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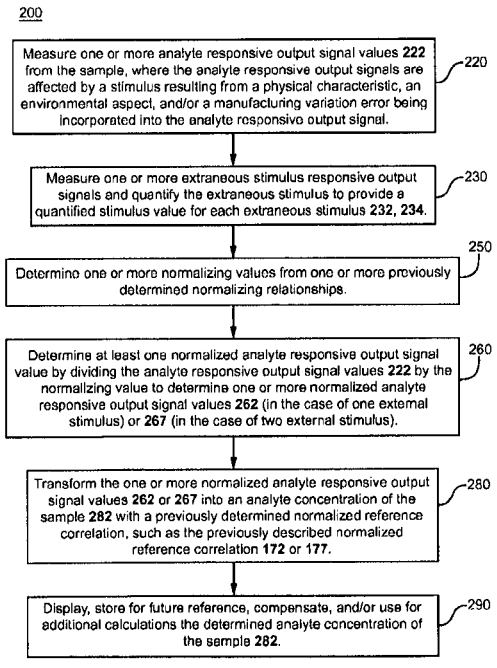

FIG.C

(57) Abstract: Biosensor system measurement devices used to determine the presence and/or concentration of an analyte in a sample include normalized calibration information relating output signal or signals the device generates in response to the analyte concentration of the sample to previously determined reference sample analyte concentrations. The measurement devices use this normalized calibration information to relate one or more output signals from an electrochemical or optical analysis of a sample to the presence and/or concentration of one or more analytes in the sample. The normalized calibration information includes a normalization relationship to normalize output signals measured by the measurement device of the biosensor system and at least one normalized reference correlation relating normalized output signals to reference sample analyte concentrations.

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Normalized Calibration of Analyte Concentration Determinations

REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application No. 61/782,520 entitled "Calibration of Analyte Concentration Determinations" filed March 14, 2013, which is incorporated by reference in its entirety.

BACKGROUND

[002] Biosensor systems provide an analysis of a biological fluid sample, such as blood, serum, plasma, urine, saliva, interstitial, or intracellular fluid. Typically, the systems include a measurement device that analyzes a sample residing in a test sensor. The sample usually is in liquid form and in addition to being a biological fluid, may be the derivative of a biological fluid, such as an extract, a dilution, a filtrate, or a reconstituted precipitate. The analysis performed by the biosensor system determines the presence and/or concentration of one or more analytes, such as alcohol, glucose, uric acid, lactate, cholesterol, bilirubin, free fatty acids, triglycerides, proteins, ketones, phenylalanine or enzymes, in the biological fluid. For example, a person with diabetes may use a biosensor system to determine the A1c or glucose level in blood for adjustments to diet and/or medication.

[003] In blood samples including hemoglobin (Hb), the presence and/or concentration of total hemoglobin (THb) and glycated hemoglobin (HbA1c) may be determined. HbA1c (%-A1c) is a reflection of the state of glucose control in diabetic patients, providing insight into the average glucose control over the three months preceding the test. For diabetic individuals, an accurate measurement of %-A1c assists in determining how well the patient is controlling blood glucose levels with diet and/or medication over a longer term than provided by an instantaneous

measure of blood glucose level. As an instantaneous blood glucose measurement does not indicate blood glucose control other than when the measurement is made.

[004] Biosensor systems may be designed to analyze one or more analytes and may use different volumes of biological fluids. Some systems may analyze a single drop of blood, such as from 0.25-15 microliters (μL) in volume. Biosensor systems may be implemented using bench-top, portable, and like measurement devices. Portable measurement devices may be hand-held and allow for the identification and/or quantification of one or more analytes in a sample. Examples of portable measurement systems include the Contour® meters of Bayer HealthCare in Tarrytown, New York, while examples of bench-top measurement systems include the Electrochemical Workstation available from CH Instruments in Austin, Texas.

[005] Biosensor systems may use optical and/or electrochemical methods to analyze the biological fluid. In some optical systems, the analyte concentration is determined by measuring light that has interacted with or been absorbed by a light-identifiable species, such as the analyte or a reaction or product formed from a chemical indicator reacting with the analyte. In other optical systems, a chemical indicator fluoresces or emits light in response to the analyte when illuminated by an excitation beam. The light may be converted into an electrical output signal, such as current or potential, which may be similarly processed to the output signal from an electrochemical system. In either optical system, the system measures and correlates the light with the analyte concentration of the sample.

[006] In light-absorption optical systems, the chemical indicator produces a reaction product that absorbs light. A chemical indicator such as tetrazolium along with an enzyme such as diaphorase may be used. Tetrazolium usually forms formazan (a chromagen) in response to the redox reaction of the analyte. An incident input beam from a light source is directed toward the sample. The light source may be a laser, a light emitting diode, or the like. The incident beam may

have a wavelength selected for absorption by the reaction product. As the incident beam passes through the sample, the reaction product absorbs a portion of the incident beam, thus attenuating or reducing the intensity of the incident beam. The incident beam may be reflected back from or transmitted through the sample to a detector. The detector collects and measures the attenuated incident beam (output signal). The amount of light attenuated by the reaction product is an indication of the analyte concentration in the sample.

[007] In light-generated optical systems, the chemical indicator fluoresces or emits light in response to the analyte redox reaction. A detector collects and measures the generated light (output signal). The amount of light produced by the chemical indicator is an indication of the analyte concentration in the sample and is represented as a current or potential from the detector.

[008] An example of an optical system using reflectance is a laminar flow %-A1c system that determines the concentration of A1c hemoglobin in blood. These systems use immunoassay chemistry where the blood is introduced to the test sensor of the biosensor system where it reacts with reagents and then flows along a reagent membrane. When contacted by the blood, A1c antibody coated color beads release and move along with the blood to a detection Zone 1. Because of the competition between the A1c in the blood sample and an A1c peptide present in detection Zone 1 for the color beads, color beads not attached to the A1c antibody are captured at Zone 1 and are thus detected as the A1c signal from the change in reflectance. The total hemoglobin (THb) in the blood sample also is reacting with other blood treatment reagents and moves downstream into detection Zone 2, where it is measured at a different wavelength. For determining the concentration of A1c in the blood sample, the reflectance signal is proportional to the A1c analyte concentration (%-A1c), but is affected by the THb content of the blood. For the THb measurement, however, the reflectance in Zone 2 is inversely proportional to the

THb (mg/mL) of the blood sample, but is not appreciably affected by the A1c content of the blood.

[009] In electrochemical systems, the analyte concentration of the sample is determined from an electrical signal generated by an oxidation/reduction or redox reaction of the analyte or a measurable species responsive to the analyte concentration when an input signal is applied to the sample. The input signal may be a potential or current and may be constant, variable, or a combination thereof such as when an AC signal is applied with a DC signal offset. The input signal may be applied as a single pulse or in multiple pulses, sequences, or cycles. An enzyme or similar species may be added to the sample to enhance the electron transfer from the analyte during the redox reaction. The enzyme or similar species may react with a single analyte, thus providing specificity to a portion of the generated output signal. A redox mediator may be used as the measurable species to maintain the oxidation state of the enzyme and/or assist with electron transfer from the analyte to an electrode. Thus, during the redox reaction, an enzyme or similar species may transfer electrons between the analyte and the redox mediator, while the redox mediator transfers electrons between itself and an electrode of the test sensor.

[0010] Electrochemical biosensor systems usually include a measurement device having electrical contacts that connect with the electrical conductors of the test sensor. The conductors may be made from conductive materials, such as solid metals, metal pastes, conductive carbon, conductive carbon pastes, conductive polymers, and the like. The electrical conductors connect to working and counter electrodes, and may connect to reference and/or other electrodes that extend into a sample reservoir depending on the design of the test sensor. One or more electrical conductors also may extend into the sample reservoir to provide functionality not provided by the electrodes.

[0011] In many biosensor systems, the test sensor may be adapted for use outside, inside, or partially inside a living organism. When used outside a living

organism, a sample of the biological fluid may be introduced into a sample reservoir in the test sensor. The test sensor may be placed in the measurement device before, after, or during the introduction of the sample for analysis. When inside or partially inside a living organism, the test sensor may be continually immersed in the sample or the sample may be intermittently introduced to the test sensor. The test sensor may include a reservoir that partially isolates a volume of the sample or be open to the sample. When open, the test sensor may take the form of a fiber or other structure placed in contact with the biological fluid. Similarly, the sample may continuously flow through the test sensor, such as for continuous monitoring, or be interrupted, such as for intermittent monitoring, for analysis.

[0012] The measurement device of an electrochemical biosensor system applies an input signal through the electrical contacts to the electrical conductors of the test sensor. The electrical conductors convey the input signal through the electrodes into the sample present in the sample reservoir. The redox reaction of the analyte generates an electrical output signal in response to the input signal. The electrical output signal from the test sensor may be a current (as generated by amperometry or voltammetry), a potential (as generated by potentiometry/galvanometry), or an accumulated charge (as generated by coulometry). The measurement device may have the processing capability to measure and correlate the output signal with the presence and/or concentration of one or more analytes in the sample.

[0013] In coulometry, a potential is applied to the sample to exhaustively oxidize or reduce the analyte. A biosensor system using coulometry is described in U.S. Patent No. 6,120,676. In amperometry, an electric signal of constant potential (voltage) is applied to the electrical conductors of the test sensor while the measured output signal is a current. Biosensor systems using amperometry are described in U.S. Patent Nos. 5,620,579; 5,653,863; 6,153,069; and 6,413,411. In voltammetry, an electric signal of varying potential is applied to a sample of biological fluid, while

the measured output is current. In gated amperometry and gated voltammetry, pulsed inputs are used as described in WO 2007/013915 and WO 2007/040913, respectively.

[0014] Primary output signals are responsive to the analyte concentration of the sample and are obtained from an analytic input signal. Output signals that are substantially independent of signals responsive to the analyte concentration of the sample include signals responsive to temperature and signals substantially responsive to interferents, such as the hematocrit or acetaminophen content of a blood sample when the analyte is glucose, for example. Output signals substantially not responsive to analyte concentration may be referred to as secondary output signals, as they are not primary output signals responsive to the alteration of light by the analyte or analyte responsive indicator, the electrochemical redox reaction of the analyte, or the electrochemical redox reaction of the analyte responsive redox mediator. Secondary output signals are responsive to the physical or environmental characteristics of the biological sample. Secondary output signals may arise from the sample or from other sources, such as a thermocouple that provides an estimate of an environmental characteristic of the sample. Thus, secondary output signals may be determined from the analytic input signal or from another input signal.

[0015] When arising from the sample, secondary output signals may be determined from the electrodes used to determine the analyte concentration of the sample, or from additional electrodes. Additional electrodes may include the same reagent composition as the electrodes used to determine the analyte concentration of the sample, a different reagent composition, or no reagent composition. For example, a reagent composition may be used that reacts with an interferent or an electrode lacking reagent composition may be used to study one or more physical characteristics of the sample, such as whole blood hematocrit.

[0016] During sample analysis, there may be more than one stimulus affecting the primary output signal analyzed by the measurement device. These stimuli

include the analyte concentration of the sample, the physical characteristics of the sample, the environmental aspects of the sample, the manufacturing variations between test sensor lots, and the like. Since the primary goal of the analysis is to determine the presence and/or concentration of the analyte in the sample, the analyte concentration of the sample is referred to as the primary stimulus. All other stimuli that affect the output signal are referred to as extraneous stimulus. Thus, the primary output signals include a major effect from the primary stimulus – the analyte concentration of the sample– but also include some effect from one or more extraneous stimulus. In contrast, the secondary output signals include a major effect from one or more extraneous stimulus, and may or may not include a major effect from the primary stimulus.

[0017] The measurement performance of a biosensor system is defined in terms of accuracy and precision. Accuracy reflects the combined effects of systematic and random error components. Systematic error, or trueness, is the difference between the average value determined from the biosensor system and one or more accepted reference values for the analyte concentration of the biological fluid. Trueness may be expressed in terms of mean bias, with larger mean bias values representing lower trueness and thereby contributing to less accuracy. Precision is the closeness of agreement among multiple analyte readings in relation to a mean. One or more error in the analysis contributes to the bias and/or imprecision of the analyte concentration determined by the biosensor system. A reduction in the analysis error of a biosensor system therefore leads to an increase in accuracy and/or precision and thus an improvement in measurement performance.

[0018] Bias may be expressed in terms of "absolute bias" or "percent bias". Absolute bias is the difference between the determined concentration and the reference concentration, and may be expressed in the units of the measurement, such as mg/dL, while percent bias may be expressed as a percentage of the absolute bias value over the reference concentration, or expressed as a percentage of the

absolute bias over either the cut-off concentration value or the reference concentration of the sample. For example, if the cut-off concentration value is100 mg/dL ,then for glucose concentrations less than 100 mg/dL, percent bias is defined as (the absolute bias over 100 mg/dL) * 100; for glucose concentrations of 100 mg/dL and higher, percent bias is defined as the absolute bias over the accepted reference value of analyte concentration * 100.

[0019] Accepted reference values for the analyte glucose in blood samples are preferably obtained with a reference instrument, such as the YSI 2300 STAT PLUS™ available from YSI Inc., Yellow Springs, Ohio. Other reference instruments and ways to determine percent bias may be used for other analytes. For the %-A1c measurements, the error may be expressed as either absolute bias or percent bias against the %-A1c reference value for the therapeutic range of 4 – 12%. Accepted reference values for the %-A1c in blood samples may be obtained with a reference instrument, such as the Tosoh G7 instrument available from Tosoh Corp, Japan.

[0020] Hematocrit bias refers to the average difference (systematic error) between the reference glucose concentration obtained with a reference instrument and experimental glucose readings obtained from the measurement device and the test sensor of a biosensor system for samples containing differing hematocrit levels. The difference between the reference and values obtained from the biosensor system results from the varying hematocrit level between specific blood samples and may be generally expressed as a percentage as follows: %Hct-Bias = 100% x (G_m – G_{ref})/G_{ref}, where G_m is the determined glucose concentration at a specific hematocrit level and G_{ref} is the reference glucose concentration at a sample hematocrit level. The larger the absolute value of the %Hct-bias, the more the hematocrit level of the sample (expressed as %Hct, the percentage of red blood cell volume/sample volume) is reducing the accuracy of the glucose concentration determined from the biosensor system.

[0021] For example, if different blood samples containing identical glucose concentrations, but having hematocrit levels of 20, 40, and 60%, are analyzed, three different glucose concentrations will be reported by a biosensor system based on one set of calibration constants (slope and intercept of the 40% hematocrit containing blood sample, for instance). Thus, even though the glucose concentration of the different blood samples is the same, the system will report that the 20% hematocrit sample contains more glucose than the 40% hematocrit sample, and that the 60% hematocrit sample contains less glucose than the 40% hematocrit sample. "Hematocrit sensitivity" is an expression of the degree to which changes in the hematocrit level of a sample affect the bias values for an analysis performed with the biosensor system. Hematocrit sensitivity may be defined as the numerical values of the percent biases per percent hematocrit, thus bias/%-bias per %Hct.

[0022] Biosensor systems may provide an output signal during the analysis of the biological fluid including error from multiple error sources. These error sources contribute to the total error, which may be reflected in an abnormal output signal, such as when one or more portions or the entire output signal is non-responsive or improperly responsive to the analyte concentration of the sample.

[0023] The total error in the output signal may originate from one or more error contributors, such as the physical characteristics of the sample, the environmental aspects of the sample, the operating conditions of the system, the manufacturing variation between test sensor lots, and the like. Physical characteristics of the sample include hematocrit (red blood cell) concentration, interfering substances, such as lipids and proteins, and the like. Interfering substances for glucose analyses also may include ascorbic acid, uric acid, acetaminophen, and the like. Environmental aspects of the sample include temperature, oxygen content of the air, and the like. Operating conditions of the system include underfill conditions when the sample size is not large enough, slow-filling of the test sensor by the sample, intermittent electrical contact between the

sample and one or more electrodes of the test sensor, degradation of the reagents that interact with the analyte after the test sensor was manufactured, and the like. Manufacturing variations between test sensor lots include changes in the amount and/or activity of the reagents, changes in the electrode area and/or spacing, changes in the electrical conductivity of the conductors and electrodes, and the like. A test sensor lot is preferably made in a single manufacturing run where lot-to-lot manufacturing variation is substantially reduced or eliminated. There may be other contributors or a combination of error contributors that cause error in the analysis.

[0024] Percent bias, mean percent bias, percent bias standard deviation (SD), percent coefficient of variance (%-CV), and hematocrit sensitivity are independent ways to express the measurement performance of a biosensor system. Additional ways may be used to express the measurement performance of a biosensor system.

[0025] Percent bias is a representation of the accuracy of the biosensor system in relation to a reference analyte concentration, while the percent bias standard deviation reflects the accuracy of multiple analyses, with regard to error arising from the physical characteristics of the sample, the environmental aspects of the sample, the operating conditions of the system, and the manufacturing variations between test sensors. Thus, a decrease in percent bias standard deviation represents an increase in the measurement performance of the biosensor system across multiple analyses. The percent coefficient of variance may be expressed as 100%*(SD of a set of samples)/(the average of multiple readings taken from the same set of samples) and reflects precision of multiple analyses. Thus, a decrease in percent bias standard deviation represents an increase in the measurement performance of the biosensor system across multiple analyses.

[0026] Increasing the measurement performance of the biosensor system by reducing error from these or other sources means that more of the analyte concentrations determined by the biosensor system may be used for accurate therapy by the patient when blood glucose is being monitored, for example.

Additionally, the need to discard test sensors and repeat the analysis by the patient also may be reduced.

[0027] Biosensor systems may have a single source of uncompensated output signals responsive to a redox or light-based reaction of the analyte, such as the counter and working electrodes of an electrochemical system. Biosensor systems also may have the optional ability to determine or estimate temperature, such as with one or more thermocouples or other means. In addition to these systems, biosensor systems also may have the ability to generate secondary output signals external to those from the analyte or from a mediator responsive to the analyte. For example, in an electrochemical test sensor, one or more electrical conductors also may extend into the sample reservoir to provide functionality not provided by the working and counter electrodes. Such conductors may lack one or more of the working electrode reagents, such as the mediator, thus allowing for the subtraction of a background interferent signal from the working electrode signal.

[0028] Many biosensor systems include one or more methods to compensate for errors associated with an analysis, thus attempting to improve the measurement performance of the biosensor system. Compensation methods may increase the measurement performance of a biosensor system by providing the biosensor system with the ability to compensate for error in the analyses, thus increasing the accuracy and/or precision of the concentration values obtained from the system. Conventional error compensation methods for physical and environmental error contributors are traditionally developed in a laboratory as these types of errors can be reproduced in a controlled environment.

[0029] How the measurement device of the biosensor system is calibrated in the laboratory affects the measurement performance of the system in the hands of the user. Thus, an ongoing concern in the context of calibrating a measurement device is that of all the error parameters that may affect the measurement performance of the measurement device in use, which error parameters should be

calibrated for in the laboratory before the measurement device is used for analyzing the analyte concentration of samples.

[0030] Error parameters are variables, the values of which are determined from the analysis, such as the intermediate signals from the primary output signal, or from secondary output signals independent of the analyte responsive output signal, such as thermocouples, additional electrodes, and the like. Error parameters may be any variables responsive to one or more errors in the output signal. Thus, these variables with their discrete values may be the currents or potentials measured from the intermediate signals from a primary output signal, or from secondary output signals, such as from thermocouple currents or voltages, additional electrode currents or voltages, and the like. Other error parameters may be determined from these or other primary or secondary output signals.

[0031] A point of diminishing returns or even poorer measurement performance may result if the measurement device is calibrated for too many or non-optimal error parameters. Furthermore, the more parameters that are considered in the calibration, the less useful the calibration information stored in the measurement device may be for later compensation of the analysis from error parameters determined during the analysis. These calibration issues become even more complex when the analysis being performed includes multiple output signals including analyte concentration-responsive (primary output signals) and/or non-analyte responsive signals (secondary output signals). The present invention avoids or ameliorates at least some of the disadvantages of measurement devices using conventional calibration techniques.

SUMMARY

[0032] In one aspect, the invention provides a method for determining an analyte concentration in a sample that includes generating at least one output signal from a sample; measuring at least one analyte responsive output signal value from the at least one output signal, where the at least one analyte responsive output signal value is affected by at least one extraneous stimulus; measuring at least one extraneous stimulus responsive output signal from the sample; determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal; determining at least one normalizing value from at least one normalizing relationship; determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

[0033] In another aspect of the invention, there is a method for calibrating a measurement device of a biosensor system that includes measuring at least two analyte responsive output signals from a sample, where the analyte responsive output signals are affected by at least one extraneous stimulus; determining a reference correlation between at least one reference sample analyte concentration and the at least two analyte responsive output signals; measuring at least one extraneous stimulus responsive output signal from the sample; determining at least two quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal; determining a normalizing relationship between the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values; determining a normalizing value from the normalizing relationship and the at least two quantified extraneous stimulus values; determining at least two normalized analyte responsive output signals from the at least two analyte responsive output signals and the normalizing value; and determining a

normalized reference correlation between the at least two normalized analyte responsive output signals and the least one reference sample analyte concentration.

[0034] In another aspect of the invention, there is an analyte measurement device that includes electrical circuitry connected to a sensor interface, where the electrical circuitry includes a processor connected to a signal generator and a storage medium; where the processor is capable of measuring at least one analyte responsive output signal value from a sample, where the at least one analyte responsive output signal value is affected by at least one extraneous stimulus; where the processor is capable of measuring at least one extraneous stimulus responsive output signal from the sample; where the processor is capable of determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal; where the processor is capable of determining at least one normalizing value from at least one normalizing relationship; where the processor is capable of determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and where the processor is capable of determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

[0035] In another aspect of the invention, there is a biosensor system for determining an analyte concentration in a sample that includes a test sensor having a sample interface adjacent to a reservoir formed by a base, where the test sensor is capable of generating at least one output signal from a sample; and a measurement device having a processor connected to a sensor interface, the sensor interface having electrical communication with the sample interface, and the processor having electrical communication with a storage medium; where the processor is capable of measuring at least one analyte responsive output signal value from the at least one output signal, where the at least one analyte responsive output signal value

is affected by at least one extraneous stimulus; where the processor is capable of measuring at least one extraneous stimulus responsive output signal from the sample; where the processor is capable of determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal; where the processor is capable of determining at least one normalizing value from at least one normalizing relationship; where the processor is capable of determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and where the processor is capable of determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The invention can be better understood with reference to the following drawings and description. The components in the figures are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the invention.

[0037] FIG. A represents a calibration method of determining calibration information for incorporation into a measurement device with a reduced extraneous stimulus effect.

[0038] FIG. B represents an optional calibration method of also considering a second extraneous stimulus with the calibration information.

[0039] FIG. C represents an analysis method of determining the analyte concentration of a sample with a reduced extraneous stimulus effect using a normalized reference correlation.

[0040] FIG. 1A shows the A1c reflectance signals recorded from the Zone 1 detector/s of the measurement device versus reference sample analyte concentrations (%-A1c) at four THb (total hemoglobin) concentrations (85 mg/mL, 125 mg/mL, 175 mg/mL, and 230 mg/mL).

[0041] FIG. 1B shows the comparatively constant THb output signals at four levels of THb reference sample concentrations (85 mg/mL, 125 mg/mL, 175 mg/mL, and 230 mg/mL) as determined from the Zone 2 detectors of the measurement device.

[0042] FIG. 1C shows the individual A1c reflectance signals recorded from the Zone 1 detector/s of the measurement device separated for the four different THb concentrations in blood samples.

[0043] FIG. 1D also provides an example of determining the normalization relationship **140**, which establishes the correlation between the synthesized extraneous stimulus responsive output signals at a single A1c concentration and the secondary output signals responsive to the sample THb concentrations.

[0044] FIG. 1E provides an example of the determination of normalized analyte responsive output signals from the normalizing value.

[0045] FIG. 1F provides an example of the determination of a normalized reference correlation from combining the normalized analyte responsive output signal values of FIG. 1E.

[0046] FIG. 1G provides another example of the determination of a normalized reference correlation from the normalized analyte responsive output signal values of FIG. 1E.

[0047] FIG. 1H compares the normalized analyte responsive output signals to the normalized reference correlation in the form of a normalized calibration curve

from FIG. 1G by superimposing the normalized analyte responsive output signal values on the curve.

[0048] FIG. 2A represents the normalization relationships for both channels of an A1c measurement device having two detection channels.

[0049] FIG. 2B represents the individual normalized calibration curves for Ch1 and Ch3 of the A1c measurement device.

[0050] FIG. 2C shows the normalized A1c reflectance signals from the two individual channels (Ch1 & Ch3) for the reference samples.

[0051] FIG. 2D shows the normalizing relationship determined by first averaging the A1c reflectance output signals from Ch1 and Ch3 of the measurement device.

[0052] FIG. 2E shows the normalized reference correlation in the form of a normalized calibration curve determined for the averaged A1c reflectance signals from Ch1 and Ch3 of the measurement device.

[0053] FIG. 3A plots the currents obtained from the measurement device versus reference sample analyte concentrations for glucose at different temperatures and 40% Hct.

[0054] FIG. 3B separates these primary output signal currents by the temperature at which they were recorded.

[0055] FIG. 3C shows the correlations between the synthesized extraneous stimulus responsive output signals obtained at two separate single glucose concentration of 100 and 500 mg/dL versus the quantified extraneous stimulus (temperatures) to determine the normalization relationships.

[0056] FIG. 3D provides an example of the determination of normalized analyte responsive output signals from the normalizing value at 100 mg/dL.

[0057] FIG. 3E provides an example of the determination of a normalized reference correlation from the normalized analyte responsive output signal values of FIG. 3D.

[0058] FIG. 3F plots the %-bias attributable to the different temperatures (6.0° C, 10.9° C, 15.9° C, 22.0° C, 30.4° C, 35.1° C, and 40.0° C) before and after normalization.

[0059] FIG. 4A shows the output signal currents from the measurement device for reference samples including known glucose concentrations for the tested temperatures (6.0° C, 10.9° C, 15.9° C, 22.0° C, 30.4° C, 35.1° C, and 40.0° C) and for the tested Hct reference sample concentrations (0%, 20%, 40%, 55%, 70%).

[0060] FIG. 4B represents the temperature normalizing relationships at 40% Hct and at two separate single glucose concentrations of 100 and 500 mg/dL in blood sample, and is the same as previously represented in FIG. 3C, as the same temperature stimulus reduction is being performed.

[0061] FIG. 4C plots the temperature normalized analyte responsive output signal values from FIG. 4A versus reference sample analyte concentration for glucose at the Hct reference sample concentrations tested in this example.

[0062] FIG. 4D plots the synthesized signals determined from the secondary output signal responsive to the hematocrit concentration of the sample verses temperature for reference samples including a 40% hematocrit concentration.

[0063] FIG. 4E shows the temperature normalized reference correlation for Hct where reference sample %Hct concentrations were plotted against the temperature normalized Hct electrode output currents.

[0064] FIG. 4F represents the second normalizing relationship determined between the resulting temperature normalized analyte responsive output signals and the reference sample %-Hct values – the second extraneous stimulus.

[0065] FIG. 4G graphically represents the reduction in error introduced by the extraneous stimulus of hematocrit as represented in FIG. 4C provided through the use of the temperature and Hct normalized analyte responsive output signal values at the selected glucose concentration of 100 mg/dL.

[0066] FIG. 4H provides an example of the determination of a normalized reference correlation from combining the temperature and hematocrit normalized analyte responsive output signal values of FIG. 4G.

[0067] FIG. 4I graphically represents the %-bias of the analyte concentrations that were determined by a measurement device using a conventional reference correlation (%bias_raw), a temperature normalized reference correlation (%bias_T), and a temperature and Hct normalized reference correlation (%bias_T/Hct).

[0068] FIG. 5 depicts a schematic representation of a biosensor system that determines an analyte concentration in a sample of a biological fluid.

DETAILED DESCRIPTION

[0069] Measurement devices in biosensor systems that are used to determine the presence and/or concentration of an analyte in a sample include normalized calibration information relating output signal or signals the device generates in response to the analyte concentration of the sample to previously determined reference sample analyte concentrations. The measurement devices use this normalized calibration information to relate one or more output signals from an electrochemical or optical analysis of a sample to the presence and/or concentration of one or more analytes in the sample.

[0070] The present application discloses methods to determine normalized calibration information in a factory, laboratory or similar setting for use in sample analysis of analyte concentration(s), methods to determine the analyte concentration(s) of a sample using normalized calibration information that is stored in a measurement device of a biosensor system for use during sample analysis, and a biosensor system that uses normalized calibration information to determine the presence and/or concentration of the analyte(s) in the sample. The normalized calibration information includes a normalizing relationship used to determine normalized output signals from measured output signals and a normalized reference correlation relating the normalized output signals determined during the analysis to a reference sample analyte concentration. The normalized calibration information is useful in biosensor systems that generate at least one primary output signal responsive to an analyte but include or are affected by error from at least one extraneous stimulus and that generate at least one secondary output signal responsive to the at least one extraneous stimulus

[0071] During sample analysis, the primary stimulus and one or more extraneous stimulus affect the one or more output signals analyzed by the measurement device. The primary stimulus is the analyte concentration of the sample. The extraneous stimulus includes all other stimuli (except the analyte concentration) that affect the output signal such as the physical characteristics of the sample, the environmental aspects of the sample, manufacturing variations between test sensor lots, and the like. The one or more output signals analyzed by the measurement device may include primary output signals and secondary output signals. The primary output signals include a major effect from the primary stimulus – the analyte concentration of the sample -- but also include some effect from one or more extraneous stimulus. In contrast, the secondary output signals include a major effect from the extraneous stimuli, and may or may not include a major effect from the primary stimulus. Preferably, the secondary output signals are solely responsive to the one or more extraneous stimulus.

[0072] The measurement of %-A1c in blood samples, thus the concentration of glycated hemoglobin (%-A1c or A1c) in the total hemoglobin (THb) content of a blood sample, may be accomplished by an immunoassay method using a laminar flow analysis. Conventionally, in the laminar flow analysis two independent signals are measured, primary output signals for the A1c and secondary output signals for the THb. In this type of A1c system, the Zone 1 detectors provide the primary output signal while the Zone 2 detectors provide the secondary output signal. The primary output signals from the Zone 1 detector/s depends on the A1c concentration of the sample, but also on the THb concentration of the sample. The secondary output signals from the Zone 2 detector/s depend on the THb concentration of the sample, but are substantially independent of the A1c concentration of the sample.

[0073] Conventional calibration in these systems focuses on establishing a relationship between the known %-A1c value of reference samples, the reflectance primary output signals determined from the Zone 1 detector/s of the measurement device responsive to A1c when these samples are analyzed by the biosensor system, and the secondary output reflectance signals determined from the Zone 2 detector/s of the measurement device responsive to the THb content of the sample when these samples are analyzed by the biosensor system. Thus, there are three stimuli for potential consideration in determining the calibration information to store in the measurement device for later use during an analysis (reference sample analyte concentration, primary output signals from the measurement device, and secondary output signals from the measurement device).

[0074] In contrast to such conventional methods, a significant benefit of the presently disclosed calibration methods in an A1c biosensor system arises from the ability to use the laboratory determined calibration information in later compensation techniques when two of the stimuli (reference sample analyte concentration (%-A1c, primary stimulus) and secondary THb output signals (an extraneous stimulus)) are reduced to one (reference sample analyte concentration for

%-A1c). One method of accomplishing this reduction of stimuli is through the described normalization methods.

[0075] The normalization method reduces the dependence of the primary output A1c signal from the measurement device on THb sample concentration by generating a normalized output signal from the A1c responsive reflectance values determined by the measurement device. Then a normalized reference correlation is determined between the generated normalized output signals and the reference sample analyte concentrations. The normalization relationship used to determine the normalized output signals and the normalized reference correlation are stored in the measurement device. In use, the primary output signals measured from the Zone 1 detector/s of the measurement device as normalized by the described normalization procedure remain responsive to A1c, but become substantially independent of the secondary output signals measured from the Zone 2 detector/s responsive to the total hemoglobin content of the sample (THb).

[0076] In a glucose analysis system, calibration generally focuses on establishing a relationship between the known reference sample analyte concentrations for glucose, the electrical or optical primary output signals determined from the sample, and the secondary output signals responsive to temperature and/or the hematocrit (Hct) content of the sample. These secondary output signals may be determined from a thermistor, a dedicated Hct electrode, and the like, or from one or more estimates of these values originating from the primary output signals.

[0077] In these glucose analysis systems, the electrical or optical primary output signals responsive to the glucose concentration of the sample also depends on the temperature of the sample and/or the Hct content of the sample. The temperature and Hct information provided by the secondary output signals of the measurement device is substantially independent of the glucose concentration of the sample. Thus, in addition to the reference sample analyte concentration, there are

at least two (glucose and temperature responsive signals) or three (glucose, temperature, and Hct responsive signals) stimuli to consider for determining the calibration information to store in the measurement device for later use during an analysis.

[0078] An example of a conventional method of addressing this calibration in a glucose system is to generate a line or curve representing the reference correlation between multiple reference sample analyte concentrations for glucose and the corresponding output signals of the measurement device at a known temperature, and/or hematocrit concentration. This reference correlation is stored in the measurement device for later use during the analysis. As optical detectors convert light to a voltage and/or amperage, this process is similar for optical or electrochemical biosensor systems. Thus, a reference correlation may be determined for the known reference sample analyte concentration at 20 °C and a 40% sample Hct, for example, and stored in the measurement device. This process may be repeated for multiple Hct sample concentrations at the selected temperature, for example, and these reference correlations also stored in the measurement device. However, in this conventional technique, during the analysis the measurement device must select which of the multiple reference correlations to use or to interpolate between for a specific analysis. Thus, the measurement device is attempting to select the best reference correlation of those it has to fit the actual analysis – a process fraught with potential issues. The goal of the later analysis of a sample by the biosensor system is to transform the output signal determined by the measurement device into the analyte concentration of the sample using the previously determined reference correlation or correlations stored in the device.

[0079] In contrast to a conventional direct conversion of the output signal to a concentration by the reference correlation, a significant benefit of the presently disclosed calibration methods arises from the ability to use the laboratory determined calibration information stored in the measurement device in later

compensation techniques if at least two of these stimuli (reference sample analyte concentration for glucose and secondary temperature output signals) are reduced to one (reference sample analyte concentration for glucose). For example, the temperature dependence of the reference correlation on temperature may be reduced or preferably removed through the described normalization methods to make the reference correlation unitless. Similarly, the Hct dependence of the reference correlation also may be reduced or preferably removed through the described normalization methods.

[0080] The normalization method reduces the dependence of the primary output glucose signal from the measurement device on temperature or temperature and sample %-Hct by generating a normalized output signal from the glucose responsive current values determined by the measurement device. Then a normalized reference correlation is determined between the generated normalized output signals and the reference sample analyte concentrations. The normalization relationship used to determine the normalized output signals and the normalized reference correlation are stored in the measurement device. In use, the primary output signals responsive to glucose as measured by the measurement device as normalized by the described normalization procedure remain responsive to glucose, but become substantially independent of the secondary output signals responsive to temperature or temperature and sample %-Hct.

[0081] For either analysis type, the normalization method may be represented by the following expression: Normalized Output Signal = (analyte responsive signal including the effect of one primary stimulus and at least one extraneous stimulus)/(at least one extraneous stimulus signal) where the effect of the primary stimulus is the effect the measurement device is attempting to detect and/or quantify. Thus, while two or more factors affect the outcome of the analysis, one or more factor is normalized to reduce the factors affecting the outcome of the analysis to one. The analyte responsive primary output signal may be the reflectance output

from the Zone 1 detector/s of an A1c analysis system or the current output responsive to the electrochemical redox reaction of glucose or a glucose concentration responsive mediator in an electrochemical analysis system, for example. Primary output signals from other types of analyses also may be used with the normalization method. The extraneous stimulus may be THb in an A1c analysis system, for example, or temperature and/or hematocrit in a glucose analysis system, for example. Thus, the extraneous stimulus arises from the secondary output signals of the analysis.

[0082] FIG. A represents a calibration method **100** of determining normalized calibration information for incorporation into a measurement device of a biosensor system with a reduced stimulus effect. Preferably, the calibration method **100** is performed during factory calibration of the measurement device. The calibration method **100** also may be performed in a laboratory or similar setting. The calibration method may be performed by the measurement device, one or more analytical devices such as a computer, or a combination of the measurement and analytical devices.

[0083] In analyte responsive output signal measurement **110**, analyte responsive output signals are measured from a reference sample, where the analyte responsive output signals are affected by at least one extraneous stimulus resulting from a physical characteristic, an environmental aspect, and/or a manufacturing variation error being incorporated into the analyte responsive output signals. At least two analyte responsive output signals are measured. Preferably, at least four, and more preferably at least 6 analyte responsive output signals are measured from the reference sample. Optical and/or electrochemical methods may be used to analyze the reference samples. FIG. 1A, as addressed further below, provides an example of the analyte responsive output signal measurement **110** in an A1c analysis system. FIG. 3A, as addressed further below, provides an example of the analyte responsive output signal measurement **110** in a glucose analysis system.

[0084] In reference correlation determination **120**, a reference correlation **122** is determined between one or more reference sample analyte concentrations **124** and one or more output signals. The reference correlation **122** relates the reference sample analyte concentrations **124** to the output signals as determined by the measurement device **126**. The reference sample analyte concentration of the reference samples may be determined using a reference instrument, by mixing or altering known sample analyte concentrations, and the like.

[0085] In extraneous stimulus quantification **130**, one or more extraneous stimulus responsive output signals are measured from the reference samples and the extraneous stimulus quantified to determine at least two quantified extraneous stimulus values **132**. The stimulus responsive output signals may be measured concurrently with the analyte responsive output signals or at different times. Preferably, the stimulus responsive output signals are measured concurrently with the analyte responsive output signals. FIG. 1B, as addressed further below, provides an example of the extraneous stimulus quantification **130** in an A1c analysis system. In a glucose system, for example as represented in Table 3, when temperature is the extraneous stimulus, multiple analyses are performed at a target temperature and the actual temperature for each analysis averaged.

[0086] The extraneous stimulus signals may be directly quantified, such as when an optical detector or electrode outputs a specific voltage and/or amperage. The extraneous stimulus signals may be indirectly quantified, such as when a thermistor provides a specific voltage and/or amperage that is reported as a temperature in degrees Celsius, for example. The extraneous stimulus signals also may be indirectly quantified, such as when the Hct concentration of a sample is determined from a specific voltage and/or amperage measured from an Hct electrode, for example. The extraneous stimulus signals may be directly or indirectly quantified and then modified to provide the quantified extraneous stimulus values **132**, such as when the directly or indirectly quantified extraneous

stimulus value is transformed into a concentration. The quantified extraneous stimulus values **132** may be determined by averaging multiple values, such as multiple temperature readings recorded at the same target temperature. The extraneous stimulus may be quantified through other techniques. For example, analysis method **200**, as described further below provides an example of extraneous stimulus quantification.

[0087] In normalizing relationship determination **140**, a normalizing relationship **142** is determined between the analyte responsive output signals and the quantified extraneous stimulus values **132** for the analyte concentration of the one or more reference sample analyte concentrations selected. Preferably, a regression technique is applied to the analyte responsive output signals and the quantified extraneous stimulus values **132** to determine the normalizing relationship at single selected analyte concentration. FIG. 1C, as addressed further below, provides an example of how a single analyte concentration was selected in an A1c analysis system and used to determine synthesized extraneous stimulus responsive output signals responsive to the quantified extraneous stimulus signals for THb. FIG. 3B, as addressed further below, provides an example of how one of two analyte concentrations was selected in a glucose analysis system and used to determine synthesized extraneous stimulus responsive output signals responsive to the quantified extraneous stimulus signals for temperature. Thus, a synthesized extraneous stimulus responsive output signal was determined from the primary output signals at a single selected sample analyte concentration. The synthesized extraneous stimulus responsive output signal may be thought of as the extraneous stimulus responsive output signal extracted from the combined primary output signal from the measurement device that includes both the primary and the extraneous stimulus. Similarly, the normalizing relationship **142** may be thought of as a reference correlation for the extraneous stimulus.

[0088] FIG. 1D, as addressed further below, provides an example of how the normalizing relationship determination **140** may be implemented in an A1c analysis system using the synthesized extraneous stimulus responsive output signal values. An example normalizing relationship as determined for the A1c analysis system also is shown in FIG. 1D. FIG. 3C, as addressed further below, provides an example of how the normalizing relationship determination **140** may be implemented in a glucose analysis system using the synthesized extraneous stimulus responsive primary output signals. Example normalizing relationships as determined for the glucose analysis system also are shown in FIG. 3C.

[0089] Linear or non-linear (such as polynomial) regression techniques may be used to determine the normalizing relationship **142**. Linear or non-linear regression techniques include those available in the MINITAB® version 14 or version16 statistical packages (MINTAB, INC., State College, PA), Microsoft Excel, or other statistical analysis packages providing regression techniques. Preferably, polynomial regression is used to determine the normalizing relationship **142**. For example in MS Excel version 2010, the Linear Trendline Option accessible through the Trendline Layout Chart Tool may be selected to perform linear regression, while the Polynomial Trendline Option may be chosen to perform a non-linear polynomial regression. Other regression techniques may be used to determine the normalizing relationship **142**. The normalizing relationship **142** is preferably stored in the measurement device as a portion of the calibration information.

[0090] When linear regression is used, the normalizing relationship **142** will be in the form of $Y = mX + b$, where m is the slope and b is the intercept of the regression line. When non-linear regression is used, the normalizing relationship **142** will be in a form of $Y = b_2*X^2 + b_1*X + b_0$, and the like, where b_2, b_1 and b_0 are the coefficients of the polynomial. In both the linear or polynomial regression equations, Y is the calculated synthesized extraneous stimulus responsive output signal responsive to the extraneous stimulus portion of the primary output signal at a

single selected analyte concentration, and X is the quantified extraneous stimulus signals/values. When a value of X (the quantified extraneous stimulus signal value) is entered into either one of the relationships (linear or polynomial equations), an output value Y, representing the normalizing value (NV) is generated from the normalizing relationship.

[0091] If a second extraneous stimulus is adversely affecting the analyte responsive output signals and will be addressed by the calibration information, the normalizing relationship determination **140** is repeated for a second extraneous stimulus. An example of how a second normalizing relationship may be determined to address a second extraneous stimulus is found regarding FIG. 4, as addresses further below.

[0092] In normalizing value determination **150**, a normalizing value **152** is determined from the normalizing relationship **142** by inputting the quantified extraneous stimulus values **132** into the normalizing relationship **142** and solving for the normalizing value **152.**

[0093] In normalized output signal determination **160**, one or more normalized analyte responsive output signals are determined from one or more analyte responsive output signals and the normalizing value. Preferably, the analyte responsive output signals are divided by the normalizing value **152** to provide normalized analyte responsive output signals **162.** This preferably reduces the effect of the extraneous stimulus on the analyte responsive output signals. FIG. 1E, as addressed further below, provides an example of the normalized output signal determination **160** in an A1c analysis system. FIG. 3D, as addressed further below, provides an example of the normalized output signal determination **160** in a glucose analysis system at a single selected sample analyte concentration (100 mg/dL).

[0094] In normalized reference correlation determination **170**, a normalized reference correlation **172** is determined between the normalized analyte responsive output signals **162** and the reference sample analyte concentrations **124**. Preferably, a regression technique is applied to the normalized analyte responsive output signals **162** and the reference sample analyte concentrations **124** to determine the normalized reference correlation **172**. Linear or non-linear (such as polynomial) regression techniques may be used, such as those available in the MINITAB® version 14 or version16 statistical packages (MINTAB, INC., State College, PA), Microsoft Excel, or another statistical analysis package providing regression techniques. Preferably, polynomial regression is used to determine the normalized reference correlation **172**.

[0095] For example in MS Excel version 2010, the Linear Trendline Option accessible through the Trendline Layout Chart Tool may be selected to perform linear analysis, while the Polynomial Trendline Option may be chosen to perform a non-linear polynomial analysis. Other regression techniques may be used to determine the normalized reference correlation **172**. FIG. 1F, as addressed further below, provides an example of the normalized reference correlation determination **170** in an A1c analysis system. FIG. 1G represents the determined normalized reference correlation **172** expressed as a normalized calibration curve. FIG. 3E, as addressed further below, provides an example of the normalized reference correlation determination **170** in a glucose analysis system.

