise times above and/or below a specific time point that a sensor has been disconnected from sensor electronics, for example, sensors having been disconnected from sensor electronics for at least 5, 10, 15, 30, 60, 90 or 120 minutes (e.g. a time range of 5 minutes to infinity etc.), or sensors having been disconnected from sensor electronics for less than 5, 10, 15, 30, 60, 90 or 120 minutes (e.g. a time range of 0 - 5 minutes etc.). The time ranges can comprise windows of time that a sensor has been disconnected from sensor electronics, for example, sensors having been disconnected from sensor electronics from between 1-5 minutes, 1-10 minutes, 5-10 minutes, 5-15 minutes, 10-30 minutes, 10-60 minutes, 10-90 minutes or 10-120 minutes etc.

[0099] Typically, the initialization protocol is selected from the group consisting of: a first initialization scheme comprising a first series of voltage pulses and a second initialization scheme comprising a second series of voltage pulses, wherein the first initialization scheme is selected if the disconnection time falls within a first time range and the second initialization scheme is selected if the disconnection time falls within a second time range. Once selected, the inventive method can preferably include applying the selected initialization protocol to the sensor. The group may further comprise a third initialization scheme comprising the application of no voltage to the sensor, wherein the third initialization scheme is selected if the disconnection time is less than the first time range and the second time range. Alternatively, the third initialization scheme may be selected if the disconnection time falls within a third time range. There may be additional initialization schemes and time ranges as desired. Preferably, the first initialization scheme is a hard initialization scheme, the second initialization scheme is a soft initialization scheme, and the third initialization scheme is a no voltage initialization scheme, all three of which are discussed herein.

[0100] As noted above, there can be three disconnection time ranges, and three respective types of initialization. These three types of initialization may include a hard initialization scheme, for those sensors disconnected for more than a certain amount of time, such as 2 hours, a soft initialization scheme, for those sensors disconnected less than that first amount of time but more than a smaller amount of time, such as 10 minutes, and a no voltage initialization scheme for those sensors disconnected less than the smaller amount of time. This allows for sensors having been disconnected long enough to need a complete, hard initialization, sensors that can be initialized using an intermediate, soft initialization, and sensors that really don't need an initialization because they've been disconnected for such a short period of time. In practice, there could be only the hard and no voltage initiation schemes, or only hard and soft, or only soft and no voltage initialization.

[0101] Preferably, there are three disconnection time ranges, and three respective types of initialization. As shown in FIG. 4, when a sensor is connected to sensor electronics at step 401 the system determines whether the sensor is a new sensor or a reconnected sensor at step 405. If the sensor is a new sensor, the system goes to initialization scheme 1 at step 430 and FIG. 5. If the sensor is not a new sensor, the system determines whether the sensor disconnection time is within a certain range, for example less than 10 minutes, at step 410. If the sensor disconnection time is within that range, then initialization scheme 3 is selected at step 415 and FIG. 7. If the sensor disconnection time is not within that range, then it is determined whether the sensor disconnection time is within a second disconnection range, for example 10-120 minutes, at step 420. If the sensor disconnection time is within that range, then initialization scheme 2 is selected at step 425 and FIG. 6. If the sensor disconnection time is not within that range, then it will fall within the remaining range of time, for example greater than 120 minutes, and initialization scheme 1 is initialized at step 430 and FIG. 5.

[0102] Although a particular selection process is shown in FIG. 4, it is possible that the particular process could be different. For example, the disconnection time could be compared to a lookup table or it could be steps in a different order, however a programmer sees suitable to prepare the process such that one of three initialization schemes is selected based on the disconnection time ranges.

[0103] A sample hard initialization scheme (initialization scheme 1) is shown in FIG. 5. A hard initialization is preferably used for new sensors or when the sensor has been disconnected from the sensor electronics for greater than a certain amount of time. Initially, hydration of the sensor may be performed at step 501. Hydration techniques may be conventional techniques or other techniques described herein. After hydration, if performed, a hard voltage initialization is performed at step 505. The hard voltage initialization may be performed using voltage switching, pulsing, or stepping, as described herein. An example hard voltage initialization is shown in FIG. 10. After up to 5 minutes of hydration, a voltage switching scheme is employed until the 20 minute mark. Thus, in the example shown in FIG. 10, if 5 minutes of hydration is

performed, 15 minutes of hard initialization voltage switching is performed, switching between 1.07V for 2 minutes and -0.55V for 1 minute. The particular example in the figure is illustrative and different voltages and time periods could also be used. For example, additional voltages could be positive or negative 0, 280, 535, 585, 635 and 1.070mV.

[0104] After the hard voltage initialization at 505, stabilization is performed at step 510. The stabilization may be performed by applying the operating voltage, for example 535mV, for a certain amount of time, for example 16 minutes. At step 515, the system determines whether the sensor is stable. Metrics of glucose sensor signal stability are known in the art and described, for example, in WO/2011/163294. Sensor stability can be determined, for example, by determining whether the sensor exhibits a fixed current profile in the presence of unchanging glucose concentrations. Sensor stability can be determined, for example, by determining whether the sensor has achieved 90% of a maximum unchanged signal in the presence of unchanging glucose concentrations. Sensor stability can be determined, for example, by determining whether the sensor exhibits limiting current in the presence of unchanging glucose concentrations.

[0105] If the sensor is not stable (e.g. does not exhibit a fixed current profile in the presence of unchanging glucose concentrations), the system performs additional stabilization until a maximum stabilization time or a maximum additional stabilization time is reached (e.g. a preselected time for stabilizing the sensor such as 15, 30, 45, 60, 90, 120, 180 or more minutes). In the example shown in FIG. 5, the system determines whether there has been stabilization for less than a maximum stabilization time, such as 30 minutes, at step 515. If not, then additional stabilization is performed at step 510. The additional stabilization can be for the same amount of time as the original stabilization time or a different amount of time. For example, it might be useful to have a smaller secondary stabilization time because the sensor has already been stabilizing for a period of time and may just need a short amount of time to stabilize. Also, the system could be set up to have a series of small stabilization times, such as 1 or 5 minutes followed by stabilization checks. The stabilization check could be going on during the stabilization period such that there is not a loop type stabilization process but instead a continuous stabilization with stabilization checks until stabilization is reached. If the sensor does not become stabilized after a maximum amount of time, the sensor is not useable and should be removed and replaced. This is shown in FIG. 5 as step 525. As shown in FIG. 5, if the sensor is stable, it is calibrated at step 530. Calibration may be performed using a blood glucose meter as described in U.S. patent application serial no. 09/334,996, filed June 17, 1999, entitled "Characteristic Monitor With A Characteristic Meter and Method of Using the Same," and U.S. patent application serial no. 11/931,866, filed October 31, 2007, entitled "Modified Sensor Calibration Algorithm," or by other calibration methods. Documents US2011230735 and US2008000779 disclose implanted glucose measurements systems with multiple voltage switching initialization schemes. Calibration methods use a real time glucose value taken by blood glucose meter using the traditional finger-prick method (and analysis of the blood taken therefrom) and using that real value to calibrate the values being obtained by the sensor inside the body and related sensor electronics. These methods or other calibration methods may be used with the present invention.

[0106] After calibration, sensing may begin at step 535. It is further possible, although it may not be as efficient, that there may be a stabilization period with no check whether or not the sensor is stable at the end of the stabilization period.

[0107] A sample soft voltage initialization scheme, initialization scheme 2, is shown in FIG. 6. The soft initialization is used for sensors that have been previously connected to sensor electronics and are being reconnected. As shown in FIG. 4, the soft initialization is ideally not used for sensors that have been disconnected for more than a predetermined amount of time, such as 2 hours. However, it is possible that a soft initialization may be useful for any disconnected sensor that is being reconnected, without a maximum disconnection period of time. With or without the maximum disconnection time, there may also be a minimum disconnection time for using the soft initialization, such as 10 minutes.

[0108] In the example shown in FIG. 6, when initialization scheme 2 is selected, the soft voltage initialization is applied at step 601. It is generally not necessary to include a hydration step prior to the soft voltage initialization, because the sensor should remain inside a user's body. However, it is possible to do so if desired, for example if for some reason the user removes a replaceable sensor from the body and then replaces it prior to reconnection. The soft initialization procedure may involve a series of potential steps to the sensor using a processor. The number of potential steps could range from 2 to 20 steps. It is also possible to have more of a voltage switching or pulsing type initialization. There may be more than 20 steps or there may be several steps repeated as a sequence (e.g., V1, V2, V3, V1, V2, V3, etc., where V1, V2 and V3 each are stepped voltages). The sequence of steps may last between about 1 and about 10 minutes. It is possible to have more or less time if desired, such as 8 minutes. One example of the soft voltage initialization is shown in FIG. 8A. As can be seen, a potential of 0.535V is applied for 2 minutes. Then a potential of 1.07V is applied for 2 minutes, after which the operating potential of 0.535V can be applied. Another example of the soft voltage initialization is shown in FIG. 8B, where a series of 8 potential steps are used to gradually step down from an initial potential of 1.07V to the operating potential of 0.535V.

[0109] FIGs. 9A and 9B show the difference in response time with and without a soft initialization according to an example of the present invention. FIG. 9A shows the signal response (iSig) of the sensor when the sensor is reconnected to the processor and sensor electronics after 2 hours of disconnection without any soft initialization. The start-up time (i.e., the time to reach 90% of the expected response) is over 60 minutes long. FIG. 9B shows the signal response when the sensor is reconnected to the processor after 2 hours of disconnect using the soft initialization shown in FIG. 8A. In

the case in FIG. 9B, the start up time is less than 30 minutes, showing that the time can be greatly reduced even using a simple soft initialization method.

[0110] Other methods of hard voltage initialization for a sensor may be used, including those discussed herein and in U.S. Pat. Nos. 5,320,725; 6,251,260 and U.S. Patent Application No. 2005/0161346.

[0111] A sample soft initialization is shown in FIG. 11. In the example shown in FIG. 11, the sensor is disconnected for between 10 and 120 minutes. When reconnected, the soft initialization starts with 2 minutes of 0.535V potential and then 2 minutes of 1.07V. The system them starts the operating voltage of 0.535V. The particular example in the figure is illustrative and different voltages and time periods could also be used. Some additional examples are shown in FIG. 14-17. FIG. 14 shows a potential step of 0.535V for 2 minutes, a potential step of -0.55V for 1 minute, and a potential step of 1.07V for 2 minutes, which are then followed by operating potential, e.g. at 0.535V. FIG. 15 shows a step potential sequence of 0.535V for 1 minute, 1.07V for one minute, 0.535V for 1 minute, 0.85V for 1 minute, 0.535V for 1 minute, and 0.65V for 1 minute, followed by operating potential, e.g. at 0.535V. FIG. 16 shows a series of 8 potential steps that gradually steps down the voltage from 1.07V to an operation potential of 0.535V. FIG. 17 shows a potential step of 0.535V for 2 minutes then 1.07V for 2 minutes followed by operating voltage of 0.535V.

[0112] FIGs. 18 and 19 show boxplots of recovery time, which in those FIGs. is defined as the time for the sensor to reach 90% of limiting current, for certain soft initialization schemes. In FIG. 18, the schemes are 2 minute rampdown with 10 steps (1801), 2 minutes at 0.535V and 2 minutes at 1.07V (1802), 2 minutes at 1.07V (1803), 30 seconds at 1.07V (1804), 4 minute rampdown with 10 steps (1805), 5 minutes at 0.535V and 2 minutes at 1.07V (1806), 60 seconds at 1.07V (1807), 4 minutes at 0.535V and 1 minute at -0.55V and 2 minutes at 1.07V (1808), and a stepdown scheme (1809). In FIG. 19, a boxplot is shown of the sensor recovery time based on the time of soft initialization, regardless of the soft initialization sequence used.

[0113] Continuing with FIG. 6, after the soft voltage initialization is applied at step 601, stabilization is performed at step 605. The stabilization may be performed by applying the operating voltage, for example 535mV, for a certain amount of time, for example 10, 16, 20, or 26 minutes. At step 610, the system can determine whether the sensor is stable. If the sensor is not stable, the system performs additional stabilization until a maximum stabilization time or a maximum additional stabilization time is reached. In the example shown in FIG. 6, the system can determine whether there has been stabilization for less than a maximum stabilization time, such as 30 minutes, at step 615. If not, then additional stabilization is performed at step 605. As with initialization scheme 1, the additional stabilization can be for the same amount of time as the original stabilization time or a different amount of time. The system could be set up to have a series of small stabilization times, such as 1 or 5 minutes followed by stabilization checks. The stabilization check could be going on during the stabilization period such that there is not a loop type stabilization process but instead a continuous stabilization with stabilization checks until stabilization is reached. If the sensor does not become stabilized after a maximum amount of time, the sensor is not useable and should be removed and replaced. This is shown in FIG. 6 as step 620. As shown in FIG. 6, if the sensor is stable, it is calibrated at step 625. Calibration may be performed using a blood glucose meter as discussed above or by other calibration methods. After calibration, sensing may begin at step 630.

[0114] A third scheme, initialization scheme 3, is shown in FIG. 7. It may be desired that sensors disconnected for a short period of time not be subjected to a new initialization, as this limited period of disconnection is insufficient for the sensor to need any initialization. A sample graph of initialization scheme 3 is shown in FIG. 12. In FIG. 12, the sensor has been disconnected for less than 10 minutes, so the system merely applies the operating voltage of 0.535V for a stabilization period of 10 minutes before moving on to sensing at the operating voltage. It is possible that this stability time be more or less, depending on how long of a stabilization period is desired. As with initialization scheme 1 and 2, there may be a stabilization check. As shown in FIG. 7, a sensor that has fallen within the proper disconnection time range is stabilized at step 701. The stabilization may be performed by applying the operating voltage, for example 535mV, for a certain amount of time, for example 10 minutes. Other time ranges could be employed, such as 16, 20 or 26 minutes. At step 705, the system determines whether the sensor is stable. If the sensor is not stable, the system performs additional stabilization until a maximum stabilization time or a maximum additional stabilization time is reached. In the example shown in FIG. 7, the system determines whether there has been stabilization for less than a maximum stabilization time, such as 30 minutes, at step 710. If not, then additional stabilization is performed at step 701. The additional stabilization can be for the same amount of time as the original stabilization time or a different amount of time. As with the other initialization schemes, the system could be set up to have a series of small stabilization times, such as 1 or 5 minutes followed by stabilization checks. The stabilization check could be going on during the stabilization period such that there is not a loop type stabilization process but instead a continuous stabilization with stabilization checks until a stabilization is reached. If the sensor does not become stabilized after a maximum amount of time, the sensor is not useable and should be removed and replaced. This is shown in FIG. 7 as step 715. Typically, no calibration is required for sensors falling under this initialization scheme, although it is of course possible to recalibrate if desired. Thus, sensing begins at step 720.

