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(54) **Systems and methods for improving electrochemical analyte sensors**

System und Verfahren zur Verbesserung von elektrochemischen Analytsensoren

Système et procédé pour l'amélioration de capteurs d'analyte

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Description

Field of the Invention

[0001] The present invention relates generally to systems and methods involving the electrochemical detection or measurement of analytes.

Background of the Invention

[0002] A variety of sensors are known that use an electrochemical cell to provide output signals by which the presence or absence of an analyte in a sample can be determined. For example in an electrochemical cell, an analyte (or a species derived from it) that is electro-active generates a detectable signal at an electrode, and this signal can be used to detect or measure the presence and/or amount within a biological sample. In some conventional sensors, an enzyme is provided that reacts with the analyte to be measured, and the byproduct of the reaction is qualified or quantified at the electrode. An enzyme has the advantage that it can be very specific to an analyte and also, when the analyte itself is not sufficiently electro-active, can be used to interact with the analyte to generate another species which is electro-active and to which the sensor can produce a desired output. In one conventional amperometric glucose oxidase-based glucose sensor, immobilized glucose oxidase catalyses the oxidation of glucose to form hydrogen peroxide, which is then quantified by amperometric measurement (for example, change in electrical current) through a polarized electrode.

[0003] One problem with electrochemical sensors is that they can electrochemically react not only with the analyte to be measured (or by-product of the enzymatic reaction with the analyte), but additionally can react with other electroactive species that are not intentionally being measured (for example, interfering species), which causes an increase in signal strength due to these "interfering species". In other words, interfering species are compounds with an oxidation or reduction potential that overlaps with the analyte to be measured (or by product of the enzymatic reaction with the analyte). For example, in a conventional amperometric glucose oxidase-based glucose sensor wherein the sensor measures hydrogen peroxide, interfering species such as acetaminophen, ascorbate, and urate, are known to produce inaccurate signal strength when they are not properly controlled. Moreover, signal interference can result from effects, such as local ischemia, or the like, which cause the signal to produce erroneous output.

[0004] Some glucose sensors utilize a membrane system that blocks at least some interfering species, such as ascorbate and urate. In some such examples, at least one layer of the membrane assembly includes a porous structure that has a relatively impermeable matrix with a plurality of "micro holes" or pores of molecular dimensions, such that transfer through these materials is primarily due to passage of species through the pores (for example, the layer acts as a microporous barrier or sieve blacking interfering species of a particular size). In other such examples, at least one layer of the membrane assembly defines a permeability that allows selective dissolution and diffusion of species as a solute through the layer. Unfortunately, it is difficult to find membranes that are satisfactory or reliable in use, especially in vivo, which effectively block all interferants and/or interfering species.

[0005] US4805624 discloses an improved low-potential electrochemical sensors and method for rapid, accurate, in vitro and in vivo measurement of the concentration of carbohydrates in organic or biological fluids by cyclic voltammetric or coulometric scan within a restricted voltage domain and identifying one or more oxidation and/or reduction current peaks, with the concentration of the carbohydrate being a linear function of the current output.

[0006] US2002/123048 discloses a microelectromechanical systems (MEMS) and integrated circuit (IC) based bio-sensor capable of sensing or detecting various ionic molecules and macromelecules (DNA, RNA or protein).

[0007] US6275717 discloses a method of calibrating an analyte sensor in vivo, by providing a first predetermined stimulus to the sensor when the sensor is applied to a subject to produce a first sensor signal, measuring the first sensor signal, and determining a calibration function based on the first measured sensor signal resulting from the predetermined stimulus.

[0008] US2003/119208 discloses an electrochemical immunosensor including a biological sensor layer with an antigen or a ligand residue immobilized thereon, and a biochemical analyte detection kit and method for electrochemically signaling a biological reaction occurring in the biological sensor layer.

Summary of the Invention

[0009] Accordingly, the preferred embodiments provide systems and methods for improving the quality of analyte-measuring devices by identifying interfering species on an analyte signal. The preferred embodiments further provide systems and methods for reducing or eliminating the effects of interfering species on an analyte signal by obtaining differential measurements based on multiple bias potential settings.

[0010] In a first embodiment, a method for identifying an interfering species using an analyte-measuring device is provided, the method comprising providing at least one electrochemical sensor; measuring a first signal output obtained

at a first bias potential setting; measuring a second signal output obtained at a second bias potential setting; and comparing the first signal output with the second signal output to determine a differential measurement, thereby identifying a presence of an interfering species in a liquid.

[0011] In an aspect of the first embodiment, the interfering species is negatively identified when the differential measurement is below a set threshold.

[0012] In an aspect of the first embodiment, the interfering species is positively identified when the differential measurement is above a set threshold.

[0013] In an aspect of the first embodiment, the method further comprises calculating an analyte concentration from the differential measurement, wherein the step of calculating is performed when interfering species are positively identified.

[0014] In an aspect of the first embodiment, the sensor is configured to switch between the first bias potential setting and the second bias potential setting.

[0015] In an aspect of the first embodiment, the step of providing comprises providing a first sensor at the first bias potential setting and a second sensor at the second bias potential setting.

[0016] In an aspect of the first embodiment, the interfering species is acetaminophen.

[0017] In an aspect of the first embodiment, the analyte measuring device is a glucose sensor.

[0018] In an aspect of the first embodiment, the liquid comprises blood.

[0019] In an aspect of the first embodiment, the liquid is a bodily fluid, such as interstitial fluid.

[0020] The invention provides a method for measuring an analyte concentration in a continuous and transcutaneous electrochemical sensor, the method comprising:

scanning the electrochemical sensor by

(i) varying a bias potential applied to the electrochemical sensor, and
(ii) measuring signal outputs of the electrochemical sensor as the bias potential is varied;

comparing the signal outputs; and
calculating an analyte concentration measurement based on the comparison of the signal outputs.

[0021] The invention also provides a device for measuring an analyte concentration, the device comprising:

a continuous and transcutaneous electrochemical sensor comprising two electrodes; and
electronic circuitry operatively coupled to the two electrodes, wherein the electronic circuitry is configured to

(i) scan the electrochemical sensor by varying a bias potential between the two electrodes, and measure signal outputs of at least one of the two electrodes as the bias potential is varied, and
(ii) compare the signal outputs; and
(iii) calculate an analyte concentration measurement based on the signal outputs.

[0022] In an aspect of the first embodiment, the method further comprises deriving an analyte concentration from the first signal output and the second signal output to determine an analyte concentration.

[0023] In a second embodiment, an analyte-measuring device for measuring a concentration of an analyte and identifying an interfering species is provided, the device comprising at least one electrochemical sensor configured to provide a differential measurement of a current output signal at a first bias potential and at a second bias potential, wherein the differential measurement is employed to identify a species interfering with the analyte concentration.

[0024] In an aspect of the second embodiment, the electrochemical sensor is configured to switch between the first bias potential setting and the second bias potential setting.