[0096] When linear regression is used, the normalized reference correlation **172** will be in the form of $Y=mX+b$, where m is slope and b is an intercept of the regression line. When non-linear regression is used, such as a polynomial, the normalized reference correlation **172** may be in a form of $Y=b_2*X^2+b_1*X+b_0$, and the like, where b_2, b_1 and b_0 are the coefficients of the polynomial. The normalized reference correlation **172** is preferably stored in the measurement device as a portion of the calibration information for later use during the analysis of a sample.

In the measurement device, Y is the normalized analyte responsive output signal value determined during the analysis, and X is the analyte concentration of the sample as determined from the normalized reference correlation **172**. As discussed further below, for the linear normalized reference correlation, an X value (the sample analyte concentration) may be solved for when inputting a Y value (a value of the normalized output signal) into the equation. For a normalized reference correlation in the form of a 2nd order polynomial, the normalized reference correlation **172** may be expressed in the form of a normalized calibration curve as $X = c_2*Y^2 + c_1*Y + c_0$ where c_2, c_1 and c_0 are coefficients for the equation. A normalized output signal input to this relationship will generate an analyte concentration.

[0097] FIG. B represents an optional calibration method **102** that considers a second extraneous stimulus with the normalized calibration information. Calibration method **102** provides normalized calibration information from the second extraneous stimulus for incorporation into a measurement device of a biosensor system with a reduced stimulus effect. Preferably, the calibration method **102** also is performed during factory calibration of the measurement device. The calibration method **102** also may be performed in a laboratory or similar setting. The calibration method may be performed by the measurement device, one or more analytical devices such as a computer, or a combination of the measurement and analytical devices. Calibration method **102** combines with calibration method **100** to provide normalized calibration information from a first extraneous stimulus and a second extraneous stimulus. Thus, FIG. A and FIG. B may be combined when determining calibration information for the measurement device of the biosensor system.

[0098] If a second extraneous stimulus adversely affecting the analyte responsive output signals is considered, such as the hematocrit concentration of the sample when the first extraneous stimulus is temperature, at least two second

quantified extraneous stimulus values **134** may be determined in accord with the extraneous stimulus quantification **130**. FIG. 4D and FIG. 4E, as addressed further below, provide an example of the determination of second quantified extraneous stimulus values **134** in a glucose analysis system.

[0099] Then a second normalizing relationship **147** may be determined in accord with the normalizing relationship determination **140**, but where the second normalizing relationship **147** is determined between the normalized analyte responsive output signals **162** and the second quantified extraneous stimulus values **134** at a single selected sample analyte concentration. The second normalizing relationship **147** is preferably stored in the measurement device as a portion of the calibration information. FIG. 4F, as addressed further below, provides an example of the determination of a second normalizing relationship **147** in a glucose analysis system.

[00100] In the case of the second extraneous stimulus, a second normalizing value determination **155** is performed. A second normalizing value **157** is determined from the second normalizing relationship **147** by inputting the second quantified extraneous stimulus values **134** into the second normalizing relationship **147** and solving for the second normalizing value **157**.

[00101] In the case of the second extraneous stimulus, a second normalized output signal determination **165** is performed. Second normalized analyte responsive output signals **167** are determined by dividing the normalized analyte responsive output signals **162** by the second normalizing value **157**. FIG. 4G, as addressed further below, provides an example of determining second normalized analyte responsive output signals **167** in a glucose analysis system.

[00102] In the case of the second extraneous stimulus, a second normalized reference correlation determination **175** is performed. A second normalized reference correlation **177** is determined between the second normalized analyte

responsive output signals **167** and the reference sample analyte concentrations **124** by a regression technique, as previously described. FIG. 4H, as addressed further below, provides an example of determining a second normalized reference correlation **177** in a glucose analysis system.

[00103] The second normalized reference correlation **177** is preferably stored in the measurement device as a portion of the calibration information. In this case, the normalized reference correlation **172** does not need to be stored in the measurement device and is preferably not used during the analysis. Similarly, three or more extraneous stimulus may be considered by the calibration information, where each extraneous stimulus is represented by an individual normalizing relationship stored in the measurement device in addition to a single normalized reference correlation prepared for the combined extraneous stimulus represented by the individual normalizing relationships.

[00104] FIG. C represents an analysis method **200** of determining the analyte concentration of a sample with a reduced extraneous stimulus effect using a normalized reference correlation. The analysis method **200** is preferably performed when a user activates a measurement device of a biosensor system to analyze a sample, such as blood. Preferably, the sample is blood including red blood cells. Optical and/or electrochemical methods may be used to analyze the sample.

[00105] In analysis analyte responsive output signal measurement **220**, one or more analyte responsive output signal values **222** are measured from the sample, where the analyte responsive output signal values are affected by one or more extraneous stimulus, such as a physical characteristic, an environmental aspect, and/or a manufacturing variation, that results in an error being incorporated into the analyte responsive output signal values. The analyte responsive output signal values **222** are measured from one or more output signals generated from the sample using optical and/or electrochemical methods, such as gated amperometry, gated voltammetry, or the like.

[00106] In analysis extraneous stimulus quantification **230**, one or more extraneous stimulus responsive output signals are measured. One or more quantified extraneous stimulus values are determined in response to the extraneous stimulus responsive output signals. From method **100**, a single or first quantified extraneous stimulus value **232** may be determined in response to a first extraneous stimulus. Methods **100** and **102** may be combined to determine a first quantified extraneous stimulus value **232** in response to a first extraneous stimulus and a second quantified extraneous stimulus value **234** in response to a second extraneous stimulus. Other quantified extraneous stimulus values may be determined. Thus, a quantified extraneous stimulus value is determined for each extraneous stimulus addressed by the calibration information. The quantified extraneous stimulus responsive output signals are measured from one or more output signals generated from the sample using optical and/or electrochemical methods, such as gated amperometry, gated voltammetry, or the like

[00107] In analysis normalizing value determination **250**, one or more previously determined normalizing relationships are used to determine one or more normalizing values. Examples of previously determined normalizing relationships are the previously described normalizing relationship **142** and the previously described second normalizing relationship **147**. For example, one or more of the analyte responsive output signal values **222** and the quantified extraneous stimulus value **232** are input into the normalizing relationship **142**. Similarly, one or more of the analyte responsive output signal values **222** and the quantified extraneous stimulus value **234** are input into the second normalizing relationship **147**. In this way, extraneous stimulus value **232** or **234** may be input to the normalizing relationship **142** or **147** to determine the normalizing value. Thus, one or more analyte responsive output signal values and one or more quantified extraneous stimulus values are input into one or more normalizing relationships to determine one or more normalizing values.

[00108] In normalized analyte responsive output signal determination **260**, at least one normalized analyte responsive output signal value is determined in response to the one or more analyte responsive output signal values and one or more normalizing values. The one or more analyte responsive output signal values **222** are divided by the normalizing value to determine one or more normalized analyte responsive output signal values **262** (in the case of one external stimulus) or **267** (in the case of two external stimulus). Preferably, one analyte responsive output signal value is used to determine one normalized analyte responsive output signal value.

[00109] In analysis analyte concentration determination **280**, one or more analyte concentrations in the sample are determined in response to one or more normalized reference correlations and one or more normalized analyte responsive output signals. Preferably, a previously determined normalized reference correlation, such as the previously described normalized reference correlation **172** or **177**, transforms the one or more normalized analyte responsive output signal values **262** or **267** into an analyte concentration of the sample **282**. Preferably, the previously described normalized reference correlation **172** or **177** is transforms one normalized analyte responsive output signal value into an analyte concentration of the sample. When two or more analyte concentrations of the sample are determined, the analyte concentrations may be averaged to provide an average analyte concentration of the sample.

[00110] In **290**, the analyte concentration of the sample **282** may be displayed, stored for future reference, compensated, and/or used for additional calculations.

[00111] Thus, in the analysis method **200** the normalized reference correlation **172** or **177** is incorporated into the measurement device and used similarly to how a conventional reference correlation would be used to translate primary output signal values into determined analyte concentrations of the sample. Except that in the analysis method **200**, instead of primary output signal values being transformed by

the reference correlation **122**, the normalized analyte responsive output signal value/s **262** or **267** are transformed by the normalized reference correlation **172** or **177**, respectively, to provide the analyte concentration of the sample with reduced effect from one or more extraneous stimulus.

[00112] An example of the calibration method **100** for determining calibration information with a reduced extraneous stimulus effect for incorporation into the measurement device using this normalization process for calibration is shown in FIG. 1 for an A1c analysis system. In this example, the sample is blood; the sample analyte is the A1c in the blood samples and the sample analyte concentration is the sample %-A1c. The A1c is the primary stimulus while the THb is the extraneous stimulus. The numerical values calculated throughout FIG. 1 would be different for a different analysis system or even a different A1c analysis system. This method is represented with the plots in FIG. 1B through FIG. 1H.

[00113] FIG. 1A shows A1c reflectance signals recorded from the Zone 1 detector/s of the measurement device versus reference sample analyte concentrations (%-A1c) at four THb concentrations (85 mg/mL, 125 mg/mL, 175 mg/mL, and 230 mg/mL). The %-A1c measurement was repeated twice for each reference sample of blood including a known concentration of A1c. Because the A1c reflectance signals measured from the Zone 1 detector/s of the measurement device are THb dependent, the A1c reflectance signals are spread out for the same %-A1c reference sample analyte concentration. Thus, even though the actual A1c concentration was identical for a set of reference samples, the measured A1c reflectance signals measured from the Zone 1 detector/s for the reference sample set was different due to the THb extraneous stimulus. The equation shown in the figure represents a conventional reference correlation for this analysis where the output signals from the measurement device are directly translated into analyte concentrations by this equation. Note the relatively low R^2 correlation of 0.6272

between the determined reference correlation ($Y=-0.0006x^2+0.0263x+0.2239$) and the output signals from the reference samples.

[00114] FIG. 1B shows the comparatively constant THb output signals at the four THb reference sample concentrations (85 mg/mL, 125 mg/mL, 175 mg/mL, and 230 mg/mL) as determined from the Zone 2 detectors of the measurement device. Thus, for each THb concentration, an average signal value of the extraneous stimulus THb was determined. For example, a quantified extraneous stimulus signal value of ~0.76 was determined from FIG. 1B at the 85 mg/mL THb sample concentration by averaging. Methods other than averaging may be used to quantify the extraneous stimulus from the secondary output signals.

[00115] FIG. 1C shows the individual A1c reflectance signals recorded from the Zone 1 detector/s of the measurement device separated for the four different THb concentrations in blood samples. This allows a single sample analyte concentration to be selected from which synthesized extraneous stimulus responsive output signal values may be determined from the primary output signals. In this example, linear regression lines were determined at each of the 4 THb sample concentrations using the general relationship (R_{A1c} = Slope*%-A1c + Int, where R_{A1c} is the output signal from the measurement device, Slope and Int are the slope and intercept, respectively of the linear regression lines at each THb sample concentration, and %-A1c is the sample analyte concentration). Other regression techniques may be used.

[00116] The regression equations determined at the 85 THb mg/mL and 230 THb mg/mL are shown on the figure, but regression equations at 127 and 175 mg/mL THb also were determined. In this example, the single selected sample analyte concentration of 9%-A1c was selected to determine the synthesized extraneous stimulus responsive output signal values from the primary output signals. Thus, in this example, the reference sample analyte concentration of 9% provided an ~0.36 A1c synthesized extraneous stimulus responsive output signal value for

the 85 mg/mL THb samples from the 85 mg/mL THb regression line and an ~0.44 A1c synthesized extraneous stimulus responsive output signal value for the 230 mg/mL THb samples from the 230 mg/mL THb regression line.

[00117] Synthesized extraneous stimulus responsive output signal values can be determined in other ways than determining regression lines and "back determining" a primary output signal value from a selected reference sample analyte concentration. For example, synthesized extraneous stimulus responsive output signal values may be selected from the measured primary output signal values at one reference sample %-A1c concentration for all four THb levels. A single THb reflectance signal measured concurrently is paired with the A1c reflectance signal to form the four pairs of A1c and THb data and to construct the plot of A1c reflectance vs. THb reflectance, which will also lead to the normalizing relationship.

[00118] While the single selected sample analyte concentration of 9 %-A1c was chosen in FIG. 1C, reference sample analyte concentrations of 6 through 11 %-A1c also may preferably be selected. Thus, the single selected sample analyte concentration at which to determine the synthesized extraneous stimulus responsive output signal values is preferably near the middle of the range of reference sample analyte concentrations, but can be on either side of the middle to provide the desired measurement performance to the analysis system.

[00119] Table A, below, shows the data pairs collected from averaging the THb signals at the same level of THb and the corresponding synthesized THb responsive output signals calculated at a single %-A1c concentration (in this example 9% A1c) through the above general regression relationship (R_{A1c} = Slope*%-A1c + Int) as in Fig. 1C.

THb (mg/mL)	**85**	**125**	**175**	**230**
THb/70 (mg/mL)*	1.214	1.786	2.5	3.286
Quantified (Avg.) secondary output signal from Fig.1B	0.7572	0.7302	0.7069	0.6796
Synthesized THb Responsive Output Signal Values at A1c Conc. (9) from Fig 1C	0.3659	0.3964	0.4183	0.4400

Table A: Synthesized and Average THb Signal Values

*The samples were diluted to obtain signals appropriate for the detectors.

[00120] FIG. 1D is a correlation plot of these four pairs of data where the synthesized extraneous stimulus responsive output signals extracted from the A1c output signal in Y-axis is plotted against the THb signals (secondary output signals) in the X-axis, the extraneous stimulus. FIG. 1D also provides an example of determining the normalization relationship **140**, which establishes the correlation between the synthesized extraneous stimulus responsive output signals at a single A1c concentration and the secondary output signals responsive to the sample THb concentrations.

[00121] A regression technique, in this case polynomial (a_2*THb^2 + a_1*THb + a_0, where a_2, a_1 and a_0 are the coefficients of the 2nd order polynomial normalization function from curve-fitting and THb is the quantified extraneous stimulus value for THb), was then used to determine the normalizing relationship **142** between the synthesized extraneous stimulus responsive output signals at a single selected

sample analyte concentration and the quantified extraneous stimulus signals. The specific normalization relationship for the A1c analysis data from this example is shown in FIG. 1D as $Y=-3.34X^2+3.85X-0.63$, thus showing the specific 2nd order polynomial coefficients for this example, where Y is the calculated synthesized extraneous stimulus responsive output signal responsive to the extraneous stimulus at a single selected analyte concentration, and X is the quantified extraneous stimulus signals/values. A different analysis would have different regression coefficients. When a value of X (the quantified extraneous stimulus signal value) is entered into the 2nd order polynomial, a value of Y is generated through this normalizing relationship, which is the normalizing value (NV).

[00122] FIG. 1E provides an example of the determination of normalized analyte responsive output signals **162** using the normalizing value. Thus, the A1c reflectance signals from FIG. 1C are converted to normalized primary output signal values using the normalization relationship of FIG. 1D and the normalizing value. The determination of normalized analyte responsive output signals from the normalizing relationship and the normalizing value may be represented by the relationship $NR_{A1c} = R_{A1c}/NV_{A1c}$, where NR_{A1c} are the THb normalized analyte responsive output signals, R_{A1c} are the A1c reflectance signals from the measurement device, and NV_{A1c} is the normalizing value.

[00123] Preferably, the determination of normalized analyte responsive output signals is performed for all or the majority of the analyte responsive output signal to determine the calibration information. However, a subset of the analyte responsive output signal may be used depending on the analysis system. Thus, in FIG. 1E, the analyte responsive output signal values from FIG. 1C were normalized by being divided with the corresponding normalizing values through the normalizing relationship determined in FIG. 1D using the normalizing value from FIG. 1F to provide the normalized analyte responsive output signal values shown in FIG. 1E, which are then combined into FIG. 1F.

[00124] FIG. 1F provides an example of the determination of a normalized reference correlation from the normalized analyte responsive output signals of FIG. 1E. NR_{A1c} was plotted vs. the reference sample analyte concentrations (%-A1c) and curve-fitted by a regression technique to provide the normalized reference correlation. A regression technique, in this case 2nd order polynomial (a_2*%-A1c^2 + a_1*%-A1c + a_0, where a_2, a_1, and a_0 are coefficients of the polynomial and %-A1c is the analyte concentration of the reference samples), was used to determine the normalized reference correlation.

[00125] The specific normalized reference correlation for the A1c analysis data from this example is shown in FIG. 1F as $y=-0.1119X^2+0.0697X+0.538$, thus showing the specific 2nd order polynomial coefficients for this example. A different analysis would have different coefficients. Also shown in FIG. 1F is the $R^2=0.9663$, showing the excellent agreement between the normalized primary output signals and the reference sample analyte concentrations for %-A1c. In this determination of the normalized reference correlation, the normalized primary output signal was the dependent variable, while the reference sample analyte concentrations for %-A1c was the independent variable for the regression. Thus, this normalized reference correlation may be thought of as outputting the normalized analyte responsive output signal values from the reference sample analyte concentrations for %-A1c.

[00126] FIG. 1G provides another example of the determination of a normalized reference correlation from the normalized analyte responsive output signal values of FIG. 1E. In FIG. 1G, the normalized analyte responsive output signal was the independent variable, while the reference sample analyte concentration for %-A1c was the dependent variable for the regression. Thus, the horizontal x and vertical y axes are reversed. In this example, the determined normalized reference correlation was $y=28.26X^2 - 28.996X+0.522$ and the R^2 correlation was 0.962, again showing the excellent agreement between the normalized analyte responsive output signals and the reference sample analyte

concentrations for %-A1c. A different analysis would have different regression coefficients. Thus, this normalized reference correlation may be thought of as outputting the reference sample analyte concentrations for %-A1c from the normalized analyte responsive output signal values.

[00127] A normalized reference correlation expressed in this way may be considered a "normalized calibration curve". Such a normalized calibration curve providing sample analyte concentrations is preferred for storage in the measurement device for use during the analysis **200** as the biosensor system determines an analyte concentration from the primary output signal, and not the reverse as would be obtained from the normalized reference correlation of FIG. 1F. Thus, when a value of X (the normalized output signal) is entered into the 2nd order polynomial equation, a value of Y (the analyte concentration) is obtained.

[00128] FIG. 1H compares the normalized analyte responsive output signals to the normalized reference correlation in the form of a normalized calibration curve from FIG. 1G by superimposing the normalized analyte responsive output signal values on the curve. Another point of interest is the comparison of the R^2 correlation value of 0.6272 determined in FIG. 1A for the conventional reference correlation and R^2 correlation value of 0.9663 determined in FIG. 1F for the normalized reference correlation. The approximately 54% (0.9663-0.6272/0.6272*100) improvement in the normalized reference correlation establishes the superiority of the normalized output signal values/normalized reference correlation in determining analyte sample concentrations in comparison to the conventional measured output signal values/reference correlation.

[00129] The resultant calibration information including the normalizing relationship and the normalized reference correlation may be stored in the measurement device in the form of a look-up table, one or more equations, and the like. Other relationships also may be stored in the measurement device. The

calibration information is used by the processor of the measurement device during sample analysis to determine the analyte concentration of the sample.

[00130] In a measurement device with one primary output signal, the above techniques may be used to determine calibration information for the one primary output signal. However, for measurement devices with more than one primary output signal, calibration information may be determined for each primary output signal, and the analyte concentrations determined from the different calibration information combined. For example, in an A1c measurement device having more than one detector for Zone 1 with which to determine the primary stimulus, calibration information may be determined for each detector channel and then the final analyte concentration determined by averaging the initial analyte concentration determined from each detector channel.

[00131] Alternatively, for measurement devices with more than one primary output signal of the same primary stimulus, the output signals initially may be combined and calibration information determined for the combined signal. The independent output signals may then be transformed into analyte concentrations using the combined calibration information to provide initial analyte concentrations that are then combined to provide the analyte concentration of the sample, or the combined output signals may be transformed by the calibration information determined for the combined signal to provide the analyte concentration of the sample. For example, in an A1c measurement device having more than one detector for Zone 1, the output signals from both detectors may be averaged and calibration information determined for the averaged output signals from both detectors. Then, the averaged output signal may be transformed into the analyte concentration of the sample by the calibration information determined from the averaged output signal or the output signal from both channels transformed by the calibration information determined from the averaged output signal to provide two

initial analyte concentrations, which are then averaged to provide the final analyte concentration of the sample.

[00132] The examples described with regard to FIG. 2 show the benefit of determining independent calibration information for each of two individual detector channels of a measurement device, where each of the two output signal channels includes both A1c and THb responsive information. The numerical values calculated throughout FIG. 2 would be different for a different analysis system or even a different A1c analysis system.

[00133] FIG. 2A represents the normalization relationships for both channels of an A1c measurement device having two detection channels. Thus, for this example, FIG. 2A shows the two separate normalizing relationships for the primary output signals from the Zone 1 channel one detector (Ch1) and the secondary output signals from the Zone 2 channel two detector (Ch2); and for the primary output signals from the Zone 1 channel three detector (Ch3) and the secondary output signals from the Zone 2 channel four detector (Ch4). Thus, Ch1 and Ch3 provide A1c responsive output signals, while Ch2 and Ch4 provide THb responsive output signals.

[00134] FIG. 2B represents the individual normalized calibration curves for Ch1 and Ch3 of the A1c measurement device. Also plotted on the figure are the normalized output signals determined from Ch1/Ch2, the normalized output signals determined from Ch3/Ch4, and the average of these normalized output signals. A polynomial regression technique was used to determine the normalized reference correlations in the form of normalized calibration curves, as previously described.

[00135] FIG. 2C shows the normalized A1c reflectance signals from the two individual channels (Ch1 & Ch3) for the reference samples. Averaging may be performed for the two initial %-A1c concentrations to provide the final A1c concentration. The mean and percent bias standard deviation (SD) values in Table 1

and in Table 2 below show the separate individual channels results, as well as the average A1c results for the calibration and measurement device sample analyses, respectively. For both the calibration, using reference samples, and analyses, performed with the measurement device using the calibration information, the averaged determined analyte concentrations are improved over the individual channel results. From Table 2, the Ch1 bias standard deviation was reduced by nearly nine percent (8.8%) (5.58-5.09/5.58*100), while the Ch2 bias standard deviation was reduced by over 18% (18.3%) (6.23-5.09/6.23*100) for the average. Thus, the bias standard deviation was reduced by an average of greater than 10% (13.5%) (8.8+18.3/2) for the averaged determined analyte concentrations.

[00136]

	%-bias1	%-bias3	%-bias_Avg
Mean	0.274	0.295	0.156
SD	5.25	5.52	3.97

Table 1: Calibration

	%-bias1	%-bias3	%-bias_Avg
Mean	0.055	0.184	0.120
SD	5.58	6.23	5.09

Table 2: Analysis

[00137] In addition to determining calibration information for each channel, and then combining the intermediate sample concentrations determined for each channel, the output signals from each channel may be first combined and then used to determine calibration information for the combined signal. FIG. 2D shows the normalizing relationship determined by first averaging the A1c reflectance output signals from Ch1 and Ch3 of the measurement device. Thus, the same output signals used to determine the two normalizing relationships represented in FIG. 2A were first averaged. FIG. 2E shows the normalized reference correlation in the form

of a normalized calibration curve determined for the averaged A1c reflectance signals from Ch1 and Ch3 of the measurement device. Output signals from each channel of the measurement device can then be converted to initial analyte concentrations with this calibration information and the initial analyte concentrations averaged to determine a final sample analyte concentration.

[00138] An example of the calibration method **100** for determining calibration information with a reduced extraneous stimulus effect for temperature on the primary output signal from an electrochemical glucose analysis system is shown in FIG. 3. In this example, the sample is the blood and the sample analyte is the glucose (the primary stimulus). The sample analyte concentration is the sample glucose concentration and the extraneous stimulus are temperature and hematocrit.

[00139] For the temperature effect, the currents measured by the measurement device from reference samples at 40% Hct (the %-Hct at which the conventional reference correlation relating output currents and reference sample analyte concentrations was determined) and at different temperatures were normalized. In this type of glucose system, the working and counter electrodes provide the primary output signal while the temperature sensor provides the secondary output signal. This process is represented with the plots in FIG. 3A through FIG. 3F. The numerical values calculated throughout FIG. 3 would be different for a different analysis system or even a different glucose analysis system.

[00140] FIG. 3A plots the currents obtained from the measurement device versus reference sample analyte concentrations for glucose at different temperatures and 40% Hct. The currents become more widely spread due to changes in temperature at higher sample glucose concentrations. While the currents determined by the measurement device from reference samples including ~80 mg/dL of glucose in blood were closely grouped around ~75 nA, the currents determined by the measurement device from reference samples including ~320 mg/dL and ~580 mg/dL of glucose were widely spaced. In fact, as shown in

FIG. 3A a linear regression line determined from these currents showed an R^2 correlation of only 0.6. This figure may be thought of as showing the effect of an extraneous stimulus on analyte responsive output signals as previously observed in FIG. 1C. In FIG. 1C the extraneous stimulus was sample THb, while in FIG. 3A it was temperature.

[00141] FIG. 3B separates these primary output signal currents by the temperature at which they were recorded. Thus, temperature is the extraneous stimulus that adversely affects the analyte responsive output signal currents from the measurement device, even though the analyte concentrations of the reference samples are identical at each temperature. In this example, linear regression lines were determined at each of the 5 temperatures using the general relationship $i_G = Slope*G_{Ref} + Int$, where i_G is the glucose responsive current from the measurement device and G_{Ref} is the reference sample analyte concentration for glucose from which to determine the synthesized extraneous stimulus responsive output signal values. Other techniques may be used to determine the synthesized extraneous stimulus responsive output signal values.

[00142] In FIG. 3B, two sample glucose concentrations of 100 and 500 mg/dL were selected at which to determine the synthesized extraneous stimulus responsive output signal values at their corresponding temperatures. Thus, unlike in the A1c system where the single selected sample analyte concentration of 9% was selected, this example shows that synthesized extraneous stimulus responsive output signal values may be determined at more than one single selected sample analyte concentration. Single selected sample analyte concentrations other than 100 and 500 mg/dL may be used.

[00143] Table 3, below, provides the synthesized extraneous stimulus responsive output signal values obtained for each temperature at 100 and 500 mg/dL glucose sample analyte concentration from the individual regression lines by using the regression equations similar to that previously described with regard to the

A1c example (i_G = Slope*G_{Ref} + Int). The temperatures values in the table are averages from all the measured temperatures when performing the analysis of the reference samples at the target temperatures. Thus, Table 3 forms two sets of pairs at the selected single glucose concentration of 100 or 500 mg/dL, each set containing seven pairs of output signals-temperatures data.

Avg. Temp, C	6.0	10.9	15.9	22.0	30.4	35.1	40.0
500 mg/dL	205.78	283.53	373.96	462.61	639.89	705.54	809.11
100 mg/dL	41.16	56.71	74.79	92.52	127.98	141.11	161.82

Table 3: Synthesized Output Signal Values

Thus, FIG. 3B separates the output currents from the measurement device by temperature, as opposed to THb sample concentration as described in FIG. 1C. Only five correlation lines were plotted for five of the seven temperatures tested, in order not to crowd the plot.

[00144] FIG. 3C shows the correlations between the synthesized extraneous stimulus responsive output signals obtained at two separate single glucose concentration of 100 and 500 mg/dL versus the quantified extraneous stimulus (temperatures) to determine the normalization relationships. Fig. 3C also provides an example of determining the normalization relationship **140**, which considers temperature for normalization of the analyte responsive output signals. The vertical Y-axis of FIG. 3C shows the extraneous stimulus responsive values as synthesized from the regression lines of FIG. 3B and determined at the single selected sample analyte concentrations of 100 and 500 mg/dL glucose for the five temperatures. The horizontal X-axis of FIG. 3C shows the average value determined at each target temperature for the extraneous stimulus temperature.

[00145] A regression technique, in this case polynomial ($a_2*T^2 + a_1*T + a_0$, where a_2, a_1 and a_0 are the coefficients of the 2nd order polynomial normalization function from curve-fitting and T is the quantified extraneous stimulus value for temperature), was then used to determine the normalizing relationship **142** between the synthesized extraneous stimulus responsive output signals at a single selected sample analyte concentration and the quantified extraneous stimulus signals. The specific normalization relationship for the 100 and 500 mg/dL glucose analysis data from this example is shown in FIG. 3C as $y=0.0104X^2+3.0646x+22.366$ (100 mg/dL) and $y=0.05214X^2+15.3228x+111.832$ (500 mg/dL), thus showing the specific 2nd order polynomial coefficients for this example, where Y is the calculated synthesized extraneous responsive output signal responsive to the extraneous stimulus signal at a single selected analyte concentration, and X is the quantified extraneous stimulus signals/values. A different analysis would have different coefficients. When a value of X (the quantified extraneous stimulus signal value) is entered into the 2nd order polynomial, a value of Y is generated through this normalizing relationship, which is the normalizing value (NV). This figure may be thought of similarly as to FIG. 1D; however, in this example, normalizing values may be determined at two reference sample analyte concentrations.

[00146] FIG. 3D provides an example of the determination of normalized analyte responsive output signals **162** from the normalizing value at 100 mg/dL. Thus, the analyte responsive output signals from the vertical y-axis of FIG. 3B were converted to normalized primary output signal values by dividing the analyte responsive output signals with their corresponding normalizing values obtained from the normalization relationship of FIG. 3C. The determination of the normalized analyte responsive output signals from the normalizing relationship and the normalizing value may be represented by the relationship $Ni_G = i_{measured}/NV_{Temp}$, where Ni_G are the temperature normalized analyte responsive output signals, $i_{measured}$ are the glucose responsive currents from the measurement device, and NV_{Temp} is the normalizing value determined from temperature normalization. Thus, the five

individual lines of FIG. 3B for the different temperatures collapsed into a group of closely packed lines as represented in FIG. 3D. As previously discussed, preferably, the determination of normalized analyte responsive output signals is performed for all or the majority of the analyte responsive output signal to determine the calibration information.

[00147] FIG. 3E provides an example of the determination of a normalized reference correlation from the normalized analyte responsive output signal values of FIG. 3D. N_{IG} was plotted vs. the reference sample analyte concentrations and curve-fitted by a regression technique to provide the normalized reference correlation. A regression technique, in this case linear (Y=Slope*X + Int), was used to determine the normalized reference correlation, where during the analysis **200** Y is the normalized primary output signal determined by the measurement device and X is the reference analyte concentration of the sample. Thus, when a Y value (the normalized output signal) is entered into the linear regression equation, an X value (the analyte concentration) is obtained by solving the equation.

[00148] The specific normalized reference correlation for the glucose analysis data from this example is shown in FIG. 3E as Y=0.01033X - 0.14082, thus showing the specific linear coefficients for this example. A different analysis would have different coefficients. Also shown in FIG. 3E is the R^2=0.9946, showing the excellent agreement between the normalized primary output signals and the reference sample analyte concentrations. Thus, this normalized reference correlation may be thought of as providing determined sample analyte concentrations for glucose from the normalized analyte responsive output signal values.

[00149] For the temperatures measured (6.0° C, 10.9° C, 15.9° C, 22.0° C, 30.4° C, 35.1° C, and 40.0° C), the average temperatures, the regression slope obtained at each temperature using a conventional reference correlation, and the regression slope obtained at each temperature using the normalized reference

correlation at the 100 mg/dL glucose reference sample analyte concentration are tabulated in Table 4, below.

Temp °C	Conventional Reference Correlation Slopes	Normalized Reference Correlation Slopes
6.0	0.412	0.0103
10.9	0.567	0.0099
15.9	0.748	0.0101
22.0	0.925	0.0097
30.4	1.280	0.0102
35.1	1.411	0.0099
40.0	1.618	0.0100
Mean slope	0.9944	0.0100147
SD, slope	0.4532	0.00023014
%-CV	45.6	2.3

Table 4: Summary of Normalization for Temperature Stimulus

[00150] The improvement in measurement performance may be better appreciated by looking at the mean response slopes and the %-CV of the slopes before and after normalization. The %-CV of the response slopes determined with primary output signals from the measurement device and a conventional reference correlation was 45.6%. In contrast, the %-CV of the response slopes determined with the described normalized primary output signals and normalized reference correlation was reduced to 2.3%, an approximate 95% reduction (45.6-2.3/45.6*100). This reduction is graphically represented when the normalized output signal currents are transformed into sample analyte concentrations with the normalized reference correlation of FIG. 3E in comparison to when the underlying currents from the measurement device are transformed by the conventional reference correlation of FIG. 3A.

[00151] FIG. 3F plots the %-bias of the determined glucose concentrations attributable to the different temperatures (6.0° C, 10.9° C, 15.9° C, 22.0° C, 30.4° C, 35.1° C, and 40.0° C) before and after normalization. The measured currents showed a %-bias spread of approximately ± 60 when transformed by the conventional reference correlation, while the normalized currents showed a %-bias spread of approximately ± 20. Thus, an approximate 3X reduction in %-bias would be expected for sample analyte concentrations determined with a biosensor system including a measurement device including calibration information in accord with the present method in comparison to sample analyte concentrations determined with a measurement device including calibration information provided by a conventional method lacking normalization reduction of the temperature stimulus.

[00152] Once the effect of temperature is reduced, the effect of a second extraneous stimulus, such as sample hematocrit also may be substantially reduced using a two-step normalization process, thus the combination of FIG. A and FIG. B. In this type of glucose system, the working and counter electrodes provide the primary output signal while a temperature sensor preferably provides a secondary output signal and a hematocrit electrode preferably provides an additional secondary output signal. The secondary output signals responsive to temperature and hematocrit may arise in other ways, as previously discussed. The step-wise normalization by temperature and then by sample hematocrit was generally performed by normalizing the output currents from the measurement device at multiple temperatures (as described above) and then normalizing the resulting temperature normalized output signal currents for multiple Hct sample concentrations using a hematocrit normalization relationship.

[00153] An example of the calibration method **102** for determining calibration information with a reduced secondary extraneous stimulus effect for hematocrit on the primary output signal from an electrochemical glucose analysis system is shown in FIG. 4. In this example, the sample analyte is glucose (the primary stimulus) and

the sample analyte concentration is the glucose concentration in the sample of blood. Hematocrit concentration in the blood sample is the second extraneous stimulus in addition to the first extraneous stimulus, temperature. This method is represented with the plots in FIG. 4A through FIG. 4I. The numerical values calculated throughout FIG. 4 would be different for a different analysis system or even a different glucose analysis system.

[00154] FIG. 4A shows the output signal currents from the measurement device for reference samples including known glucose concentrations for the tested temperatures (6.0° C, 10.9° C, 15.9° C, 22.0° C, 30.4° C, 35.1° C, and 40.0° C) and for the tested Hct reference sample concentrations (0%, 20%, 40%, 55%, 70%). The secondary output signals obtained from a hematocrit electrode were used to obtain the Hct responsive output currents from the reference samples having known hematocrit concentrations. As expected, the currents determined by the measurement device from reference samples including ~80mg/dL glucose analyte concentration were closely grouped around ~75 nA, while the currents determined by the measurement device from reference samples including ~320 mg/dL and ~580 mg/dL glucose analyte concentrations were widely spaced.

[00155] FIG. 4B represents the temperature normalizing relationships at 40% Hct and at two separate single glucose concentrations of 100 and 500 mg/dL in blood sample, and is the same as previously represented in FIG. 3C, as the same temperature stimulus reduction is being performed. Temperature normalization was the first step taken in this example to reduce the effect of extraneous stimulus from temperature, as the same temperature stimulus reduction was performed. From FIG. 4B, normalized analyte responsive output signals with a reduction in the effect of the temperature stimulus were determined as previously described.

[00156] FIG. 4C plots the temperature normalized analyte responsive output signal values from FIG. 4A versus reference sample analyte concentration for glucose at the Hct reference sample concentrations tested in this example. As

expected, significant spread in the normalized currents is observed at higher glucose concentrations for the different Hct concentrations, even though the underlying sample analyte concentration is the same. FIG. 4C may be thought of as being similar to FIG. 3B, but showing the effect of the second extraneous stimulus, hematocrit as opposed to temperature.

[00157] Temperature as an error parameter or an extraneous stimulus is preferably measured concurrently with the primary stimulus and its value is independent of other factors. The hematocrit concentration in the blood samples is provided along with the glucose concentration, but the hematocrit responsive secondary output signals are temperature-dependent. Therefore, temperature is also an extraneous stimulus for the Hct responsive output signals and the effect of temperature is preferably reduced by normalization. The procedure involved is first to construct the Hct responsive currents plot against the temperature at a single selected Hct concentration. Then, a Hct normalized calibration curve is determined that provides the calculated %-Hct values from the temperature normalized Hct output signals for later use.

[00158] Synthesized Hct output signal values were generated similarly as previously described for A1c and glucose with regard to FIG. 1C and FIG. 3B, respectively. In this determination, which is not shown in a figure, the current recorded from the Hct electrode for the reference samples at each reference sample hematocrit concentration was plotted on the vertical y-axis while the known reference sample hematocrit concentrations were plotted on the horizontal X-axis. A regression line was plotted for each temperature (6.0° C, 10.9° C, 15.9° C, 22.0° C, 30.4° C, 35.1° C, and 40.0° C) and a synthesized Hct output signal value was determined at a 40% sample hematocrit concentration for each temperature.

[00159] FIG. 4D plots the synthesized signals determined from the secondary output signal responsive to the hematocrit concentration of the sample verses temperature for reference samples including a 40% hematocrit concentration. From

the above operation, seven pairs of the synthesized Hct output signals from a single selected Hct concentration of 40% and the temperatures, at which the reference samples were analyzed, were obtained and plotted. A regression technique, in this instance polynomial, was then used to determine a specific normalizing relationship for Hct as shown in the figure, but having the general form $NV_{Hct} = (b_2*T^2 + b_1*T + b_0$, where b_2, b_1 and b_0 are the coefficients of the 2nd order polynomial normalization function from curve-fitting and T is the temperature). A Hct normalizing value was determined, and normalized Hct electrode currents were determined with the general relationship $Ni\_{Hct} = i\_{Hct}/NV_{Hct}$, where Ni_{Hct} are the temperature normalized Hct electrode currents, i_{Hct} are the Hct responsive currents from the Hct electrode, and NV_{Hct} is the Hct normalizing value.

[00160] FIG. 4E shows the temperature normalized reference correlation for Hct where reference sample %Hct concentrations were plotted against the temperature normalized Hct electrode output currents. Other interferents may be similarly treated if the biosensor system provides a secondary output signal responsive to the interferent.

[00161] FIG. 4F represents the second normalizing relationship determined between the resulting temperature normalized analyte responsive output signals and the reference sample %-Hct values – the second extraneous stimulus. FIG. 4F established the correlation between the temperature normalized output signals and the sample %-Hct concentrations. That is, at the single selected glucose concentration of either 100 or 500 mg/dL, the temperature normalized output signals are substantively responsive to the Hct concentration, the second extraneous stimulus.

[00162] A regression technique, in this case polynomial ($c_2*Hct^2 + c_1*Hct + c_0$, where c_2, c_1 and c_0 are the coefficients of the 2nd order polynomial normalization function from curve-fitting and Hct is the second quantified extraneous stimulus value for Hct), was then used to determine the normalizing relationship between the

synthesized second extraneous stimulus responsive output signals at a single selected sample analyte concentration and the quantified second extraneous stimulus values (reference sample hematocrit concentrations of 0%, 20%, 40%, 55%, and 70%. The specific normalization relationship for the 100 and 500 mg/dL glucose analysis data from this example is shown in FIG. 4F as $y=-0.00008X^2-0.00456X+1.31152$ (100 mg/dL) and $y=-0.0004X^2-0.0228X+6.5577$ (500 mg/dL), thus showing the specific 2nd order polynomial coefficients for this example, where Y is the calculated synthesized second extraneous stimulus responsive output signal responsive to the second extraneous stimulus (Hct) at a single selected analyte concentration, and X is the quantified second extraneous stimulus values. A different analysis would have different coefficients. When a value of X (the quantified second extraneous stimulus signal value) is entered into the 2nd order polynomial, a value of Y is generated through this normalizing relationship, which is the normalizing value (NV).

[00163] Second normalized analyte responsive output signals **167** were then determined from the normalizing value at 100 mg/dL. Thus, the temperature normalized output signals from the vertical Y-axis of FIG. 4C were then converted to second normalized primary signal values using the normalization relationship of FIG. 4F with their corresponding normalizing values. The determination of the normalized analyte responsive signals from the normalizing value may be represented by the relationship $Nic = i_{measured}/NV_{Temp-Hct}$, where Nic are the temperature and hematocrit normalized analyte responsive signals, $i_{measured}$ are the glucose responsive currents from the measurement device, and $NV_{Temp-Hct}$ is the normalizing value determined from temperature and hematocrit normalization.

[00164] FIG. 4G graphically represents the reduction in error introduced by the extraneous stimulus of hematocrit as represented in FIG. 4C provided through the use of the temperature and Hct normalized analyte responsive output signal values at the selected glucose concentration of 100 mg/dL. Thus, this figure may be

thought of similarly as to FIG. 3C; however, in this example, both temperature and hematocrit normalized currents are used. Regression equations are shown for the lower (0%) and upper (70%) limit Hct concentrations. In relation to FIG. 4C, the divergence between the upper and lower Hct limits has been reduced from approximately 4 normalized output signal units (FIG. 4C) to approximately 0.25 output signal units (FIG. 4G) at ~600 mg/dL, an approximate 93% reduction (4-0.25/4*100) in divergence between the regression lines.

[00165] FIG. 4H provides an example of the determination of a normalized reference correlation from combining the temperature and hematocrit normalized analyte responsive output signal values of FIG. 4G. The temperature and hematocrit normalized signals were plotted on the vertical Y-axis versus the reference sample analyte concentrations for glucose and curve-fitted by a regression technique to provide the normalized reference correlation. A regression technique, in this case linear (Y=Slope*X + Int), was used to determine the normalized reference correlation, where during the analysis **200** Y is a normalized primary output signal value determined by the measurement device and X is the determined analyte concentration of the sample.

[00166] The specific normalized reference correlation for the glucose analysis data from this example is shown in FIG. 4H as Y=0.0104X - 0.1339, thus showing the specific linear coefficients for this example. A different analysis would have different coefficients. Also shown in FIG. 4H is the R^2=0.9828, showing the excellent agreement between the normalized primary output signals and the reference sample analyte concentrations for glucose. Thus, the normalized reference correlation relates the normalized output signals and the sample analyte concentration. When a normalized output signal is input into the normalized reference correlation, a sample analyte concentration is generated. FIG. 4H may be thought of as being similar to FIG. 3E except incorporating both temperature and Hct normalization into the calibration information.

[00167] For the hematocrit concentrations provided from the blood samples (0%, 20%, 40%, 55%, and 70%), the slopes of the reference correlations with temperature and temperature/hematocrit normalizations are tabulated in Table 5, where Slope/T is the slope from the temperature normalized reference correlation and Slope/T/H is the slope from the temperature and hematocrit normalized reference correlation.

%Hct	Slope/T FIG. 4C	Slope/T/H FIG. 4G
0	0.0133	0.0105
20	0.0126	0.0107
40	0.0105	0.0105
55	0.0082	0.0101
70	0.0058	0.0102
Mean slope	0.0101	0.0104
SD, slope	0.0031	0.0002
%CV	30.7	2.3

Table 5: Summary of Normalization for Temperature and Hematocrit Stimuli

[00168] The improvement in measurement performance may be better appreciated by looking at the mean response slopes and the %-CV of the slopes for temperature normalization alone and after normalization for both temperature and hematocrit. In this example, the %-CV of the response slopes determined with a temperature normalized reference correlation was 30.7%. In contrast, the %-CV of the response slopes determined with the described temperature and hematocrit normalized reference correlation was reduced to 2.3%, an approximate 92% reduction (30.7-2.3/30.7*100) in %-CV providing a substantial increase in measurement performance to the biosensor system.