[0115] The methods can further comprise applying a stabilization voltage to the sensor (e.g. a voltage designed to enhance sensor stability), for example after applying the selected initialization voltage, for a first stabilization time. The

method may further include determining whether the sensor is stable after applying the first stabilization voltage; and if the sensor is not stable, applying a second stabilization voltage to the sensor for a second stabilization time. Example stabilization time periods include times less than forty minutes, such as 10, 16, 20, and 26 minutes, or 30 minutes. The second stabilization time may be the same or different than the first stabilization time.

[0116] The invention may comprise an improved method of detecting and/or facilitating sensor hydration. For detection of hydration (e.g. the level or degree of implanted sensor hydration), voltage pulses are preferably applied to the sensor immediately after insertion of the sensor and prior to sensor initialization using the sensor processor. The response (iSig) to this voltage pulse will be used for detection of hydration. One pre-initialization voltage pulse scheme for detecting hydration is a set of two alternating voltages, such as 0.0V and 0.2V. Other potential voltages could be used, for example alternating voltages between 0.0V and a second voltage of between 0.1V and 0.535V. The sensor response (iSig) is recorded at a high sampling rate, such as every 1 second. The sensor is considered hydrated when the response to the voltage pulse is above a certain hydration threshold, such as 100nA. Once the sensor is considered hydrated, the sensor undergoes initialization. If the threshold is not met after a certain amount of time, for example 5 minutes or up to about 20 minutes, the sensor will be considered not ready and will not undergo initialization. Instead, more similar pulses, which may be the same as the original pulses, are applied until the threshold is met. There may be a maximum hydration time period after which the sensor will be considered non-functioning and should be removed and replaced by a new sensor. FIG. 13 is an example graph showing the sensor response during hydration detection according to the example shown above.

[0117] The invention may include detecting hydration of the sensor prior to applying the selected initiation protocol, wherein detecting hydration includes applying a series of hydration pulses (voltages selected to detect or facilitate sensor hydration) to the sensor for a first hydration time; recording the current response of the sensor during application of the series of hydration pulses; and comparing the current response to a predetermined hydration threshold. Application of the series of hydration pulses may be terminated if the current response reaches or exceeds the predetermined hydration threshold. Detecting hydration may further include applying a second series of hydration pulses to the sensor for a second hydration time if the current response does not reach the predetermined hydration threshold during the first predetermined hydration time. The predetermined hydration threshold may be 100 nA or 50 nA, for example. Example hydration pulses may be a series of 0 V and 2 V pulses, for example for 20 seconds or 2 minutes each.

[0118] The hydration detection described above may be used in combination with other methods, for the same or different sensors. For example, in some methods where more than one sensor is used, the hydration detection described above may be used with respect to one sensor and a different hydration detection may be used with respect to the other sensor. The sensors should become hydrated at roughly the same time, so this would serve as a check to make sure that they hydration detection methods are all correlating properly.

[0119] One example of another method to determine hydration includes using a processor that detects whether a sensor is sufficiently hydrated for analyte detection comprising a computer usable media including at least one computer program embedded therein that is capable of calculating an impedance value; and comparing the impedance value against a threshold to determine if the sensor is sufficiently hydrated for analyte detection. In related methods, detecting whether a sensor is sufficiently hydrated for analyte detection includes comprising calculating an open circuit potential value between at least two electrodes of the sensor and comparing the open circuit potential value against a threshold to determine if the sensor sufficiently hydrated for analyte detection. Typically, the open circuit potential value is the impedance value (and optionally this value is an approximation of a sum of polarization resistance and solution resistance). Optionally, the open circuit potential value is compared against an another threshold to determine if the sensor sufficiently hydrated for analyte detection. This can solve problems that occur when a user attempts to initialize a sensor that is not fully hydrated (e.g. compromising the accuracy and/or lifetime of the sensor).

[0120] The invention may include a fuse element that can be triggered after a predetermined period of time or event so as to interrupt a flow of electrical current within the apparatus (i.e. so as to disable the sensor), as disclosed in U.S. Patent Application Serial No. 12/184,046 (filed July 31, 2008).

[0121] The invention may comprise a processor that is capable of comparing a first signal received from a working electrode in response to a first working potential with a second signal received from a working electrode in response to a second working potential, wherein the comparison of the first and second signals at the first and second working potentials can be used to identify a signal generated by an interfering compound. These methods are further discussed in U.S. Application Serial Nos. 12/184,046 (filed July 31, 2008).

[0122] The sensor may switch between a high potential to a low potential (e.g. with a frequency of less than 3, 2 or 1 seconds). In such a case, the sensor may not discharge, with for example sensor elements acting as a sort of capacitor. In this context, the invention can include a circuit discharge element that facilitates sensor circuit discharge (e.g. if discharge is not sufficient to reach a specific potential such as 535 millivolts). A variety of such circuit discharge elements known in the art can be adapted for use with sensor examples of the invention (see, e.g. U.S. Pat. Nos. 4,114,627; 4,373,531; 4,858,610; 4,991,583; and 5,170,806, 5,486,201, 6,661,275 and U.S. Patent Application No. 20060195148). Optionally for example, a sensor charge can be removed by connecting it through a discharging switch element, and

optionally a discharging resistor element.

[0123] Sensors of the invention can also be incorporated in to a wide variety of medical systems known in the art. Sensors of the invention can be used, for example, in a closed loop infusion systems designed to control the rate that medication is infused into the body of a user. Such a closed loop infusion system can include a sensor and an associated meter which generates an input to a controller which in turn operates a delivery system (e.g. one that calculates a dose to be delivered by a medication infusion pump). In such contexts, the meter associated with the sensor may also transmit commands to, and be used to remotely control, the delivery system. Typically, the sensor is a subcutaneous sensor in contact with interstitial fluid to monitor the glucose concentration in the body of the user, and the liquid infused by the delivery system into the body of the user includes insulin. Illustrative systems are disclosed for example in U.S. Pat. Nos. 6,558,351 and 6,551,276; PCT Application Nos. US99/21703 and US99/22993; as well as WO 2004/008956 and WO 2004/009161.

[0124] A number of articles, U.S. patents and patent application describe the state of the art with the common methods and materials disclosed herein and further describe various elements (and methods for their manufacture) that can be used in the sensor designs disclosed herein. These include for example, U.S. Pat. Nos. 6,413,393; 6,368,274; 5,786,439; 5,777,060; 5,391,250; 5,390,671; 5,165,407, 4,890,620, 5,390,671, 5,390,691, 5,391,250, 5,482,473, 5,299,571, 5,568,806; United States Patent Application 20020090738; as well as PCT International Publication Numbers WO 01/58348, WO 03/034902, WO 03/035117, WO 03/035891, WO 03/023388, WO 03/022128, WO 03/022352, WO 03/023708, WO 03/036255, WO03/036310 and WO 03/074107.

[0125] Typical sensors for monitoring glucose concentration of diabetics are further described in Shichiri, et al.: "In Vivo Characteristics of Needle-Type Glucose Sensor-Measurements of Subcutaneous Glucose Concentrations in Human Volunteers," Horm. Metab. Res., Suppl. Ser. 20:17-20 (1988); Bruckel, et al.: "In Vivo Measurement of Subcutaneous Glucose Concentrations with an Enzymatic Glucose Sensor and a Wick Method," Klin. Wochenschr. 67:491-495 (1989); and Pickup, et al.: "In Vivo Molecular Sensing in Diabetes Mellitus: An Implantable Glucose Sensor with Direct Electron Transfer," Diabetologia 32:213-217 (1989). Other sensors are described in, for example Reach, et al., in ADVANCES IN IMPLANTABLE DEVICES, A. Turner (ed.), JAI Press, London, Chap. 1, (1993).

[0126] Various publication citations are referenced throughout the specification. In addition, certain text from related art is reproduced herein to more clearly delineate the various examples of the invention.

[0127] Various of the disclosed components of the apparatus, such as the disconnection timer and the initialization protocol selector may be realized in hardware or in software residing in a suitably programmed computer.

Claims

1. A method of initializing an analyte sensor, said method comprising:

using a disconnection timer to determine a disconnection time, wherein the disconnection time is the amount of time the sensor has been disconnected from sensor electronics,
using an initialization protocol selector to select an initialization protocol based on the disconnection time, the initialization protocol being selected from the group comprising:

(a) a first initialization scheme comprising a first series of voltage pulses and,
(b) a second initialization scheme comprising a second series of voltage pulses,

wherein the first initialization scheme is selected if the disconnection time falls within a first time range and the second initialization scheme is selected if the disconnection time falls within a second time range; and
applying the selected initialization protocol to the sensor.

2. The method of claim 1, wherein said group further comprises:

(c) a third initialization scheme comprising the application of no voltage to sensor,

wherein the third initialization scheme is selected if the disconnection time less than the first time range and the second time range.

3. The method of claim 1 or 2, further comprising applying a stabilization voltage to the sensor, after applying the selected initialization voltage, for a first stabilization time.

4. The method of claim 3, further comprising:

determining whether the sensor is stable after applying the first stabilization voltage; and
if the sensor is not stable, applying a second stabilization voltage to the sensor for a second stabilization time.

5. The method of claim 4, further comprising calibrating the sensor if the sensor is stable.

6. The method of claim 5, wherein calibrating the sensor includes measuring blood glucose using a blood glucose meter and/or is performed only if the disconnection time falls within the first or second time range.

7. The method of any one of claims 4 to 6, wherein if the sensor is not stable after a predetermined maximum stabilization time, the initialization protocol is ended so that a new sensor may be connected to the sensor electronics, optionally wherein the predetermined maximum stabilization time is 30 minutes or more.

8. The method of any one of the preceding claims, wherein the determining a disconnection time includes measuring the current output of the sensor and comparing the measured current output to a disconnection threshold value.

9. The method of claim 8, wherein the determining a disconnection time further includes comparing the current output to a reconnection threshold value, optionally wherein the disconnection threshold value is 0.6 nA or less.

10. The method of any one of the preceding claims, wherein the first time range is a disconnection time of greater than 120 minutes and/or the second time range is 10 minutes to 120 minutes.

11. The method of any one of the preceding claims, wherein the second initialization scheme comprises application of at least two voltages to the sensor for a predetermined second initialization time, optionally wherein the at least two voltages are a series of stepped down voltages and/or the predetermined second initialization time is less than 30 minutes.

12. The method of any one of the preceding claims, further comprising detecting hydration of the sensor prior to applying the selected initialization protocol, wherein detecting hydration includes:

applying a series of hydration pulses to the sensor for a first hydration time;
recording the current response of the sensor during application of the series of hydration pulses; and
comparing the current response to a predetermined hydration threshold;
optionally wherein application of the series of hydration pulses is terminated if the current response reaches or exceeds the predetermined hydration threshold.

13. The method of claim 12, wherein the detecting hydration further includes applying a second series of hydration pulses to the sensor for a second hydration time if the current response does not reach the predetermined hydration threshold during the first predetermined hydration time.

14. The method of claim 12, wherein the predetermined hydration threshold is 100 nA or more.

15. Apparatus for initializing an analyte sensor, said apparatus comprising:

a disconnection timer configured to determine the amount of time that said analyte sensor has been disconnected from sensor electronics,
an initialization protocol selector configured to select an initialization protocol based on said disconnection time, the initialization protocol selector being configured to select from the group comprising:

(a) a first initialization scheme comprising a first series of voltage pulses, and
(b) a second initialization scheme comprising a second series of voltage pulses,

wherein the initialization protocol selector is configured to select the first initialization scheme if the disconnection time falls within a first time range and to select the second initialization scheme if the disconnection time falls within a second time range,
said apparatus being configured to apply the selected initialization protocol to the analyte sensor.

Patentansprüche

1. Verfahren zum Initialisieren eines Analytsensors, das Verfahren umfassend:

   Verwenden eines Unterbrechungszeitgebers zum Bestimmen einer Unterbrechungszeit, wobei die Unterbrechungszeit die Zeit ist, während der die Verbindung des Sensors zur Sensorelektronik getrennt war,
   Verwenden eines Initialisierungsprotokollselektors, um basierend auf der Unterbrechungszeit ein Initialisierungsprotokoll zu wählen, wobei das Initialisierungsprotokoll aus der Gruppe gewählt ist, die Folgendes umfasst:

   (a) ein erstes Initialisierungsschema, umfassend eine erste Reihe von Spannungsimpulsen und,
   (b) ein zweites Initialisierungsschema, umfassend eine zweite Reihe von Spannungsimpulsen,

   wobei das erste Initialisierungsschema ausgewählt ist, wenn die Unterbrechungszeit in einen ersten Zeitbereich fällt, und das zweite Initialisierungsschema gewählt ist, wenn die Unterbrechungszeit in einen zweiten Zeitbereich fällt; und
   Anwenden des gewählten Initialisierungsprotokolls auf den Sensor.

2. Verfahren nach Anspruch 1, wobei die Gruppe ferner umfasst:

   (c) ein drittes Initialisierungsschema, umfassend kein Anlegen einer Spannung an den Sensor,

   wobei das dritte Initialisierungsschema ausgewählt ist, wenn die Unterbrechungszeit weniger ist als der erste Zeitbereich und der zweite Zeitbereich.

3. Verfahren nach Anspruch 1 oder 2, ferner umfassend ein Anlegen einer Stabilisierungsspannung an den Sensor, nach einem Anlegen der gewählten Initialisierungsspannung, über eine erste Stabilisierungszeit.

4. Verfahren nach Anspruch 3, ferner umfassend:

   Bestimmen, ob der Sensor nach einem Anlegen der ersten Stabilisierungsspannung stabil ist; und
   wenn der Sensor nicht stabil ist, Anlegen einer zweiten Stabilisierungsspannung an den Sensor über eine zweite Stabilisierungszeit.