[0025] In an aspect of the second embodiment, the device further comprises a first sensor at the first bias potential setting and a second sensor at the second bias potential setting.

[0026] In an aspect of the second embodiment, the analyte comprises glucose and the interfering species comprises acetaminophen.

[0027] In a third embodiment, a method for identifying a signal interference in an analyte-measuring device is provided, the method comprising providing at least one electrochemical sensor; measuring a first signal output obtained at a first bias potential setting; measuring a second signal output at a second bias potential setting; comparing the first signal output with the second signal output to determine a differential measurement, thereby identifying an interference in the signal outputs.

[0028] In an aspect of the third embodiment, the method further comprises deriving an analyte concentration from the first signal output and the second signal output to determine an analyte concentration.

[0029] In an aspect of the third embodiment, the method further comprises measuring a third signal output at a third bias potential setting indicative of an additional interference in the signal outputs.

[0030] In an aspect of the third embodiment, the analyte comprises glucose and the interfering species comprises acetaminophen.

[0031] In a fourth embodiment, an analyte-measuring device for measuring a concentration of analyte and identifying interference in signal output is provided, the device comprising the device comprising at least one electrochemical sensor configured to provide a differential measurement of a current output signal at a first bias potential setting and at a second bias potential setting, whereby an interference within the analyte concentration measurement signal is determined.

[0032] In an aspect of the fourth embodiment, the device is configured to derive an analyte concentration from the measurements at the first potential bias setting and at the second bias potential setting.

[0033] In an aspect of the fourth embodiment, the analyte comprises glucose and the interfering species comprises acetaminophen.

Brief Description of the Drawings

[0034]

Fig. I is a circuit diagram of a potentiostat that controls a typical three-electrode system.

Fig. 2 is a schematic graph of current vs. voltage obtained from cyclic voltammetry of hydrogen peroxide and acetaminophen.

Fig. 3 is a graph that shows the effects of bias potential on the measurement of glucose and acetaminophen.

Detailed Description of the Preferred Embodiment

[0035] The following description and examples illustrate some exemplary embodiments of the disclosed invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a certain exemplary embodiment should not be deemed to limit the scope of the present invention.

Definitions

[0036] In order to facilitate an understanding of the disclosed invention, a number of terms are defined below.

[0037] 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 detect an analyte. In one embodiment, the sensor includes an electrochemical cell that has a working electrode (anode), a reference electrode and a counter electrode (cathode) 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. The counter electrode typically has a greater electrochemically reactive surface area than the working electrode. 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.

[0038] The term "signal output," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an analog or digital signal directly related to the measured analyte from the analyte-measuring device. The term broadly encompasses a single point, or alternatively, a plurality of time spaced data points from a substantially continuous glucose sensor, which comprises individual measurements taken at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes or longer.

[0039] The term "electrochemical cell," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a device in which chemical energy is converted to electrical energy. Such a cell typically consists of two or more electrodes held apart from each other and in contact with an electrolyte solution. Connection of the electrodes to a source of direct electric current renders one of them negatively charged and the other positively charged. Positive ions in the electrolyte migrate to the negative electrode (cathode) and there combine with one or more electrons, losing part or all of their charge and becoming new ions having lower charge or neutral atoms or molecules; at the same time, negative ions migrate to the positive electrode (anode) and transfer one or more electrons to it, also becoming new ions or neutral particles. The overall effect of the two processes is the transfer of electrons from the negative ions to the positive ions, a chemical reaction.

[0040] The term "potentiostat," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an electrical system that controls the potential between the working and reference electrodes of a three-

electrode cell at a preset value independent of resistance changes between the electrodes. It forces whatever current is necessary to flow between the working and counter electrodes to keep the desired potential, as long as the needed cell voltage and current do not exceed the compliance limits of the potentiostat.

[0041] The term "bias potential," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the voltage difference between two points in a circuit, which is the cause of the flow of a current, if sufficient analyte is present.

[0042] The term "differential measurement," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the difference between multiple signal output measurements at different bias potential settings.

[0043] The terms "interferants" and "interfering species," as used herein, are broad terms and are used in their ordinary sense, including, without limitation, effects and/or species that interfere with the measurement of an analyte of interest in a sensor to produce a signal that does not accurately represent the analyte measurement. In one example of an electrochemical sensor, interfering species are compounds with an oxidation or reduction potential that overlaps with the analyte to be measured. In another example of an enzyme-based electrochemical sensor, local ischemia is an interferant that produces error in the output signal due to lack of sufficient oxygen to react with the enzyme.

Overview

[0044] The preferred embodiments relate to the use of an analyte-measuring device that measures a concentration of analyte or a substance indicative of the concentration or presence of the analyte. In some embodiments, the analyte-measuring device measures glucose, lactate, oxygen, or the like. In some embodiments, the analyte-measuring device is a continuous device, for example a subcutaneous, transdermal, or intravascular device. In some embodiments, the device can analyze a plurality of intermittent blood samples. In some embodiments, the device can analyze a single blood sample. The analyte-measuring device can use any method of analyte-measurement, including enzymatic, chemical, physical, electrochemical, or the like.

[0045] The analyte-measuring device uses any known method, including invasive, minimally invasive, and non-invasive sensing techniques, to provide an output signal indicative of the concentration of the analyte. The output signal is typically a raw signal that is used to provide a useful value of the analyte to a user, such as a patient or doctor, who may be using the device.

[0046] In one embodiment, the analyte-measuring device measures glucose using a transcutaneous glucose sensor, such as described in co-pending U.S. Provisional Patent Application Nos. 60/587,787 and 60/614,683. In another embodiment, the analyte-measuring device measures glucose using an electrochemical cell with a membrane system, such as described in U.S. Patent 6,001,067 and U.S. Published Patent Application 2003/0032874. In this embodiment, the membrane system provides an interference domain including a thin membrane that can limit diffusion of high molecular weight species. The interference domain serves to allow certain analytes and other substances that are to be measured by the electrodes to pass through, while preventing passage of other substances, including interfering species, such as ascorbate and urate. In one exemplary embodiment, the interference domain is constructed from polyurethane and has a thickness of about 0.1 to 5 microns. Although the interference domain does successfully block some interfering species described above, it does not sufficiently block other interfering species, such as acetaminophen.

[0047] 4-Acetaminophenol (4-AAP, common name acetaminophen. or paracetamol) is a nonprescription medication useful in the treatment of mild pain or fever, for example, acetaminophen can be found in Tylenol®. Acetaminophen is a commonly taken medication, and when ingested, can cause transient, non-glucose related signal artifacts in a glucose-measurement device. It is noted that much of the description of the preferred embodiments focuses on identifying acetaminophen, a known interfering species in the art of amperometric glucose sensors because it generates a positive signal independent of glucose concentration (for example, when measuring hydrogen peroxide). However, the preferred embodiments can be implemented to identify numerous other known interfering species in other known electrochemically-based analyte-measuring devices.