[00169] FIG. 4I graphically represents the %-bias of the analyte (glucose) concentrations determined by the measurement device of a biosensor system using a conventional reference correlation (%bias_raw), a temperature normalized reference

correlation (%bias_T), and a temperature and Hct normalized reference correlation (%bias_T/Hct). The figure establishes that the output currents including the temperature and hematocrit stimuli in combination show a %-bias of nearly ±100% when directly transformed with a conventional reference correlation into sample analyte concentrations. Removal of the temperature stimulus from the calibration information allows the measurement device to determine analyte concentrations with a %-bias of approximately ±50%, while further removal of the Hct stimulus reduces the %-bias to approximately ±30%. Thus, an approximately 70% reduction in %-bias was observed with the described normalized calibration information in relation to conventional calibration information. This is a substantial improvement in relation to conventional systems with regard to the measurement performance the biosensor system may provide from the calibration information without additional compensation.

[00170] FIG. 5 depicts a schematic representation of a biosensor system **500** that determines an analyte concentration in a sample of a biological fluid. Biosensor system **500** includes a measurement device **502** and a test sensor **504**. The measurement device **502** may be implemented in an analytical instrument, including a bench-top device, a portable or hand-held device, or the like. Preferably the measurement device **502** is implemented in a hand-held device. The measurement device **502** and the test sensor **504** may be adapted to implement an electrochemical sensor system, an optical sensor system, a combination thereof, or the like.

[00171] The biosensor system **500** determines the analyte concentration of the sample using the calibration information developed in accord with the previously described normalization techniques and stored in the measurement device **502**. The calibration information from one or both of the calibration methods **100** and **102** may be stored in the measurement device **502**. The calibration information includes one or more normalizing relationships and one or more normalized

reference correlations. One or both calibration methods **100** and **102** may be stored in the measurement device **502** so the normalized calibration information may be determined by the measurement device **502**. The analysis method **200** may be stored in the measurement device for implementation by the biosensor system **500**. The method of measurement device calibration may improve the measurement performance of the biosensor system **500** in determining the analyte concentration of the sample. The biosensor system **500** may be utilized to determine analyte concentrations, including those of glucose, A1c, uric acid, lactate, cholesterol, bilirubin, and the like. While a particular configuration is shown, the biosensor system **500** may have other configurations, including those with additional components.

[00172] The test sensor **504** has a base **506** that forms a reservoir **508** and a channel **510** with an opening **512**. The reservoir **508** and the channel **510** may be covered by a lid with a vent. The reservoir **508** defines a partially-enclosed volume. The reservoir **508** may contain a composition that assists in retaining a liquid sample such as water-swellable polymers or porous polymer matrices. Reagents may be deposited in the reservoir **508** and/or the channel **510**. The reagents may include one or more enzymes, binders, mediators, and like species. The reagents may include a chemical indicator for an optical system. The test sensor **504** has a sample interface **514** adjacent to the reservoir **508**. The test sensor **504** may have other configurations.

[00173] In an optical sensor system, the sample interface **514** has an optical portal or aperture for viewing the sample. The optical portal may be covered by an essentially transparent material. The sample interface **514** may have optical portals on opposite sides of the reservoir **508**.

[00174] In an electrochemical system, the sample interface **514** has conductors connected to a working electrode **532** and a counter electrode **534** from which the analytic output signal may be measured. The sample interface **514** also may include

conductors connected to one or more additional electrodes **536** from which secondary output signals may be measured. The electrodes may be substantially in the same plane or in more than one plane. The electrodes may be disposed on a surface of the base **506** that forms the reservoir **508**. The electrodes may extend or project into the reservoir **508**. A dielectric layer may partially cover the conductors and/or the electrodes. The sample interface **514** may have other electrodes and conductors.

[00175] The measurement device **502** includes electrical circuitry **516** connected to a sensor interface **518** and an optional display **520**. The electrical circuitry **516** includes a processor **522** connected to a signal generator **524**, an optional temperature sensor **526**, and a storage medium **528**.

[00176] The signal generator **524** is capable of providing an electrical input signal to the sensor interface **518** in response to the processor **522**. In optical systems, the electrical input signal may be used to operate or control the detector and light source in the sensor interface **518**. In electrochemical systems, the electrical input signal may be transmitted by the sensor interface **518** to the sample interface **514** to apply the electrical input signal to the sample of the biological fluid. The electrical input signal may be a potential or current and may be constant, variable, or a combination thereof, such as when an AC signal is applied with a DC signal offset. The electrical input signal may be applied continuously or as multiple excitations, sequences, or cycles. The signal generator **524** also may be capable of recording an output signal from the sensor interface as a generator-recorder.

[00177] The optional temperature sensor **526** is capable of determining the ambient temperature of the measurement device **502**. The temperature of the sample may be estimated from the ambient temperature of the measurement device **502**, calculated from the output signal, or presumed to be the same or similar to the ambient temperature of the measurement device **502**. The temperature may be

measured using a thermister, thermometer, or other temperature sensing device. Other techniques may be used to determine the sample temperature.

[00178] The storage medium **528** may be a magnetic, optical, or semiconductor memory, another storage device, or the like. The storage medium **528** may be a fixed memory device, a removable memory device, such as a memory card, remotely accessed, or the like.

[00179] The processor **522** is capable of implementing the analyte analysis method using computer readable software code and the calibration information stored in the storage medium **528**. The processor **522** may start the analyte analysis in response to the presence of the test sensor **504** at the sensor interface **518**, the application of a sample to the test sensor **504**, in response to user input, or the like. The processor **522** is capable of directing the signal generator **524** to provide the electrical input signal to the sensor interface **518**. The processor **522** is capable of receiving the sample temperature from the temperature sensor **526**. The processor **522** is capable of receiving the output signals from the sensor interface **518**.

[00180] In electrochemical systems, the analyte responsive primary output signal is generated from the working and counter electrodes **532**, **534** in response to the reaction of the analyte in the sample. Secondary output signals also may be generated from additional electrodes **536**. In optical systems, the detector or detectors of the sensor interface **518** receive the primary and any secondary output signals. The output signals may be generated using an optical system, an electrochemical system, or the like. The processor **522** is capable of determining analyte concentrations from output signals using the calibration information stored in the storage medium **528**. The results of the analyte analysis may be output to the display **520**, a remote receiver (not shown), and/or may be stored in the storage medium **528**.

[00181] The calibration information relating reference sample analyte concentrations and output signals from the measurement device **502** may be represented graphically, mathematically, a combination thereof, or the like. The calibration information is preferably represented as correlation equations, which may be represented by a program number (PNA) table, another look-up table, or the like that is stored in the storage medium **528**.

[00182] Instructions regarding implementation of the analyte analysis also may be provided by the computer readable software code stored in the storage medium **528**. The code may be object code or any other code describing or controlling the described functionality. The data from the analyte analysis may be subjected to one or more data treatments, including the determination of decay rates, K constants, ratios, functions, and the like in the processor **522**.

[00183] In electrochemical systems, the sensor interface **518** has contacts that connect or electrically communicate with the conductors in the sample interface **514** of the test sensor **504**. The sensor interface **518** is capable of transmitting the electrical input signal from the signal generator **524** through the contacts to the connectors in the sample interface **514**. The sensor interface **518** also is capable of transmitting the output signal from the sample through the contacts to the processor **522** and/or signal generator **524**.

[00184] In light-absorption and light-generated optical systems, the sensor interface **518** includes a detector that collects and measures light. The detector receives light from the test sensor **504** through the optical portal in the sample interface **514**. In a light-absorption optical system, the sensor interface **518** also includes a light source such as a laser, a light emitting diode, or the like. The incident beam may have a wavelength selected for absorption by the reaction product. The sensor interface **518** directs an incident beam from the light source through the optical portal in the sample interface **514**. The detector may be positioned at an angle such as 45° to the optical portal to receive the light reflected

back from the sample. The detector may be positioned adjacent to an optical portal on the other side of the sample from the light source to receive light transmitted through the sample. The detector may be positioned in another location to receive reflected and/or transmitted light.

[00185] The optional display **520** may be analog or digital. The display **520** may include a LCD, a LED, an OLED, a vacuum fluorescent display, or other display adapted to show a numerical reading. Other display technologies may be used. The display **520** electrically communicates with the processor **522**. The display **520** may be separate from the measurement device **502**, such as when in wireless communication with the processor **522**. Alternatively, the display **520** may be removed from the measurement device **502**, such as when the measurement device **502** electrically communicates with a remote computing device, medication dosing pump, and the like.

[00186] In use, a liquid sample for analysis is transferred into the reservoir **508** by introducing the liquid to the opening **512**. The liquid sample flows through the channel **510**, filling the reservoir **508** while expelling the previously contained air. The liquid sample chemically reacts with the reagents deposited in the channel **510** and/or reservoir **508**.

[00187] The test sensor **502** is disposed in relation to the measurement device **502**, such that the sample interface **514** is in electrical and/or optical communication with the sensor interface **518**. Electrical communication includes the transfer of input and/or output signals between contacts in the sensor interface **518** and conductors in the sample interface **514**. Optical communication includes the transfer of light between an optical portal in the sample interface **514** and a detector in the sensor interface **518**. Optical communication also includes the transfer of light between an optical portal in the sample interface **514** and a light source in the sensor interface **518**.

[00188] The processor **522** is capable of directing the signal generator **524** to provide an input signal to the sensor interface **518** of the test sensor **504**. In an optical system, the sensor interface **518** is capable of operating the detector and light source in response to the input signal. In an electrochemical system, the sensor interface **518** is capable of providing the input signal to the sample through the sample interface **514**. The test sensor **504** is capable of generating one or more output signals in response to the input signal. The processor **522** is capable of receiving the output signals generated in response to the redox reaction of the analyte in the sample as previously discussed.

[00189] The processor **522** is capable of transforming the output signal using the analysis method and the calibration information stored in the storage medium **528** to determine an initial analyte concentration of the sample. The processor **522** may then report this initial analyte concentration as the final analyte concentration of the sample. Alternatively, the processor **522** may further process this initial analyte concentration of the sample using a compensation system. More than one compensation and/or other functions also may be implemented by the processor **522**.

[00190] To provide a clear and more consistent understanding of the specification and claims of this application, the following definitions are provided.

[00191] "Average" or "Averaged" or "Averaging" includes the combination of two or more variables to form an average variable. A variable may be a numerical value, an algebraic or scientific expression, or the like. For example, averaging may be performed by adding the variables and dividing the sum by the number of variables; such as in the equation $AVG = (a+b+c)/3$, where AVG is the average variable and a, b, and c are the variables. In another example, averaging includes modifying each variable by an averaging coefficient and then adding the modified variables to form a weighted average; such as in the equation $W_{AVG} = 0.2*a + 0.4*b + 0.4*c$, where W_{AVG} is the weighted average, 0.2, 0.4 and 0.4

are the averaging coefficients, and a, b, and c are the variables. The averaging coefficients are numbers between 0 and 1; and if added, will provide a sum of 1 or substantially 1. Other averaging methods may be used.

[00192] "Measurable species" addresses a species the biosensor system is designed to determine the presence and/or concentration of in the sample and may be the analyte of interest or a mediator whose concentration in the sample is responsive to that of the analyte of interest.

[00193] While various embodiments of the invention have been described, it will be apparent to those of ordinary skill in the art that other embodiments and implementations are possible within the scope of the invention.

WHAT IS CLAIMED IS:

1. A method for determining an analyte concentration in a sample, comprising:

generating at least one output signal from a sample;

measuring at least one analyte responsive output signal value from the at least one output signal, where the at least one analyte responsive output signal value is affected by at least one extraneous stimulus;

measuring at least one extraneous stimulus responsive output signal from the sample;

determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal;

determining at least one normalizing value from at least one normalizing relationship;

determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and

determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

2. The method of claim 1, where the determining at least one normalizing value comprises inputting the at least one analyte responsive output signal value and the at least one quantified extraneous stimulus value into the at least one normalizing relationship.

3. The method of claim 1 or 2, where the determining at least one normalized analyte responsive output signal value comprises dividing the at least one analyte responsive output signal value by the at least one normalizing value.

4. The method of claim 3, where one analyte responsive output signal value is used to determine one normalized analyte responsive output signal value.

5. The method of any one of the preceding claims, where the determining at least one analyte concentration comprises the at least one normalized reference correlation transforming the at least one normalized analyte responsive output signal value into the at least one analyte concentration.

6. The method of any one of the preceding claims, further comprising determining an average analyte concentration of the sample from at least two analyte concentrations.

7. The method of any one of the preceding claims, where the determining at least one normalizing value comprises inputting the at least one analyte responsive output signal value and the at least one quantified extraneous stimulus value into the at least one normalizing relationship.

8. The method of any one of the preceding claims, further comprising:

determining the normalizing relationship between at least two analyte responsive output signals and at least two quantified extraneous stimulus values;

determining the at least two quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal;

measuring at least one extraneous stimulus responsive output signal from at least one reference sample; and

determining a reference correlation between a reference sample analyte concentration of the at least one reference sample and at least two analyte responsive output signals;

determining the at least one normalized reference correlation between at least two normalized analyte responsive output signals and the reference sample analyte concentration; and

determining the at least two normalized analyte responsive output signals from the at least two analyte responsive output signals and the normalizing value.

9. The method of claim 8, where determining the normalizing relationship comprises applying a normalizing relationship regression technique to the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values at a single selected analyte concentration, and where determining the at least one normalized reference correlation comprises applying a normalized reference correlation regression technique to the at least two normalized analyte responsive output signals and the at least one reference sample analyte concentration.

10. The method of claim 8, further comprising:

determining at least two second quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal;

determining a second normalizing relationship between the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values;

determining at least two second normalized analyte responsive output signals from the at least two normalized analyte responsive output signals and a second normalizing value; and

determining a second normalized reference correlation between the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

11. The method of claim 10, where the determining a second normalizing relationship comprises applying a second normalizing relationship regression technique to the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values at a single selected analyte concentration, and where determining a second normalized reference correlation

comprises applying a second normalized reference correlation regression technique to the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

12. The method of any one of the preceding claims, where the at least one extraneous stimulus comprises at least one of a physical characteristic, an environmental aspect, and a manufacturing variation.

13. The method of any one of the preceding claims, where the at least one analyte concentration comprises at least one of glycated hemoglobin and glucose, and where the sample comprises blood, and where the at least one extraneous stimulus comprises at least one of temperature, total hemoglobin, and hematocrit.

14. An analyte measurement device, comprising electrical circuitry connected to a sensor interface, where the electrical circuitry includes a processor connected to a signal generator and a storage medium; where the processor is capable of implementing any one of the methods of claims1 through 13.

15. A biosensor system for determining an analyte concentration in a sample, comprising:

a test sensor having a sample interface adjacent to a reservoir formed by a base, where the test sensor is capable of generating at least one output signal from a sample; and

a measurement device having a processor connected to a sensor interface, the sensor interface having electrical communication with the sample interface, and the processor having electrical communication with a storage medium;

where the processor is capable of implementing any one of the methods of claims1 through 13.

16. Each and every novel feature herein disclosed.

17. A method for determining an analyte concentration in a sample, comprising:

generating at least one output signal from a sample;

measuring at least one analyte responsive output signal value from the at least one output signal, where the at least one analyte responsive output signal value is affected by at least one extraneous stimulus;

measuring at least one extraneous stimulus responsive output signal from the sample;

determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal;

determining at least one normalizing value from at least one normalizing relationship;

determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and

determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

18. The method of claim 17, where the at least one extraneous stimulus is at least one of a physical characteristic, an environmental aspect, and a manufacturing variation.

19. The method of claim 17, where the determining at least one quantified extraneous stimulus value comprises determining a first quantified extraneous stimulus value in response to a first extraneous stimulus.

20. The method of claim 19, where the determining at least one quantified extraneous stimulus value further comprises determining a second quantified extraneous stimulus value in response to a second extraneous stimulus.

21. The method of claim 17, where the determining at least one normalizing value comprises inputting the at least one analyte responsive output signal value and the at least one quantified extraneous stimulus value into the at least one normalizing relationship.

22. The method of claim 17, where the determining at least one normalized analyte responsive output signal value comprises dividing the at least one analyte responsive output signal value by the at least one normalizing value.

23. The method of claim 22, where one analyte responsive output signal value is used to determine one normalized analyte responsive output signal value.

24. The method of claim 17, where the determining at least one analyte concentration comprises the at least one normalized reference correlation transforming the at least one normalized analyte responsive output signal value into the at least one analyte concentration.

25. The method of claim 17, further comprising determining an average analyte concentration of the sample from at least two analyte concentrations.

26. The method of claim 17, where the at least one analyte concentration comprises at least one of glycated hemoglobin and glucose, and where the sample comprises blood.

27. The method of claim 17, where the at least one extraneous stimulus is at least one of temperature, total hemoglobin, and hematocrit.

28. The method of claim 17, where the determining at least one normalizing value comprises inputting the at least one analyte responsive output signal value and the at least one quantified extraneous stimulus value into the at least one normalizing relationship.

29. The method of claim 17, further comprising:

determining the normalizing relationship between at least two analyte responsive output signals and at least two quantified extraneous stimulus values;

determining the at least two quantified extraneous stimulus values from at least one extraneous stimulus responsive output signal;

measuring at least one extraneous stimulus responsive output signal from at least one reference sample ; and

determining a reference correlation between a reference sample analyte concentration of the at least one reference sample and at least two analyte responsive output signals.

30. The method of claim 29, where the determining the normalizing relationship comprises applying a regression technique to the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values at a single selected analyte concentration.

31. The method of claim 29, further comprising:

determining the normalized reference correlation between at least two normalized analyte responsive output signals and the at least one reference sample analyte concentration; and

determining the at least two normalized analyte responsive output signals from the at least two analyte responsive output signals and the normalizing value.

32. The method of claim 31, where the determining a normalized reference correlation comprises applying a regression technique to the at least two normalized analyte responsive output signals and the at least one reference sample analyte concentration.

33. The method of claim 31, further comprising:

determining at least two second quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal; and

determining a second normalizing relationship between the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values.

34. The method of claim 33, where the determining a second normalizing relationship comprises applying a regression technique to the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values at a single selected analyte concentration.

35. The method of claim 33, further comprising:

determining at least two second normalized analyte responsive output signals from the at least two normalized analyte responsive output signals and a second normalizing value; and

determining a second normalized reference correlation between the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

36. The method of claim 35, where the determining a second normalized reference correlation comprises applying a regression technique to the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

37. A method for calibrating a measurement device of a biosensor system, comprising:

measuring at least two analyte responsive output signals from a sample, where the analyte responsive output signals are affected by at least one extraneous stimulus;

determining a reference correlation between at least one reference sample analyte concentration and the at least two analyte responsive output signals;

measuring at least one extraneous stimulus responsive output signal from the sample;

determining at least two quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal;

determining a normalizing relationship between the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values;

determining a normalizing value from the normalizing relationship and the at least two quantified extraneous stimulus values;

determining at least two normalized analyte responsive output signals from the at least two analyte responsive output signals and the normalizing value; and

determining a normalized reference correlation between the at least two normalized analyte responsive output signals and the least one reference sample analyte concentration.

38. The method of claim 37, where the at least one extraneous stimulus is at least one of a physical characteristic, an environmental aspect, and a manufacturing variation.

39. The method of claim 37, where the measuring at least two analyte responsive output signals comprises measuring at least four analyte responsive output signals.

40. The method of claim 37, where the measuring at least two analyte responsive output signals comprises measuring at least six analyte responsive output signals.

41. The method of claim 37, further comprising the measuring the at least one extraneous stimulus responsive output signal concurrently with the measuring at least two analyte responsive output signals from the sample.

42. The method of claim 37, further comprising directly quantifying the at least two quantified extraneous stimulus values

43. The method of claim 37, further comprising indirectly quantifying the at least two quantified extraneous stimulus values

44. The method of claim 37, where the determining a normalizing relationship comprises applying a regression technique to the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values at a single selected analyte concentration.

45. The method of claim 37, where the determining at least two normalized analyte responsive output signals comprises dividing the at least two analyte responsive output signals by the normalizing value.

46. The method of claim 37, where the determining a normalized reference correlation comprises applying a regression technique to the at least two normalized analyte responsive output signals and the at least one reference sample analyte concentration.

47. The method of claim 37, where the normalized reference correlation comprises a normalized calibration curve.

48. The method of claim 37, further comprising storing the normalizing relationship and the normalized reference correlation in a measurement device.

49. The method of claim 37, where the at least one analyte concentration comprises at least one of glycated hemoglobin and glucose, and where the sample comprises blood.

50. The method of claim 37, where the at least one extraneous stimulus comprises at least one of temperature, total hemoglobin, and hematocrit.

51. The method of claim 37, further comprising:

determining at least two second quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal;

determining a second normalizing relationship between the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values;

determining a second normalizing value from the second normalizing relationship and the at least two second quantified extraneous stimulus values;

determining at least two second normalized analyte responsive output signals from the at least two normalized analyte responsive output signals and the second normalizing value; and

determining a second normalized reference correlation between the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

52. The method of claim 51, where the determining a second normalizing relationship comprises applying a regression technique to the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values at a single selected analyte concentration.

53. The method of claim 51, where the determining at least two second normalized analyte responsive output signals comprises dividing the at least two normalized analyte responsive output signals by the second normalizing value.

54. The method of claim 51, where the determining a second normalized reference correlation comprises applying a regression technique to the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

55. The method of claim 51 where the second normalized reference correlation comprises a second normalized calibration curve.

56. The method of claim 51, further comprising storing the second normalizing relationship and the second normalized reference correlation in a measurement device.

57. The method of claim 51, where the at least one analyte concentration comprises at least one of glycated hemoglobin and glucose, and where the sample comprises blood.

58. The method of claim 51, where the at least one extraneous stimulus is at least one of temperature, total hemoglobin, and hematocrit.

59. An analyte measurement device, comprising:

electrical circuitry connected to a sensor interface, where the electrical circuitry includes a processor connected to a signal generator and a storage medium;

where the processor is capable of measuring at least one analyte responsive output signal value from a sample, where the at least one analyte responsive output signal value is affected by at least one extraneous stimulus;

where the processor is capable of measuring at least one extraneous stimulus responsive output signal from the sample;

where the processor is capable of determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal;

where the processor is capable of determining at least one normalizing value from at least one normalizing relationship;

where the processor is capable of determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and

where the processor is capable of determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

60. The analyte measurement device of claim 59, where the at least one extraneous stimulus is at least one of a physical characteristic, an environmental aspect, and a manufacturing variation.

61. The analyte measurement device of claim 59, where the processor is capable of determining an average analyte concentration of the sample from at least two analyte concentrations.

62. The analyte measurement device of claim 59, where the at least one analyte concentration comprises at least one of glycated hemoglobin and glucose, and where the sample comprises blood.

63. The analyte measurement device of claim 59, where the at least one extraneous stimulus is at least one of temperature, total hemoglobin, and hematocrit.

64. The analyte measurement device of claim 59, where the at least one normalizing relationship and the at least one normalized reference correlation are stored in the storage medium.

65. The analyte measurement device of claim 59, where the measurement device further comprises at least two detection channels.

66. A biosensor system for determining an analyte concentration in a sample, comprising:

a test sensor having a sample interface adjacent to a reservoir formed by a base, where the test sensor is capable of generating at least one output signal from a sample; and

a measurement device having a processor connected to a sensor interface, the sensor interface having electrical communication with the sample interface, and the processor having electrical communication with a storage medium;

where the processor is capable of measuring at least one analyte responsive output signal value from the at least one output signal, where the at least one analyte responsive output signal value is affected by at least one extraneous stimulus;

where the processor is capable of measuring at least one extraneous stimulus responsive output signal from the sample;

where the processor is capable of determining at least one quantified extraneous stimulus value in response to the at least one extraneous stimulus output signal;

where the processor is capable of determining at least one normalizing value from at least one normalizing relationship;

where the processor is capable of determining at least one normalized analyte responsive output signal value in response to the at least one analyte responsive output signal value and the at least one normalizing value; and

where the processor is capable of determining at least one analyte concentration in the sample in response to at least one normalized reference correlation and the at least one normalized analyte responsive output signal.

67. The biosensor system of claim 67, where the at least one extraneous stimulus is at least one of a physical characteristic, an environmental aspect, and a manufacturing variation.

68. The biosensor system of claim 67, where the processor is capable of determining an average analyte concentration of the sample from at least two analyte concentrations.

69. The biosensor system of claim 67, where the at least one analyte concentration comprises at least one of glycated hemoglobin and glucose, and where the sample comprises blood.

70. The biosensor system of claim 67, where the at least one extraneous stimulus is at least one of temperature, total hemoglobin, and hematocrit.

71. The biosensor system of claim 67, where the at least one normalizing relationship and the at least one normalized reference correlation are stored in the storage medium.

72. The biosensor system of claim 67,

where the processor is capable of measuring at least two analyte responsive output signals;

where the processor is capable of determining a reference correlation between at least one reference sample analyte concentration and the at least two analyte responsive output signals;

where the processor is capable of measuring at least one extraneous stimulus responsive output signal from the sample;

where the processor is capable of determining at least two quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal;

where the processor is capable of determining the normalizing relationship between the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values;

where the processor is capable of determining a normalizing value from the normalizing relationship and the at least two quantified extraneous stimulus values;

where the processor is capable of determining at least two normalized analyte responsive output signals from the at least two analyte responsive output signals and the normalizing value; and

where the processor is capable of determining the normalized reference correlation between the at least two normalized analyte responsive output signals and the at least one reference sample analyte concentration.

73. The biosensor system of claim 71, where the processor is capable of determining the normalizing relationship by applying a regression technique to the at least two analyte responsive output signals and the at least two quantified extraneous stimulus values at a single selected analyte concentration.

74. The biosensor system of claim 71, where the processor is capable of determining the normalized reference correlation by applying a regression technique to the at least two normalized analyte responsive output signals and the at least one reference sample analyte concentration.

75. The biosensor system of claim 71, further comprising:

where the processor is capable of determining at least two second quantified extraneous stimulus values from the at least one extraneous stimulus responsive output signal;

where the processor is capable of determining a second normalizing relationship between the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values;

where the processor is capable of determining a second normalizing value from the second normalizing relationship and the at least two second quantified extraneous stimulus values;

where the processor is capable of determining at least two second normalized analyte responsive output signals from the at least two normalized analyte responsive output signals and the second normalizing value; and

where the processor is capable of determining a second normalized reference correlation between the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

76. The biosensor system of claim 74, where the processor is capable of determining the second normalizing relationship by applying a regression technique to the at least two normalized analyte responsive output signals and the at least two second quantified extraneous stimulus values at a single selected analyte concentration.

77. The biosensor system of claim 74, where the processor is capable of determining the second normalized reference correlation by applying a regression technique to the at least two second normalized analyte responsive output signals and the at least one reference sample analyte concentration.

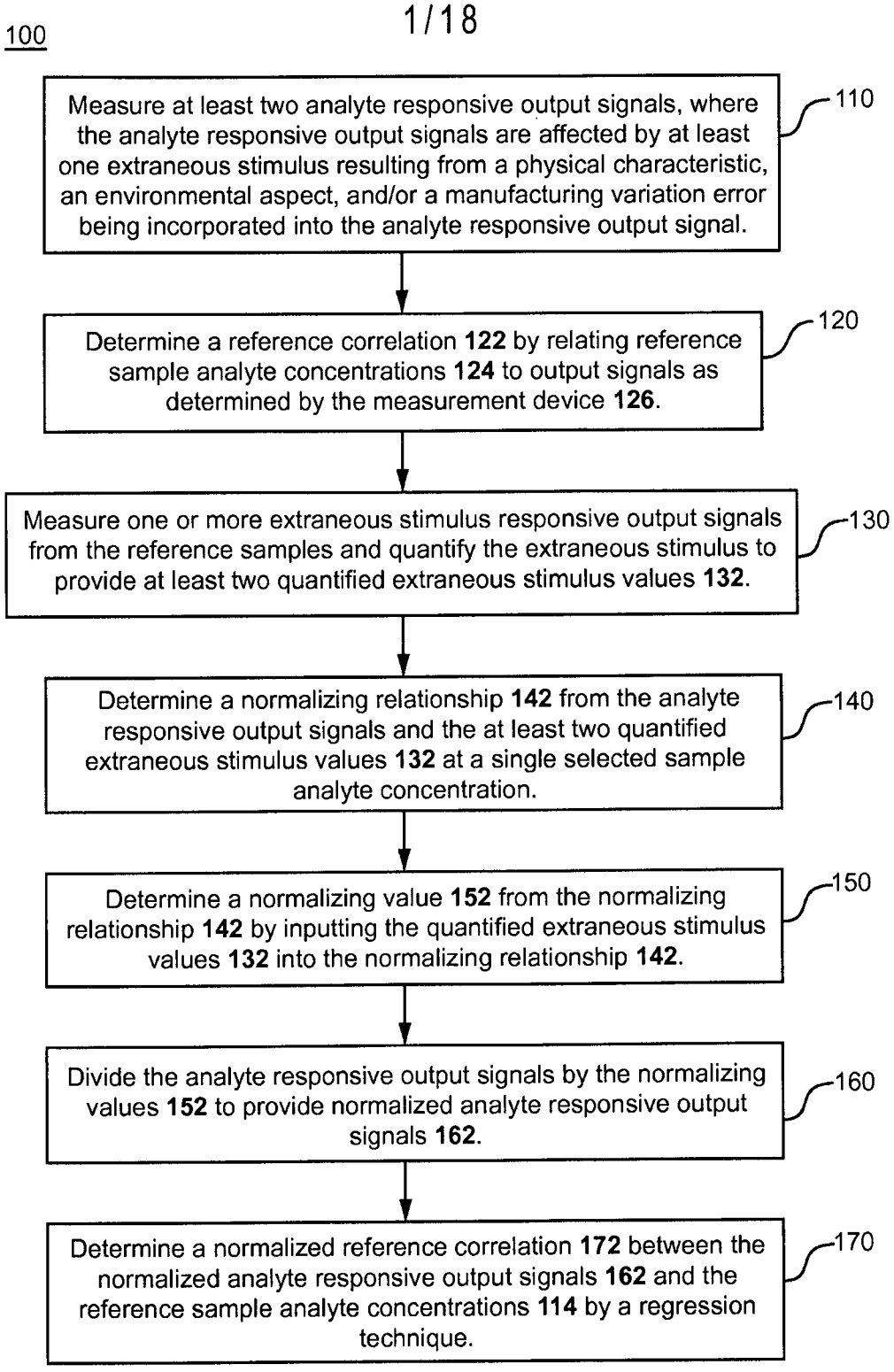
100
Measure at least two analyte responsive output signals, where the analyte responsive output signals are affected by at least one extraneous stimulus resulting from a physical characteristic, an environmental aspect, and/or a manufacturing variation error being incorporated into the analyte responsive output signal.
110
Determine a reference correlation 122 by relating reference sample analyte concentrations 124 to output signals as determined by the measurement device 126.
120
Measure one or more extraneous stimulus responsive output signals from the reference samples and quantify the extraneous stimulus to provide at least two quantified extraneous stimulus values 132.
130
Determine a normalizing relationship 142 from the analyte responsive output signals and the at least two quantified extraneous stimulus values 132 at a single selected sample analyte concentration.
140
Determine a normalizing value 152 from the normalizing relationship 142 by inputting the quantified extraneous stimulus values 132 into the normalizing relationship 142.
150
Divide the analyte responsive output signals by the normalizing values 152 to provide normalized analyte responsive output signals 162.
160
Determine a normalized reference correlation 172 between the normalized analyte responsive output signals 162 and the reference sample analyte concentrations 114 by a regression technique.
170

FIG. A

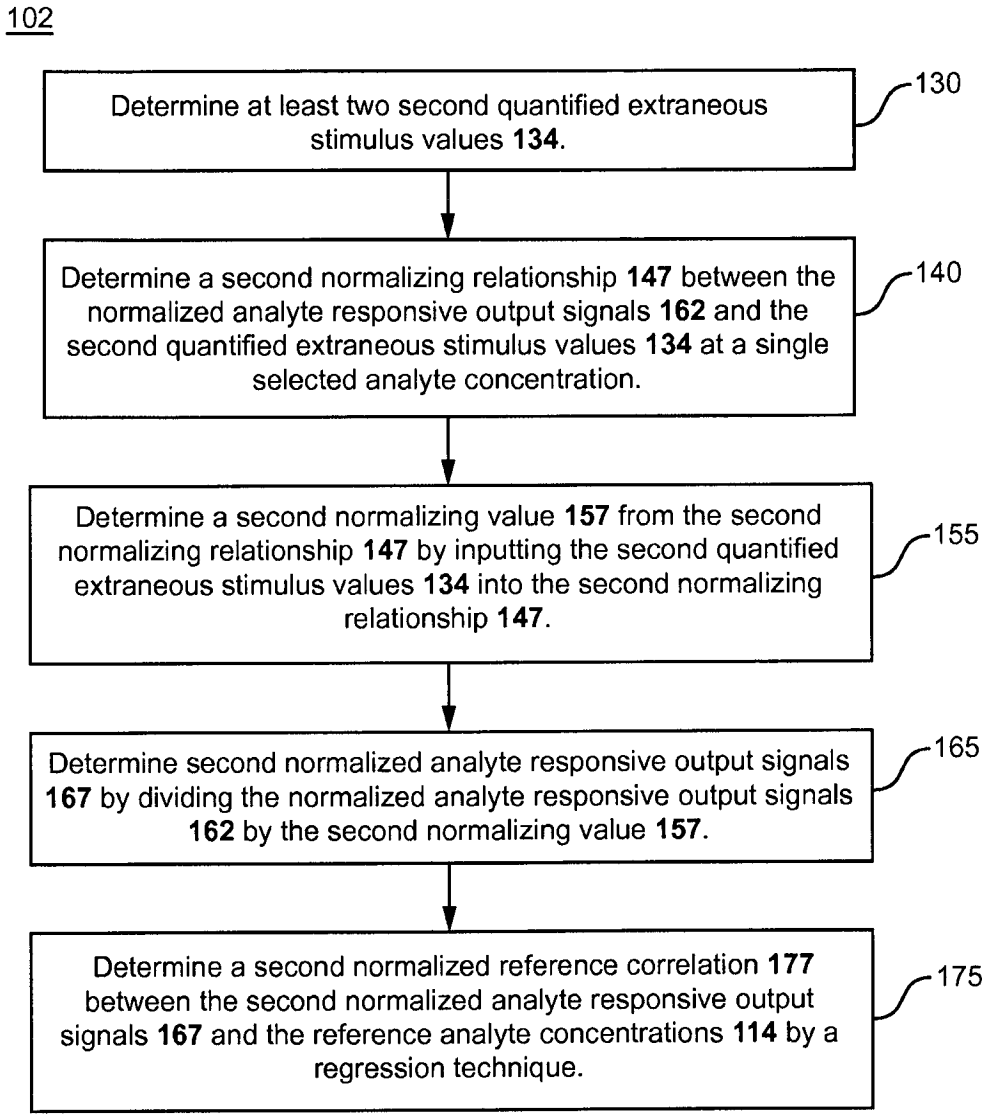
102
Determine at least two second quantified extraneous stimulus values 134.
130
Determine a second normalizing relationship 147 between the normalized analyte responsive output signals 162 and the second quantified extraneous stimulus values 134 at a single selected analyte concentration.
140
Determine a second normalizing value 157 from the second normalizing relationship 147 by inputting the second quantified extraneous stimulus values 134 into the second normalizing relationship 147.
155
Determine second normalized analyte responsive output signals 167 by dividing the normalized analyte responsive output signals 162 by the second normalizing value 157.
165
Determine a second normalized reference correlation 177 between the second normalized analyte responsive output signals 167 and the reference analyte concentrations 114 by a regression technique.
175

FIG.B

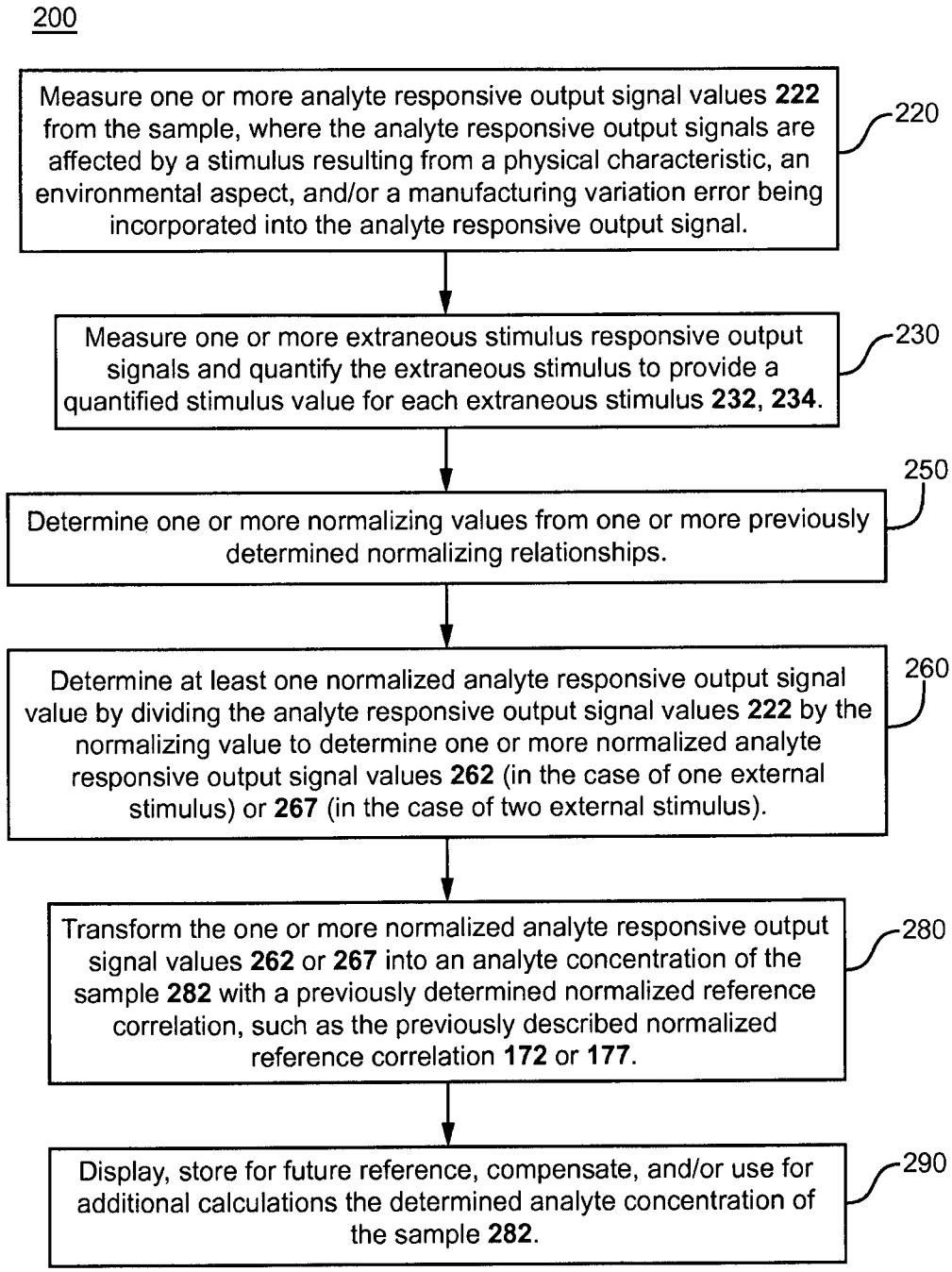
200
Measure one or more analyte responsive output signal values 222 from the sample, where the analyte responsive output signals are affected by a stimulus resulting from a physical characteristic, an environmental aspect, and/or a manufacturing variation error being incorporated into the analyte responsive output signal.
220
Measure one or more extraneous stimulus responsive output signals and quantify the extraneous stimulus to provide a quantified stimulus value for each extraneous stimulus 232, 234.
230
Determine one or more normalizing values from one or more previously determined normalizing relationships.
250
Determine at least one normalized analyte responsive output signal value by dividing the analyte responsive output signal values 222 by the normalizing value to determine one or more normalized analyte responsive output signal values 262 (in the case of one external stimulus) or 267 (in the case of two external stimulus).
260
Transform the one or more normalized analyte responsive output signal values 262 or 267 into an analyte concentration of the sample 282 with a previously determined normalized reference correlation, such as the previously described normalized reference correlation 172 or 177.
280
Display, store for future reference, compensate, and/or use for additional calculations the determined analyte concentration of the sample 282.
290

FIG.C

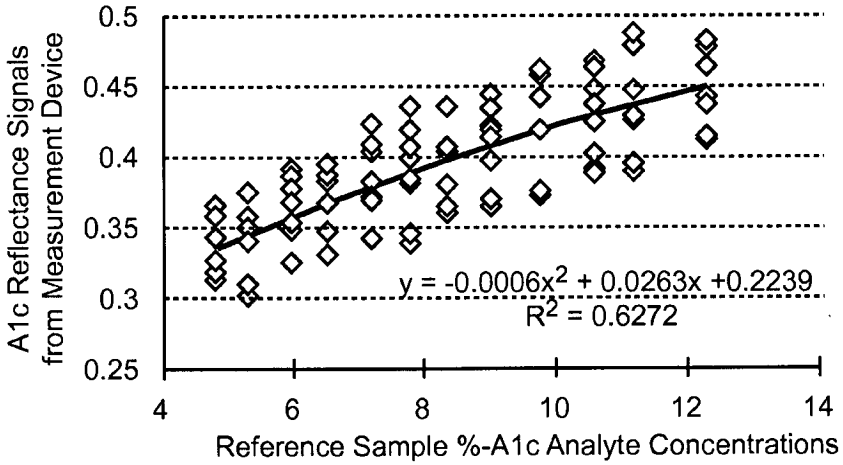
A1c Reflectance Signals from Measurement Device
0.5
0.45
0.4
0.35
0.3
0.25
y = -0.0006x2 + 0.0263x +0.2239
R2 = 0.6272
4
6
8
10
12
14
Reference Sample %-A1c Analyte Concentrations

FIG.1A

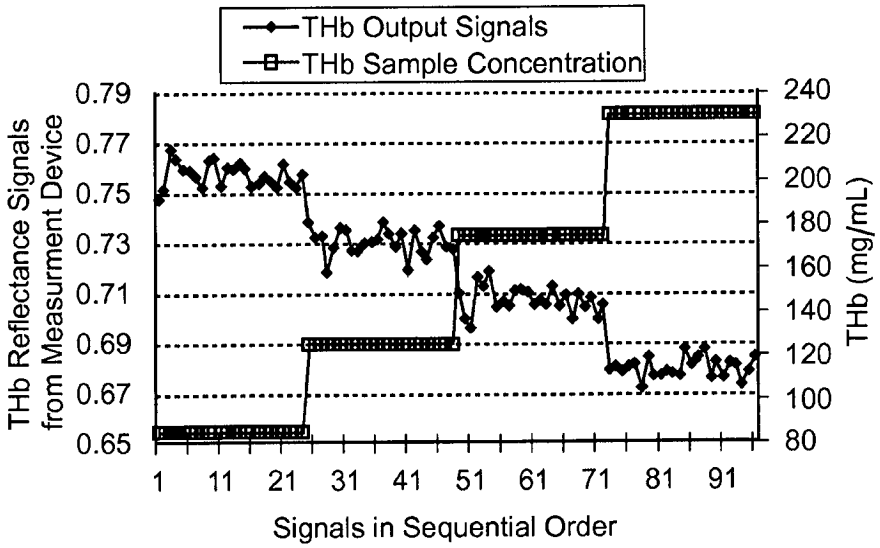
THb Output Signals
THb Sample Concentration
THb Reflectance Signals from Measurment Device
0.79
0.77
0.75
0.73
0.71
0.69
0.67
0.65
240
220
200
180
160
140
120
100
80
THb (mg/mL)
1
11
21
31
41
51
61
71
81
91
Signals in Sequential Order