5. Verfahren nach Anspruch 4, ferner umfassend ein Kalibrieren des Sensors, wenn der Sensor stabil ist.

6. Verfahren nach Anspruch 5, wobei ein Kalibrieren des Sensors ein Messen von Blutzucker unter Verwendung eines Blutzuckermessgeräts umfasst und/oder nur durchgeführt wird, wenn die Unterbrechungszeit in den ersten oder zweiten Zeitbereich fällt.

7. Verfahren nach einem der Ansprüche 4 bis 6, wobei, wenn der Sensor nach einer festgelegten maximalen Stabilisierungszeit nicht stabil ist, das Initialisierungsprotokoll beendet ist, damit ein neuer Sensor mit der Sensorelektronik verbunden werden kann, optional wobei die festgelegte maximale Stabilisierungszeit 30 Minuten oder mehr ist.

8. Verfahren nach einem der vorangehenden Ansprüche, wobei das Bestimmen einer Unterbrechungszeit ein Messen des Stromausgangs des Sensors und ein Vergleichen des gemessenen Stromausgangs mit einem Unterbrechungsschwellenwert umfasst.

9. Verfahren nach Anspruch 8, wobei das Bestimmen einer Unterbrechungszeit ferner ein Vergleichen des Stromausgangs mit einem Wiederverbindungsschwellenwert umfasst, optional wobei der Unterbrechungsschwellenwert 0,6 nA oder weniger ist.

10. Verfahren nach einem der vorangehenden Ansprüche, wobei der erste Zeitbereich eine Unterbrechungszeit ist, die größer ist als 120 Minuten und/oder der zweite Zeitbereich 10 Minuten bis 120 Minuten ist.

11. Verfahren nach einem der vorangehenden Ansprüche, wobei das zweite Initialisierungsschema ein Anlegen von mindestens zwei Spannungen an den Sensor über eine festgelegte zweite Initialisierungszeit umfasst, optional wobei die mindestens zwei Spannungen eine Reihe von abwärtsgeregelten Spannungen sind und/oder die festgelegte zweite Initialisierungszeit weniger als 30 Minuten ist.

12. Verfahren nach einem der vorangehenden Ansprüche, ferner umfassend ein Erfassen von Hydratation des Sensors vor einem Anwenden des gewählten Initialisierungsprotokolls, wobei ein Erfassen von Hydration umfasst:

Anwenden einer Reihe von Hydratationsimpulsen auf den Sensor über eine erste Hydratationszeit;
Aufzeichnen der Stromantwort des Sensors während einer Anwendung der Reihe von Hydratationsimpulsen; und
Vergleichen der Stromantwort mit einer festgelegten Hydratationsschwelle;
optional wobei eine Anwendung der Reihe von Hydratationsimpulsen beendet ist, wenn die Stromantwort die festgelegte Hydratationsschwelle erreicht oder überschreitet.

13. Verfahren nach Anspruch 12, wobei das Erfassen einer Hydration ferner ein Anwenden einer zweiten Reihe von Hydratationsimpulsen auf den Sensor über eine zweite Hydratationszeit umfasst, wenn die Stromantwort die festgelegte Hydratationsschwelle während der ersten festgelegten Hydratationszeit nicht erreicht.

14. Verfahren nach Anspruch 12, wobei die festgelegte Hydratationsschwelle 100 nA oder mehr ist.

15. Gerät zum Initialisieren eines Analytsensors, das Gerät umfassend:

einen Unterbrechungszeitgeber, der konfiguriert ist, um die Zeit zu bestimmen, über die die Verbindung des Analytsensors zur Sensorelektronik getrennt war,
einen Initialisierungsprotokollselektor, der konfiguriert ist, um basierend auf der Unterbrechungszeit ein Initialisierungsprotokoll zu wählen, wobei der Initialisierungsprotokollselektor konfiguriert ist, um aus der Gruppe zu wählen, die Folgendes umfasst:

(a) ein erstes Initialisierungsschema, umfassend eine erste Reihe von Spannungsimpulsen, und
(b) ein zweites Initialisierungsschema, umfassend eine zweite Reihe von Spannungsimpulsen,

wobei der Initialisierungsprotokollselektor konfiguriert ist, um das erste Initialisierungsschema zu wählen, wenn die Unterbrechungszeit in einen ersten Zeitbereich fällt, und das zweite Initialisierungsschema zu wählen, wenn die Unterbrechungszeit in einen zweiten Zeitbereich fällt,
wobei das Gerät konfiguriert ist, um das gewählte Initialisierungsprotokoll auf den Analytsensor anzuwenden.

Revendications

1. Procédé d'initialisation d'un capteur d'analyte, ledit procédé comprenant :

l'utilisation d'un temporisateur de déconnexion pour déterminer un temps de déconnexion, dans lequel le temps de déconnexion est la durée pendant laquelle le capteur a été déconnecté du système électronique relatif au capteur,
l'utilisation d'un sélecteur de protocole d'initialisation pour sélectionner un protocole d'initialisation en fonction du temps de déconnexion, le protocole d'initialisation étant choisi dans le groupe comprenant :

(a) un premier schéma d'initialisation comprenant une première série d'impulsions de tension et,
(b) un deuxième schéma d'initialisation comprenant une deuxième série de d'impulsions de tension

dans laquelle le premier schéma d'initialisation est sélectionné si le temps de déconnexion si situe dans une première plage temporelle et le deuxième schéma d'initialisation est sélectionné si le temps de déconnexion se situe dans une deuxième plage temporelle ; et
l'application du protocole d'initialisation sélectionné au capteur.

2. Procédé selon la revendication 1, dans lequel ledit groupe comprend en outre :

(c) un troisième schéma d'initialisation comprenant l'application de l'absence de tension au capteur,

le troisième schéma d'initialisation étant sélectionné si le temps de déconnexion est inférieur à la première plage temporelle et à la deuxième plage temporelle.

3. Procédé selon la revendication 1 ou 2, comprenant en outre l'application d'une tension de stabilisation au capteur, après l'application de la tension d'initialisation sélectionnée, pour un premier temps de stabilisation.

4. Procédé selon la revendication 3, comprenant en outre :

la détermination de savoir si le capteur est stable après l'application de la première tension de stabilisation ; et si le capteur n'est pas stable, l'application d'une deuxième tension de stabilisation au capteur pour un deuxième temps de stabilisation.

5. Procédé selon la revendication 4, comprenant en outre l'étalonnage du capteur si le capteur est stable.

6. Procédé selon la revendication 5, dans lequel l'étalonnage du capteur comprend la mesure du glucose sanguin au moyen d'un glucomètre sanguin et/ou n'est réalisé que si le temps de déconnexion se situe dans la première ou la deuxième plage temporelle.

7. Procédé selon l'une quelconque des revendications 4 à 6, dans lequel si le capteur n'est pas stable après un temps de stabilisation maximal prédéterminé, le protocole d'initialisation est terminé de manière à ce qu'un nouveau capteur puisse être connecté au système électronique relatif au capteur, éventuellement dans lequel le temps de stabilisation maximal prédéterminé est de 30 minutes ou plus.

8. Procédé selon l'une quelconque des revendications précédentes, dans lequel la détermination d'un temps de déconnexion comprend la mesure de la sortie de courant du capteur et la comparaison de la sortie de courant mesurée à une valeur seuil de déconnexion.

9. Procédé selon la revendication 8, dans lequel la détermination d'un temps de déconnexion comprend en outre la comparaison de la sortie de courant à une valeur seuil de reconnexion, éventuellement dans lequel la valeur seuil de déconnexion est de 0,6 nA ou moins.

10. Procédé selon l'une quelconque des revendications précédentes, dans lequel la première plage temporelle est un temps de déconnexion supérieur à 120 minutes et/ou la deuxième plage temporelle est de 10 minutes à 120 minutes.

11. Procédé selon l'une quelconque des revendications précédentes, dans lequel le deuxième schéma d'initialisation comprend l'application d'au moins deux tensions au capteur pour un deuxième temps d'initialisation prédéterminé, éventuellement dans lequel les au moins deux tensions sont une série de tensions abaissées et/ou le deuxième temps d'initialisation prédéterminé est de moins de 30 minutes.

12. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre la détection de l'hydratation du capteur avant l'application du protocole d'initialisation sélectionné, l'hydratation de la détection comprenant :

l'application d'une série d'impulsions d'hydratation au capteur pour un premier temps d'hydratation ;
l'enregistrement de la réponse de courant du capteur pendant l'application de la série d'impulsions d'hydratation ; et
la comparaison de la réponse de courant à un seuil d'hydratation prédéterminé ;
l'application de la série d'impulsions d'hydratation étant éventuellement terminée si la réponse de courant atteint ou excède le seuil d'hydratation prédéterminé.

13. Procédé selon la revendication 12, dans lequel l'hydratation de la détection comprend en outre l'application d'une deuxième série d'impulsions d'hydratation au capteur pour un deuxième temps d'hydratation si la réponse de courant n'atteint pas le seuil d'hydratation prédéterminé pendant le premier temps d'hydratation prédéterminé.

14. Procédé selon la revendication 12, dans lequel le seuil d'hydratation prédéterminé est de 100 nA ou plus.

15. Appareil destiné à initialiser un capteur d'analyte, ledit appareil comprenant :

un temporisateur de déconnexion conçu pour déterminer la durée pendant laquelle ledit capteur d'analyte a été déconnecté du système électronique relatif au capteur,
un sélecteur de protocole d'initialisation conçu pour sélectionner un protocole d'initialisation en fonction dudit temps de déconnexion, le sélecteur de protocole d'initialisation étant conçu pour sélectionner dans le groupe

comprenant :

(a) un premier schéma d'initialisation comprenant une première série d'impulsions de tension, et
(b) un deuxième schéma d'initialisation comprenant une deuxième série d'impulsions de tension,

dans lequel le sélecteur de protocole d'initialisation est conçu pour sélectionner le premier schéma d'initialisation si le temps de déconnexion se situe dans une première plage temporelle et pour sélectionner le deuxième schéma d'initialisation si le temps de déconnexion se situe dans une deuxième plage temporelle,
ledit appareil étant conçu pour appliquer le protocole d'initialisation sélectionné au capteur d'analyte.

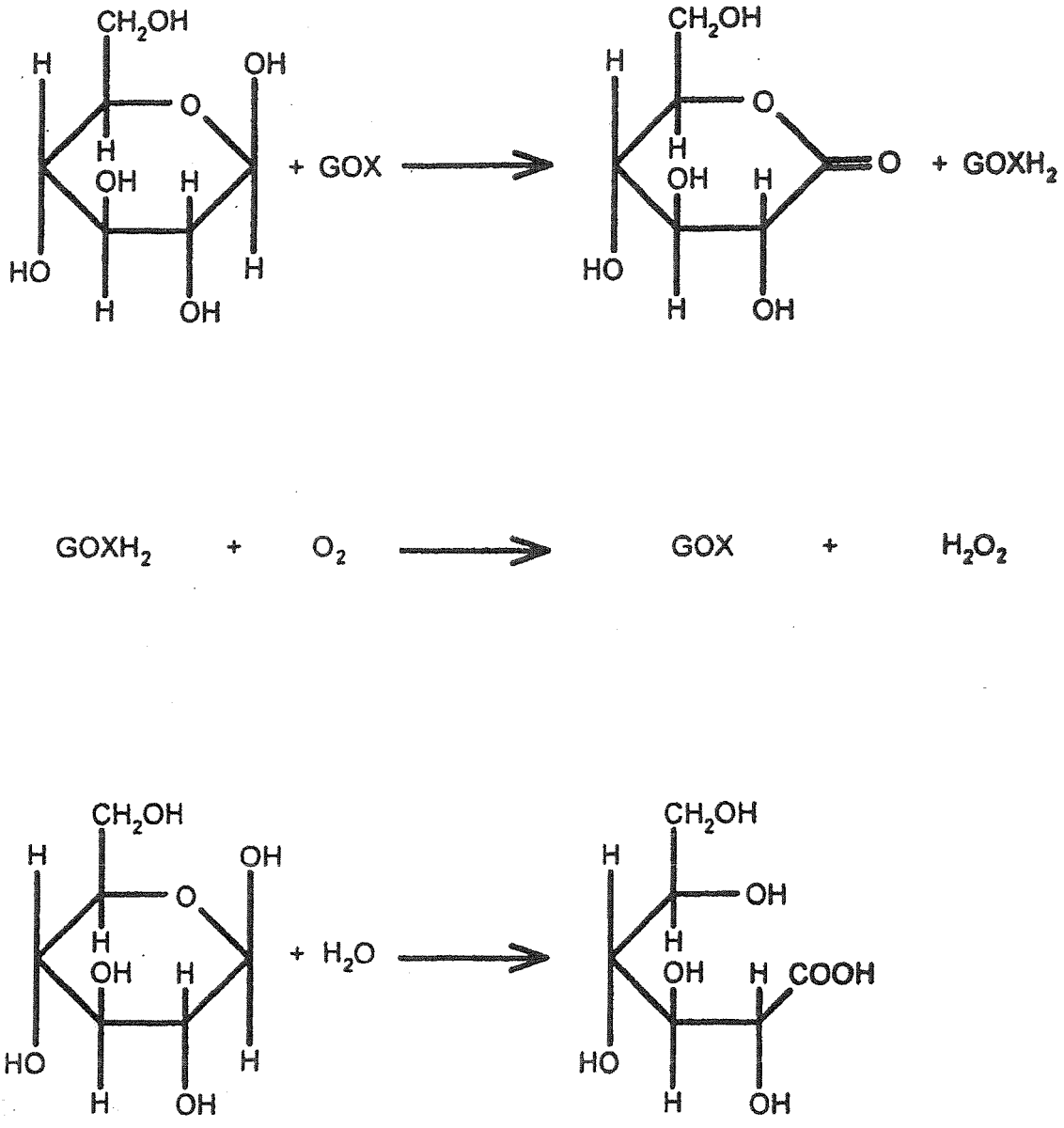

CH2OH
H
OH
O
H
OH
H
HO
H
H
OH
+ GOX
CH2OH
H
O
H
OH
H
O
+ GOXH2
HO
H
OH
GOXH2 + O2
GOX + H2O2
CH2OH
H
OH
O
H
OH
H
HO
H
H
OH
+ H2O
CH2OH
H
OH
H
OH
H
COOH
HO
H
OH