Description

[0048] Fig. 1 is a circuit diagram of a conventional potentiostat that controls a typical three-electrode system of an electrochemical cell, which can be employed with an electrochemical sensor such as described above. The potentiostat includes a working electrode (10), a reference electrode (12), and a counter electrode (14). Conventionally, the voltage applied to the working electrode (10) is a constant value (for example, +1.2V with respect to battery ground) and the voltage applied to the reference electrode (12) is also set at a constant value (for example, +0.6V with respect to battery ground) such that the bias potential (V_{BIAS}) applied between the working and reference electrodes is set at a constant value (for example, +0.6V). The counter electrode is configured to have a constant current (equal to the current being measured by the working electrode), which is accomplished by driving the voltage at the counter electrode (14) to a potential that balances the current going through the working electrode (10) such that current does not pass through the

reference electrode (12). In addition, the counter electrode acts as a negative feedback circuit to maintain the desired voltage at the reference electrode.

[0049] In one embodiment of a glucose sensor such as described herein, a membrane system that contains glucose oxidase catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate, such as described above. Therefore, for each glucose molecule metabolized there is an equivalent change in molecular concentration in the co-reactant O_2 and the product H_2O_2. Consequently, one can use an electrode (for example, working electrode (10)) to monitor the concentration-induced current change in either the co-reactant or the product (for example, H_2O_2) to determine glucose concentration. However, if an interfering species exists with an oxidation or reduction potential that overlaps with the co-reactant or the product (for example, H_2O_2), then the current change does not accurately reflect glucose concentration. Additionally, if an oxygen deficiency exists, such that insufficient oxygen is present to react with an analyte at the enzyme for example, then the current change similarly does not accurately reflect glucose concentration.

[0050] It is noted that a glucose sensor signal obtained from glucose when the bias potential is set between about +0.35V and about +0.75V is substantially constant under standard physiologic conditions. In contrast, a glucose sensor signal obtained from interfering species when the same bias potentials are set (between about +0.35V and about +0.75V) is not substantially constant under standard physiologic conditions. Current-voltage curves are known for various analytes and are available in the literature, for example such as described by Lerner, H.; Giner, J.; Soeldner, J. S.; Colton, C. K. An implantable electrochemical glucose sensor. Ann N Y Acad Sci 1984, 428, 263-278. Fig. 2 is a schematic graph of current vs. voltage obtained from cyclic voltammetry (also known as a CV-curve) for hydrogen peroxide and acetaminophen. The x-axis represents bias potential applied to an electrochemical cell in Volts (V); the y-axis represents current output measured by the working electrode of the electrochemical cell in nanoAmps (nA). The schematic graph generally shows current output of an electrochemical enzyme-based glucose sensor as the bias potential is varied from about 0.1V to about 1.0V. Current output is shown without units because it is the differential response, rather than the actual measurement, of signal output that is being generally taught herein, As illustrated by the graph, acetaminophen (22) increases the total signal (24), resulting in an inaccurate glucose measurement that is significantly higher than the actual value.

[0051] The hydrogen peroxide curve (20) can be obtained by exposing an electrochemical sensor to glucose (without acetaminophen) and varying the bias potential from about 0.1 V to about 1.0V. The graph shows the response of the glucose sensor to hydrogen peroxide; generally, the current increases at a relatively constant rate from about 0.1V to about 0.4V, after which it plateaus until about 0.6V, and then continues to increase at a slightly slower rate.

[0052] The acetaminophen curve (22) can be obtained by exposing an electrochemical sensor to acetaminophen (without glucose), and varying the bias potential from about 0.1V to about 1.0V. The graph shows the response of the glucose sensor to acetaminophen; generally, the acetaminophen curve (22) increases relatively slowly from about 0.1V to about 0.4V, showing a minimal current output of the acetaminophen signal (at 0.4V) relative to the higher glucose signal (at 4.0V). From 0.4V to 0.6V, the acetaminophen. curve (22) increases to a value at 0.6V approximately equal to the value of the hydrogen peroxide signal at that same bias potential, after which the acetaminophen. curve (22) continues to increase at a slightly slower rate.

[0053] The total signal (24) shows the curve that can be obtained by exposing an electrochemical sensor to glucose and acetaminophen. It is particularly noted that at 0.6 V, acetaminophen. adds significantly to the signal output, which cause erroneously high readings of the glucose concentration when a presence or amount of acetaminophen is unknowingly introduced. In other words, the output signal of an electrochemical sensor may not be indicative of the actual glucose concentration due to signal interference from acetaminophen. Therefore, the preferred embodiments provide systems and methods for identifying the presence of an interfering species and optionally deriving and analyte value therefrom.

[0054] In general, the preferred embodiments measure the difference between the sensor signal at low and high bias potential settings, hereinafter referred to as the "differential measurement," which at the minimum enables identification of signal contribution from the interfering species. A differential measurement that is relatively low or shows substantial equivalence (for example, below a set threshold) identifies a substantially glucose-only signal. In contrast, a differential measurement that is relatively higher or does not show substantial equivalence (for example, above a set threshold) identifies the presence of interfering species (for example, acetaminophen) on a glucose signal.

[0055] In some embodiments, the differential measurement can be obtained from a single analyte-measuring device with multiple sensors. In one such example, the first sensor can be biased at a voltage of about +0.4V and the second sensor can be biased at a voltage about +0.6V. The two sensors can be provided under the same membrane system or separate membrane systems. The two sensors can share the same reference and/or counter electrodes or can utilize separate reference and/or counter electrodes.

[0056] In some embodiments, the differential measurement can be obtained by switching the bias potential of a single sensor between the two measurement potentials. The bias potentials can be held at each respective setting (high and low bias settings) for as short as milliseconds to as long as minutes or hours. Pulsed amperometric detection (PED) is one method of quickly switching voltages, such as described in Bisenberger, M.; Brauchle, C.; Hampp, N. A triple-step

potential waveform at enzyme multisensors with thick-film gold electrodes for detection of glucose and sucrose. Sensors and Actuators 1995, B, 181-189. In some embodiments, bias potential settings are held long enough to allow equilibration.

[0057] Fig. 3 is a graph that illustrates an experiment wherein acetaminophen was identified as an interfering species during glucose measurements. The experiment measured glucose and glucose with acetaminophen at different bias potential settings. The x-axis represents bias potential (V); the y-axis represents the sensor signal (current) measured by the sensor in nanoAmps (nA). The glucose sensor was constructed such as described in U.S. Patent 6,001,067 and U.S. Published Patent Application 2003-0032874 A1. Initially, the glucose sensor was set with a bias potential of about +0.6V and placed in a solution with a glucose concentration of 400 mg/dL (no acetaminophen). The resulting current output was about 9.2 nA. Then, the bias potential of the glucose sensor was set to +0.4V and maintained with the sensor in the 400-mg/dL glucose solution. The resulting current output settled at about 8.7 nA.