FIG.1B

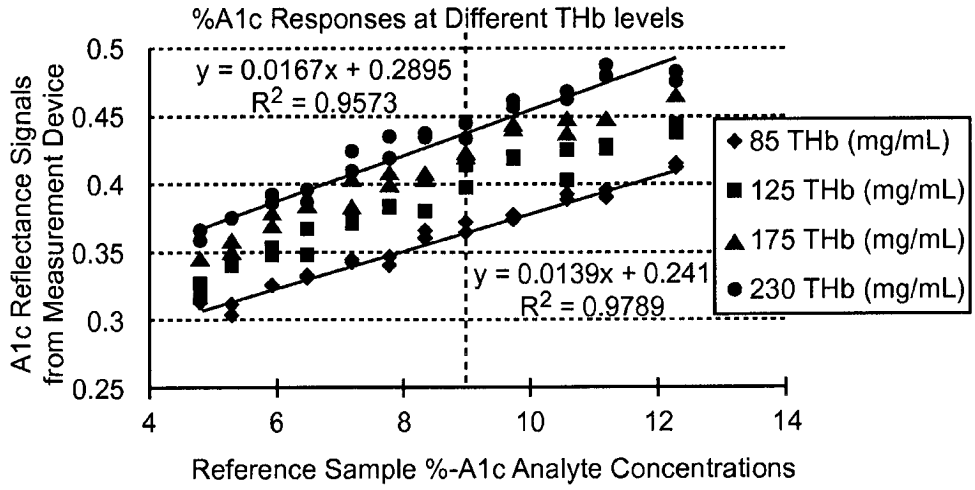
%A1c Responses at Different THb levels
y = 0.0167x + 0.2895
R2 = 0.9573
y = 0.0139x + 0.241
R2 = 0.9789
85 THb (mg/mL)
125 THb (mg/mL)
175 THb (mg/mL)
230 THb (mg/mL)
A1c Reflectance Signals from Measurement Device
0.5
0.45
0.4
0.35
0.3
0.25
4
6
8
10
12
14
Reference Sample %-A1c Analyte Concentrations

FIG.1C

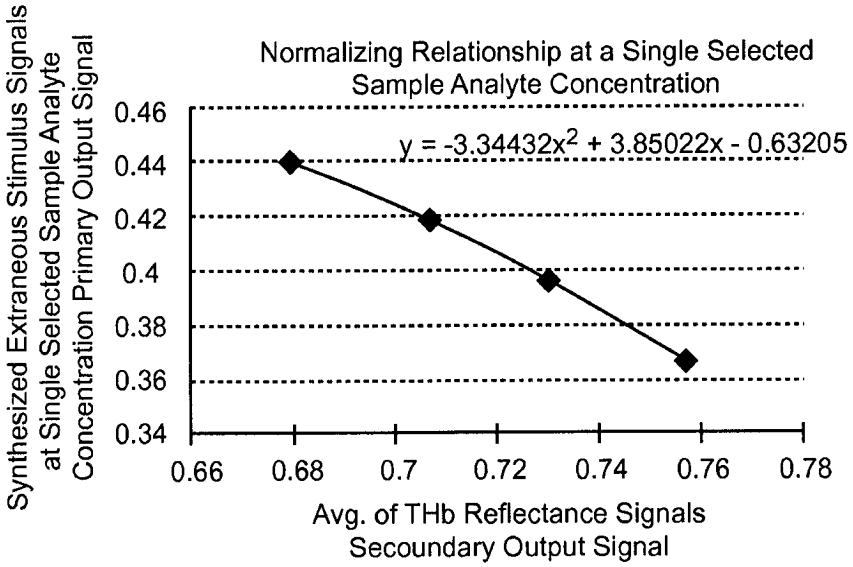
Normalizing Relationship at a Single Selected Sample Analyte Concentration
y = -3.34432x2 + 3.85022x - 0.63205
Synthesized Extraneous Stimulus Signals at Single Selected Sample Analyte Concentration Primary Output Signal
0.46
0.44
0.42
0.4
0.38
0.36
0.34
0.66
0.68
0.7
0.72
0.74
0.76
0.78
Avg. of THb Reflectance Signals Secoundary Output Signal

FIG.1D

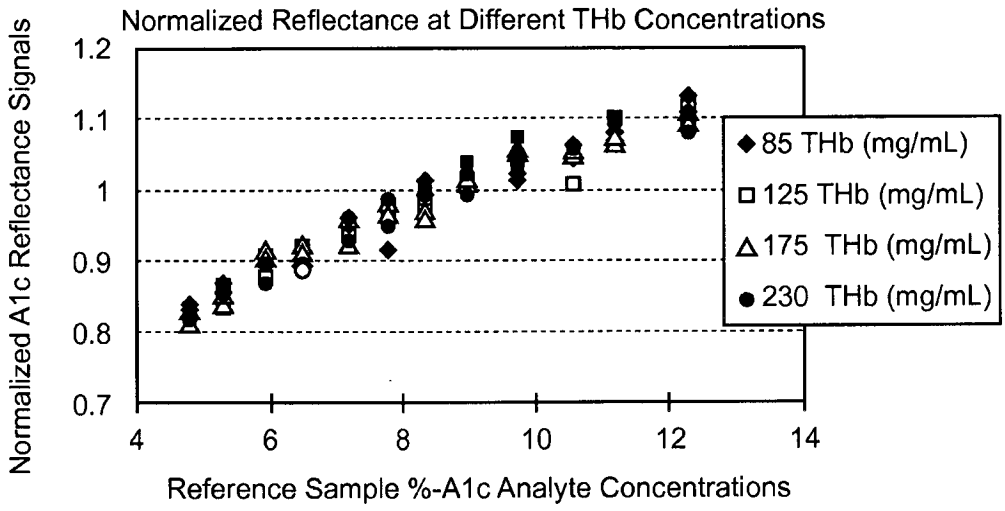
Normalized Reflectance at Different THb Concentrations
Normalized A1c Reflectance Signals
1.2
1.1
1
0.9
0.8
0.7
4
6
8
10
12
14
Reference Sample %-A1c Analyte Concentrations
85 THb (mg/mL)
125 THb (mg/mL)
175 THb (mg/mL)
230 THb (mg/mL)

FIG.1E

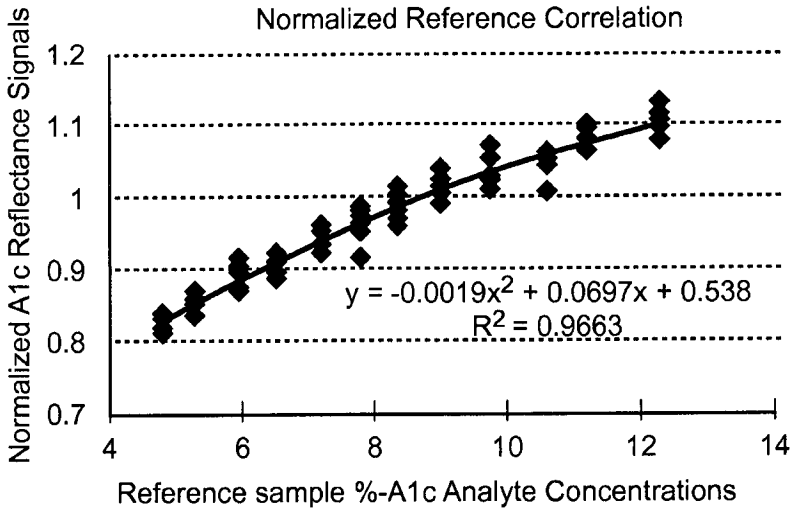
Normalized Reference Correlation
Normalized A1c Reflectance Signals
1.2
1.1
1
0.9
0.8
0.7
4
6
8
10
12
14
Reference sample %-A1c Analyte Concentrations
y = -0.0019x2 + 0.0697x + 0.538
R2 = 0.9663

FIG.1F

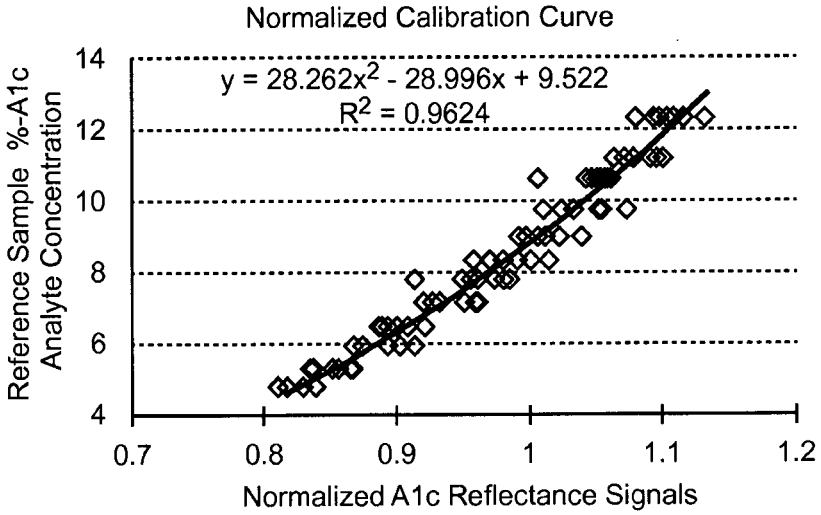
Normalized Calibration Curve
y = 28.262x2 - 28.996x + 9.522
R2 = 0.9624
Reference Sample %-A1c
Analyte Concentration
14
12
10
8
6
4
0.7
0.8
0.9
1
1.1
1.2
Normalized A1c Reflectance Signals

FIG.1G

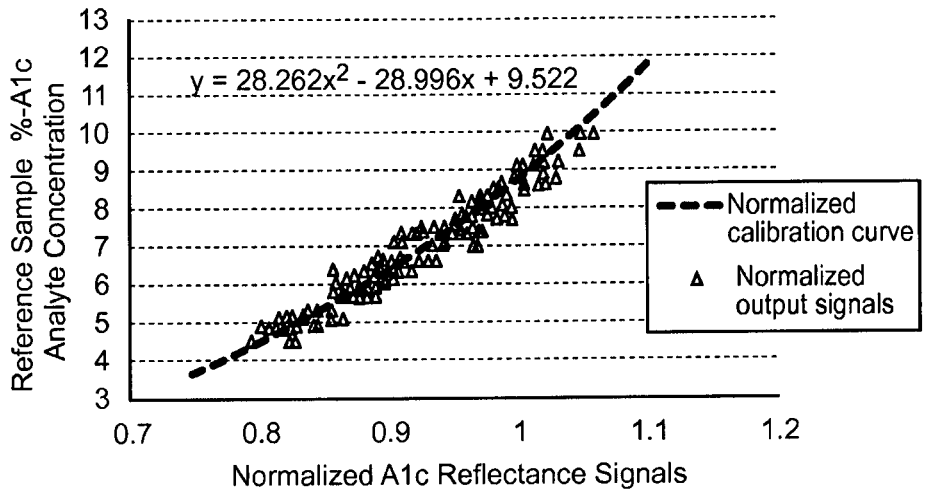
y = 28.262x2 - 28.996x + 9.522
Reference Sample %-A1c
Analyte Concentration
13
12
11
10
9
8
7
6
5
4
3
0.7
0.8
0.9
1
1.1
1.2
Normalized A1c Reflectance Signals
Normalized calibration curve
Normalized output signals

FIG.1H

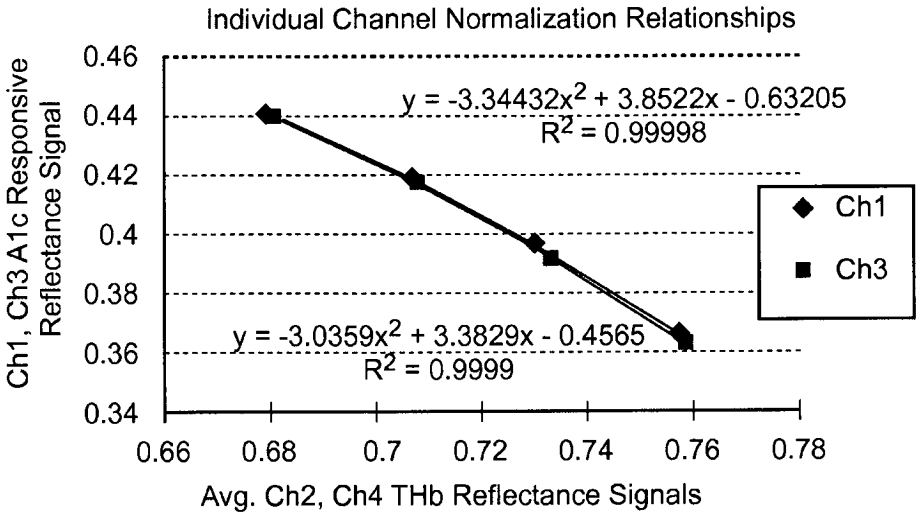
Individual Channel Normalization Relationships
Ch1, Ch3 A1c Responsive Reflectance Signal
0.46
0.44
0.42
0.4
0.38
0.36
0.34
y = -3.34432x2 + 3.8522x - 0.63205
R2 = 0.99998
y = -3.0359x2 + 3.3829x - 0.4565
R2 = 0.9999
Ch1
Ch3
0.66
0.68
0.7
0.72
0.74
0.76
0.78
Avg. Ch2, Ch4 THb Reflectance Signals

FIG.2A

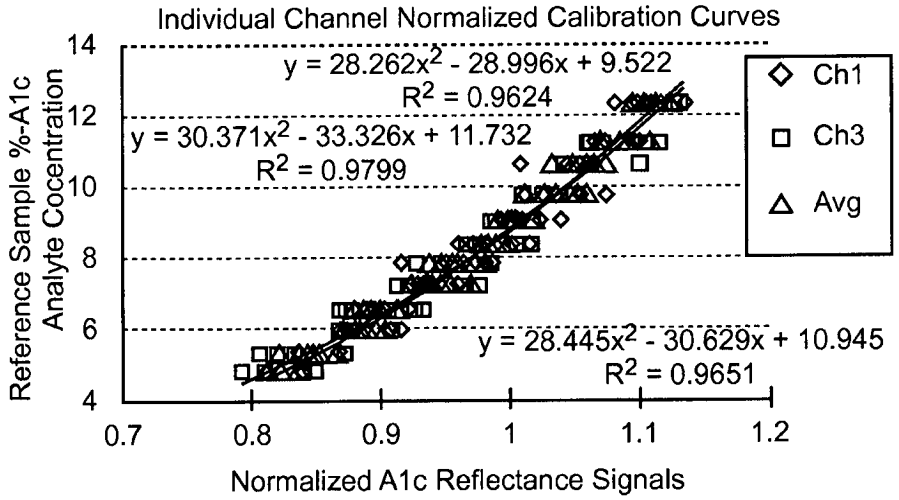
Individual Channel Normalized Calibration Curves
Reference Sample %-A1c Analyte Cocentration
14
12
10
8
6
4
y = 28.262x2 - 28.996x + 9.522
R2 = 0.9624
y = 30.371x2 - 33.326x + 11.732
R2 = 0.9799
y = 28.445x2 - 30.629x + 10.945
R2 = 0.9651
Ch1
Ch3
Avg
0.7
0.8
0.9
1
1.1
1.2
Normalized A1c Reflectance Signals

FIG.2B

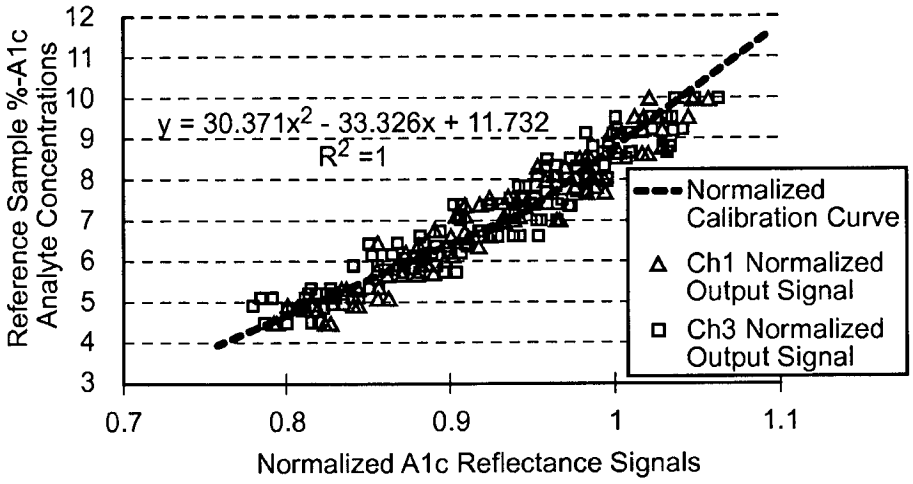
Reference Sample %-A1c Analyte Concentrations
12
11
10
9
8
7
6
5
4
3
y = 30.371x2 - 33.326x + 11.732
R2 =1
Normalized Calibration Curve
Ch1 Normalized Output Signal
Ch3 Normalized Output Signal
0.7
0.8
0.9
1
1.1
Normalized A1c Reflectance Signals

FIG.2C

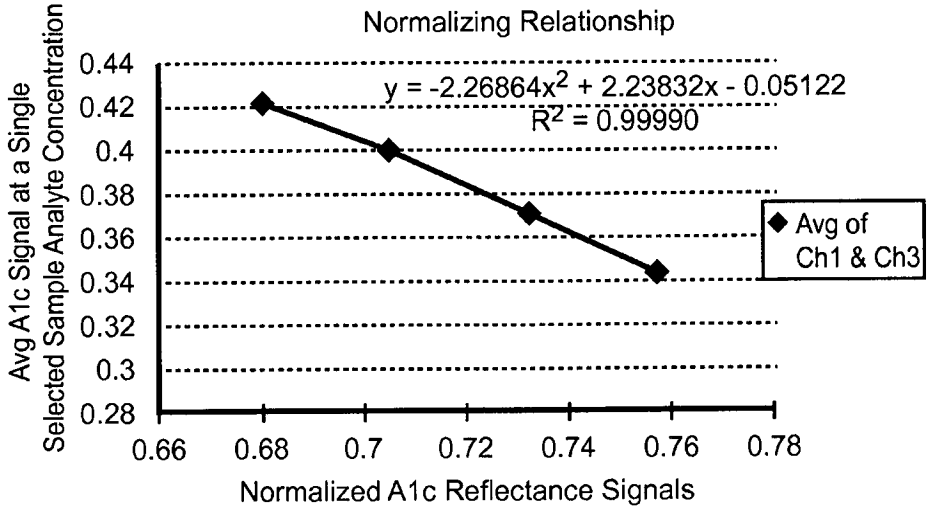
Normalizing Relationship
Avg A1c Signal at a Single Selected Sample Analyte Concentration
0.44
0.42
0.4
0.38
0.36
0.34
0.32
0.3
0.28
y = -2.26864x2 + 2.23832x - 0.05122
R2 = 0.99990
Avg of Ch1 & Ch3
0.66
0.68
0.7
0.72
0.74
0.76
0.78
Normalized A1c Reflectance Signals

FIG.2D

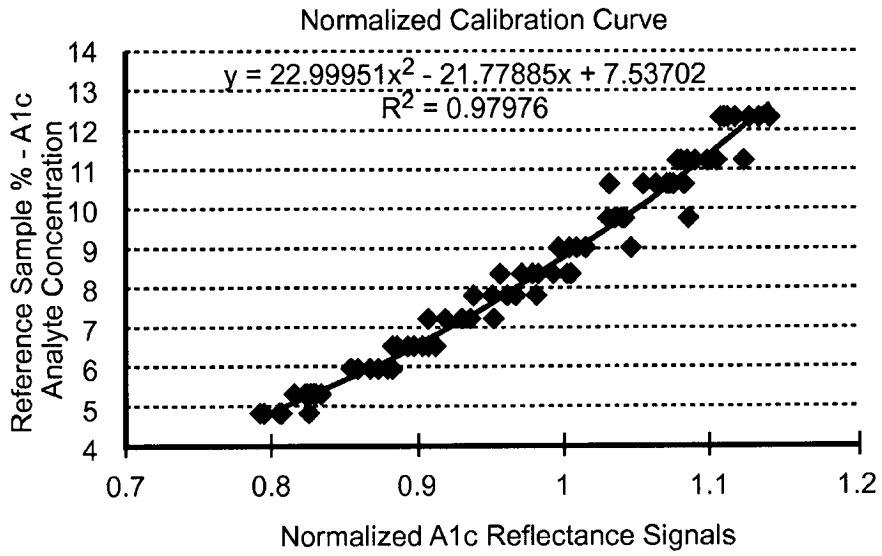
Normalized Calibration Curve
y = 22.99951x2 - 21.77885x + 7.53702
R2 = 0.97976
Reference Sample % - A1c Analyte Concentration
14
13
12
11
10
9
8
7
6
5
4
0.7
0.8
0.9
1
1.1
1.2
Normalized A1c Reflectance Signals

FIG.2E

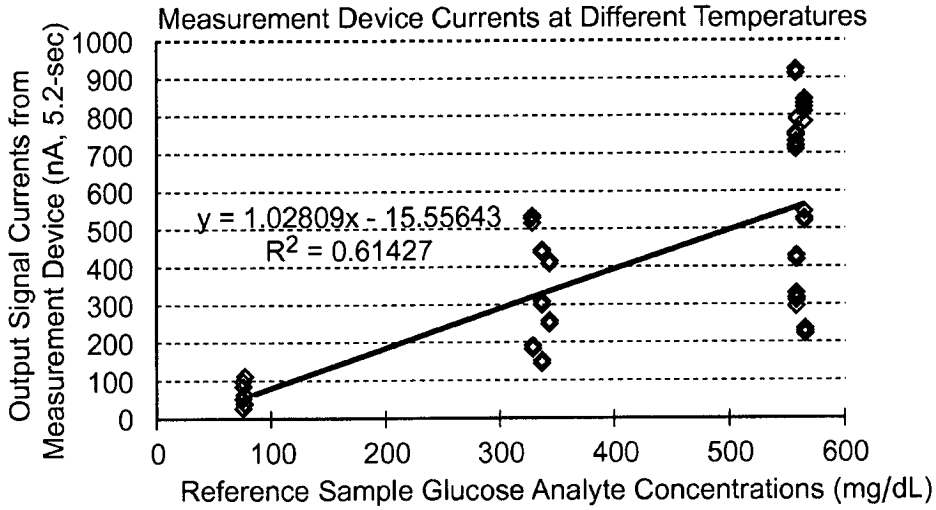
Measurement Device Currents at Different Temperatures
Output Signal Currents from Measurement Device (nA, 5.2-sec)
1000
900
800
700
600
500
400
300
200
100
0
y = 1.02809x - 15.55643
R2 = 0.61427
0
100
200
300
400
500
600
Reference Sample Glucose Analyte Concentrations (mg/dL)

FIG.3A

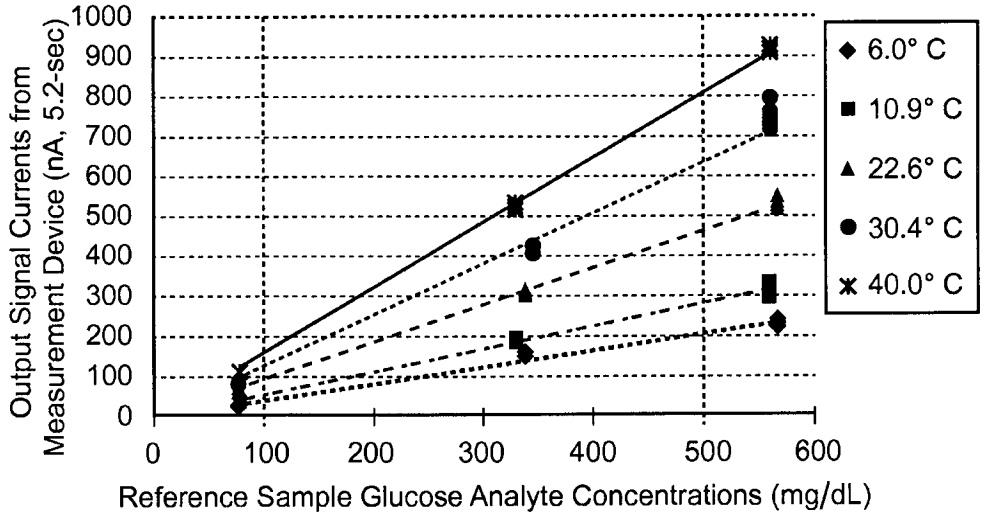
Output Signal Currents from Measurement Device (nA, 5.2-sec)
1000
900
800
700
600
500
400
300
200
100
0
0
100
200
300
400
500
600
Reference Sample Glucose Analyte Concentrations (mg/dL)
6.0° C
10.9° C
22.6° C
30.4° C
40.0° C

FIG.3B

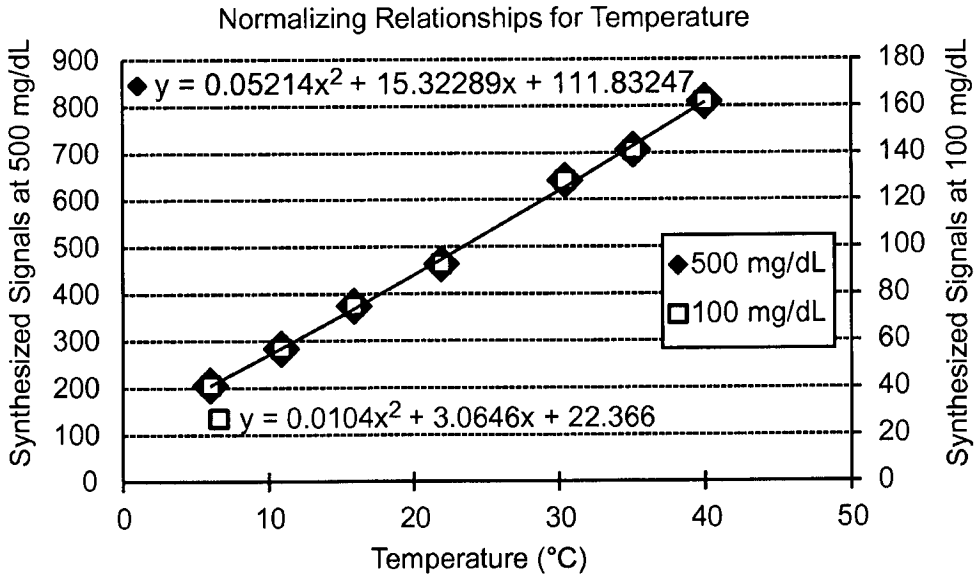
Normalizing Relationships for Temperature
Synthesized Signals at 500 mg/dL
900
800
700
600
500
400
300
200
100
0
y = 0.05214x2 + 15.32289x + 111.83247
500 mg/dL
100 mg/dL
y = 0.0104x2 + 3.0646x + 22.366
180
160
140
120
100
80
60
40
20
0
Synthesized Signals at 100 mg/dL
0
10
20
30
40
50
Temperature (°C)

FIG.3C

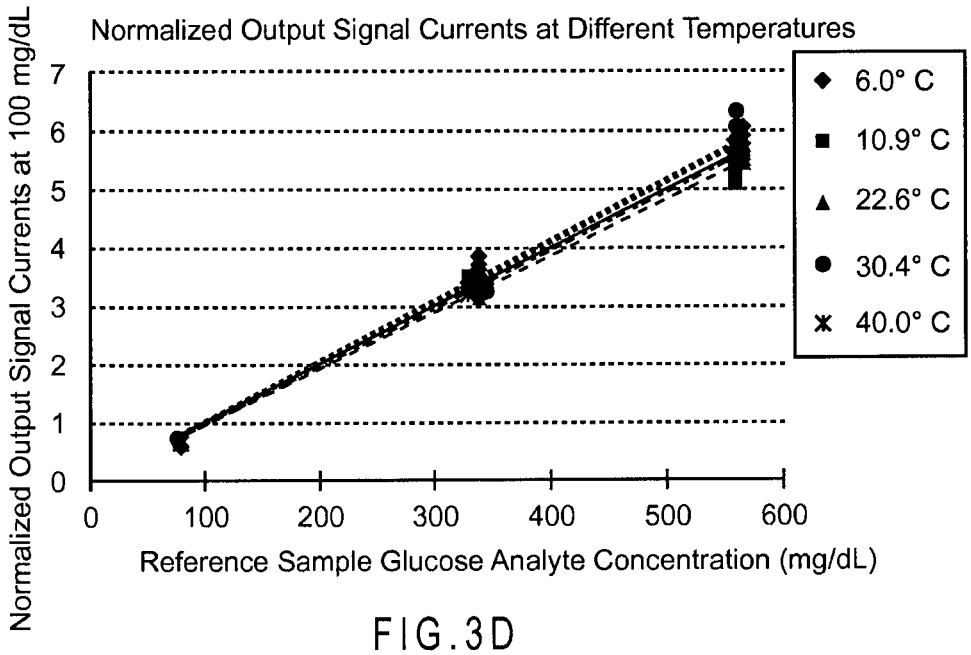
Normalized Output Signal Currents at Different Temperatures
Normalized Output Signal Currents at 100 mg/dL
0
1
2
3
4
5
6
7
0
100
200
300
400
500
600
Reference Sample Glucose Analyte Concentration (mg/dL)
6.0° C
10.9° C
22.6° C
30.4° C
40.0° C

FIG.3D

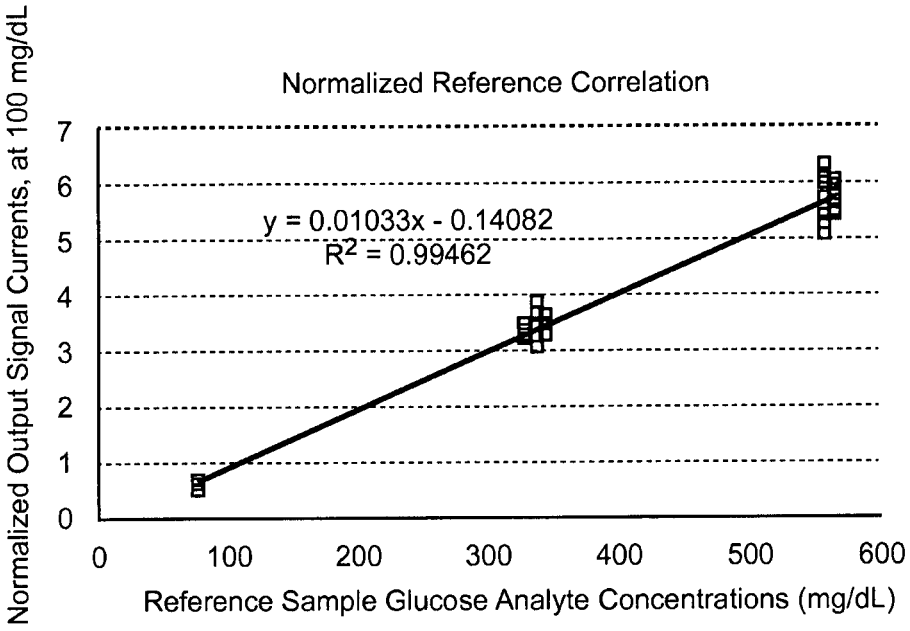
Normalized Reference Correlation
Normalized Output Signal Currents, at 100 mg/dL
y = 0.01033x - 0.14082
R2 = 0.99462
0
1
2
3
4
5
6
7
0
100
200
300
400
500
600
Reference Sample Glucose Analyte Concentrations (mg/dL)

FIG.3E

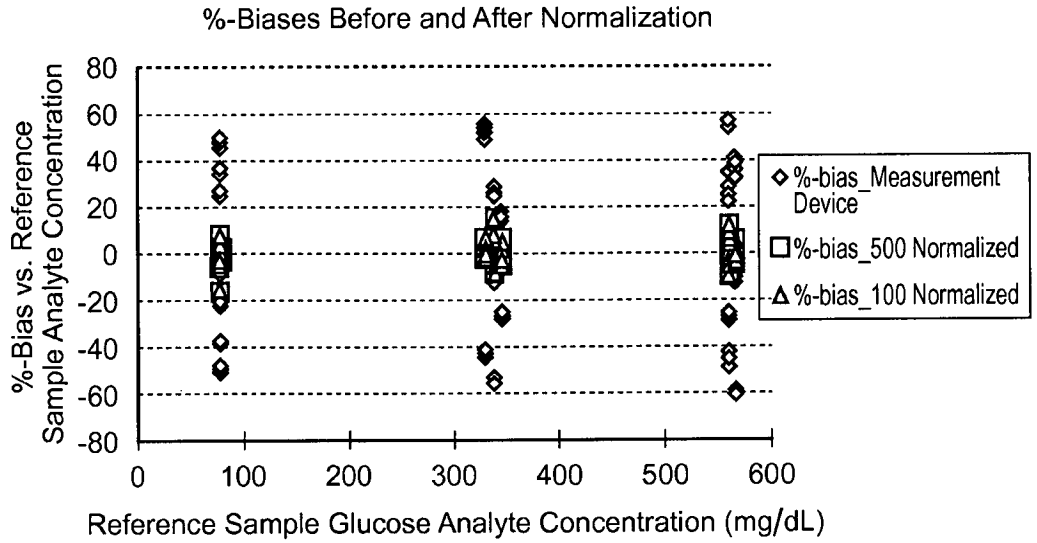
%-Biases Before and After Normalization
%-Bias vs. Reference Sample Analyte Concentration
80
60
40
20
0
-20
-40
-60
-80
0
100
200
300
400
500
600
Reference Sample Glucose Analyte Concentration (mg/dL)
%-bias_Measurement Device
%-bias_500 Normalized
%-bias_100 Normalized

FIG.3F

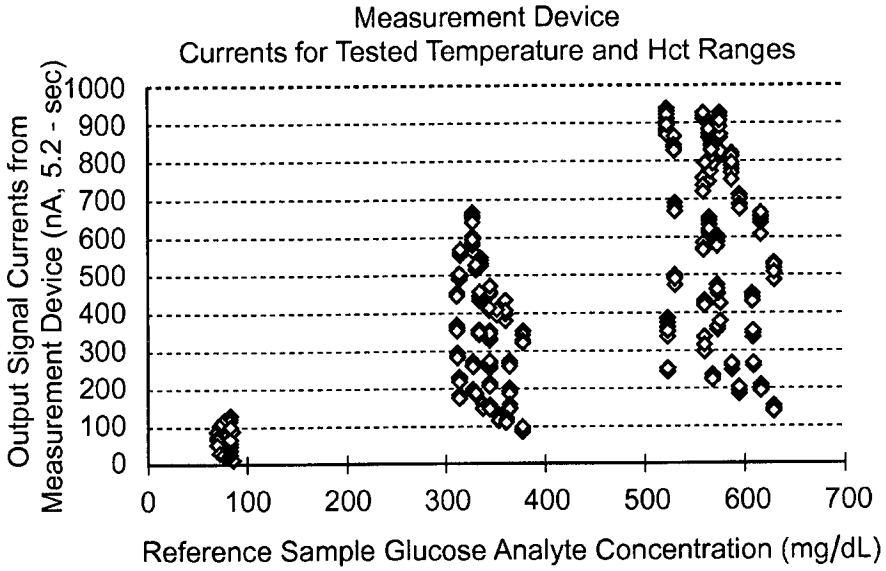
Measurement Device
Currents for Tested Temperature and Hct Ranges
Output Signal Currents from Measurement Device (nA, 5.2 - sec)
1000
900
800
700
600
500
400
300
200
100
0
0
100
200
300
400
500
600
700
Reference Sample Glucose Analyte Concentration (mg/dL)

FIG.4A

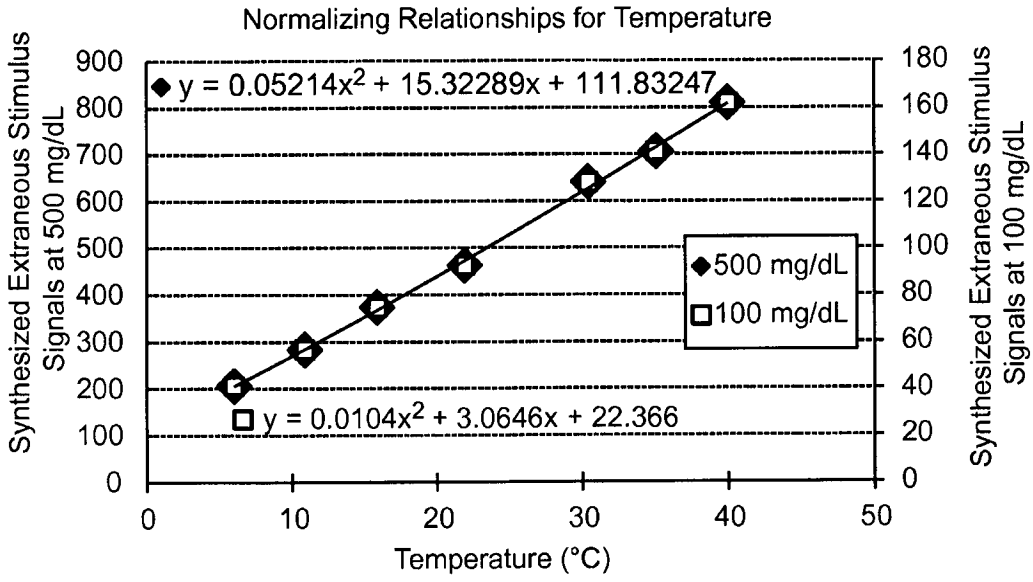
Normalizing Relationships for Temperature
Synthesized Extraneous Stimulus Signals at 500 mg/dL
Synthesized Extraneous Stimulus Signals at 100 mg/dL
y = 0.05214x2 + 15.32289x + 111.83247
y = 0.0104x2 + 3.0646x + 22.366
500 mg/dL
100 mg/dL
Temperature (°C)

FIG.4B

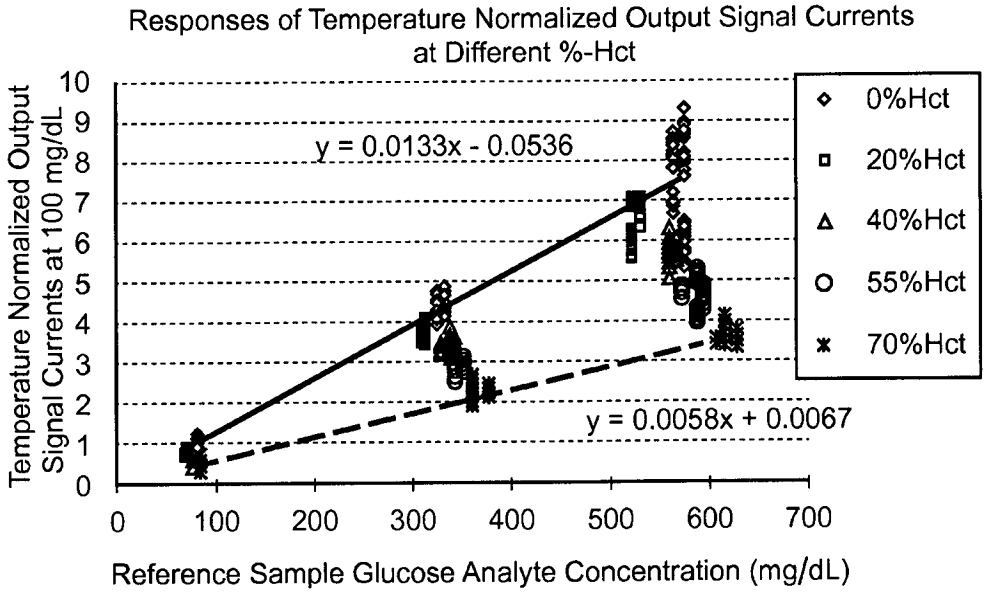
Responses of Temperature Normalized Output Signal Currents at Different %-Hct
Temperature Normalized Output Signal Currents at 100 mg/dL
y = 0.0133x - 0.0536
y = 0.0058x + 0.0067
0%Hct
20%Hct
40%Hct
55%Hct
70%Hct
Reference Sample Glucose Analyte Concentration (mg/dL)

FIG.4C

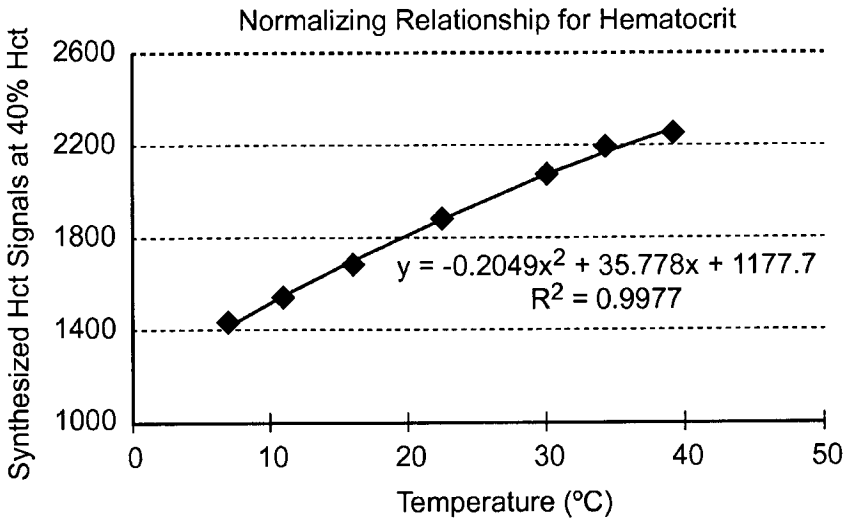
Normalizing Relationship for Hematocrit
Synthesized Hct Signals at 40% Hct
2600
2200
1800
1400
1000
y = -0.2049x2 + 35.778x + 1177.7
R2 = 0.9977
0
10
20
30
40
50
Temperature (°C)

FIG.4D

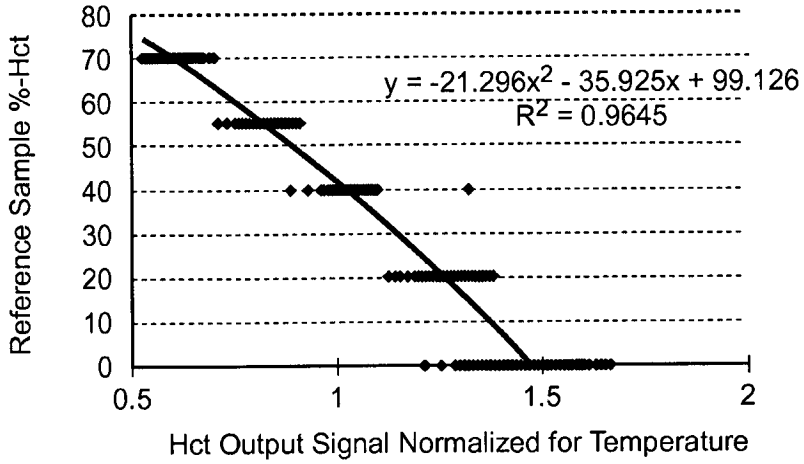
Reference Sample %-Hct
80
70
60
50
40
30
20
10
0
y = -21.296x2 - 35.925x + 99.126
R2 = 0.9645
0.5
1
1.5
2
Hct Output Signal Normalized for Temperature

FIG.4E

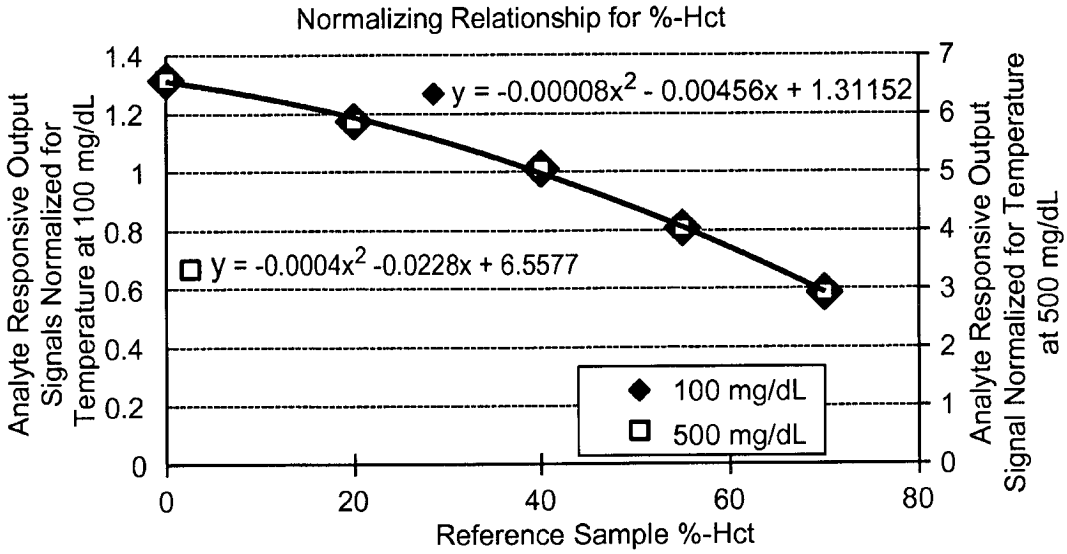
Normalizing Relationship for %-Hct
y = -0.00008x2 - 0.00456x + 1.31152
y = -0.0004x2 -0.0228x + 6.5577
100 mg/dL
500 mg/dL
Analyte Responsive Output Signals Normalized for Temperature at 100 mg/dL
Analyte Responsive Output Signal Normalized for Temperature at 500 mg/dL
Reference Sample %-Hct
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
1
2
3
4
5
6
7
0
20
40
60
80