FIG. 1

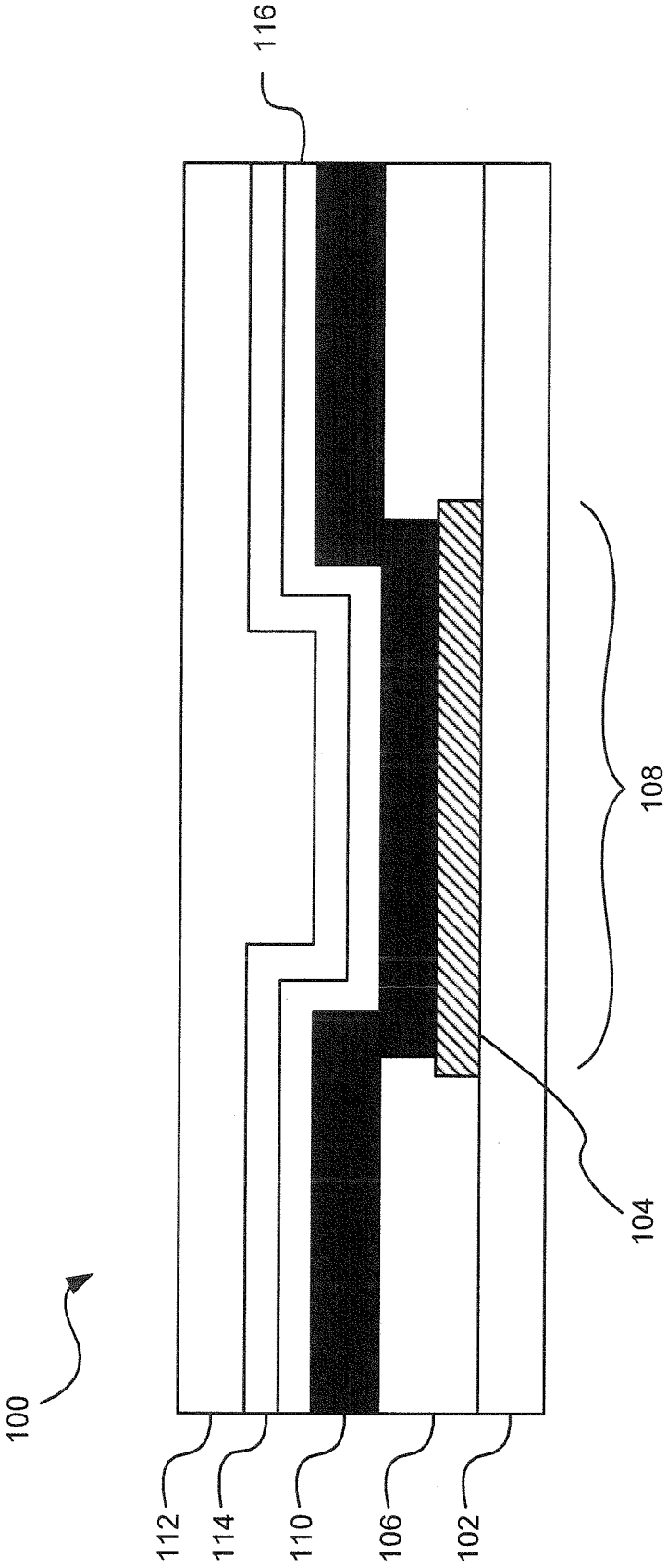


FIG. 2

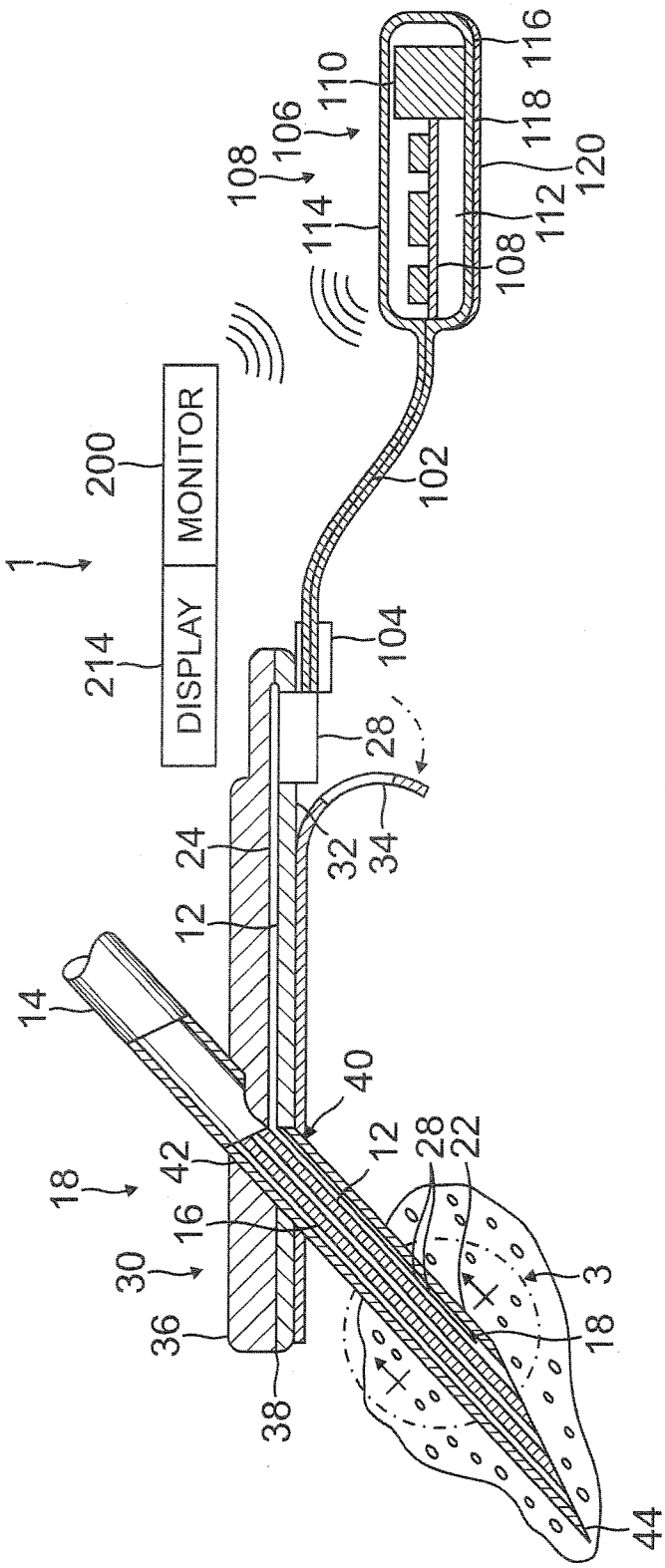

1
200
MONITOR
214
DISPLAY
102
104
106
108
110
112
114
116
118
120
28
32
34
24
12
14
40
42
18
16
30
36
38
22
3
44

FIG. 3

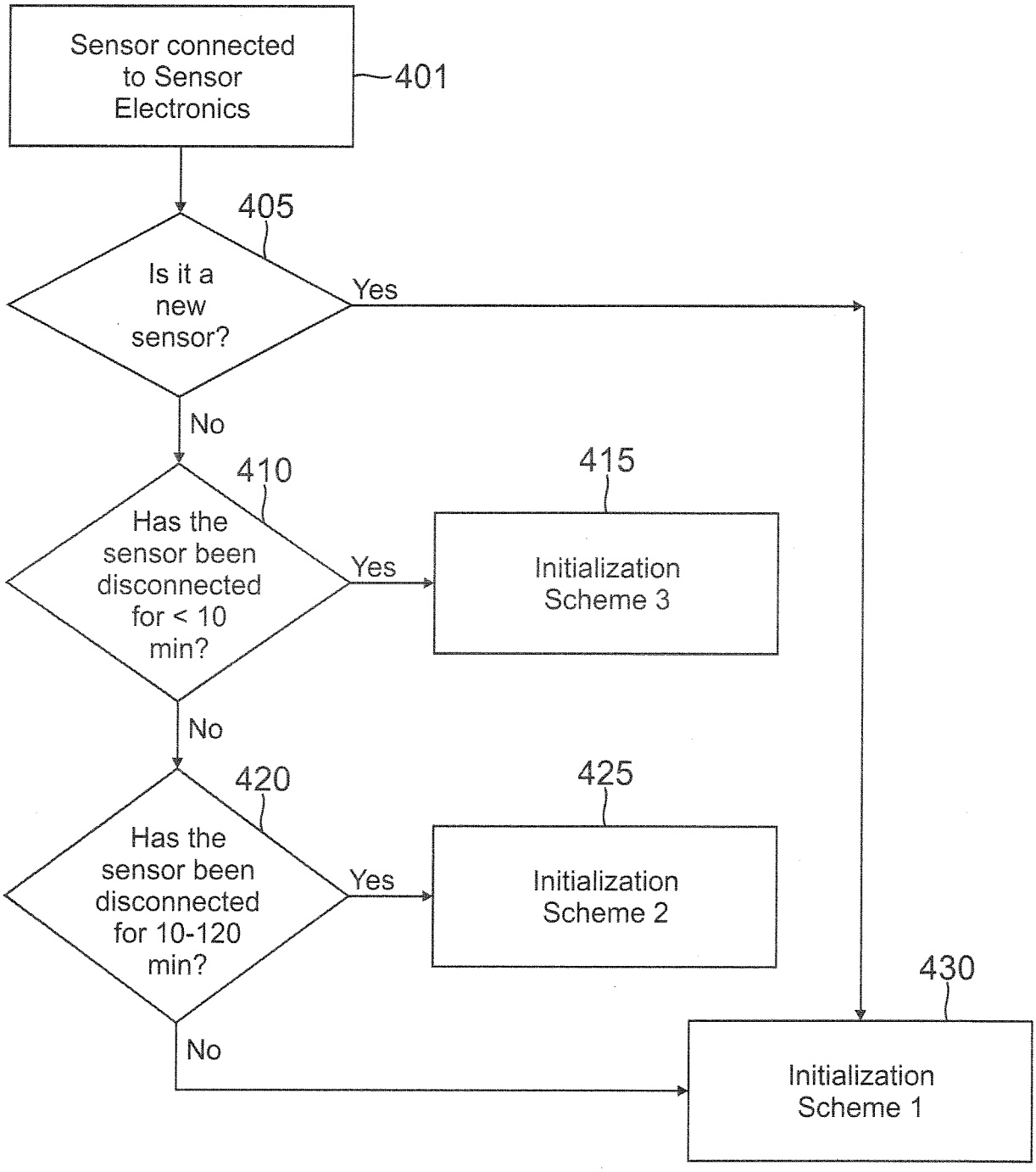

Sensor connected to Sensor Electronics
401
405
Is it a new sensor?
Yes
No
410
Has the sensor been disconnected for < 10 min?
415
Yes
Initialization Scheme 3
No
420
Has the sensor been disconnected for 10-120 min?
425
Yes
Initialization Scheme 2
No
430
Initialization Scheme 1

FIG. 4

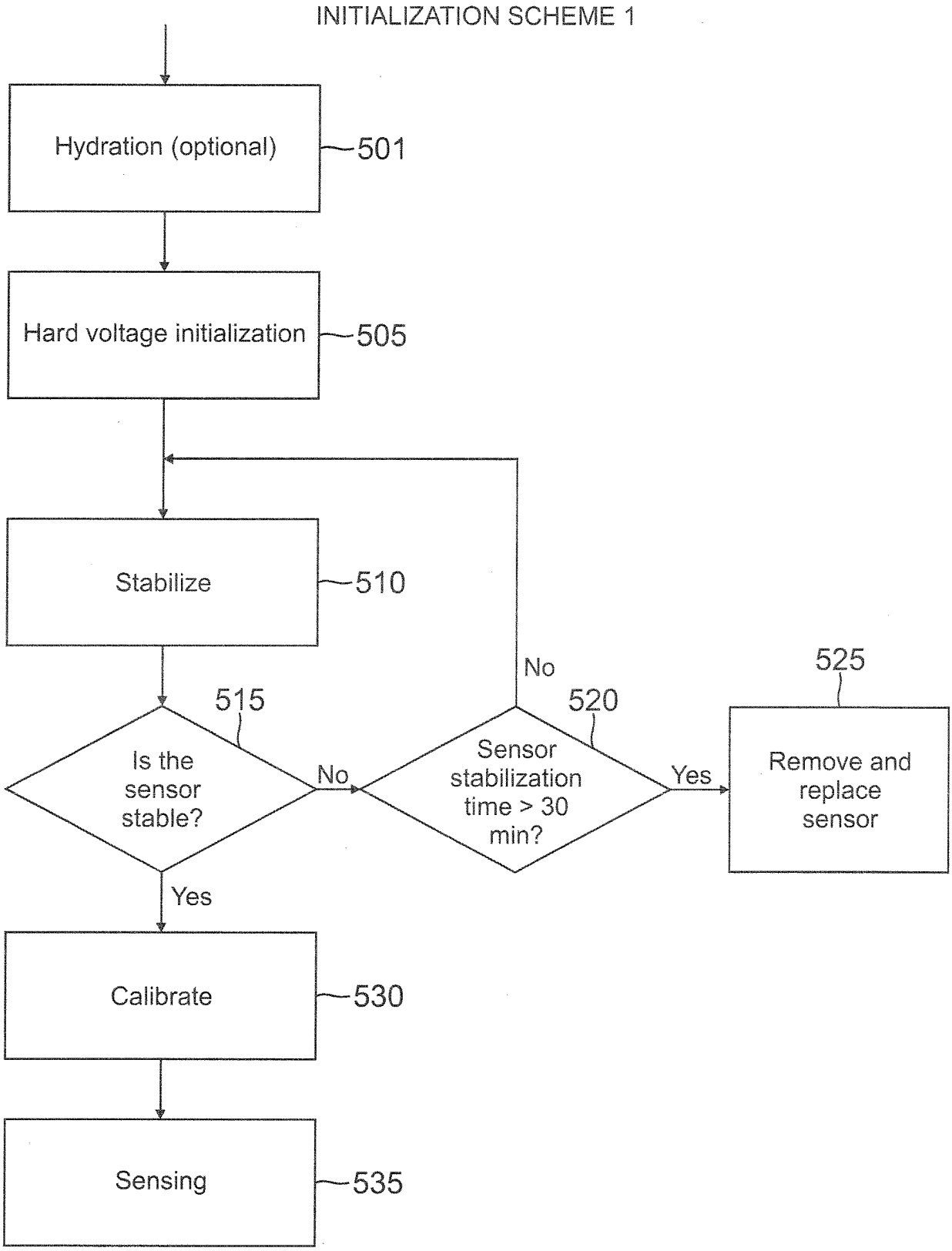

INITIALIZATION SCHEME 1
Hydration (optional)
501
Hard voltage initialization
505
Stabilize
510
515
Is the sensor stable?
No
520
Sensor stabilization time > 30 min?
No
Yes
525
Remove and replace sensor
Yes
Calibrate
530
Sensing
535

