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(71) Applicant: **ASCENSIA DIABETES CARE HOLDINGS AG** [CH/CH]; Peter-Merian-Str. 90, 4052 Basel (CH).

(72) Inventor: **WU, Huan-Ping**; 14374 Shoreline Drive, Granger, IN 46530 (US).

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(54) **Title**: IMPROVED BIOSENSOR SYSTEM ANALYTE MEASUREMENT

(57) **Abstract**: Methods and biosensor systems for compensating an analyte measurement are provided. The methods and systems determine a secondary output signal based on the measured primary output signal in order to better approximate the effects of an extraneous stimulus on the primary output signal under actual measurement conditions. The methods and systems according to the present disclosure may provide a more accurate analyte measurement, and may be particularly useful in detecting and compensating an analyte measurement during an off-condition.

IMPROVED BIOSENSOR SYSTEM ANALYTE MEASUREMENT

CROSS-REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application Serial No. 62/162,298, filed on May 15, 2015, which is herein incorporated by reference in its entirety.

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BACKGROUND

[0003] 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 (also referred to as a meter) that analyzes a sample residing in a test sensor (also referred to as a test strip or a sensor strip). The sample usually is a biological fluid, though may be a derivative, such as an extract, a dilution, a filtrate, or a reconstituted precipitate (as used from here on in, the term "biological fluid" includes derivatives thereof). The analysis performed by the biosensor system may determine 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, which may be useful in the diagnosis and/or treatment of certain conditions.

[0004] For example, a person with diabetes may use a biosensor system to determine the A1c (glycated hemoglobin) or glucose level in blood for adjustments to diet and/or medication. In blood samples that include hemoglobin (Hb), the presence and/or concentration of total hemoglobin (THb) and Alc may be determined. A1c level (%-A1c) is a reflection of the state of glucose control in a patient, providing insight into the average glucose control over the two to three months preceding the test. For diabetic individuals, an accurate measurement of %-A1c provides a better indication of how well the individual is controlling blood glucose levels

with diet and/or medication over a longer term than an instantaneous measure of blood glucose level, which only indicates blood glucose control at the time the measurement is made.

[0005] 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 in a range of 0.25-15 microliters (μL) in volume. Biosensor systems may be implemented using bench-top, portable, and other types of 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 (Whippany, New Jersey), while examples of bench-top measurement systems include the Electrochemical Workstation available from CH Instruments in Austin, Texas, and the bench-top model "YSI 2300 STAT Plus™ Glucose & Lactate Analyzer," and related models from the Yellow Springs Instrument Company, now known as YSI Inc. (referred to herein as "YSI" reference values).

[0006] 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, and 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 continuously flowed through the test sensor, such as for continuous monitoring; or the sample may be intermittently introduced to or flowed through the test sensor, such as for intermittent monitoring. 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.

[0007] Biosensor systems typically provide one or more primary input signals (collectively referred to as the primary input signal) to a sample of biological fluid, and measure one or more primary output signals (collectively referred to as the primary output signal) generated from the sample to determine the analyte concentration. The primary output signal is generated as a result of an interaction between the primary input signal and the analyte, or between the primary input signal and a species indicative of the analyte, and is typically correlated with the analyte concentration. Biosensor systems may use optical and/or electrochemical methods to analyze the biological fluid.

[0008] In optical systems, the primary input signal is typically a light beam generated from a light source, giving rise to a measurement of a sample's transmittance or reflectance of the light beam. In some optical systems, the analyte or species indicative of the analyte may absorb or shift the wavelength of the incident light beam (primary input signal), so that the resulting primary (light) output signal has reduced intensity or is wavelength-shifted with respect to the primary input signal. In other optical systems, a chemical indicator may fluoresce or emit light in response to the analyte when illuminated by a primary (light) input signal). In either optical system, the measured primary (light) output signal) may be converted into an electrical output signal, such as current or potential, and the system measures the primary (light) output signal and correlates the primary output signal with the analyte concentration of the sample.

[0009] In electrochemical systems, the analyte concentration of the sample is determined from an electrical signal generated by a redox reaction of the analyte or of a measurable species responsive to the analyte concentration when a primary (electrical) input signal is applied to the sample. The primary 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 primary 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] The measurement device of an electrochemical biosensor system applies a primary input signal through the electrical contacts to the electrical conductors of the test sensor. The electrical conductors convey the primary input signal through the electrodes into the sample present in the sample reservoir. The redox reaction of the analyte generates a primary (electrical) output signal in response to the primary input signal. The primary (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 primary output signal with the presence and/or concentration of one or more analytes in the sample.

[0011] In either optical or electrochemical biosensor systems, the conversion of the primary output signal to indicate the presence and/or concentration of the target analyte(s) is typically accomplished using a conversion function. A conversion function is a calculation method that converts the primary output signal to a concentration of the target analyte(s). For example, a conversion function may involve using a reference correlation between the primary output signal and the analyte concentration with a linear, nonlinear, or polynomial relationship. The conversion function reflects a correlation under a set of assumptions regarding the conditions of the testing and sample, and deviations from these assumptions may introduce error in the calculated analyte concentration.

[0012] The generation and measurement of the primary output signal is designed to be primarily responsive to the analyte(s) concentration that is the target or objective of the biosensor measurement, but the measured primary output signal inevitably also includes contributions from extraneous stimuli, such as deviations from the assumptions underlying the correlation. Such extraneous stimuli include those arising from physical or environmental characteristics of the sample, such as interfering substances (*e.g.*, hematocrit (Hct), acetaminophen, lipids, proteins, ascorbic acid, uric acid, *etc.*), ambient temperature, humidity, and the like; operating conditions of the system, such as underfill conditions when the sample size is insufficient for the system to carry out a measurement, intermittent electrical contact between the sample and one or more electrodes in the test sensor, degradation of the reagents, and the like; and manufacturing variations between test sensor lots, such as changes in the amount and/or activity of the reagents, changes in the electrode area and/or spacing, and the like; *etc.*.

[0013] Extraneous stimuli affect both the accuracy and precision of the measurement and analysis of the target analyte(s). Such erroneous measurements can cause frustration for the biosensor system's end user, who may need to discard test sensors and provide additional samples in order to repeat measurements, and who also may face uncertain treatment choices because of the inaccurate information. Thus, there has been an ongoing need to quantify and offset the effects of extraneous stimuli in order to remove or minimize those effects from the target analyte concentration.

[0014] When an extraneous stimulus arises from the physical or environmental characteristics of the sample, its effect may be quantified from a secondary output signal that is either extracted from the primary output signal, or measured by dedicated means or a dedicated

detection channel. For example, in electrochemical systems, a secondary output signal due to an interfering substance (such as Hct) may be extracted from the primary output signals (such as, for example, the current ratios of R4/3, R5/4 and R6/5 disclosed in PCT Publication No. WO 2009/108239 entitled, "Slope-Based Compensation" and the potential sequence of gated amperometry with a Hct pulse disclosed in PCT Publication No. WO 2011/156152 A1 entitled, "Slope-Based Compensation Including Secondary Output Signals") used to determine the target analyte concentration of the sample, or measured using a dedicated electrode that may include the same reagent composition as the electrodes used to determine the target analyte concentration of the sample, a different reagent composition (*e.g.*, one that reacts with the interferent), or no reagent composition. In optical systems, for example, a secondary output signal due to an interfering substance (such as THb) may be measured using a dedicated optical channel focused at a wavelength or an angle indicative of the interfering substance (such as, for example, the reflectance measurements disclosed in PCT Publication No. WO 2013/043839 A1 entitled "Analysis Compensation Including Segmented Signals" and PCT Publication No. WO 2014/159077 A1 entitled "Normalized Calibration of Analyte Concentration Determination"). In some instances, the secondary output signal may be correlated with a value for the extraneous stimulus; for example, a temperature sensor incorporated into a biosensor system may measure a secondary output signal due to temperature and correlate that secondary output signal with a temperature value, thus providing a separate measurement of the ambient temperature of the sample.

[0015] As used herein, the term "secondary output signal" may describe the raw signal extracted from the primary output signal or measured by a dedicated sensor, electrode, detection channel or the like, or may describe the extraneous stimulus value correlated with the raw signal, depending on the context of the particular measurement or calculation being done.

[0016] The conversion function used to convert the primary output signal to analyte concentration may utilize the secondary output signals to compensate for the effects of those extraneous stimuli. For example, the measured temperature value may be used to compensate the primary output signal to more accurately determine the analyte concentration, as discussed, for example, in U.S. Patent No. 7,781,222 ("Temperature-Adjusted Analyte Determination for Biosensor System"). In another example, the conversion function may involve a multivariable regression with secondary output signals, as discussed, for example, in U.S. Patent No. 8,744,776 ("Method of Determining Analyte Concentration Based on Complex Index Functions") and PCT Publication No. WO 2011/119533 A1 ("Residual

Compensation for a Biosensor"). Normalization may also be used to remove or minimize the effect of extraneous stimuli from the primary output signal, as discussed, for example, in PCT Publication No. WO 2014/159077 A1 ("Normalized Calibration of Analyte Concentration Determinations").

[0017] While incorporating such compensation methods into conversion functions can improve biosensor system measurement performance, shortcomings remain. Such compensation methods are typically developed and implemented in a laboratory, where error conditions can be reproduced in a controlled environment. For portable measurement devices, particularly hand-held devices used by most consumers, such a controlled laboratory environment may not accurately reflect the conditions under which the measurements are made, so the compensation methods developed under controlled laboratory conditions may not accurately compensate for the effects of the extraneous stimuli on the primary output signal under actual measurement conditions. For example, the temperature measured by a temperature sensor incorporated in a biosensor system is assumed to reflect the temperature of the biological fluid sample, but that assumption may fail under certain operating conditions, such as when a hand-held measuring device is kept in a car during winter weather (*e.g.*, 0° - 10°C) or summer weather (*e.g.*, 40° - 45°C) and then used immediately with a test sensor that had been kept indoors at room temperature (*e.g.*, 22° - 25° C). In another example, a Hct signal measurement may itself be erroneous due, for example, to a failure of a dedicated electrode.

[0018] Such a situation, where the secondary output signal does not match the reference value assumed by the compensation method and/or does not match the secondary output signal expected from the primary output signal, is referred to as an "off-condition." When an analyte determination is made under an off-condition, using the generated secondary output signal to compensate the primary output signal may introduce additional error into the analyte determination. Currently-available biosensor systems and methods cannot determine when such an off-condition occurs and so cannot determine when the conversion function requires additional adjustment to compensate for such errors due to the secondary output signals.

[0019] The methods and systems disclosed herein avoid or ameliorate at least some of these disadvantages in the prior art.

SUMMARY

[0020] In one aspect, the present disclosure provides a method of determining an analyte concentration in a biological fluid sample. A primary output signal that is primarily

responsive to the analyte concentration is measured, and a secondary output signal that is responsive to an extraneous stimulus that affects the primary output signal is generated. A secondary output signal is back-calculated based on the measured primary output signal, and the generated secondary output signal is adjusted using the back-calculated secondary output signal. The measured primary output signal is converted to an analyte concentration using a conversion function with the adjusted secondary output signal used to compensate for the effect of the extraneous stimulus on the measured output signal.

[0021] In another aspect, the present disclosure provides a method of compensating an analyte measurement in an off-condition by measuring a primary output signal that is primarily responsive to the analyte concentration in a biological fluid sample and generating a secondary output signal that is responsive to an extraneous stimulus that affects the primary output signal. The measured primary output signal is converted to a preliminary analyte concentration using a conversion function with the generated secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal. A first back-calculated secondary output signal is determined based on the measured primary output signal and the preliminary analyte concentration. If an off-condition is determined to exist, then a first adjusted secondary output signal is determined using the first back-calculated secondary output signal to adjust the generated secondary output signal. The measured primary output signal is converted to a first analyte concentration value using the conversion function with the first adjusted secondary output signal to compensate for the effect of the extraneous stimulus on the primary output signal. In some implementations, a second back-calculated secondary output signal is determined based on the measured primary output signal and the first analyte concentration value; if an off-condition is determined to exist based on the first and second back-calculated secondary output signals, then a second adjusted secondary output signal is determined using the second back-calculated secondary output signal to adjust the first adjusted secondary output signal, and the measured primary output signal is converted to a second analyte concentration value using the conversion function and the second adjusted secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal.

[0022] In another aspect, the present disclosure provides a method of compensating an analyte measurement in an off-temperature condition by measuring a primary output signal and generating a temperature measurement using a temperature sensor. The measured primary output signal is converted into a preliminary analyte concentration using a conversion function with the temperature measurement to compensate for the effect of temperature on the

measured primary output signal. A first back-calculated temperature is determined from the measured primary output signal and the preliminary analyte concentration. If an off-temperature condition is determined to exist, then the temperature measurement is adjusted using the first back-calculated temperature, and the measured primary output signal converted into a first analyte concentration using the conversion function with the first adjusted temperature to adjust for the effect of the temperature on the measured primary output signal.

[0023] In another aspect, the present disclosure provides a biosensor system for implementing one or more of the methods disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIGURE 1A illustrates a conventional (prior art) approach to compensating for the effect of an extraneous stimulus in an analyte determination.

[0025] FIGURE 1B illustrates a cyclic approach to compensating for the effect of an extraneous stimulus in an analyte determination.

[0026] FIGURE 2A represents one embodiment of a method of determining an analyte concentration.

[0027] FIGURE 2B represents another embodiment of a method of determining an analyte concentration.

[0028] FIGURE 2C represents another embodiment of a method of determining an analyte concentration.

[0029] FIGURE 2D represents another embodiment of a method of determining an analyte concentration.

[0030] FIGURE 3A shows a graph of primary output signal versus meter temperature for three YSI reference glucose samples.

[0031] FIGURE 3B shows a graph of the primary output signals extrapolated to 22°C versus YSI reference glucose levels.

[0032] FIGURE 3C shows a graph of normalized primary output signal determined by two normalization methods versus temperature.

[0033] FIGURE 3D shows a table summarizing the estimated accuracy of temperature back-calculated using the normalization functions shown in FIGURE 3C.

[0034] FIGURE 3E represents the primary output signals as a function of the Hct signals of the Hct dedicated electrode at three different reference glucose concentrations.

[0035] FIGURE 3F represents a normalizing function for the Hct signals extrapolated at i_{Hct} = 2000 mV versus YSI reference glucose levels.

[0036] FIGURE 3G represents the normalized reference correlation for back-calculating the Hct Signals determined by the normalized output signals.

[0037] FIGURE 3H represents the primary A1c signals (reflectance) as a function of the THb signals from a dedicated detection channel at four different reference %-A1c concentrations.

[0038] FIGURE 3I represents a normalizing function for the THb signals extrapolated at R_{THb} = 0.7 versus reference %-A1c levels.

[0039] FIGURE 3J represents the normalized reference correlation for back-calculating the THb signals where the THb signal is plotted against the normalized A1c signals.

[0040] FIGURE 3K illustrates one embodiment of a method of generating normalized calibration information that may be used to back-calculate a secondary output signal.

[0041] FIGURE 4A represents one embodiment of a method of determining an off-condition in an analyte concentration determination.

[0042] FIGURE 4B represents another embodiment of a method of determining an off-condition in an analyte concentration determination.

[0043] FIGURE 5A shows a plot of measured primary output signals for three different whole blood (WB) glucose concentrations taken with the sensor/sample and meter at seven different temperatures.

[0044] FIGURE 5B shows a plot of measured primary output signals for four different WB glucose concentrations taken with the sensor/sample at 22°C and the meter at six different temperatures.

[0045] FIGURE 5C shows a plot of bias/%-bias in an analyte determination using a conventional one-way conversion function with temperature compensation in an off-temperature condition and the meter temperature at which the primary output signals were measured.

[0046] FIGURE 6A shows a plot of back-calculated temperatures based on a measured primary output signal and the meter temperature at which the primary output signals were measured.

[0047] FIGURE 6B shows a plot of bias/%-bias in an analyte determination using a conventional (one-way) application of a conversion function with temperature compensation (*), a complete one cycle application of the conversion function with temperature compensation (◆), and a selected one cycle application of the conversion function with temperature compensation applied in off-temperature conditions only (□), and the meter temperature at which the primary output signals were measured.

[0048] FIGURE 7A represents one embodiment of a method of compensating an analyte measurement in an off-temperature condition.

[0049] FIGURE 7B shows a plot of bias/%-bias in an analyte determination using a cyclic application of a conversion function with temperature compensation with two different weight coefficients.

[0050] FIGURE 8 represents one embodiment of a biosensor system according to the present disclosure.

DETAILED DESCRIPTION

[0051] The present disclosure introduces a concept of back-calculating a secondary output signal based on the measured primary output signal and using the back-calculated secondary output signal to help compensate for the effect of an extraneous stimulus on the primary output signal in an analyte determination. A back-calculated secondary output signal based on the measured primary output signal better reflects the effect of the extraneous stimulus under the actual conditions under which the primary output signal was measured, and so may be used to determine when an off-condition occurs and to help compensate for the errors introduced by the off-condition, thereby improving the accuracy of the analyte concentration determination.

[0052] FIGURE 1A illustrates a conventional approach to compensating for the effect of an extraneous stimulus in an analyte determination. A biosensor system makes a measurement of a primary output signal. The measured primary output signal is primarily responsive to an analyte concentration in a biological fluid sample, but will include responses from extraneous stimuli (such as temperature, Hct, THb, *etc.*) that will affect the accuracy and precision of the analyte determination. To compensate for the effects from an extraneous stimulus, the biosensor system may generate a secondary output signal that is responsive to the extraneous stimulus, for example, by extracting the secondary output signal from the measured primary output signal, or by making a separate measurement of the secondary output signal. In a conventional compensation approach, the measured primary output signal and the generated secondary output signal are inputted into a conversion function that uses the generated secondary output signal to compensate the measured primary output signal for the effect of the extraneous stimulus while converting the measured primary output signal into an analyte concentration.

[0053] This one-way process of inputting the measured primary output signal and the generated secondary output signal into the conversion function to determine the analyte

concentration, while it may be effective in reducing the effect of the extraneous stimulus in the analyte determination, fails to detect errors associated with the generated secondary output signal. Such errors may arise, for example, when the generated secondary output signal itself is in error due to a faulty detection channel, such as may occur in detecting a THb signal, or due to a failure of a dedicated electrode, such as may occur in detecting a Hct signal, or when the generated secondary output signal does not reflect the actual condition of the biological fluid sample when the primary output signal is measured, such as may occur when the measuring device's temperature sensor does not represent the temperature of the sensor/sample. When an erroneous secondary output signal is inputted into the conversion function, a large error may result when compensating the measured primary output signal for the effect of the extraneous stimulus, and so may compromise the accuracy of the analyte concentration determination.

[0054] FIGURE 1B illustrates a cyclic approach, according to this present disclosure, for compensating for the effect of an extraneous stimulus in an analyte determination. In accordance to this disclosure, the cyclic process may begin as above, with a measured primary output signal and a generated secondary output signal being inputted into a conversion function to determine a preliminary analyte concentration. The process then generates a new input to cycle back into the conversion function to better compensate for the effect of the extraneous stimulus. This cyclic process involves back-calculating a secondary output signal based on the measured primary output signal using, for example, the measured primary output signal itself, the preliminary analyte concentration and/or other information derived from the measured primary output signal and/or preliminary analyte concentration. The back-calculated secondary output signal is used to adjust the generated secondary output signal by, for example, adding a portion of the back-calculated secondary output signal or a parameter that depends on the back-calculated secondary output signal to the generated secondary output signal, or replacing the generated secondary output signal with the back-calculated secondary output signal. The adjusted secondary output signal (along with the measured primary output signal) is inputted into the conversion function to determine a first compensated analyte concentration. This cyclic process may be implemented for one cycle, or multiple cycles, for example, for a predetermined number of cycles, or until certain criteria are satisfied.

[0055] It has been found that, by using the back-calculated secondary output signal to adjust the generated secondary output signal, the adjusted secondary output signal that is inputted into the conversion function better reflects the actual conditions under which the primary output signal was measured and also helps correct for errors in the generated secondary output

signal. Thus, cyclic processes of the present disclosure may provide improved accuracy of analyte determinations.

[0056] FIGURES 2A-2D illustrate some steps involved in different implementations of a cyclic process according to the present disclosure.

[0057] FIGURE 2A shows a flow chart 200 illustrating some steps in a one-cycle implementation of a method of determining an analyte concentration according to the present disclosure. Using a biosensor system, a primary output signal is measured at step 201. The primary output signal is designed to be primarily responsive to the analyte concentration.

[0058] At step 202, a secondary output signal is generated. The secondary output signal is responsive to an extraneous stimulus that affects the measured primary output signal and may be generated, for example, by extracting the secondary output signal from the measured primary output signal (such as, for example, extracting the current ratios of R4/3, R5/4 and R6/5 as secondary output signals responsive to Hct levels, as disclosed in PCT Publication No. WO 2009/108239 entitled, "Slope-Based Compensation," or using the potential sequence of gated amperometry with a Hct pulse, as disclosed in WO 2011/156152 A1 entitled, "Slope-Based Compensation Including Secondary Output Signals"), or by making a separate measurement of the secondary output signal using a separate sensor, a separate detection channel or electrode, or the like (such as, for example, using a temperature sensor to make a temperature measurement, or a dedicated optical channel to measure a reflectance signal responsive to THb levels, as disclosed in WO 2013/043839 A1 entitled "Analysis Compensation Including Segmented Signals" and WO 2014/159077 A1 entitled "Normalized Calibration of Analyte Concentration Determination"). Steps 201 and 202 may be performed in any order, or may occur simultaneously.

[0059] At step 203, a back-calculated secondary output signal is determined based on the measured primary output signal using the measured primary output signal itself and/or information derived from the measured primary output signal, such as a preliminary analyte concentration. Some embodiments of a method for back-calculating a secondary output signal will be shown and discussed below and with reference to FIGURES 3A-3J.

[0060] At step 204, the back-calculated secondary output signal is used to adjust the secondary output signal generated by the biosensor system. At step 205, the measured primary output signal is converted into the analyte concentration using a conversion function with the adjusted secondary output signal (from step 204) being used to compensate for the effect of the extraneous stimulus on the measured primary output signal.

[0061] FIGURE 2B shows a flow chart 210 illustrating some steps in a one-cycle implementation of a method of compensating an analyte measurement in an off-condition according to the present disclosure. Using a biosensor system, a primary output signal is measured at step 211, and a secondary output signal generated at step 212. Steps 211 and 212 may be performed in any order, or may occur simultaneously. At step 213, the measured primary output signal is converted into a preliminary analyte concentration using a conversion function with the generated secondary output signal used to compensate for the effect of an extraneous stimulus on the measured primary output signal. At step 214, a back-calculated secondary output signal is determined based on the measured primary output signal, as will be discussed further below and with regard to FIGURES 3A-3J. Step 215 queries whether an off-condition exists. An "off-condition" may occur when the generated secondary output signal does not match the reference value assumed by a compensation method incorporated into the conversion function and/or does not match the secondary output signal expected based on the measured primary output signal; some embodiments of a method for determining whether an off-condition exists will be shown and discussed below, with reference to FIGURES 4A and 4B.

[0062] If an off-condition is determined to not exist (*i.e.*, the answer to the query of 215 is "NO"), then additional or further compensation for the effect of the extraneous stimulus may not be needed or desired, so at step 216, the preliminary analyte concentration may be reported by the biosensor system as the analyte measurement.

[0063] If an off-condition is determined to exist (*i.e.*, the answer to the query of 215 is "YES"), then additional compensation for the effect of the extraneous stimulus may be needed or desired, so, at step 217, the generated secondary output signal is adjusted using the back-calculated secondary output signal. In some implementations, the generated secondary output signal may be replaced by the back-calculated secondary output signal; in other words, the adjusted secondary output signal may be equated to the back-calculated secondary output signal. In other implementations, a portion of the back-calculated secondary output signal may be used to adjust the generated secondary output signal. In still other implementations, a portion of the difference between the back-calculated secondary output signal and the generated secondary output signal may be added to the generated secondary output signal to adjust it. At step 218, the measured primary output signal is converted into the analyte measurement using the conversion function with the adjusted secondary output signal to compensate for the effect of the extraneous stimulus, and the analyte measurement reported in step 219.

[0064] FIGURE 2C shows a flow chart 220 that illustrates some steps in a multiple cycle implementation of a method of compensating an analyte measurement in an off-condition according to the present disclosure. In the implementation shown in flow chart 220, cyclic compensation is repeated until an off-condition no longer exists.

[0065] Using a biosensor system, a primary output signal is measured at step 221, and a secondary output signal generated at step 222. Steps 221 and 222 may be performed in any order, or may occur simultaneously. At step 223, the measured primary output signal is converted into a preliminary analyte concentration using a conversion function with the generated secondary output signal used to compensate for the effect of an extraneous stimulus on the measured primary output signal.

[0066] A counter, n, may be used to keep track of the number of cycles used, and at step 224, n is set to 1. A cycle begins at step 225, where an n^{th} back-calculated secondary output signal is determined based on the measured primary output signal and the $(n\text{-}1)^{th}$ analyte concentration, as will be discussed further below and with regard to FIGURES 3A-3J; for n=1, the $(n\text{-}1)^{th}$ analyte concentration is the preliminary analyte concentration that was determined in step 223. Step 226 queries whether an off-condition exists; some embodiments of a method for determining whether an off-condition exists will be shown and discussed below, with reference to FIGURES 4A and 4B.

[0067] If the query of 226 returns "NO", then the $(n\text{-}1)^{th}$ analyte concentration is reported as the analyte measurement, as shown at step 230.

[0068] If the query of 226 returns "YES", then, at step 227, an n^{th} adjusted secondary output signal is determined by, for example, using the n^{th} back-calculated secondary output signal to adjust the $(n\text{-}1)^{th}$ adjusted secondary output signal; for n=1, the $(n\text{-}1)^{th}$ adjusted secondary output signal is the generated secondary output signal from step 222. In some implementations, the n^{th} back-calculated secondary output signal may be used to replace the $(n\text{-}1)^{th}$ adjusted secondary output signal; in other words, the n^{th} adjusted secondary output signal may be equated to the n^{th} back-calculated secondary output signal. In other implementations, a portion of the n^{th} back-calculated secondary output signal may be used to adjust the $(n\text{-}1)^{th}$ generated secondary output signal. In still other implementations, a portion of the difference between the n^{th} back-calculated secondary output signal and the $(n\text{-}1)^{th}$ adjusted secondary output signal may be added to the $(n\text{-}1)^{th}$ adjusted secondary output signal to determine the n^{th} adjusted secondary output signal.

[0069] At step 228, the measured primary output signal is converted to an n^{th} analyte concentration using the conversion function with the n^{th} adjusted secondary output signal to compensate for the effect of the extraneous stimulus.

[0070] At step 229, the counter, n, is increased by one, *i.e.*, $n = n + 1$, and another cycle begins at step 225. The cycle (steps 225-229) is repeated until the off-condition no longer exists (*i.e.*, the query of 226 returns "NO"), at which point the $(n\text{-}1)^{th}$ analyte concentration is reported as the analyte measurement (step 230).

[0071] FIGURE 2D shows a flow chart 240 that illustrates some steps in another multiple cycle implementation of a method of compensating an analyte measurement in an off-condition according to the present disclosure. In the implementation shown in flow chart 240, cyclic compensation is repeated for a pre-determined (fixed) number of cycles.

[0072] Using a biosensor system, a primary output signal is measured at step 241, and a secondary output signal generated at step 242. Steps 241 and 242 may be performed in any order, or may occur simultaneously. At step 243, the measured primary output signal is converted into a preliminary analyte concentration using a conversion function with the generated secondary output signal used to compensate for the effect of an extraneous stimulus on the measured primary output signal.

[0073] Step 244 queries whether an off-condition exists; some embodiments of a method for determining whether an off-condition exists will be shown and discussed below, with reference to FIGURES 4A and 4B.

[0074] If the query of 244 returns "NO", then the preliminary analyte concentration is reported as the analyte measurement, as shown at step 251.

[0075] If the query of 244 returns "YES", then cyclic compensation is performed. A counter, n, may be used to keep track of the number of cycles used, and at step 245, n is set to 1. A cycle begins at step 246, where an n^{th} back-calculated secondary output signal is determined based on the measured primary output signal and the $(n\text{-}1)^{th}$ analyte concentration, as will be discussed further below and with regard to FIGURES 3A-3J; for n=1, the $(n\text{-}1)^{th}$ analyte concentration is the preliminary analyte concentration that was determined in step 243.

[0076] At step 247, an n^{th} adjusted secondary output signal is determined by, for example, using the n^{th} back-calculated secondary output signal to adjust the $(n\text{-}1)^{th}$ adjusted secondary output signal; for n=1, the $(n\text{-}1)^{th}$ adjusted secondary output signal is the generated secondary output signal from step 242. In some implementations, the n^{th} back-calculated secondary output signal may be used to replace the $(n\text{-}1)^{th}$ adjusted secondary output signal; in other words, the n^{th} adjusted secondary output signal may be equated to the n^{th} back-calculated

secondary output signal. In other implementations, a portion of the n^{th} back-calculated secondary output signal may be used to adjust the $(n\text{-}1)^{th}$ generated secondary output signal. In still other implementations, a portion of the difference between the n^{th} back-calculated secondary output signal and the $(n\text{-}1)^{th}$ adjusted secondary output signal may be added to the $(n\text{-}1)^{th}$ adjusted secondary output signal to determine the n^{th} adjusted secondary output signal.

[0077] At step 248, the measured primary output signal is converted to an n^{th} analyte concentration using the conversion function with the n^{th} adjusted secondary output signal to compensate for the effect of the extraneous stimulus.

[0078] Step 249 queries whether n is equal to the pre-determined number of cycles, N. If the query of step 249 returns "YES," then the n^{th} analyte concentration is reported as the analyte measurement, as shown in step 252. If the query of step 249 returns "NO", then the counter, n, is increased by one, *i.e.*, $n = n + 1$, at step 250, and another cycle begins at step 246. The cycle (steps 246-250) is repeated until $n = N$ (*i.e.*, the query of 249 returns "YES"), at which point the n^{th} analyte concentration is reported as the analyte measurement (step 252).

[0079] A secondary output signal may be back-calculated from the measured primary output signal in different ways, such as using a correlation of the secondary output signal to a parameter or other information derived from the measured primary output signal. For example, temperature may be back-calculated using a correlation between temperature and the decay constant parameter from a gated amperometry measurement, as discussed, for example, in U.S. Patent No. 8,425,757, which is hereby incorporated by reference its entirety.

[0080] Another way of back-calculating a secondary output signal uses a correlation between the secondary output signals and normalized primary output signals. As discussed above, the measured primary output signal depends on a number of variables, primarily on analyte concentration but also on extraneous stimuli such as %-Hct, THb value, temperature, etc. Normalization reduces the dependency of the primary output signal from these many variables to fewer variables, preferably to just one variable. PCT Publication No. WO 2014/159077A1, entitled "Normalized Calibration of Analyte Concentration Determinations," provides a more detailed discussion of normalization generally and is hereby incorporated by reference in its entirety. Normalization of the primary output signal to eliminate the dependency of the primary output signal on analyte concentration so that the primary output signal becomes dependent on an extraneous stimulus only may be accomplished by various methods. For example, the primary output signal may be normalized by dividing the primary output signal by a unity function value of the analyte concentration; alternatively, a normalization function

may be generated, and a ratio of the primary output signal to the normalization function value used as the normalized primary output signal.

[0081] FIGURES 3A-3J illustrate some ways to generate a normalization function and a normalized primary output signal that has had its dependency on analyte concentration eliminated and is dependent only on a secondary output signal. Back-calculating the secondary output signal may be accomplished using a correlation between the secondary output signal and normalized primary output signal. FIGURE 3K shows a flowchart that summarizes some steps illustrated in FIGURES 3A-3I for generating a normalization function and normalized calibration information that may be used to back-calculate a secondary output signal.

[0082] FIGURES 3A-3D illustrate some aspects of normalization as applied to normalize a primary output signal that is primarily responsive to glucose concentration to be dependent on temperature only.

[0083] FIGURE 3A shows a plot of glucose signal (the primary output signal in this example) as a function of temperature (the secondary output signal in this example) at three glucose concentrations. The glucose signals (reported as the ending current at 5.2 seconds in a gated amperometry potential sequence, "Currents at 5.2s (mV)") were measured from YSI glucose reference samples (glucose level of 78.4 mg/dL (◆), 329.5 mg/dL (□), and 559.8 mg/dL(△)) are plotted against the temperature as measured by the temperature sensor in the meter ("Temperature, C"). In generating the data shown in FIGURE 3A, the sensor/sample temperature and the meter temperature were kept the same. A line is fitted through the plotted data for each YSI glucose reference sample, and the corresponding regression equation for each line also shown in FIGURE 3A.

[0084] FIGURE 3B shows the glucose signals extrapolated to a designated temperature (22°C; see the vertical dashed line in FIGURE 3A) and plotted against the reference glucose concentrations. The extrapolated glucose signal values were obtained by inputting the designated temperature (22°C) into the regression equations for each YSI glucose reference sample, resulting in the following three extrapolated values: 65.77, 316.86 and 553.12 (current counts, mV). A line is fitted through the extrapolated values plotted in FIGURE 3B and a regression analysis performed to produce a normalization function shown as follows (Eq. (1)):

$$y = 1.0122x - 14.577 \quad (1)$$

where y corresponds to the primary output signal value that may be used as a normalization function value and x corresponds to glucose (analyte) concentration. In this embodiment, the

regression equation is a linear function of analyte concentration, but in other embodiments, the regression equation may be a polynomial or other type of function.