[0058] Next, 3.0 mg/dL acetaminophen was added to the 400 mg/dL glucose solution with the +0.4V bias potential maintained on the sensor. The resulting current output increased slightly and settled at about 9.9 nA. Finally, the bias potential was returned to +0.6V while the glucose sensor remained in the glucose and acetaminophen solution. The resulting current output settled at about 16.2nA.

[0059] Table 1 shows a comparison of the signal at the two bias potentials in the presence of glucose only and in the presence of glucose and acetaminophen. A small differential measurement is observed in the presence of glucose only (about 0.5 nA or 6%). In contrast, a large differential measurement is observed in the presence of glucose and acetaminophen (about 6.3 nA or 71%). Therefore, by measuring current at +0.4 V and +0.6 V bias, a quality assessment of the glucose measurement can be obtained from the measurement differential (delta) in current.

Table 1.

Bias	Glucose	Glucose and Acetaminophen
+0.4V	8.7 nA	9.9 nA
+0.6 V	9.2 nA	16.2 nA
Differential Measurement	0.5 nA	6.3 nA

[0060] In some embodiments, the device can utilize the differential measurements as a measure of accuracy for the device. If interfering species (for example, acetaminophen or interference from low oxygen, for example) is observed, the device can be programmed to discontinue glucose information to the patient until an insignificant differential measurement is restored, for example.

[0061] In some embodiments, when the device measures a level of inaccuracy, the signal measurements can be adjusted to provide a more accurate glucose signal. Namely, the measured difference in current between the signals can be utilized to calculate the glucose signal without the interfering species. For example, the following first and second equations represent the relationship between the glucose and acetaminophen signal at first and second bias potentials, respectively:

$$Y_{0.4V} = \alpha[A] + \beta[B] \qquad \text{(Equation 1)}$$

$$Y_{0.6V} = \delta[A] + \gamma[B] \qquad \text{(Equation 2)}$$

[0062] In these equations, *Y* represents the total current of the signal output of the sensor in nanoAmps at each respective bias potential setting, [A] represents the concentration of glucose, [B] represents the concentration of acetaminophen, and α, β, δ, and γ represent constants associated with glucose and acetaminophen at each respective bias potential setting. When these constants are known, glucose measurements can be taken at 0.4V and 0.6V, after which Equations 1 and 2 can be solved to determine the signal concentration due to glucose and acetaminophen separately, thereby enabling the reporting of the true glucose signal.

[0063] In some embodiments, these constants (α, β, δ, and γ) can be obtained by *in vitro* and/or *in vivo* calibration. *In vitro* calibration of α and δ can be accomplished by measuring a sensor exposed to a known concentration of glucose solution [A] (namely, without acetaminophen) at bias potential settings of 0.4V and 0.6V to obtain $Y_{0.4V}$ and $Y_{0.6V}$, respectively; by knowing [A], $Y_{0.4V}$, and $Y_{0.6V}$, the glucose-specific portions of Equations 1 and 2 ($Y_{0.4V} = \alpha[A]$and $Y_{0.6V} = \delta[A]$) can be solved to determine α and δ. Similarly, *in vitro* calibration of β and γ can be accomplished by measuring a sensor exposed to a known concentration of acetaminophen solution [B] (namely, without glucose) at bias potential settings of 0.4V and 0.6V to obtain $Y_{0.4V}$ and $Y_{0.6V}$, respectively; by knowing [B], $Y_{0.4V}$, and $Y_{0.6V}$, the acetaminophen-

specific portions of Equations 1 and 2 ($Y_{0.4V} = \beta[B]$ and $Y_{0.6V} = \gamma[B]$) can be solved to determine β and γ.

[0064] In some embodiments, the device can benefit from *in vivo* calibration of the constants. In one such example, an acetaminophen-free *in vivo* environment is created. The glucose concentration is then measured (for example, using a blood glucose meter, Yellow Springs Instrument (YSI), or the like), from which α and δ can be calculated such as described with reference to the *in vitro* glucose constants calibration, above. Similarly, acetaminophen constants β and γ can be calculated empirically (*in vivo*) and the ratio of glucose constants (α and δ) to acetaminophen constants (β and γ) *in vivo* can be determined. Using the known ratio of glucose constants to acetaminophen constants, Equations 1 and 2 can be solved to determine the glucose signal without the interfering species.

[0065] While certain examples of calibration *in vitro* and *in vivo* have been provided, other calibration methods can be applied to the preferred embodiments to determine glucose and acetaminophen concentrations. Additionally, although specific examples have been drawn toward a glucose sensor that eliminates acetaminophen. as an interfering species, the concepts can by applied to other analyte sensors with other interfering species. Furthermore, multiple (more than two) analytes and/or interfering species can be determined using the concepts described here by increasing the number of measurements taken. Even more, the bias potentials settings can be altered and/or optimized using information obtained from CV-curve for the various analytes being measured.

[0066] In some embodiments, Equations 1 and 2 can further include a baseline, (for example, ($Y_{0.4V}=\alpha[A]+\beta[B]+C$) and ($Y_{0.6V}=\delta[A]+\gamma[B]+C$)). However, in some embodiments, other processes can be used to compensate for baseline (for example, during calibration of the sensor).

[0067] While not wishing to be bound by theory, it is believed that a wide variety of interfering species for a wide variety of analyte-measuring devices can utilize methods described herein, including comparing current values at multiple bias potential settings to assess the quality of the analyte measurement, identify interfering species, and calculate substantially interference-free analyte concentration measurements.

[0068] In some embodiments, periodic or regular cyclic voltammograms are performed (scanned) to determine information about a variety of interferants based on the shape of the curve or the data that forms the curve. This embodiment can be advantageous for determining the optimal bias potential setting for measurement of the analyte of interest, or settings for identifying and/or reducing signal effects of one or multiple interferants. Additionally, this embodiment provides a means by which the sensor can periodically or regularly scan for a variety of transient interferants (for example, acetaminophen).

[0069] In another aspect of the preferred embodiments, measurements taken at different bias potential settings are used to measure interference in the signal due to low oxygen levels. In one embodiment, H_2O_2 concentration (analyte byproduct of glucose and oxygen) is measured with a first bias potential (for example, about 0.6V). The O_2 concentration can then be measured at a second bias potential that is set much lower than the first (for example, about -0.6V). In practice, the first bias potential can be set to measure H_2O_2 on a regular basis, while the second bias potential measures O_2 periodically or intermittently (for example, about -0.6 V). The first and second measurements can be made using two distinct sensors or by switching the bias potential of one sensor, for example using pulsed amperometric detection (PED). In one such example, the first and second bias potentials can be set by controlling the reference electrode set potential using a resistor switch network, digital-to-analog converter (DAC), or the like.