FIG. 5

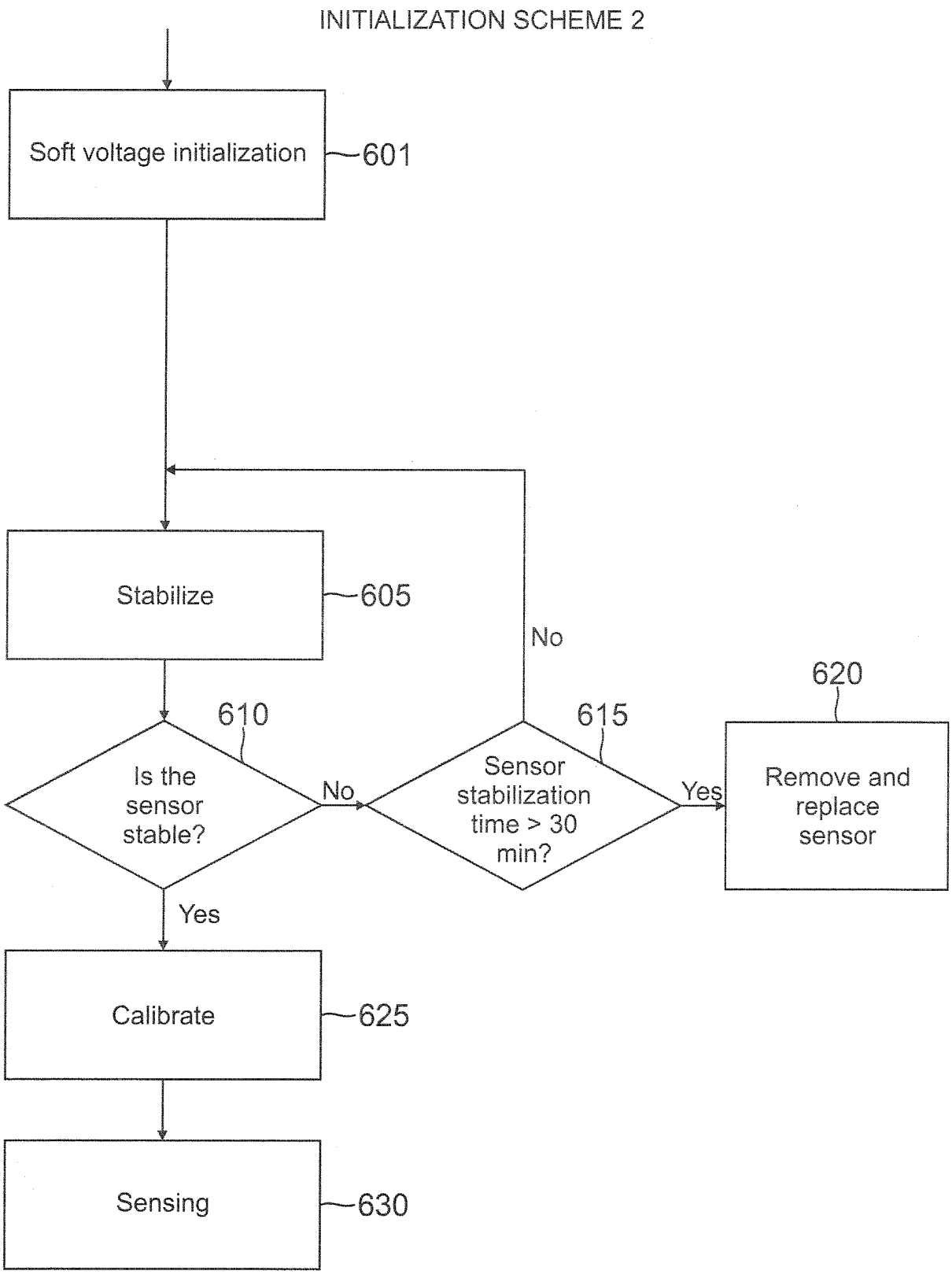

INITIALIZATION SCHEME 2
Soft voltage initialization
601
Stabilize
605
No
620
610
615
Is the sensor stable?
No
Sensor stabilization time > 30 min?
Yes
Remove and replace sensor
Yes
Calibrate
625
Sensing
630

FIG. 6

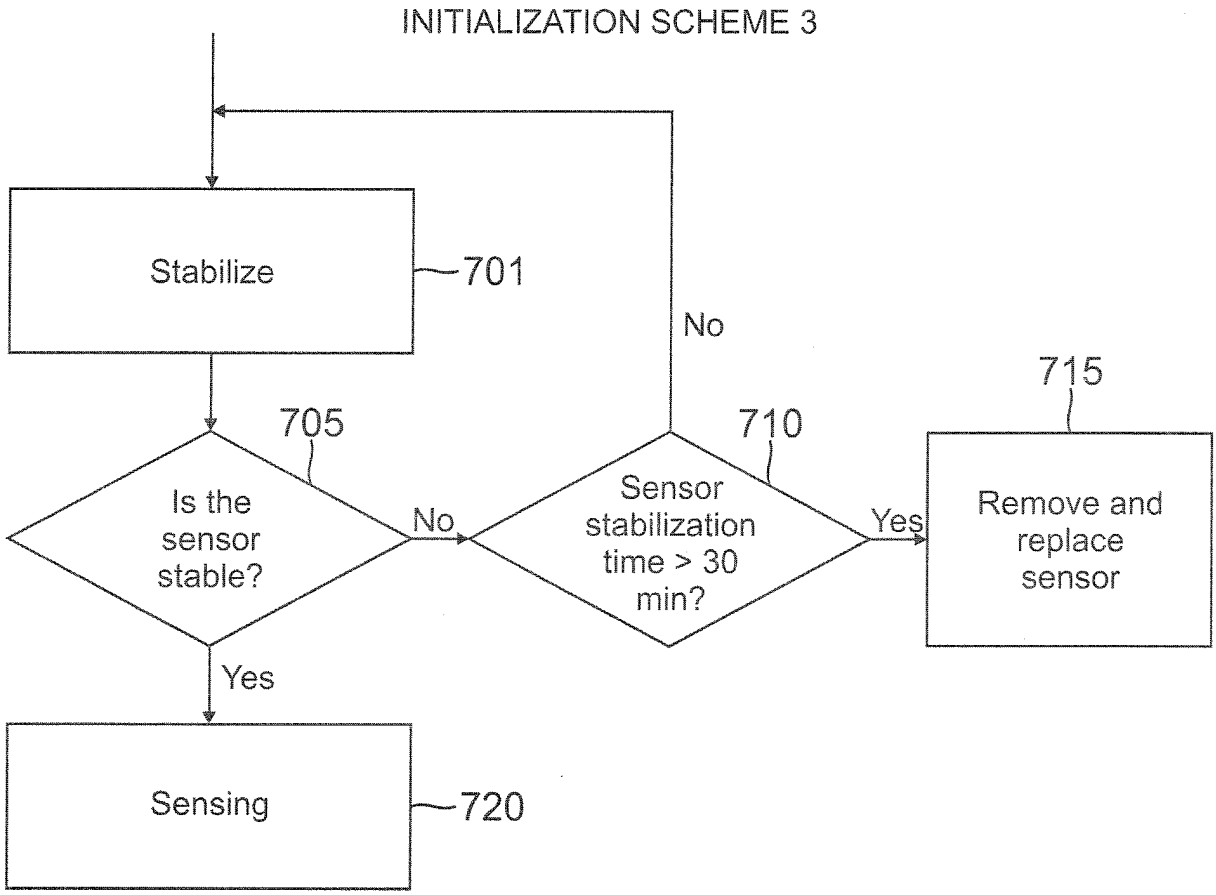

INITIALIZATION SCHEME 3
Stabilize
701
705
Is the sensor stable?
No
710
Sensor stabilization time > 30 min?
Yes
715
Remove and replace sensor
No
Yes
Sensing
720

FIG. 7

FIG. 8A

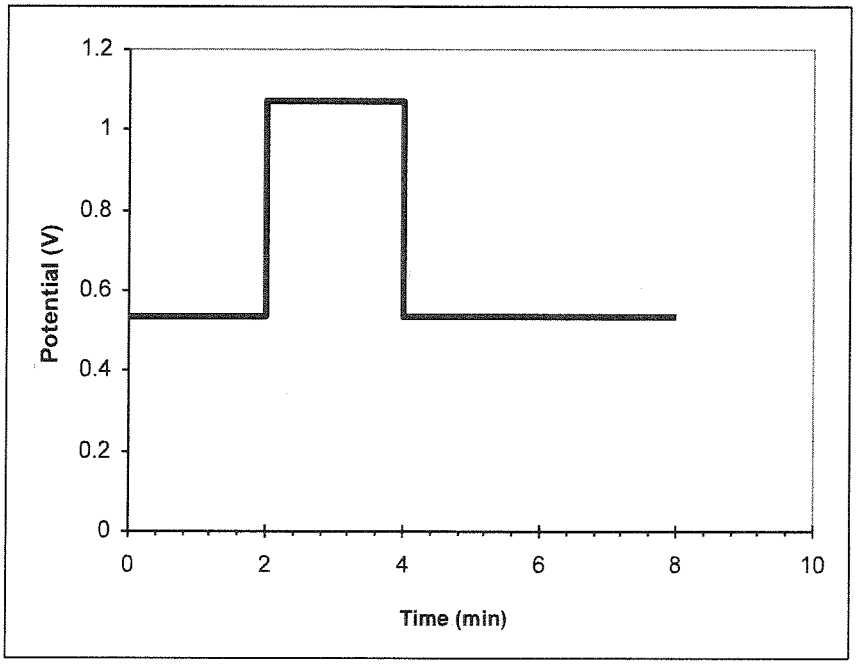

1.2
1
0.8
0.6
0.4
0.2
0
Potential (V)
0
2
4
6
8
10
Time (min)

FIG. 8B

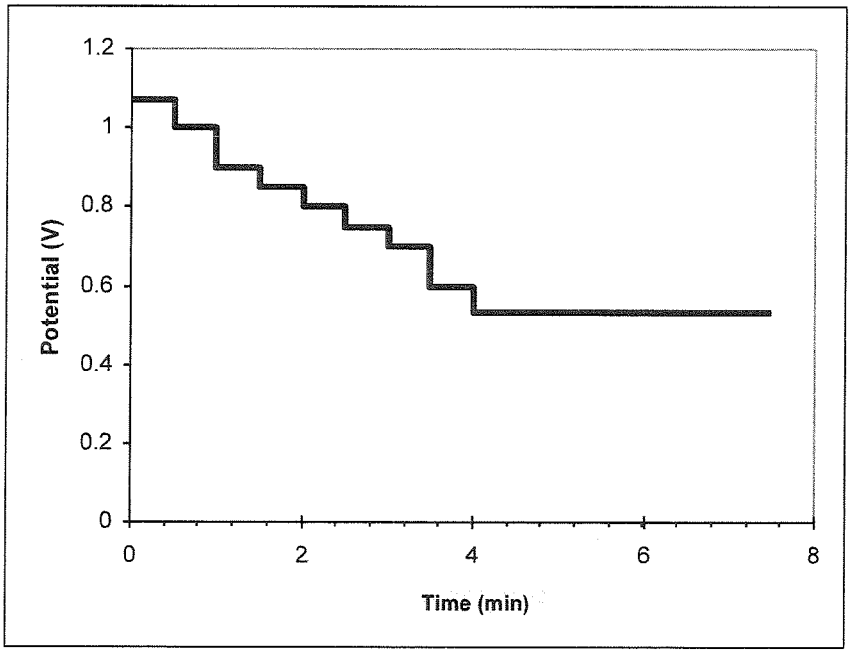

1.2
1
0.8
0.6
0.4
0.2
0
Potential (V)
0
2
4
6
8
Time (min)