[0085] FIGURE 3C plots normalized glucose signals ("Normalized Currents") against temperature ("Temperature, C"), which establishes the correlation between the normalized primary output signals and temperature. FIGURE 3C includes normalized glucose signals determined by two different normalization methods. Normalized glucose signals determined as a ratio of the measured glucose signals ($i_{5.2}$) to the unity function value of the known YSI reference glucose concentration value (*i.e.*, a normalization current value taken at the numerical value of the known analyte concentration) are plotted using diamonds (◆). Normalized glucose signals plotted using open squares (□) were determined by dividing the measured glucose signals ($i_{5.2}$) by the normalization function values for the known YSI reference glucose concentration values (x) determined by Eq. (1). A regression analysis of the two normalized glucose signals plotted against temperature in FIGURE 3C generates a linear regression function for each as follows:

$$y_{(\blacklozenge)} = 0.0333x_{(\blacklozenge)} + 0.1962 \quad (2)$$

$$y_{(\square)} = 0.0354x_{(\square)} + 0.2077 \quad (3)$$

where $y_{(\blacklozenge)}$ corresponds to the glucose signal normalized by taking a ratio to a unity function of the known YSI reference concentrations and $y_{(\square)}$ corresponds to the glucose signal normalized by taking a ratio to the normalization function value (Eq. (1)), and $x_{(\blacklozenge)}$ and $x_{(\square)}$ correspond to temperature. The two plots shown in FIGURE 3C and Equations (2) and (3) show the relationship between normalized glucose signals and temperature. Equations (2) and (3) may be rewritten to express temperature as a function of normalized glucose signal as follows:

$$x_{(\blacklozenge)} = \frac{y_{(\blacklozenge)} - 0.1962}{0.0333} \quad (4)$$

$$x_{(\square)} = \frac{y_{(\square)} - 0.2077}{0.0354} \quad (5)$$

[0086] The relationship between normalized glucose signals and temperature, as expressed by, for example, Equations (4) or (5), may be used as normalized calibration information to back-calculated temperature (secondary output signal) by normalizing the measured glucose (primary output) signal to the normalization value derived from a corresponding glucose (analyte) concentration and applying the normalized calibration information to the normalized glucose (primary output) signal.

[0087] FIGURE 3D shows the estimated accuracy of temperatures back-calculated using Equations (4) and (5). The back-calculated temperature (T_{calc}) using either Equation (4) or (5)

shows no mean bias relative to the measured temperature (T_{meas}), that is to say that the mean $\Delta T = T_{calc} - T_{meas}$ is 0.0° C. Both equations show equivalent accuracy as a method of back-calculating temperatures.

[0088] FIGURES 3E-3G illustrate some aspects of normalization as applied to normalize a primary output signal that is primarily responsive to glucose concentration to be dependent on Hct signal (secondary output signal) only.

[0089] FIGURE 3E shows a plot of glucose signal (i_G, the primary output signal in this example) as a function of Hct signal (i_{Hct}, the secondary output signal in this example) at three glucose concentrations. The glucose signals (reported as the ending current at 5.2 seconds in a gated amperometry potential sequence, "Glucose Currents, i_5.2s") from each of the YSI glucose reference samples (glucose level of 74.9 mg/dL (◆), 348.7 mg/dL (■), and 528.3 mg/dL(▲)) are plotted against the Hct signals as measured by a dedicated Hct electrode ("Hct Electrode Currents (mV)"). Regression equations corresponding to the plotted data for each YSI reference sample are also shown. In the biosensor system used to generate the data shown in FIGURE 3E, the expected average Hct current count is 2500 mV for 20% Hct, 2000 mV for 42% Hct, 1680 mV for 60% Hct and 1150 mV for 70% Hct, and both i_G and i_{Hct} decrease with increasing %Hct.

[0090] FIGURE 3F shows glucose signals extrapolated to a designated value for the Hct Electrode Current (2000 mV; see vertical dashed line in FIGURE 3E) and plotted against the YSI reference glucose levels (mg/dL). The extrapolated glucose signal values were obtained by inputting the designated Hct signal value (2000 mV) into the regression equation for each YSI reference glucose sample, resulting in the following three extrapolated values: 70.01, 352.8 and 585.7. A line is fitted through the extrapolated values plotted in FIGURE 3F and a regression analysis performed to produce a normalization function shown as follows (Eq. (6)):

$$y = 0.000582x^2 + 0.786148x + 7.848238 \quad (6)$$

where y corresponds to the glucose signal value that may be used as a normalization function value and x corresponds to glucose (analyte) concentration.

[0091] FIGURE 3G plots normalized glucose signals ("Normalized currents") against Hct signal (mV), which establishes the correlation between the normalized glucose signals and Hct signal. FIGURE 3G includes normalized glucose signals determined by two different normalization methods. Normalized glucose signals determined as a ratio of the measured glucose signal ($i_{5.2}$) to the unity function value of the known YSI reference glucose concentration (*i.e.*, a normalization current value taken at the numerical value of the known analyte concentration) are plotted using diamonds (◆). Normalized glucose signals plotted

using open squares (□) were determined by dividing the measured glucose signal ($i_{5,2}$) by the normalization function values for the known analyte concentration values (x) determined by Eq. (6). A regression analysis of the two normalized glucose signals plotted against Hct signal in FIGURE 3G generates a linear regression function for each as follows:

$$y_{(\blacklozenge)} = 0.000447x_{(\blacklozenge)} + 0.116934 \quad (7)$$

$$y_{(\square)} = 0.000442x_{(\square)} + 0.114668 \quad (8)$$

where $y_{(\blacklozenge)}$ corresponds to the normalized glucose signal obtained by taking a ratio of the glucose signal to unity function of the known YSI reference concentrations and $y_{(\square)}$ corresponds to the normalized glucose signal obtained by taking a ratio of the glucose signal to the normalization function value (Eq. (6)), and $x_{(\square)}$ and $x_{(\blacklozenge)}$ correspond to Hct signal. The two plots shown in FIGURE 3G and Equations (7) and (8) show the relationship between normalized glucose signals and Hct signal. Equations (7) and (8) may be rewritten to express Hct signal as a function of normalized glucose signal and used as normalized calibration information to back-calculate Hct (secondary output) signal by inputting the normalized measured glucose (primary output) signal corresponding to a glucose (analyte) concentration.

[0092] FIGURES 3H-3J illustrate some aspects of normalization as applied to normalize a primary output signal that is primarily responsive to %-A1c level to be dependent on THb signal (secondary output signal) only.

[0093] FIGURE 3H shows a plot of A1c signals (R_{A1c}, the primary output signal in this example) as a function of THb signal (R_{THb}, the secondary output signal in this example) at four %-A1c levels. The A1c signals (reported as reflectance of a first wavelength measured from a first detection zone using a laminar flow A1c biosensor system) from each of the reference samples (%A1c level of 4.8 (◆), 6.5 (□), 9(Δ) and 12.3 (●)) are plotted against THb signals (measured as reflectance of a second wavelength from a second detection zone). Curves are fitted through data from each reference sample, and regression equations corresponding to each curve are also shown.

[0094] FIGURE 3I shows the A1c signals extrapolated to a THb reflectance signal (R_{THb}) value of 0.7, which corresponds to an average THb concentration (~150 mg/mL) (see vertical dashed line in FIGURE 3H), plotted against the reference %-A1c level. The extrapolated A1c signal values were obtained by inputting the R_{THb} designated value (0.7) into the regression equation for each %-A1c reference sample, resulting in the following four extrapolated values: 0.31602, 0.35704, 0.40483 and 0.43732. A regression analysis of the extrapolated A1c signal data plotted in FIGURE 3I generates the normalization function (Eq. (9)):

$$y = -0.0015x^2 + 0.0414x + 0.1508 \quad (9)$$

where y corresponds to the A1c signal value that may be used as a normalization function value and x corresponds to %-A1c level (analyte concentration). In this example, the regression equation (Eq. (9)) is a second order polynomial function of analyte concentration.

[0095] FIGURE 3J plots THb signals values against the normalized A1c signals,,which establishes the correlation between THb signals and normalized A1c signals. The normalized A1c signals plotted in FIGURE 3J were determined as a ratio of the measured A1c signal to the normalization function value for the known analyte concentration values (x) determined by Eq. (9). A regression analysis of the THb signals plotted against normalized A1c signals in FIGURE 3J generates a second order polynomial regression function as follows:

$$y = -0.6086x^2 + 0.8276x + 0.4826 \quad (10)$$

where y corresponds to THb signal and x corresponds to the normalized A1c signal. Equation (10) may be used as normalized calibration information to back-calculate a THb (secondary output) signal by inputting the normalized measured A1c (primary output) signal corresponding to %-A1c (analyte concentration).

[0096] FIGURE 3K summarizes some steps for one embodiment of generating a normalization function and normalized calibration information that may be used to back-calculate a secondary output signal in accordance with the present disclosure. In implementing the steps shown in flow chart 300, a biosensor system is used to measure reference primary output signals from a plurality of reference samples at step 301. The reference primary output signals are primarily responsive to a primary stimulus, and each reference sample is associated with a known value of the primary stimulus. At step 302, the biosensor system generates a secondary output signal for each measured reference primary output signal. The generated secondary output signal is responsive to an extraneous stimulus that affects the measured reference primary output signal. Steps 301 and 302 may be performed in any order, or may occur simultaneously.

[0097] At step 303, the measured reference primary output signals for each reference sample (from step 301) are correlated to the generated secondary output signals (from step 302). In some implementations, a regression analysis may be performed on the correlated data from step 303 to generate a regression equation that relates measured reference primary output signal to generated secondary output signal.

[0098] At step 304, for each reference sample, a reference primary output signal value is extrapolated to a designated value of the secondary output signal. The designated value of the secondary output signal is typically a value around the mid-point of the range of generated

secondary output signals (from step 302); however, any value within the range of generated secondary output signals may be used as the designated value to which a reference primary output signal value is extrapolated. In implementations that generate the first regression equation that relates measured reference primary output signal to generated secondary output signal, the first regression equation may be used to extrapolate the reference primary output signal value by inputting the designated value of the secondary output signal.

[0099] At step 305, the extrapolated reference primary output signal values (from step 304) are correlated to their known primary stimulus values in order to generate a normalization function by, for example, regression analysis of the correlated data.

[0100] The normalization function is then used, at step 306, to normalize each measured reference primary output signal at its corresponding known primary stimulus value. Normalization is typically carried out by dividing the measured primary output signal by a normalization function value. In this embodiment, the normalization function value is determined by inputting the known primary stimulus value into the normalization function generated at step 305.

[0101] At step 307, the normalized reference primary output signals (from step 306) are correlated to the generated secondary output signals (from step 302) to generate normalized calibration information. This normalized calibration information may be used in some embodiments of the present disclosure in order to back-calculate a secondary output signal based on the measured primary output signal. In some implementations, the normalized calibration information may be represented as a regression equation that relates normalized primary output signals to secondary output signals and results from a regression analysis of the correlated data from step 307.

[0102] FIGURES 4A-4B illustrate different embodiments to determine whether an off-condition exists. The flow chart 400 in FIGURE 4A illustrates some steps in determining whether an off-condition exists based on a difference between the generated secondary output signal and a reference value for the extraneous stimulus established during calibration of the biosensor system. For example, the standard reference correlation of the primary output signal to analyte concentration is typically established at a reference temperature (such as 25°C) and a reference hematocrit level (such as 42%). For biosensor measurements at a temperature or hematocrit level that differ from the reference value, the effect of temperature or hematocrit on the primary output signal is typically compensated by the conversion function so that the analyte concentration is reported at the reference temperature and hematocrit level values. However, if the difference between the generated secondary output

signal and the reference value is too large, an off-condition may exist and the typical compensation methods may introduce additional error into the analyte determination.

[0103] In implementing the steps shown in the flow chart 400, a biosensor system generates a secondary output signal at step 401 and determines a difference between the generated secondary output signal and a reference value at step 402. Step 403 queries whether the absolute value of the difference determined at step 402 is greater than or equal to a threshold value. In implementations where repeated cycles are carried out, a difference between an n^{th} adjusted secondary output signal, or an n^{th} back-calculated secondary output signal, and a reference value may be determined, and an off-condition may exist when the absolute value of this difference is greater than or equal to the threshold value. The threshold value is typically set depending on the sensitivity desired for detecting an off-condition, and may be varied (for example, progressively reduced) from one cycle to the next. If the query of step 403 returns "NO", then an off-condition does not exist (as shown at 404). If the query of step 403 returns "YES", then an off-condition does exist (as shown at 405), and, in some implementations, a notification of the off-condition may be provided at step 406. The notification may take any form, for example, a warning message on a display incorporated with the biosensor system, a red light indicator on the biosensor system indicating that an error may exist, and the like. The notification may also include instructions for correcting the off-condition or to repeat the measurement.

[0104] The flow chart 410 of FIGURE 4B illustrates some steps in determining whether an off-condition exists based on a difference between the generated secondary output signal and an expected extraneous stimulus value based on the measured primary output signal. At steps 411 and 412, a biosensor system measures a primary output signal and generates a secondary output signal. Steps 411 and 412 may be performed in any order, or may occur simultaneously. At step 413, a back-calculated secondary output signal is determined based on the measured primary output signal; the back-calculated secondary output signal reflects the expected extraneous stimulus value based on the measured output signal. At step 414, a difference between the generated secondary output signal from step 412 and the back-calculated secondary output signal from step 413 is determined. Step 415 queries whether the absolute value of the difference determined at step 414 is greater than or equal to a preset value. In implementations where repeated cycles are carried out, a difference between an n^{th} back-calculated secondary output signal and an $(n\text{-}1)^{th}$ back-calculated, or $(n\text{-}1)^{th}$ adjusted, secondary output signal and may be determined, and an off-condition may exist when the absolute value of this difference is greater than or equal to the preset value. The preset value

is typically set depending on the sensitivity desired for detecting an off-condition, and may be varied (for example, progressively reduced) from one cycle to the next. If the query of step 415 returns "NO", then an off-condition does not exist (as shown at 416). If the query of ste 415 returns "YES", then an off-condition does exist (as shown at 418); in some implementations, a notification of the off-condition (as discussed previously, with regard to step 406 in FIGURE 4A) may be provided at step 419.

[0105] In some implementations according to the present disclosure, an off-condition may be determined based on a combination of the criteria discussed with regard to FIGs. 4A and 4B. That is, an off-condition may be determined to exist when the absolute value of the difference between the generated secondary output signal and the reference value is greater than or equal to a threshold value, and the absolute value of the difference between the generated secondary output signal and the back-calculated secondary output signal is greater than or equal to a preset value.

[0106] The error introduced into an analyte measurement by an off-condition may be illustrated by FIGURES 5A-5C, which illustrate the effect of an "off-temperature condition." An off-temperature condition may occur, for example, when a hand-held meter is kept in a car during winter weather (*e.g.*, 0° - 10° C) or summer weather (*e.g.*, 40° - 45° C) and then used with a test sensor that had been kept at room temperature (*e.g.*, 22° - 25° C). Given that heat transfer between the test sensor and the meter through the interfacing contacts is expected to be minimal within a short time, the test sensor/sample temperature is expected to remain relatively unchanged, regardless of the meter temperature.

[0107] When a temperature sensor or other temperature measuring device is incorporated into a biosensor system, it is assumed that the temperature measured by such device accurately reflects the temperature of the test sensor and of the sample, but such devices are typically incorporated into the meter, not the sensor. Methods that include temperature compensation for determining analyte concentration typically use the temperature measured by such devices to compensate the primary output signal. Under an off-temperature condition, however, the measured temperature may not accurately reflect the sensor/sample temperature, so temperature compensated measurements using the measured temperature will introduce error into the calculated analyte concentration.

[0108] FIGURE 5A shows a plot of primary output signal (Currents at 5.2s (mV)) from samples with three different glucose concentrations (70, 350 and 550 mg/dL) as measured by a biosensor system at seven temperatures, with the meter and sensor/sample at the same temperature: 5°C (♦), 10°C (□), 15°C (▲), 25°C (×), 35°C (✳), 40°C (●) and 45°C (+).

The measured primary output signals at different glucose concentrations varied with temperature, with the variance increasing as the concentration increases. Conversion functions including temperature compensation, such as that discussed in U.S. Patent No. 7,781,222 ("Temperature-Adjusted Analyte Determination for Biosensor System"), have been developed to compensate for such temperature-related variances in primary output signals when converting the primary output signal into an analyte concentration.

[0109] FIGURE 5B shows a plot of primary output signal (Current at 5.2s (mV)) from samples with four different glucose concentrations (86, 170, 335 and 564 mg/dL) as measured by a biosensor system with the sensor/sample at ~22°C and the meter stored at six different temperatures (22°C, 5°C, 10°C, 15°C, 35°C, 45°C) resulting in average temperature measurements as follows: 21.9°C (♦), 6°C (□), 10.3°C (▲), 15.7°C (×), 34.1°C (✳) and 43.7°C (○). Even though the measured meter temperatures vary greatly, the sensor/sample temperature remains relatively stable, as reflected in the measured primary output signals remaining relatively unchanged for each glucose concentration. If a conversion function with temperature compensation is applied to these data using the measured meter temperature to compensate for the effect of temperature, the measured meter temperature would introduce a potentially large error into the analyte determination.

[0110] FIGURE 5C shows the error in glucose concentration (plotted as bias/%-bias) for data in FIGURE 5B determined using a conventional conversion function with temperature compensation due to an off-temperature condition, when the measured meter temperature does not accurately represent the sensor/sample temperature. The bias/%-bias data (◆) are plotted sequentially along with the average meter temperatures (△) at 22°C, 5.5°C, 10.5°C, 15.5°C, 22.5°C, 34°C, 39.5°C, and 43.5°C (the sensor/sample were at ~22°C). As can be seen in FIGURE 5C, the larger the difference between the sensor/sample and the measured meter temperature, the larger the error in the analyte concentration.

[0111] Using a back-calculated temperature in the compensation, rather than the measured temperature, may help alleviate such error due to an off-temperature condition. Such a back-calculated temperature better reflects the temperature of the sample under the actual measurement conditions. FIGURE 6A shows back-calculated temperatures based on the primary output signals measured under off-temperature conditions (sensor/sample temperature at ~22°C; average meter temperatures at 22°C, 5.5°C, 10.5°C, 15.5°C, 22.5°C, 34°C, 39.5°C, and 43.5°C). The back-calculated temperatures (◆) shown in FIGURE 6A were generated from the same data as the bias/%-bias data shown in FIGURE 5C, using the normalizing calibration information embodied by Equation (4), above (*see also* FIGURE 3C and

accompanying text). These back-calculated temperatures are shown to be closer to the sensor/sample temperature of ~22°C than the measured meter temperatures (△). Furthermore, inputting the back-calculated temperatures into the same standard conversion function with temperature compensation that was used to generate the data shown in FIGURE 5C produces more accurate analyte concentration determinations with reduced error (smaller bias/%-bias), as shown in FIGURE 6B.

[0112] FIGURE 6B shows the error in glucose concentration (plotted as bias/%-bias) determined using a one-way application of a conventional conversion function with temperature compensation as shown in FIGURE 1A (×) (this is the same data shown in FIGURE 5C), a complete one cycle application of the same conventional conversion function with back-calculated temperature for compensation (◆) (as outlined in FIGURE 2A), and a selected one cycle application of the same conventional conversion function with back-calculated temperature for compensation applied only when an off-temperature condition is detected (□) (as outlined in FIGURE 2B), plotted along with the average measured meter temperature (△). Back-calculated temperatures were determined were determined using the normalizing calibration information embodied by Equation (4), above (*see also* FIGURE 3C and accompanying text). During off-temperature conditions, the complete and selected one cycle applications both reduced the error in terms of bias/%-bias on average from ~20% down to ~10% compared to the results of the conventional one-way application; at more extreme off-temperature conditions, such as at an average measured meter temperature ~5°C, the error is reduced from ~20% to ~5%. When applied during no off-temperature conditions (*e.g.*, measured meter temperature ~22°C), the one cycle application had comparable error of ~10% as the conventional one-way approach; but applying compensation only during off-temperature conditions, as done in the selected one cycle application minimized the chance of producing unnecessary biases.

[0113] FIGURES 7A-7B illustrate some steps and results from some embodiments of a method of compensating an analyte measurement in an off-temperature condition, using a cyclic compensation approach according to the present disclosure.

[0114] The embodiment of a cyclic compensation process shown in FIGURE 7A includes the steps of back-calculating temperature based on a previously determined analyte concentration, determining a temperature difference between the back-calculated temperature and the temperature used for compensation in the previously determined analyte concentration, detecting an off-temperature condition using the determined temperature difference, and, if an off-temperature condition is detected, adjusting the temperature and re-calculating an analyte

concentration using the adjusted temperature to compensate for the effect of temperature on the measured primary output signal; the process is repeated until no off-temperature condition is detected, at which point the determined analyte concentration is reported as the analyte measurement.

[0115] More specifically, in the flowchart 700 shown in FIGURE 7A, the process begins at step 701, with a biosensor system measuring a primary output signal. At step 702, a temperature measurement (T^0) is generated using the biosensor system (the superscript "0" used with "T" herein designates the temperature measurement made using the biosensor system, regardless of any subscript that may be appended to "T"). Steps 701 and 702 may be performed in any order, or may occur simultaneously. At step 703, the measured primary output signal is converted into a preliminary analyte concentration (G^0) using a conversion function with the temperature measurement (T^0) to compensate for the effect of temperature on the measured primary output signal.

[0116] In the embodiment shown in FIGURE 7A, an initial determination of whether an off-temperature condition may exist occurs at step 704. The initial determination in this embodiment is based on whether the absolute value of a difference between the temperature measurement (T^0) and a reference temperature (T_{ref}) is greater than or equal to a threshold value. For example, if the threshold value is set at 7°C, then an off-temperature condition may exist when $|T^0 - T_{ref}| \geq 7°C$. If an off-temperature condition is determined to possibly exist at this initial query (*i.e.*, the query at step 704 returns "YES"), then the cyclic compensation process may proceed (as discussed further below). If, however, the initial query at step 704 returns "NO", then no off-temperature condition may exist and the process may proceed directly to step 709 where the preliminary analyte concentration (G^0) may be reported as the analyte measurement. The threshold value may be set at any value (*e.g.*, 10, 7, 5, 3, 2, or 1°C) depending on the sensitivity desired for detecting an off-temperature condition.

[0117] The cyclic compensation process shown in FIGURE 7A may take more than one cycle, so a counter (n) is used to track each cycle and is set to n=1 at step 705.

[0118] At step 706, an n^{th} back-calculated temperature (T^n) is determined based on the $(n\text{-}1)^{th}$ analyte concentration (G^{n-1}). In other words, an n^{th} back-calculated temperature (T^n) is determined as a function of the $(n\text{-}1)^{th}$ analyte concentration, *i.e.*, $T^n = f(G^{n-1})$.

[0119] At step 707, an n^{th} temperature difference (ΔT^n) is determined as follows:

$$\Delta T^n = T^n - T^{n-1}{}_{adj} \quad (11)$$

where T^n is the n^{th} back-calculated temperature (from step 706) and, for n=1, T^{n-1}_{adj} is the temperature measurement (T^0) generated by biosensor system at step 702.

[0120] An off-temperature condition is detected by querying at step 708 whether the absolute value of the n^{th} temperature difference is greater than or equal to a preset value, *i.e.*, $|\Delta T^n| \geq$ preset value. For example, if the preset value is set at 5°C, then an off-temperature condition would be detected when $|\Delta T^n| \geq 5°C$, that is when the n^{th} back-calculated temperature (T^n) differs from the previously adjusted temperature (T^{n-1}_{adj}) by 5°C or more. The preset value may be set at any value (*e.g.*, 10, 7, 5, 3, 2, or 1°C) depending on the sensitivity desired for detecting an off-temperature condition; it also may be set to progressively decrease, for example, with each cycle, or the like.

[0121] If no off-temperature condition is detected based on the n^{th} temperature difference, (ΔT^n) (*i.e.*, the query of 708 returns "NO"), then the $(n\text{-}1)^{th}$ analyte concentration (G^{n-1}) is reported by the biosensor system as the analyte measurement at step 709.

[0122] If an off-temperature condition is detected based on n^{th} temperature difference, (ΔT^n) (*i.e.*, the query of 708 returns "YES"), then an n^{th} adjusted temperature (T^n_{adj}) is determined at step 710 as follows:

$$T^n_{adj} = T^{n-1}_{adj} + WC\Delta T^n \quad (12)$$

where, for n=1, T^{n-1}_{adj} is the temperature measurement (T^0) generated by biosensor system at step 702, ΔT^n is the n^{th} temperature difference (from step 707), and WC is a weighting coefficient that may be any value from zero (0) up to and including one (1). The weighting coefficient (WC) is used to determine how much of the n^{th} back-calculated temperature (T^n) to use to adjust the previously adjusted temperature (T^{n-1}_{adj}). When WC=1, then the n^{th} back-calculated temperature (T^n) completely replaces the previously adjusted temperature, so that $T^n_{adj} = T^n$.

[0123] At step 711, an n^{th} analyte concentration (G^n) is determined by converting the measured primary output signal (from step 701) using the conversion function with the n^{th} adjusted temperature (T^n_{adj}, from step 710) to compensate for the effect of temperature on the measured primary output signal. The counter, n, is advanced by one (*i.e.*, n=n+1) at step 712, and another cycle started at step 706. The cycle of steps 706-712 may be repeated until the query at 708 returns "NO" and an off-temperature condition is not detected based on the n^{th} temperature difference (ΔT^n), at which point the $(n\text{-}1)^{th}$ analyte concentration (G^{n-1}) is reported by the biosensor system as the analyte measurement at step 709.

[0124] FIGURE 7B illustrate the effect of WC on a cyclic temperature compensation process applied for one cycle of steps 706 – 711 according to the implementation shown in FIGURE

7A. FIGURE 7B plots the error in terms of bias/%-bias from a one cycle application of the conversion function with temperature compensation using the back-calculated temperature to fully compensate for the effect of temperature (*i.e.*, WC=1) (□) and a one cycle application of the conversion function with temperature compensation using a portion of the back-calculated temperature to partially compensate for the effect of temperature (*i.e.*, WC=0.65) (◆), plotted along with the average measured meter temperature (Δ). Compared to the error from a conventional one-way application of a standard conversion function with temperature compensation (see FIGURE 6B, one-way data plotted using (×)), the system error is reduced from ~20% to ~5% using WC=1 and to ~15% using WC=0.65 at more extreme off-temperature conditions (*e.g.*, measured meter temperature at ~5°C). Using the back-calculated temperature to fully compensate for the effect of temperature (WC=1) may in some instances over-compensate for the effect of temperature, for example, at less extreme off-temperature conditions (*e.g.*, measured meter temperature at ~35°C); thus, in some instances, it may be desirable to use WC<1 to compensate for the effect of an extraneous stimulus in a more gradual manner.

[0125] Table 1 below shows data generated using an embodiment of a cyclic compensation method similar to that shown in the flowchart 700 of FIGURE 7A to compensate the temperature effect in an analyte determination during an off-temperature condition. The data in Table 1 were generated using a biosensor system, three YSI reference glucose samples (glucose concentration levels of 85.9, 169.8 and 84.0 mg/dL) and sensors stored at ~22°C and meters stored at 5°C, 22°C and 40°C. The back-calculated temperatures (T^n) were determined using the normalizing calibration information embodied by Equation (4), above (*see also* FIGURE 3C and accompanying text). The weighting coefficient (WC) was set equal to 1 (*i.e.*, WC=1) so that $T^n_{adj}=T^n$.

Table 1: Summary of cyclic compensation process for T^n_{adj} and G^n

	YSI	T^0	G^0	bias/ %-bias	$T^0 - T_{ref}$	Initial Off-T Y/N?[a]			
-	85.9	21.9	87.4	1.6%	-3.1	N			
-	169.8	5.7	201.5	18.7%	-19.3	Y			
-	84.0	39.0	68.8	-15.2%	14.1	Y			
n	YSI	T^{n-1}_{adj}	G^{n-1}	T^n	ΔT^n	Off-T Y/N?	T^n_{adj}	G^n	bias/ %-bias
1	85.9	21.9	87.4	20.5	-1.4	N[b]	--	--	--

1	169.8	5.7	201.5	16.7	11.0	Y[b]	16.7	175.2	3.2%
1	84.0	39.0	68.8	30.8	-8.2	Y[b]	30.8	80.2	-4.5%
2	85.9	21.9	--	--	--	--	--	--	--
2	169.8	16.7	175.2	19.9	3.2	N[b], Y[c]	19.9	172.0[b]	1.3%[b]
2	84.0	30.8	80.2	25.9	-4.9	N[b], Y[c]	25.9	88.7[b]	5.6%[b]
3	85.9	21.9	--	--	--	--	--	--	--
3	169.8	19.9	172.0[b]	20.3	0.4	N[c], N[d]	20.3	--	--
3	84.0	25.9	88.7[b]	23.0	-2.9	N[c], Y[d]	23.0	93.8[c]	9.8%[c]
4	85.9	21.9	--	--	--	--	--	--	--
4	169.8	20.3	--	--	--	--	--	--	--
4	84.0	23.0	93.8[c]	21.5	-1.5	N[d]	21.5	--	--

Notes:

T^0 = temperature measurement

G^0 = preliminary analyte concentration ($=f(T^0)$)

$T_{ref} = 25°C$

T^n = n^{th} back-calculated temperature ($=f(G^{n-1})$)

$\Delta T^n = T^n - T^{n-1}{}_{adj}$

[a] Initial off-T criterion: $|T^0 - T_{ref}| \geq 7°C$ (threshold value)

[b] Off-T criterion: $|\Delta T^n| \geq 5°C$ (preset value)

[c] Off-T criterion: $|\Delta T^n| \geq 3°C$ (preset value)

[d] Off-T criterion: $|\Delta T^n| \geq 2°C$ (preset value)

$T^n{}_{adj}$ = n^{th} adjusted temperature (here WC=1, therefore $T^n{}_{adj} = T^n$)

$G^n = f(T^n{}_{adj})$

bias/%-bias = $(G^n - YSI)/YSI$

[0126] As shown in FIGURE 7A, the process begins with a biosensor system measuring a primary output signal and generating a temperature measurement (T^0). A preliminary glucose concentration (G^0) is determined using the temperature measurement (T^0) to compensate for the effect of temperature on the measured primary output signal. As seen in Table 1, the preliminary analyte concentrations at measured meter temperatures (T^0) of 5.7 and 39.1°C for YSI samples having glucose concentration levels of 169.8 and 84.0 mg/dL, respectively, have bias/%-biases larger than ±10%. Applying the initial criterion of $|T^0 - T_{ref}| \geq 7°C$ (threshold value), an off-temperature condition may exist for YSI samples having glucose concentration levels of 169.8 and 84.0 mg/dL, but an off-temperature condition does not exist for the YSI

sample having a glucose concentration of 85.9 mg/dL with a measured meter temperature of 21.9°C, so no cyclic compensation may be necessary for this sample measurement. In some embodiments, such as the one shown in FIGURE 7A, if the initial off-temperature criterion is not met, then no cyclic compensation is applied and back-calculating a temperature is not necessary. For purposes of illustrating a second off-temperature criterion based on a back-calculated temperature, the data shown in Table 1 includes a first back-calculated temperature and $|\Delta T^n|$ calculated for the YSI sample having a glucose concentration of 85.9 mg/dL, for which no off-temperature condition was detected based on the initial criterion.

[0127] A first back-calculated temperature (T^1, for n=1) is determined based on the preliminary analyte concentration (G^0). Applying the criterion of $|\Delta T^1 = T^1 - T^0| \geq 5°C$ (preset value), no off-temperature condition is detected for the YSI sample having a glucose concentration of 85.9 mg/dL with a measured meter temperature of 21.9°C, therefore no cyclic compensation is performed on this sample measurement. An off-temperature condition is detected for YSI samples having glucose concentration levels of 169.8 and 84.0 mg/dL, so for these two YSI samples, a first adjusted temperature (T^1_{adj}) is calculated (using WC=1, so that $T^1_{adj} = T^1$) and cycled as an input to determine a first analyte concentration (G^1). Compared to the preliminary analyte concentration of these two YSI samples, the error in the first analyte concentration (G^1) has been reduced to within ±5%.

[0128] For n=2, a second back-calculated temperature (T^2) is determined based on the first analyte concentration (G^1). If the preset value is kept the same, so that the same criterion of $|\Delta T^n| \geq 5°C$ is applied, then no off-temperature condition is detected for these YSI samples (169.8 and 84.0 mg glucose/dL) and no further cyclic compensation is performed. However, if the preset value is reduced and a criterion of $|\Delta T^n| \geq 3°C$ is applied, then an off-temperature condition is detected for both of these YSI samples, and a second adjusted temperature (T^2_{adj}) is calculated (using WC=1, so that $T^2_{adj} = T^2$) and cycled as an input to determine a second analyte concentration (G^2). The error in the second analyte concentration (G^2) for these two YSI samples remains less than ±10%, so within presently acceptable performance limits. Additionally, the second back-calculated temperature values (T^2) are closer to the expected value of the meter temperature (~22°C) than the first back-calculated temperatures (T^1).