[0070] Consequently in this alternative embodiment, by monitoring both H_2O_2 and O_2, including one analyte being measured either on demand or on both analytes being measured periodically, the two measurements can be utilized to determine interference due to transient ischemic conditions, for example. Namely, local ischemia can affect sensor performance *in vivo* due to low O_2 levels that compromise the glucose oxidase reaction and thus signal output of the sensor. If a simultaneous drop of sufficient magnitude and rate are noticed in both signals, an ischemic event is likely occurring. If a drop in H_2O_2 (namely, of sufficient magnitude and rate) is noticed without a similar drop in O_2, then no ischemic event is likely, but rather a true glucose concentration change. Conversely, if a drop in O_2 (namely, of sufficient magnitude and rate) is noticed without a similar drop in H_2O_2, then an ischemic event is likely, but not significant enough to compromise the integrity of the H_2O_2 measurement via the glucose oxidase reaction. Consequently, detection of low O_2 (ischemia) and its resulting effects on the sensor signal output can be used to cease data output (for example, because the output may be erroneous and result in misdiagnosis), trigger a message to the user (for example, to suggest a change of position and/or caution them about the data output), or compensate for the signal loss due to the effects of local ischemia (for example, using algorithms that measure and eliminate the signal error due to ischemia).

[0071] While the methods herein have been described in relation to acetaminophen as an interfering species, the methods can be modified so as to apply to a wide variety of interfering species and to a wide variety of analyte-measuring devices.

[0072] Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in copending U.S. Application No. 10/695,636 filed October 28, 2003 and entitled, "SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE"; U.S. Application No. 10/648,849 filed August 22, 2003 and entitled, "SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM"; U.S. Application No. 10/646,333 filed August 22, 2003 entitled, "OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE

SENSOR"; U.S. Application No. 10/647,065 filed August 22,2003 entitled, "POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES"; U.S. Application No. 10/633,367 filed August 1, 2003 entitled, "SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA"; U.S. Application No. 09/916,386 filed July 27, 2001 and entitled "MEMBRANE FOR USE WITH IMPLANTABLE DEVICES"; U.S. Appl. No. 091916,'711 filed July 27, 2001 and entitled "SENSOR HEAD FOR USE WITH IMPLANTABLE DEVICE"; U.S. Appl. No. 09/447,227 filed November 22, 1999 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS"; U.S. Appl. No. 10/153,356 filed May 22, 2002 and entitled "TECHNIQUES TO IMPROVE POLYURETHANE MEMBRANES FOR IMPLANTABLE GLUCOSE SENSORS"; U.S. Appl. No. 09/489,588 filed January 21, 2000 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS"; U.S. Appl. No. 09/636,369 filed August 11, 2000 and entitled "SYSTEMS AND METHODS FOR REMOTE MONITORING AND MODULATION OF MEDICAL DEVICES"; and U.S. Appl. No. 09/916,858 filed July 27, 2001 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS," as well as issued patents including U.S. 6,001,067 issued December 14, 1999 entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS"; U.S. 4,994,167 issued February 19, 1991 and entitled "BIOLOGICAL FLUID MEASURING DEVICE"; and U.S. 4,757,022 filed July 12, 1988 and entitled "BIOLOGICAL FLUID MEASURING DEVICE."

[0073] The above description provides several methods and materials of the invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this application or practice of the invention provided herein.

[0074] Each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

Claims

1. A method for measuring an analyte concentration in a continuous and transcutaneous electrochemical sensor, the method comprising:

   scanning the electrochemical sensor by

   (i) varying a bias potential applied to the electrochemical sensor, and
   (ii) measuring signal outputs of the electrochemical sensor as the bias potential is varied;

   comparing the signal outputs; and
   calculating an analyte concentration measurement based on the comparison of the signal outputs.

2. The method of claim 1, wherein the electrochemical sensor comprises a plurality of electrodes and wherein varying the bias potential comprises varying the bias potential between two electrodes of the plurality of electrodes.

3. The method of claim 2, wherein the two electrodes comprise a working electrode and a reference electrode and wherein the signal outputs are measured by measuring a current output of the working electrode.

4. The method of claim 1, wherein when the electrochemical sensor is a glucose sensor measuring hydrogen peroxide, the bias potential is varied from 0.1 V to 1.0V to account for the presence of acetaminophen.

5. The method of claim 1, wherein the bias potential is varied in accordance with cyclic voltammetry.

6. The method of claim 1, wherein the signal outputs comprise current values and wherein comparing the signal outputs comprises comparing a first current value associated with a first bias potential of the varying bias potential with a second current value associated with a second, different bias potential of the varying bias potential.

7. The method of claim 1, wherein comparing the signal outputs comprises comparing cyclic voltammogram curves.

8. The method of claim 1, wherein the signal outputs represent analyte measurements and wherein comparing the signal outputs comprises assessing the quality and/or level of accuracy of the analyte measurements.

9. The method of claim 1, wherein comparing the signal outputs comprises identifying and/or reducing signal effects of one or multiple interferants.

10. The method of claim 1, wherein the scanning is performed periodically or regularly.

11. A device for measuring an analyte concentration, the device comprising:

a continuous and transcutaneous electrochemical sensor comprising two electrodes; and
electronic circuitry operatively coupled to the two electrodes, wherein the electronic circuitry is configured to

(i) scan the electrochemical sensor by varying a bias potential between the two electrodes, and measure signal outputs of at least one of the two electrodes as the bias potential is varied;
(ii) compare the signal outputs; and
(iii) calculate an analyte concentration measurement based on the signal outputs.

12. The device of claim 11, wherein the two electrodes comprise a working electrode and a reference electrode and wherein the signal outputs are measured by measuring a current output of the working electrode.

13. The device of claim 11, wherein the electronic circuitry is operatively coupled to a third electrode and wherein the third electrode is a counter electrode.

14. The device of claim 11, wherein when the device is a glucose sensor measuring hydrogen peroxide, the electronic circuitry is configured to vary the biasing potential between 0.1V to 1.0V to account for the presence of acetaminophen.

15. The device of claim 11, wherein the electronic circuitry is configured to vary the biasing potential in accordance with cyclic voltammetry.

16. The device of claim 11, wherein the signal outputs comprise current values.

17. The device of claim 11, wherein the signal outputs comprise cyclic voltammogram curves.

18. The device of claim 11, wherein the electronic circuitry is configured to assess the quality and/or level of accuracy of the analyte measurements based on the signal outputs.

19. The device of claim 11, wherein the electronic circuitry is configured to identify and/or reduce signal effects of one or multiple interferants based on the signal outputs.

20. The device of claim 11, wherein the electronic circuitry is configured to periodically or regularly scan the electrochemical sensor.