FIG.4F

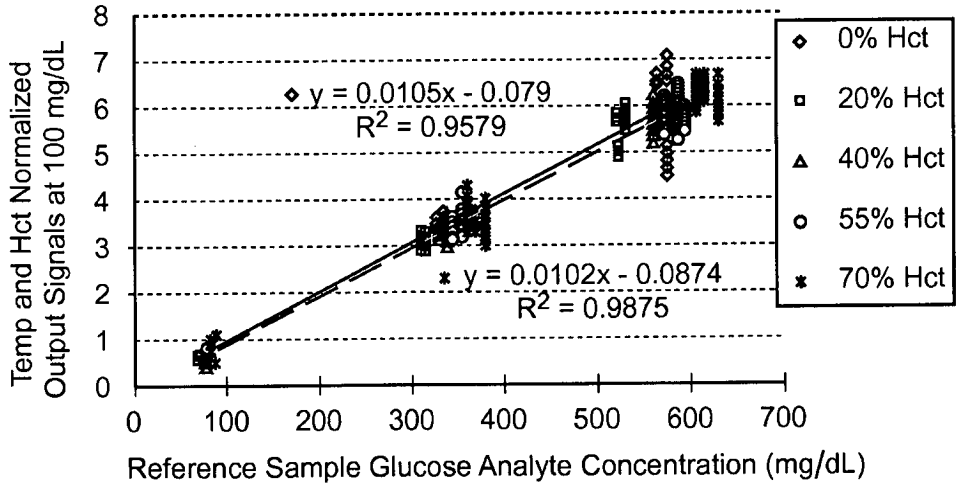
y = 0.0105x - 0.079
R2 = 0.9579
y = 0.0102x - 0.0874
R2 = 0.9875
0% Hct
20% Hct
40% Hct
55% Hct
70% Hct
Temp and Hct Normalized Output Signals at 100 mg/dL
Reference Sample Glucose Analyte Concentration (mg/dL)
0
1
2
3
4
5
6
7
8
0
100
200
300
400
500
600
700

FIG.4G

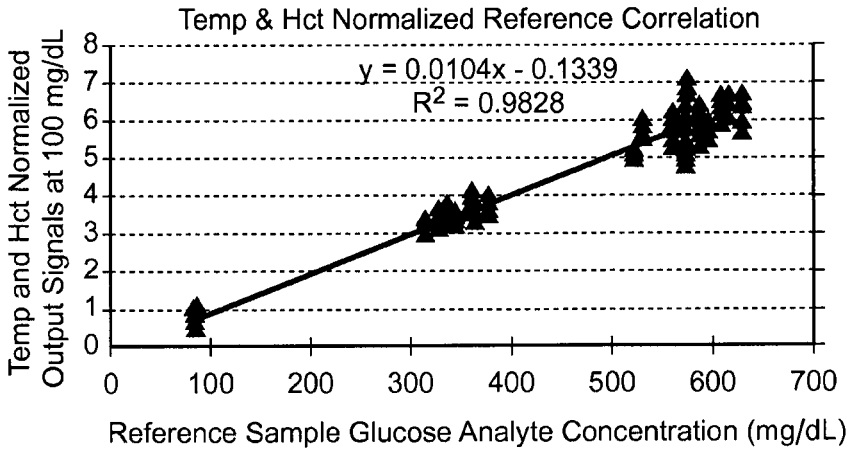
Temp & Hct Normalized Reference Correlation
y = 0.0104x - 0.1339
R2 = 0.9828
Temp and Hct Normalized Output Signals at 100 mg/dL
0
1
2
3
4
5
6
7
8
0
100
200
300
400
500
600
700
Reference Sample Glucose Analyte Concentration (mg/dL)

FIG.4H

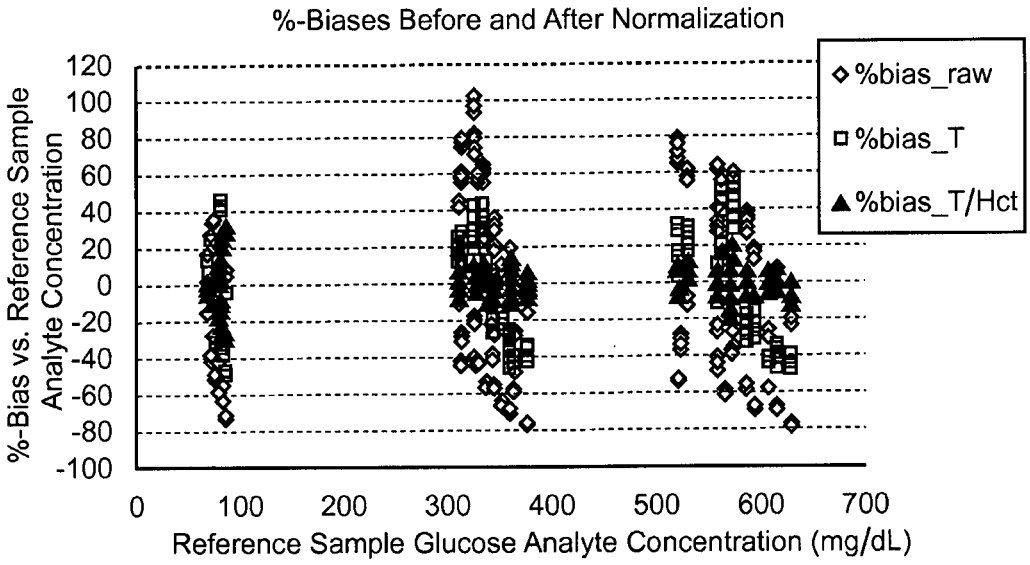
%-Biases Before and After Normalization
%bias_raw
%bias_T
%bias_T/Hct
%-Bias vs. Reference Sample Analyte Concentration
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
100
200
300
400
500
600
700
Reference Sample Glucose Analyte Concentration (mg/dL)

FIG.4I

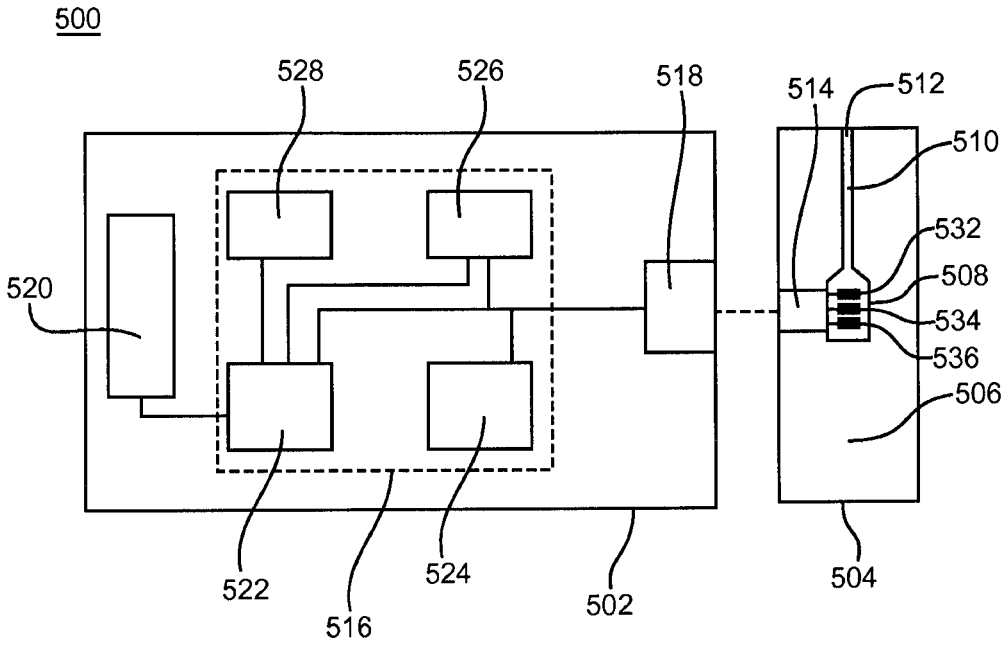
500
528
526
518
514
512
510
532
508
534
536
506
520
522
516
524
502
504

FIG.5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/021870

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/72 G01N27/327
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/156152 A1 (BAYER HEALTHCARE LLC [US]; HUANG DIJIA [US]; WU PING [US]) 15 December 2011 (2011-12-15)	1-77
Y	the whole document in particular: claims 1,34,48,49,60,66,67 paragraphs [0013], [0067] - paragraph [00121]	13,26, 49,57,69

X	WO 2011/119533 A1 (BAYER HEALTHCARE LLC [US]; WU HUAN-PING [US]; HARRISON BERN [US]; MAUR) 29 September 2011 (2011-09-29)	1-77
Y	the whole document	13,26, 49,57,69

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2014	27/06/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tuynman, Antonin

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/021870

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/108239 A2 (BAYER HEALTHCARE LLC [US]; WU HUAN-PING [US]) 3 September 2009 (2009-09-03)	1-77
Y	the whole document	13,26, 49,57,69

X	WO 2010/077660 A1 (BAYER HEALTHCARE LLC [US]; WU HUAN-PING [US]; JUNG SUNG-KWON [US]) 8 July 2010 (2010-07-08)	1-77
Y	the whole document	13,26, 49,57,69

Y	EP 1 978 361 A2 (BAYER HEALTHCARE LLC [US]) 8 October 2008 (2008-10-08) the whole document	13,26, 49,57,69

X,P	WO 2013/043839 A1 (BAYER HEALTHCARE LLC [US]; WU HUAN-PING [US]) 28 March 2013 (2013-03-28)	1-77
L	the whole document	

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/021870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011156152 A1	15-12-2011	CA 2798938 A1	15-12-2011
		CN 103210310 A	17-07-2013
		EP 2577302 A1	10-04-2013
		JP 2013528289 A	08-07-2013
		KR 20130109088 A	07-10-2013
		SG 186179 A1	30-01-2013
		US 2011301857 A1	08-12-2011
		WO 2011156152 A1	15-12-2011
WO 2011119533 A1	29-09-2011	CA 2793878 A1	29-09-2011
		CN 103003692 A	27-03-2013
		EP 2550530 A1	30-01-2013
		JP 2013522647 A	13-06-2013
		KR 20130016311 A	14-02-2013
		RU 2012144625 A	27-04-2014
		US 2011231105 A1	22-09-2011
		WO 2011119533 A1	29-09-2011
WO 2009108239 A2	03-09-2009	CA 2708038 A1	03-09-2009
		CN 101999073 A	30-03-2011
		CN 103760356 A	30-04-2014
		EP 2223104 A2	01-09-2010
		JP 2011506966 A	03-03-2011
		RU 2010128653 A	20-01-2012
		TW 200933147 A	01-08-2009
		US 2009177406 A1	09-07-2009
		WO 2009108239 A2	03-09-2009
WO 2010077660 A1	08-07-2010	CA 2743440 A1	08-07-2010
		CN 102239406 A	09-11-2011
		CN 102854232 A	02-01-2013
		EP 2373984 A1	12-10-2011
		JP 2012511160 A	17-05-2012
		RU 2011128010 A	20-01-2013
		US 2011297554 A1	08-12-2011
		WO 2010077660 A1	08-07-2010
EP 1978361 A2	08-10-2008	EP 1978361 A2	08-10-2008
		US 2008248581 A1	09-10-2008
		WO 2008124063 A1	16-10-2008
WO 2013043839 A1	28-03-2013	KR 20140063829 A	27-05-2014
		TW 201314195 A	01-04-2013
		US 2013071869 A1	21-03-2013
		WO 2013043839 A1	28-03-2013

(19)中华人民共和国国家知识产权局

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代理人 梁兴龙 曹正建
(51)Int.Cl.
G01N 33/72(2006.01)
G01N 27/327(2006.01)

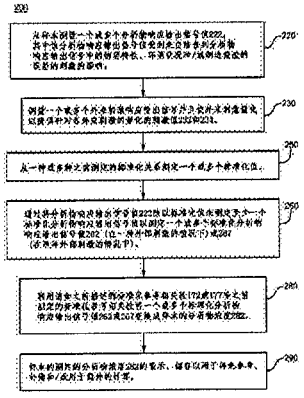
权利要求书8页 说明书28页 附图13页

(54)发明名称

分析物浓度测定的标准化校准

(57)摘要

用来测定样本中分析物的有无和/或浓度的生物传感器系统测量装置包括标准化校准信息，该标准化校准信息使该装置响应于样本的分析物浓度生成的输出信号与之前测定的参考样本分析物浓度相联系。该测量装置利用这种标准化校准信息使来自样本的电化学或光学分析的一个或多个输出信号与样本中一种或多种分析物的有无和/或浓度相联系。标准化校准信息包括使由生物传感器系统的测量装置测量的输出信号标准化的标准化关系和使标准化输出信号与参考样本分析物浓度相联系的至少一种标准化参考相关性。



CN 105378484 A

1. 一种测定样本中分析物浓度的方法，包括：

从样本生成至少一个输出信号；

从所述至少一个输出信号测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；

从所述样本测量至少一个外来刺激响应输出信号；

响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；

从至少一种标准化关系测定至少一个标准化值；

响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和

响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定所述样本中的至少一个分析物浓度。

2. 如权利要求 1 所述的方法，其中测定至少一个标准化值包括向所述至少一种标准化关系中输入所述至少一个分析物响应输出信号值和所述至少一个量化的外来刺激值。

3. 如权利要求 1 或 2 所述的方法，其中测定至少一个标准化分析物响应输出信号值包括将所述至少一个分析物响应输出信号值除以所述至少一个标准化值。

4. 如权利要求 3 所述的方法，其中一个分析物响应输出信号值被用来测定一个标准化分析物响应输出信号值。

5. 如前述权利要求中任一项所述的方法，其中测定至少一个分析物浓度包括将所述至少一个标准化分析物响应输出信号值变换成所述至少一个分析物浓度的所述至少一种标准化参考相关性。

6. 如前述权利要求中任一项所述的方法，还包括从至少两个分析物浓度测定所述样本的平均分析物浓度。

7. 如前述权利要求中任一项所述的方法，其中测定至少一个标准化值包括向所述至少一种标准化关系中输入所述至少一个分析物响应输出信号值和所述至少一个量化的外来刺激值。

8. 如前述权利要求中任一项所述的方法，还包括：

测定至少两个分析物响应输出信号和至少两个量化的外来刺激值之间的标准化关系；

从所述至少一个外来刺激响应输出信号测定所述至少两个量化的外来刺激值；

从至少一个参考样本测量至少一个外来刺激响应输出信号；

测定所述至少一个参考样本的参考样本分析物浓度和至少两个分析物响应输出信号之间的参考相关性；

测定至少两个标准化分析物响应输出信号和所述参考样本分析物浓度之间的至少一种标准化参考相关性；和

从所述至少两个分析物响应输出信号和所述标准化值测定所述至少两个标准化分析物响应输出信号。

9. 如权利要求 8 所述的方法，其中测定所述标准化关系包括在单个选定的分析物浓度下向所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值应用标准化关系回归技术，以及其中测定所述至少一种标准化参考相关性包括向所述至少两个标准化分

析物响应输出信号和至少一个参考样本分析物浓度应用标准化参考相关性回归技术。

10. 如权利要求 8 所述的方法，还包括：

从所述至少一个外来刺激响应输出信号测定至少两个第二量化的外来刺激值；

测定所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值之间的第二标准化关系；

从所述至少两个标准化分析物响应输出信号和第二标准化值测定至少两个第二标准化分析物响应输出信号；和

测定所述至少两个第二标准化分析物响应输出信号和至少一个参考样本分析物浓度之间的第二标准化参考相关性。

11. 如权利要求 10 所述的方法，其中测定第二标准化关系包括在单个选定的分析物浓度下向所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值应用第二标准化关系回归技术，以及其中测定第二标准化参考相关性包括向所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用第二标准化参考相关性回归技术。

12. 如前述权利要求中任一项所述的方法，其中所述至少一种外来刺激包括物理特性、环境状况和制造偏差中的至少一种。

13. 如前述权利要求中任一项所述的方法，其中所述至少一个分析物浓度包括糖化血红蛋白和葡萄糖中的至少一种，其中所述样本包括血液，以及其中所述至少一种外来刺激包括温度、总血红蛋白和血细胞比容中的至少一种。

14. 一种分析物测量装置，包括与传感器接口连接的电路，其中所述电路包括与信号发生器和存储介质连接的处理器；其中所述处理器能够实施权利要求 1 ～ 13 中任一项所述的方法。

15. 一种用于测定样本中分析物浓度的生物传感器系统，包括：

测试传感器，所述测试传感器具有邻近由基部形成的储器的样本接口，其中所述测试传感器能够从样本生成至少一个输出信号；和

测量装置，所述测量装置具有与传感器接口连接的处理器，所述传感器接口与所述样本接口电连通，以及所述处理器与存储介质电连通；

其中所述处理器能够实施权利要求 1 ～ 13 中任一项所述的方法。

16. 本文公开的各个新颖性特征。

17. 一种测定样本中分析物浓度的方法，包括：

从样本生成至少一个输出信号；

从所述至少一个输出信号测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；

从所述样本测量至少一个外来刺激响应输出信号；

响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；

从至少一种标准化关系测定至少一个标准化值；

响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和

响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定

所述样本中的至少一个分析物浓度。

18. 如权利要求 17 所述的方法，其中所述至少一种外来刺激是物理特性、环境状况和制造偏差中的至少一种。

19. 如权利要求 17 所述的方法，其中测定至少一个量化的外来刺激值包括响应于第一外来刺激测定第一量化的外来刺激值。

20. 如权利要求 19 所述的方法，其中测定至少一个量化的外来刺激值还包括响应于第二外来刺激测定第二量化的外来刺激值。

21. 如权利要求 17 所述的方法，其中测定至少一个标准化值包括向所述至少一种标准化关系中输入所述至少一个分析物响应输出信号值和所述至少一个量化的外来刺激值。

22. 如权利要求 17 所述的方法，其中测定至少一个标准化分析物响应输出信号值包括将所述至少一个分析物响应输出信号值除以所述至少一个标准化值。

23. 如权利要求 22 所述的方法，其中一个分析物响应输出信号值被用来测定一个标准化分析物响应输出信号值。

24. 如权利要求 17 所述的方法，其中测定至少一个分析物浓度包括将所述至少一个标准化分析物响应输出信号值变换成所述至少一个分析物浓度的所述至少一种标准化参考相关性。

25. 如权利要求 17 所述的方法，还包括从至少两个分析物浓度测定所述样本的平均分析物浓度。

26. 如权利要求 17 所述的方法，其中所述至少一个分析物浓度包括糖化血红蛋白和葡萄糖中的至少一种，以及其中所述样本包括血液。

27. 如权利要求 17 所述的方法，其中所述至少一种外来刺激是温度、总血红蛋白和血细胞比容中的至少一种。

28. 如权利要求 17 所述的方法，其中测定至少一个标准化值包括向所述至少一种标准化关系中输入所述至少一个分析物响应输出信号值和所述至少一个量化的外来刺激值。

29. 如权利要求 17 所述的方法，还包括：

测定至少两个分析物响应输出信号和至少两个量化的外来刺激值之间的标准化关系；

从至少一个外来刺激响应输出信号测定所述至少两个量化的外来刺激值；

从至少一个参考样本测量至少一个外来刺激响应输出信号；和

测定所述至少一个参考样本的参考样本分析物浓度和至少两个分析物响应输出信号之间的参考相关性。

30. 如权利要求 29 所述的方法，其中测定所述标准化关系包括在单个选定的分析物浓度下向所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值应用回归技术。

31. 如权利要求 29 所述的方法，还包括：

测定至少两个标准化分析物响应输出信号和至少一个参考样本分析物浓度之间的标准化参考相关性；和

从所述至少两个分析物响应输出信号和所述标准化值测定所述至少两个标准化分析物响应输出信号。

32. 如权利要求 31 所述的方法，其中测定标准化参考相关性包括向所述至少两个标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用回归技术。

33. 如权利要求 31 所述的方法，还包括：

从所述至少一个外来刺激响应输出信号测定至少两个第二量化的外来刺激值；和

测定所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值之间的第二标准化关系。

34. 如权利要求 33 所述的方法，其中测定第二标准化关系包括在单个选定的分析物浓度下向所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值应用回归技术。

35. 如权利要求 33 所述的方法，还包括：

从所述至少两个标准化分析物响应输出信号和第二标准化值测定至少两个第二标准化分析物响应输出信号；和

测定所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度之间的第二标准化参考相关性。

36. 如权利要求 35 所述的方法，其中测定第二标准化参考相关性包括向所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用回归技术。

37. 一种用于校准生物传感器系统的测量装置的方法，包括：

从样本测量至少两个分析物响应输出信号，其中所述分析物响应输出信号受到至少一种外来刺激的影响；

测定至少一个参考样本分析物浓度和所述至少两个分析物响应输出信号之间的参考相关性；

从所述样本测量至少一个外来刺激响应输出信号；

从所述至少一个外来刺激响应输出信号测定至少两个量化的外来刺激值；

测定所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值之间的标准化关系；

从所述标准化关系和所述至少两个量化的外来刺激值测定标准化值；

从所述至少两个分析物响应输出信号和所述标准化值测定至少两个标准化分析物响应输出信号；和

测定所述至少两个标准化分析物响应输出信号和所述至少一个参考样本分析物浓度之间的标准化参考相关性。

38. 如权利要求 37 所述的方法，其中所述至少一种外来刺激是物理特性、环境状况和制造偏差中的至少一种。

39. 如权利要求 37 所述的方法，其中所述测量至少两个分析物响应输出信号包括测量至少 4 个分析物响应输出信号。

40. 如权利要求 37 所述的方法，其中所述测量至少两个分析物响应输出信号包括测量至少 6 个分析物响应输出信号。

41. 如权利要求 37 所述的方法，还包括与从所述样本测量至少两个分析物响应输出信号同时测量所述至少一个外来刺激响应输出信号。

42. 如权利要求 37 所述的方法，还包括使所述至少两个量化的外来刺激值直接量化。

43. 如权利要求 37 所述的方法，还包括使所述至少两个量化的外来刺激值间接量化。

44. 如权利要求 37 所述的方法，其中测定标准化关系包括在单个选定的分析物浓度下向所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值应用回归技术。

45. 如权利要求 37 所述的方法，其中测定至少两个标准化分析物响应输出信号包括将所述至少两个分析物响应输出信号除以所述标准化值。

46. 如权利要求 37 所述的方法，其中测定标准化参考相关性包括向所述至少两个标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用回归技术。

47. 如权利要求 37 所述的方法，其中所述标准化参考相关性包括标准化校准曲线。

48. 如权利要求 37 所述的方法，还包括在测量装置中储存所述标准化关系和所述标准化参考相关性。

49. 如权利要求 37 所述的方法，其中所述至少一个分析物浓度包括糖化血红蛋白和葡萄糖中的至少一种，以及其中所述样本包括血液。

50. 如权利要求 37 所述的方法，其中所述至少一种外来刺激包括温度、总血红蛋白和血细胞比容中的至少一种。

51. 如权利要求 37 所述的方法，还包括：

从所述至少一个外来刺激响应输出信号测定至少两个第二量化的外来刺激值；

测定所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值之间的第二标准化关系；

从第二标准化关系和所述至少两个第二量化的外来刺激值测定第二标准化值；

从所述至少两个标准化分析物响应输出信号和第二标准化值测定至少两个第二标准化分析物响应输出信号；和

测定所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度之间的第二标准化参考相关性。

52. 如权利要求 51 所述的方法，其中测定第二标准化关系包括在单个选定的分析物浓度下向所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值应用回归技术。

53. 如权利要求 51 所述的方法，其中测定至少两个第二标准化分析物响应输出信号包括将所述至少两个标准化分析物响应输出信号除以第二标准化值。

54. 如权利要求 51 所述的方法，其中测定第二标准化参考相关性包括向所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用回归技术。

55. 如权利要求 51 所述的方法，其中第二标准化参考相关性包括第二标准化校准曲线。

56. 如权利要求 51 所述的方法，还包括在测量装置中储存第二标准化关系和第二标准化参考相关性。

57. 如权利要求 51 所述的方法，其中所述至少一个分析物浓度包括糖化血红蛋白和葡萄糖中的至少一种，以及其中所述样本包括血液。

58. 如权利要求 51 所述的方法，其中所述至少一种外来刺激是温度、总血红蛋白和血细胞比容中的至少一种。

59. 一种分析物测量装置，包括：

与传感器接口连接的电路，其中所述电路包括与信号发生器和存储介质连接的处理器；

其中所述处理器能够从样本测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；

其中所述处理器能够从所述样本测量至少一个外来刺激响应输出信号；

其中所述处理器能够响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；

其中所述处理器能够从至少一种标准化关系测定至少一个标准化值；

其中所述处理器能够响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和

其中所述处理器能够响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定所述样本中的至少一个分析物浓度。

60. 如权利要求 59 所述的分析物测量装置，其中所述至少一种外来刺激是物理特性、环境状况和制造偏差中的至少一种。

61. 如权利要求 59 所述的分析物测量装置，其中所述处理器能够从至少两个分析物浓度测定所述样本的平均分析物浓度。

62. 如权利要求 59 所述的分析物测量装置，其中所述至少一个分析物浓度包括糖化血红蛋白和葡萄糖中的至少一种，以及其中所述样本包括血液。

63. 如权利要求 59 所述的分析物测量装置，其中所述至少一种外来刺激是温度、总血红蛋白和血细胞比容中的至少一种。

64. 如权利要求 59 所述的分析物测量装置，其中所述至少一种标准化关系和所述至少一种标准化参考相关性储存在所述存储介质中。

65. 如权利要求 59 所述的分析物测量装置，其中所述测量装置还包括至少两个检测通道。

66. 一种用于测定样本中分析物浓度的生物传感器系统，包括：

测试传感器，所述测试传感器具有邻近由基部形成的储器的样本接口，其中所述测试传感器能够从样本生成至少一个输出信号；和

测量装置，所述测量装置具有与传感器接口连接的处理器，所述传感器接口与所述样本接口电连通，以及所述处理器与存储介质电连通；

其中所述处理器能够从所述至少一个输出信号测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；

其中所述处理器能够从所述样本测量至少一个外来刺激响应输出信号；

其中所述处理器能够响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；

其中所述处理器能够从至少一种标准化关系测定至少一个标准化值；

其中所述处理器能够响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和

其中所述处理器能够响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定所述样本中的至少一个分析物浓度。

67. 如权利要求 67 所述的生物传感器系统，其中所述至少一种外来刺激是物理特性、环境状况和制造偏差中的至少一种。

68. 如权利要求 67 所述的生物传感器系统，其中所述处理器能够从至少两个分析物浓度测定所述样本的平均分析物浓度。

69. 如权利要求 67 所述的生物传感器系统，其中所述至少一个分析物浓度包括糖化血红蛋白和葡萄糖中的至少一种，以及其中所述样本包括血液。

70. 如权利要求 67 所述的生物传感器系统，其中所述至少一种外来刺激是温度、总血红蛋白和血细胞比容中的至少一种。

71. 如权利要求 67 所述的生物传感器系统，其中所述至少一种标准化关系和所述至少一种标准化参考相关性储存在所述存储介质中。

72. 如权利要求 67 所述的生物传感器系统，

其中所述处理器能够测量至少两个分析物响应输出信号；

其中所述处理器能够测定至少一个参考样本分析物浓度和所述至少两个分析物响应输出信号之间的参考相关性；

其中所述处理器能够从所述样本测量至少一个外来刺激响应输出信号；

其中所述处理器能够从所述至少一个外来刺激响应输出信号测定至少两个量化的外来刺激值；

其中所述处理器能够测定所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值之间的标准化关系；

其中所述处理器能够从所述标准化关系和所述至少两个量化的外来刺激值测定标准化值；

其中所述处理器能够从所述至少两个分析物响应输出信号和所述标准化值测定至少两个标准化分析物响应输出信号；和

其中所述处理器能够测定所述至少两个标准化分析物响应输出信号和所述至少一个参考样本分析物浓度之间的标准化参考相关性。

73. 如权利要求 71 所述的生物传感器系统，其中所述处理器能够通过在单个选定的分析物浓度下向所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值应用回归技术来测定所述标准化关系。

74. 如权利要求 71 所述的生物传感器系统，其中所述处理器能够通过向所述至少两个标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用回归技术来测定所述标准化参考相关性。

75. 如权利要求 71 所述的生物传感器系统，还包括：

其中所述处理器能够从所述至少一个外来刺激响应输出信号测定至少两个第二量化的外来刺激值；

其中所述处理器能够测定所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值之间的第二标准化关系；

其中所述处理器能够从第二标准化关系和所述至少两个第二量化的外来刺激值测定第二标准化值；

其中所述处理器能够从所述至少两个标准化分析物响应输出信号和第二标准化值测

定至少两个第二标准化分析物响应输出信号；和

其中所述处理器能够测定所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度之间的第二标准化参考相关性。

76. 如权利要求 74 所述的生物传感器系统，其中所述处理器能够通过在单个选定的分析物浓度下向所述至少两个标准化分析物响应输出信号和所述至少两个第二量化的外来刺激值应用回归技术来测定第二标准化关系。

77. 如权利要求 74 所述的生物传感器系统，其中所述处理器能够通过向所述至少两个第二标准化分析物响应输出信号和所述至少一个参考样本分析物浓度应用回归技术来测定第二标准化参考相关性。

分析物浓度测定的标准化校准

[0001] 相关申请的参照

[0002] 本申请要求于2013年3月14日提交的发明名称为“分析物浓度测定的校准”的美国临时申请No.61/782,520的权益，其全部内容通过引用的方式并入本文。

背景技术

[0003] 生物传感器系统提供对诸如血液、血清、血浆、尿、唾液、细胞间液或细胞内液等生物流体样本的分析。通常，该系统包括分析存在于测试传感器中的样本的测量装置。该样本通常为液态形式并且除了为生物流体之外，还可以是生物流体的衍生物，例如提取物、稀释物、滤出液或复原沉淀。由生物传感器系统进行的分析测定生物流体中诸如乙醇、葡萄糖、尿酸、乳酸酯、胆固醇、胆红素、游离脂肪酸、甘油三酸酯、蛋白质、酮类、苯丙氨酸或酶等一种或多种分析物的有无和/或浓度。例如，糖尿病患者可以使用生物传感器系统来测定血液中的A1c或葡糖糖水平以调节日常饮食和/或用药。

[0004] 在含有血红蛋白(Hb)的血液样本中，可以测定总血红蛋白(THb)和糖化血红蛋白(HbA1c)的有无和/或浓度。HbA1c(A1c%)是糖尿病患者葡萄糖控制状态的反映，提供对在测试之前三个月的平均葡萄糖控制的深入认识。对于糖尿病病人来说，A1c%的精确测量有助于测定在比由血糖水平的瞬时测量提供的期间更长的时期内患者用日常饮食和/或用药对血糖水平控制得有多好。由于瞬时血糖测量不表示当进行测量时之外的血糖控制。

[0005] 生物传感器系统可以设计成分析一种或多种分析物并且可以使用不同体积的生物流体。一些系统可以分析例如体积为0.25～15微升(μL)的一滴血液。生物传感器系统可以使用台式、便携式等测量装置来实现。便携式测量装置可以手持并且允许识别和/或量化样本中的一种或多种分析物。便携式测量系统的例子包括Tarrytown,New York的Bayer HealthCare的Contour®计量仪，而台式测量系统的例子包括可从Austin,Texas的CH Instruments得到的电化学工作站。

[0006] 生物传感器系统可以利用光学和/或电化学方法来分析生物流体。在一些光学系统中，分析物浓度通过测量与光可识别的样品相互作用或被光可识别的样品吸收的光来测定，例如该光可识别的样品为分析物或从与分析物反应的化学指示剂形成的反应或产物。在其他光学系统中，化学指示剂响应于当被激发光束照亮时的分析物发荧光或发射光。该光可以转换成诸如电流或电位等电输出信号，可以对其进行与来自电化学系统的输出信号类似的处理。在任一光学系统中，该系统测量光并且使光与样本的分析物浓度相关联。

[0007] 在光吸收光学系统中，化学指示剂产生吸收光的反应产物。可以将诸如四唑等化学指示剂与诸如心肌黄酶等酶一起使用。四唑通常响应于分析物的氧化还原反应形成甲臜(发色团)。来自光源的入射输入光束朝向样本照射。该光源可以是激光器和发光二极管等。入射光束可以具有选定为由反应产物吸收的波长。随着入射光束穿过样本，反应产物吸收一部分的入射光束，因而减弱或降低入射光束的强度。入射光束可以从样本反射回来或透过样本到达检测器。检测器聚集并测量减弱的入射光束(输出信号)。被反应产物减弱的光的量为样本中分析物的浓度的指示。

[0008] 在光产生光学系统中，化学指示剂响应于分析物的氧化还原反应发荧光或发射光。检测器聚集并测量所产生的光（输出信号）。由化学指示剂产生的光的量为样本中分析物的浓度的指示并且表示为来自检测器的电流或电位。

[0009] 利用反射率的光学系统的一个例子是测定血液中 A1c 血红蛋白浓度的层流 A1c% 系统。这些系统利用其中将血液引入生物传感器系统的测试传感器（在那里其与试剂反应然后沿着试剂膜流动）的免疫测定化学。当被血液接触时，A1c 抗体包被的彩珠释放并与血液一起移动到检测区 1。由于血液样本中的 A1c 和检测区 1 中的存在的 A1c 肽之间对彩珠的竞争，而使得没有附着到 A1c 抗体上的彩珠在区 1 被捕获，因而从反射率的变化检测为 A1c 信号反射率。血液样本中的总血红蛋白（THb）也与其他血液处理试剂反应并向下游移动到检测区 2 中，在那里以不同的波长对其进行测量。对于血液样本中的 A1c 浓度的测定，反射率信号与 A1c 分析物浓度（A1c%）成正比，但是受到血液 THb 含量的影响。然而，对于 THb 测量，区 2 中的反射率与血液样本的 THb(mg/mL) 成反比，但是不会明显受到血液 A1c 含量的影响。

[0010] 在电化学系统中，样本的分析物浓度从当向样本施加输入信号时由分析物的氧化 / 还原或氧化还原反应产生的电信号或响应于分析物浓度的可测量物质测定。输入信号可以是电位或电流并且可以是恒定的、可变的或其组合（例如当施加具有 DC 信号偏移的 AC 信号时）。输入信号可以作为单脉冲或以多个脉冲、多个序列或多个周期施加。酶或类似物质可以添加到样本中以加强氧化还原反应期间来自分析物的电子转移。酶或类似物质可以与一种分析物反应，因而提供与所产生的输出信号的一部分的特异性。氧化还原介体可以用作可测量物质以维持酶的氧化状态和 / 或协助来自分析物的电子转移到电极。因此，在氧化还原反应期间，酶或类似物质可以在分析物和氧化还原介体之间转移电子，同时氧化还原介体在其本身和测试传感器的电极之间转移电子。

[0011] 电化学生物传感器系统通常包括具有与测试传感器的电导体连接的电触头的测量装置。该导体可以由诸如固体金属、金属浆料、导电碳、导电碳浆和导电聚合物等导电材料制成。电导体与工作电极和对电极连接，并且取决于测试传感器的设计可以与延伸到样本储器中的参比电极和 / 或其他电极连接。一个或多个电导体也可以延伸到样本储器中以提供电极未提供的功能性。

[0012] 在许多生物传感器系统中，测试传感器可以适于在活的有机体的外部、内部或部分在其内部使用。当在活的有机体的外部使用时，生物流体的样本可以引入测试传感器中的样本储器中。测试传感器可以在引入用于分析的样本之前、之后或期间放置在测量装置中。当在活的有机体内部或部分在其内部使用时，测试传感器可以连续浸没在样品中或样本可以间歇地引入测试传感器中。测试传感器可以包括部分地隔离样本体积的储器或对样本开放。当对样本开放时，测试传感器可以采取与生物流体接触地放置的纤维或其他结构的形式。类似地，样本可以连续流经测试传感器（例如针对连续监测）或被中断（例如针对间歇监测）以进行分析。

[0013] 电化学生物传感器系统的测量装置通过电触头向测试传感器的电导体施加输入信号。电导体通过电极将输入信号传递到样本储器中存在的样本中。分析物的氧化还原反应响应于输入信号产生电输出信号。来自测试传感器的电输出信号可以是电流（通过安培法或伏安法产生的）、电位（通过电位测定法 / 电流测定法产生的）或蓄积的电荷（通过电

量分析法产生的）。该测量装置可以具有测量输出信号并使输出信号与样本中一种或多种分析物的有无和／或浓度相关联的处理能力。

[0014] 在电量分析法中，向样本上施加电位以使分析物彻底地氧化或还原。在美国专利No.6,120,676中描述了利用电量分析法的生物传感器系统。在安培法中，将恒定电位（电压）的电信号施加到测试传感器的电导体，同时测量的输出信号是电流。在美国专利No.5,620,579、5,653,863、6,153,069和6,413,411中描述了利用安培法的生物传感器系统。在伏安法中，将变化电位的电信号施加到生物流体的样本上，同时测量的输出是电流。在门控安培法和门控伏安法中，如分别在WO 2007/013915和WO 2007/040913中描述的使用脉冲输入。

[0015] 主输出信号响应于样本的分析物浓度并从分析的输入信号获得。例如，当分析物为葡萄糖时，基本上独立于响应于样本的分析物浓度的信号的输出信号包括响应于温度的信号和基本上响应于血液样本的诸如血细胞比容或对乙酰氨基酚含量等干扰物的信号。基本上不响应于分析物浓度的输出信号可以被称作次级输出信号，因为它们不是响应于由分析物或分析物响应指示剂、分析物的电化学氧化还原反应或分析物响应的氧化还原介体的电化学氧化还原反应引起的光的改变的主输出信号。次级输出信号响应于生物样本的物理或环境特性。次级输出信号可以产生于样本或其他源，例如提供对样本的环境特性的评价的热电偶等。因此，次级输出信号可以从分析的输入信号或从其他输入信号测定。

[0016] 当产生于样本时，次级输出信号可以从用来测定样本的分析物浓度的电极或从附加电极测定。附加电极可以含有与用来测定样本的分析物浓度的电极相同的试剂组合物、不同的试剂组合物或不含有试剂组合物。例如，可以使用与干扰物反应的试剂组合物或可以使用缺乏试剂组合物的电极来研究诸如全血血细胞比容等样本的一种或多种物理特性。

[0017] 在样本分析期间，可以存在影响由测量装置分析的主输出信号的多于一种的刺激。这些刺激包括样本的分析物浓度、样本的物理特性、样本的环境状况、测试传感器批次间的制造偏差等。由于分析的首要目标是测定样本中分析物的有无和／或浓度，所以样本的分析物浓度被称作主刺激。影响输出信号的所有其他刺激被称作外来刺激。因此，主输出信号包括来自主刺激（样本的分析物浓度）的主要效果，而且也包括来自一种或多种外来刺激的一些效果。相比而言，次级输出信号包括来自一种或多种外来刺激的主要效果，并且可以包括或可以不包括来自主刺激的主要效果。

[0018] 生物传感器系统的测量性能从准确度和精度方面进行定义。准确度反映系统和随机误差分量的复合效应。系统误差或真实度是从生物传感器系统测定的平均值和生物流体的分析物浓度的一个或多个采纳的参考值之间的差。真实度可以从平均偏差方面表示，其中较大的平均偏差值表示较低的真实度，从而导致较低的准确度。精度是与平均数相关的多个分析物读数的一致接近度。分析中的一种或多种误差导致由生物传感器系统测定的分析物浓度的偏差和／或不精确性。因此，生物传感器系统分析误差的减小引起准确度和／或精度的提高，因而提高测量性能。

[0019] 偏差可以从“绝对偏差”或“偏差百分比”方面表示。绝对偏差是测定浓度和参考浓度之间的差并且可以以诸如mg/dL等测量的单位表示，偏差百分比可以表示为绝对偏差值除以参考浓度的百分比或表示为绝对偏差除以样本的截止浓度值或参考浓度的百分比。例如，如果截止浓度值为100mg/dL，那么对于小于100mg/dL的葡萄糖浓度来说，偏差百分

比定义为（绝对偏差除以 100mg/dL)*100；对于 100mg/dL 以上的葡萄糖浓度来说，偏差百分比定义为绝对偏差除以分析物浓度的采纳的参考值 *100。

[0020] 血液样本中分析物葡萄糖的采纳的参考值优选利用诸如可从 Yellow Springs, Ohio 的 YSI Inc. 得到的 YSI 2300STAT PLUS™等标准仪器获得。测定偏差百分比的其他标准仪器和方式可以用于其他分析物。对于 A1c% 测量，误差可以表示为绝对偏差或相对于有效药浓度范围为 4 ～ 12% 的 A1c% 参考值的偏差百分比。血液样本中 A1c% 的采纳的参考值可以利用诸如可从日本 Tosoh Corp 得到的 Tosoh G7 仪器等标准仪器获得。

[0021] 血细胞比容偏差是指利用标准仪器获得的参考葡萄糖浓度和从用于含有不同血细胞比容水平的样本的生物传感器系统的测量装置和测试传感器获得的实验葡萄糖读数之间的平均差（系统误差）。参考值和从生物传感器系统获得的值之间的差由特定血液样本之间变化的血细胞比容水平所引起并且通常可以表示为如下的百分数：% Hct-Bias = 100% ×$(G_m-G_{ref})/G_{ref}$，其中 G_m 是在特定的血细胞比容水平下的测定的葡萄糖浓度，G_{ref} 是在样本血细胞比容水平下的参考葡萄糖浓度。% Hct-bias 的绝对值越大，样本的血细胞比容水平（表示为 Hct%，红细胞容积 / 样品体积的百分比）使从生物传感器系统测定的葡萄糖浓度的准确度降低得越多。

[0022] 例如，如果对含有相同的葡萄糖浓度但是具有 20、40 和 60% 的血细胞比容水平的不同的血液样本进行分析，那么生物传感器系统基于一组校准常数（例如，含有 40% 血细胞比容的血液样本的斜率和截距）将报告三个不同的葡萄糖浓度。因此，即使不同血液样本的葡萄糖浓度相同，该系统也将报告 20% 血细胞比容样本含有比 40% 血细胞比容样本更多的葡萄糖，以及 60% 血细胞比容样本含有比 40% 血细胞比容样本更少的葡萄糖。“血细胞比容灵敏度”是样本血细胞比容水平的变化对利用生物传感器系统进行的分析的偏差值影响程度的表示。血细胞比容灵敏度可以定义为偏差百分比 / 血细胞比容百分比的数字值，因此表示为偏差% /Hct%。

[0023] 生物传感器系统可以在包括来自多个误差源的误差的生物流体的分析期间提供输出信号。这些误差源促成总误差，该总误差可以反映在异常的输出信号中，例如当输出信号的一部分或多部分或全部不响应于或不适当地响应于样本的分析物浓度时。