[0129] For n=3, a third back-calculated temperature (T^3) is determined based on the second analyte concentration (G^2) for these two YSI samples (169.8 and 84.0 mg glucose/dL). Applying the criterion of $|\Delta T^n| \geq 3°C$, no off-temperature condition is detected for either sample, so no further cyclic compensation is performed. If desired, for example, to drive the back-calculated temperature closer to the sample/sensor temperature, the preset value may be

reduced further, for example, a criterion of $|\Delta T^n| \geq 2°C$ is applied. With the preset value set at 2°C, an off-temperature condition is detected for the YSI sample having 84.0 mg glucose/dL, and another cycle of compensation applied to this sample measurement, with a third adjusted temperature (T^3_{adj}) calculated (using WC=1, so that $T^3_{adj} = T^3$) and cycled as an input to determine a third analyte concentration (G^3).

[0130] For n=4, a fourth back-calculated temperature (T^4) is determined based on the third analyte concentration (G^3) for the YSI sample having 84.0 mg glucose/dL. Applying the criterion of $|\Delta T^n| \geq 2°C$, no off-temperature condition is detected, so no further cyclic compensation is performed. As can be seen in Table 1, the fourth back-calculated temperature (T^4) is even closer to the expected meter temperature than any of the previously back-calculated temperatures.

[0131] Reviewing the data in Table 1, it can be seen that repeated cyclic compensation, particularly used in conjunction with progressively reducing the preset value and refining the off-temperature criterion, may be used to gradually drive the back-calculated temperature to the expected sensor/sample temperature. Progressively reducing the preset value, however, does not necessarily result in a concomitant progressive reduction in the error in the analyte concentration as other error sources may become more expressed. However, the error in the analyte concentration remains within presently acceptable performance limits (*e.g.*, ±10%).

[0132] Table 2 below shows data generated using an embodiment of a cyclic compensation method similar to that shown in flowchart 240 of FIGURE 2D to compensate the hematocrit effect in an analyte determination. In this embodiment, after an initial determination that an off-condition exists based on $|i_{Hct\_Ref} - i^0_{Hct}| \geq 300$ (threshold value) and $|\Delta i^1_{Hct} = i^0_{Hct} - i^1_{Hct}| \geq 300$ (preset value), the cyclic compensation process was carried out for a pre-determined number of cycles, in this case $N = 9$. The data in Table 2 were generated from a YSI reference sample having a glucose concentration level of 245 mg/dL and 38% Hct, using a biosensor system having a dedicated Hct electrode. The first line of data includes the data generated directly from the biosensor measurement (i^0_{Hct}, G^0). The back-calculated hematocrit signals (i^n_{Hct}) were determined using the normalizing calibration information embodied by Equation (8), above (*see also* FIGURE 3G and accompanying text) and were used in calculating the n^{th} analyte concentration (*i.e.*, $G^n = f(i^n_{Hct})$). In order to monitor the progress of the cyclic compensation, the off-condition criteria and bias/%-bias were calculated for each cycle.

[0133] The generated Hct signal (i^0_{Hct} = 791.5 mV) is low compared to the reference value (i_{Hct_Ref} = 2000 mV, so $|i_{Hct\_Ref} - i^0_{Hct}|$ = 1208.5 mV) and also low compared to the first back-

calculated Hct signal (i^{1}_{Hct} = 1271.8 mV, so $|\Delta i^{1}_{Hct} = i^{0}_{Hct} - i^{1}_{Hct}|$ = 480.3 mV), which indicate an off-condition exists. The preliminary glucose concentration (G^0) has a %-bias of 38.3%. The data in Table 2 show that after 9 cycles of compensation using the back-calculated Hct signal, the %-bias in glucose concentration is reduced to less than 10%.

Table 2: Summary of cyclic compensation process for i^{n}_{Hct} and G^n

n	YSI	%Hct	i^{0}_{Hct}	G^0 (bias/ %-bias)	$i_{Hct\text{-}ref} - i^{0}_{Hct}$	i^{n}_{Hct}	G^n (bias/ %-bias)	$i_{Hct\text{-}ref} - i^{n}_{Hct}$	Δi^{n}_{Hct}
1	245	38	791.5	338.2 (38.5%)	1208.5	1271.8	329.1 (34.6%)	728.2	480.3
2	--	--	--	--	--	1321.1	319.6 (30.7%)	678.9	49.3
3	--	--	--	--	--	1376.4	309.7 (26.7%)	623.6	55.2
4	--	--	--	--	--	1436.9	299.8 (22.6%)	563.1	60.5
5	--	--	--	--	--	1501.5	290.2 (18.7%)	498.5	64.7
6	--	--	--	--	--	1568.5	281.6 (15.2%)	431.5	67.0
7	--	--	--	--	--	1632.3	274.6 (12.3%)	367.7	63.8
8	--	--	--	--	--	1687.6	268.8 (9.9%)	312.4	55.3
9	--	--	--	--	--	1735.6	263.9 (7.9%)	264.4	48.0

Notes:

i^{0}_{Hct} = generated Hct signal

G^0 = preliminary analyte concentration ($=f(i^{0}_{Hct})$)

$i_{Hct\text{-}ref}$ = 2000

i^{n}_{Hct} = n^{th} back-calculated Hct signal ($=f(G^{n-1})$)

$\Delta i^{n}_{Hct} = i^{n}_{Hct} - i^{n-1}_{Hct}$

$G^n = f(i^{n}_{Hct})$

bias/%-bias = $(G^n - YSI)/YSI$

Off-T criteria: $|i_{Hct\text{-}ref} - i^{n}_{Hct}| \geq 300$ (threshold value) and $|\Delta i^{n}_{Hct}| \geq 300$ (preset value)

[0134] The methods of the present disclosure that may be implemented may be in an electrochemical biosensor system, an optical system, a combination thereof, or the like. FIGURE 8 depicts a schematic representation of one embodiment of a biosensor system 800 in which the methods of the present disclosure may be implemented. The biosensor system

800 includes a measurement device 802 and a test sensor 804. The measurement device 802 may be implemented in an analytical instrument, including a bench-top device, a portable or hand-held device, or the like.

[0135] The biosensor system 800 typically determines the analyte concentration of the sample using calibration information stored in the measurement device 802. The biosensor system 800 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 800 may have other configurations and may include additional components.

[0136] The test sensor 804 typically has a base 806 that forms a reservoir 808 and a channel 810 with an opening 812. The reservoir 808 and the channel 810 may be covered by a lid with a vent. The reservoir 808 defines a partially-enclosed volume and 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 808 and/or the channel 810. The reagents may include one or more enzymes, binders, mediators, and like species, and/or a chemical indicator. The test sensor 804 has a sample interface 814 adjacent to the reservoir 808. The test sensor 804 may have other configurations.

[0137] In an electrochemical system, the sample interface 814 has conductors or contacts electrically connected to a working electrode (not shown) and a counter electrode (not shown) from which the output signal may be measured. The sample interface 814 also may include conductors or contacts electrically connected to one or more additional electrodes (not shown) 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 806 that forms the reservoir 808. The electrodes may extend or project into the reservoir 808. A dielectric layer may partially cover the conductors and/or the electrodes. The sample interface 814 may have other electrodes and conductors and contacts.

[0138] In an optical sensor system, the sample interface 814 typically has one or more optical portals or apertures for probing the sample with light.

[0139] The measurement device 802 includes electrical circuitry 816 connected to a sensor interface 818 and an optional display 820. The electrical circuitry 816 includes a processor 822 connected to a signal generator 824, a temperature sensor 826, and a storage medium 828.

[0140] The signal generator 824 is capable of providing an electrical input signal to the sensor interface 818 in response to the processor 822. In an optical system, the electrical input signal

may be used to operate or control the detector and light source in the sensor interface 818. In an electrochemical system, the electrical input signal may be transmitted via the sensor interface 818 to the sample interface 814 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 824 also may be capable of recording an output signal from the sensor interface as a generator-recorder.

[0141] The temperature sensor 826 is capable of measuring the ambient temperature of the measurement device 802, and may be a thermister, thermometer, or other temperature sensing device.

[0142] The storage medium 828 may be a magnetic, optical, or semiconductor memory, another storage device, or the like. The storage medium 828 may be a fixed memory device, a removable memory device, such as a memory card, remotely accessed, or the like. The storage medium 828 may store the computer-programmed instructions and calibration and other information used in the analyte measurement, analysis and/or methods of the present disclosure (such as threshold values and the preset values used to detect an off-condition).

[0143] The storage medium 828 also may store a normalization function and/or normalized calibration information that may be used to back-calculate a secondary output signal from a measured primary output signal according to the methods of the present disclosure. Such a normalization function and/or normalized calibration information may be represented graphically, for example as shown in FIGs. 3B-3C, 3F-3G and 3I-3J, or mathematically, for example as shown in Equations (1)-(5), (6)-(8) and (9)-(10), or as a combination thereof, or the like. The normalization function and normalized calibration information are preferably represented as equations, which may be represented by a program number (PNA) table, another look-up table, or the like.

[0144] The processor 822 is configured to execute computer-programmed instructions to implement the analyte measurement and analysis including the methods of the present disclosure. The processor 822 also may be configured to interact with the signal generator 824 to, for example, provide the electrical input signal to the sensor interface 818; with the temperature sensor 826 to, for example, generate and receive a temperature measurement (T^0); and with the sensor interface 818 to, for example, receive a primary and/or other secondary output signal(s) from the test sensor 804.

[0145] In an electrochemical system, the primary output signal is measured using the working

and counter electrodes in response to the reaction of the analyte in the sample. Secondary output signals also may be measured from additional electrodes. In optical systems, the detector or detectors of the sensor interface 818 may receive the primary and some secondary output signals.

[0146] The processor 822 may be further configured to execute computer-programmed instructions to start the analyte measurement and analysis (including the methods of this disclosure) in response to the presence of the test sensor 804 at the sensor interface 818, the application of a sample to the test sensor 804, user input, or the like. The results of the analyte analysis may be outputted to the display 820, a remote receiver (not shown), and/or may be stored in the storage medium 828.

[0147] Instructions to implement an analyte measurement, which may include determining an off-condition, back-calculating a secondary output signal based on a measured primary output signal, and/or cyclic compensation methods, may be provided by the computer readable software code stored in the storage medium 828. 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 822.

[0148] The foregoing description has been presented for the purpose of illustrating certain aspects of the present disclosure and is not intended to limit the disclosure. Persons skilled in the relevant art will appreciate that many additions, modifications, variations and improvements may be implemented in light of the above teachings and still fall within the scope of the present disclosure.

CLAIMS

I claim:

1. A method of determining an analyte concentration in a biological fluid sample, the method comprising:

measuring a measured primary output signal from the biological fluid sample, the measured primary output signal being primarily responsive to the analyte concentration in the biological fluid sample;

generating a generated secondary output signal, the generated secondary output signal being responsive to an extraneous stimulus affecting the measured primary output signal;

back-calculating a back-calculated secondary output signal based on the measured primary output signal;

adjusting the generated secondary output signal using the back-calculated secondary output signal to derive an adjusted secondary output signal; and

converting the measured primary output signal to the analyte concentration value using a conversion function with the adjusted secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal.

2. The method of claim 1, wherein the generated secondary output signal is extracted from the measured primary output signal.

3. The method of claim 1, wherein the generated secondary output signal is measured separately from the measured primary output signal.

4. The method of claim 1, wherein the extraneous stimulus is temperature.

5. The method of claim 1, wherein the extraneous stimulus is hematocrit (Hct).

6. The method of claim 1, wherein the extraneous stimulus is total hemoglobin (THb).

7. The method of any of claims 1-6, wherein back-calculating a secondary output signal based on the measured primary output signal comprises:

converting the measured primary output signal to a preliminary analyte concentration using the conversion function with the generated secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal;

normalizing the measured primary output signal relative to the preliminary analyte concentration to derive a normalized measured primary output signal; and

applying normalized calibration information to the normalized measured primary output signal, the normalized calibration information relating the normalized primary output signal to the secondary output signal.

8. The method of any of claims 1-7, wherein adjusting the generated secondary output signal comprises substituting the back-calculated secondary output signal for the generated secondary output signal.

9. The method of any of claims 1-7, wherein adjusting the generated secondary output signal comprises:

determining a difference by subtracting the generated secondary output signal from the back-calculated secondary output signal;

determining an adjustment amount by multiplying the difference with a weighting coefficient, wherein the weighting coefficient is a positive number not greater than 1; and

adding the adjustment amount to the generated secondary output signal.

10. A method of compensating an analyte measurement in an off-condition, the method comprising:

measuring a measured primary output signal from a biological fluid sample, the measured primary output signal being primarily responsive to an analyte concentration in the biological fluid sample;

generating a generated secondary output signal, the generated secondary output signal being responsive to an extraneous stimulus affecting the measured primary output signal;

converting the measured primary output signal to a preliminary analyte concentration using a conversion function with the generated secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal;

determining a first back-calculated secondary output signal from the measured primary output signal and the preliminary analyte concentration;

determining whether an off-condition exists; and

if the off-condition exists:

determining a first adjusted secondary output signal using the first back-calculated secondary output signal to adjust the generated secondary output signal; and

converting the measured primary output signal to a first analyte concentration using the conversion function with the first adjusted secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal.

11. The method of claim 10, wherein determining a first back-calculated secondary output signal from the measured primary output signal and the preliminary analyte concentration comprises:

normalizing the measured primary output signal relative to the preliminary analyte concentration to derive a normalized measured primary output signal; and

applying normalized calibration information to the normalized measured primary output signal, the normalized calibration information relating the normalized primary output signal to the secondary output signal.

12. The method of any of claims 10-11, wherein determining whether an off-condition exists comprises:

determining a first difference between the generated secondary output signal and the first back-calculated secondary output signal, wherein the off-condition exists when the absolute value of said first difference is greater than or equal to a first preset value.

13. The method of any of claims 10-11, wherein determining whether an off-condition exists comprises:

determining a second difference between the generated secondary output signal and a reference value, wherein the off-condition exists when the absolute value of said second difference is greater than or equal to a first threshold value.

14. The method of any of claims 10-13, further comprising:

determining a second back-calculated secondary output signal from the measured primary output signal and the first analyte concentration;

determining whether a second off-condition exists based on the first back-calculated secondary output signal; and

if the second off-condition exists:

determining a second adjusted secondary output signal using the second back-calculated secondary output signal to adjust the first adjusted secondary output signal; and

converting the measured primary output signal to a second analyte concentration using the conversion function with the second adjusted secondary output signal to compensate for the effect of the extraneous stimulus on the measured primary output signal.

15. The method of claim 14, wherein determining a second back-calculated secondary output signal from the measured primary output signal and the first analyte concentration comprises:

normalizing the measured primary output signal relative to the first analyte concentration to derive a normalized measured primary output signal; and

applying normalized calibration information to the normalized measured primary output signal, the normalized calibration information relating the normalized primary output signal to the secondary output signal.

16. The method of any of claims 14-15, wherein determining whether a second off-condition exists based on the first back-calculated secondary output signal comprises:

determining a third difference between the first back-calculated secondary output signal and the second back-calculated secondary output signal, wherein the off-condition exists when the absolute value of said third difference is greater than or equal to a second preset value.

17. The method of any of claims 14-15, wherein determining whether a second off-condition exists based on the first back-calculated secondary output signal comprises:

determining a fourth difference between the first back-calculated secondary output signal and the reference value, wherein the off-condition exists when the absolute value of said fourth difference is greater than or equal to a second threshold value.

18. A method of compensating an analyte measurement in an off-temperature condition, the method comprising:

measuring a measured primary output signal from a biological fluid sample, the measured primary output signal being primarily responsive to an analyte concentration in the biological fluid sample;

generating a temperature measurement using a temperature sensor;

converting the measured primary output signal to a preliminary analyte concentration using a conversion function with the temperature measurement to compensate for the effect of temperature on the measured primary output signal;

determining a first back-calculated temperature based on the measured primary output signal and the preliminary analyte concentration;

determining whether an off-temperature condition exists; and

if the off-temperature condition exists:

determining a first adjusted temperature using the first back-calculated temperature to adjust the temperature measurement; and

converting the measured primary output signal to a first analyte concentration using the conversion function with the first adjusted temperature to compensate for the effect of temperature on the measured primary output signal.

19. The method of claim 18, wherein determining a first back-calculated temperature from the measured primary output signal and the preliminary analyte concentration comprises:

normalizing the measured primary output signal relative to the preliminary analyte concentration to derive a normalized measured primary output signal; and

applying normalized calibration information to the normalized measured primary output signal, the normalized calibration information relating the normalized measured primary output signal to temperature.

20. The method of any of claims 18-19, wherein determining whether an off-temperature condition exists comprises:

determining a first difference between the first back-calculated temperature and the temperature measurement, wherein the off-temperature condition exists when the absolute value of said first difference is greater than or equal to a first preset value.

21. The method of any of claims 18-19, wherein determining whether an off-temperature condition exists comprises:

determining a second difference between the first temperature measurement and a reference temperature, wherein the off-temperature condition exists when the absolute value of said second difference is greater than or equal to a first threshold value.

22. The method of any of claims 18-21, further comprising:

determining a second back-calculated temperature based on the measured primary output signal and the first analyte concentration;

determining whether a second off-temperature condition exists based on the first back-calculated temperature; and

if the second off-temperature condition exists:

determining a second adjusted temperature using the second back-calculated temperature to adjust the first adjusted temperature; and

converting the measured primary output signal to a second analyte concentration using the conversion function with the second adjusted temperature to compensate for the effect of temperature on the measured primary output signal.

23. The method of claim 22, wherein determining a second back-calculated temperature from the measured primary output signal and the first analyte concentration comprises:

normalizing the measured primary output signal relative to the first analyte concentration to derive a normalized measured primary output signal; and

applying normalized calibration information to the normalized measured primary output signal, the normalized calibration information relating the normalized primary output signal to temperature.

24. The method of any of claims 22-23, wherein determining whether a second off-temperature condition exists based on the first back-calculated temperature comprises:

determining a third difference between the first back-calculated temperature and the second back-calculated temperature, wherein the second off-temperature condition exists when the absolute value of said third difference is greater than or equal to a second preset value.

25. The method of any of claims 22-23, wherein determining whether a second off-temperature condition exists based on the first back-calculated temperature comprises:

determining a fourth difference between the first back-calculated temperature and the reference temperature, wherein the second off-temperature condition exists when the absolute value of said fourth difference is greater than or equal to a second threshold value.

26. A biosensor system for determining an analyte concentration in a biological fluid sample, the biosensor system comprising:

a test sensor having a base and a sample interface,

the base having formed therein a reservoir for receiving the biological fluid sample, and

the sample interface being disposed adjacent to the reservoir; and

a measuring device configured to interface with the test sensor and having a sensor interface, a storage medium and a processor, the processor being connected with the sensor interface and the storage medium and being configured to execute computer-programmed instructions to:

receive, via the sensor interface, a measured primary output signal measured from the biological fluid sample in the reservoir, the measured primary output signal being primarily responsive to the analyte concentration;

receive a generated secondary output signal, the generated secondary output signal being responsive to an extraneous stimulus affecting the measured primary output signal;

back-calculate a back-calculated secondary output signal based on the measured primary output signal;

adjust the generated secondary output signal using the back-calculated secondary output signal to derive an adjusted generated secondary output signal; and

convert the measured primary output signal to the analyte concentration using a conversion function that is stored in the storage medium, wherein the conversion function uses the adjusted generated secondary output signal to compensate for the effect of extraneous stimulus on the measured primary output signal.

27. A biosensor system for determining an analyte concentration in a biological fluid sample in an off-condition, the biosensor system comprising:

a test sensor having a base and a sample interface,

the base having formed therein a reservoir for receiving the biological fluid sample, and

the sample interface being disposed adjacent to the reservoir; and

a measuring device configured to interface with the test sensor and having a sensor interface, a storage medium and a processor, the processor being connected with the sensor interface and the storage medium and being configured to execute computer-programmed instructions to:

receive, via the sensor interface, a measured primary output signal measured from the biological fluid sample in the reservoir, the measured primary output signal being primarily responsive to the analyte concentration;

receive a generated secondary output signal, the generated secondary output signal being responsive to an extraneous stimulus affecting the measured primary output signal;

back-calculate a back-calculated secondary output signal based on the measured primary output signal;

determine whether an off-condition exists; and

if the off-condition exists, adjust the generated secondary output signal using the back-calculated secondary output signal to derive an adjusted generated secondary output signal, and convert the measured primary output signal to the analyte concentration using the conversion function and the adjusted generated secondary output signal to compensate for the effect of the extraneous stimulus.

28. A biosensor system for determining an analyte concentration in a biological fluid sample in an off-temperature condition, the biosensor system comprising:

a test sensor having a base and a sample interface,

the base having formed therein a reservoir for receiving the biological fluid sample, and

the sample interface being disposed adjacent to the reservoir; and

a measuring device configured to interface with the test sensor and having a sensor interface, a temperature sensor, a storage medium and a processor, the processor being connected with the sensor interface, temperature sensor and the storage medium and being configured to execute computer-programmed instructions to:

receive, via the sensor interface, a measured primary output signal measured from the biological fluid sample in the reservoir, the measured primary output signal being primarily responsive to the analyte concentration;

receive a temperature measurement from the temperature sensor;

convert the measured primary output signal to a preliminary analyte concentration using a conversion function that is stored in the storage medium, wherein the conversion function uses the temperature measurement to compensate for the effect of temperature on the measured primary output signal;

back-calculate a back-calculated temperature based on the measured primary output signal and the preliminary analyte concentration;

determine whether an off-temperature conditions exists; and

if the off-temperature condition exists, adjust the temperature measurement using the back-calculated temperature to derive an adjusted temperature measurement, and convert the measured primary output signal to the analyte concentration using the conversion function and the adjusted temperature measurement to compensate for the effect of temperature on the measured primary output signal.

29. A method of back-calculating a secondary output signal based on a primary output signal, wherein the primary output signal is primarily responsive to a primary stimulus and the secondary output signal is responsive to an extraneous stimulus that affects the primary output signal, the method comprising:

normalizing the primary output signal to a corresponding value for the primary stimulus to derive a normalized primary output signal; and

applying normalized calibration information to the normalized primary output signal, the normalized calibration information relating the normalized primary output signal to the secondary output signal.

30. The method of claim 29, wherein the normalized calibration information is generated by:

measuring measured reference primary output signals from a plurality of reference samples, wherein each reference sample is associated with a known value of the primary stimulus;

generating a generated secondary output signal corresponding to each of the measured reference primary output signals;

correlating the measured reference primary output signals to the generated secondary output signals for each reference sample;

extrapolating, from the measured reference primary output signals for each reference sample, an extrapolated reference primary output signal value to a designated value of the secondary output signal;

correlating each extrapolated reference primary output signal value to its corresponding known value of the primary stimulus to generate a normalization function, wherein the normalization function, when applied to the primary output signal, eliminates the dependency of the primary output signal on the primary stimulus;

using the normalization function to normalize the measured reference primary output signals to derive normalized reference primary output signals; and

correlating the normalized reference primary output signals to the generated secondary output signals to generate the normalized calibration information.

31. The method of claim 30, wherein normalizing the primary output signal to the primary stimulus comprises:

using the normalization function to derive a normalization function value from the corresponding primary stimulus value; and

dividing the primary output signal by the normalization function value to determine the normalized primary output signal.

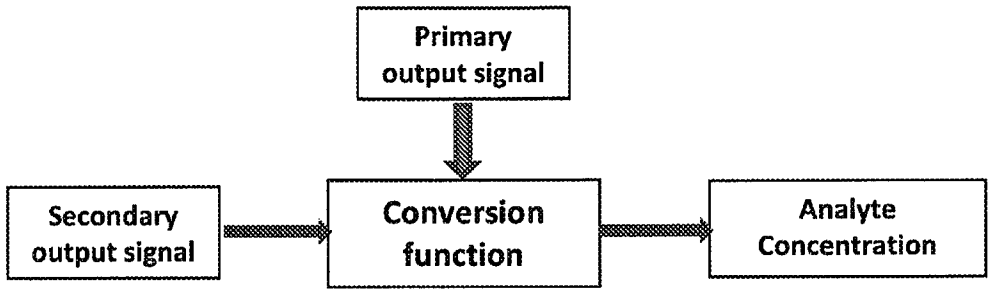
32. The method of any of claims 29-31, wherein the primary output signal is measured using a biosensor system and the primary stimulus is an analyte concentration.

33. The method of any of claims 29-32, wherein the extraneous stimulus is temperature.

34. The method of any of claims 29-32, wherein the extraneous stimulus is hematocrit (Hct).

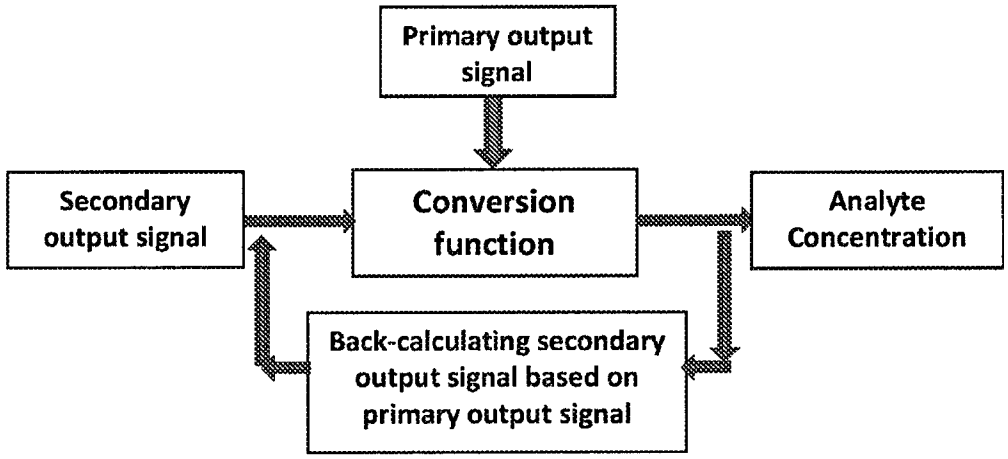
35. The method of any of claims 29-32, wherein the extraneous stimulus is total hemoglobin (THb).

FIGURE 1A (PRIOR ART)



One-way process

FIGURE 1B



Cyclic process

FIGURE 2A

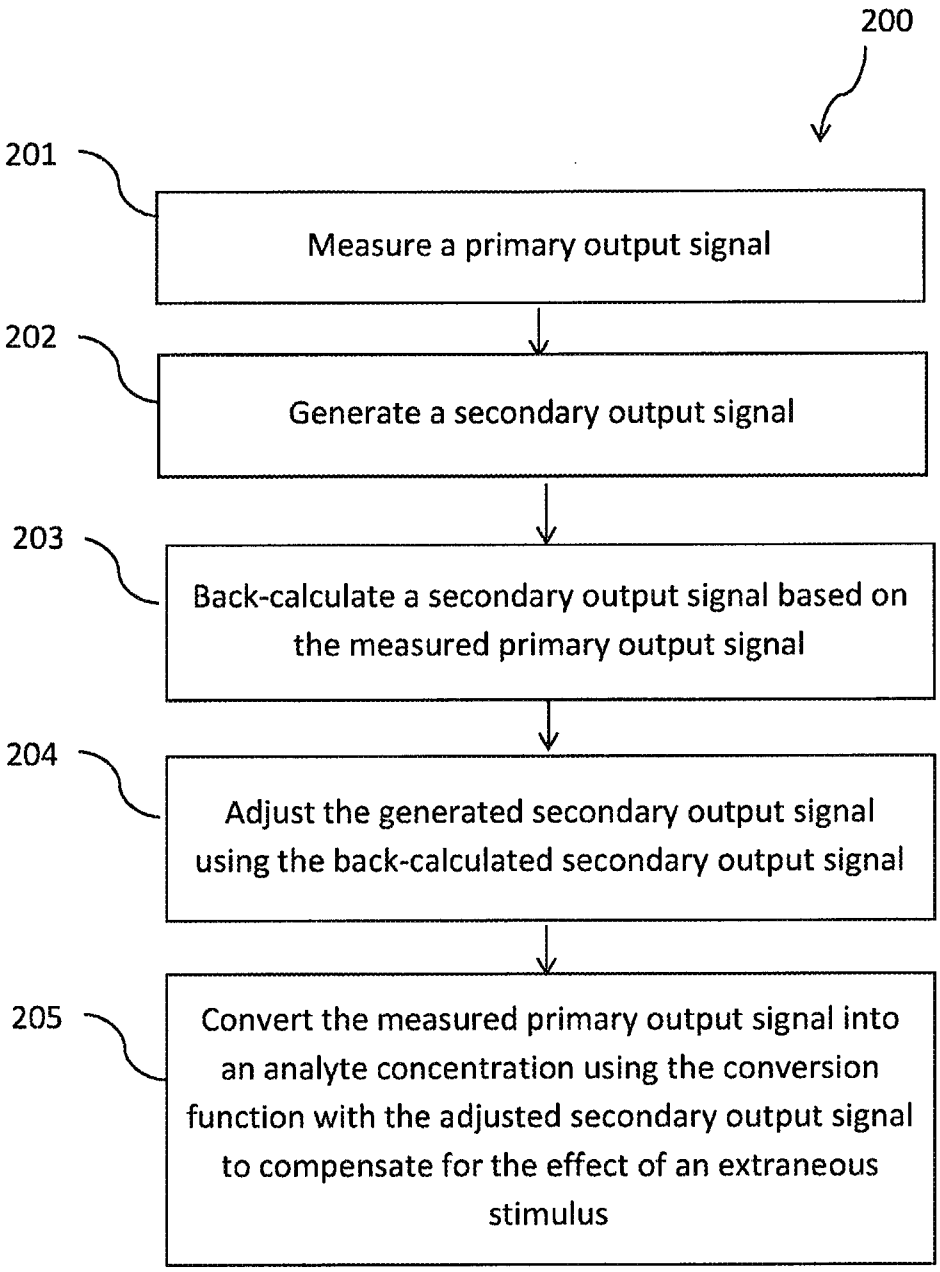

200
201
Measure a primary output signal
202
Generate a secondary output signal
203
Back-calculate a secondary output signal based on the measured primary output signal
204
Adjust the generated secondary output signal using the back-calculated secondary output signal
205
Convert the measured primary output signal into an analyte concentration using the conversion function with the adjusted secondary output signal to compensate for the effect of an extraneous stimulus

FIGURE 2B

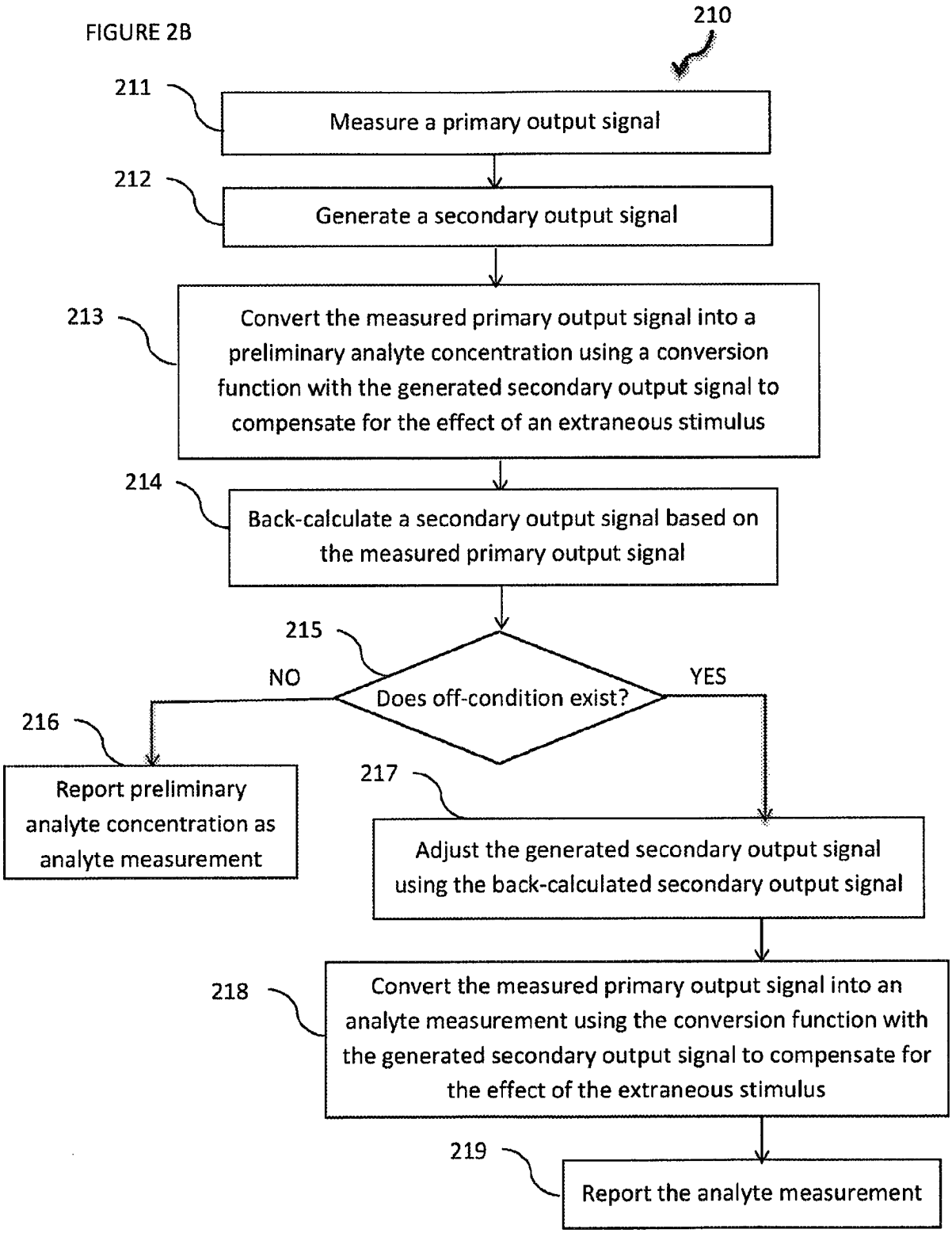

210
211
Measure a primary output signal
212
Generate a secondary output signal
213
Convert the measured primary output signal into a preliminary analyte concentration using a conversion function with the generated secondary output signal to compensate for the effect of an extraneous stimulus
214
Back-calculate a secondary output signal based on the measured primary output signal
215
Does off-condition exist?
NO
YES
216
Report preliminary analyte concentration as analyte measurement
217
Adjust the generated secondary output signal using the back-calculated secondary output signal
218
Convert the measured primary output signal into an analyte measurement using the conversion function with the generated secondary output signal to compensate for the effect of the extraneous stimulus
219
Report the analyte measurement