Patentansprüche

1. Verfahren zum Messen einer Analytkonzentration in einem kontinuierlichen und transkutanen elektrochemischen Sensor, umfassend:

Abtasten des elektrochemischen Sensors durch

(i) Variieren einer an den elektrochemischen Sensor angelegten Vorspannung und
(ii) Messen von Ausgangssignalen des elektrochemischen Sensors, während die Vorspannung variiert wird,

Vergleichen der Ausgangssignale und
Berechnen einer Analytkonzentrationsmessung auf der Grundlage des Vergleichs der Ausgangssignale.

2. Verfahren nach Anspruch 1, wobei der elektrochemische Sensor eine Vielzahl von Elektroden umfasst und wobei Variieren der Vorspannung Variieren der Vorspannung zwischen zwei Elektroden der Vielzahl von Elektroden umfasst.

3. Verfahren nach Anspruch 2, wobei die zwei Elektroden eine Arbeitselektrode und eine Bezugselektrode umfassen und wobei die Ausgangssignale durch Messen eines Stromausgangs der Arbeitselektrode gemessen werden.

4. Verfahren nach Anspruch 1, wobei, wenn es sich beim elektrochemischen Sensor um einen Glucose-Sensor handelt, der Wasserstoffperoxid misst, die Vorspannung von 0,1V bis 1,0 V variiert wird, um die Gegenwart von Acetaminophen nachzuweisen.

5. Verfahren nach Anspruch 1, wobei die Vorspannung gemäß Cyclovoltammetrie variiert wird.

6. Verfahren nach Anspruch 1, wobei die Ausgangssignale Stromwerte umfassen und wobei Vergleichen der Ausgangssignale Vergleichen eines zu einer ersten Vorspannung der variierenden Vorspannung gehörenden ersten Stromwerts mit einem zu einer zweiten, anderen Vorspannung der variierenden Vorspannung gehörenden zweiten Stromwert umfasst.

7. Verfahren nach Anspruch 1, wobei Vergleichen der Ausgangssignale Vergleichen von Cyclovoltammogrammkurven umfasst.

8. Verfahren nach Anspruch 1, wobei die Ausgangssignale Analytmessungen darstellen und wobei Vergleichen der Ausgangssignale Bewerten der Qualität und/oder des Genauigkeitsgrads der Analytmessungen umfasst.

9. Verfahren nach Anspruch 1, wobei Vergleichen der Ausgangssignale Ermitteln und/oder Verringern von Signalauswirkungen eines oder mehrerer Störstoffe umfasst.

10. Verfahren nach Anspruch 1, wobei das Abtasten periodisch oder regelmäßig durchgeführt wird.

11. Einrichtung zum Messen einer Analytkonzentration, umfassend:

einen zwei Elektroden umfassenden kontinuierlichen und transkutanen elektrochemischen Sensor und
eine mit den zwei Elektroden wirkverbundene elektronische Schaltungsanordnung, wobei die elektronische Schaltungsanordnung dafür konfiguriert ist,

(i) den elektrochemischen Sensor durch Variieren einer Vorspannung zwischen den zwei Elektroden abzutasten und Ausgangssignale mindestens einer der zwei Elektroden zu messen, während die Vorspannung variiert wird,
(ii) die Ausgangssignale zu vergleichen und
(iii) auf der Grundlage der Ausgangssignale eine Analytkonzentrationsmessung zu berechnen.

12. Einrichtung nach Anspruch 11, wobei die zwei Elektroden eine Arbeitselektrode und eine Bezugselektrode umfassen und wobei die Ausgangssignale durch Messen eines Stromausgangs der Arbeitselektrode gemessen werden.

13. Einrichtung nach Anspruch 11, wobei die elektronische Schaltungsanordnung mit einer dritten Elektrode wirkverbunden ist und wobei es sich bei der dritten Elektrode um eine Gegenelektrode handelt.

14. Einrichtung nach Anspruch 11, wobei, wenn es sich bei der Einrichtung um einen Glucose-Sensor handelt, der Wasserstoffperoxid misst, die elektronische Schaltungsanordnung dafür konfiguriert ist, die Vorspannung zwischen 0,1 V bis 1,0 V zu variieren, um die Gegenwart von Acetaminophen nachzuweisen.

15. Einrichtung nach Anspruch 11, wobei die elektronische Schaltungsanordnung dafür konfiguriert ist, die Vorspannung gemäß Cyclovoltammetrie zu variieren.

16. Einrichtung nach Anspruch 11, wobei die Ausgangssignale Stromwerte umfassen.

17. Einrichtung nach Anspruch 11, wobei die Ausgangssignale Cyclovoltammogrammkurven umfassen.

18. Einrichtung nach Anspruch 11, wobei die elektronische Schaltungsanordnung dafür konfiguriert ist, die Qualität und/oder den Genauigkeitsgrad der Analytmessungen auf der Grundlage der Ausgangssignale zu bewerten.

19. Einrichtung nach Anspruch 11, wobei die elektronische Schaltungsanordnung dafür konfiguriert ist, Signalauswirkungen eines oder mehrerer Störstoffe auf der Grundlage der Ausgangssignale zu ermitteln und/oder zu verringern.

20. Einrichtung nach Anspruch 11, wobei die elektronische Schaltungseinrichtung dafür konfiguriert ist, den elektroche-

mischen Sensor periodisch oder regelmäßig abzutasten.

Revendications

1. Procédé de mesure d une concentration d analyte dans un capteur électrochimique continu et transcutané, le procédé comprenant :

   le balayage du capteur électrochimique

   (i) en faisant varier un potentiel de polarisation appliqué au capteur électrochimique et
   (ii) en mesurant des sorties de signaux du capteur électrochimique lors de la variation du potentiel de polarisation ;

   la comparaison des sorties de signaux ; et
   le calcul d une mesure de concentration d analyte sur la base de la comparaison des sorties de signaux.

2. Procédé selon la revendication 1, dans lequel le capteur électrochimique comprend une pluralité d électrodes et dans lequel la variation du potentiel de polarisation comprend la variation du potentiel de polarisation entre deux électrodes de la pluralité d électrodes.

3. Procédé selon la revendication 2, dans lequel les deux électrodes comprennent une électrode de travail et une électrode de référence et dans lequel les sorties de signaux sont mesurées en mesurant une sortie de courant de l électrode de travail.

4. Procédé selon la revendication 1, dans lequel, lorsque le capteur électrochimique est un capteur de glucose mesurant le peroxyde d hydrogène, le potentiel de polarisation est soumis à une variation de 0,1 V à 1,0 V pour tenir compte de la présence d acétaminophène.

5. Procédé selon la revendication 1, dans lequel le potentiel de polarisation est soumis à une variation en fonction d une voltammétrie cyclique.

6. Procédé selon la revendication 1, dans lequel les sorties de signaux comprennent des valeurs de courant et dans lequel la comparaison des sorties de signaux comprend la comparaison d une première valeur de courant associée à un premier potentiel de polarisation du potentiel de polarisation variable avec une seconde valeur de courant associée à un second potentiel de polarisation différent du potentiel de polarisation variable.