[0024] 输出信号的总误差可源自一种或多种误差促成因素，例如样本的物理特性、样本的环境状况、系统的操作条件、测试传感器批次间的制造偏差等。样本的物理特性包括血细胞比容（红细胞浓度）以及诸如脂类和蛋白质等干扰物质等。葡萄糖分析的干扰物质还可以包括抗坏血酸、尿酸和对乙酰氨基酚等。样本的环境状况包括温度和空气中的氧含量等。系统的操作条件包括当样本尺寸不够大时的未充满条件、由样本进行的测试传感器的缓慢填充、样本和测试传感器的一个或多个电极之间的间歇电接触、在制造测试传感器之后与分析物相互作用的试剂的降解等。测试传感器批次间的制造偏差包括试剂的量和 / 或活性的变化、电极面积和 / 或间距的变化、导体和电极的电导率的变化等。测试传感器批次优选以其中基本上减小或消除批次间的制造偏差的单个制造周期制成。可以存在造成分析误差的其他促成因素或误差促成因素的组合。

[0025] 偏差百分比、平均偏差百分比、偏差百分比的标准差 (SD)、方差系数百分比 (CV%) 和血细胞比容灵敏度是表示生物传感器系统的测量性能的独立方式。可以使用额外的方式来表示生物传感器系统的测量性能。

[0026] 偏差百分比是与参考分析物浓度相关的生物传感器系统准确度的表示，而偏差百分比标准差反映关于由样本的物理特性、样本的环境状况、系统的操作条件和测试传感器之间的制造偏差引起的误差的多个分析的准确度。因此，偏差百分比标准差的降低表示多个分析中的生物传感器系统的测量性能的提高。方差系数百分比可以表示为100%*(一组样本的SD)/(取自同一组样本的多个读数的平均值)并反映多个分析的精度。因此，偏差百分比标准差的降低表示多个分析中的生物传感器系统的测量性能的提高。

[0027] 例如，通过减小来自这些或其他源的误差来提高生物传感器系统的测量性能意味着由生物传感器系统测定的更多的分析物浓度可以用于当监测血糖时患者的精确治疗。另外，也可以减少对丢弃测试传感器和由患者进行的重复分析的需要。

[0028] 生物传感器系统可以具有响应于分析物的氧化还原或光系反应的未补偿的输出信号的单个源，例如电化学系统的对电极和工作电极。生物传感器系统也可以具有例如利用一个或多个热电偶或其他装置测定或估计温度的任选的能力。除了这些系统之外，生物传感器系统也可以具有生成来自分析物或来自响应于分析物的介体的输出信号之外的次级输出信号的能力。例如，在电化学测试传感器中，一个或多个电导体也可以延伸到样本储器中以提供工作电极和对电极未提供的功能性。这种导体可能缺少诸如介体等工作电极试剂中的一种或多种，因而允许从工作电极信号减去背景干扰信号。

[0029] 许多生物传感器系统包括补偿与分析相关联的误差的一种或多种方法，因而试图提高生物传感器系统的测量性能。补偿方法可以通过为生物传感器系统提供补偿分析误差的能力来提高生物传感器系统的测量性能，因而提高从该系统获得的浓度值的准确度和/或精度。物理和环境误差促成因素的常规误差补偿方法传统上在实验室进行开发，因为这些类型的误差可以在受控的环境中再现。

[0030] 在实验室中如何对生物传感器系统的测量装置进行校准影响由使用者掌握的系统的测量性能。因此，在校准测量装置的上下文中持续关注的是在使用中可能影响测量装置的测量性能的所有误差参数，这些误差参数应当在将该测量装置用于分析样本的分析物浓度之前在实验室中进行校准。

[0031] 误差参数是变量，它们的值从诸如来自主输出信号的中间信号的分析或从独立于分析物响应输出信号的次级输出信号(例如热电偶和附加电极等)测定。误差参数可以是响应于输出信号的一种或多种误差的任意变量。因此，具有它们的离散值的这些变量可以是从来自主输出信号的中间信号或从次级输出信号(例如从热电偶电流或电压以及附加电极电流或电压等)测量的电流或电位。其他误差参数可以从这些或其他主输出信号或次级输出信号确定。

[0032] 如果对测量装置进行太多或非最优误差参数的校准，那么可能产生效果递减点或者甚至是更差的测量性能。此外，在校准中考虑越多的参数，在测量装置中储存的校准信息对于从在分析期间测定的误差参数进行的后面分析的补偿可能越无用。当正在进行的分析包括多个输出信号(包括分析物浓度响应(主输出信号)和/或非分析物响应信号(次级输出信号))时，这些校准问题变得更复杂。本发明利用常规校准技术避免或改善了测量装置的至少一些缺点。

发明内容

[0033] 在一个方面，本发明提供了一种测定样本中分析物浓度的方法，包括：从样本生成至少一个输出信号；从所述至少一个输出信号测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；从所述样本测量至少一个外来刺激响应输出信号；响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；从至少一种标准化关系测定至少一个标准化值；响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定所述样本中的至少一个分析物浓度。

[0034] 在本发明的另一个方面中，提供了一种用于校准生物传感器系统的测量装置的方法，包括：从样本测量至少两个分析物响应输出信号，其中所述分析物响应输出信号受到至少一种外来刺激的影响；测定至少一个参考样本分析物浓度和所述至少两个分析物响应输出信号之间的参考相关性；从所述样本测量至少一个外来刺激响应输出信号；从所述至少一个外来刺激响应输出信号测定至少两个量化的外来刺激值；测定所述至少两个分析物响应输出信号和所述至少两个量化的外来刺激值之间的标准化关系；从所述标准化关系和所述至少两个量化的外来刺激值测定标准化值；从所述至少两个分析物响应输出信号和所述标准化值测定至少两个标准化分析物响应输出信号；和测定至少两个标准化分析物响应输出信号和所述至少一个参考样本分析物浓度之间的标准化参考相关性。

[0035] 在本发明的另一个方面中，提供了一种分析物测量装置，包括：与传感器接口连接的电路，其中所述电路包括与信号发生器和存储介质连接的处理器；其中所述处理器能够从样本测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；其中所述处理器能够从所述样本测量至少一个外来刺激响应输出信号；其中所述处理器能够响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；其中所述处理器能够从至少一种标准化关系测定至少一个标准化值；其中所述处理器能够响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和其中所述处理器能够响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定所述样本中的至少一个分析物浓度。

[0036] 在本发明的另一个方面中，提供了一种用于测定样本中分析物浓度的生物传感器系统，包括：测试传感器，所述测试传感器具有邻近由基部形成的储器的样本接口，其中所述测试传感器能够从样本生成至少一个输出信号；和测量装置，所述测量装置具有与传感器接口连接的处理器，所述传感器接口与所述样本接口电连通，以及所述处理器与存储介质电连通；其中所述处理器能够从所述至少一个输出信号测量至少一个分析物响应输出信号值，其中所述至少一个分析物响应输出信号值受到至少一种外来刺激的影响；其中所述处理器能够从所述样本测量至少一个外来刺激响应输出信号；其中所述处理器能够响应于所述至少一个外来刺激响应输出信号测定至少一个量化的外来刺激值；其中所述处理器能够从至少一种标准化关系测定至少一个标准化值；其中所述处理器能够响应于所述至少一个分析物响应输出信号值和所述至少一个标准化值测定至少一个标准化分析物响应输出信号值；和其中所述处理器能够响应于至少一种标准化参考相关性和所述至少一个标准化分析物响应输出信号测定所述样本中的至少一个分析物浓度。

附图说明

[0037] 参照以下附图和说明可以更好地理解本发明。附图中的部件不一定是成比例的，而是强调说明本发明的原理。

[0038] 图 A 示出了用于结合到具有减少的外来刺激效果的测量装置中的测定校准信息的校准方法。

[0039] 图 B 示出了也考虑到具有校准信息的第二外来刺激的任选的校准方法。

[0040] 图 C 示出了利用标准化参考相关性测定具有减少的外来刺激效果的样本的分析物浓度的分析方法。

[0041] 图 1A 示出了在四个 THb（总血红蛋白）浓度 (85mg/mL、125mg/mL、175mg/mL 和 230mg/mL) 下的从测量装置的区 1 检测器记录的 A1c 反射率信号相对于参考样本分析物浓度 (A1c％）的图。

[0042] 图 1B 示出了如从测量装置的区 2 检测器测定的在四个 THb 参考样本浓度水平 (85mg/mL、125mg/mL、175mg/mL 和 230mg/mL) 下的相对恒定的 THb 输出信号。

[0043] 图 1C 示出了为血液样本中四个不同的 THb 浓度分离开的从测量装置的区 1 检测器记录的各自的 A1c 反射率信号。

[0044] 图 1D 也提供了测定标准化关系 140 的例子，其在单个 A1c 浓度下的合成的外来刺激响应输出信号和响应于样本 THb 浓度的次级输出信号之间建立相关性。

[0045] 图 1E 提供了从标准化值测定标准化分析物响应输出信号的例子。

[0046] 图 1F 提供了从将图 1E 的标准化分析物响应输出信号值组合测定标准化参考相关性的例子。

[0047] 图 1G 提供了从图 1E 的标准化分析物响应输出信号值测定标准化参考相关性的另一个例子。

[0048] 图 1H 通过使标准化分析物响应输出信号值叠加在图 1G 的标准化校准曲线上来将标准化分析物响应输出信号与该曲线的形式的标准化参考相关性进行比较。

[0049] 图 2A 示出了针对具有两个检测通道的 A1c 测量装置的两个通道的标准化关系。

[0050] 图 2B 示出了 A1c 测量装置的 Ch1 和 Ch3 的各自标准化校准曲线。

[0051] 图 2C 示出了针对参考样本的来自两个各自通道 (Ch1&Ch3) 的标准化 A1c 反射率信号。

[0052] 图 2D 示出了通过首先对来自测量装置的 Ch1 和 Ch3 的 A1c 反射率输出信号求平均所测定的标准化关系。

[0053] 图 2E 示出了针对来自测量装置的 Ch1 和 Ch3 的平均 A1c 反射率信号测定的标准化校准曲线形式的标准化参考相关性。

[0054] 图 3A 绘制了在不同的温度和 40Hct％下的从测量装置获得的电流相对于葡萄糖的参考样本分析物浓度的图。

[0055] 图 3B 将这些主输出信号电流按温度分开，在该温度下记录了这些主输出信号电流。

[0056] 图 3C 示出了在两个单独的单个葡萄糖浓度 100 和 500mg/dL 下获得的合成的外来刺激响应输出信号相对于量化的外来刺激（温度）之间的相关性以测定标准化关系。

[0057] 图 3D 提供了在 100mg/dL 下从标准化值测定标准化分析物响应输出信号的例子。

[0058] 图 3E 提供了从图 3D 的标准化分析物响应输出信号值测定标准化参考相关性的例子。

[0059] 图 3F 绘制了在标准化之前和之后归因于不同的温度（6.0℃、10.9℃、15.9℃、22.0℃、30.4℃、35.1℃和 40.0℃）的偏差%。

[0060] 图 4A 示出了针对测试温度（6.0℃、10.9℃、15.9℃、22.0℃、30.4℃、35.1℃和 40.0℃）和测试 Hct 参考样本浓度（0%、20%、40%、55%、70%）的相对于包含已知葡萄糖浓度的参考样本的来自测量装置的输出信号电流。

[0061] 图 4B 示出了在血液样本中 40Hct%和两个单独的单个葡萄糖浓度 100 和 500mg/dL 下的温度标准化关系，并且与之前图 3C 中所示的相同，因为正在进行相同的温度刺激降低。

[0062] 图 4C 绘制了在本实施例中测试的 Hct 参考样本浓度下的来自图 4A 的温度标准化分析物响应输出信号值相对于葡萄糖的参考样本分析物浓度的图。

[0063] 图 4D 绘制了针对包含 40%血细胞比容浓度的参考样本的从响应于样本的血细胞比容浓度的次级输出信号测定的合成的信号相对于温度的图。

[0064] 图 4E 示出了 Hct 的温度标准化参考相关性，其中绘制了参考样本 Hct%浓度相对温度标准化 Hct 电极输出电流的图。

[0065] 图 4F 示出了在所产生的温度标准化分析物响应输出信号和参考样本 Hct%值（第二外来刺激）之间确定的第二标准化关系。

[0066] 图 4G 通过图形示出了在选定的葡萄糖浓度 100mg/dL 下的通过利用温度和 Hct 标准化分析物响应输出信号值所提供的由如图 4C 所示的血细胞比容的外来刺激所引入的误差的减小。

[0067] 图 4H 提供了从将图 4G 的温度和血细胞比容标准化分析物响应输出信号值进行组合来测定标准化参考相关性的例子。

[0068] 图 4I 通过图形示出了由测量装置利用常规参考相关性（偏差% _raw）、温度标准化参考相关性（偏差% _T）以及温度和 Hct 标准化参考相关性（偏差% _T/Hct）所测定的分析物浓度的偏差%。

[0069] 图 5 绘出了测定生物流体的样本中分析物浓度的生物传感器系统的示意图。

具体实施方式

[0070] 用来测定样本中分析物的有无和 / 或浓度的生物传感器系统中的测量装置包括标准化校准信息，该标准化校准信息使该装置响应于样本的分析物浓度生成的输出信号与之前测定的参考样本分析物浓度相联系。该测量装置利用这种标准化校准信息使来自样本的电化学或光学分析的一个或多个输出信号与样本中一种或多种分析物的有无和 / 或浓度相联系。

[0071] 本申请公开了用于分析物浓度的样本分析的在工厂、实验室或类似环境中测定标准化校准信息的方法、利用储存在在样本分析期间所使用的生物传感器系统的测量装置中的标准化校准信息测定样本的分析物浓度的方法和利用标准化校准信息来测定样本中分析物的有无和 / 或浓度的生物传感器系统。标准化校准信息包括用来从测量的输出信号测

定标准化输出信号的标准化关系和使在分析期间测定的标准化输出信号与参考样本分析物浓度相联系的标准化参考相关性。标准化校准信息在响应于分析物生成至少一个主输出信号但是包括来自至少一种外来刺激的误差或受到其影响并且响应于至少一种外来刺激生成至少一个次级输出信号的生物传感器系统中是有用的。

[0072] 在样本分析期间，主刺激和一种或多种外来刺激影响由测量装置分析的一个或多个输出信号。主刺激是样本的分析物浓度。外来刺激包括影响输出信号的所有其他刺激（除了分析物浓度之外），例如样本的物理特性、样本的环境状况和测试传感器批次间的制造偏差等。由测量装置分析的一个或多个输出信号可以包括主输出信号和次级输出信号。主输出信号包括来自主刺激（样本的分析物浓度）的主要效果，而且也包括来自一种或多种外来刺激的一些效果。相比而言，次级输出信号包括来自外来刺激的主要效果，并且可以包括或可以不包括来自主刺激的主要效果。优选地，次级输出信号唯一地响应于一种或多种外来刺激。

[0073] 血液样本中 A1c％的测量，因而是血液样本的总血红蛋白（THb）含量中糖化血红蛋白浓度（A1c％或 A1c）的测量，可以通过利用层流分析的免疫测定法来完成。通常，在层流分析中，测量两种独立的信号，针对 A1c 的主输出信号和针对 THb 的次级输出信号。在这种类型的 A1c 系统中，区 1 检测器提供主输出信号，而区 2 检测器提供次级输出信号。来自区 1 检测器的主输出信号取决于样本的 A1c 浓度，但是也取决于样本的 THb 浓度。来自区 2 检测器的次级输出信号取决于样本的 THb 浓度，但是基本上独立于样本的 A1c 浓度。

[0074] 这些系统中的常规校准着重建立参考样本的已知 A1c％值、当这些样本由生物传感器系统进行分析时响应于 A1c 从测量装置的区 1 检测器测定的反射率主输出信号和当这些样本由生物传感器系统进行分析时响应于样本的 THb 含量从测量装置的区 2 检测器测定的次级输出反射率信号之间的关系。因此，在测定校准信息时存在三种潜在考虑的刺激以储存在测量装置中以备将来在分析期间使用（参考样本分析物浓度、来自测量装置的主输出信号和来自测量装置的次级输出信号）。

[0075] 与这种常规方法相比，本公开的校准方法在 A1c 生物传感器系统中的重大益处起因于，当刺激中的两种（参考样本分析物浓度（A1c％，主刺激）和次级 THb 输出信号（外来刺激））减少到一种（A1c％的参考样本分析物浓度）时，在以后的补偿技术中利用实验室测定的校准信息的能力。实现这种刺激减少的一种方法是通过所描述的标准化方法。

[0076] 标准化方法通过从由测量装置测定的 A1c 响应反射率值生成标准化输出信号来降低来自测量装置的主输出 A1c 信号对 THb 样本浓度的依赖性。然后确定生成的标准化输出信号和参考样本分析物浓度之间的标准化参考相关性。用来测定标准化输出信号的标准化关系和标准化参考相关性储存在测量装置中。在使用中，如通过所描述的标准化程序标准化的从测量装置的区 1 检测器测量的主输出信号仍然响应于 A1c，但是变得基本上独立于响应于样本的总血红蛋白含量（THb）的从区 2 检测器测量的次级输出信号。

[0077] 在葡萄糖分析系统中，校准通常着重建立葡萄糖的已知参考样本分析物浓度、从样本测定的电学或光学主输出信号和响应于温度和／或样本的血细胞比容（Hct）含量的次级输出信号之间的关系。这些次级输出信号可以从热敏电阻器和专用 Hct 电极等测定或从源自主输出信号的这些值的一个或多个估计值测定。

[0078] 在这些葡萄糖分析系统中，响应于样本的葡萄糖浓度的电学或光学主输出信号也

取决于样本的温度和 / 或样本的 Hct 含量。由测量装置的次级输出信号提供的温度和 Hct 信息基本上独立于样本的葡萄糖浓度。因此，除了参考样本分析物浓度之外，还存在测定校准信息所考虑的至少两种（葡萄糖和温度响应信号）或三种（葡萄糖、温度和 Hct 响应信号）刺激以储存在测量装置中以备将来在分析期间使用。

[0079] 在葡萄糖系统中处理这种校准的常规方法的例子是生成表示在已知温度和 / 或血细胞比容浓度下的葡萄糖的多个参考样本分析物浓度和测量装置的对应输出信号之间的参考相关性的直线或曲线。这种参考相关性储存在测量装置中以备将来在分析期间使用。由于光学检测器将光转换成电压和 / 或安培数，所以对于光学或电化学生物传感器系统来说，这个过程是类似的。因此，例如，参考相关性可以在 20℃和 40％样本 Hct 下对已知参考样本分析物浓度进行测定并且可以储存在测量装置中。可以对在选定温度下的多个 Hct 样本浓度重复进行这个过程，并且例如，这些参考相关性也储存在测量装置中。然而，在这种常规技术中，在分析期间，对于特定的分析来说，测量装置必须选择使用多个参考相关性中的哪个或将其插入其间。因此，测量装置尝试选择那些中最好的参考相关性，其必须适合实际分析（充满潜在问题的处理）。由生物传感器系统进行的样本的后续分析的目标是使用之前测定的参考相关性或储存在该装置中的相关性将由测量装置测定的输出信号变换成样本的分析物浓度。

[0080] 与常规的通过参考相关性将输出信号直接转换成浓度相比，本公开的校准方法的重大益处起因于，如果这些刺激中的至少两种（葡萄糖的参考样本分析物浓度和次级温度输出信号）减少到一种（葡萄糖的参考样本分析物浓度），那么将储存在测量装置中的实验室测定的校准信息用于后续补偿技术中的能力。例如，参考相关性对温度的温度依赖性可以通过所描述的标准化方法降低或优选去除以使参考相关性无单位。类似地，参考相关性的 Hct 依赖性也可以通过所描述的标准化方法降低或优选去除。

[0081] 标准化方法通过从由测量装置测定的葡萄糖响应电流值生成标准化输出信号来降低来自测量装置的主输出葡萄糖信号对温度或温度和样本 Hct％的依赖性。然后，确定生成的标准化输出信号和参考样本分析物浓度之间的标准化参考相关性。用来测定标准化输出信号的标准化关系和标准化参考相关性储存在测量装置中。在使用中，如通过所描述的标准化程序标准化的如由测量装置测量的响应于葡萄糖的主输出信号仍然响应于葡萄糖，但是变得基本上独立于响应于温度或温度和样本 Hct％的次级输出信号。

[0082] 对于任一分析类型来说，标准化方法都可以由下式表示：标准化输出信号＝（包括一种主刺激和至少一种外来刺激的效果的分析物响应信号）/（至少一种外来刺激信号），其中主刺激的效果是测量装置尝试检测和 / 或量化的效果。因此，在两种以上的因素影响分析的结果时，使一种或多种因素标准化以将影响分析结果的因素减少为一种。例如，分析物响应主输出信号可以是来自 A1c 分析系统的区 1 检测器的反射率输出或电化学分析系统中响应于葡萄糖的电化学氧化还原反应或葡萄糖浓度响应介体的电流输出。来自其他类型的分析的主输出信号也可以与标准化方法一起使用。外来刺激可以是例如 A1c 分析系统中的 THb，或者是例如在葡萄糖分析系统中的温度和 / 或血细胞比容。因此，外来刺激起因于分析的次级输出信号。

[0083] 图 A 示出了用于结合到具有减少的刺激效果的生物传感器系统的测量装置中的测定标准化校准信息的校准方法 100。优选地，校准方法 100 在测量装置的工厂校准期间进

行。校准方法 100 也可以在实验室或类似环境中进行。该校准方法可以通过测量装置、诸如计算机等一种或多种分析装置或测量装置和分析装置的组合进行。

[0084] 在分析物响应输出信号测量 110 中，分析物响应输出信号从参考样本进行测量，其中该分析物响应输出信号受到结合到分析物响应输出信号中的物理特性、环境状况和 / 或制造偏差的误差中的至少一种外来刺激的影响。测量至少两个分析物响应输出信号。优选地，从参考样本测量至少 4 个，更优选至少 6 个分析物响应输出信号。光学和 / 或电化学方法可以用来分析参考样本。图 1A，如下文所述，提供了在 A1c 分析系统中的分析物响应输出信号测量 110 的例子。图 3A，如下文所述，提供了在葡萄糖分析系统中的分析物响应输出信号测量 110 的例子。

[0085] 在参考相关性测定 120 中，测定在一个或多个参考样本分析物浓度 124 和一个或多个输出信号之间的参考相关性 122。参考相关性 122 使参考样本分析物浓度 124 与如由测量装置 126 测定的输出信号相联系。参考样本的参考样本分析物浓度可以使用标准仪器以及通过混合或改变已知样本分析物浓度等来测定。

[0086] 在外来刺激量化 130 中，从参考样本测量一个或多个外来刺激响应输出信号并且使外来刺激量化以测定至少两个量化的外来刺激值 132。刺激响应输出信号可以与分析物响应输出信号同时或不同时地进行测量。优选地，刺激响应输出信号与分析物响应输出信号同时进行测量。图 1B，如下文所述，提供了在 A1c 分析系统中的外来刺激量化 130 的例子。在葡萄糖系统中，例如如表 3 所示，当温度是外来刺激时，在目标温度和实际温度进行多个分析以使各分析平均。

[0087] 例如，当光学检测器或电极输出特定的电压和 / 或安培数时，可以使外来刺激信号直接量化。例如，当热敏电阻器提供报告为摄氏温度的温度的特定的电压和 / 或安培数时，可以使外来刺激信号间接量化。例如，当样本的 Hct 浓度从从 Hct 电极测量的特定电压和 / 或安培数测定时，也可以使外来刺激信号间接量化。例如，当将直接或间接量化的外来刺激值变换成浓度时，可以使外来刺激信号直接或间接量化，然后对其进行修正以提供量化的外来刺激值 132。量化的外来刺激值 132 可以通过对在同一目标温度下记录的诸如多个温度读数等多个值求平均来测定。外来刺激可以通过其他技术进行量化。例如，分析方法 200，如下面进一步描述的，提供了外来刺激量化的例子。

[0088] 在标准化关系测定 140 中，对所选定的一个或多个参考样本分析物浓度的分析物浓度来说，标准化关系 142 在分析物响应输出信号和量化的外来刺激值 132 之间进行测定。优选地，将回归技术应用于分析物响应输出信号和量化的外来刺激值 132 以测定在单个选定的分析物浓度下的标准化关系。图 1C，如下文所述，提供了在 A1c 分析系统中如何选定单个分析物浓度并将其用来响应于 THb 的量化的外来刺激信号测定合成的外来刺激响应输出信号的例子。图 3B，如下文所述，提供了在葡萄糖分析系统中如何选定两个分析物浓度中的一个并将其用来响应于温度的量化的外来刺激信号测定合成的外来刺激响应输出信号的例子。因此，在单个选定的样本分析物浓度下从主输出信号测定合成的外来刺激响应输出信号。合成的外来刺激响应输出信号可以看成从来自同时包括主刺激和外来刺激的测量装置的组合的主输出信号提取的外来刺激响应输出信号。类似地，标准化关系 142 可以看成外来刺激的参考相关性。

[0089] 图 1D，如下文所述，提供了在使用合成的外来刺激响应输出信号值的 A1c 分析系

统中可以如何实现标准化关系测定 140 的例子。图 1D 也示出了如为 A1c 分析系统测定的标准化关系的例子。图 3C，如下文所述，提供了在使用合成的外来刺激响应主输出信号的葡萄糖分析系统中可以如何实现标准化关系测定 140 的例子。图 3C 也示出了如为葡萄糖分析系统测定的标准化关系的例子。

[0090] 线性或非线性（例如多项式）回归技术可以用来测定标准化关系 142。线性或非线性回归技术包括在MINITAB®版本 14 或版本 16 统计软件包 (MINTAB, INC., State College, PA)、Microsoft Excel 或提供回归技术的其他统计分析软件包中可获得那些回归技术。优选地，多项式回归用来测定标准化关系 142。

[0091] 例如，在 MS Excel 版本 2010 中，可以选择可通过趋势线布局图表工具 (Trendline Layout Chart Tool) 访问的线性趋势线选项 (Linear Trendline Option) 来进行线性回归，同时可以选择多项式趋势线选项 (Polynomial Trendline Option) 来进行非线性多项式回归。其他回归技术可以用来测定标准化关系 142。标准化关系 142 优选作为校准信息的一部分储存在测量装置中。

[0092] 当使用线性回归时，标准化关系 142 会是 $Y = mX+b$ 的形式，其中 m 是回归线的斜率和 b 是回归线的截距。当使用非线性回归时，标准化关系 142 会是 $Y = b_2*X^2+b_1*X+b_0$ 等的形式，其中 b_2、b_1 和 b_0 是多项式的系数。在线性和多项式回归方程中，Y 是在单个选定的分析物浓度下响应于主输出信号的外来刺激部分计算的合成的外来刺激响应输出信号，X 是量化的外来刺激信号 / 值。当将 X 的值（量化的外来刺激信号值）输入到关系（线性或多项式方程）中的任一个中时，从标准化关系生成表示标准化值 (NV) 的输出值 Y。

[0093] 如果第二外来刺激对分析物响应输出信号产生不利影响并且将由校准信息进行处理，那么对第二外来刺激重复进行标准化关系测定 140。如下文所述，图 4 中发现可以如何测定第二标准化关系以处理第二外来刺激的例子。

[0094] 在标准化值测定 150 中，通过将量化的外来刺激值 132 输入到标准化关系 142 中并且求解标准化值 152 来从标准化关系 142 测定标准化值 152。

[0095] 在标准化输出信号测定 160 中，从一个或多个分析物响应输出信号和标准化值测定一个或多个标准化分析物响应输出信号。优选地，将分析物响应输出信号除以标准化值 152 以提供标准化分析物响应输出信号 162。这优选降低外来刺激对分析物响应输出信号的影响。图 1E，如下文所述，提供了在 A1c 分析系统中的标准化输出信号测定 160 的例子。图 3D，如下文所述，提供了在单个选定的样本分析物浓度 (100mg/dL) 下的在葡萄糖分析系统中的标准化输出信号测定 160 的例子。

[0096] 在标准化参考相关性测定 170 中，测定在标准化分析物响应输出信号 162 和参考样本分析物浓度 124 之间的标准化参考相关性 172。优选地，将回归技术应用到标准化分析物响应输出信号 162 和参考样本分析物浓度 124 以测定标准化参考相关性 172。可以使用线性或非线性（例如多项式）回归技术，例如在MINITAB®版本 14 或版本 16 统计软件包 (MINTAB, INC., State College, PA)、Microsoft Excel 或提供回归技术的另一种统计分析软件包中可得到的那些回归技术。优选地，多项式回归用来测定标准化参考相关性 172。

[0097] 例如，在 MS Excel 版本 2010 中，可以选择可通过趋势线布局图表工具访问的线性趋势线选项来进行线性分析，同时可以选择多项式趋势线选项来进行非线性多项式分析。

其他回归技术可以用来测定标准化参考相关性 172。图 1F，如下文所述，提供了在 A1c 分析系统中的标准化参考相关性测定 170 的例子。图 1G 示出了表示为标准化校准曲线的测定的标准化参考相关性 172。图 3E，如下文所述，提供了在葡萄糖分析系统中的标准化参考相关性测定 170 的例子。

[0098] 当使用线性回归时，标准化参考相关性 172 会是 $Y = mX+b$ 的形式，其中 m 是回归线的斜率并且 b 是回归线 - 的截距。当使用诸如多项式等非线性回归时，标准化参考相关性 172 可以是 $Y = b_2*X^2+b_1*X+b_0$ 等的形式，其中 b_2、b_1 和 b_0 是多项式的系数。标准化参考相关性 172 优选作为校准信息的一部分储存在测量装置中以备将来在样本的分析期间使用。在测量装置中，Y 是在分析期间测定的标准化分析物响应输出信号值，X 是如从标准化参考相关性 172 测定的样本的分析物浓度。如下文进一步讨论的，对于线性标准化参考相关性，当将 Y 值（标准化输出信号的值）输入到方程式中时可以求解 X 值（样本分析物浓度）。对于二次多项式形式的标准化参考相关性，标准化参考相关性 172 可以以标准化校准曲线的形式表示为 $X = c_2*Y^2+c_1*Y+c_0$，其中 c_2、c_1 和 c_0 是方程式的系数。输入到这种关系的标准化输出信号将生成分析物浓度。

[0099] 图 B 示出了考虑到具有标准化校准信息的第二外来刺激的任选的校准方法 102。校准方法 102 提供了用于结合到具有减少的刺激效果的生物传感器系统的测量装置中的来自第二外来刺激的标准化校准信息。优选地，校准方法 102 也在测量装置的工厂校准期间进行。校准方法 102 也可以在实验室或类似环境中进行。该校准方法可以通过测量装置、诸如计算机等一种或多种分析装置或测量装置和分析装置的组合进行。校准方法 102 与校准方法 100 组合以提供来自第一外来刺激和第二外来刺激的标准化校准信息。因此，当为生物传感器系统的测量装置测定校准信息时可以使图 A 和图 B 组合。

[0100] 如果考虑到对分析物响应输出信号产生不利影响的第二外来刺激，例如当第一外来刺激是温度时样本的血细胞比容浓度，那么可以按照外来刺激量化 130 测定至少两个第二量化的外来刺激值 134。图 4D 和图 4E，如下文所述，提供了在葡萄糖分析系统中的测定第二量化的外来刺激值 134 的例子。

[0101] 然后，可以按照标准化关系测定 140 测定第二标准化关系 147，但是其中在单个选定的样本分析物浓度下测定在标准化分析物响应输出信号 162 和第二量化的外来刺激值 134 之间的第二标准化关系 147。第二标准化关系 147 优选作为校准信息的一部分储存在测量装置中。图 4F，如下文所述，提供了在葡萄糖分析系统中的测定第二标准化关系 147 的例子。

[0102] 在第二外来刺激的情况下，进行第二标准化值测定 155。通过将第二量化的外来刺激值 134 输入到第二标准化关系 147 中并求解第二标准化值 157 来从第二标准化关系 147 测定第二标准化值 157。

[0103] 在第二外来刺激的情况下，进行第二标准化输出信号测定 165。通过将标准化分析物响应输出信号 162 除以第二标准化值 157 来测定第二标准化分析物响应输出信号 167。图 4G，如下文所述，提供了在葡萄糖分析系统中的测定第二标准化分析物响应输出信号 167 的例子。

[0104] 在第二外来刺激的情况下，进行第二标准化参考相关性测定 175。如之前所述，通过回归技术测定在第二标准化分析物响应输出信号 167 和参考样本分析物浓度 124 之间的

第二标准化参考相关性 177。图 4H，如下文所述，提供了在葡萄糖分析系统中测定第二标准化参考相关性 177 的例子。

[0105] 第二标准化参考相关性 177 优选作为校准信息的一部分储存在测量装置中。在这种情况下，标准化参考相关性 172 不必储存在测量装置中并且优选不在分析期间使用。类似地，校准信息可以考虑三种以上的外来刺激，其中各外来刺激除了为由各自的标准化关系表示的组合的外来刺激所准备的单一标准化参考相关性之外还由储存在测量装置中的各自的标准化关系表示。

[0106] 图 C 示出了利用标准化参考相关性测定具有减少的外来刺激效果的样本的分析物浓度的分析方法 200。当使用者激活生物传感器系统的测量装置以分析诸如血液等样本时，优选进行分析方法 200。优选地，样本是包含红细胞的血液。光学和 / 或电化学方法可以用来分析样本。

[0107] 在分析分析物响应输出信号测量 220 中，从样本测量一个或多个分析物响应输出信号值 222，其中该分析物响应输出信号值受到诸如物理特性、环境状况和 / 或制造偏差等一种或多种外来刺激的影响，该外来刺激导致结合到分析物响应输出信号中的值中的误差。从利用光学和 / 或电化学方法（例如门控安培法和门控伏安法等）从样本生成的一个或多个输出信号测量分析物响应输出信号值 222。

[0108] 在分析外来刺激量化 230 中，测量一个或多个外来刺激响应输出信号。响应于外来刺激响应输出信号测定一个或多个量化的外来刺激值。从方法 100 可知，可以响应于第一外来刺激测定单个或第一量化的外来刺激值 232。方法 100 和 102 可以组合以响应于第一外来刺激测定第一量化的外来刺激值 232 以及响应于第二外来刺激测定第二量化的外来刺激值 234。可以测定其他量化的外来刺激值。因此，针对由校准信息处理的各外来刺激测定量化的外来刺激值。从利用光学和 / 或电化学方法（例如门控安培法和门控伏安法等）从样本生成的一个或多个输出信号测量量化的外来刺激响应输出信号。

[0109] 在分析标准化值测定 250 中，一种或多种之前测定的标准化关系用来测定一个或多个标准化值。之前测定的标准化关系的例子是之前描述的标准化关系 142 和之前描述的第二标准化关系 147。例如，将分析物响应输出信号值 222 和量化的外来刺激值 232 中的一个或多个输入标准化关系 142 中。类似地，将分析物响应输出信号值 222 和量化的外来刺激值 234 中的一个或多个输入第二标准化关系 147 中。以这种方式，外来刺激值 232 或 234 可以输入标准化关系 142 或 147 中以测定标准化值。因此，将一个或多个分析物响应输出信号值和一个或多个量化的外来刺激值输入一种或多种标准化关系中以测定一个或多个标准化值。

[0110] 在标准化分析物响应输出信号测定 260 中，响应于一个或多个分析物响应输出信号值和一个或多个标准化值测定至少一个标准化分析物响应输出信号值。将一个或多个分析物响应输出信号值 222 除以标准化值以测定一个或多个标准化分析物响应输出信号值 262（在一种外部刺激的情况下）或 267（在两种外部刺激的情况下）。优选地，一个分析物响应输出信号值用来测定一个标准化分析物响应输出信号值。

[0111] 在分析分析物浓度测定 280 中，响应于一种或多种标准化参考相关性和一个或多个标准化分析物响应输出信号测定样本中的一个或多个分析物浓度。优选地，诸如之前描述的标准化参考相关性 172 或 177 等之前测定的标准化参考相关性将一个或多个标准化分

析物响应输出信号值 262 或 267 变换成样本的分析物浓度 282。优选地，之前描述的标准化参考相关性 172 或 177 将一个标准化分析物响应输出信号值变换成样本的分析物浓度。当测定样本的两个以上的分析物浓度时，可以对分析物浓度求平均以提供样本的平均分析物浓度。

[0112] 在 290 中，样本的分析物浓度 282 可以被显示、储存以用于将来参考、补偿和 / 或用于额外的计算。

[0113] 因此，在分析方法 200 中，将标准化参考相关性 172 或 177 结合到测量装置中并且与常规参考相关性会如何用来将主输出信号值转化成测定的样本分析物浓度类似地使用。除了在分析方法 200 中之外，不是主输出信号值被参考相关性 122 变换，而是标准化分析物响应输出信号值 262 或 267 分别被标准化参考相关性 172 或 177 变换以提供具有减少的来自一种或多种外来刺激的效果的样本的分析物浓度。

[0114] 图 1 所示的利用校准的这种标准化过程测定用于结合到测量装置中的具有减少的外来刺激效果的校准信息的校准方法 100 的例子是针对 A1c 分析系统。在本实施例中，样本是血液；样本分析物是血液样本中的 A1c 并且样本分析物浓度是样本 A1c%。A1c 是主刺激，而 THb 是外来刺激。整个图 1 计算的数字值对于不同的分析系统或甚至不同的 A1c 分析系统将是不同的。这种方法用图 1B ～图 1H 中的图表示。

[0115] 图 1A 示出了在四个 THb 浓度 (85mg/mL、125mg/mL、175mg/mL 和 230mg/mL) 下的从测量装置的区 1 检测器记录的 A1c 反射率信号相对于参考样本分析物浓度 (A1c%) 的图。对包含已知浓度的 A1c 的各血液参考样本重复进行两次 A1c%测量。因为从测量装置的区 1 检测器测量的 A1c 反射率信号是依赖 THb 的，所以对于同一 A1c%参考样本分析物浓度来说 A1c 反射率信号是分散开的。因此，即使对于一组参考样本来说实际 A1c 浓度是相同的，从区 1 检测器测量的针对参考样本组的测量的 A1c 反射率信号也由于 THb 外来刺激而不同。附图中所示出的方程式示出了用于这种分析的常规参考相关性，其中通过这个方程式将来自测量装置的输出信号直接转化成分析物浓度。注释了测定的参考相关性 ($Y = -0.0006x^2+0.0263x+0.2239$) 和来自参考样本的输出信号之间的较低的 R^2相关性 0.6272。

[0116] 图 1B 示出了如从测量装置的区 2 检测器测定的在四个 THb 参考样本浓度 (85mg/mL、125mg/mL、175mg/mL 和 230mg/mL) 下的相对恒定的 THb 输出信号。因此，对于各 THb 浓度来说，测定外来刺激 THb 的平均信号值。例如，在 85mg/mL THb 样本浓度下通过求平均从图 1B 测定～ 0.76 的量化的外来刺激信号值。求平均之外的方法可以用来量化来自次级输出信号的外来刺激。

[0117] 图 1C 示出了为血液样本中四个不同的 THb 浓度分离开的从测量装置的区 1 检测器记录的各自的 A1c 反射率信号。这允许选择单一样本分析物浓度，在该浓度下可以从主输出信号测定合成的外来刺激响应输出信号值。在本实施例中，利用一般关系 (R_{A1c}= Slope*A1c% +Int，其中 R_{A1c}是来自测量装置的输出信号，Slope 和 Int 分别是在各 THb 样本浓度下的线性回归线的斜率和截距，A1c%是样本分析物浓度) 在 4 个 THb 样本浓度的各个浓度下测定线性回归线。可以使用其他回归技术。

[0118] 在附图上示出了在 85THb mg/mL 和 230THb mg/mL 下测定的回归方程，但是也测定了在 127 和 175mg/mL THb 下的回归方程。在本实施例中，选择单个选定的样本分析物浓度

9A1c%来从主输出信号测定合成的外来刺激响应输出信号值。因此，在本实施例中，参考样本分析物浓度9%从85mg/mL THb回归线对85mg/mL THb样本提供了～0.36A1c合成的外来刺激响应输出信号值以及从230mg/mL THb回归线对230mg/mL THb样本提供了～0.44A1c合成的外来刺激响应输出信号值。

[0119] 合成的外来刺激响应输出信号值可以以从选定的参考样本分析物浓度测定回归线以及"回测定"主输出信号值之外的其他方式来测定。例如，对于所有的四个THb水平可以在一个参考样本A1c%浓度下从测量的主输出信号值选择合成的外来刺激响应输出信号值。同时测量的单个THb反射率信号与A1c反射率信号配对以形成四对A1c和THb数据并构建A1c反射率相对于THb反射率的曲线图，这也将形成标准化关系。

[0120] 虽然图1C中选择了单个选定的样本分析物浓度9A1c%，但是也可以优选选择6～11A1c%的参考样本分析物浓度。因此，在其下测定合成的外来刺激响应输出信号值的单个选定的样本分析物浓度优选在参考样本分析物浓度范围的中间附近，但是可以在中间的任一边以向分析系统提供所希望的测量性能。

[0121] 下面的表A示出了从在同一水平的THb下的THb信号的平均值和通过如图1C中的上述一般回归关系(R_{A1c}= Slope*A1c% +Int)在单个A1c%浓度(在本实施例中为9A1c%)下计算的对应合成的THb响应输出信号收集的数据对。

[0122]

THb (mg/mL)	85	125	175	230
THb/70 (mg/mL)*	1.214	1.786	2.5	3.286
来自图1B的量化的(平均)次级输出信号	0.7572	0.7302	0.7069	0.6796
来自图1C的在A1c浓度(9)下的合成的THb响应输出信号值	0.3659	0.3964	0.4183	0.4400

[0123] 表A：合成的和平均THb信号值

[0124] *对样本进行稀释以获得适于检测器的信号。

[0125] 图1D是这四对数据的相关性曲线图，其中在Y轴上绘制了从A1c输出信号提取的合成的外来刺激响应输出信号，在X轴上绘制了THb信号(次级输出信号)，即外来刺激。图1D也提供了测定标准化关系140的例子，其在单个A1c浓度下的合成的外来刺激响应输出信号和响应于样本THb浓度的次级输出信号之间建立相关性。

[0126] 回归技术，在这种情况下为多项式(a_2*THb^2+a_1*THb+a_0，其中a_2、a_1和a_0是曲线拟合的二次多项式标准化函数的系数并且THb是针对THb的量化的外来刺激值)，然后用来测定在单个选定的样本分析物浓度下的合成的外来刺激响应输出信号和量化的外来刺激信号之间的标准化关系142。针对来自本实施例的A1c分析数据的特定的标准化关系在图1D中作为$Y = -3.34X^2+3.85X-0.63$示出，因而示出了针对本实施例的特定的二次多项式系数，其中Y是在单个选定的分析物浓度下响应于外来刺激计算的合成的外来刺激响应输出信号，X是量化的外来刺激信号/值。不同的分析将具有不同的回归系数。当将X的值(量化的外来刺激信号值)输入到二次多项式中时，Y的值通过这种标准化关系生成，其是标准化值(NV)。

[0127] 图1E提供了利用标准化值测定标准化分析物响应输出信号162的例子。因此，利

用图 1D 的标准化关系和标准化值将来自图 1C 的 A1c 反射率信号转换成标准化主输出信号值。从标准化关系和标准化值测定标准化分析物响应输出信号可以通过关系 $NR_{A1c} = R_{A1c}/NV_{A1c}$ 表示，其中 NR_{A1c} 是 THb 标准化分析物响应输出信号，R_{A1c} 是来自测量装置的 A1c 反射率信号，NV_{A1c} 是标准化值。

[0128] 优选地，对分析物响应输出信号的全部或大部分进行标准化分析物响应输出信号的测定以测定校准信息。然而，取决于分析系统可以使用一子组分析物响应输出信号。因此，在图 1E 中，来自图 1C 的分析物响应输出信号值利用来自图 1F 的标准化值通过图 1D 中测定的标准化关系经过除以对应的标准化值来进行标准化以提供在图 1E 中所示的标准化分析物响应输出信号值，其然后被组合到图 1F 中。

[0129] 图 1F 提供了从图 1E 的标准化分析物响应输出信号测定标准化参考相关性的例子。绘制了 NR_{A1c} 相对于参考样本分析物浓度（A1c％）的图并且通过回归技术对其进行曲线拟合以提供标准化参考相关性。回归技术，在这种情况下为二次多项式（a_2*A1c％^{2}+a_1*A1c％ +a_0，其中 a_2、a_1 和 a_0 是多项式的系数并且 A1c％是参考样本的分析物浓度），用来测定标准化参考相关性。