FIGURE 2C

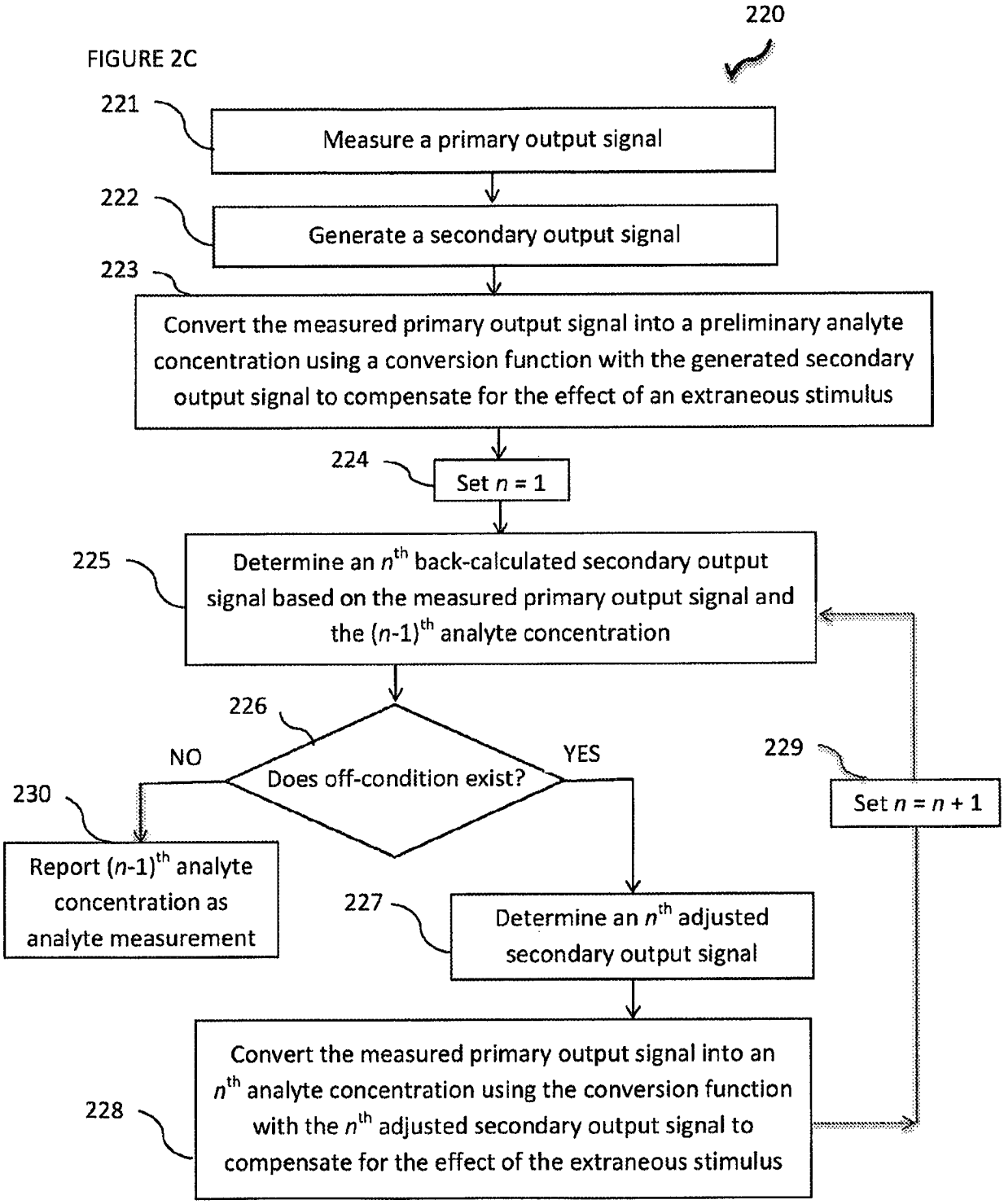

220
221
Measure a primary output signal
222
Generate a secondary output signal
223
Convert the measured primary output signal into a preliminary analyte concentration using a conversion function with the generated secondary output signal to compensate for the effect of an extraneous stimulus
224
Set n = 1
225
Determine an nth back-calculated secondary output signal based on the measured primary output signal and the (n-1)th analyte concentration
226
Does off-condition exist?
NO
YES
230
Report (n-1)th analyte concentration as analyte measurement
227
Determine an nth adjusted secondary output signal
228
Convert the measured primary output signal into an nth analyte concentration using the conversion function with the nth adjusted secondary output signal to compensate for the effect of the extraneous stimulus
229
Set n = n + 1

FIGURE 2D

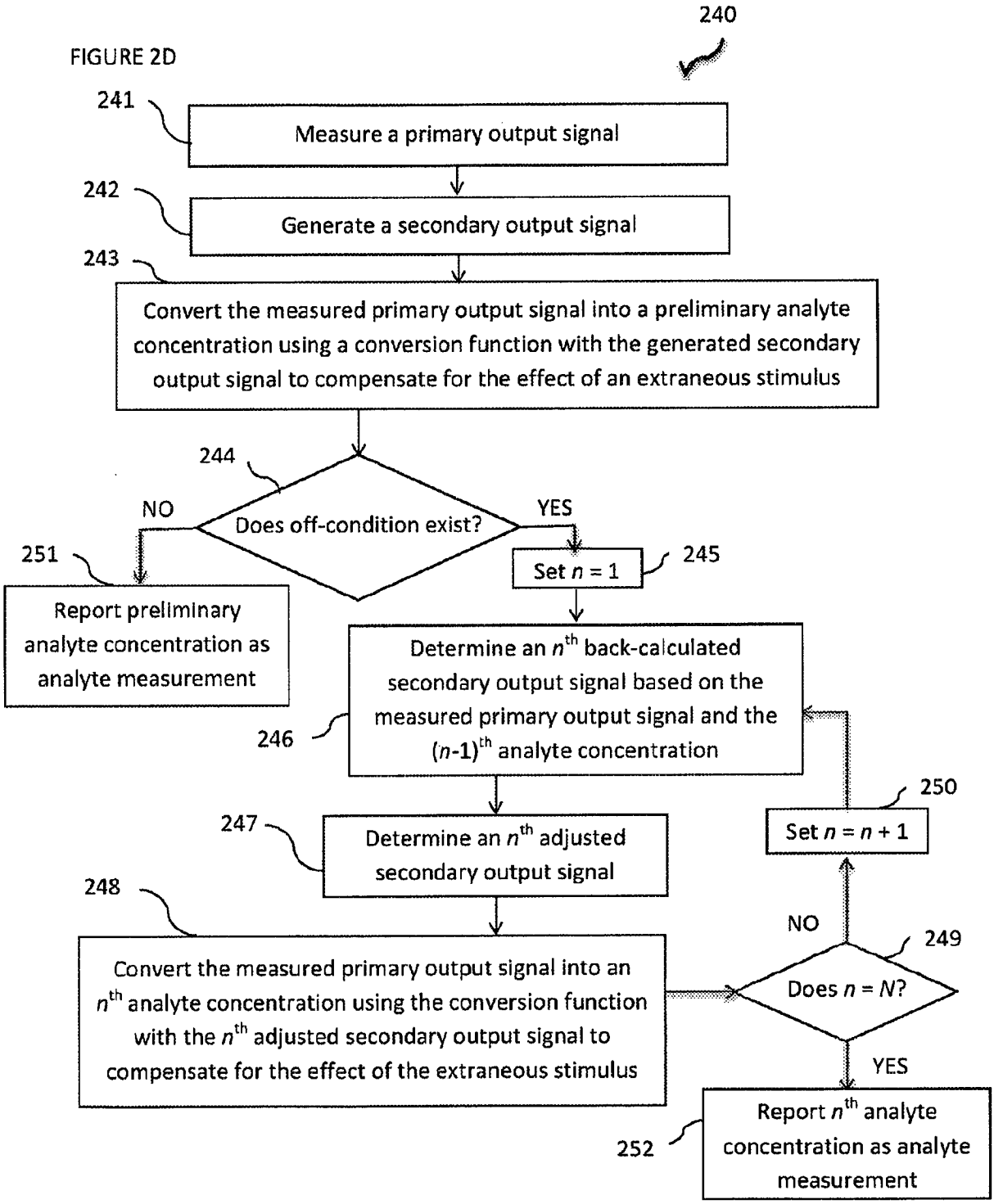

240
241
Measure a primary output signal
242
Generate a secondary output signal
243
Convert the measured primary output signal into a preliminary analyte concentration using a conversion function with the generated secondary output signal to compensate for the effect of an extraneous stimulus
244
Does off-condition exist?
NO
YES
251
Report preliminary analyte concentration as analyte measurement
Set n = 1
245
Determine an nth back-calculated secondary output signal based on the measured primary output signal and the (n-1)th analyte concentration
246
247
Determine an nth adjusted secondary output signal
248
Convert the measured primary output signal into an nth analyte concentration using the conversion function with the nth adjusted secondary output signal to compensate for the effect of the extraneous stimulus
250
Set n = n + 1
NO
249
Does n = N?
YES
252
Report nth analyte concentration as analyte measurement

FIGURE 3A

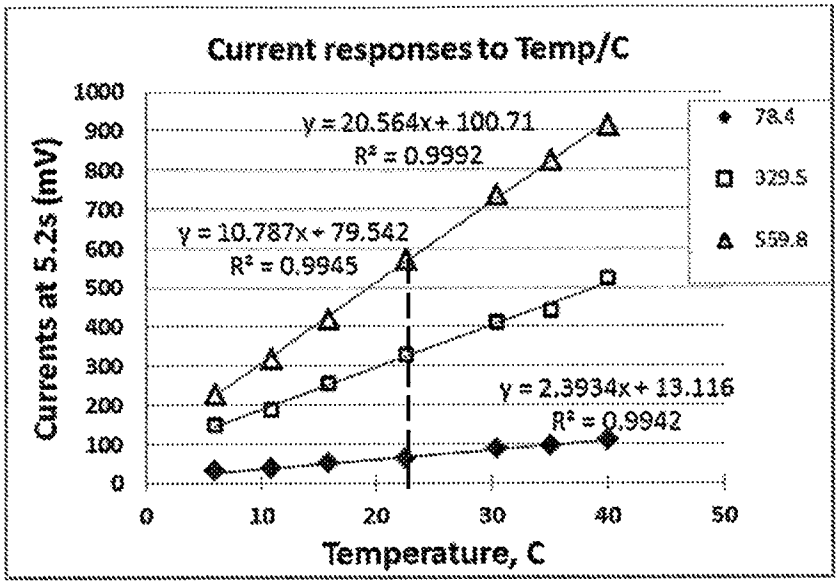


FIGURE 3B

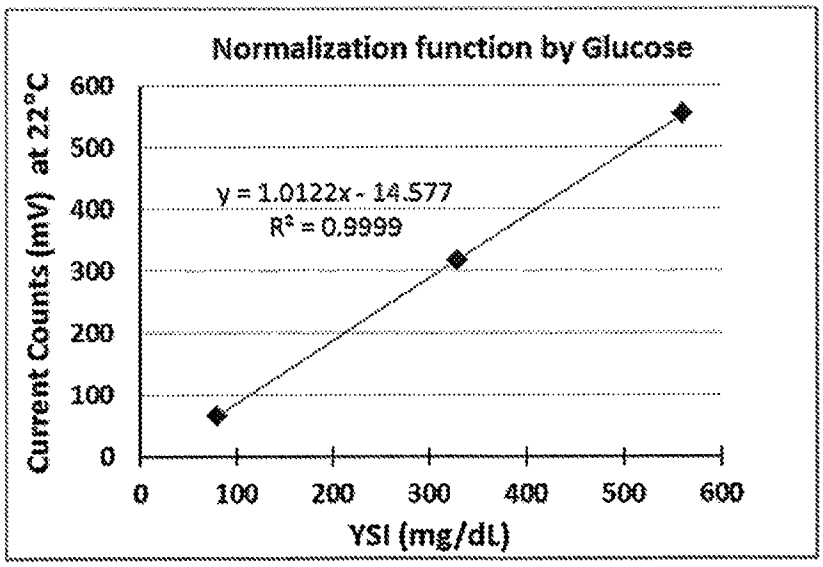


FIGURE 3C

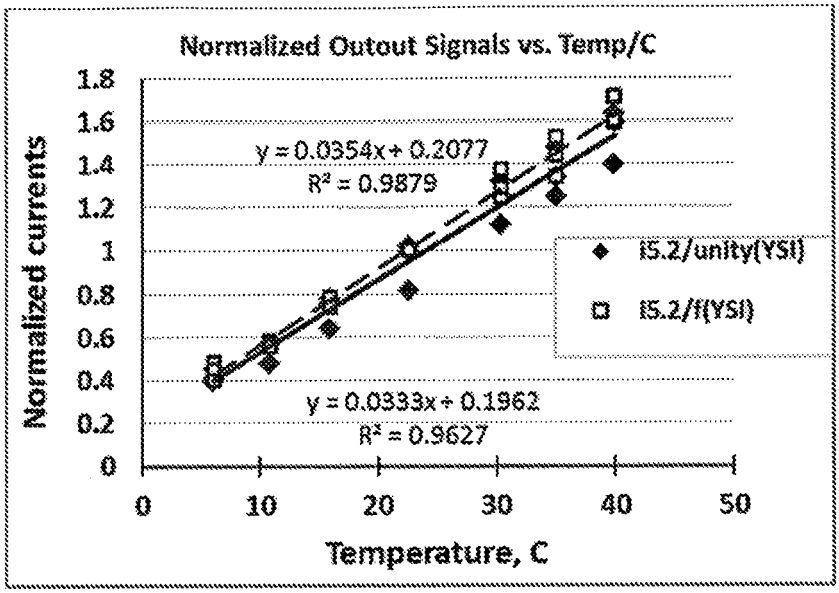


FIGURE 3D

Estimated accuracy of back-calculated temperatures		
	$\Delta T = T_{calc} - T_{meas}$	
	Eq. (4) (♦)	**Eq. (5)** (□)
Mean, °C	0.0	0.0
SD, °C	2.4	1.3

FIGURE 3E

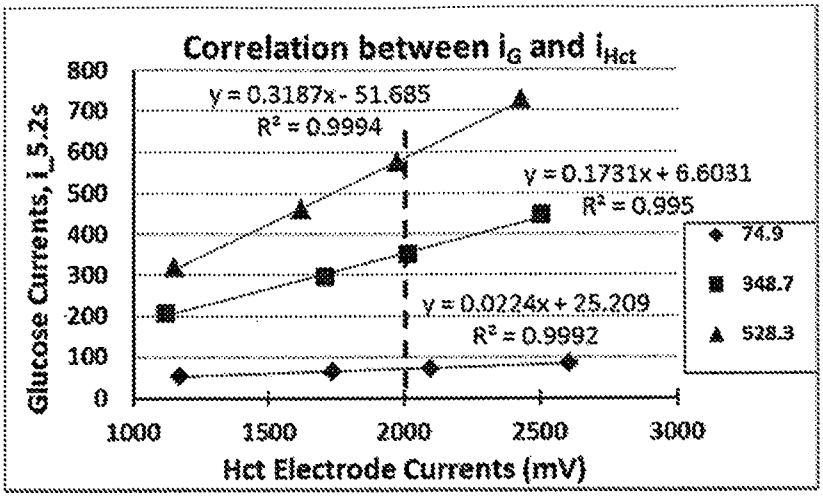


FIGURE 3F

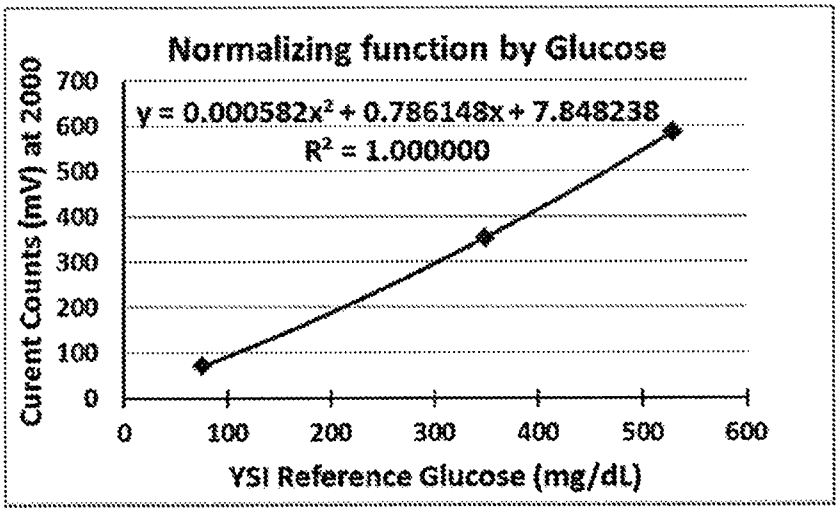


FIGURE 3G

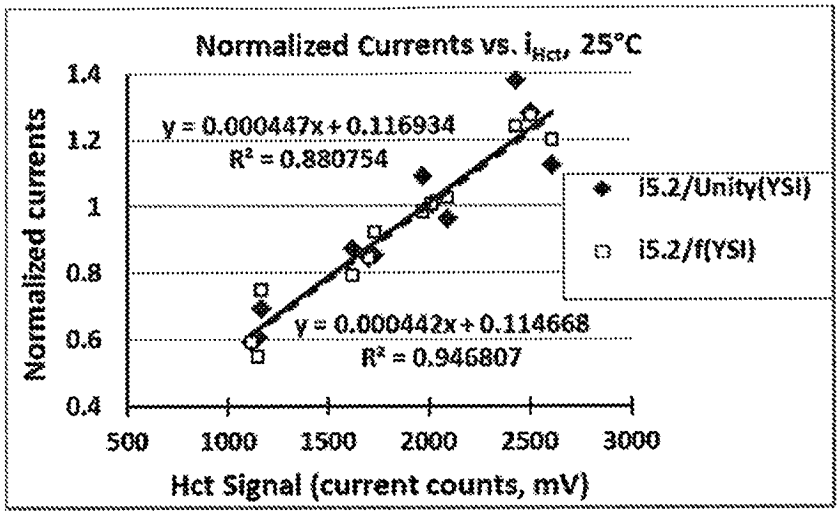


FIGURE 3H

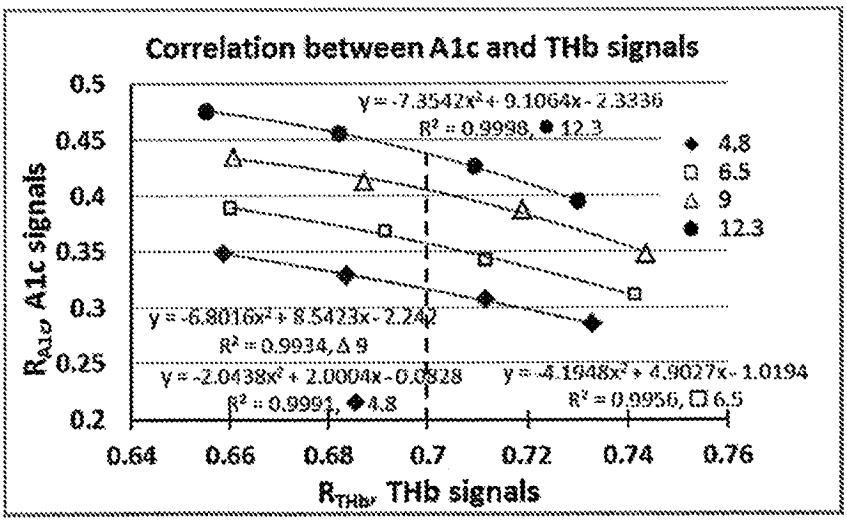


FIGURE 3I

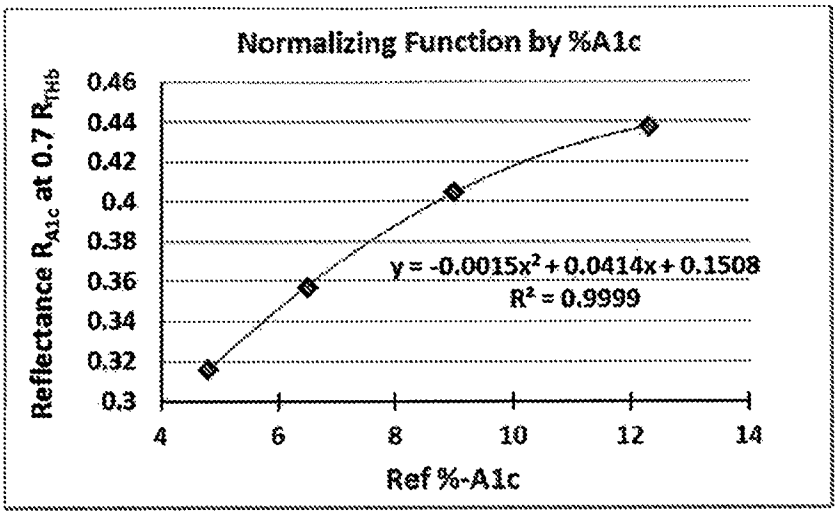


FIGURE 3J

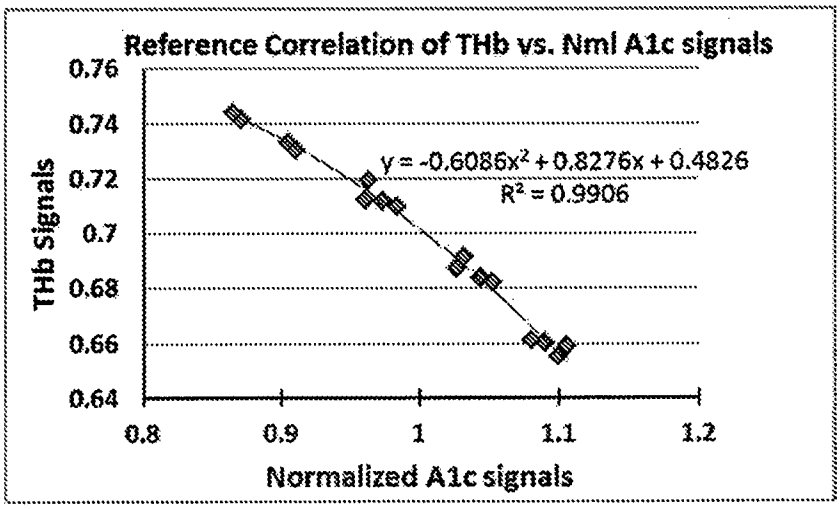


FIGURE 3K

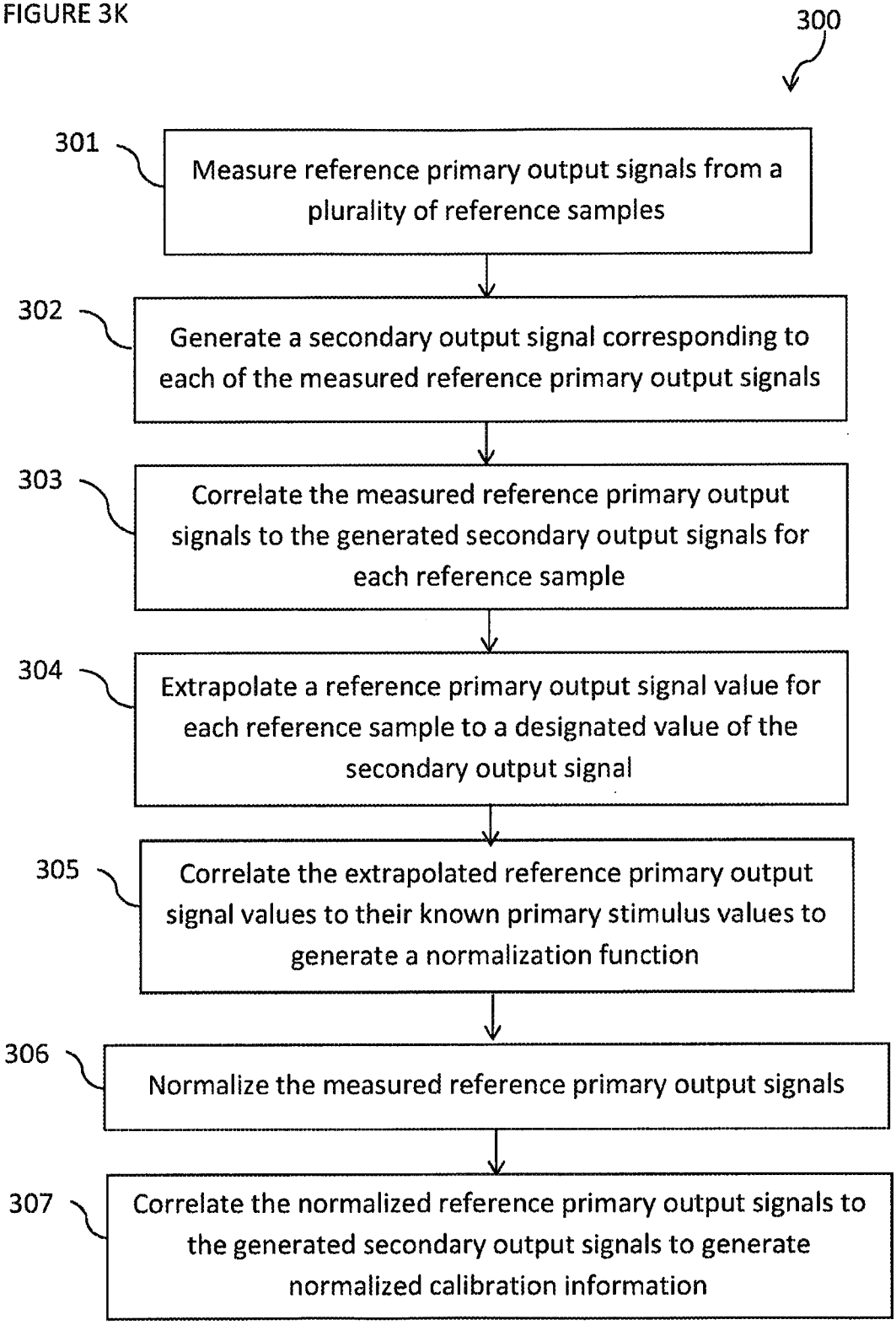

300
301
Measure reference primary output signals from a plurality of reference samples
302
Generate a secondary output signal corresponding to each of the measured reference primary output signals
303
Correlate the measured reference primary output signals to the generated secondary output signals for each reference sample
304
Extrapolate a reference primary output signal value for each reference sample to a designated value of the secondary output signal
305
Correlate the extrapolated reference primary output signal values to their known primary stimulus values to generate a normalization function
306
Normalize the measured reference primary output signals
307
Correlate the normalized reference primary output signals to the generated secondary output signals to generate normalized calibration information

FIGURE 4A

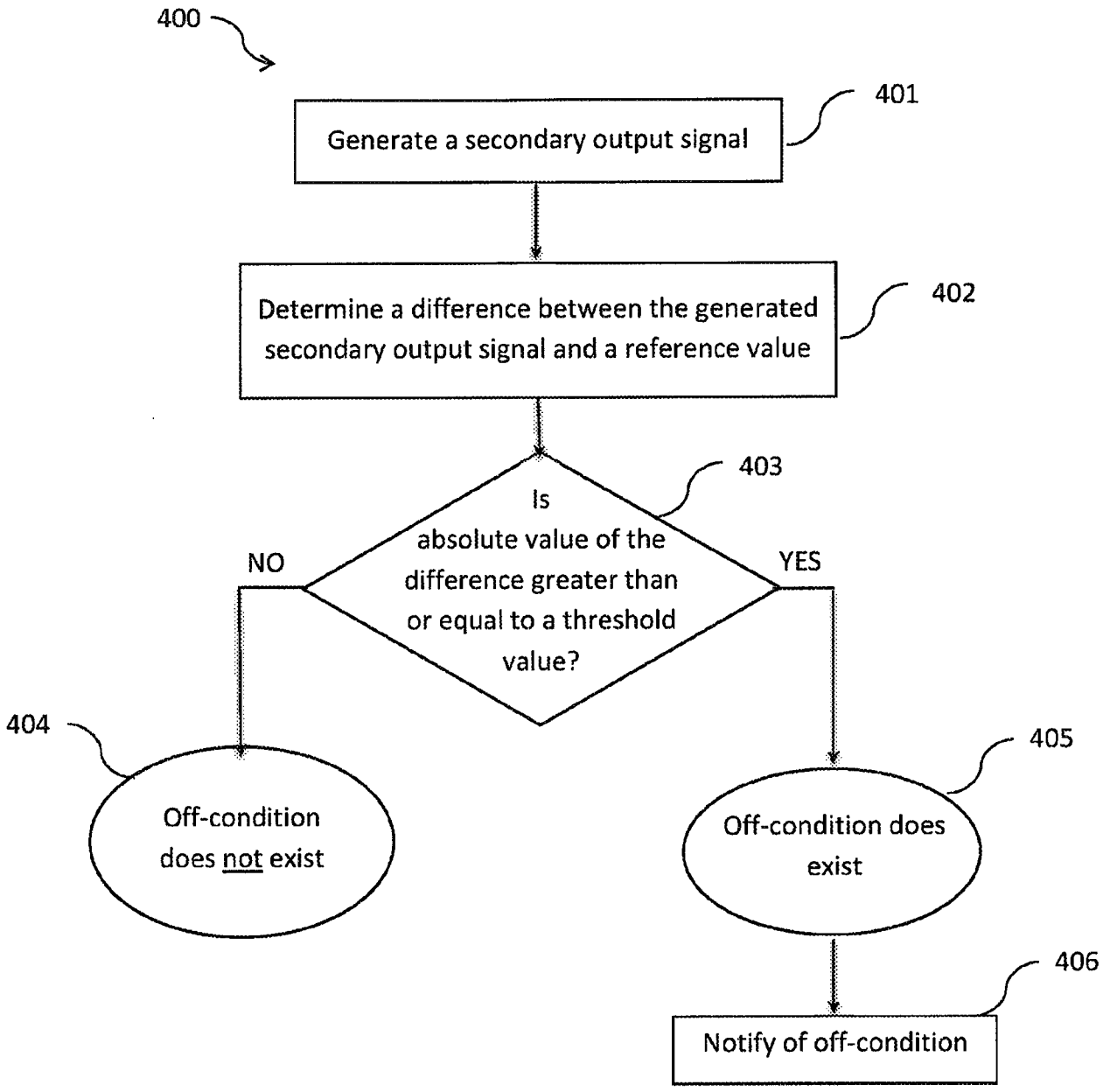

400
401
Generate a secondary output signal
402
Determine a difference between the generated secondary output signal and a reference value
403
Is absolute value of the difference greater than or equal to a threshold value?
NO
YES
404
Off-condition does not exist
405
Off-condition does exist
406
Notify of off-condition