7. Procédé selon la revendication 1, dans lequel la comparaison des sorties de signaux comprend la comparaison de courbes cycliques de voltammogrammes.

8. Procédé selon la revendication 1, dans lequel les sorties de signaux représentent des mesures d analytes et dans lequel la comparaison des sorties de signaux comprend l évaluation de la qualité et/ou du niveau de précision des mesures d analytes.

9. Procédé selon la revendication 1, dans lequel la comparaison des sorties de signaux comprend l identification et/ou la réduction d effets de signaux d un ou plusieurs interférants multiples.

10. Procédé selon la revendication 1, dans lequel le balayage est effectué de manière périodique ou régulière.

11. Dispositif de mesure d une concentration d analyte, le dispositif comprenant :

    un capteur électrochimique continu et transcutané comprenant deux électrodes ; et
    un circuit électronique couplé en service aux deux électrodes, dans lequel le circuit électronique est configuré pour :

    (i) balayer le capteur électrochimique en faisant varier un potentiel de polarisation entre les deux électrodes et mesurer les sorties de signaux d au moins l une des deux électrodes lors de la variation du potentiel de polarisation ;

(ii) comparer les sorties de signaux ; et
(iii) calculer une mesure de concentration d analyte sur la base des sorties de signaux.

12. Dispositif selon la revendication 11, dans lequel les deux électrodes comprennent une électrode de travail et une électrode de référence et dans lequel les sorties de signaux sont mesurées en mesurant une sortie de courant de l électrode de travail.

13. Dispositif selon la revendication 11, dans lequel le circuit électronique est couplé en service à une troisième électrode et dans lequel la troisième électrode est une contre-électrode.

14. Dispositif selon la revendication 11, dans lequel, lorsque le dispositif est un capteur de glucose mesurant le peroxyde d hydrogène, le circuit électronique est configuré pour faire varier le potentiel de polarisation entre 0,1 V et 1,0 V pour tenir compte de la présence d acétaminophène.

15. Dispositif selon la revendication 11, dans lequel le circuit électronique est configuré pour faire varier le potentiel de polarisation en fonction d une voltammétrie cyclique.

16. Dispositif selon la revendication 11, dans lequel les sorties de signaux comprennent des valeurs de courant.

17. Dispositif selon la revendication 11, dans lequel les sorties de signaux comprennent des courbes cycliques de voltammogrammes.

18. Dispositif selon la revendication 11, dans lequel le circuit électronique est configuré pour évaluer la qualité et/ou le niveau de précision des mesures d analytes sur la base des sorties de signaux.

19. Dispositif selon la revendication 11, dans lequel le circuit électronique est configuré pour identifier et/ou réduire des effets de signaux d un ou plusieurs interférants sur la base des sorties de signaux.

20. Dispositif selon la revendication 11, dans lequel le circuit électronique est configuré pour balayer le capteur électrochimique de manière périodique ou régulière.