[0130] 针对来自本实施例的 A1c 分析数据的特定的标准化参考相关性在图 1F 中作为 $y = -0.1119X^2+0.0697X+0.538$ 示出，因而示出了针对本实施例的特定的二次多项式系数。不同的分析将具有不同的系数。图 1F 中也示出了 $R^2 = 0.9663$，示出了标准化主输出信号和 A1c％的参考样本分析物浓度之间良好的吻合性。在标准化参考相关性的这种测定中，标准化主输出信号是因变量，而 A1c％的参考样本分析物浓度是回归的自变量。因此，这种标准化参考相关性可以看成从 A1c％的参考样本分析物浓度输出标准化分析物响应输出信号值。

[0131] 图 1G 提供了从图 1E 的标准化分析物响应输出信号值测定标准化参考相关性的另一个例子。在图 1G 中，标准化分析物响应输出信号是自变量，而 A1c％的参考样本分析物浓度是回归的因变量。因此，横轴 x 和纵轴 y 是相反的。在本实施例中，测定的标准化参考相关性是 $y = 28.26X^2-28.996X+0.522$ 并且 R^2 相关性是 0.962，再次示出了标准化分析物响应输出信号和 A1c％的参考样本分析物浓度之间良好的吻合性。不同的分析将具有不同的回归系数。因此，这种标准化参考相关性可以看成从标准化分析物响应输出信号值输出 A1c％的参考样本分析物浓度。

[0132] 以这种方式表达的标准化参考相关性可以被认为是“标准化校准曲线”。提供样本分析物浓度的这种标准化校准曲线优选储存在测量装置中以备将来如在生物传感器系统从主输出信号测定分析物浓度时在分析 200 期间使用，而不是相反如将从图 1F 的标准化参考相关性获得。因此，当将 X 的值（标准化输出信号）输入到二次多项式方程中时，获得 Y 的值（分析物浓度）。

[0133] 图 1H 通过使标准化分析物响应输出信号值叠加在图 1G 的标准化校准曲线上来将标准化分析物响应输出信号与该曲线的形式的标准化参考相关性进行比较。另一个兴趣点是针对常规参考相关性的在图 1A 中测定的 R^2 相关性值 0.6272 和针对标准化参考相关性的在图 1F 中测定的 R^2 相关性值 0.9663 的比较。与常规测量的输出信号值 / 参考相关性相比，标准化参考相关性中的大约 54％（0.9663-0.6272/0.6272*100）的改进在测定分析物样本浓度中建立了标准化输出信号值 / 标准化参考相关性的优越性。

[0134] 包含标准化关系和标准化参考相关性的所产生的校准信息可以以查询表以及一个或多个方程式等的形式储存在测量装置中。其他关系也可以储存在测量装置中。在样本分析期间校准信息被测量装置的处理器用来测定样本的分析物浓度。

[0135] 在具有一种主输出信号的测量装置中，以上技术可以用来测定针对一种主输出信号的校准信息。然而，对于具有多于一种的主输出信号的测量装置，可以针对各主输出信号测定校准信息，以及从组合的不同的校准信息测定分析物浓度。例如，在具有多于一个的利用其测定主刺激的区 1 检测器的 A1c 测量装置中，校准信息可以针对各检测器通道进行测定，然后通过对从各检测器通道测定的初始分析物浓度求平均来测定最终分析物浓度。

[0136] 可选择地，对于具有同一主刺激的多于一种的主输出信号的测量装置，输出信号起初可以组合并且可以针对组合的信号测定校准信息。独立的输出信号然后可以利用组合的校准信息变换成分析物浓度以提供然后组合以提供样本的分析物浓度的初始分析物浓度，或者组合的输出信号可以通过针对组合的信号测定的校准信息变换以提供样本的分析物浓度。例如，在具有多于一个的区 1 检测器的 A1c 测量装置中，可以对来自两个检测器的输出信号求平均并且可以针对来自两个检测器的平均的输出信号测定校准信息。然后，平均的输出信号可以通过从平均的输出信号测定的校准信息变换成样本的分析物浓度或者来自两个通道的输出信号通过从平均的输出信号测定的校准信息变换成样本的分析物浓度以提供两个初始分析物浓度，然后对这两个初始分析物浓度求平均以提供样本最终的分析物浓度。

[0137] 图 2 所述的实施例示出了针对测量装置的两个各自检测器通道中的每个测定独立校准信息的益处，其中两个输出信号通道中的每个都包括 A1c 和 THb 响应信息。整个图 2 计算的数字值对于不同的分析系统或甚至不同的 A1c 分析系统将是不同的。

[0138] 图 2A 示出了针对具有两个检测通道的 A1c 测量装置的两个通道的标准化关系。因此，对于本实施例来说，图 2A 示出了针对来自区 1 通道一检测器 (Ch1) 的主输出信号和来自区 2 通道二检测器 (Ch2) 的次级输出信号以及针对来自区 1 通道三检测器 (Ch3) 的主输出信号和来自区 2 通道四检测器 (Ch4) 的次级输出信号的两个单独的标准化关系。因此，Ch1 和 Ch3 提供了 A1c 响应输出信号，同时 Ch2 和 Ch4 提供了 THb 响应输出信号。

[0139] 图 2B 示出了 A1c 测量装置的 Ch1 和 Ch3 的各自标准化校准曲线。在图上也绘制了从 Ch1/Ch2 测定的标准化输出信号、从 Ch3/Ch4 测定的标准化输出信号以及这些标准化输出信号的平均值。如之前所述，多项式回归技术用来测定标准化校准曲线形式的标准化参考相关性。

[0140] 图 2C 示出了针对参考样本的来自两个各自通道 (Ch1&Ch3) 的标准化 A1c 反射率信号。可以对两个初始 A1c%浓度求平均以提供最终 A1c 浓度。下面的表 1 和表 2 中的平均值和偏差百分比标准差 (SD) 值分别示出了单独的各自通道结果以及针对校准和测量装置样本分析的平均 A1c 结果。对于利用参考样本的两个校准以及利用校准信息通过测量装置进行的分析来说，相对于各自的通道结果改进了平均的测定分析物浓度。从表 2 可知，对于平均值来说，Ch1 偏差标准差减小了近百分之九 (8.8%) (5.58-5.09/5.58*100)，而 Ch2 偏差标准差减小了 18%以上 (18.3%) (6.23-5.09/6.23*100)。因此，对于平均的测定分析物浓度来说，偏差标准差平均减小了大于 10% (13.5%) (8.8+18.3/2) 的值。

[0141]

	偏差% 1	偏差% 3	偏差% _Avg
平均值	0.274	0.295	0.156
SD	5.25	5.52	3.97

[0142] 表 1 :校准

[0143]

	偏差% 1	偏差% 3	偏差% _Avg
平均值	0.055	0.184	0.120
SD	5.58	6.23	5.09

[0144] 表 2 :分析

[0145] 除了针对各通道测定校准信息然后将针对各通道测定的中间样本浓度组合之外，来自各通道的输出信号也可以首先进行组合然后用来针对组合的信号测定校准信息。图 2D 示出了通过首先对来自测量装置的 Ch1 和 Ch3 的 A1c 反射率输出信号求平均所测定的标准化关系。因此，对用来测定图 2A 中所示的两种标准化关系的相同输出信号首先求平均。图 2E 示出了针对来自测量装置的 Ch1 和 Ch3 的平均 A1c 反射率信号测定的标准化校准曲线形式的标准化参考相关性。来自测量装置的各通道的输出信号然后可以利用这种校准信息转换成初始分析物浓度并且可以对初始分析物浓度求平均以测定最终样本分析物浓度。

[0146] 图 3 示出了对来自电化学葡萄糖分析系统的主输出信号具有减少的温度外来刺激效果的测定校准信息的校准方法 100 的例子。在本实施例中，样本是血液并且样本分析物是葡萄糖（主刺激）。样本分析物浓度是葡萄糖的样本浓度并且外来刺激是温度和血细胞比容。

[0147] 对于温度效果，使在 40Hct%（在该 Hct%下测定使输出电流和参考样本分析物浓度相联系的常规参考相关性）和不同的温度下由测量装置从参考样本测量的电流标准化。在这种类型的葡萄糖系统中，工作电极和对电极提供主输出信号，同时温度传感器提供次级输出信号。这个过程由图 3A ～图 3F 中的图表示。整个图 3 计算的数字值对于不同的分析系统或甚至不同的葡萄糖分析系统将是不同的。

[0148] 图 3A 绘制了在不同的温度和 40Hct%下的从测量装置获得的电流相对于葡萄糖的参考样本分析物浓度的图。在较高的葡萄糖的样本浓度下电流由于温度的变化而变得更广泛地分布。虽然由测量装置从血液中包含～ 80mg/dL 的葡萄糖的参考样本测定的电流紧紧围绕～ 75nA，但是由测量装置从包含～ 320mg/dL 和～ 580mg/dL 的葡萄糖参考样本测定的电流广泛地间隔开。事实上，如图 3A 所示，从这些电流测定的线性回归线显示出了仅 0.6 的 R^2 相关性。该图可以看成显示如之前在图 1C 中观察到的外来刺激对分析物响应输出信号的效果。在图 1C 中，外来刺激是样本 THb，而在图 3A 中其是温度。

[0149] 图 3B 将这些主输出信号电流按温度分开，在该温度下记录了这些主输出信号电流。因此，即使参考样本的分析物浓度在各温度下是相同的，温度也是对来自测量装置的分析物响应输出信号电流产生不利影响的外来刺激。在本实施例中，利用一般关系 $i_G=$

Slope*G_{Ref}+Int 在 5 个温度的各个温度下测定线性回归线，其中 i_G是来自测量装置的葡萄糖响应电流，G_{Ref}是葡萄糖的参考样本分析物浓度，从该浓度测定合成的外来刺激响应输出信号值。其他技术可以用来测定合成的外来刺激响应输出信号值。

[0150] 在图 3B 中，选择两个葡萄糖的样本浓度 100 和 500mg/dL，在该浓度下测定在它们对应的温度下的合成的外来刺激响应输出信号值。因此，与其中选择单个选定的样本分析物浓度 9％的 A1c 系统中不同，本实施例示出了可以在多于一个的单个选定的样本分析物浓度下测定合成的外来刺激响应输出信号值。可以使用 100 和 500mg/dL 之外的单个选定的样本分析物浓度。

[0151] 下表 3 通过利用与之前相对于 A1c 实施例所述的相似的回归方程（i_G= Slope*G_{Ref}+Int）从各自的回归线提供了在 100 和 500mg/dL 葡萄糖样本分析物浓度下针对各温度获得的合成的外来刺激响应输出信号值。当在目标温度下进行参考样本的分析时，表中的温度值从所有测量的温度求平均。因此，表 3 形成了在选定的单个葡萄糖浓度 100 或 500mg/dL 下的两组对，各组含有 7 对输出信号 - 温度数据。

[0152]

平均温度，℃	6.0	10.9	15.9	22.0	30.4	35.1	40.0
500mg/dL	205.78	283.53	373.96	462.61	639.89	705.54	809.11
100mg/dL	41.16	56.71	74.79	92.52	127.98	141.11	161.82

[0153] 表 3 :合成的输出信号值

[0154] 因此，与图 1C 所述的按 THb 样本浓度分开相对，图 3B 将来自测量装置的输出电流按温度分开。仅针对测试的七个温度中的五个温度绘制了相关性线，以使得曲线图不拥挤。

[0155] 图 3C 示出了在两个单独的单个葡萄糖浓度 100 和 500mg/dL 下获得的合成的外来刺激响应输出信号相对于量化的外来刺激（温度）之间的相关性以测定标准化关系。图 3C 也提供了测定标准化关系 140 的例子，其将温度考虑用于分析物响应输出信号的标准化。图 3C 的纵轴 y 示出了针对五个温度的如从图 3B 的回归线合成并且在单个选定的葡萄糖样本分析物浓度 100 和 500mg/dL 下测定的外来刺激响应值。图 3C 的横轴 x 示出了在各目标温度下针对外来刺激温度测定的平均值。

[0156] 回归技术，在这种情况下为多项式（$a_2*T^2+a_1*T+a_0$，其中 a_2、a_1和 a_0是曲线拟合的二次多项式标准化函数的系数和 T 是针对温度的量化的外来刺激值），然后用来测定在单个选定的样本分析物浓度下的合成的外来刺激响应输出信号和量化的外来刺激信号之间的标准化关系 142。针对来自本实施例的 100 和 500mg/dL 葡萄糖分析数据的特定的标准化关系在图 3C 中表示为 $y = 0.0104X^2+3.0646x+22.366$（100mg/dL）和 $y = 0.05214X^2+15.3228x+111.832$（500mg/dL），因而示出了针对本实施例的特定的二次多项式系数，其中 Y 是在单个选定的分析物浓度下响应于外来刺激信号计算的合成的外来响应输出信号，X 是量化的外来刺激信号 / 值。不同的分析将具有不同的系数。当将 X 的值（量化的外来刺激信号值）输入到二次多项式中时，Y 的值通过这种标准化关系生成，其是标准化值（NV）。该图可以被看成与图 1D 类似；然而，在本实施例中，标准化值可以在两个参考样本分析物浓度下测定。

[0157] 图3D提供了在100mg/dL下从标准化值测定标准化分析物响应输出信号162的例子。因此，来自图3B的纵轴y的分析物响应输出信号通过将分析物响应输出信号除以从图3C的标准化关系获得的它们的对应标准化值而转换成标准化主输出信号值。从标准化关系和标准化值测定标准化分析物响应输出信号可以通过关系 $Ni_G = i_{measured}/NIV_{Temp}$ 表示，其中 Ni_G 是温度标准化分析物响应输出信号，$i_{measured}$ 是来自测量装置的葡萄糖响应电流，NV_{Temp} 是从温度标准化测定的标准化值。因此，针对不同的温度的图3B的五个各自的线如图3D所示归化成一组紧密堆叠的线。如之前所讨论的，优选地，对分析物响应输出信号的全部或大部分进行标准化分析物响应输出信号的测定以测定校准信息。

[0158] 图3E提供了从图3D的标准化分析物响应输出信号值测定标准化参考相关性的例子。绘制出了 Ni_G 相对于参考样本分析物浓度的图并且通过回归技术对其进行曲线拟合以提供标准化参考相关性。回归技术，在这种情况下为线性的 (Y = Slope*X+Int)，用来测定标准化参考相关性，其中在分析200期间，Y是由测量装置测定的标准化主输出信号并且X是样本的参考分析物浓度。因此，当将Y值（标准化输出信号）输入到线性回归方程中时，通过求解该方程式获得X值（分析物浓度）。

[0159] 针对来自本实施例的葡萄糖分析数据的特定的标准化参考相关性在图3E中表示为 Y = 0.01033X-0.14082，因而示出了本实施例的线性系数。不同的分析将具有不同的系数。在图3E中也示出了 $R^2 = 0.9946$，示出了标准化主输出信号和参考样本分析物浓度之间良好的吻合性。因此，这种标准化参考相关性可以看成从标准化分析物响应输出信号值提供针对葡萄糖的测定的样本分析物浓度。

[0160] 针对测量的温度 (6.0℃、10.9℃、15.9℃、22.0℃、30.4℃、35.1℃和40.0℃)，下表4中列出了在100mg/dL葡萄糖参考样本分析物浓度下的平均温度、利用常规参考相关性在各温度下获得的回归斜率和利用标准化参考相关性在各温度下获得的回归斜率。

[0161]

温度℃	常规参考相关性斜率	标准化参考相关性斜率
6.0	0.412	0.0103
10.9	0.567	0.0099
15.9	0.748	0.0101
22.0	0.925	0.0097
30.4	1.280	0.0102
35.1	1.411	0.0099
40.0	1.618	0.0100
平均斜率	0.9944	0.0100147
SD，斜率	0.4532	0.00023014

CV%	45.6	2.3

[0162] 表 4 :针对温度刺激的标准化的总结

[0163] 通过观察在标准化之前和之后的平均响应斜率和斜率的 CV%可以更好地理解测量性能的改进。利用来自测量装置的主输出信号和常规参考相关性测定的响应斜率的CV%为 45.6%。相比而言,利用所描述的标准化主输出信号和标准化参考相关性测定的响应斜率的 CV%降到了 2.3%,大约减少 95% (45.6-2.3/45.6*100)。与当来自测量装置的潜在电流由图 3A 的常规参考相关性变换时相比,当标准化输出信号电流利用图 3E 的标准化参考相关性变换成样本分析物浓度时,通过图形示出了这种降低。

[0164] 图 3F 绘制出了在标准化之前和之后归因于不同的温度 (6.0℃、10.9℃、15.9℃、22.0℃、30.4℃、35.1℃和 40.0℃) 的测定的葡萄糖浓度的偏差%。测量的电流当由常规参考相关性变换时显示出大约 ±60 的偏差%分布,同时标准化电流显示出大约 ±20 的偏差%分布。因此,与利用包含由缺少温度刺激的标准化降低的常规方法提供的校准信息的测量装置测定的样本分析物浓度相比,期望利用包括包含按照本方法的校准信息的测量装置的生物传感器系统测定的样本分析物浓度具有偏差%的大约 3 倍的降低。

[0165] 一旦温度的效果降低,那么也可以利用两步标准化过程基本上降低诸如样本血细胞比容等第二外来刺激的效果,因而将图 A 和图 B 进行组合。在这种类型的葡萄糖系统中,工作电极和对电极提供主输出信号,同时温度传感器优选提供次级输出信号并且血细胞比容电极优选提供额外的次级输出信号。响应于温度和血细胞比容的次级输出信号可能以如之前所讨论的其他方式产生。通过温度然后通过样本血细胞比容的逐步标准化通常通过使在多个温度下 (如上所述) 来自测量装置的输出电流标准化、然后利用血细胞比容标准化关系使针对多个 Hct 样本浓度所产生的温度标准化输出信号电流标准化来进行。

[0166] 图 4 示出了对来自电化学葡萄糖分析系统的主输出信号具有血细胞比容的减少的次级外来刺激效果的测定校准信息的校准方法 102 的例子。在本实施例中,样本分析物是葡萄糖 (主刺激) 并且样本分析物浓度是血液样本中的葡萄糖浓度。血液样本中的血细胞比容浓度是除了第一外来刺激温度之外的第二外来刺激。这个方法由图 4A ～图 4I 中的图表示。整个图 4 计算的数字值对于不同的分析系统或甚至不同的葡萄糖分析系统将是不同的。

[0167] 图 4A 示出了针对测试温度 (6.0℃、10.9℃、15.9℃、22.0℃、30.4℃、35.1℃和 40.0℃) 和测试 Hct 参考样本浓度 (0%、20%、40%、55%、70%) 的相对于包含已知葡萄糖浓度的参考样本的来自测量装置的输出信号电流。从血细胞比容电极获得的次级输出信号用来从具有已知血细胞比容浓度的参考样本获得 Hct 响应输出电流。正如预期的那样,由测量装置从包含～ 80mg/dL 葡萄糖分析物浓度的参考样本测定的电流紧紧围绕～ 75nA,而由测量装置从包含～ 320mg/dL 和～ 580mg/dL 葡萄糖分析物浓度的参考样本测定的电流广泛地间隔开。

[0168] 图 4B 示出了在血液样本中 40Hct%和两个单独的单个葡萄糖浓度 100 和 500mg/dL 下的温度标准化关系,并且与之前图 3C 中所示的相同,因为正在进行相同的温度刺激降低。温度标准化是在本实施例中采取的第一步以降低来自温度的外来刺激的效果,因为进行了同样的温度刺激降低。从图 4B 可知,如之前所述测定了具有减少的温度刺激的效果的

标准化分析物响应输出信号。

[0169] 图4C绘制了在本实施例中测试的Hct参考样本浓度下的来自图4A的温度标准化分析物响应输出信号值相对于葡萄糖的参考样本分析物浓度的图。正如预期的那样，即使潜在的样本分析物浓度相同，那么也观察到了对于不同的Hct浓度在较高的葡萄糖浓度下的标准化电流的显著分布。图4C可以看成与图3B相似，但是示出了与温度相对的第二外来刺激血细胞比容的效果。

[0170] 作为误差参数或外来刺激的温度优选与主刺激同时测量并且其值独立于其他因素。血液样本中的血细胞比容浓度与葡萄糖浓度一起提供，但是血细胞比容响应次级输出信号是依赖于温度的。因此，温度也是Hct响应输出信号的外来刺激并且温度的效果优选通过标准化降低。所涉及的程序首先是构建在单个选定的Hct浓度下Hct响应电流相对于温度的曲线。然后，测定从温度标准化Hct输出信号提供计算的Hct%值的Hct标准化校准曲线以备将来使用。

[0171] 与如之前分别相对于图1C和图3B针对A1c和葡萄糖所述的类似地生成合成的Hct输出信号值。在图中未示出的这种测定中，在各参考样本血细胞比容浓度下从参考样本的Hct电极记录的电流绘制在纵轴y上，而已知参考样本血细胞比容浓度绘制在横轴x上。针对各温度(6.0℃、10.9℃、15.9℃、22.0℃、30.4℃、35.1℃和40.0℃)绘制回归线并且针对各温度在40%样本血细胞比容浓度下测定合成的Hct输出信号值。

[0172] 图4D绘制了针对包含40%血细胞比容浓度的参考样本的从响应于样本的血细胞比容浓度的次级输出信号测定的合成的信号相对于温度的图。从以上操作可知，获得并绘制出了来自在其下分析参考样本的单个选定的Hct浓度40%和温度的7对合成的Hct输出信号。回归技术，在这种情况下为多项式，然后用来测定如图所示的，但是具有通式$NV_{Hct}=(b_2*T^2+b_1*T+b_0$，其中$b_2$、$b_1$和$b_0$是曲线拟合的二次多项式标准化函数的系数并且T是温度)的针对Hct的特定的标准化关系。测定Hct标准化值，并且利用一般关系$Ni_{}_{Hct}=i_{}_{Hct}/NV_{Hct}$测定标准化Hct电极电流，其中$Ni_{}_{Hct}$是温度标准化Hct电极电流，$i_{}_{Hct}$是来自Hct电极的Hct响应电流，$NV_{Hct}$是Hct标准化值。

[0173] 图4E示出了Hct的温度标准化参考相关性，其中绘制了参考样本Hct%浓度相对温度标准化Hct电极输出电流的图。如果生物传感器系统响应于干扰物提供次级输出信号，那么其他干扰物可以类似处理。

[0174] 图4F示出了在所产生的温度标准化分析物响应输出信号和参考样本Hct%值(第二外来刺激)之间确定的第二标准化关系。图4F建立了温度标准化输出信号和样本Hct%浓度之间的相关性。即，在100或500mg/dL的单个选定的葡萄糖浓度下，温度标准化输出信号基本上响应于Hct浓度(第二外来刺激)。

[0175] 回归技术，在这种情况下为多项式($c_2*Hct2+c_1*Hct+c_0$，其中c_2、c_1和c_0是曲线拟合的二次多项式标准化函数的系数并且Hct是针对Hct的第二量化的外来刺激值)，然后用来测定在单个选定的样本分析物浓度下的合成的第二外来刺激响应输出信号和量化的第二外来刺激值(参考样本血细胞比容浓度0%、20%、40%、55%和70%)之间的标准化关系。针对来自本实施例的100和500mg/dL葡萄糖分析数据的特定的标准化关系在图4F中表示为$y=-0.00008X^2-0.00456X+1.31152$(100mg/dL)和$y=-0.0004X^2-0.0228X+6.5577$(500mg/dL)，因而示出了针对本实施例的特定的二次多项式系数，其中Y是在单个选定的分

析物浓度下响应于第二外来刺激 (Hct) 的计算的合成的第二外来刺激响应输出信号，X 是量化的第二外来刺激值。不同的分析将具有不同的系数。当将 X 的值（量化的第二外来刺激信号值）输入到二次多项式时，Y 的值通过这种标准化关系生成，其是标准化值 (NV)。

[0176] 然后在 100mg/dL 下从标准化值测定第二标准化分析物响应输出信号 167。因此，来自图 4C 的纵轴 y 的温度标准化输出信号然后利用具有它们对应的标准化值的图 4F 的标准化关系转换成第二标准化主信号值。从标准化值测定标准化分析物响应信号可以通过关系 $Ni_G = i_{measured}/_{NVTemp-Hct}$ 表示，其中 Ni_G 是温度和血细胞比容标准化分析物响应信号，$i_{measured}$ 是来自测量装置的葡萄糖响应电流，$NV_{Temp-Hct}$ 是从温度和血细胞比容标准化测定的标准化值。

[0177] 图 4G 通过图形示出了在选定的葡萄糖浓度 100mg/dL 下的通过利用温度和 Hct 标准化分析物响应输出信号值所提供的由如图 4C 所示的血细胞比容的外来刺激所引入的误差的减小。因此，该图可以被看成是类似于图 3C ;然而，在本实施例中，同时使用温度和血细胞比容标准化电流。针对下限 (0%) 和上限 (70%) Hct 浓度示出了回归方程。相对于图 4C，在～ 600mg/dL 下的上限和下限 Hct 之间的发散度已从大约 4 个标准化输出信号单位（图 4C) 降低到大约 0.25 个输出信号单位（图 4G)，回归线之间的发散度降低了约 93% (4-0.25/4*100)。

[0178] 图 4H 提供了从将图 4G 的温度和血细胞比容标准化分析物响应输出信号值进行组合来测定标准化参考相关性的例子。相对于葡萄糖的参考样本分析物浓度的温度和血细胞比容标准化信号绘制在纵轴 y 上并且通过回归技术对其进行曲线拟合以提供标准化参考相关性。回归技术，在这种情况下为线性的 (Y = Slope*X+Int)，用来测定标准化参考相关性，其中在分析 200 期间，Y 是由测量装置测定的标准化主输出信号值并且 X 是测定的样本分析物浓度。

[0179] 针对来自本实施例的葡萄糖分析数据的特定的标准化参考相关性在图 4H 中表示为 Y = 0.0104X-0.1339，因而示出了本实施例的线性系数。不同的分析将具有不同的系数。在图 4H 中也示出了 $R^2 = 0.9828$，示出了标准化主输出信号和葡萄糖的参考样本分析物浓度之间良好的吻合性。因此，标准化参考相关性使标准化输出信号和样本分析物浓度相联系。当将标准化输出信号输入标准化参考相关性中时，产生样本分析物浓度。图 4H 可以看成与图 3E 类似，不同之处在于同时将温度和 Hct 标准化结合到校准信息中。

[0180] 对于从血液样本提供的血细胞比容浓度 (0%、20%、40%、55%和 70%)，表 5 中列出了具有温度和温度 / 血细胞比容标准化的参考相关性的斜率，其中 Slope/T 是来自温度标准化参考相关性的斜率并且 Slope/T/H 是来自温度和血细胞比容标准化参考相关性的斜率。

[0181]

Hct%	Slope/T 图 4C	Slope/T/H 图 4G
0	0.0133	0.0105
20	0.0126	0.0107

[0182]

40	0.0105	0.0105
55	0.0082	0.0101
70	0.0058	0.0102
平均斜率	0.0101	0.0104
SD，斜率	0.0031	0.0002
%CV	30.7	2.3

[0183] 表 5 :针对温度和血细胞比容刺激的标准化的总结

[0184] 通过观察单独针对温度标准化以及在同时针对温度和血细胞比容的标准化之后的平均响应斜率和斜率的 CV%，可以更好地理解测量性能的改进。在本实施例中，通过温度标准化参考相关性测定的响应斜率的 CV%是 30.7%。相比而言，通过所描述的温度和血细胞比容标准化参考相关性测定的响应斜率的 CV%降到了 2.3%，CV%降低大约 92%(30.7-2.3/30.7*100)，对生物传感器系统的测量性能提供了大幅提高。

[0185] 图 4I 通过图形示出了由生物传感器系统的测量装置利用常规参考相关性（偏差% _raw)、温度标准化参考相关性（偏差% _T）以及温度和 Hct 标准化参考相关性（偏差% _T/Hct）测定的分析物（葡萄糖）浓度的偏差%。图中建立了包含温度和血细胞比容刺激的输出电流组合示出了当直接通过常规参考相关性变换成样本分析物浓度时的近±100%的偏差%。从校准信息去除温度刺激允许测量装置测定偏差%为大约 ±50%的分析物浓度，而进一步去除 Hct 刺激将偏差%降低到大约 ±30%。因此，相对于常规校准信息，利用描述的标准化校准信息观察到偏差%降低大约 70%。就生物传感器系统在没有额外补偿的情况下可以从校准信息提供的测量性能而言，这是相对于常规系统的大幅改进。

[0186] 图 5 绘出了测定生物流体的样本中分析物浓度的生物传感器系统 500 的示意图。生物传感器系统 500 包括测量装置 502 和测试传感器 504。测量装置 502 可以以分析仪器来实现，包括台式装置和便携式或手持式装置等。优选地，测量装置 502 以手持式装置实现。测量装置 502 和测试传感器 504 可以适于实现电化学传感器系统、光学传感器系统及其组合等。

[0187] 生物传感器系统 500 利用按照之前描述的标准化技术开发并储存在测量装置 502 中的校准信息测定样本的分析物浓度。来自校准方法 100 和 102 中的一种或两种的校准信息可以储存在测量装置 502 中。校准信息包括一种或多种标准化关系和一种或多种标准化参考相关性。一种或两种校准方法 100 和 102 可以储存在测量装置 502 中，因此标准化校准信息可以由测量装置 502 测定。分析方法 200 可以储存在测量装置中以由生物传感器系统 500 实现。测量装置校准的方法可以提高生物传感器系统 500 在测定样本的分析物浓度时的测量性能。生物传感器系统 500 可以被用来测定分析物浓度，包括葡萄糖、A1c、尿酸、乳酸酯、胆固醇和胆红素等的浓度。虽然示出了特定的构造，但是生物传感器系统 500 可以具有其他构造，包括具有额外的部件的那些构造。

[0188] 测试传感器 504 具有形成储器 508 和具有开口 512 的通道 510 的基部 506。储器 508 和通道 510 可以由带有通风口的盖子覆盖。储器 508 限定部分封闭的容积。储器 508 可以包含诸如吸水膨胀聚合物或多孔聚合物基质等有助于保存液体样本的组合物。试剂可以沉积在储器 508 和 / 或通道 510 中。试剂可以包括一种或多种酶、粘合剂、介体及类似的物质。试剂可以包括用于光学系统的化学指示剂。测试传感器 504 具有邻近储器 508 的样本接口 514。测试传感器 504 可以具有其他构造。

[0189] 在光学传感器系统中，样本接口 514 具有用于观察样本的光门或窗口。光门可以由基本上透明的材料覆盖。样本接口 514 可以在储器 508 的相反侧具有光门。

[0190] 在电化学系统中，样本接口 514 具有与从其可以测量分析输出信号的工作电极 532 和对电极 534 连接的导体。样本接口 514 还可以包括与一个或多个附加电极 536 连接的导体，从该附加电极可以测量次级输出信号。电极可以基本上位于同一平面上或位于多于一个的平面上。电极可以设置在形成储器 508 的基部 506 的表面上。电极可以延伸或突出到储器 508 中。介电层可以部分覆盖导体和 / 或电极。样本接口 514 可以具有其他电极和导体。

[0191] 测量装置 502 包括与传感器接口 518 连接的电路 516 和任选的显示器 520。电路 516 包括与信号发生器 524、任选的温度传感器 526 和存储介质 528 连接的处理器 522。

[0192] 信号发生器 524 能够响应于处理器 522 向传感器接口 518 提供电输入信号。在光学系统中，电输入信号可以用来操作或控制传感器接口 518 中的检测器和光源。在电化学系统中，电输入信号可以由传感器接口 518 传递到样本接口 514 以向生物流体的样本施加电输入信号。电输入信号可以是电位或电流并且可以是恒定的、可变的或其组合，例如当施加具有 DC 信号偏移的 AC 信号时。电输入信号可以连续或作为多个激励、序列或周期施加。信号发生器 524 也是可以作为生成器 - 记录器而能够记录来自感器接口的输出信号。

[0193] 任选的温度传感器 526 能够测定测量装置 502 的环境温度。样本的温度可以从测量装置 502 的环境温度估计、从输出信号计算或假定为与测量装置 502 的环境温度相同或相似。温度可以使用热敏电阻、温度计或其他温度感测装置测量。其他技术可以用来测定样本温度。

[0194] 存储介质 528 可以是磁、光学或半导体存储器以及其他存储装置等。存储介质 528 可以是固定存储装置以及诸如存储卡等远程访问的可移动存储装置等。

[0195] 处理器 522 能够利用储存在存储介质 528 中的计算机可读软件代码和校准信息实施分析物分析方法。处理器 522 可以响应于测试传感器 504 在传感器接口 518 上的有无以及响应于使用者输入向测试传感器 504 施加样本等起动分析物分析。处理器 522 能够指导信号发生器 524 向传感器接口 518 提供电输入信号。处理器 522 能够接收来自温度传感器 526 的样本温度。处理器 522 能够接收来自传感器接口 518 的输出信号。

[0196] 在电化学系统中，分析物响应主输出信号响应于样本中分析物的反应从工作电极 532 和对电极 534 生成。次级输出信号也可以从附加电极 536 生成。在光学系统中，传感器接口 518 的检测器接收主输出信号和任意次级输出信号。输出信号可以利用光学系统和电化学系统等生成。处理器 522 能够利用储存在存储介质 528 中的校准信息从输出信号测定分析物浓度。分析物分析的结果可以输出到显示器 520、远程接收器（未示出）和 / 或可以储存在存储介质 528 中。

[0197] 使参考样本分析物浓度和来自测量装置 502 的输出信号相联系的校准信息可以以图形、数学及其组合等表示。校准信息优选表示为相关方程式，其可以由储存在存储介质 528 中的程序号 (PNA) 表或其他查询表等表示。

[0198] 关于实施分析物分析的指令也可以由储存在存储介质 528 中的计算机可读软件代码提供。该代码可以是目标代码或描述或控制所述的功能性的任意其他代码。来自分析物分析的数据可以经受一种或多种数据处理，包括处理器 522 中衰减率、K 常数、比率、函数

等的测定。

[0199] 在电化学系统中，传感器接口 518 具有与测试传感器 504 的样本接口 514 中的导体连接或电连通的触头。传感器接口 518 能够通过触头将来自信号发生器 524 的电输入信号传递到样本接口 514 中的连接器。传感器接口 518 也能够通过触头将来自样本的输出信号传递到处理器 522 和 / 或信号发生器 524。

[0200] 在光吸收和光产生光学系统中，传感器接口 518 包括聚集并测量光的检测器。检测器通过样本接口 514 中的光门接收来自测试传感器 504 的光。在光吸收光学系统中，传感器接口 518 也包括诸如激光和发光二极管等光源。入射光束可以具有选定为由反应产物吸收的波长。传感器接口 518 引导来自光源的入射光束通过样本接口 514 中的光门。检测器可以与光门成诸如 45° 等的角度定位以接收从样本反射回来的光。检测器可以邻近在样本的与光源相对的另一侧的光门定位以接收透过样本的光。检测器可以位于其他位置以接收反射的和 / 或透光的光。

[0201] 任选的显示器 520 可以是模拟的或数字的。显示器 520 可以包括 LCD、LED、OLED、真空荧光显示器或适于显示数字读数的其他显示器。可以利用其他显示技术。显示器 520 与处理器 522 电连通。显示器 520 可以与测量装置 502 分离开，例如当与处理器 522 无线通信时。可选择地，显示器 520 可以从测量装置 502 去除，例如当测量装置 502 与远程计算设备及药计量泵等电连通时。

[0202] 在使用中，通过将用于分析的液体样本引入开口 512 中来将该液体转移到储器 508 中。液体样本流经通道 510，在排出先前容纳的空气的同时填充储器 508。液体样本与沉积在通道 510 和 / 或储器 508 中的试剂进行化学反应。

[0203] 测试传感器 504 相对于测量装置 502 设置，使得样本接口 514 与传感器接口 518 电和 / 或光学连通。电连通包括在传感器接口 518 中的触头和样本接口 514 中的导体之间传递输入和 / 或输出信号。光学连通包括在样本接口 514 中的光门和传感器接口 518 中的检测器之间传输光。光学连通也包括在样本接口 514 中的光门传感器接口 518 中的光源之间传输光。

[0204] 处理器 522 能够指导信号发生器 524 向测量装置 502 的传感器接口 518 提供输入信号。在光学系统中，传感器接口 518 能够响应于输入信号操作检测器和光源。在电化学系统中，传感器接口 518 能够通过样本接口 514 向样本提供输入信号。测试传感器 504 能够响应于输入信号生成一个或多个输出信号。如之前所讨论的，处理器 522 能够接收响应于样本中分析物的氧化还原反应生成的输出信号。

[0205] 处理器 522 能够利用储存在存储介质 528 中的分析方法和校准信息变换输出信号以测定样本的初始分析物浓度。处理器 522 然后可以将这个初始分析物浓度报告为样本的最终分析物浓度。可选择地，处理器 522 可以利用补偿系统进一步处理样本的这个初始分析物浓度。多于一种的补偿和 / 或其他功能也可以由处理器 522 实现。

[0206] 为了提供对本申请说明书和权利要求书清楚以及更一致的理解，提供了以下定义。

[0207] “平均值”或“平均”或“求平均”包括两个以上变量的组合以形成平均变量。变量可以是数字值、代数式或科学表述等。例如，求平均可以通过使变量相加并且使和除以变量数来进行；例如在方程式 AVG = (a+b+c)/3 中，其中 AVG 是平均变量并且 a、b 和 c 是变量。

在另一个例子中，求平均包括通过平均化系数来修改各变量然后将修改的变量相加来形成加权平均值；例如在方程式 W_{AVG} = 0.2*a+0.4*b+0.4*c 中，其中 W_{AVG} 是加权平均值，0.2、0.4 和 0.4 是平均化系数，a、b 和 c 是变量。平均化系数是 0 和 1 之间的数；并且如果相加，将提供 1 或基本上为 1 的和。可以使用其他求平均的方法。

[0208] “可测量物质”表示生物传感器系统被设计成测定样本中它的有无和/或浓度的物质，并且可以是目标分析物或者样本中它的浓度响应于目标分析物的浓度的介体。

[0209] 虽然已经描述了本发明的各种实施方案，但本领域技术人员显然可以在本发明的范围做出其他实施方案和实施方式。

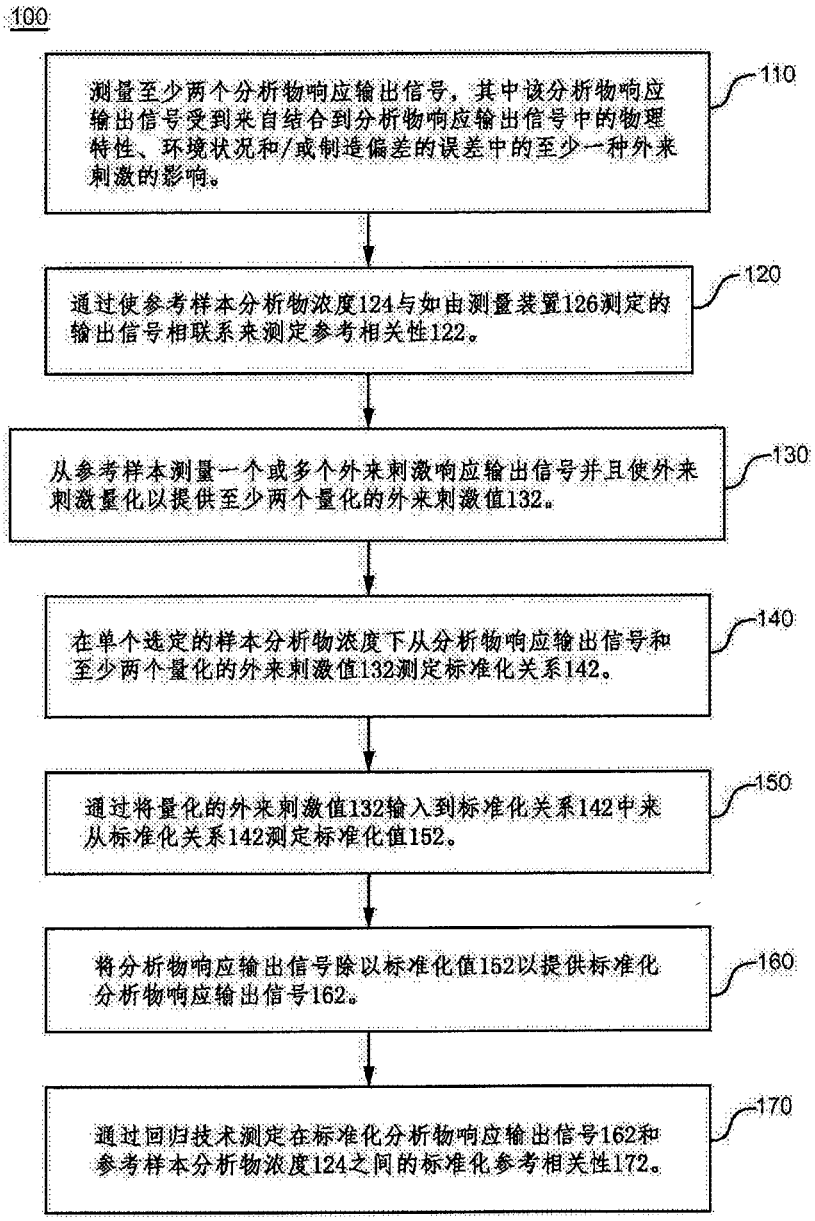

100
测量至少两个分析物响应输出信号，其中该分析物响应输出信号受到来自结合到分析物响应输出信号中的物理特性、环境状况和/或制造偏差的误差中的至少一种外来刺激的影响。
110
通过使参考样本分析物浓度124与如由测量装置126测定的输出信号相联系来测定参考相关性122。
120
从参考样本测量一个或多个外来刺激响应输出信号并且使外来刺激量化以提供至少两个量化的外来刺激值132。
130
在单个选定的样本分析物浓度下从分析物响应输出信号和至少两个量化的外来刺激值132测定标准化关系142。
140
通过将量化的外来刺激值132输入到标准化关系142中来从标准化关系142测定标准化值152。
150
将分析物响应输出信号除以标准化值152以提供标准化分析物响应输出信号162。
160
通过回归技术测定在标准化分析物响应输出信号162和参考样本分析物浓度124之间的标准化参考相关性172。
170

图 A

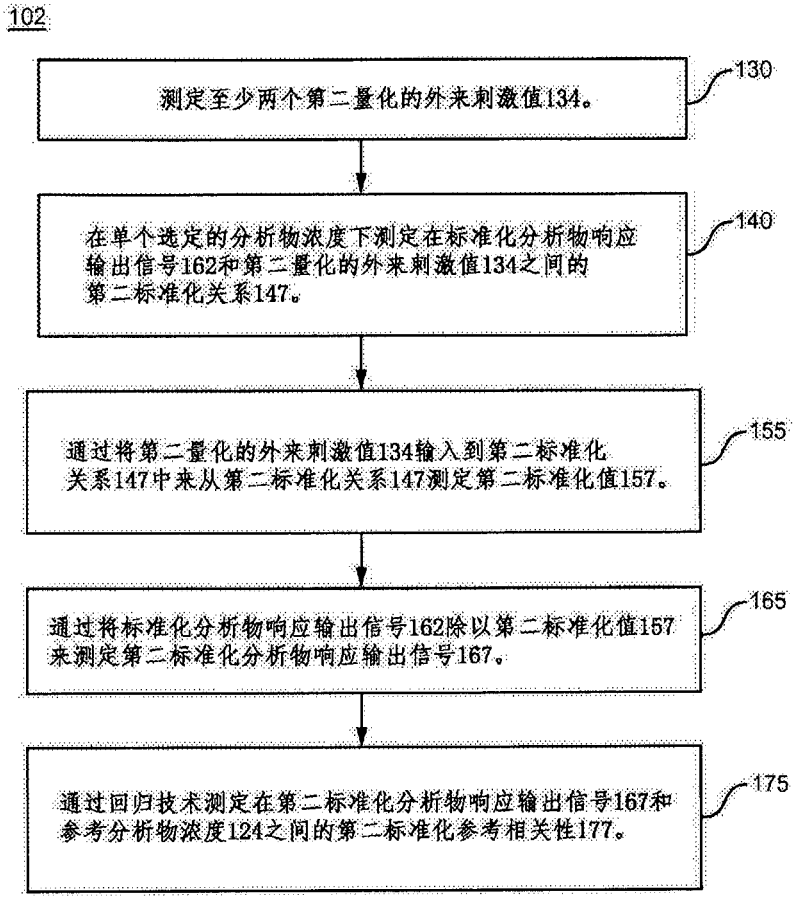

102
测定至少两个第二量化的外来刺激值134。
130
在单个选定的分析物浓度下测定在标准化分析物响应输出信号162和第二量化的外来刺激值134之间的第二标准化关系147。
140
通过将第二量化的外来刺激值134输入到第二标准化关系147中来从第二标准化关系147测定第二标准化值157。
155
通过将标准化分析物响应输出信号162除以第二标准化值157来测定第二标准化分析物响应输出信号167。
165
通过回归技术测定在第二标准化分析物响应输出信号167和参考分析物浓度124之间的第二标准化参考相关性177。
175