FIGURE 4B

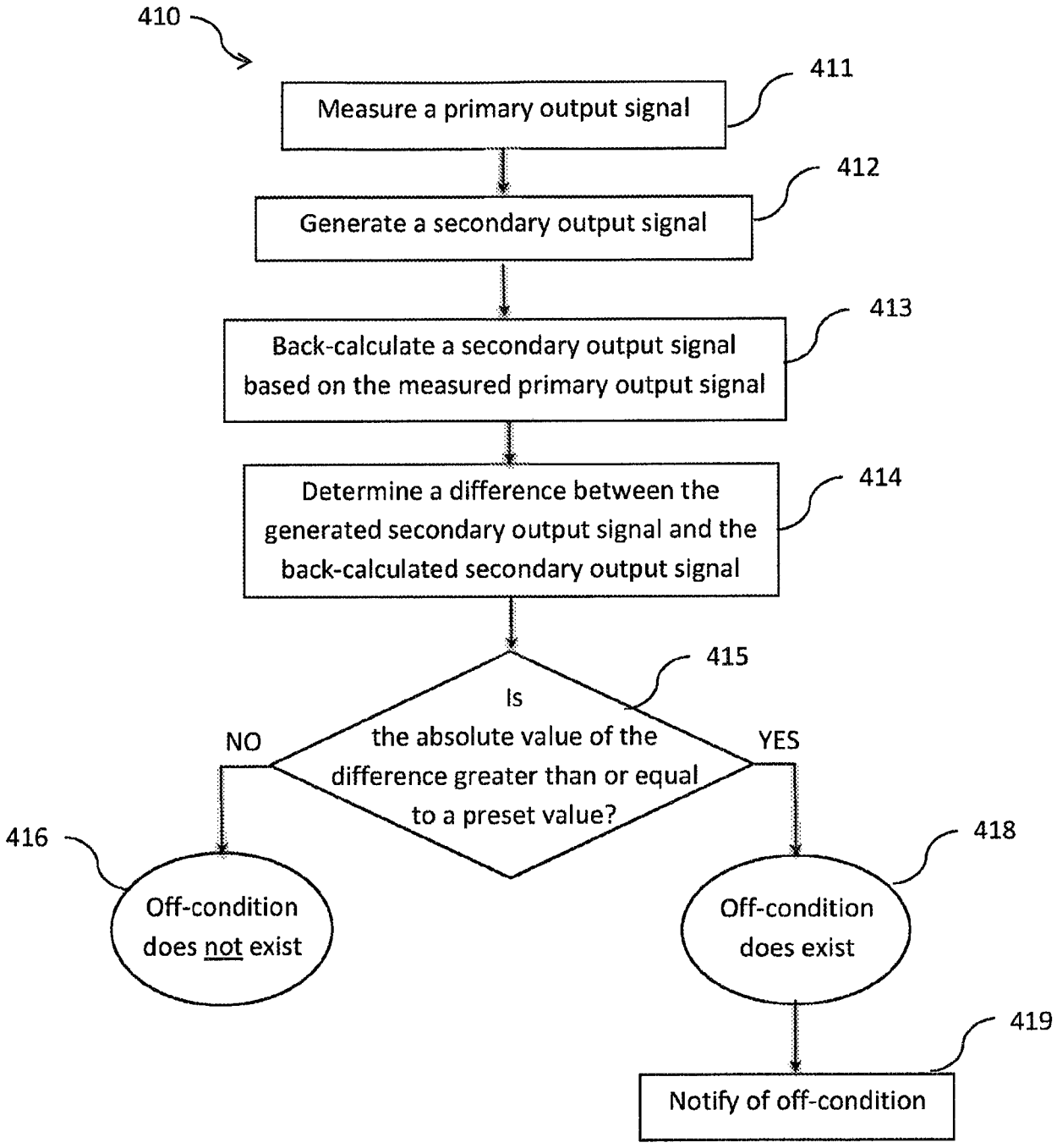

410
Measure a primary output signal
411
Generate a secondary output signal
412
Back-calculate a secondary output signal based on the measured primary output signal
413
Determine a difference between the generated secondary output signal and the back-calculated secondary output signal
414
Is the absolute value of the difference greater than or equal to a preset value?
415
NO
YES
416
Off-condition does not exist
418
Off-condition does exist
419
Notify of off-condition

FIGURE 5A

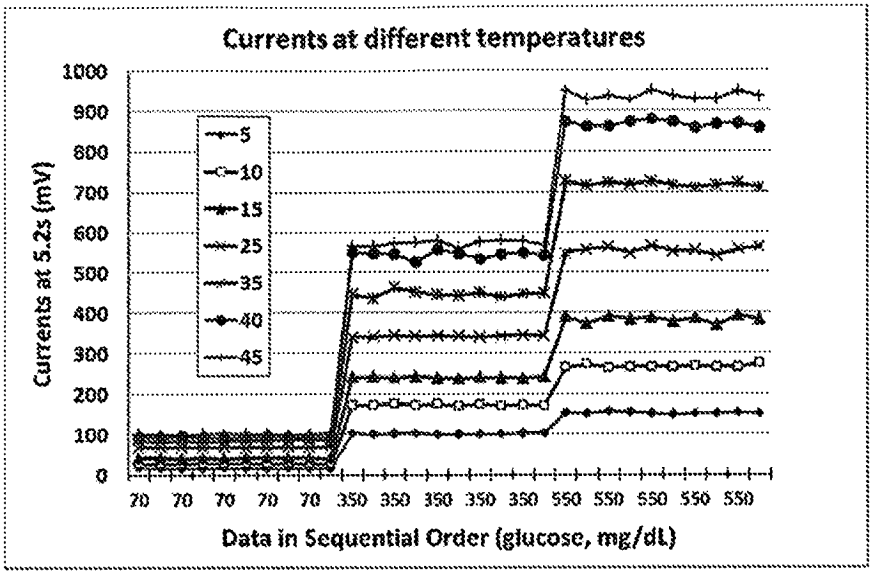


FIGURE 5B

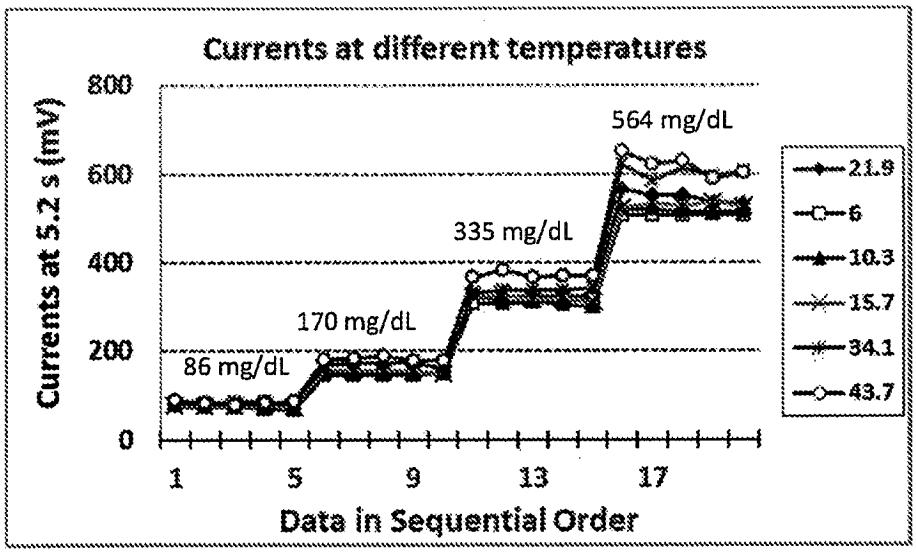


FIGURE 5C

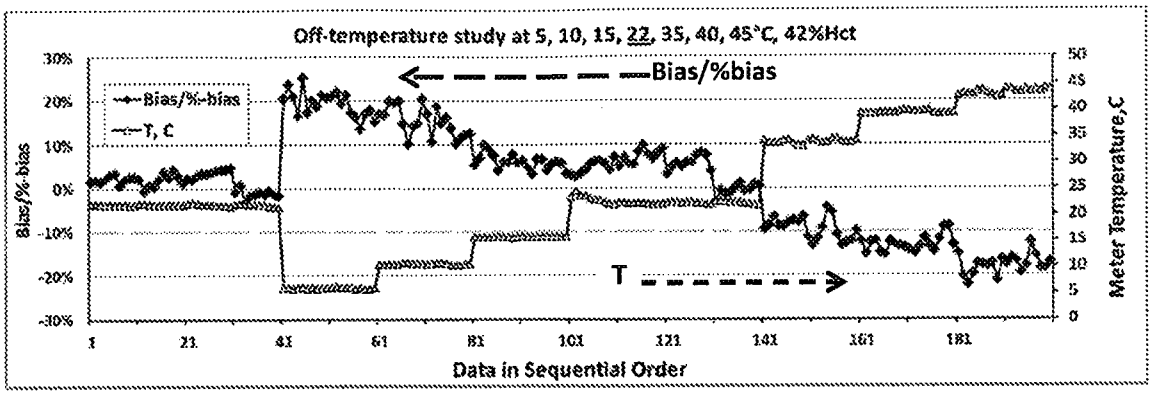

Off-temperature study at 5, 10, 15, 22, 35, 40, 45°C, 42%Hct
Bias/%bias
T
Bias/%-bias
T, C
Bias/%-bias
Meter Temperature,C
Data in Sequential Order
30%
20%
10%
0%
-10%
-20%
-30%
1
21
41
61
81
101
121
141
161
181
50
45
40
35
30
25
20
15
10
5
0

FIGURE 6A

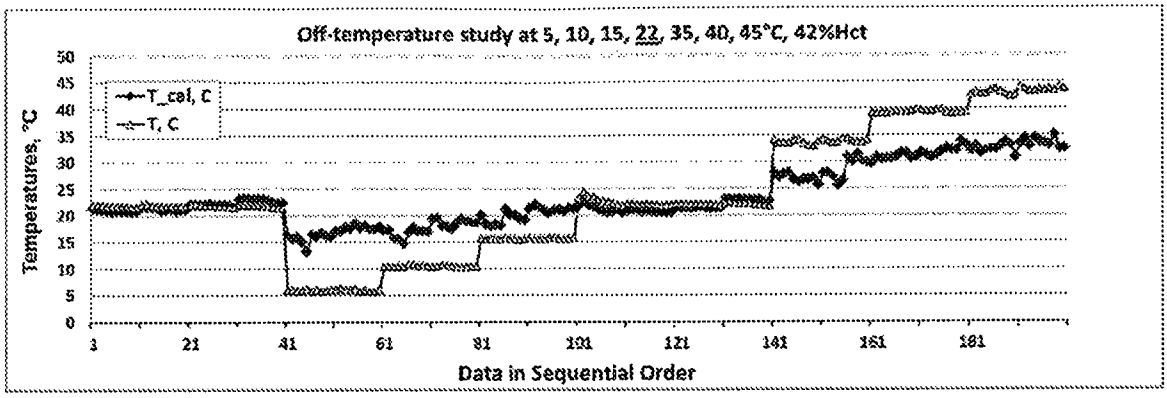


FIGURE 6B

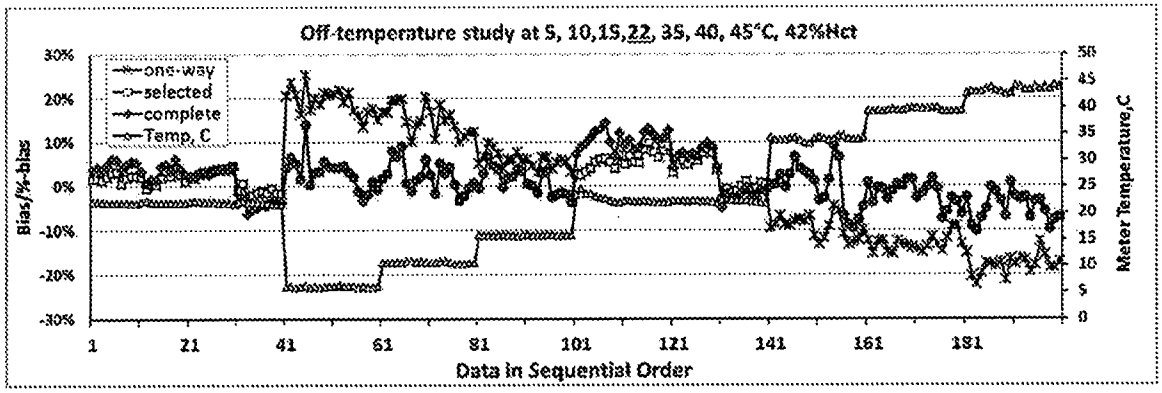


FIGURE 7A

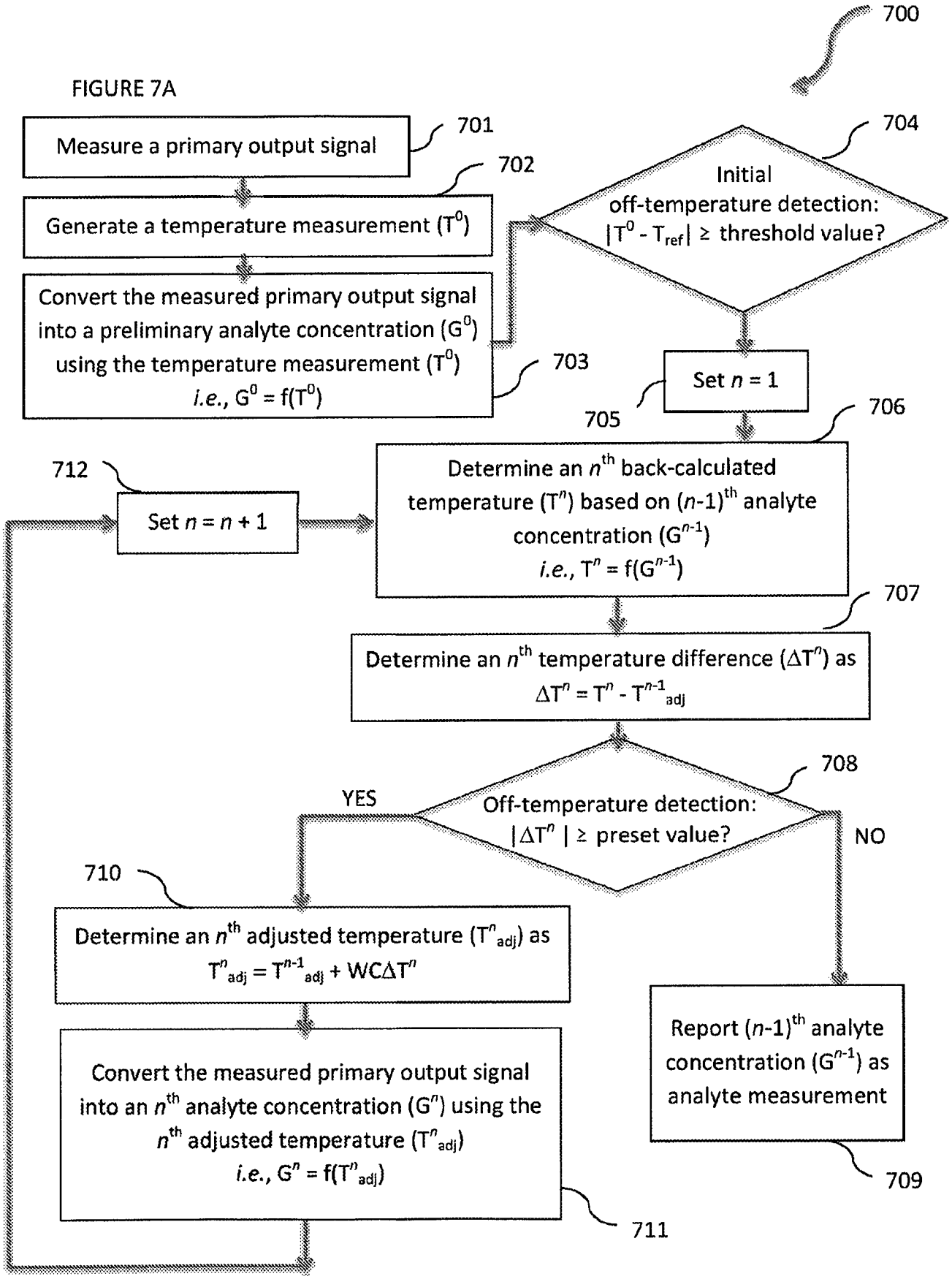

700
Measure a primary output signal
701
Generate a temperature measurement (T^0)
702
Convert the measured primary output signal into a preliminary analyte concentration (G^0) using the temperature measurement (T^0)
i.e., $G^0 = f(T^0)$
703
Initial off-temperature detection: $|T^0 - T_{ref}| \geq$ threshold value?
704
Set $n = 1$
705
Determine an n^{th} back-calculated temperature (T^n) based on $(n\text{-}1)^{th}$ analyte concentration (G^{n-1})
i.e., $T^n = f(G^{n-1})$
706
Determine an n^{th} temperature difference (ΔT^n) as
$\Delta T^n = T^n - T^{n-1}_{adj}$
707
Off-temperature detection: $|\Delta T^n| \geq$ preset value?
708
YES
NO
Determine an n^{th} adjusted temperature (T^n_{adj}) as
$T^n_{adj} = T^{n-1}_{adj} + WC\Delta T^n$
710
Convert the measured primary output signal into an n^{th} analyte concentration (G^n) using the n^{th} adjusted temperature (T^n_{adj})
i.e., $G^n = f(T^n_{adj})$
711
Report $(n\text{-}1)^{th}$ analyte concentration (G^{n-1}) as analyte measurement
709
Set $n = n + 1$
712

FIGURE 7B

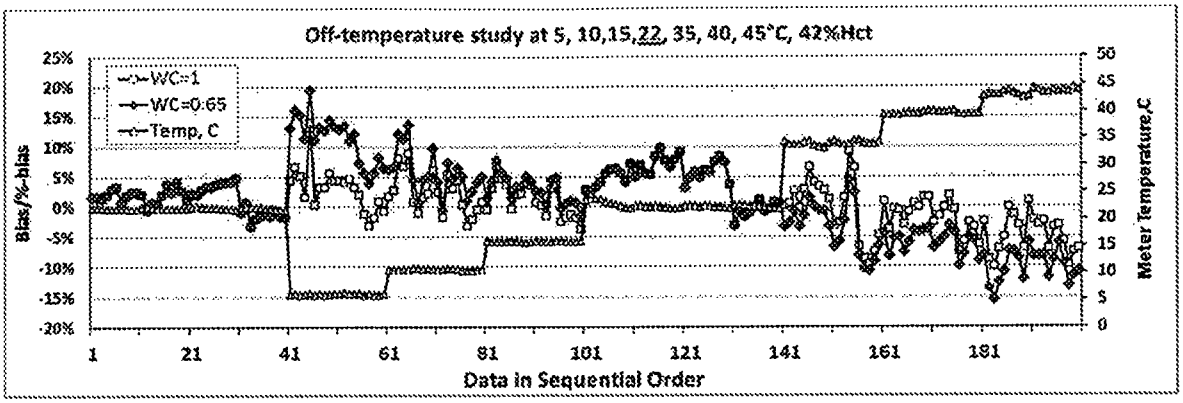
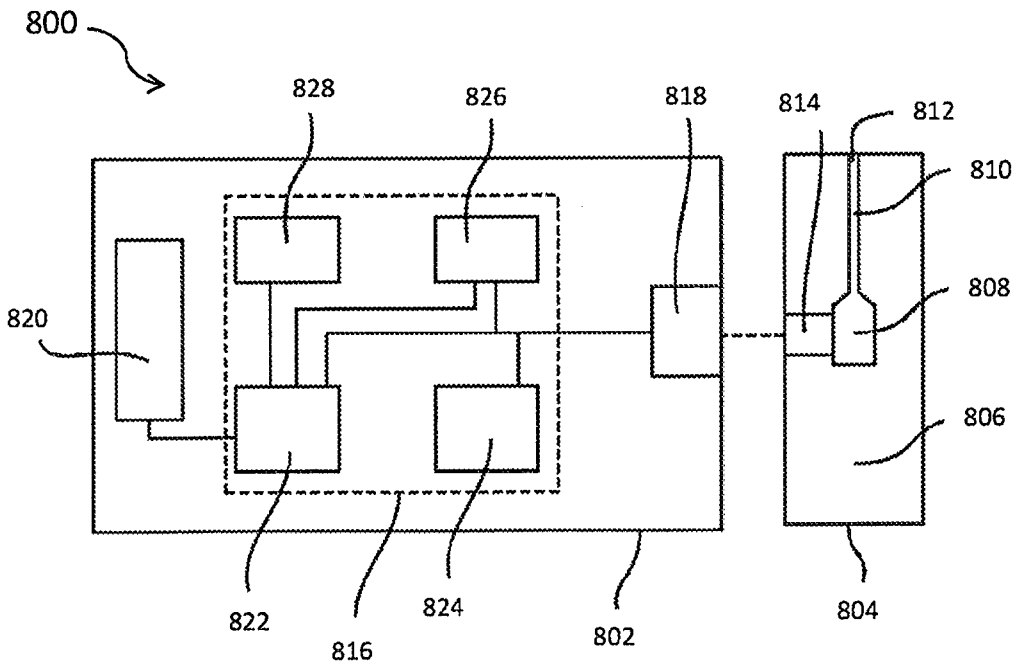


FIGURE 8



INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. 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, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/100651 A1 (BAYER HEALTHCARE LLC [US]; WU HUAN-PING [US]; NELSON CHRISTINE D [US]) 7 September 2007 (2007-09-07)	1-4,7-33
Y	claims 1-3,24-32; figure 112	5,6,34, 35

X	GB 2 512 842 A (SPHERE MEDICAL LTD [GB]) 15 October 2014 (2014-10-15)	1-4,7-33
Y	claims 1,11-15; figures 4-7	5,6,34, 35

X	WO 2012/059743 A2 (GAS SENSING SOLUTIONS LTD [GB]; MACGREGOR CALUM JOHN [GB]; GIBSON DESM) 10 May 2012 (2012-05-10)	1-4,7-33
Y	claims 1-4, 17; figure 1	5,6,34, 35

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[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

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"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
12 July 2016	19/07/2016

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	Pinheiro Vieira, E

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/203942 A1 (UCHIYAMA MOTONORI [JP]) 25 August 2011 (2011-08-25)	1-5,7-34
Y	claims 21-37; figures 4,6,48-53	6,35

X	WO 2014/159077 A1 (BAYER HEALTHCARE LLC [US]) 2 October 2014 (2014-10-02) cited in the application page 39; claims 15,17,29,66,70; figures 1-5	1-35

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/052800

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(71)申请人 安晟信医疗科技控股公司
地址 瑞士巴塞尔
(72)发明人 伍焕平
(74)专利代理机构 北京信慧永光知识产权代理有限责任公司 11290
代理人 王新春 曹正建
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权利要求书6页 说明书22页 附图17页

(54)发明名称

改进的生物传感器系统分析物测量

(57)摘要

本发明提供了用于补偿分析物测量的方法和生物传感器系统。该方法和系统基于测量的主输出信号来确定次级输出信号，以便更好地接近在实际测量条件下外来刺激对主输出信号的影响。根据本公开的方法和系统可以提供更准确的分析物测量，并且在异常条件期间检测和补偿分析物测量时可以特别有用。

CN 107636452 A

1.一种用于测定生物流体样本中分析物浓度的方法，所述方法包括：

从所述生物流体样本测量测量的主输出信号，所述测量的主输出信号主要响应于所述生物流体样本中的所述分析物浓度；

生成生成的次级输出信号，所述生成的次级输出信号响应于影响所述测量的主输出信号的外来刺激；

基于所述测量的主输出信号来反向计算反向计算的次级输出信号；

使用所述反向计算的次级输出信号来调节所述生成的次级输出信号，以导出调节的次级输出信号；并且

使用利用所述调节的次级输出信号来补偿所述外来刺激对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成分析物浓度值。

2.根据权利要求1所述的方法，其中，所述生成的次级输出信号是从所述测量的主输出信号中提取的。

3.根据权利要求1所述的方法，其中，所述生成的次级输出信号是与所述测量的主输出信号分开测量的。

4.根据权利要求1所述的方法，其中，所述外来刺激为温度。

5.根据权利要求1所述的方法，其中，所述外来刺激为血细胞比容(Hct)。

6.根据权利要求1所述的方法，其中，所述外来刺激为总血红蛋白(THb)。

7.根据权利要求1～6中任一项所述的方法，其中，基于所述测量的主输出信号来反向计算次级输出信号包括：

使用利用所述生成的次级输出信号来补偿所述外来刺激对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成初步分析物浓度；

使所述测量的主输出信号相对于所述初步分析物浓度标准化，以导出标准化的测量的主输出信号；并且

将标准化的校准信息应用至所述标准化的测量的主输出信号，所述标准化的校准信息使所述标准化的主输出信号与所述次级输出信号相联系。

8.根据权利要求1～7中任一项所述的方法，其中，调节所述生成的次级输出信号包括：用所述反向计算的次级输出信号代替所述生成的次级输出信号。

9.根据权利要求1～7中任一项所述的方法，其中，调节所述生成的次级输出信号包括：

通过从所述反向计算的次级输出信号中减去所述生成的次级输出信号来确定差值；

通过将所述差值乘以加权系数来确定调节量，其中，所述加权系数为不大于1的正数；并且

将所述调节量添加至所述生成的次级输出信号。

10.一种补偿在异常条件下的分析物测量的方法，所述方法包括：

从生物流体样本测量测量的主输出信号，所述测量的主输出信号主要响应于所述生物流体样本中的分析物浓度；

生成生成的次级输出信号，所述生成的次级输出信号响应于影响所述测量的主输出信号的外来刺激；

使用利用所述生成的次级输出信号来补偿所述外来刺激对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成初步分析物浓度；

从所述测量的主输出信号和所述初步分析物浓度确定第一反向计算的次级输出信号；

确定是否存在异常条件；以及

如果存在所述异常条件，那么：

使用所述第一反向计算的次级输出信号来调节所述生成的次级输出信号以确定第一调节的次级输出信号；并且

使用利用所述第一调节的次级输出信号来补偿所述外来刺激对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成第一分析物浓度。

11.根据权利要求10所述的方法，其中，从所述测量的主输出信号和所述初步分析物浓度确定第一反向计算的次级输出信号包括：

使所述测量的主输出信号相对于所述初步分析物浓度标准化，以导出标准化的测量的主输出信号；并且

将标准化的校准信息应用至所述标准化的测量的主输出信号，所述标准化的校准信息使所述标准化的主输出信号与所述次级输出信号相联系。

12.根据权利要求10～11中任一项所述的方法，其中，确定是否存在异常条件包括：

确定所述生成的次级输出信号和所述第一反向计算的次级输出信号之间的第一差值，其中，当所述第一差值的绝对值大于或等于第一预设值时，存在所述异常条件。

13.根据权利要求10～11中任一项所述的方法，其中，确定是否存在异常条件包括：

确定所述生成的次级输出信号和参考值之间的第二差值，其中，当所述第二差值的绝对值大于或等于第一阈值时，存在所述异常条件。

14.根据权利要求10～13中任一项所述的方法，进一步包括：

从所述测量的主输出信号和所述第一分析物浓度确定第二反向计算的次级输出信号；

基于所述第一反向计算的次级输出信号来确定是否存在第二异常条件；并且

如果存在所述第二异常条件，那么：

使用所述第二反向计算的次级输出信号来调节所述第一调节的次级输出信号以确定第二调节的次级输出信号；并且

使用利用所述第二调节的次级输出信号来补偿所述外来刺激对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成第二分析物浓度。

15.根据权利要求14所述的方法，其中，从所述测量的主输出信号和所述第一分析物浓度确定第二反向计算的次级输出信号包括：

使所述测量的主输出信号相对于所述第一分析物浓度标准化，以导出标准化的测量的主输出信号；并且

将标准化的校准信息应用至所述标准化的测量的主输出信号，所述标准化的校准信息使所述标准化的主输出信号与所述次级输出信号相联系。

16.根据权利要求14～15中任一项所述的方法，其中，基于所述第一反向计算的次级输出信号来确定是否存在第二异常条件包括：

确定所述第一反向计算的次级输出信号和所述第二反向计算的次级输出信号之间的第三差值，其中，当所述第三差值的绝对值大于或等于第二预设值时，存在所述异常条件。

17.根据权利要求14～15中任一项所述的方法，其中，基于所述第一反向计算的次级输出信号来确定是否存在第二异常条件包括：

确定第一反向计算的次级输出信号和所述参考值之间的第四差值，其中，当所述第四差值的绝对值大于或等于第二阈值时，存在所述异常条件。

18.一种补偿在异常温度条件下的分析物测量的方法，所述方法包括：

从生物流体样本测量测量的主输出信号，所述测量的主输出信号主要响应于所述生物流体样本中的分析物浓度；

使用温度传感器生成温度测量值；

使用利用所述温度测量值来补偿温度对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成初步分析物浓度；

基于所述测量的主输出信号和所述初步分析物浓度来确定第一反向计算的温度；

确定是否存在异常温度条件；并且

如果存在所述异常温度条件，那么：

使用所述第一反向计算的温度来调节所述温度测量值以确定第一调节的温度；并且

使用利用所述第一调节的温度来补偿温度对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成第一分析物浓度。

19.根据权利要求18所述的方法，其中，从所述测量的主输出信号和所述初步分析物浓度确定第一反向计算的温度包括：

使所述测量的主输出信号相对于所述初步分析物浓度标准化，以导出标准化的测量的主输出信号；并且

将标准化的校准信息应用至所述标准化的测量的主输出信号，所述标准化的校准信息使所述标准化的测量的主输出信号与温度相联系。

20.根据权利要求18～19中任一项所述的方法，其中，确定是否存在异常温度条件包括：

确定所述第一反向计算的温度和所述温度测量值之间的第一差值，其中，当所述第一差值的绝对值大于或等于第一预设值时，存在所述异常温度条件。

21.根据权利要求18～19中任一项所述的方法，其中，确定是否存在异常温度条件包括：

确定所述温度测量值和参考温度之间的第二差值，其中，当所述第二差值的绝对值大于或等于第一阈值时，存在所述异常温度条件。

22.根据权利要求18～21中任一项所述的方法，进一步包括：

基于所述测量的主输出信号和所述第一分析物浓度来确定第二反向计算的温度；

基于所述第一反向计算的温度来确定是否存在第二异常温度条件；并且

如果存在所述第二异常温度条件，那么：

使用所述第二反向计算的温度来调节所述第一调节的温度以确定第二调节的温度；并且

使用利用所述第二调节的温度来补偿温度对所述测量的主输出信号的影响的转换函数将所述测量的主输出信号转换成第二分析物浓度。

23.根据权利要求22所述的方法，其中，从所述测量的主输出信号和所述第一分析物浓度确定第二反向计算的温度包括：

使所述测量的主输出信号相对于所述第一分析物浓度标准化，以导出标准化的测量的

主输出信号;并且

将标准化的校准信息应用至所述标准化的测量的主输出信号,所述标准化的校准信息使所述标准化的主输出信号与温度相联系。

24.根据权利要求22～23中任一项所述的方法,其中,基于所述第一反向计算的温度来确定是否存在第二异常温度条件包括:

确定第一反向计算的温度和所述第二反向计算的温度之间的第三差值,其中,当所述第三差值的绝对值大于或等于第二预设值时,存在所述第二异常温度条件。

25.根据权利要求22～23中任一项所述的方法,其中,基于所述第一反向计算的温度来确定是否存在第二异常温度条件包括:

确定第一反向计算的温度和所述参考温度之间的第四差值,其中,当所述第四差值的绝对值大于或等于第二阈值时,存在所述第二异常温度条件。

26.一种用于测定生物流体样本中分析物浓度的生物传感器系统,所述生物传感器系统包括:

测试传感器,其具有基部和样本接口,

所述基部中形成有储器,用以接收所述生物流体样本,并且

所述样本接口配置成与所述储器相邻;以及

测量装置,其被构造成与所述测试传感器相互连接并具有传感器接口、存储介质和处理器,所述处理器与所述传感器接口和所述存储介质连接并被构造成执行计算机编程的指令以:

经由所述传感器接口接收从所述储器中的生物流体样本测量的测量的主输出信号,所述测量的主输出信号主要响应于所述分析物浓度;

接收生成的次级输出信号,所述生成的次级输出信号响应于影响所述测量的主输出信号的外来刺激;

基于所述测量的主输出信号来反向计算反向计算的次级输出信号;

使用所述反向计算的次级输出信号来调节所述生成的次级输出信号,以导出调节的生成的次级输出信号;并且

使用存储在所述存储介质中的转换函数将所述测量的主输出信号转换成所述分析物浓度,其中,所述转换函数使用所述调节的生成的次级输出信号来补偿外来刺激对所述测量的主输出信号的影响。

27.一种用于在异常条件下测定生物流体样本中分析物浓度的生物传感器系统,所述生物传感器系统包括:

测试传感器,其具有基部和样本接口,

所述基部中形成有储器,用以接收所述生物流体样本,并且

所述样本接口配置成与所述储器相邻;以及

测量装置,其被构造成与所述测试传感器相互连接并具有传感器接口、存储介质和处理器,所述处理器与所述传感器接口和所述存储介质连接并被构造成执行计算机编程的指令以:

经由所述传感器接口接收从所述储器中的生物流体样本测量的测量的主输出信号,所述测量的主输出信号主要响应于所述分析物浓度;

接收生成的次级输出信号，所述生成的次级输出信号响应于影响所述测量的主输出信号的外来刺激；

基于所述测量的主输出信号来反向计算反向计算的次级输出信号；

确定是否存在异常条件；并且

如果存在所述异常条件，那么：使用所述反向计算的次级输出信号来调节所述生成的次级输出信号，以导出调节的生成的次级输出信号，并且使用转换函数和所述调节的生成的次级输出信号将所述测量的主输出信号转换成所述分析物浓度，以补偿外来刺激的影响。

28.一种用于在异常温度条件下测定生物流体样本中分析物浓度的生物传感器系统，所述生物传感器系统包括：

测试传感器，其具有基部和样本接口，

所述基部中形成有储器，用以接收所述生物流体样本，并且

所述样本接口配置成与所述储器相邻；以及

测量装置，其被构造成与所述测试传感器相互连接并具有传感器接口、温度传感器、存储介质和处理器，所述处理器与所述传感器接口、所述温度传感器和所述存储介质连接并被构造成执行计算机编程的指令以：