FIG. 9A

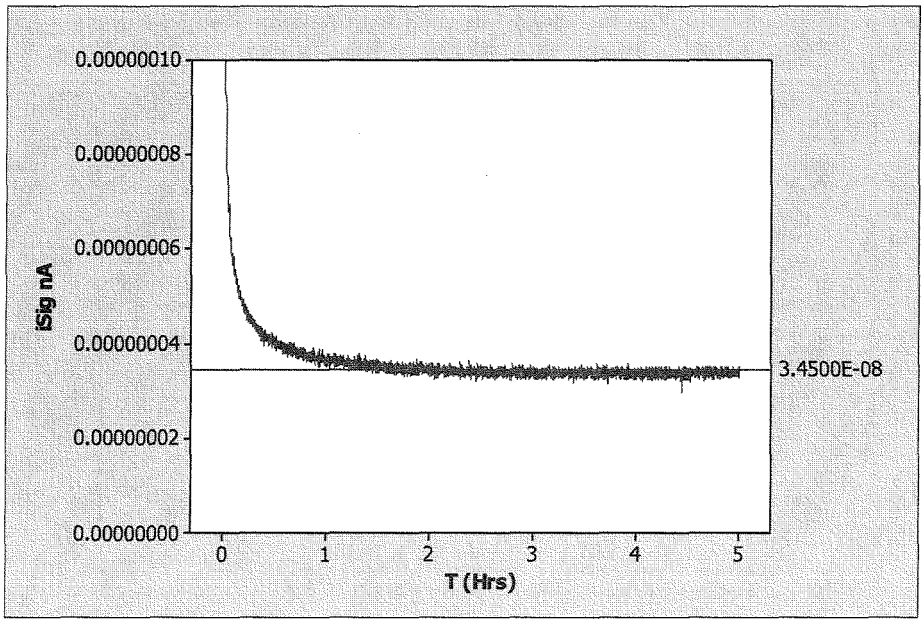
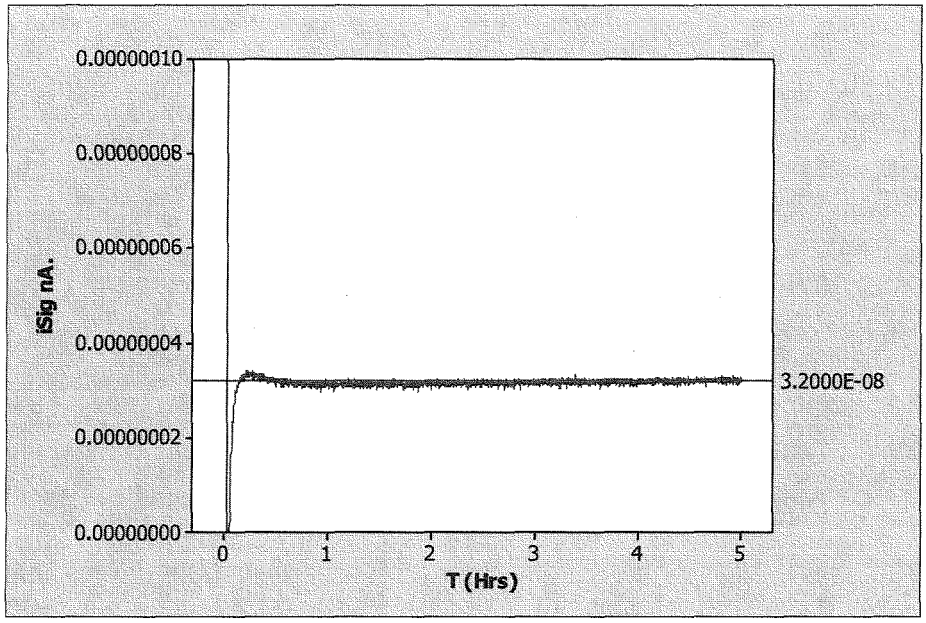

0.00000010
0.00000008
0.00000006
0.00000004
0.00000002
0.00000000
iSig nA
0
1
2
3
4
5
T (Hrs)
3.4500E-08

FIG. 9B


0.00000010
0.00000008
0.00000006
0.00000004
0.00000002
0.00000000
iSig nA.
0
1
2
3
4
5
T (Hrs)
3.2000E-08

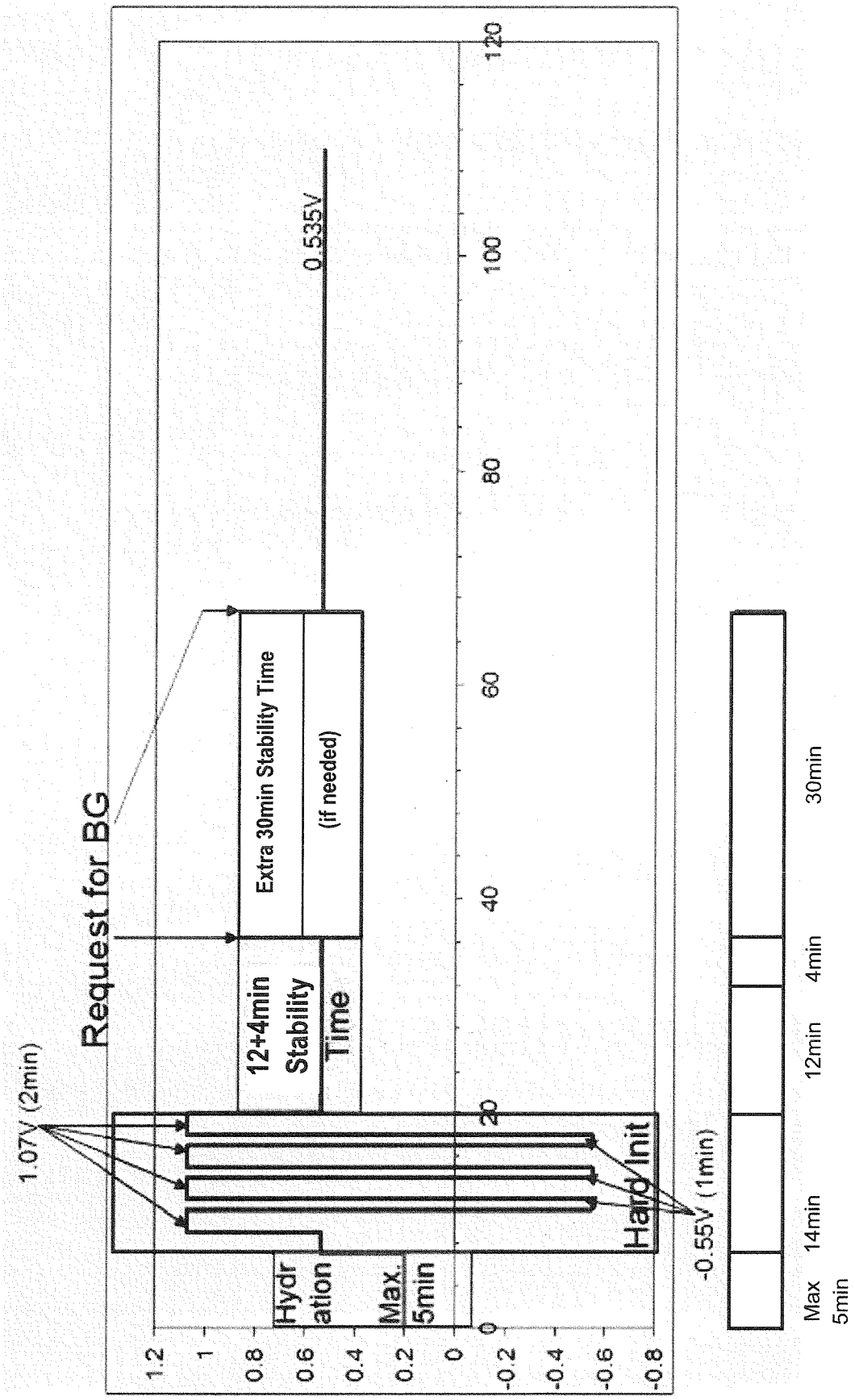

1.07V (2min)
Request for BG
12+4min Stability Time
Extra 30min Stability Time
(if needed)
0.535V
Hydration
Max. 5min
Hard Init
-0.55V (1min)
Max 5min
14min
12min
4min
30min
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
0
20
40
60
80
100
120

FIG. 10

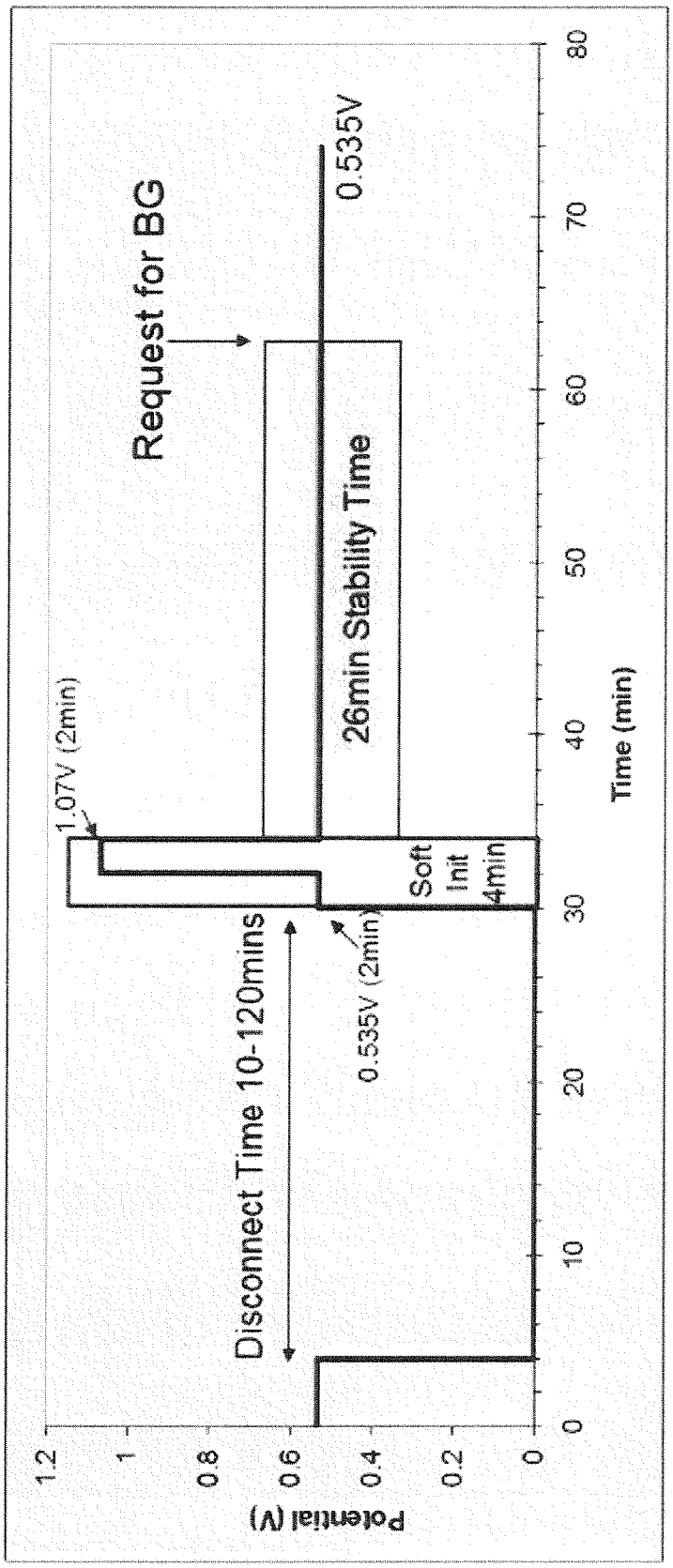

Request for BG
0.535V
26min Stability Time
1.07V (2min)
Soft
Init
4min
Disconnect Time 10-120mins
0.535V (2min)
Potential (V)
Time (min)
0
0.2
0.4
0.6
0.8
1
1.2
0
10
20
30
40
50
60
70
80

FIG. 11

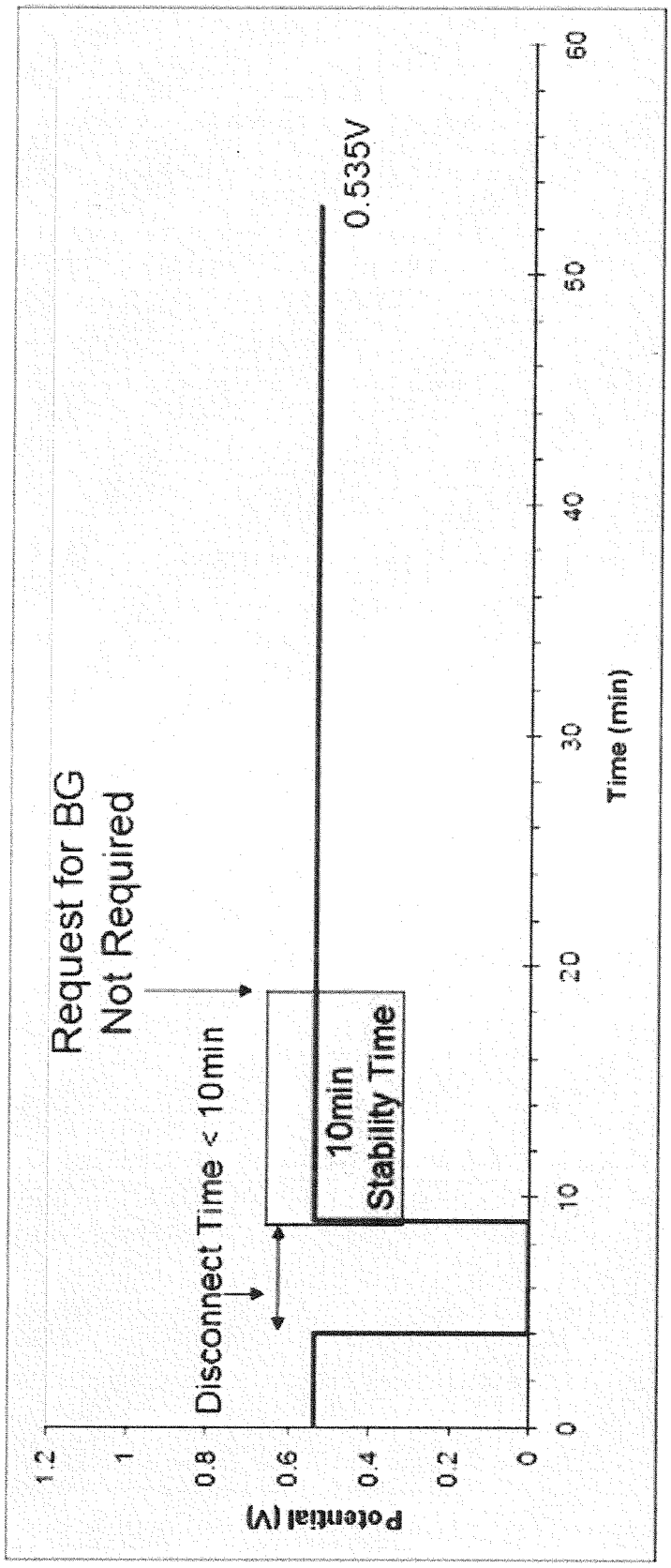

Request for BG
Not Required
Disconnect Time < 10min
10min
Stability Time
0.535V
Potential (V)
Time (min)
0
0.2
0.4
0.6
0.8
1
1.2
0
10
20
30
40
50
60