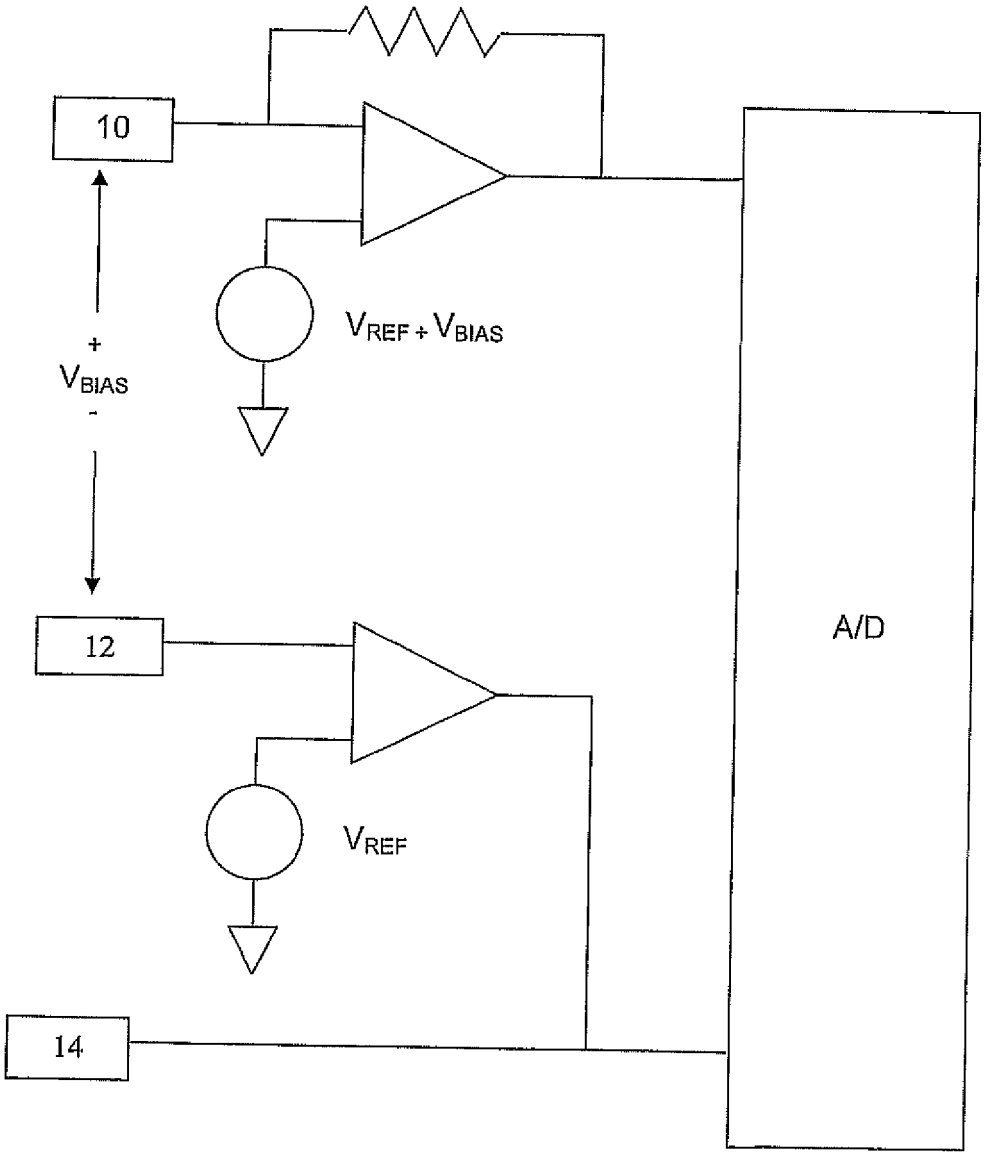

FIG. 1

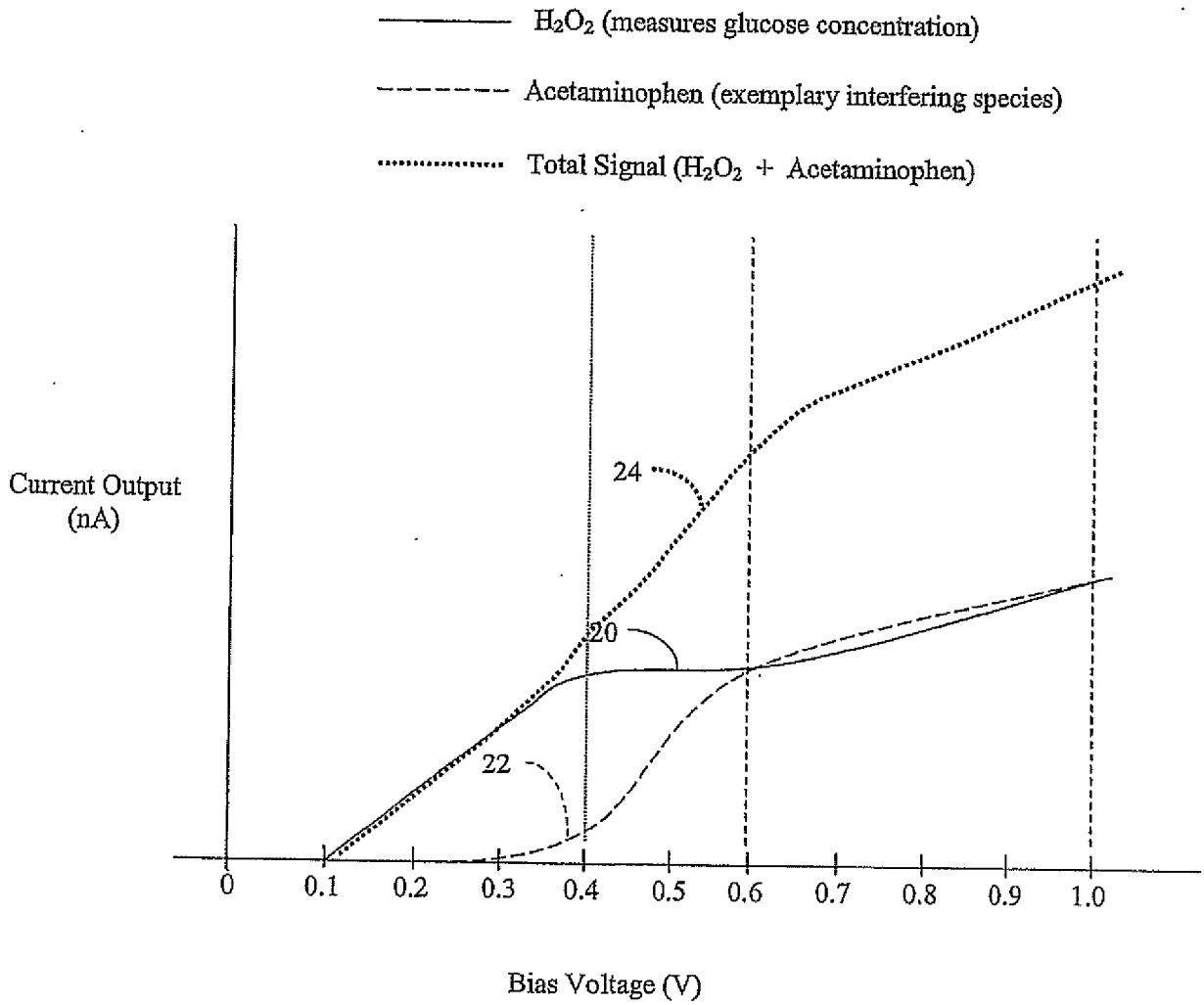
H_2O_2 (measures glucose concentration)
Acetaminophen (exemplary interfering species)
Total Signal (H_2O_2 + Acetaminophen)
Current Output (nA)
24
20
22
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Bias Voltage (V)

FIG. 2

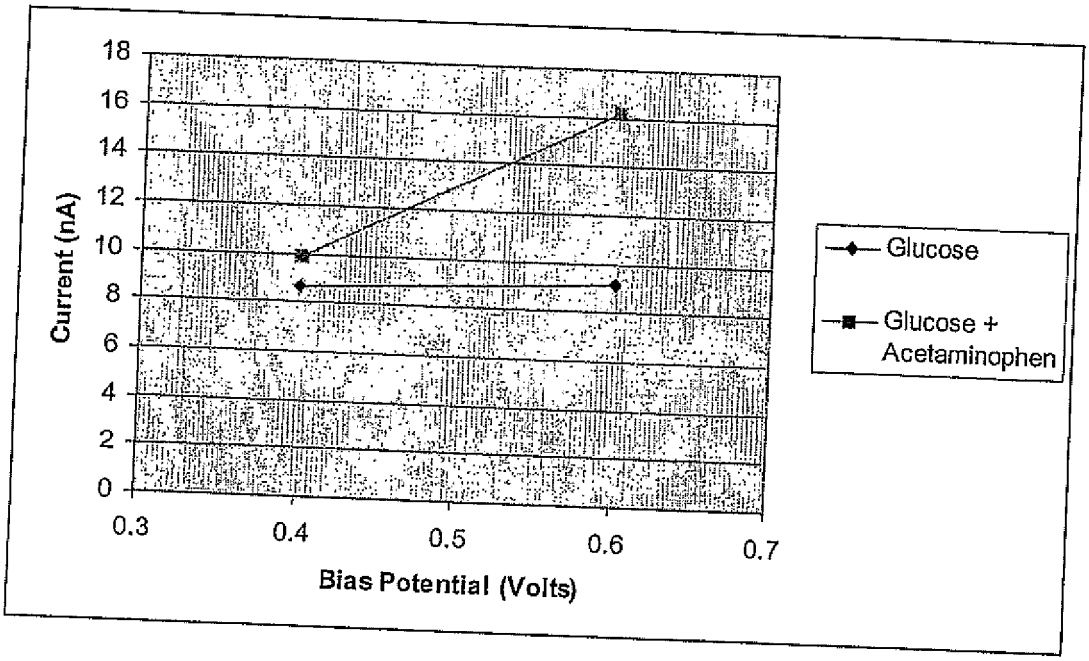
18
16
14
12
10
8
6
4
2
0
Current (nA)
0.3
0.4
0.5
0.6
0.7
Bias Potential (Volts)
Glucose
Glucose + Acetaminophen

Fig. 3

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	用于改善电化学分析物传感器的系统和方法		
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外部链接	Espacenet		

摘要(译)

提供分析物测量装置，特别是电化学传感器，用于测量多个偏置电位设置下的电流值，以评估分析物测量的质量，识别信号中的干扰，并计算基本上无干扰的分析物浓度测量值。当葡萄糖是分析物并且对乙酰氨基酚是干扰物质时，该装置和方法适合于计算基本上无干扰的分析物浓度测量值。