经由所述传感器接口接收从所述储器中的生物流体样本测量的测量的主输出信号，所述测量的主输出信号主要响应于所述分析物浓度；

从所述温度传感器中接收温度测量值；

使用存储在所述存储介质中的转换函数将所述测量的主输出信号转换成初步分析物浓度，其中，所述转换函数使用所述温度测量值来补偿温度对所述测量的主输出信号的影响；

基于所述测量的主输出信号和所述初步分析物浓度来反向计算反向计算的温度；

确定是否存在异常温度条件；并且

如果存在所述异常温度条件，那么：使用所述反向计算的温度来调节所述温度测量值，以导出调节的温度测量值，并且使用所述转换函数和所述调节的温度测量值将所述测量的主输出信号转换成所述分析物浓度，以补偿温度对所述测量的主输出信号的影响。

29.一种基于主输出信号来反向计算次级输出信号方法，其中，所述主输出信号主要响应于主刺激，所述次级输出信号响应于影响所述主输出信号的外来刺激，所述方法包括：

使所述主输出信号相对于所述主刺激的对应值标准化，以导出标准化的主输出信号；并且

将标准化的校准信息应用至所述标准化的主输出信号，所述标准化的校准信息使所述标准化的主输出信号与所述次级输出信号相联系。

30.根据权利要求29所述的方法，其中，所述标准化的校准信息通过以下方式生成：

从多个参考样本测量测量的参考主输出信号，其中，每个参考样本都与所述主刺激的已知值相关联；

生成与所述测量的参考主输出信号的各者相对应的生成的次级输出信号；

对于每个参考样本，使所述测量的参考主输出信号与所述生成的次级输出信号相关联；

对于每个参考样本，将外推的参考主输出信号值从所述测量的参考主输出信号外推到所述次级输出信号的指定值；

将每个外推的参考主输出信号值与其主刺激的对应已知值相关联，以生成标准化函数，其中，所述标准化函数在应用至所述主输出信号时会消除所述主输出信号对所述主刺激的依赖性；

使用所述标准化函数来使所述测量的参考主输出信号标准化，以导出标准化的参考主输出信号；并且

使所述标准化的参考主输出信号与所述生成的次级输出信号相关联，以生成所述标准化的校准信息。

31.根据权利要求30所述的方法，其中，使所述主输出信号相对于所述主刺激标准化包括：

使用所述标准化函数从相应的主刺激值导出标准化函数值；并且

将所述主输出信号除以所述标准化函数值，以确定所述标准化的主输出信号。

32.根据权利要求29～31中任一项所述的方法，其中，使用生物传感器系统测量所述主输出信号，并且所述主刺激为分析物浓度。

33.根据权利要求29～32中任一项所述的方法，其中，所述外来刺激为温度。

34.根据权利要求29～32中任一项所述的方法，其中，所述外来刺激为血细胞比容(Hct)。

35.根据权利要求29～32中任一项所述的方法，其中，所述外来刺激为总血红蛋白(THb)。

改进的生物传感器系统分析物测量

[0001] 相关申请的交叉引用

[0002] 本申请要求于2015年5月15日提交的美国临时专利申请No.62/162,298的优先权权益,其全部内容以引用的方式并入本文。

[0003] 版权

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背景技术

[0005] 生物传感器系统提供诸如血液、血清、血浆、尿液、唾液、间质或细胞内液等生物流体样本的分析。通常,系统包括分析驻留在测试传感器(也被称为测试条或传感器条)中的样本的测量装置(也被称为测量仪)。虽然样本通常为生物流体,但是样本可以为衍生物,诸如提取物、稀释液、滤液或重新构成的沉淀物等(从现在开始,术语"生物流体"包括其衍生物)。由生物传感器系统进行的分析可以确定生物流体中一种或多种分析物(诸如乙醇、葡萄糖、尿酸,乳酸、胆固醇、胆红素、游离脂肪酸、甘油三酸酯、蛋白质、酮、苯丙氨酸或酶等)的存在和/或浓度,这可用于诊断和/或治疗某些病症。

[0006] 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(糖化血红蛋白)或葡萄糖水平,以便调节饮食和/或药物。在包括血红蛋白(Hb)的血液样本中,可以测定总血红蛋白(THb)和A1c的存在和/或浓度。A1c水平(%-A1c)反映了患者的葡萄糖控制状态,提供对在测试前两到三个月内的平均葡萄糖控制的了解。对于糖尿病患者,相比于仅指示在进行测量时的血糖控制的血糖水平的瞬时测量,%-A1c的准确测量提供了关于患者在更长期内通过饮食和/或药物对血糖水平控制程度的更好的指示。

[0007] 生物传感器系统可以被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。一些系统可以分析单滴血液,诸如体积为0.25-15微升(μL)的范围等。生物传感器系统可以使用台式、便携式和其他类型的测量装置来实现。便携式测量装置可以是手持式的并且允许识别和/或定量样本中的一种或多种分析物。便携式测量系统的例子包括Bayer HealthCare(新泽西州惠帕尼)的Contour®测量仪,而台式测量系统的例子包括由德克萨斯州奥斯汀的CH Instruments提供的电化学工作站(Electrochemical Workstation),台式机型"YSI 2300STAT Plus™葡萄糖和乳酸分析仪"("YSI 2300STAT Plus™ Glucose & Lactate Analyzer"),以及Yellow Springs Instrument Company(现称为YSI Inc)的相关型号(本文中被称为"YSI"参考值)。

[0008] 在许多生物传感器系统中,测试传感器可以适用于活的有机体的外部、内部或部分内部。当用于活的有机体外部时,生物流体的样本可以被引入到测试传感器中的样本储器中,并且可以在将分析用样本引入之前、之后或期间,将测试传感器放置在测量装置中。当在活的有机体内部或部分内部使用时,测试传感器可以连续地浸入样本中或者样本连续

流过测试传感器，例如用于连续监测；或者样本可以间歇地被引入到测试传感器中或间歇地流过测试传感器，例如用于间歇监测。测试传感器可以包括部分地隔离一定体积的样本或者对样本开放的储器。当开放时，测试传感器可以采取放置成与生物流体接触的纤维或其它结构的形式。

[0009] 生物传感器系统通常将一个或多个主输入信号(统称为主输入信号)提供给生物流体的样本，并且测量从样本生成的一个或多个主输出信号(统称为主输出信号)，以测定分析物浓度。主输出信号由于主输入信号和分析物之间或主输入信号与指示分析物的物质之间的相互作用而生成，并且通常与分析物浓度相关。生物传感器系统可以使用光学和/或电化学方法来分析生物流体。

[0010] 在光学系统中，主输入信号通常是从光源产生的光束，从而产生样本对光束的透光率或反射率的测量。在一些光学系统中，分析物或指示分析物的物质可以吸收或改变入射光束(主输入信号)的波长，使得所得的主(光)输出信号相对于主输入信号具有降低的强度或波长被改变。在其他光学系统中，化学指示剂可以在当被主(光)输入信号照射时响应于分析物而发出荧光或发光。在任一光学系统中，测量的主(光)输出信号可以被转换成电输出信号，诸如电流或电位等，并且系统测量主(光)输出信号，并将主输出信号与样本的分析物浓度相关联。

[0011] 在电化学系统中，当主(电)输入信号施加于样本时，从响应于分析物浓度的由分析物或可测量物质的氧化还原反应生成的电信号来测定样本的分析物浓度。主输入信号可以是电位或电流，并且可以是常量、变量或其组合(例如当AC信号被施加DC信号偏移时)。主输入信号可以作为单个脉冲施加，或以多个脉冲、序列或周期施加。可以向样本中加入酶或类似物质以增强在氧化还原反应期间从分析物的电子转移。酶或类似物质可以与单个分析物反应，从而为所生成的输出信号的一部分提供特异性。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/或辅助从分析物到电极的电子转移。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，而氧化还原介体在其自身与测试传感器的电极之间转移电子。

[0012] 电化学生物传感器系统的测量装置通过电触点将主输入信号施加到测试传感器的电导体。电导体通过电极将主输入信号传送到位于样本储器中的样本中。分析物的氧化还原反应响应于主输入信号而生成主(电)输出信号。来自测试传感器的主(电)输出信号可以是(如通过电流分析法或伏安法产生的)电流、(如通过电位测定法/电流测定法产生的)电位或(如通过电量分析法产生的)累积电荷。测量装置可以具有如下处理能力：测量主输出信号，并将主输出信号与样本中的一种或多种分析物的存在和/或浓度相关联。

[0013] 在光学或电化学生物传感器系统中，通常使用转换函数来完成主输出信号的转换以指示目标分析物的存在和/或浓度。转换函数是将主输出信号转换成目标分析物的浓度的计算方法。例如，转换函数可以涉及使用具有线性、非线性或多项式关系的主输出信号和分析物浓度之间的参考相关性。转换函数反映了在针对测试条件和样本的一组假设下的相关性，与这些假设的偏差可能导致所计算的分析物浓度的误差。

[0014] 主输出信号的生成和测量被设计为主要响应于作为生物传感器测量的目标或目的的分析物浓度，但是测量的主输出信号不可避免地还包括来自外来刺激的贡献，诸如与相关性假设的偏差。这种外来刺激包括：由样本的物理特征或环境特征引起的刺激，例如干

扰物质(如血细胞比容(Hct)、对乙酰氨基酚、脂质、蛋白质、抗坏血酸、尿酸等)、环境温度、湿度等;系统的操作条件,例如当样本大小不足以使系统进行测量时的填充不足条件、样本与测试传感器中的一个或多个电极之间的间歇性电接触、试剂的降解等;以及测试传感器批次之间的制造差异,例如试剂的量和/或活性的变化、电极面积和/或间距的变化等。

[0015] 外来刺激影响目标分析物的测量和分析的准确度和精度。这种错误测量可导致生物传感器系统终端使用者感到受挫,终端使用者需要丢弃测试传感器并提供额外的样本以重复测量,并且由于不准确的信息,终端使用者也会面临不确定的治疗选择。因此,不断需要量化并抵消外来刺激的影响,以便从目标分析物浓度中去除这些影响或使这些影响最小化。

[0016] 当外来刺激源自样本的物理或环境特征时,其影响可以从次级输出信号来进行量化,该次级输出信号从主输出信号中提取,或者由专用装置或专用检测通道测得。例如,在电化学系统中,因干扰物质(诸如Hct等)而引起的次级输出信号可以从用于测定样本的目标分析物浓度的主输出信号提取(例如,在名称为"基于斜率的补偿(Slope-Based Compensation)"的PCT公开No.WO 2009/108239中披露的电流比R4/3、R5/4和R6/5,以及在名称为"包括次级输出信号的基于斜率的补偿(Slope-Based Compensation Including Secondary Output Signals)"的PCT公开No.WO 2011/156152A1中披露的具有Hct脉冲的门控电流分析的电位序列),或者可以使用专用电极测得,该专用电极可以包含与用于测定样本的目标分析物浓度的电极相同的试剂组合物、不同的试剂组合物(例如,与干扰物反应的试剂组合物)或不含试剂组合物。在光学系统中,例如,因干扰物质(例如THb)而引起的次级输出信号可以使用聚焦指示干扰物质的波长或角度的专用光学通道测得(例如,在名称为"包括分段信号的分析补偿(Analysis Compensation Including Segmented Signals)"的PCT公开No.WO2013/043839A1和名称为"分析物浓度测定的标准化校准(Normalized Calibration of Analyte Concentration Determination)"的PCT公开No.WO2014/159077A1中披露的反射率测量)。在一些情况下,次级输出信号可以与外来刺激的值相关联;例如,并入生物传感器系统中的温度传感器可以测量因温度而引起的次级输出信号,并将该次级输出信号与温度值相关联,从而提供对样本的环境温度的单独测量。

[0017] 如本文所使用的,取决于正在进行的特定测量或计算的背景,术语"次级输出信号"可以描述从主输出信号提取的原始信号或由专用的传感器、电极、检测通道等测量的原始信号,或者可以描述与原始信号相关联的外来刺激值。

[0018] 用于将主输出信号转换成分析物浓度的转换函数可以利用次级输出信号来补偿那些外来刺激的影响。例如,测量的温度值可以用于补偿主输出信号以更准确地确定分析物浓度,例如,如在美国专利No.7,781,222("生物传感器系统的温度调节的分析物测定(Temperature-Adjusted Analyte Determination for Biosensor System)")中所讨论的。在另一示例中,转换函数可以涉及具有次级输出信号的多变量回归,例如,如在美国专利No.8,744,776("基于复指数函数测定分析物浓度的方法(Method of Determining Analyte Concentration Based on Complex Index Functions)")和PCT公开No.WO2011/119533A1("生物传感器的剩余补偿(Residual Compensation for a Biosensor)")中所讨论的。标准化(Normalization)也可以用于从主输出信号中去除外来刺激的影响或将其最小化,例如,如在PCT公开No.WO2014/159077A1("分析物浓度测定的标准化校准

(Normalized Calibration of Analyte Concentration Determination)")中所讨论的。

[0019] 虽然将这种补偿方法纳入转换函数中可以改善生物传感器系统的测量性能,但仍然存在缺点。这种补偿方法通常在实验室中被开发和实施,在实验室中,可以在受控环境下再现误差条件。对于便携式测量装置,特别是大多数消费者使用的手持式装置来说,这种受控的实验室环境可能无法准确地反映进行测量的条件,因此在受控实验室条件下开发的补偿方法可能无法准确地补偿在实际测量条件下外来刺激对主输出信号的影响。例如,假设由并入生物传感器系统中的温度传感器测量的温度反映生物流体样本的温度,但是在某些操作条件下(例如,当手持式测量装置在冬季天气(例如0～10℃)或夏季天气(例如40～45℃)保存在汽车中,然后立即使用在室温(例如22～25℃)下保存在室内的测试传感器时)该假设可能不成立。在另一示例中,由于例如专用电极的故障,Hct信号测量本身可能是错误的。

[0020] 这种情况被称为"异常条件(off-condition)",在该情况中,次级输出信号与由补偿方法假设的参考值不匹配和/或与基于主输出信号预期的次级输出信号不匹配。当在异常条件下进行分析物测定时,使用生成的次级输出信号来补偿主输出信号会在分析物测定中引入额外误差。当前可用的生物传感器系统和方法不能确定何时会出现这种异常条件,因此不能确定转换函数何时需要进行额外调节以补偿因次级输出信号而引起的这种误差。

[0021] 本文公开的方法和系统避免或改善了现有技术中的这些缺点的至少一部分。

发明内容

[0022] 一方面,本公开提供了一种测定生物流体样本中分析物浓度的方法。测量主要响应于分析物浓度的主输出信号,并生成响应于影响主输出信号的外来刺激的次级输出信号。基于测量的主输出信号来反向计算次级输出信号,并且使用反向计算的次级输出信号来调节所生成的次级输出信号。使用利用调节的次级输出信号来补偿外来刺激对测量的输出信号的影响的转换函数将测量的主输出信号转换成分析物浓度。

[0023] 另一方面,本公开提供了一种通过测量主输出信号和生成次级输出信号来补偿在异常条件下的分析物测量的方法,该主输出信号主要响应于生物流体样本中的分析物浓度,该次级输出信号响应于影响主输出信号的外来刺激。使用利用生成的次级输出信号来补偿外来刺激对测量的主输出信号的影响的转换函数将测量的主输出信号转换成初步分析物浓度。基于测量的主输出信号和初步分析物浓度来确定第一反向计算的次级输出信号。如果确定存在异常条件,则使用第一反向计算的次级输出信号来调节生成的次级输出信号以确定第一调节的次级输出信号。使用利用第一调节的次级输出信号来补偿外来刺激对主输出信号的影响的转换函数将测量的主输出信号转换成第一分析物浓度值。在一些实施方案中,基于测量的主输出信号和第一分析物浓度值来确定第二反向计算的次级输出信号。如果基于第一反向计算的次级输出信号和第二反向计算的次级输出信号确定存在异常条件,则使用第二反向计算的次级输出信号来调节第一调节的次级输出信号以确定第二调节的次级输出信号,并且使用转换函数和第二调节的次级输出信号将测量的主输出信号转换成第二分析物浓度值,以补偿外来刺激对主输出信号的影响。

[0024] 另一方面,本公开提供了一种通过测量主输出信号并使用温度传感器生成温度测量值来补偿在异常温度条件下的分析物测量的方法。使用利用温度测量值来补偿温度对测

量的主输出信号的影响的转换函数将测量的主输出信号转换成初步分析物浓度。从测量的主输出信号和初步分析物浓度来确定第一反向计算的温度。如果确定存在异常温度条件，则使用第一反向计算的温度来调节温度测量值，并且使用利用第一调节的温度来调节温度对测量的主输出信号的影响的转换函数将测量的主输出信号转换成第一分析物浓度。

[0025] 另一方面，本公开提供了用于实施本文披露的一种或多种方法的生物传感器系统。

附图说明

[0026] 图1A示出了用于补偿分析物测定中外来刺激的影响的常规(现有技术)方法。

[0027] 图1B示出了用于补偿分析物测定中外来刺激的影响的循环方法。

[0028] 图2A表示测定分析物浓度的方法的一个实施例。

[0029] 图2B表示测定分析物浓度的方法的另一实施例。

[0030] 图2C表示测定分析物浓度的方法的另一实施例。

[0031] 图2D表示测定分析物浓度的方法的另一实施例。

[0032] 图3A示出了三个YSI参考葡萄糖样本的主输出信号相对于测量仪温度的图。

[0033] 图3B示出了外推到22℃的主输出信号相对于YSI参考葡萄糖水平的图。

[0034] 图3C示出了通过两种标准化方法确定的标准化的主输出信号相对于温度的图。

[0035] 图3D示出了总结使用图3C所示的标准化函数反向计算的温度的估计准确度的表格。

[0036] 图3E表示在三种不同参考葡萄糖浓度下的作为Hct专用电极的Hct信号的函数的主输出信号。

[0037] 图3F表示外推到i_{Hct}＝2000mV的Hct信号相对于YSI参考葡萄糖水平的标准化函数。

[0038] 图3G表示用于反向计算由标准化的输出信号确定的Hct信号的标准化参考相关性。

[0039] 图3H表示在四种不同参考%-A1c浓度下的作为来自专用检测通道的THb信号的函数的主A1c信号(反射率)。

[0040] 图3I表示外推到R_{THb}＝0.7的THb信号相对于参考%-A1c水平的标准化函数。

[0041] 图3J表示用于反向计算THb信号的标准化的参考相关性，其中，绘制了THb信号相对于标准化A1c信号的曲线。

[0042] 图3K示出了可用于反向计算次级输出信号的标准化的校准信息的生成方法的一个实施例。

[0043] 图4A表示分析物浓度测定中的异常条件的确定方法的一个实施例。

[0044] 图4B表示分析物浓度测定中的异常条件的确定方法的另一实施例。

[0045] 图5A示出了利用在七个不同温度下的传感器/样本和测量仪得到的三种不同全血(WB)葡萄糖浓度的测量的主输出信号的图。

[0046] 图5B示出了利用22℃下的传感器/样本和六个不同温度下的测量仪得到的四种不同WB葡萄糖浓度的测量的主输出信号的图。

[0047] 图5C示出了在异常温度条件下使用具有温度补偿的常规单向转换函数的分析物

测定中的偏差/%-偏差和测量主输出信号时的测量仪温度的图。

[0048] 图6A示出了基于测量的主输出信号的反向计算的温度和测量主输出信号时的测量仪温度的图。

[0049] 图6B示出了使用具有温度补偿的转换函数的常规(单向)应用(*)、具有温度补偿的转换函数的一个完整循环应用(◆)和仅在异常温度条件下进行的具有温度补偿的转换函数的选定的一个循环应用(□)的分析物测定中的偏差/%-偏差以及测量主输出信号时的测量仪温度的图。

[0050] 图7A表示补偿在异常温度条件下的分析物测量的方法的一个实施例。

[0051] 图7B示出了使用利用两个不同加权系数的具有温度补偿的转换函数的循环应用的分析物测定中的偏差/%-偏差的图。

[0052] 图8表示根据本公开的生物传感器系统的一个实施例。

具体实施方式

[0053] 本公开引入了如下构思,在分析物测定中,基于测量的主输出信号来反向计算次级输出信号,并使用反向计算的次级输出信号来帮助补偿外来刺激对主输出信号的影响。基于测量的主输出信号的反向计算的次级输出信号更好地反映在测量主输出信号的实际条件下外来刺激的影响,并且因此可用于确定何时出现异常条件,并帮助补偿因异常条件而引起的误差,从而提高分析物浓度测定的准确度。

[0054] 图1A示出了用于补偿分析物测定中外来刺激的影响的常规方法。生物传感器系统测量主输出信号。测量的主输出信号主要响应于生物流体样本中的分析物浓度,但会包括来自影响分析物测定的准确度和精度的外来刺激(例如温度、Hct、THb等)的响应。为了补偿来自外来刺激的影响,生物传感器系统可以例如通过从测量的主输出信号中提取次级输出信号或者通过单独测量次级输出信号来生成响应于外来刺激的次级输出信号。在常规补偿方法中,测量的主输出信号和生成的次级输出信号被输入到转换函数中,该转换函数使用生成的次级输出信号来对测量的主输出信号进行针对外来刺激的影响的补偿,同时将测量的主输出信号转换成分析物浓度。

[0055] 虽然将测量的主输出信号和生成的次级输出信号输入到转换函数中以测定分析物浓度的这种单向过程可以有效降低分析物测定中的外来刺激的影响,但是该单向过程不能检测与生成的次级输出信号相关联的误差。这种误差可能出现在如下情况中,例如,当所生成的次级输出信号本身因故障的检测通道(例如在检测THb信号时可能出现)或因专用电极故障(例如在检测Hct信号时可能出现)而出错时,或者当生成的次级输出信号不反映在测量主输出信号时生物流体样本的实际状况时(例如,当测量装置的温度传感器不代表传感器/样本的温度时可能出现)。当将错误的次级输出信号输入至转换函数中时,当对测量的主输出信号进行针对外来刺激的影响的补偿时,可能会产生较大的误差,因此可损害分析物浓度测定的准确度。

[0056] 图1B示出了根据本公开的用于补偿分析物测定中外来刺激的影响的循环方法。根据本公开,循环过程可以按如上所述开始,其中,将测量的主输出信号和生成的次级输出信号输入到转换函数中以测定初步分析物浓度。然后,该过程生成要循环回到转换函数的一个新输入,以便更好地补偿外来刺激的影响。该循环过程涉及使用例如测量的主输出信号

本身、初步分析物浓度和/或从测量的主输出信号和/或初步分析物浓度导出的其它信息，基于测量的主输出信号反向计算次级输出信号。通过例如将反向计算的次级输出信号的一部分或依赖于反向计算的次级输出信号的参数添加到生成的次级输出信号或者通过用反向计算的次级输出信号替换生成的次级输出信号来使用反向计算的次级输出信号调节生成的次级输出信号。调节的次级输出信号(与测量的主输出信号一起)被输入到转换函数中以测定第一补偿的分析物浓度。该循环过程可以实施一个循环或多个循环，例如，实施预定数量的循环，或者实施到满足某些标准为止。

[0057] 已经发现，通过使用反向计算的次级输出信号来调节生成的次级输出信号，输入到转换函数中的调节的次级输出信号会更好地反映测量主输出信号时的实际条件，并且还帮助校正生成的次级输出信号的误差。因此，本公开的循环过程可以提供分析物测定的改善的准确度。

[0058] 图2A-2D示出了包含在根据本公开的循环过程的不同实施方案中的一些步骤。

[0059] 图2A示出了流程图200，该流程图示出了根据本公开的测定分析物浓度的方法的一个循环实施方案中的一些步骤。在步骤201中，使用生物传感器系统测量主输出信号。主输出信号被设计为主要响应于分析物浓度。

[0060] 在步骤202中，生成次级输出信号。次级输出信号响应于影响测量的主输出信号的外来刺激，并且次级输出信号可以通过从测量的主输出信号中提取次级输出信号来生成(例如，如在名称为“基于斜率的补偿(Slope-Based Compensation)”的PCT公开No.WO 2009/108239中所披露的提取电流比R4/3、R5/4和R6/5作为响应于Hct水平的次级输出信号，或者如在名称为“包括次级输出信号的基于斜率的补偿(Slope-Based Compensation Including Secondary Output Signals)”的PCT公开No.WO 2011/156152A1中所披露的使用具有Hct脉冲的门控电流分析法的电位序列)、或者通过使用单独的传感器、单独的检测通道或电极等单独地测量次级输出信号来生成(例如，如在名称为“包括分段信号的分析补偿(Analysis Compensation Including Segmented Signals)”的WO2013/043839 A1和名称为“分析物浓度测定的标准化校准(Normalized Calibration of Analyte Concentration Determination)”的WO2014/159077A1中所披露的使用温度传感器进行温度测量，或使用专用光学通道来测量响应于THb水平的反射信号)。步骤201和202可以以任何顺序执行，或者可以同时进行。

[0061] 在步骤203中，使用测量的主输出信号本身和/或从测量的主输出信号导出的信息(例如，初步分析物浓度)，基于测量的主输出信号测定反向计算的次级输出信号。下面参照图3A～3J示出并讨论用于反向计算次级输出信号的方法的一些实施例。

[0062] 在步骤204中，使用反向计算的次级输出信号来调节由生物传感器系统生成的次级输出信号。在步骤205中，使用利用调节的次级输出信号(来自步骤204)来补偿外来刺激对测量的主输出信号的影响的转换函数将测量的主输出信号转换成分析物浓度。

[0063] 图2B示出了流程图210，该流程图示出了根据本公开的补偿在异常条件下的分析物测量的方法的一个循环实施方案中的一些步骤。在步骤211中，使用生物传感器系统测量主输出信号，并且在步骤212中，生成次级输出信号。步骤211和212可以以任何顺序执行，或者可以同时进行。在步骤213中，使用利用生成的次级输出信号来补偿外来刺激对测量的主输出信号的影响的转换函数将测量的主输出信号转换成初步分析物浓度。在步骤214中，基

于测量的主输出信号来测定反向计算的次级输出信号，如以下参照图3A～3J所进一步讨论的。步骤215查询是否存在异常条件。当生成的次级输出信号与由结合到转换函数中的补偿方法假设的参考值不匹配和/或与基于测量的主输出信号的预期的次级输出信号不匹配时，可能出现“异常条件”。下面参照图4A和图4B示出和讨论用于确定是否存在异常条件的方法的一些实施例。

[0064] 如果确定不存在异常条件(即215的查询的答案为“否”)，则可能不需要或不期望对外来刺激的影响进行额外或进一步补偿，因此在步骤216中，初步分析物浓度可以被生物传感器系统报告为分析物测量值。

[0065] 如果确定存在异常条件(即215的查询的答案为“是”)，则可能需要或期望对外来刺激的影响的进行额外补偿，因此，在步骤217中，使用反向计算的次级输出信号来调节生成的次级输出信号。在一些实施方案中，生成的次级输出信号可以被反向计算的次级输出信号替换。换言之，调节的次级输出信号可以等同于反向计算的次级输出信号。在其他实施方案中，反向计算的次级输出信号的一部分可以用于调节生成的次级输出信号。在另外的实施方案中，反向计算的次级输出信号和生成的次级输出信号之间的差值的一部分可以被添加到生成的次级输出信号以对生成的次级输出信号进行调节。在步骤218中，使用利用调节的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成分析物测量值，并在步骤219中报告该分析物测量值。

[0066] 图2C示出了流程图220，该流程图示出了根据本公开的补偿在异常条件下的分析物测量的方法的多个循环实施方案中一些步骤。在流程图220所示的实施方案中，重复进行循环补偿，直到不再存在异常条件。

[0067] 在步骤221中，使用生物传感器系统测量主输出信号，并且在步骤222中，生成次级输出信号。步骤221和222可以以任何顺序执行，或者可以同时进行。在步骤223中，使用利用生成的次级输出信号来补偿外来刺激对测量的主输出信号的影响的转换函数将测量的主输出信号转换成初步分析物浓度。

[0068] 可以使用计数器n来记录所使用的循环次数，并且在步骤224中，将n设定为1。在步骤225处开始循环，其中如以下参照图3A～3J所进一步讨论的，基于测量的主输出信号和第(n-1)个分析物浓度来测定第n个反向计算的次级输出信号；对于n＝1，第(n-1)个分析物浓度是在步骤223中测定的初步分析物浓度。步骤226查询是否存在异常条件。下面参照图4A和图4B示出和讨论用于确定是否存在异常条件的方法的一些实施例。

[0069] 如果226的查询返回“否”，则将第(n-1)个分析物浓度报告为分析物测量值，如步骤230所示。

[0070] 如果226的查询返回“是”，则在步骤227中，通过例如使用第n个反向计算的次级输出信号来调节第(n-1)个调节的次级输出信号来确定第n个调节的次级输出信号。对于n＝1，第(n-1)个调节的次级输出信号是来自步骤222的生成的次级输出信号。在一些实施方案中，可以使用第n个反向计算的次级输出信号来替换第(n-1)个调节的次级输出信号。换言之，第n个调节的次级输出信号可以等同于第n个反向计算的次级输出信号。在其他实施方案中，可以使用第n个反向计算的次级输出信号的一部分来调节第(n-1)个生成的次级输出信号。在另外的实施方案中，第n个反向计算的次级输出信号和第(n-1)个调节的次级输出信号之间的差值的一部分可以被添加到第(n-1)个调节的次级输出信号，以确定第n个调节

的次级输出信号。

[0071] 在步骤228中，使用利用第n个调节的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成第n个分析物浓度。

[0072] 在步骤229中，计数器n增加1，即n＝n+1，在步骤225处开始另一循环。重复循环(步骤225-229)，直到异常条件不再存在(即226的查询返回“否”)，此时将第(n-1)个分析物浓度报告为分析物测量值(步骤230)。

[0073] 图2D示出了流程图240，该流程图示出了根据本公开的补偿在异常条件下的分析物测量的方法的另一个多循环实施方案中的一些步骤。在流程图240所示的实施方案中，循环补偿重复进行预定(固定)的循环次数。

[0074] 在步骤241中，使用生物传感器系统测量主输出信号，并且在步骤242中生成次级输出信号。步骤241和242可以以任何顺序执行，或者可以同时进行。在步骤243中，使用利用生成的次级输出信号来补偿外来刺激对测量的主输出信号的影响的转换函数将测量的主输出信号转换成初步分析物浓度。

[0075] 步骤244查询是否存在异常条件；下面参照图4A和图4B示出和讨论用于确定是否存在异常条件的方法的一些实施例。

[0076] 如果244的查询返回“否”，则将初步分析物浓度报告为分析物测量值，如步骤251所示。

[0077] 如果244的查询返回“是”，则进行循环补偿。可以使用计数器n来记录所使用的循环次数，并且在步骤245中，将n设定为1。在步骤246处开始循环，其中如以下参照图3A～3J所进一步讨论的，基于测量的主输出信号和第(n-1)个分析物浓度来测定第n个反向计算的次级输出信号；对于n＝1，第(n-1)个分析物浓度是在步骤243中测定的初步分析物浓度。

[0078] 在步骤247中，通过例如使用第n个反向计算的次级输出信号来调节第(n-1)个调节的次级输出信号来确定第n个调节的次级输出信号；对于n＝1，第(n-1)个调节的次级输出信号是来自步骤242的生成的次级输出信号。在一些实施方案中，可以使用第n个反向计算的次级输出信号来替换第(n-1)个调节的次级输出信号；换言之，第n个调节的次级输出信号可以等同于第n个反向计算的次级输出信号。在其他实施方案中，可以使用第n个反向计算的次级输出信号的一部分来调节第(n-1)个生成的次级输出信号。在另外的实施方案中，第n个反向计算的次级输出信号和第(n-1)个调节的次级输出信号之间的差值的一部分可以被添加到第(n-1)个调节的次级输出信号，以确定第n个调节的次级输出信号。

[0079] 在步骤248中，使用利用第n个调节的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成第n个分析物浓度。

[0080] 步骤249查询n是否等于预定的循环次数N。如果步骤249的查询返回“是”，则将第n个分析物浓度报告为分析物测量值，如步骤252所示。如果步骤249的查询返回“否”，则在步骤250中将计数器n增加1，即n＝n+1，并且在步骤246处开始另一循环。重复循环(步骤246-250)，直到n＝N(即249的查询返回“是”)，此时将第n个分析物浓度报告为分析物测量值(步骤252)。

[0081] 可以以不同的方式从测量的主输出信号反向计算次级输出信号，例如利用次级输出信号与从测量的主输出信号导出的参数或其他信息的相关性。例如，可以使用温度和门控电流分析测量法的衰变常数参数(decay constant parameter)之间的相关性来反向计

算温度，例如，如美国专利No.8,425,757(其全部内容以引用的方式并入本文)中所讨论的。

[0082] 反向计算次级输出信号的另一种方法是使用次级输出信号和标准化的主输出信号之间的相关性。如上所述，测量的主输出信号取决于许多变量，主要取决于分析物浓度，但也取决于诸如%-Hct、THb值、温度等的外来刺激。标准化使主输出信号对这些许多变量的依赖性降低到对较少变量的依赖性，优选地，降低为仅对一个变量的依赖性。名称为"分析物浓度测定的标准化校准(Normalized Calibration of Analyte Concentration Determination)"的PCT公开No.WO2014/159077 A1一般来说提供了关于标准化的更详细的讨论，并且其全部内容以引用的方式并入本文。主输出信号的消除主输出信号对分析物浓度的依赖性以使得主输出信号变得仅依赖于外来刺激的标准化可以通过各种方法来实现。例如，可以通过将主输出信号除以分析物浓度的单位函数值(unity function value)来使主输出信号标准化；可选择地，可以生成标准化函数，并且将主输出信号与标准化函数值的比值用作标准化的主输出信号。