FIG. 12

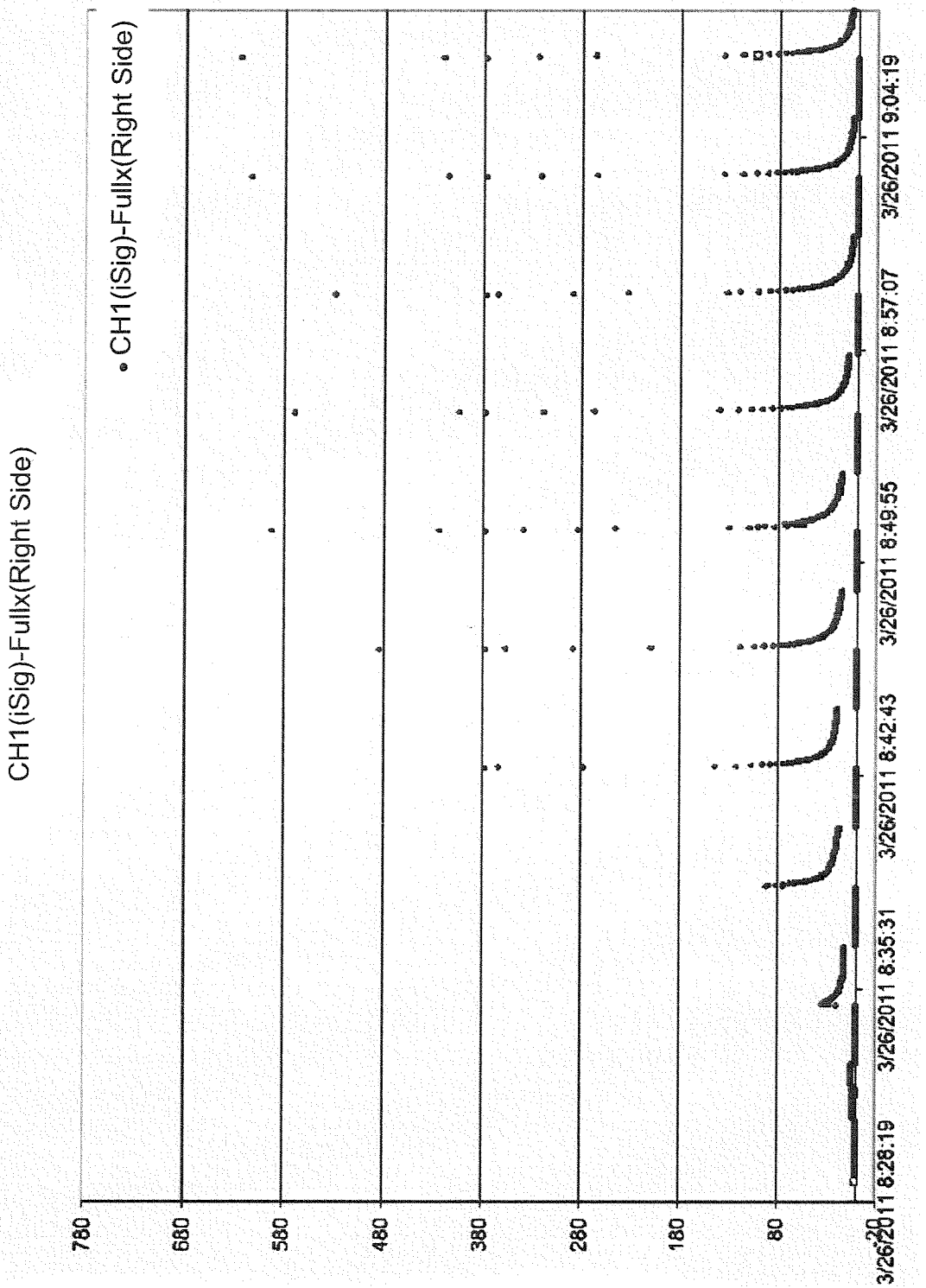

CH1(iSig)-Fullx(Right Side)
CH1(iSig)-Fullx(Right Side)
780
680
580
480
380
280
180
80
-20
3/26/2011 8:28:19
3/26/2011 8:35:31
3/26/2011 8:42:43
3/26/2011 8:49:55
3/26/2011 8:57:07
3/26/2011 9:04:19