图 B

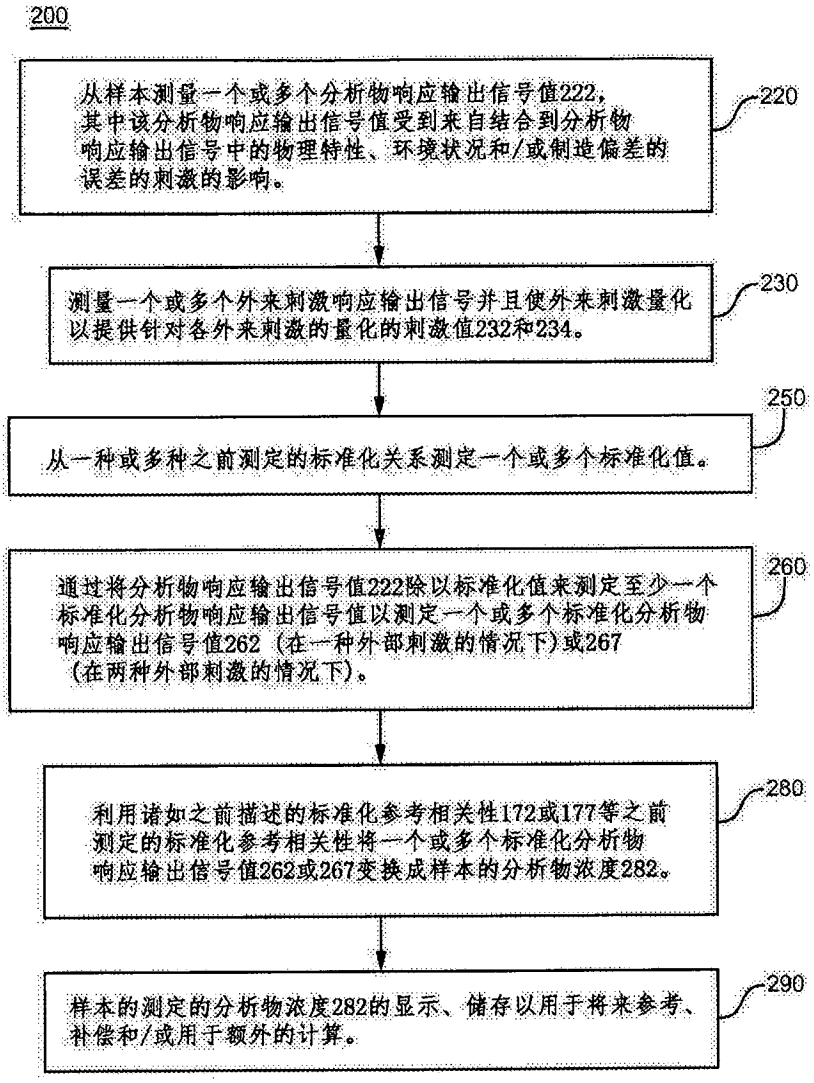

200
从样本测量一个或多个分析物响应输出信号值222，其中该分析物响应输出信号值受到来自结合到分析物响应输出信号中的物理特性、环境状况和/或制造偏差的误差的刺激的影响。
220
测量一个或多个外来刺激响应输出信号并且使外来刺激量化以提供针对各外来刺激的量化的刺激值232和234。
230
从一种或多种之前测定的标准化关系测定一个或多个标准化值。
250
通过将分析物响应输出信号值222除以标准化值来测定至少一个标准化分析物响应输出信号值以测定一个或多个标准化分析物响应输出信号值262（在一种外部刺激的情况下）或267（在两种外部刺激的情况下）。
260
利用诸如之前描述的标准化参考相关性172或177等之前测定的标准化参考相关性将一个或多个标准化分析物响应输出信号值262或267变换成样本的分析物浓度282。
280
样本的测定的分析物浓度282的显示、储存以用于将来参考、补偿和/或用于额外的计算。
290

图 C

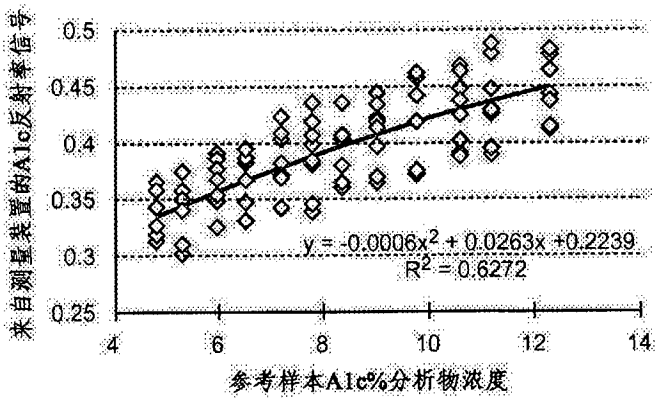

来自测量装置的A1c反射率信号
0.5
0.45
0.4
0.35
0.3
0.25
4
6
8
10
12
14
y = -0.0006x2 + 0.0263x +0.2239
R2 = 0.6272
参考样本A1c%分析物浓度

图 1A

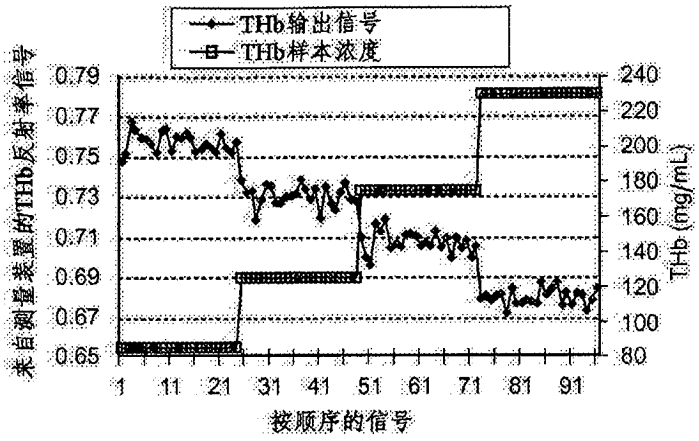

THb输出信号
THb样本浓度
来自测量装置的THb反射率信号
THb (mg/mL)
按顺序的信号

图 1B

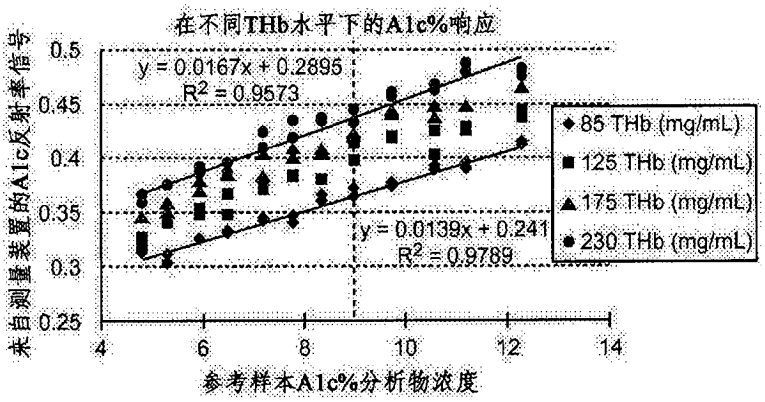

在不同THb水平下的A1c%响应
y = 0.0167x + 0.2895
R2 = 0.9573
y = 0.0139x + 0.241
R2 = 0.9789
85 THb (mg/mL)
125 THb (mg/mL)
175 THb (mg/mL)
230 THb (mg/mL)
来自测量装置的A1c反射率信号
参考样本A1c%分析物浓度

图 1C

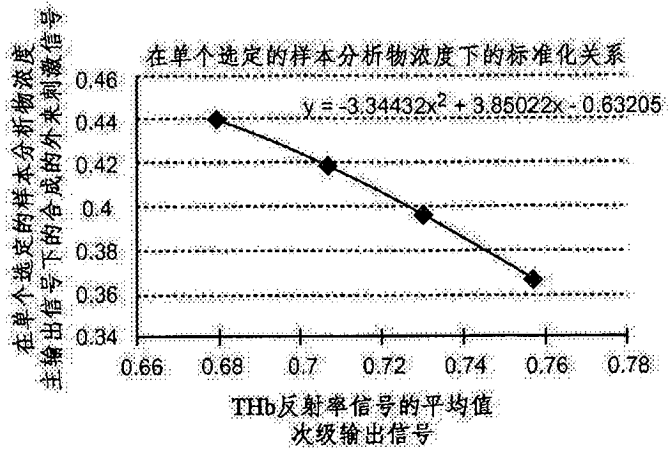

在单个选定的样本分析物浓度下的标准化关系
y = -3.34432x2 + 3.85022x - 0.63205
在单个选定的样本分析物浓度主输出信号下的合成的外来刺激信号
THb反射率信号的平均值
次级输出信号

图 1D

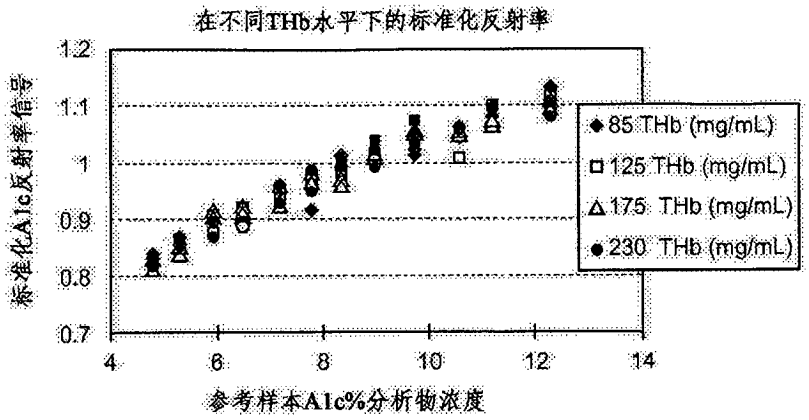

在不同THb水平下的标准化反射率
标准化A1c反射率信号
1.2
1.1
1
0.9
0.8
0.7
4
6
8
10
12
14
参考样本A1c%分析物浓度
85 THb (mg/mL)
125 THb (mg/mL)
175 THb (mg/mL)
230 THb (mg/mL)

图 1E

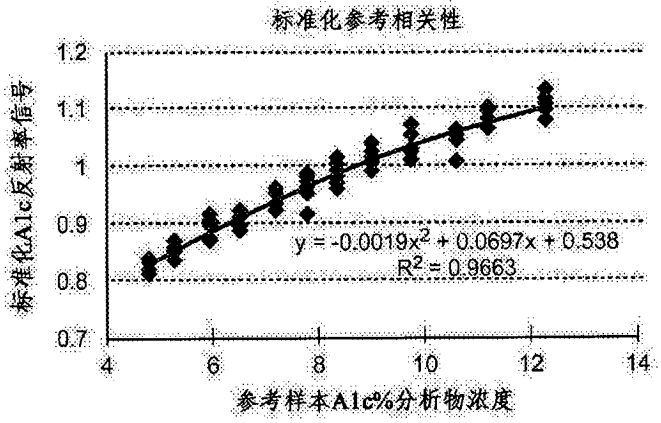

标准化参考相关性
标准化A1c反射率信号
1.2
1.1
1
0.9
0.8
0.7
y = -0.0019x2 + 0.0697x + 0.538
R2 = 0.9663
4
6
8
10
12
14
参考样本A1c%分析物浓度

图 1F

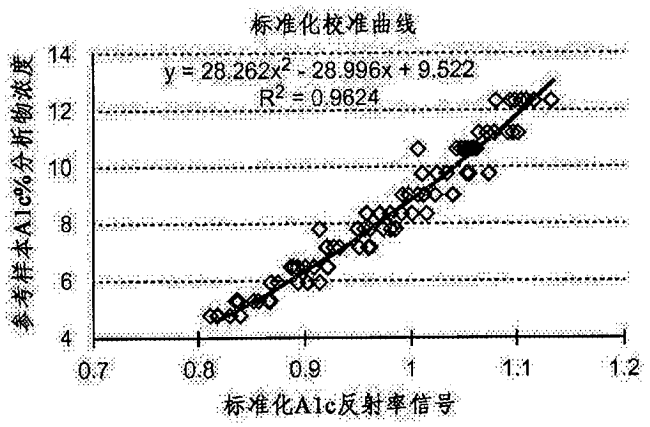

标准化校准曲线
参考样本A1c%分析物浓度
14
12
10
8
6
4
y = 28.262x2 - 28.996x + 9.522
R2 = 0.9624
0.7
0.8
0.9
1
1.1
1.2
标准化A1c反射率信号

图 1G

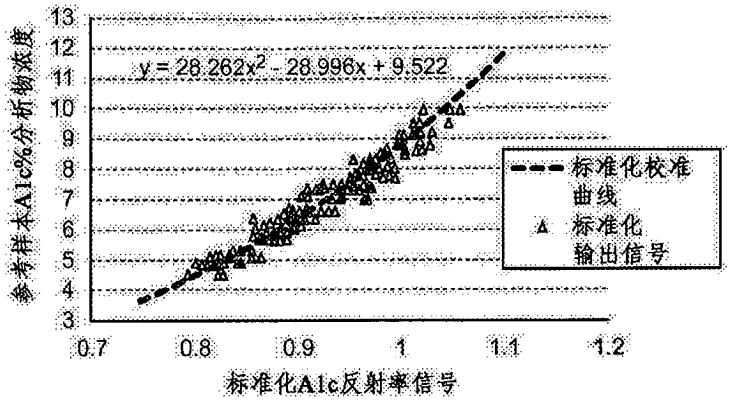

y = 28.262x² - 28.996x + 9.522
标准化校准曲线
标准化输出信号
参考样本A1c%分析物浓度
标准化A1c反射率信号

图 1H

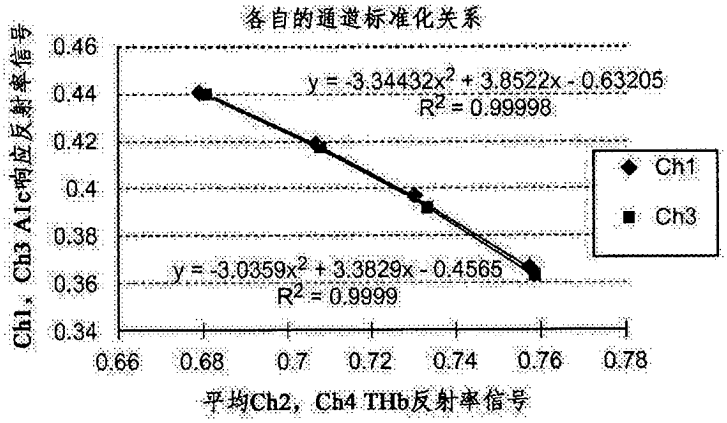

各自的通道标准化关系
y = -3.34432x² + 3.8522x - 0.63205
R² = 0.99998
y = -3.0359x² + 3.3829x - 0.4565
R² = 0.9999
Ch1
Ch3
Ch1，Ch3 A1c响应反射率信号
平均Ch2，Ch4 THb反射率信号

图 2A

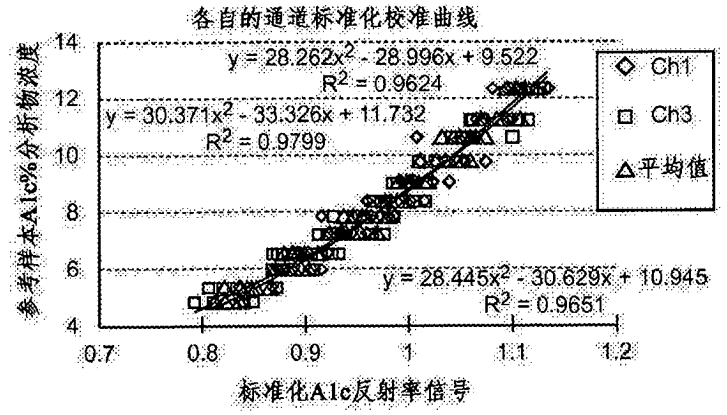

各自的通道标准化校准曲线
y = 28.262x² - 28.996x + 9.522
R² = 0.9624
y = 30.371x² - 33.326x + 11.732
R² = 0.9799
y = 28.445x² - 30.629x + 10.945
R² = 0.9651
Ch1
Ch3
平均值
参考样本A1c%分析物浓度
标准化A1c反射率信号

图 2B

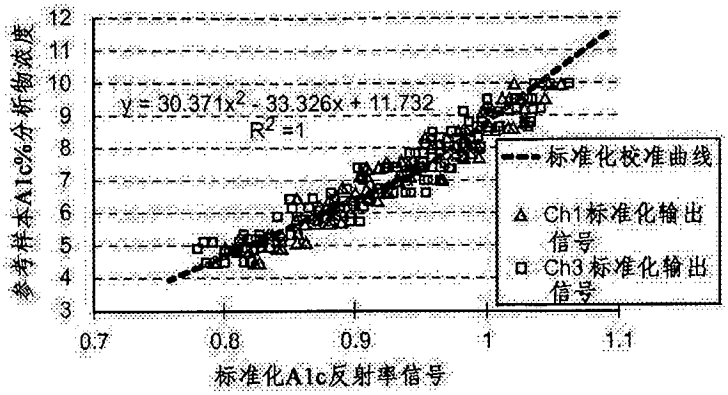

参考样本A1c%分析物浓度
y = 30.371x² - 33.326x + 11.732
R² =1
标准化校准曲线
Ch1标准化输出信号
Ch3标准化输出信号
标准化A1c反射率信号

图 2C

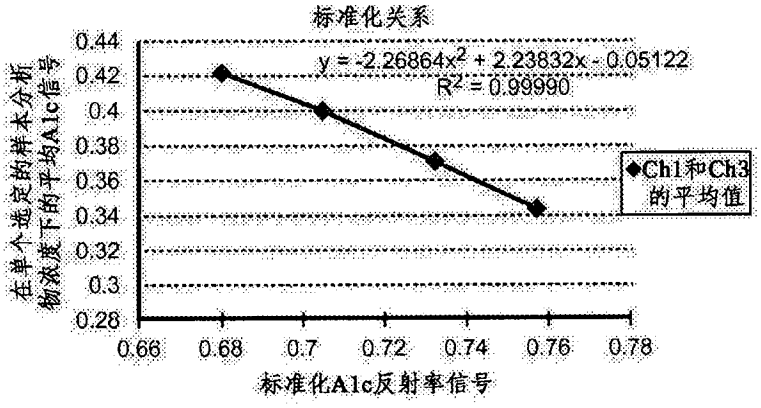

标准化关系
y = -2.26864x² + 2.23832x - 0.05122
R² = 0.99990
Ch1和Ch3的平均值
在单个选定的样本分析物浓度下的平均A1c信号
标准化A1c反射率信号

图 2D

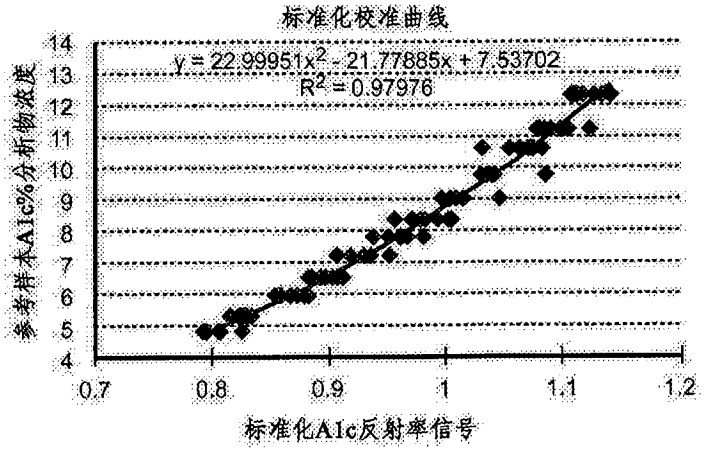

标准化校准曲线
y = 22.99951x² - 21.77885x + 7.53702
R² = 0.97976
参考样本A1c%分析物浓度
标准化A1c反射率信号

图 2E

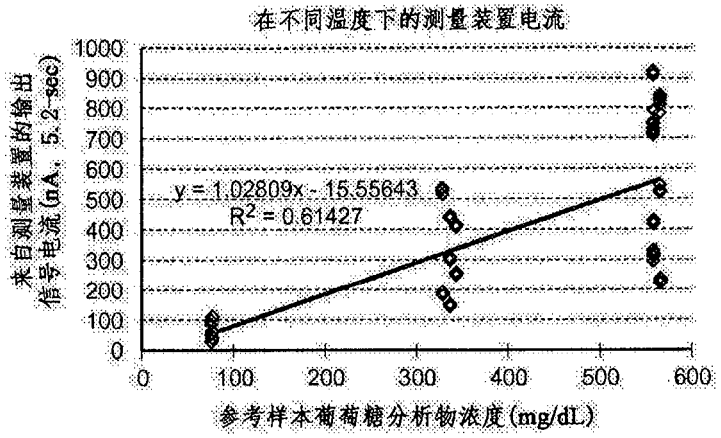

在不同温度下的测量装置电流
来自测量装置的输出信号电流(nA, 5.2-sec)
y = 1.02809x - 15.55643
R2 = 0.61427
参考样本葡萄糖分析物浓度(mg/dL)

图 3A

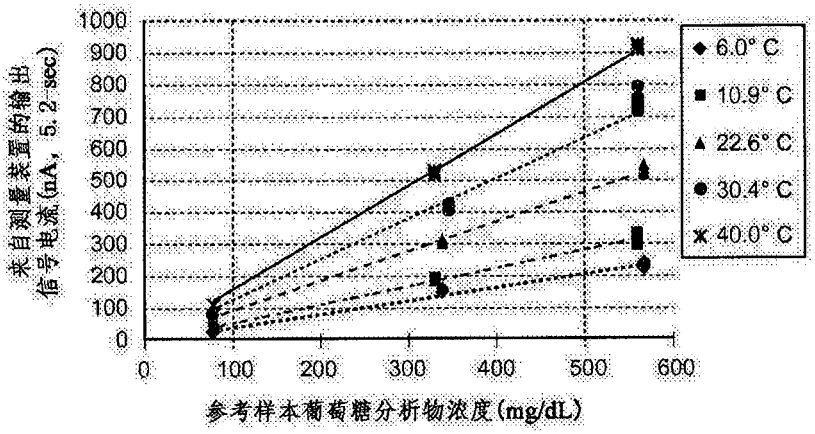

来自测量装置的输出信号电流(nA, 5.2-sec)
6.0° C
10.9° C
22.6° C
30.4° C
40.0° C
参考样本葡萄糖分析物浓度(mg/dL)

图 3B

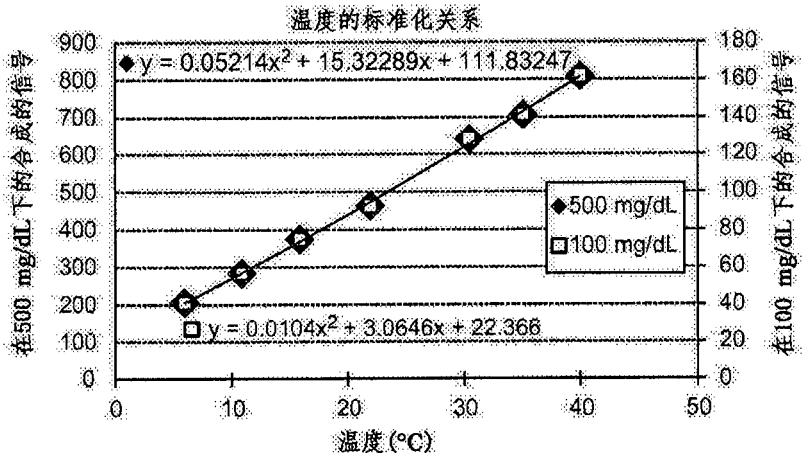

温度的标准化关系
在500 mg/dL下的合成的信号
y = 0.05214x2 + 15.32289x + 111.83247
500 mg/dL
100 mg/dL
y = 0.0104x2 + 3.0646x + 22.366
在100 mg/dL下的合成的信号
温度(°C)

图 3C

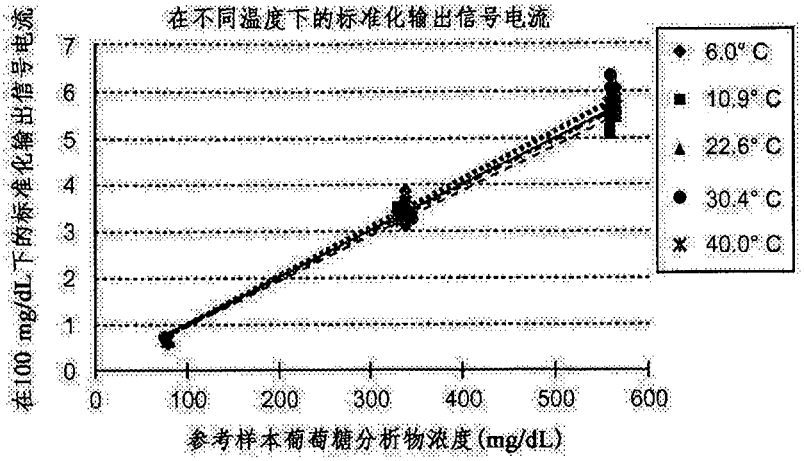

在不同温度下的标准化输出信号电流
在100 mg/dL下的标准化输出信号电流
参考样本葡萄糖分析物浓度(mg/dL)
6.0° C
10.9° C
22.6° C
30.4° C
40.0° C

图 3D

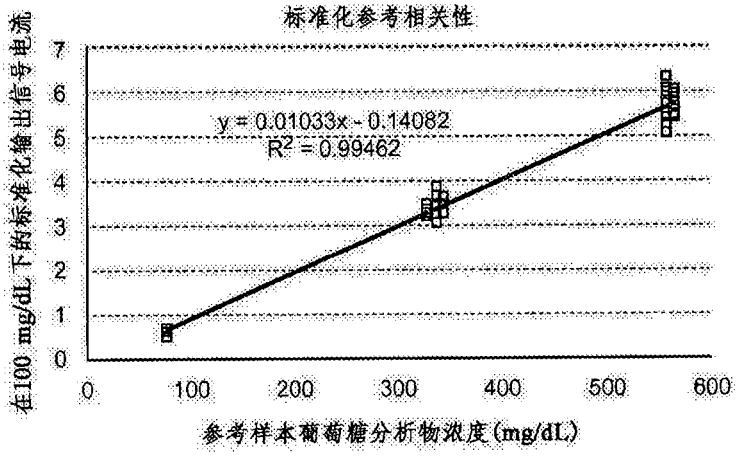

标准化参考相关性
y = 0.01033x - 0.14082
R2 = 0.99462
在100 mg/dL下的标准化输出信号电流
参考样本葡萄糖分析物浓度(mg/dL)

图 3E

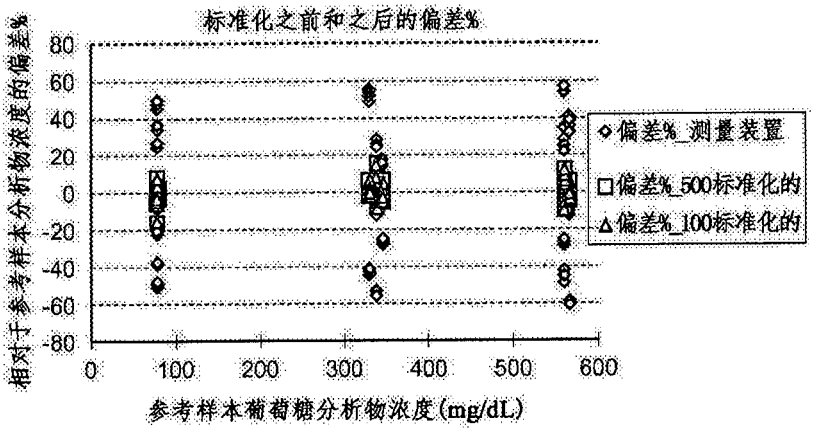

标准化之前和之后的偏差%
相对于参考样本分析物浓度的偏差%
参考样本葡萄糖分析物浓度(mg/dL)
偏差%_测量装置
偏差%_500标准化的
偏差%_100标准化的

图 3F

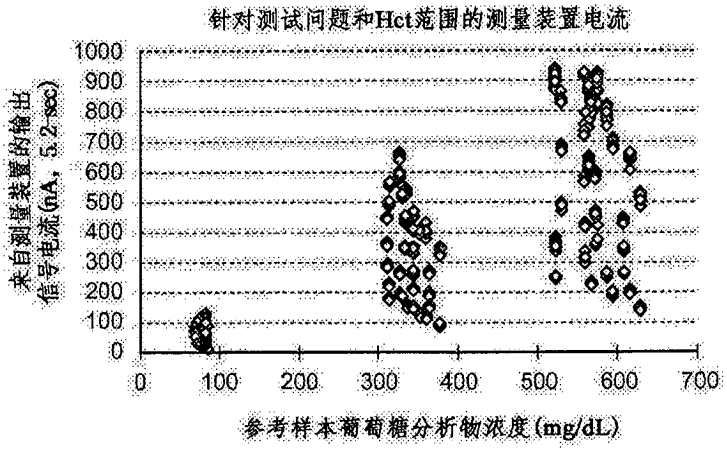

针对测试问题和Hct范围的测量装置电流
来自测量装置的输出信号电流(nA, 5.2-sec)
1000
900
800
700
600
500
400
300
200
100
0
0
100
200
300
400
500
600
700
参考样本葡萄糖分析物浓度(mg/dL)

图 4A

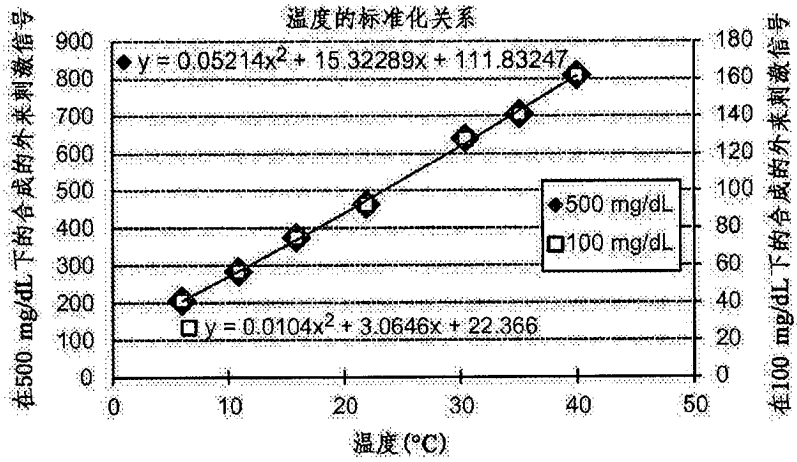

温度的标准化关系
在500 mg/dL 下的合成的外来刺激信号
在100 mg/dL 下的合成的外来刺激信号
◆ y = 0.05214x2 + 15.32289x + 111.83247
□ y = 0.0104x2 + 3.0646x + 22.366
◆500 mg/dL
□100 mg/dL
900
800
700
600
500
400
300
200
100
0
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
温度(°C)

图 4B

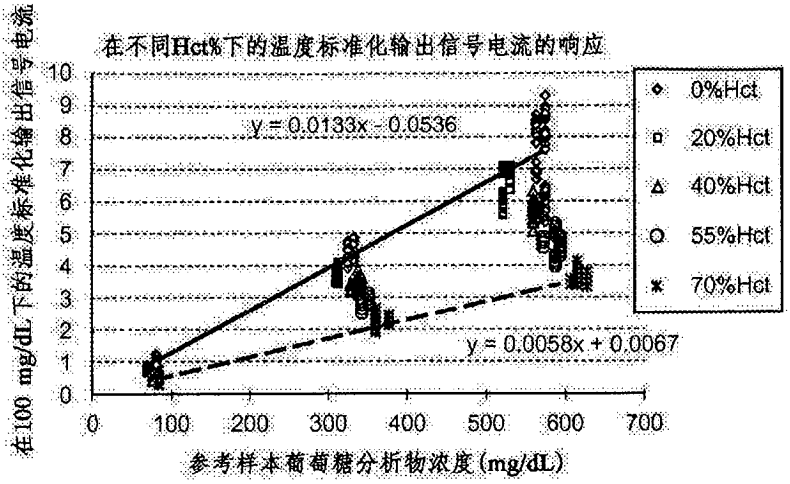

在不同Hct%下的温度标准化输出信号电流的响应
在100 mg/dL下的温度标准化输出信号电流
y = 0.0133x - 0.0536
y = 0.0058x + 0.0067
0%Hct
20%Hct
40%Hct
55%Hct
70%Hct
参考样本葡萄糖分析物浓度(mg/dL)

图 4C

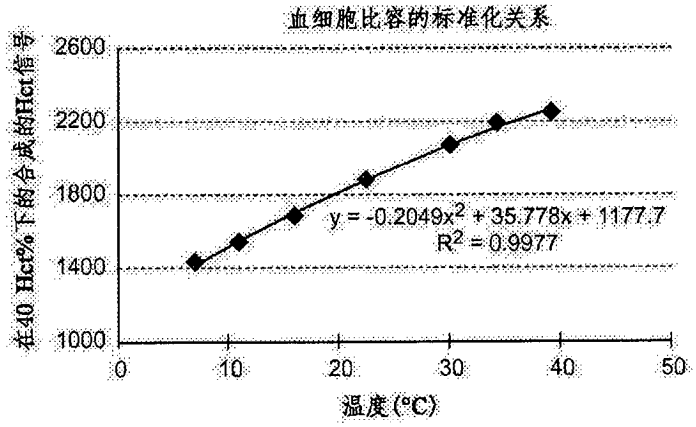

血细胞比容的标准化关系
在40 Hct%下的合成的Hct信号
y = -0.2049x² + 35.778x + 1177.7
R² = 0.9977
温度(°C)

图 4D

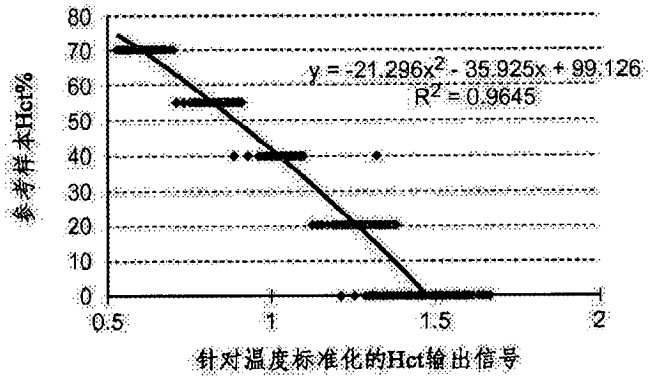

参考样本Hct%
y = -21.296x² - 35.925x + 99.126
R² = 0.9645
针对温度标准化的Hct输出信号

图 4E

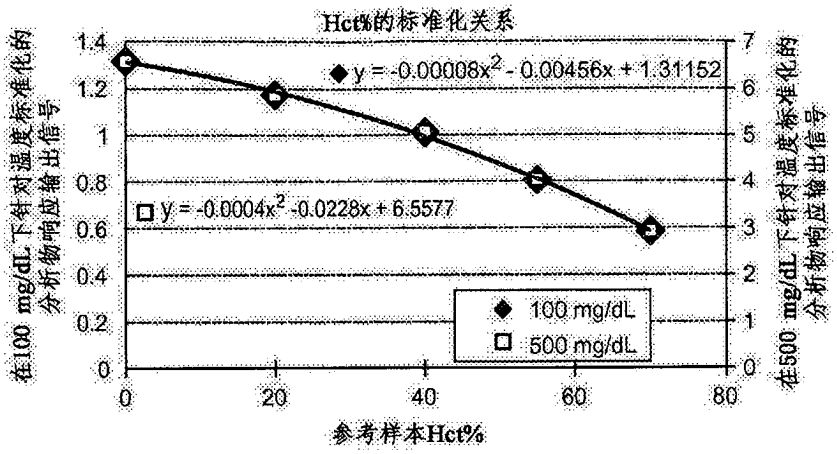

Hct%的标准化关系
y = -0.00008x2 - 0.00456x + 1.31152
y = -0.0004x2 -0.0228x + 6.5577
100 mg/dL
500 mg/dL
在100 mg/dL下针对温度标准化的分析物响应输出信号
在500 mg/dL下针对温度标准化的分析物响应输出信号
参考样本Hct%

图 4F

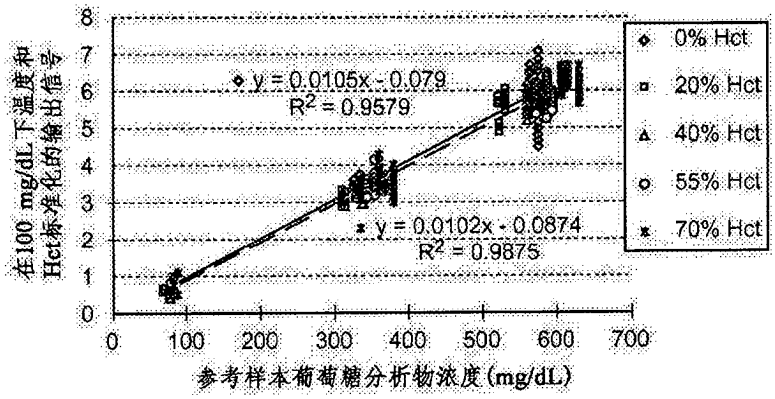

y = 0.0105x - 0.079
R2 = 0.9579
y = 0.0102x - 0.0874
R2 = 0.9875
0% Hct
20% Hct
40% Hct
55% Hct
70% Hct
在100 mg/dL下温度和Hct标准化的输出信号
参考样本葡萄糖分析物浓度(mg/dL)

图 4G

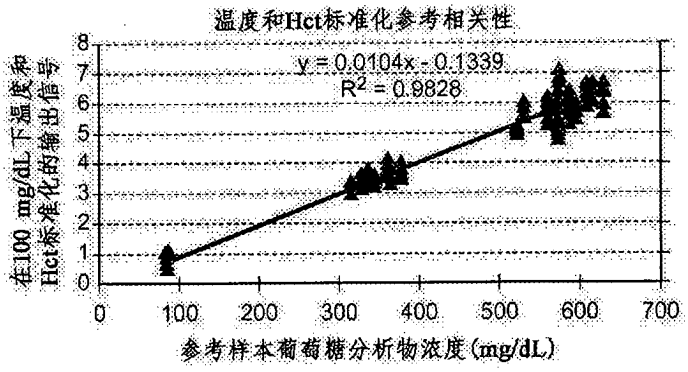

温度和Hct标准化参考相关性
y = 0.0104x - 0.1339
R2 = 0.9828
在100 mg/dL下温度和Hct标准化的输出信号
参考样本葡萄糖分析物浓度(mg/dL)

图 4H

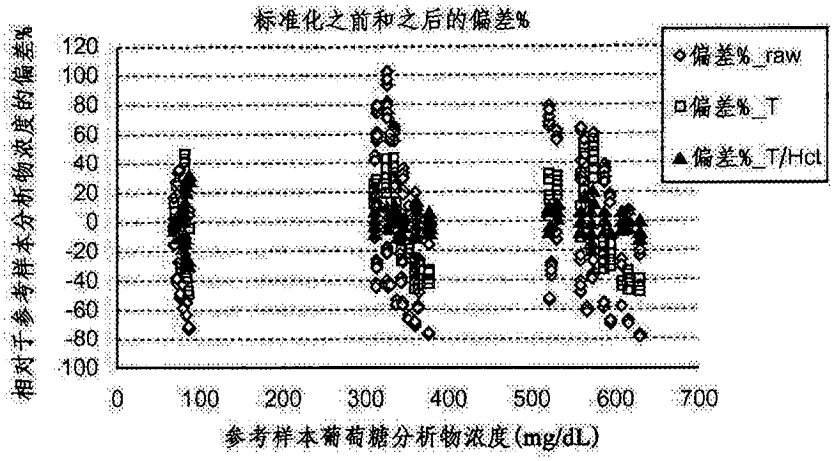

标准化之前和之后的偏差%
相对于参考样本分析物浓度的偏差%
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
100
200
300
400
500
600
700
参考样本葡萄糖分析物浓度(mg/dL)
偏差%_raw
偏差%_T
偏差%_T/Hct

图 4I

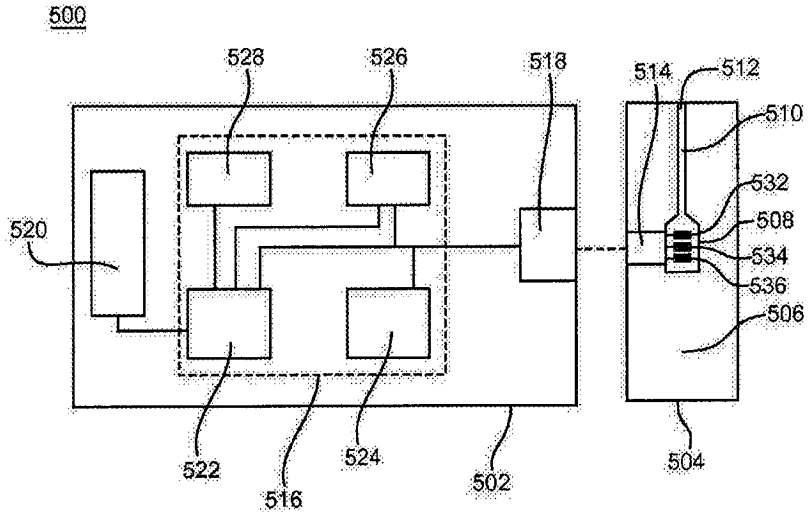

500
528
526
518
514
512
510
532
508
534
536
506
520
522
516
524
502
504

图 5

Our Ref：16HKI031-101

說明書摘要

發明名稱：分析物濃度測定的標準化校準

用來測定樣本中分析物的有無和/或濃度的生物傳感器系統測量裝置包括標準化校準信息，該標準化校準信息使該裝置響應于樣本的分析物濃度生成的輸出信號與之前測定的參考樣本分析物濃度相聯繫。該測量裝置利用這種標準化校準信息使來自樣本的電化學或光學分析的一個或多個輸出信號與樣本中一種或多種分析物的有無和/或濃度相聯繫。標準化校準信息包括使由生物傳感器系統的測量裝置測量的輸出信號標準化的標準化關係和使標準化輸出信號與參考樣本分析物濃度相聯繫的至少一種標準化參考相關性。

ABSTRACT

Title of Invention : NORMALIZED CALIBRATION OF ANALYTE CONCENTRATION DETERMINATIONS

Biosensor system measurement devices used to determine the presence and/or concentration of an analyte in a sample include normalized calibration information relating output signal or signals the device generates in response to the analyte concentration of the sample to previously determined reference sample analyte concentrations. The measurement devices use this normalized calibration information to relate one or more output signals from an electrochemical or optical analysis of a sample to the presence and/or concentration of one or more analytes in the sample. The normalized calibration information includes a normalization relationship to normalize output signals measured by the measurement device of the biosensor system and at least one normalized reference correlation relating normalized output signals to reference sample analyte concentrations.