[0083] 图3A-3J示出了生成标准化函数和标准化的主输出信号的一些方法，其中，标准化的主输出信号消除了对分析物浓度的依赖性，并且仅依赖于次级输出信号。可以使用次级输出信号与标准化的主输出信号之间的相关性来实现反向计算次级输出信号。图3K示出了总结图3A～3I中所示的用于生成可用于反向计算次级输出信号的标准化函数和标准化校准信息的一些步骤的流程图。

[0084] 图3A～3D示出了适用于将主要响应于葡萄糖浓度的主输出信号标准化为仅依赖温度的标准化的一些方面。

[0085] 图3A示出了在三种葡萄糖浓度下的作为温度(在该示例中为次级输出信号)的函数的葡萄糖信号(在该示例中为主输出信号)的图。绘制了从YSI葡萄糖参考样本(葡萄糖水平为78.4mg/dL(◆)，329.5mg(□)和559.8mg/dL(△))测量的葡萄糖信号(报告为在门控电流分析电位序列中5.2秒时的结束电流(ending current)，"5.2s时的电流(mV)")相对于由测量仪中的温度传感器测量的温度("温度,C")的图。在生成图3A所示的数据时，传感器/样本温度和测量仪温度保持相同。针对每个YSI葡萄糖参考样本的绘制数据拟合一条线，并且在图3A中也示出了每条线的相应回归方程。

[0086] 图3B示出了外推到指定温度(22℃；参见图3A中的垂直虚线)并且相对于参考葡萄糖浓度绘制的葡萄糖信号。通过将指定温度(22℃)输入到每个YSI葡萄糖参考样本的回归方程中来获得外推的葡萄糖信号值，从而得到以下三个外推值：65.77、366.86和553.12(电流计数，mV)。通过图3B中绘出的外推值拟合一条线，并进行回归分析以生成如下所示的标准化函数(方程(1))：

[0087] $y=1.0122x-14.577$ (1)

[0088] 其中，y对应于可用作标准化函数值的主输出信号值，x对应于葡萄糖(分析物)浓度。在该实施例中，回归方程是分析物浓度的线性函数，但在其他实施例中，回归方程可以是多项式或其他类型的函数。

[0089] 图3C绘制了标准化的葡萄糖信号("标准化的电流")相对于温度("温度,C")的图，其建立了标准化的主输出信号和温度之间的相关性。图3C包括由两种不同的标准化方法测定的标准化的葡萄糖信号。使用菱形(◆)绘制标准化的葡萄糖信号，该标准化的葡萄糖信号被确定为测量的葡萄糖信号($i_{5.2}$)与已知YSI参考葡萄糖浓度值的单位函数值(即，在已

知分析物浓度的数值下得到的标准化电流值)的比值。通过将测量的葡萄糖信号($i_{5.2}$)除以由方程(1)确定的已知YSI参考葡萄糖浓度值(x)的标准化函数值来确定用空心正方形(□)绘制的标准化的葡萄糖信号。在图3C中相对于温度绘制的两个标准化的葡萄糖信号的回归分析会分别生成如下的线性回归函数：

[0090] $y_{(◆)}=0.0333x_{(◆)}+0.1962$ (2)

[0091] $y_{(□)}=0.0354x_{(□)}+0.2077$ (3)其中，$y_{(◆)}$对应于通过取与已知YSI参考浓度的单位函数的比值而被标准化的葡萄糖信号，并且$y_{(□)}$对应于通过取与标准化函数值(方程(1))的比值而被标准化的葡萄糖信号，$x_{(◆)}$和$x_{(□)}$对应于温度。图3C中所示的两个图和方程(2)和(3)示出了标准化的葡萄糖信号和温度之间的关系。可以将方程(2)和(3)重写为将温度作为标准化的葡萄糖信号的函数来表示，如下所示：

[0092] $$x_{(◆)}=\frac{y_{(◆)}-0.1962}{0.0333} \quad (4)$$

[0093] $$x_{(□)}=\frac{y_{(□)}-0.2077}{0.0354} \quad (5)$$

[0094] 通过将测量的葡萄糖(主输出)信号标准化为从相应的葡萄糖(分析物)浓度导出的标准化值，并将标准化校准信息应用于标准化的葡萄糖(主输出)信号，可以将通过例如方程(4)或(5)表示的标准化的葡萄糖信号和温度之间的关系用作针对反向计算的温度(次级输出信号)的标准化的校准信息。

[0095] 图3D示出了使用方程(4)和(5)反向计算的温度的估计准确度。使用方程(4)或(5)得到的反向计算的温度(T_{calc})没有显示相对于测量的温度(T_{meas})的平均偏差)，也就是说平均$\Delta T=T_{calc}-T_{meas}$为0.0℃。作为反向计算温度的方法，两个方程显示出同等的准确度。

[0096] 图3E～3G示出了适用于将主要响应于葡萄糖浓度的主输出信号标准化为仅依赖Hct信号(次级输出信号)的标准化的一些方面。

[0097] 图3E示出了在三种葡萄糖浓度下的作为Hct信号(i_{Hct}，在该示例中为次级输出信号)的函数的葡萄糖信号(i_G，在该示例中为主输出信号)的图。绘制了从每个YSI葡萄糖参考样本(葡萄糖水平为74.9mg/dL(◆)，348.7mg(■)和528.3mg/dL(▲))测量的葡萄糖信号(报告为在门控电流分析电位序列中5.2秒时的结束电流，“葡萄糖电流，i_5.2s”)相对于由专用Hct电极测量的Hct信号(“Hct电极电流(mV)”)的图。还示出了对应于每个YSI参考样本的绘制数据的回归方程。在用于生成图3E所示数据的生物传感器系统中，对于20%Hct，预期的平均Hct电流计数为2500mV，对于42%Hct为2000mV，对于60%Hct为1680mV，对于70%Hct为1150mV，i_G和i_{Hct}均随着%Hct的增加而降低。

[0098] 图3F示出了外推到Hct电极电流的指定值(2000mV；参见图3E中的垂直虚线)并且相对于YSI参考葡萄糖水平(mg/dL)绘制的葡萄糖信号的图。通过将指定的Hct信号值(2000mV)输入到每个YSI参考葡萄糖样本的回归方程中来获得外推的葡萄糖信号值，得到以下三个外推值：70.01、352.8和585.7。通过图3F中绘出的外推值拟合一条线，并进行回归分析以生成如下所示的标准化函数(方程(6))：

[0099] $y=0.000582x^2+0.786148x+7.848238$ (6)

[0100] 其中，y对应于可用作标准化函数值的葡萄糖信号值，x对应于葡萄糖(分析物)浓度。

[0101] 图3G绘制了标准化的葡萄糖信号(“标准化的电流”)相对于Hct信号(mV)的图,其建立了标准化的葡萄糖信号和Hct信号之间的相关性。图3G包括由两种不同的标准化方法确定的标准化的葡萄糖信号。利用菱形(◆)绘制标准化的葡萄糖信号,该标准化的葡萄糖信号被确定为测量的葡萄糖信号($i_{5.2}$)与已知YSI参考葡萄糖浓度值的单位函数值(即,在已知分析物浓度的数值下得到的标准化电流值)的比值。通过将测量的葡萄糖信号($i_{5.2}$)除以由方程(6)确定的已知分析物浓度值(x)的标准化函数值来确定用空心正方形(□)绘制的标准化的葡萄糖信号。在图3G中相对于Hct信号绘制的两个标准化的葡萄糖信号的回归分析会分别生成如下的线性回归函数:

[0102] $y_{(◆)}=0.000447x_{(◆)}+0.116934$ (7)

[0103] $y_{(□)}=0.000442x_{(□)}+0.114668$ (8)

[0104] 其中,$y_{(◆)}$对应于通过取葡萄糖信号与已知YSI参考浓度的单位函数的比值而获得的标准化的葡萄糖信号,并且$y_{(□)}$对应于通过取葡萄糖信号与标准化函数值(方程(6))的比值而获得的标准化的葡萄糖信号,$x_{(◆)}$和$x_{(□)}$对应于Hct信号。图3G中所示的两个图和方程(7)和(8)示出了标准化的葡萄糖信号和Hct信号之间的关系。可以将方程(7)和(8)重写为将Hct信号作为标准化的葡萄糖信号的函数来表示,并且这两个方程可用作标准化校准信息,以通过输入对应于葡萄糖(分析物)浓度的标准化的测量的葡萄糖(主输出)信号来反向计算Hct(次级输出)信号。

[0105] 图3H～3J示出了适用于将主要响应于%-A1c水平的主输出信号标准化为仅依赖THb信号(次级输出信号)的标准化的一些方面。

[0106] 图3H示出了在四个%-A1c水平下的作为THb信号(R_{THb},在该示例中为次级输出信号)的函数的A1c信号(R_{A1c},在该示例中为主输出信号)的图。绘制了从每个参考样本(%A1c水平为4.8(◆)、6.5(□)、9(Δ)和12.3(●))测量的A1c信号(报告为使用层流A1c生物传感器系统从第一检测区域测量的第一波长的反射率)相对于THb信号(被测量为来自第二检测区域的第二波长的反射率)的图。通过每个参考样本的数据拟合曲线,并且还示出了对应于每条曲线的回归方程。

[0107] 图3I示出了相对于参考%-A1c水平绘制的外推到THb反射信号(R_{THb})值0.7(该值对应于平均THb浓度(～150mg/mL)(参见图3H中的垂直虚线))的A1c信号。通过将R_{THb}指定值(0.7)输入到每个%-A1c参考样本的回归方程中来获得外推的A1c信号值,得到以下四个外推值:0.31602、0.35704、0.4483和0.43732。图3I中绘制的外推的A1c信号数据的回归分析会生成标准化函数(方程(9)):

[0108] $y=-0.0015x^2+0.0414x+0.1508$ (9)

[0109] 其中y对应于可用作标准化函数值的A1c信号值,并且x对应于%-A1c水平(分析物浓度)。在本示例中,回归方程(方程(9))是分析物浓度的二阶多项式函数。

[0110] 图3J绘制了THb信号值相对于标准化的A1c信号的图,其建立了THb信号和标准化的A1c信号之间的相关性。将图3J中绘制的标准化的A1c信号确定为测量的A1c信号与由方程(9)确定的已知分析物浓度值(x)的标准化函数值的比值。图3J中的相对于标准化的A1c信号绘制的THb信号的回归分析会生成如下的二阶多项式回归函数:

[0111] $y=-0.6086x^2+0.8276x+0.4826$ (10)

[0112] 其中,y对应于THb信号,x对应于标准化的A1c信号。方程(10)可以用作标准化的校

准信息，以通过输入对应于%-A1c(分析物浓度)的标准化的测量的A1c(主输出)信号来反向计算THb(次级输出)信号。

[0113] 图3K总结了根据本公开的用于生成可以用于反向计算次级输出信号的标准化函数和标准化校准信息的一个实施例的一些步骤。在实施流程图300所示的步骤时，在步骤301中，使用生物传感器系统从多个参考样本中测量参考主输出信号。参考主输出信号主要响应于主刺激，并且每个参考样本与主刺激的已知值相关联。在步骤302中，生物传感器系统针对每个测量的参考主输出信号生成次级输出信号。生成的次级输出信号响应于会影响测量的参考主输出信号的外来刺激。步骤301和302可以以任何顺序执行，或者可以同时进行。

[0114] 在步骤303中，对于每个参考样本，使测量的参考主输出信号(来自步骤301)与生成的次级输出信号(来自步骤302)相关。在一些实施方案中，可以对来自步骤303的相关数据进行回归分析，以生成将测量的参考主输出信号与生成的次级输出信号相联系的回归方程。

[0115] 在步骤304中，对于每个参考样本，将参考主输出信号值外推到次级输出信号的指定值。次级输出信号的指定值通常是生成的次级输出信号(来自步骤302)的范围的中点附近的值；然而，生成的次级输出信号的范围内的任何值均可以用作参考主输出信号值被外推到的指定值。在生成将测量的参考主输出信号与生成的次级输出信号相联系的第一回归方程的实施方案中，可以使用第一回归方程通过输入次级输出信号的指定值来外推参考主输出信号值。

[0116] 在步骤305中，使外推的参考主输出信号值(来自步骤304)与其已知的主刺激值相关，以便通过例如相关数据的回归分析来生成标准化函数。

[0117] 然后，在步骤306中，使用标准化函数使每个测量的参考主输出信号(在其对应的已知主刺激值下)标准化。通常，通过将测量的主输出信号除以标准化函数值来进行标准化。在本实施例中，通过将已知主刺激值输入到在步骤305中生成的标准化函数中来确定标准化函数值。

[0118] 在步骤307中，使标准化的参考主输出信号(来自步骤306)与生成的次级输出信号(来自步骤302)相关，以生成标准化的校准信息。在本公开的一些实施例中可以使用该标准化的校准信息，以便基于测量的主输出信号来反向计算次级输出信号。在一些实施方案中，标准化的校准信息可以表示为将标准化的主输出信号与次级输出信号相联系的回归方程，并且标准化的校准信息从来自步骤307的相关数据的回归分析中得出。

[0119] 图4A～4B示出了确定是否存在异常条件的不同实施例。图4A中的流程图400示出了基于生成的次级输出信号和在生物传感器系统的校准期间建立的外来刺激的参考值之间的差值来确定是否存在异常条件的一些步骤。例如，主输出信号与分析物浓度的标准参考相关性通常在参考温度(例如25℃)和参考血细胞比容水平(例如42%)下建立。对于在不同于参考值的温度或血细胞比容水平下进行的生物传感器测量，温度或血细胞比容对主输出信号的影响通常通过转换函数来补偿，使得报告在参考温度和血细胞比容水平值下的分析物浓度。然而，如果生成的次级输出信号和参考值之间的差值太大，则可能存在异常条件，并且典型的补偿方法可能在分析物测定中引入额外误差。

[0120] 在实施流程图400中所示的步骤时，在步骤401中，生物传感器系统生成次级输出

信号，并且在步骤402中，生物传感器系统确定生成的次级输出信号与参考值之间的差值。步骤403查询在步骤402中确定的差值的绝对值是否大于或等于阈值。在执行重复循环的实施方案中，可以确定第n个调节的次级输出信号或第n个反向计算的次级输出信号与参考值之间的差值，并且当该差值的绝对值大于或等于阈值时，可能存在异常条件。阈值通常根据检测异常条件所需的灵敏度而设定，并且可以从一个循环到下一个循环发生改变(例如，逐渐减小)。如果步骤403的查询返回“否”，则不存在异常条件(如404中所示)。如果步骤403的查询返回“是”，则确实存在异常条件(如405中所示)，并且在一些实施方案中，可以在步骤406中提供异常条件的通知。该通知可以采取任何形式，例如，在合并有生物传感器系统的显示器上的警告消息、生物传感器系统上的指示可能存在错误的红光指示器等。通知还可以包括用于校正异常条件或重复测量的指令。

[0121] 图4B的流程图410示出了基于生成的次级输出信号和基于测量的主输出信号的预期的外来刺激值之间的差值来确定是否存在异常条件的一些步骤。在步骤411和412中，生物传感器系统测量主输出信号并生成次级输出信号。步骤411和412可以以任何顺序执行，或者可以同时进行。在步骤413中，基于测量的主输出信号来确定反向计算的次级输出信号；反向计算的次级输出信号反映基于测量的输出信号的预期的外来刺激值。在步骤414中，确定来自步骤412的生成的次级输出信号与来自步骤413的反向计算的次级输出信号之间的差值。步骤415查询在步骤414中确定的差值的绝对值是否大于或等于预设值。在执行重复循环的实施方案中，可以确定第n个反向计算的次级输出信号和第(n-1)个反向计算的次级输出信号或第(n-1)个调节的次级输出信号之间的差值，并且当该差值的绝对值大于或等于预设值时，可能存在异常条件。预设值通常根据检测异常条件所需的灵敏度而设定，并且可以从一个循环到另一个循环发生改变(例如，逐渐减小)。如果步骤415的查询返回“否”，则不存在异常条件(如416中所示)。如果步骤415的查询返回“是”，则确实存在异常条件(如418中所示)；在一些实施方案中，可以在步骤419中提供异常条件的通知(如先前相对于图4A中的步骤406所讨论的)。

[0122] 在根据本公开的一些实施方案中，可以基于就图4A和图4B讨论的标准的组合来确定异常条件。也就是说，当生成的次级输出信号与参考值之间的差值的绝对值大于或等于阈值以及生成的次级输出信号与反向计算的次级输出信号之间的差值的绝对值大于或等于预设值时，可以确定存在异常条件。

[0123] 图5A～5C示出了因异常条件而引入到分析物测量中的误差，这些图示出了“异常温度条件”的影响。例如，当手持式测量仪保存在冬季天气(例如0℃～10℃)或夏季天气(例如40℃～45℃)下的汽车中，然后与在室温(例如22℃～25℃)下保存的测试传感器一起使用时，可能出现异常温度条件。假设测试传感器和测量仪之间通过接口触点(interfacing contact)的热传递预期在短时间内是最小的，则无论测量仪温度如何，测试传感器/样本温度预期都将保持相对不变。

[0124] 当将温度传感器或其他温度测量装置并入到生物传感器系统中时，假设由这种装置测量的温度会准确地反映测试传感器和样本的温度，但是这些装置通常被并入测量仪中，不是传感器中。用于测定分析物浓度的包括温度补偿的方法通常使用由这些装置测量的温度来补偿主输出信号。然而，在异常温度条件下，测量的温度可能不能准确地反映传感器/样本温度，因此使用测量的温度的进行了温度补偿的测量在计算的分析物浓度中引入

了误差。

[0125] 图5A示出了通过在七个温度(5℃(◆)、10℃(□)、15℃(▲)、25℃(×)、35℃(✳)、40℃(●)以及45℃(+))下的生物传感器系统与在相同温度下的测量仪和传感器/样本测量的来自具有三种不同葡萄糖浓度(70、350和550mg/dL)的样本的主输出信号(5.2s时的电流(mV))的图。在不同葡萄糖浓度下的测量的主输出信号随着温度的变化而变化,随着浓度的增加,该变化也加剧。已经开发了如在美国专利No.7,781,222("用于生物传感器系统的温度调节的分析物测定(Temperature-Adjusted Analyte Determination for Biosensor System")中所讨论的包括温度补偿的转换函数,以便在将主输出信号转换成分析物浓度时,对主输出信号中的这种与温度相关的变化进行补偿。

[0126] 图5B示出了通过生物传感器系统测量的来自具有四种不同葡萄糖浓度(86、170、335和564mg/dL)的样本的主输出信号(5.2s时的电流(mV))的图,其中,传感器/样本处于22℃,测量仪保存在六个不同温度(22℃、5℃、10℃、15℃、35℃、45℃)下,从而得到以下平均温度测量值,21.9℃(◆)、6℃(□)、10.3℃(△)、15.7℃(×)、34.1℃(✳)和43.7℃(○)。即使测量的测量仪温度变化很大,传感器/样本温度也保持相对稳定,如测量的主输出信号针对每种葡萄糖浓度都保持相对不变所反映的那样。如果使用测量的测量仪温度补偿温度的影响而将这些数据应用于具有温度补偿的转换函数,则测量的测量仪温度将在分析物测定中引入潜在的较大误差。

[0127] 图5C示出了当测量的测量仪温度不准确表示传感器/样本温度时,针对使用具有温度补偿的常规转换函数确定的图5B中的数据的葡萄糖浓度因异常温度条件而导致的误差(绘制为偏差/%-偏差)。偏差/%-偏差数据(◆)与22℃、5.5℃、10.5℃、15.5℃、22.5℃、34℃、39.5℃和43.5℃下的平均测量仪温度(△)一起顺序地绘制(传感器/样本处于～22℃)。如从图5C可以看出的,传感器/样本与测量的测量仪温度之间的差值越大,分析物浓度的误差越大。

[0128] 在补偿中使用反向计算的温度而不使用测量的温度可有助于减轻因异常温度条件而引起的这种误差。这种反向计算的温度更好地反映了在实际测量条件下样本的温度。图6A示出了基于在异常温度条件(传感器/样本温度处于～22℃;平均测量仪温度处于22℃、5.5℃、10.5℃、15.5℃、22.5℃、34℃、39.5℃和43.5℃)下测量的主输出信号的反向计算的温度。图6A所示的反向计算的温度(◆)是使用上述方程(4)所表示的标准化校准信息(参见图3C及其相关文字)从与图5C所示的偏差/%-偏差数据相同的数据中生成的。这些反向计算的温度显示为比测量的测量仪温度(Δ)更接近～22℃的传感器/样本温度。此外,将反向计算的温度输入用于生成图5C所示的数据的具有温度补偿的相同的标准转换函数中,会生成更准确的具有减小的误差(较小的偏差/%-偏差)的分析物浓度测定,如图6B所示。

[0129] 图6B示出了与平均测量的测量仪温度(△)一起绘制的葡萄糖浓度的误差(绘制为偏差/%-偏差),该误差通过以下方式确定:如图1A所示使用具有温度补偿的常规转换函数的单向应用(×)(这是图5C中所示的相同数据)、使用利用反向计算的温度进行补偿的相同常规转换函数的一个完整循环应用(◆)(如图2A所示)以及仅在检测到异常温度条件时应用的利用反向计算的温度进行补偿的相同的常规转换函数的一个选定循环应用(□)(如图2B中所示)。使用上述方程(4)所表示的标准化校准信息(参见图3C及其相关文字)来测定反向计算的温度。在异常温度条件下,与常规单向应用的结果相比,完整循环应用和一个选定

循环应用均将作为偏差/%-偏差的误差平均从～20%降低到约～10%；在更极端的异常温度条件下，例如在平均测量的测量仪温度为～5℃下，误差从～20%降低到～5%。当在非异常温度条件(例如，测量的测量仪温度为～22℃)下应用时，一个循环应用与常规单向方法一样具有～10%的类似误差；但是仅在异常温度条件下进行补偿，如在一个选定循环应用中所做的那样，可最大限度地减少生成不必要偏差的概率。

[0130] 图7A～7B示出了使用根据本公开的循环补偿方法的补偿在异常温度条件下的分析物测量的方法的一些实施例的一些步骤和结果。

[0131] 图7A所示的循环补偿过程的实施例包括以下步骤：基于先前测定的分析物浓度反向计算温度；确定反向计算的温度和用于在先前测定的分析物浓度中进行补偿的温度之间的温度差；使用所确定的温度差来检测异常温度条件；以及如果检测到异常温度条件，则对温度进行调节并使用调节的温度来补偿温度对测量的主输出信号的影响以重新计算分析物浓度。重复该过程直到未检测到异常温度条件，此时将所测定的分析物浓度报告为分析物测量值。

[0132] 更具体地，在图7A所示的流程图700中，该过程以其中生物传感器系统测量主输出信号的步骤701开始。在步骤702中，使用生物传感器系统生成温度测量值(T^0)(这里，不论可以附加到“T”上的上标是什么，与“T”一起使用的上标“0”都表示使用生物传感器系统得出的温度测量值)。步骤701和702可以以任何顺序执行，或者可以同时进行。在步骤703中，使用利用温度测量值(T^0)来补偿温度对测量的主输出信号的影响的转换函数将测量的主输出信号转换成初步分析物浓度(G^0)。

[0133] 在图7A所示的实施例中，在步骤704中进行是否存在异常温度条件的初始判定。本实施例中的初始判定基于温度测量值(T^0)和参考温度(T_{ref})之间的差值的绝对值是否大于或等于阈值。例如，如果阈值设定为7℃，则当$|T^0-T_{ref}|\geq 7$℃时，可能存在异常温度条件。如果在该初始查询中确定很可能存在异常温度条件(即，步骤704的查询返回“是”)，则可以进行循环补偿处理(如下面进一步讨论的)。然而，如果在步骤704中的初始查询返回“否”，则可能不存在异常温度条件，并且该过程可以直接进行到其中可以将初步分析物浓度(G^0)报告为分析物测量值的步骤709。取决于检测异常温度条件所需的灵敏度，可以将阈值设定成任何值(例如，10、7、5、3、2或1℃)。

[0134] 图7A所示的循环补偿处理可进行超过一个循环，因此计数器(n)用于记录每个循环，并且在步骤705中将计数器设定为$n=1$。

[0135] 在步骤706中，基于第(n-1)个分析物浓度(G^{n-1})来确定第n个反向计算的温度(T^n)。换言之，第n个反向计算的温度(T^n)被确定为第(n-1)个分析物浓度的函数，即，$T^n=f(G^{n-1})$。

[0136] 在步骤707中，按下式确定第n个温度差(ΔT^n)：

[0137] $$\Delta T^n=T^n-T^{n-1}{}_{adj} \quad (11)$$

[0138] 其中，T^n是第n个反向的计算温度(来自步骤706)，并且对于$n=1$，$T^{n-1}{}_{adj}$是在步骤702中由生物传感器系统生成的温度测量值(T^0)。

[0139] 通过在步骤708中查询第n个温度差的绝对值是否大于或等于预设值(即，$|\Delta T^n|\geq$预设值)，来检测异常温度条件。例如，如果预设值设定为5℃，则当$|\Delta T^n|\geq 5$℃时，也就是说，当第n个反向计算的温度(T^n)与先前调节的温度($T^{n-1}{}_{adj}$)之差达到5℃以上时，将检测

到异常温度条件。取决于检测异常温度条件所需的灵敏度，预设值可以设定成任何值(例如，10、7、5、3、2或1℃)，也可以设定为例如随着每个循环逐渐减少等。

[0140] 如果基于第n个温度差(ΔT^n)没有检测到异常温度条件(即，708的查询返回“否”)，则在步骤709中，生物传感器系统将第(n-1)个分析物浓度(G^{n-1})报告为分析物测量值。

[0141] 如果基于第n个温度差(ΔT^n)检测到异常温度条件(即，708的查询返回“是”)，则在步骤710中按下式确定第n个调节的温度(T^n_{adj})：

[0142] $$T^n_{adj}=T^{n-1}_{adj}+WC\,\Delta T^n \quad (12)$$

[0143] 其中，对于n＝1，T^{n-1}_{adj}是在步骤702中由生物传感器系统生成的温度测量值(T^0)，ΔT^n是第n个温度差(来自步骤707)，WC是加权系数，其可以是从零(0)到一(1)的任何值并包括1。加权系数(WC)用于确定用于调节先前调节的温度(T^{n-1}_{adj})的第n个反向计算的温度(T^n)为多少。当WC＝1时，第n个反向计算的温度(T^n)完全取代了先前调节的温度，因此，$T^n_{adj}=T^n$。

[0144] 在步骤711中，通过使用利用第n个调节的温度(T^n_{adj}，来自步骤710)来补偿温度对测量的主输出信号的影响的转换函数来转换测量的主输出信号(来自步骤701)而确定第n个分析物浓度(G^n)。在步骤712中，计数器n加1(即，n＝n+1)，并且在步骤706中开始另一循环。可以重复步骤706～712的循环，直到708的查询返回“否”，并且基于第n个温度差(ΔT^n)未检测到异常温度条件，此时在步骤709中，生物传感器系统将第(n-1)个分析物浓度(G^{n-1})报告为分析物测量值。

[0145] 图7B示出了根据图7A所示的实施方案的WC对针对步骤706～711的一个循环适用的循环温度补偿过程的影响。图7B绘制了与平均测量的测量仪温度(△)一起绘制的作为偏差/%-偏差的误差，其中，误差来自以下转换函数的一个循环应用：具有使用反向计算的温度完全补偿温度的影响的温度补偿的转换函数(即WC＝1)(□)；以及具有使用反向计算的温度的一部分来部分地补偿温度的影响的温度补偿的转换函数(即WC＝0.65)(◆)。与来自具有温度补偿的标准转换函数的常规单向应用的误差(参见图6B，使用(×)绘制的单向数据)相比，使用WC＝1时系统误差从～20％降低到的～5％，并且在更极端的异常温度条件下(例如，测量的测量仪温度为～5℃)，使用WC＝0.65时降低到～15％。在某些情况下，使用反向计算的温度来完全补偿温度的影响(WC＝1)可能会过度补偿温度的影响，例如在不太极端的异常温度条件下(例如，测量的测量仪温度为～35℃)；因此，在某些情况下，期望使用WC<1以更渐进的方式来补偿外来刺激的影响。

[0146] 下面的表1示出了使用循环补偿方法的实施例而生成的数据，该循环补偿方法类似于图7A的流程图700所示的方法，以便补偿在异常温度条件下分析物测定中的温度影响。使用生物传感器系统、三个YSI参考葡萄糖样本(葡萄糖浓度为85.9、169.8和84.0mg/dL)和在～22℃下储存的传感器以及在5℃、22°和40℃下储存的测量仪生成表1中的数据。反向计算的温度(T^n)使用上述方程(4)所表示的标准化校准信息(参见图3C及其相关文字)确定。将加权系数(WC)设定为等于1(即，WC＝1)，因此$T^n_{adj}=T^n$。

[0147] 表1：对于T^n_{adj}和G^n的循环补偿过程的总结

[0148]

	YSI	T^0	G^0	偏差/%-偏差	$T^0 - T_{ref}$	初始异常温度是/否?[a]			
-	85.9	21.9	87.4	1.6%	-3.1	否			
-	169.8	5.7	201.5	18.7%	-19.3	是			
-	84.0	39.0	68.8	-15.2%	14.1	是			
n	YSI	T^{n-1}_{adj}	G^{n-1}	T^n	ΔT^n	异常温度是/否?	T^n_{adj}	G^n	偏差/%-偏差
1	85.9	21.9	87.4	20.5	-1.4	否[b]	--	--	--
1	169.8	5.7	201.5	16.7	11.0	是[b]	16.7	175.2	3.2%
1	84.0	39.0	68.8	30.8	-8.2	是[b]	30.8	80.2	-4.5%
2	85.9	21.9	--	--	--	--	--	--	--
2	169.8	16.7	175.2	19.9	3.2	否[b],是[c]	19.9	172.0[b]	1.3%[b]
2	84.0	30.8	80.2	25.9	-4.9	否[b],是[c]	25.9	88.7[b]	5.6%[b]
3	85.9	21.9	--	--	--	--	--	--	--
3	169.8	19.9	172.0[b]	20.3	0.4	否[c],否[d]	20.3	--	--
3	84.0	25.9	88.7[b]	23.0	-2.9	否[c],是[d]	23.0	93.8[c]	9.8%[c]
4	85.9	21.9	--	--	--	--	--	--	--
4	169.8	20.3	--	--	--	--	--	--	--
4	84.0	23.0	93.8[c]	21.5	-1.5	否[d]	21.5	--	--

[0149] 注：

[0150] T^0=温度测量值

[0151] G^0=初步分析物浓度(=f(T^0))

[0152] T_{ref}=25℃

[0153] T^n=第n个反向计算的温度(=f(G^{n-1}))

[0154] $\Delta T^n = T^n - T^{n-1}_{adj}$

[0155] [a]初始异常温度标准：$|T^0 - T_{ref}| \geq 7$℃(阈值)

[0156] [b]异常温度标准：$|\Delta T^n| \geq 5$℃(预设值)

[0157] [c]异常温度标准：$|\Delta T^n| \geq 3$℃(预设值)

[0158] [d]异常温度标准：$|\Delta T^n| \geq 2$℃(预设值)

[0159] T^n_{adj}=第n个调节的温度(这里WC=1，因此$T^n_{adj}=T^n$)

[0160] G^n=f(T^n_{adj})

[0161] 偏差/%-偏差=(G^n-YSI)/YSI

[0162] 如图7A所示，该过程开始于生物传感器系统测量主输出信号并生成温度测量值(T^0)。使用温度测量值(T^0)补偿温度对测量的主输出信号的影响来确定初步葡萄糖浓度(G^0)。如表1所示，葡萄糖浓度水平分别为169.8和84.0mg/dL的YSI样本在测量的测量仪温

度(T^0)下的初步分析物浓度具有大于±10%的偏差/%-偏差。应用$|T^0-T_{ref}|\geq 7℃$(阈值)的初始标准,葡萄糖浓度水平为169.8和84.0mg/dL的YSI样本可能存在异常温度条件,但在测量的测量仪温度为21.9℃下的葡萄糖浓度为85.9mg/dL的YSI样本不存在异常温度条件,因此该样本测量可不需要进行循环补偿。在一些实施例中,例如图7A所示的实施例中,如果不满足初始异常温度标准,则不应用循环补偿,并且不需要反向计算温度。为了说明基于反向计算的温度的第二异常温度标准,表1所示的数据包括针对葡萄糖浓度为85.9mg/dL的YSI样本计算的第一反向计算的温度和$|\Delta T^n|$,对于该样本基于初始标准没有检测到异常温度条件。

[0163] 基于初步分析物浓度(G^0)来确定第一反向计算的温度(T^1,n=1时)。应用$|\Delta T^1=T^1-T^0|\geq 5℃$(预设值)的标准,在测量的测量仪温度为21.9℃时,对于葡萄糖浓度为85.9mg/dL的YSI样本没有检测到异常温度条件,因此对该样本测量不进行循环补偿。对于葡萄糖浓度水平为169.8和84.0mg/dL的YSI样本,检测到异常温度条件,因此对于这两个YSI样本,计算第一调节的温度(T^1_{adj})(使用WC=1,因此$T^1_{adj}=T^1$),并将该第一调节的温度作为输入进行循环以确定第一分析物浓度(G^1)。与这两个YSI样本的初步分析物浓度相比,第一分析物浓度(G^1)的误差已降至±5%以内。