FIG. 13

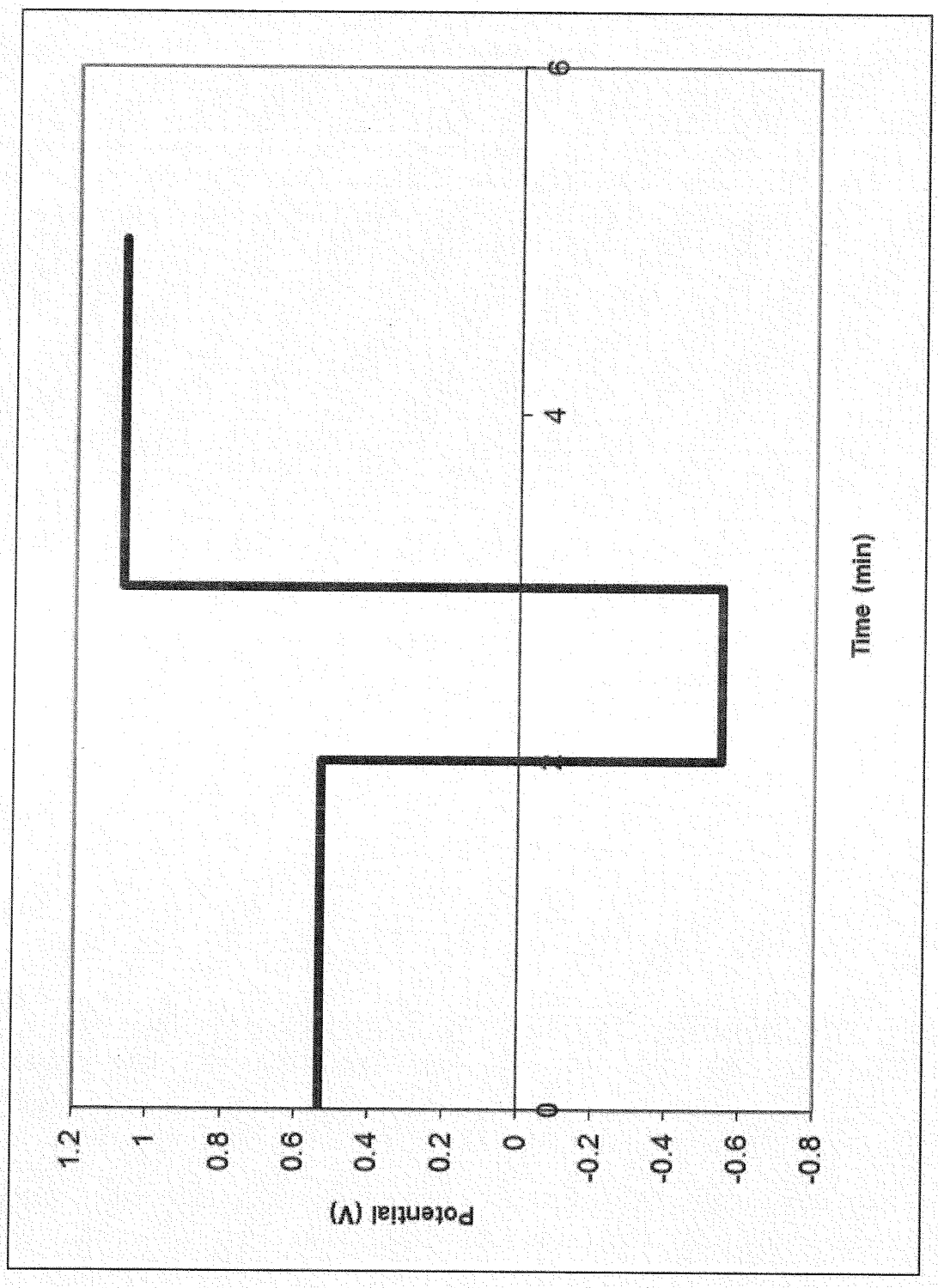


FIG. 14

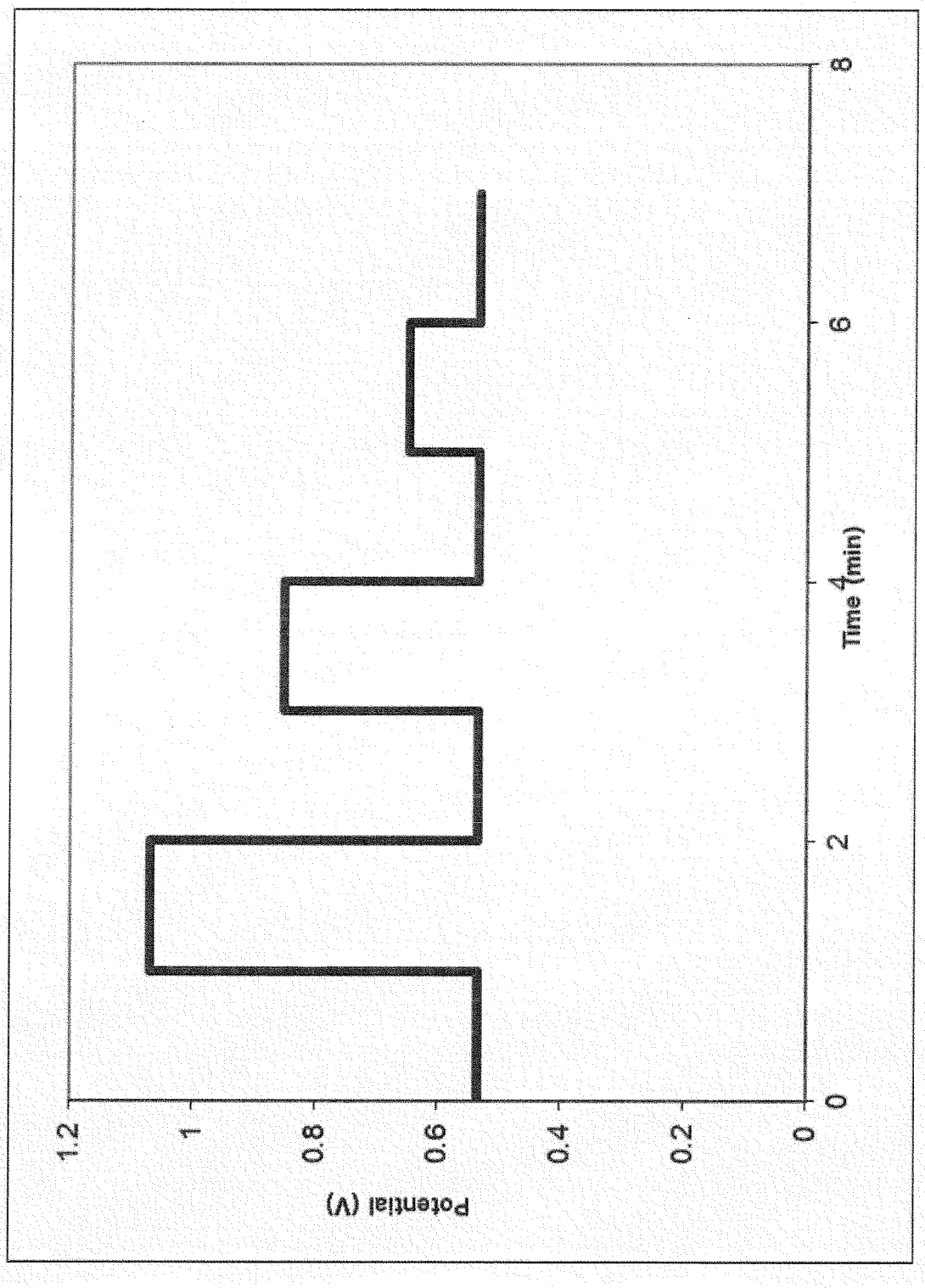


FIG. 15

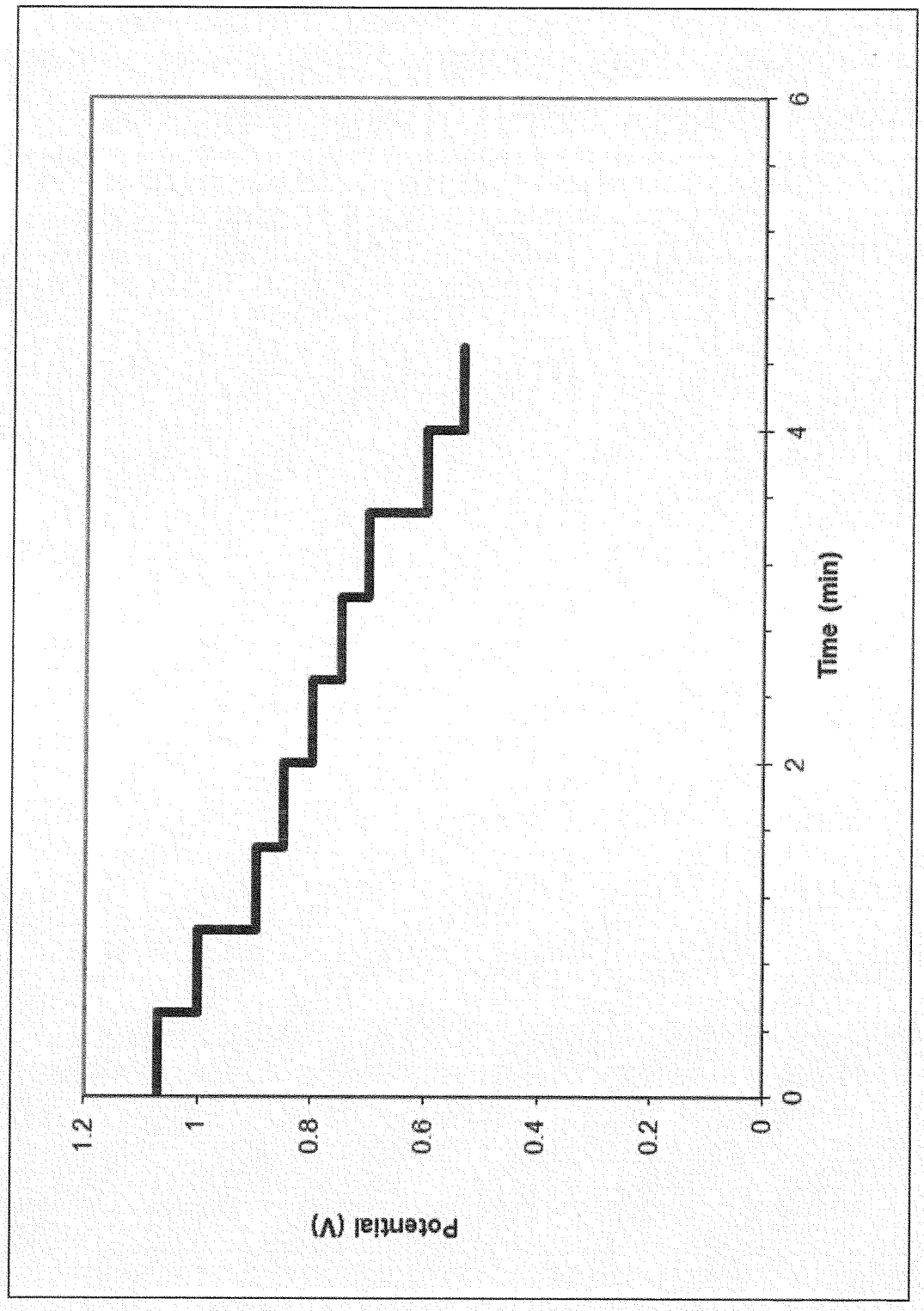


FIG. 16

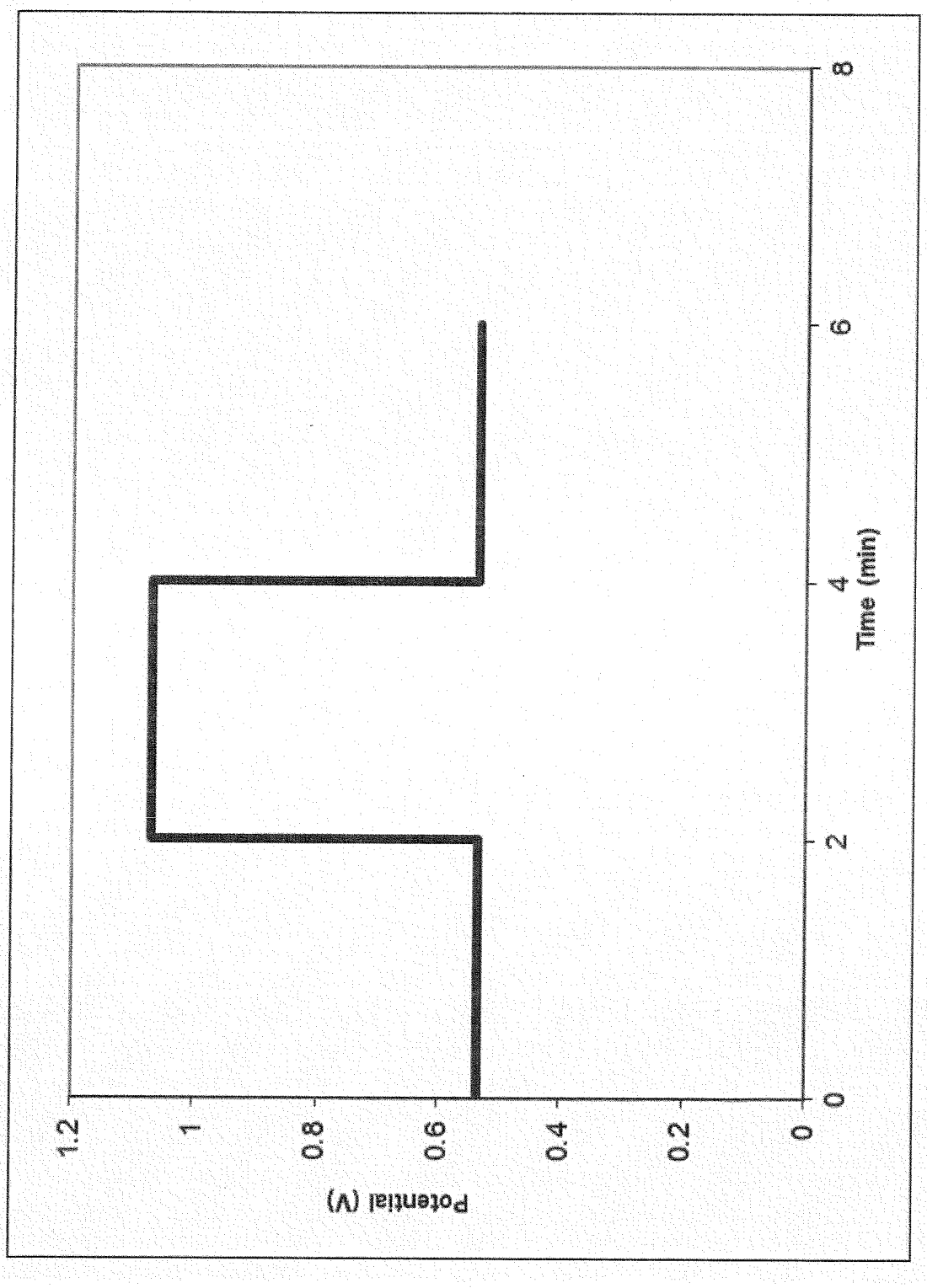


FIG. 17

FIG. 18

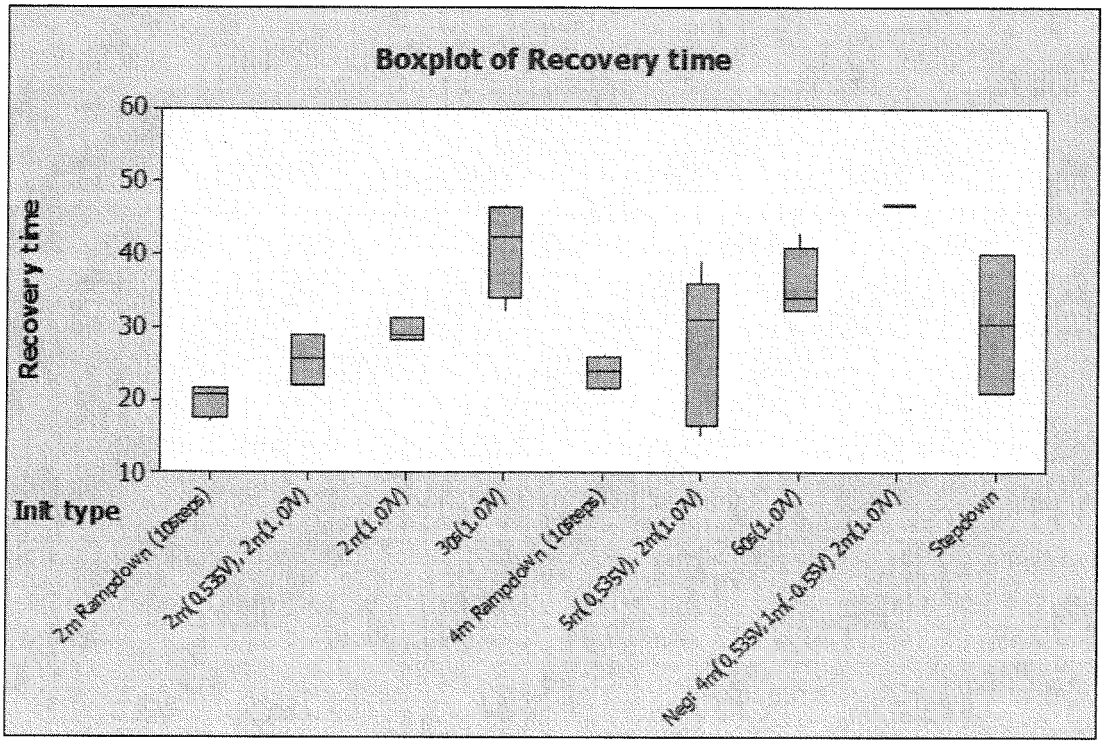
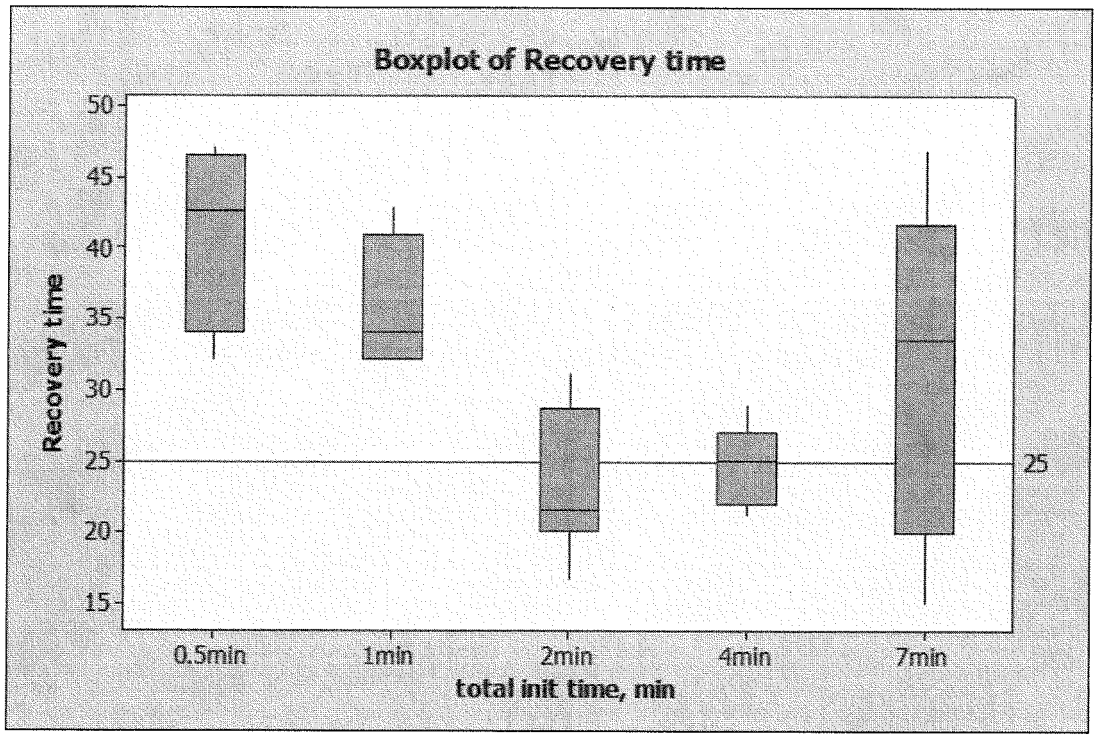

Boxplot of Recovery time
Recovery time
60
50
40
30
20
10
Init type
2m Rampdown (10steps)
2m(0.535V), 2m(1.07V)
2m(1.07V)
3m(1.07V)
4m Rampdown (10steps)
5m(0.535V), 2m(1.07V)
6m(1.07V)
Neg: 4m(0.535V),1m(-0.55V) 2m(1.07V)
Stepdown

FIG. 19


Boxplot of Recovery time
Recovery time
50
45
40
35
30
25
20
15
25
0.5min
1min
2min
4min
7min
total init time, min

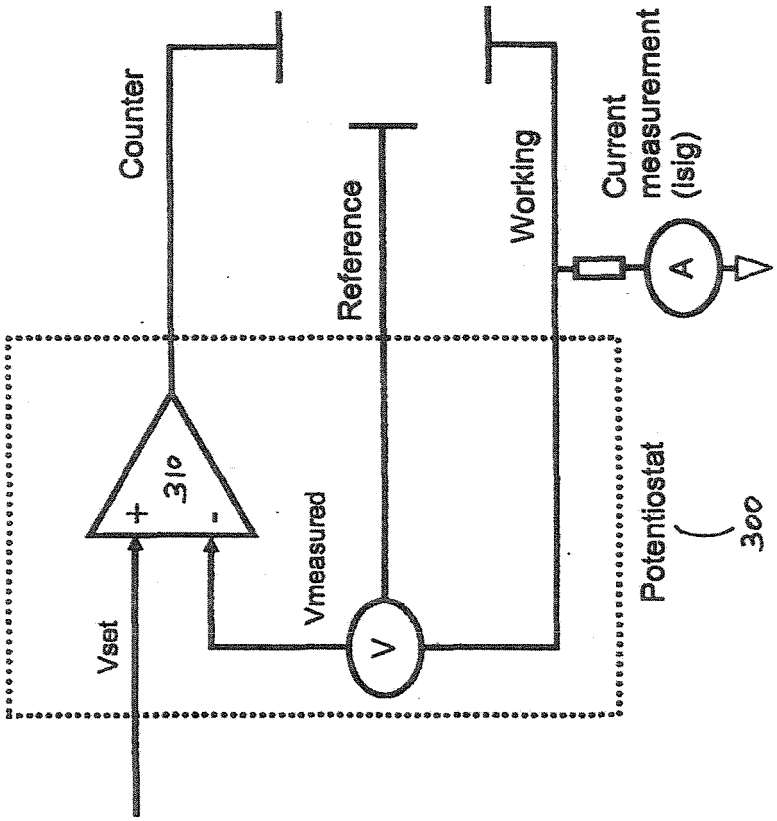

Counter
Reference
Working
Current measurement (Isig)
A
V
Vmeasured
Vset
+
310
-
Potentiostat
300

FIG. 20

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	通过施加电压来优化传感器功能的方法和系统		
公开(公告)号	EP2919653B1	公开(公告)日	2017-06-21
申请号	EP2013799433	申请日	2013-11-13
[标]申请(专利权)人(译)	美敦力迷你迈德公司		
申请(专利权)人(译)	MEDTRONIC MINIMED INC.		
当前申请(专利权)人(译)	MEDTRONIC MINIMED INC.		
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发明人	GOTTLIEB, REBECCA K. CHIU, CHIA-HUNG RAO, ASHWIN K.		
IPC分类号	A61B5/00 A61B5/055 A61B5/1473 G01N27/416 A61B5/145 A61B5/1486 A61B5/1495 G01N27/327		
CPC分类号	A61B5/0004 A61B5/055 A61B5/14532 A61B5/1473 A61B5/1486 A61B5/1495 A61B5/742 A61B2560/0204 A61B2560/0223 G01N27/3274 G01N27/4163		
优先权	13/675813 2012-11-13 US		
其他公开文献	EP2919653A1		
外部链接	Espacenet		

摘要(译)

提供了一种用于初始化分析物传感器的方法，例如葡萄糖传感器。在传感器已断开并重新连接的情况下，确定断开时间并基于断开时间选择传感器初始化协议。传感器初始化协议可以包括将第一系列电压脉冲施加到传感器。还提供了一种用于检测传感器的水合的方法。