[0164] 对于n=2,基于第一分析物浓度(G^1)来确定第二反向计算的温度(T^2)。如果预设值保持相同,则应用相同的标准$|\Delta T^n|\geq 5℃$,于是对于这些YSI样本(169.8和84.0mg葡萄糖/dL),没有检测到异常温度条件,并且不进行进一步的循环补偿。然而,如果预设值降低,并且应用$|\Delta T^n|\geq 3℃$的标准,则对于这两个YSI样本均检测到异常温度条件,并且计算第二调节的温度(T^2_{adj})(使用WC=1,因此$T^2_{adj}=T^2$),并且将该第二调节的温度作为输入进行循环以确定第二分析物浓度(G^2)。这两个YSI样本的第二分析物浓度(G^2)的误差保持小于±10%,该误差在目前可接受的性能极限内。另外,第二反向计算的温度值(T^2)比第一反向计算的温度(T^1)更接近测量仪温度(~22℃)的预期值。

[0165] 对于n=3,基于这两个YSI样本(169.8和84.0mg葡萄糖/dL)的第二分析物浓度(G^2)来确定第三反向计算的温度(T^3)。应用$|\Delta T^n|\geq 3℃$的标准,对于这两个样本,均未检测到异常温度条件,因此不进一步进行循环补偿。如果需要的话,例如,为了使反向计算的温度更接近样本/传感器温度的,可以进一步降低预设值,例如,应用$|\Delta T^n|\geq 2℃$的标准。将预设值设定为2℃时,对于具有84.0mg葡萄糖/dL的YSI样本,检测到异常温度条件,并且对该样本测量施加另一补偿循环,同时,计算第三调节的温度(T^3_{adj})(使用WC=1,因此$T^3_{adj}=T^3$),并且该第三调节的温度作为输入进行循环以确定第三分析物浓度(G^3)。

[0166] 对于n=4,基于具有84.0mg葡萄糖/dL的YSI样本的第三分析物浓度(G^3)来确定第四反向计算的温度(T^4)。应用$|\Delta T^n|\geq 2℃$的标准,未检测到异常温度条件,因此不进一步进行循环补偿。从表1可以看出,第四反向计算的温度(T^4)比任何先前反向计算的温度都更接近于预期的测量仪温度。

[0167] 回顾表1中的数据,可以看出,特别是与逐步降低预设值并提高异常温度标准结合使用的重复的循环补偿可以用于逐渐使反向计算的温度接近预期的传感器/样本温度。然而,逐步地降低预设值不一定使分析物浓度的误差伴随性地逐步降低,这是由于其他误差源可能变得更明显。

[0168] 然而,分析物浓度的误差仍然在目前可接受的性能极限内(例如,±10%)。

[0169] 下面的表2示出了使用循环补偿方法的实施例生成的数据，该循环补偿方法类似于图2D的流程图240所示用于补偿分析物测定中的血细胞比容影响的循环补偿方法。在本实施例中，在基于$|i_{Hct_Ref}-i^0_{Hct}|\geq 300$(阈值)和$|\Delta i^1_{Hct}=i^0_{Hct}-i^1_{Hct}|\geq 300$(预设值)初始判定出存在异常条件后，进行预定次数循环的循环补偿过程，在这种情况下，N=9。使用具有专用Hct电极的生物传感器系统，从具有245mg/dL的葡萄糖浓度水平和38%Hct的YSI参考样本中生成表2中的数据。第一行数据包括直接从生物传感器测量生成的数据(i^0_{Hct},G^0)。使用由以上方程(8)所表示的标准化校准信息(同样参见图3G及其相关文字)来确定反向计算的血细胞比容信号(i^n_{Hct})，并且该反向计算的血细胞比容信号用于计算第n个分析物浓度(即，$G^n=f(i^n_{Hct})$)。为了监测循环补偿的进度，计算每个循环的异常条件标准和偏差/%-偏差。

[0170] 生成的Hct信号($i^0_{Hct}=791.5$mV)与参考值相比较低($i_{Hct_Ref}=2000$mV，因此$|i_{Hct_Ref}-i^0_{Hct}|=1208.5$mV)，并且与第一反向计算的Hct信号相比也较低($i^1_{Hct}=1271.8$mV，因此$|\Delta i^1_{Hct}=i^0_{Hct}-i^1_{Hct}|=480.3$mV)，这表示存在异常条件。初步葡萄糖浓度($G^0$)的%-偏差为38.3%。表2中的数据表明，在使用反向计算的Hct信号进行了9次循环补偿后，葡萄糖浓度的%-偏差降低到10%以下。

[0171] 表2：对于i^n_{Hct}和G^n的循环补偿过程的总结

[0172]

n	YSI	%Hct	i^0_{Hct}	G^0 偏差/%-偏差	$i_{Hct-ref}-i^0_{Hct}$	i^n_{Hct}	G^n 偏差/%-偏差	$i_{Hct-ref}-i^n_{Hct}$	Δi^n_{Hct}
1	245	38	791.5	338.2 (38.5%)	1208.5	1271.8	329.1 (34.6%)	728.2	480.3
2	--	--	--	--	--	1321.1	319.6 (30.7%)	678.9	49.3
3	--	--	--	--	--	1376.4	309.7 (26.7%)	623.6	55.2
4	--	--	--	--	--	1436.9	299.8 (22.6%)	563.1	60.5
5	--	--	--	--	--	1501.5	290.2 (18.7%)	498.5	64.7
6	--	--	--	--	--	1568.5	281.6 (15.2%)	431.5	67.0
7	--	--	--	--	--	1632.3	274.6 (12.3%)	367.7	63.8
8	--	--	--	--	--	1687.6	268.8 (9.9%)	312.4	55.3

[0173]

9	--	--	--	--	--	1735.6	263.9 (7.9%)	264.4	48.0

[0174] 注：

[0175] i^0_{Hct}=生成的Hct信号

[0176] G^0=初步分析物浓度($=f(i^0_{Hct})$)

[0177] $i_{Hct-ref}=2000$

[0178] i^n_{Hct}=第n个反向计算的Hct信号($=f(G^{n-1})$)

[0179] $\Delta i^n_{Hct}=i^n_{Hct}-i^{n-1}_{Hct}$

[0180] $G^n = f(i^n_{Hct})$

[0181] 偏差/%-偏差=(G^n-YSI)/YSI

[0182] 异常标准:$|i_{Hct-ref}-i^n_{Hct}| \geq 300$(阈值)且$|\Delta i^n_{Hct}| \geq 300$(预设值)

[0183] 可以实施的本公开的方法可用于电化学生物传感器系统、光学系统及其组合等中。图8描绘了可以实施本公开的方法的生物传感器系统800的一个实施例的示意图。生物传感器系统800包括测量装置802和测试传感器804。测量装置802可以在包括台式装置、便携式或手持式装置等的分析仪器中实现。

[0184] 生物传感器系统800通常使用存储在测量装置802中的校准信息来测定样本的分析物浓度。生物传感器系统800可用于测定分析物浓度,包括葡萄糖、A1c、尿酸、乳酸、胆固醇、胆红素等的浓度。虽然示出了特定构造,但是生物传感器系统800可以具有其他构造并且可以包括额外的部件。

[0185] 测试传感器804通常具有用于形成储器808和具有开口812的通道810的基部806。储器808和通道810可以被具有通气口的盖子覆盖。储器808限定部分封闭的体积,并且可以包含帮助保持液体样本的组合物,诸如水溶胀性聚合物或多孔聚合物基质等。试剂可以沉积在储器808和/或通道810中。试剂可以包括一种或多种酶、粘合剂、介体和类似物质和/或化学指示剂。测试传感器804具有与储器808相邻的样本接口814。测试传感器804可具有其他构造。

[0186] 在电化学系统中,样本接口814具有电连接到可以从其测量输出信号的工作电极(未示出)和对电极(未示出)的导体或触点。样本接口814还可以包括电连接到可以从其测量次级输出信号的一个或多个附加电极(未示出)的导体或触点。电极可以基本上在相同平面中或在超过一个平面中。电极可以配置在用于形成储器808的基部806的表面上。电极可以延伸或突出到储器808中。电介质层可以部分地覆盖导体和/或电极。样本接口814可以具有其它电极以及导体和触点。

[0187] 在光学传感器系统中,样本接口814通常具有用于用光来探测样本的一个或多个光学入口或孔口。

[0188] 测量装置802包括连接到传感器接口818和可选显示器820的电路816。电路816包括连接到信号发生器824、温度传感器826和存储介质828的处理器822。

[0189] 响应于处理器822,信号发生器824能够向传感器接口818提供电输入信号。在光学系统中,电输入信号可用于操作或控制传感器接口818中的检测器和光源。在电化学系统中,电输入信号可以经由传感器接口818传输到样本接口814,以将电输入信号施加到生物流体的样本。电输入信号可以是电位或电流,并且可以是常数、变量或其组合(例如当AC信号被施加DC信号偏移时)。电输入信号可以连续施加,或可以作为多个激励、序列或周期施加。信号发生器824还可以作为发生器-记录器以能够记录来自传感器接口的输出信号。

[0190] 温度传感器826能够对测量装置802的环境温度进行测量,并且可以为热敏电阻、温度计或其它温度感测装置。

[0191] 存储介质828可以为磁性、光学或半导体存储器或者另一种存储装置等。存储介质828可以为可远程访问的固定存储装置、诸如存储卡等的可移动存储装置等。存储介质828可以存储用于本公开的分析物测定、分析和/或方法的计算机编程的指令以及校准和其他信息(例如用于检测异常条件的阈值和预设值)。

[0192] 根据本公开的方法，存储介质828还可以存储可以用于基于测量的主输出信号来反向计算次级输出信号的标准化函数和/或标准化的校准信息。这种标准化函数和/或标准化的校准信息可以以图形方式表示，例如如图3B～3C、3F～3G和3I～3J所示，或可以用数学表示，例如如方程(1)～(5)、(6)～(8)和(9)～(10)所示，或者可以用其组合等表示。标准化函数和标准化的校准信息优选地表示为方程，这些方程可以由程序号(PNA:program number)表、另一查找表等表示。

[0193] 处理器822被构造为执行计算机编程的指令以实施包括本公开的方法的分析物测量和分析。处理器822还可以被构造为与信号发生器824交互以例如将电输入信号提供给传感器接口818；与温度传感器826交互以例如生成并接收温度测量值(T^0)；与传感器接口818交互以例如从测试传感器804接收主输出信号和/或其他次级输出信号。

[0194] 在电化学系统中，响应于样本中分析物的反应，使用工作电极和对电极来测量主输出信号。也可以从附加电极测量次级输出信号。在光学系统中，传感器接口818的检测器可以接收主输出信号和一些次级输出信号。

[0195] 处理器822可被进一步构造为响应于传感器接口818处测试传感器804的出现、样本被施加于测试传感器804以及使用者输入等执行计算机编程的指令，以开始分析物测量和分析(包括本公开的方法)。可以将分析物分析的结果输出到显示器820、远程接收器(未示出)和/或可以存储在存储介质828中。

[0196] 可以通过存储在存储介质828中的计算机可读软件代码来提供实施分析物测量的指令，分析物测量可包括：确定异常条件、基于测量的主输出信号来反向计算次级输出信号和/或循环补偿方法。代码可以是目标代码或说明或控制所述功能的任何其他代码。来自分析物分析的数据可以在处理器822中经历一个或多个数据处理，包括确定衰减速率、K常数、比值、函数等。

[0197] 为了说明本公开的某些方面的目的给出了上述说明，该说明并不旨在限制本公开。相关领域的技术人员将理解，根据上述教导可以实现许多增加、修改、变形和改进，并且这些增加、修改、变形和改进仍然落在本公开的范围内。

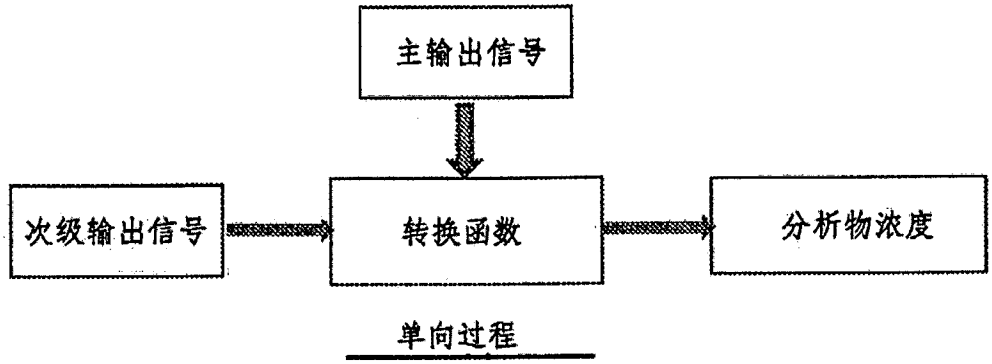
主输出信号
次级输出信号
转换函数
分析物浓度
单向过程

图1A(现有技术)

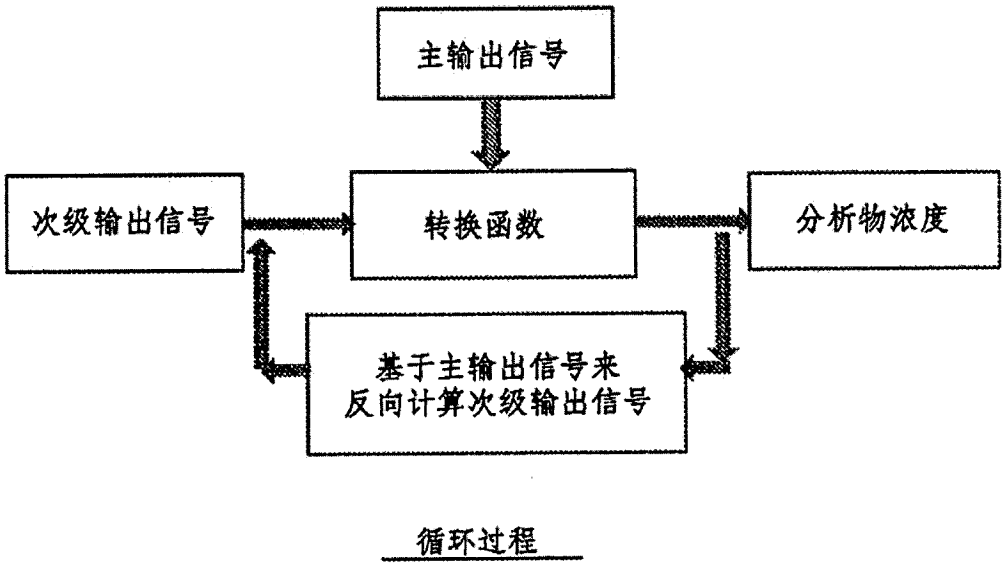
主输出信号
次级输出信号
转换函数
分析物浓度
基于主输出信号来
反向计算次级输出信号
循环过程

图1B

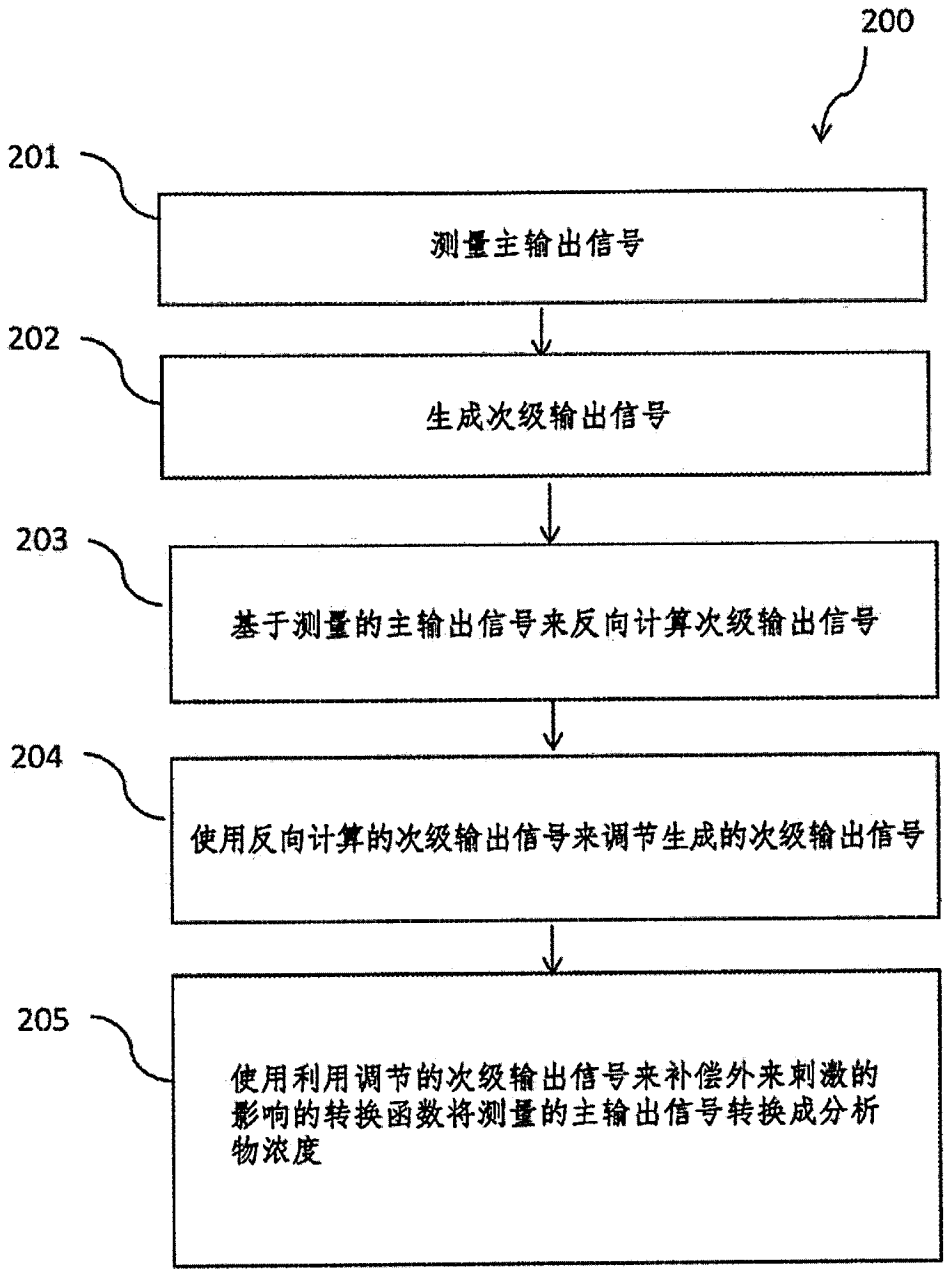
200
201
测量主输出信号
202
生成次级输出信号
203
基于测量的主输出信号来反向计算次级输出信号
204
使用反向计算的次级输出信号来调节生成的次级输出信号
205
使用利用调节的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成分析物浓度

图2A

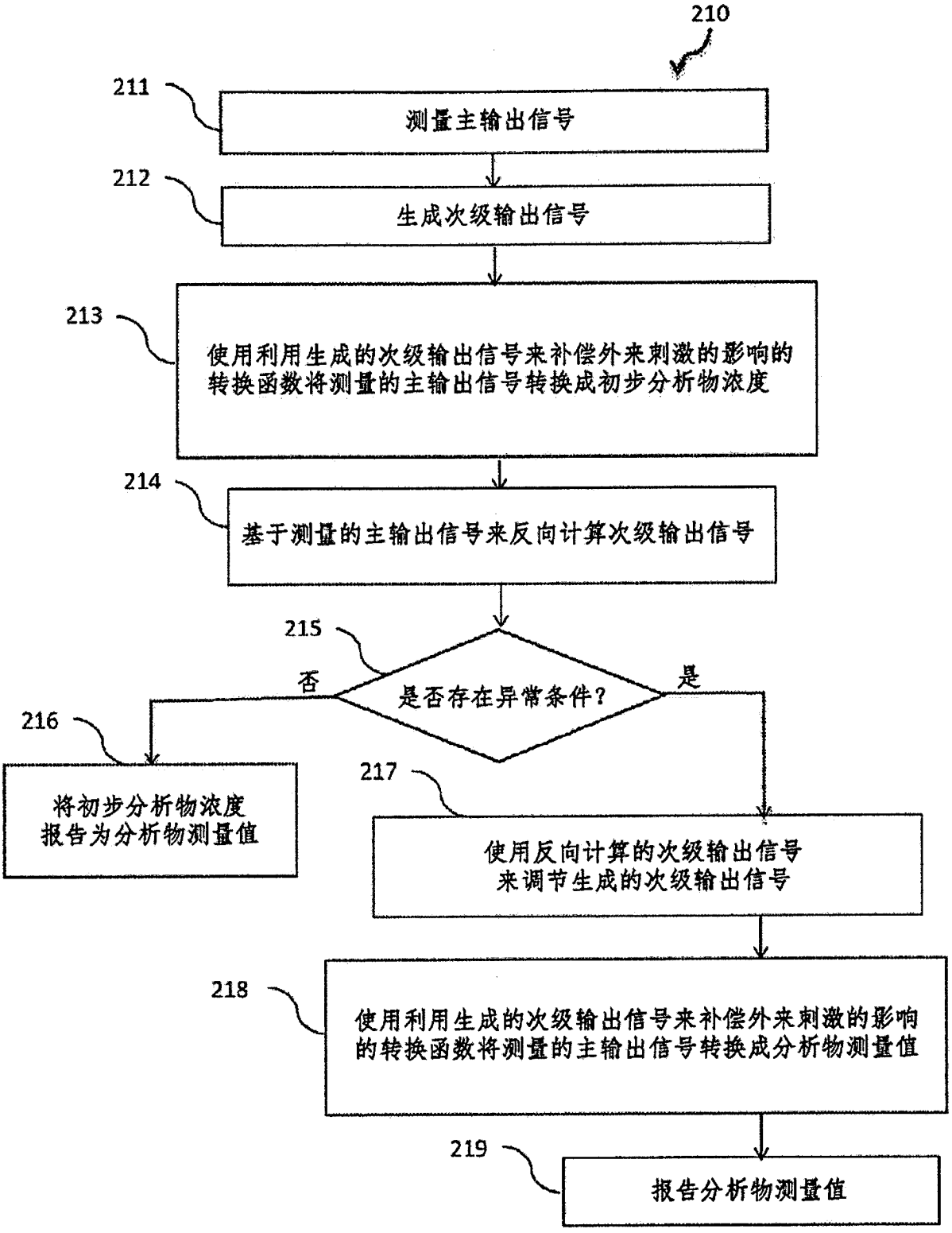
210
211
测量主输出信号
212
生成次级输出信号
213
使用利用生成的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成初步分析物浓度
214
基于测量的主输出信号来反向计算次级输出信号
215
是否存在异常条件?
否
是
216
将初步分析物浓度报告为分析物测量值
217
使用反向计算的次级输出信号来调节生成的次级输出信号
218
使用利用生成的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成分析物测量值
219
报告分析物测量值

图2B

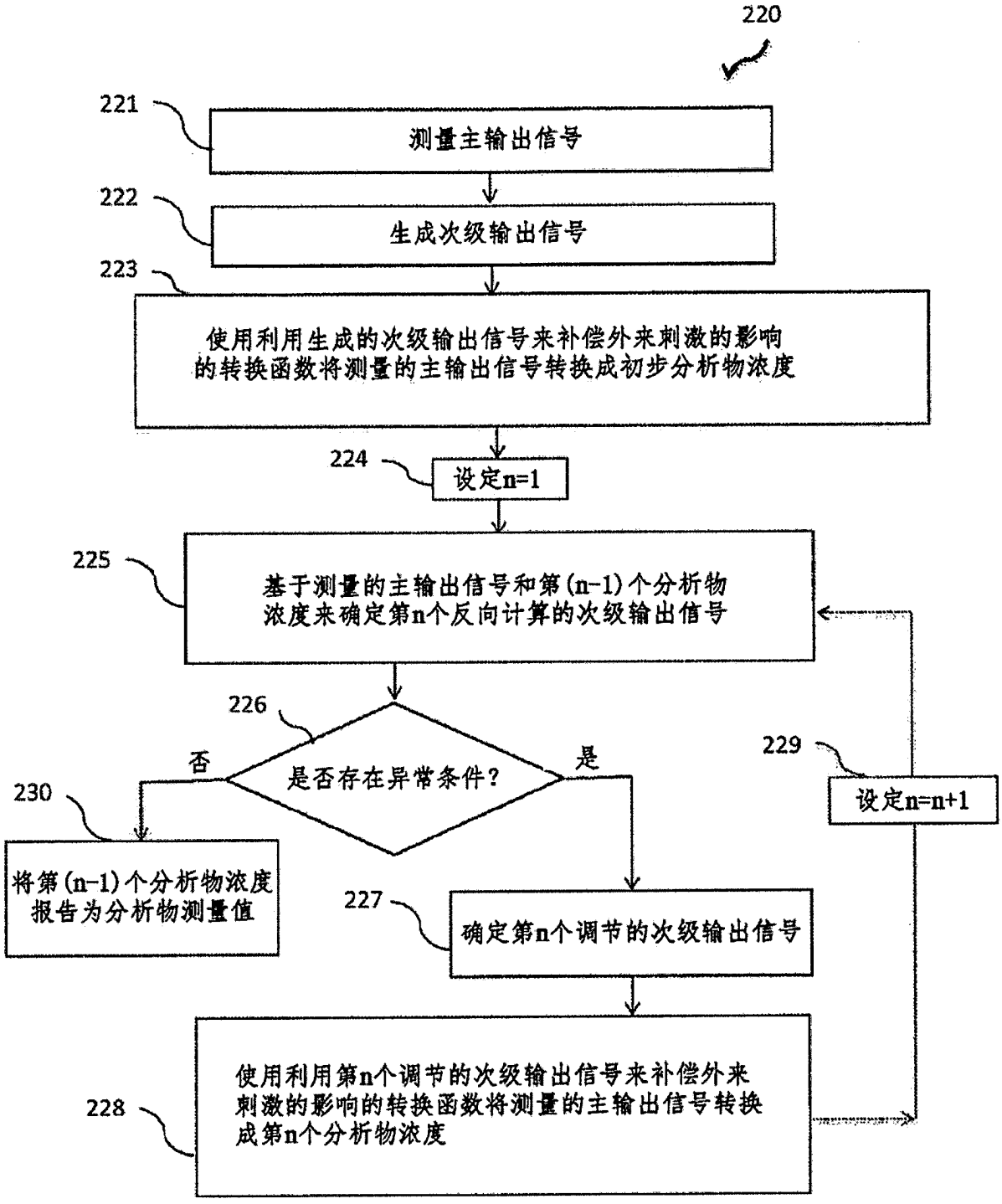
220
221
测量主输出信号
222
生成次级输出信号
223
使用利用生成的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成初步分析物浓度
224
设定n=1
225
基于测量的主输出信号和第(n-1)个分析物浓度来确定第n个反向计算的次级输出信号
226
是否存在异常条件?
否
是
229
设定n=n+1
230
将第(n-1)个分析物浓度报告为分析物测量值
227
确定第n个调节的次级输出信号
228
使用利用第n个调节的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成第n个分析物浓度

图2C

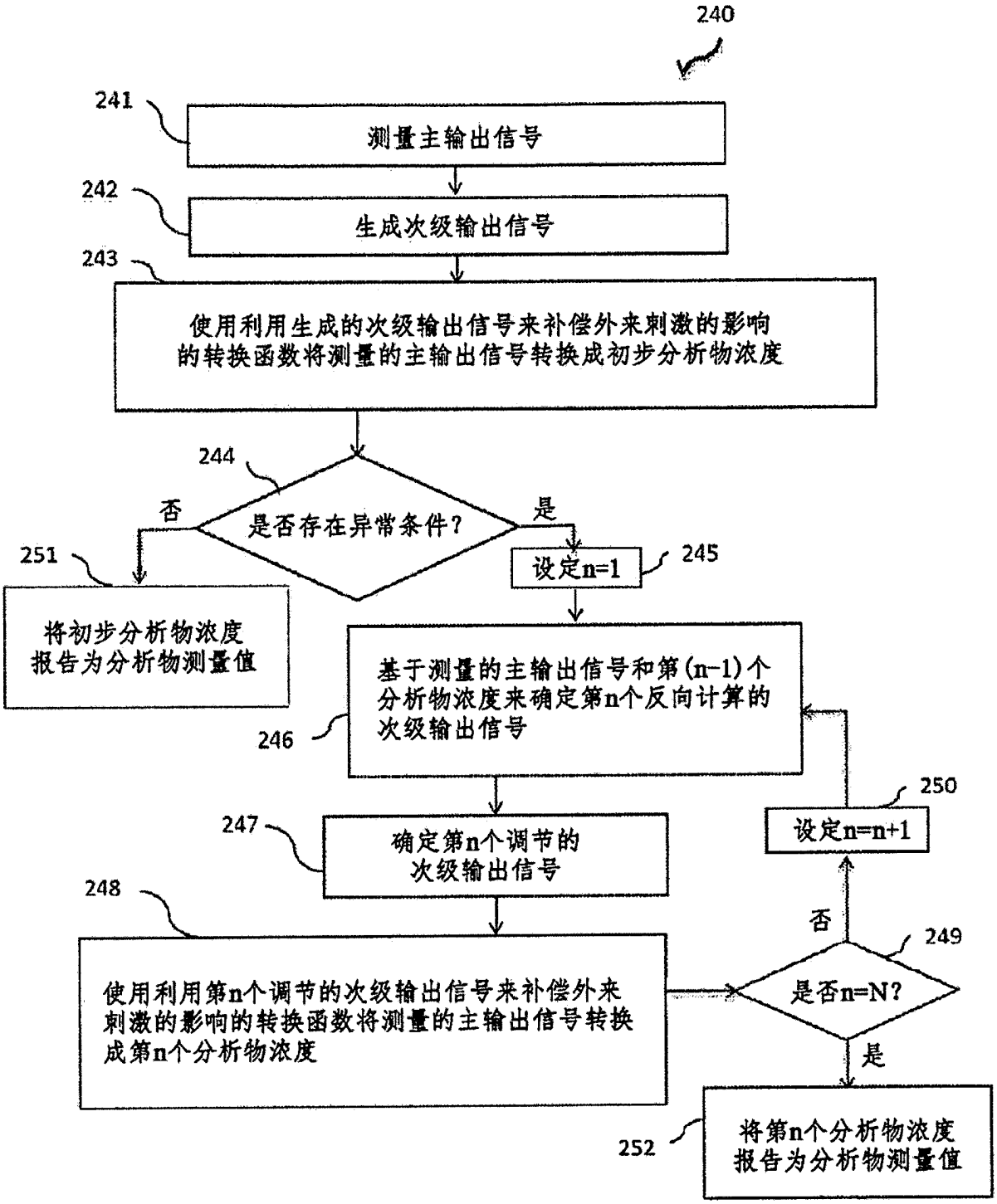
240
241
测量主输出信号
242
生成次级输出信号
243
使用利用生成的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成初步分析物浓度
244
是否存在异常条件?
否
是
251
将初步分析物浓度报告为分析物测量值
设定n=1
245
基于测量的主输出信号和第(n-1)个分析物浓度来确定第n个反向计算的次级输出信号
246
250
设定n=n+1
247
确定第n个调节的次级输出信号
248
使用利用第n个调节的次级输出信号来补偿外来刺激的影响的转换函数将测量的主输出信号转换成第n个分析物浓度
否
249
是否n=N?
是
252
将第n个分析物浓度报告为分析物测量值

图2D

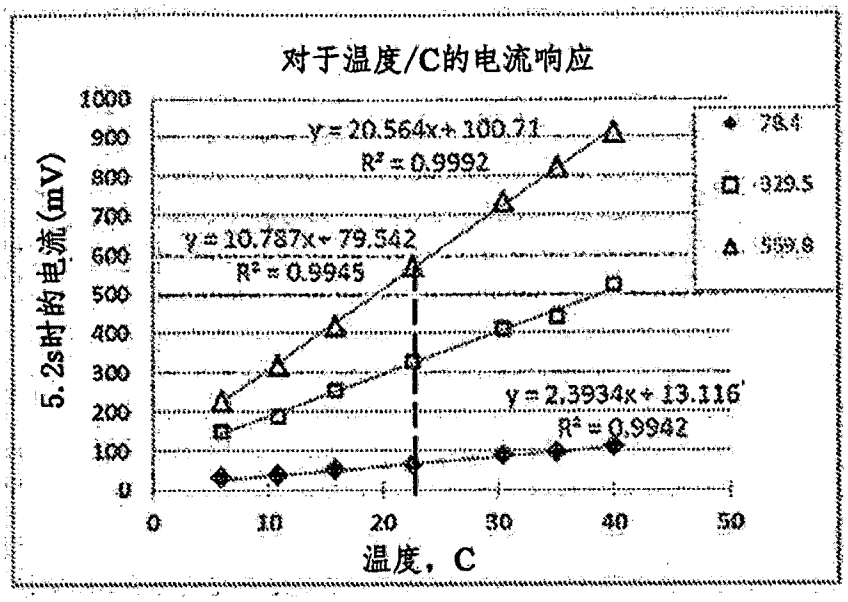
对于温度/C的电流响应
5.2s时的电流(nV)
温度，C
y = 20.564x + 100.71
R² = 0.9992
y = 10.787x + 79.542
R² = 0.9945
y = 2.3934x + 13.116
R² = 0.9942
78.4
329.5
559.8

图3A

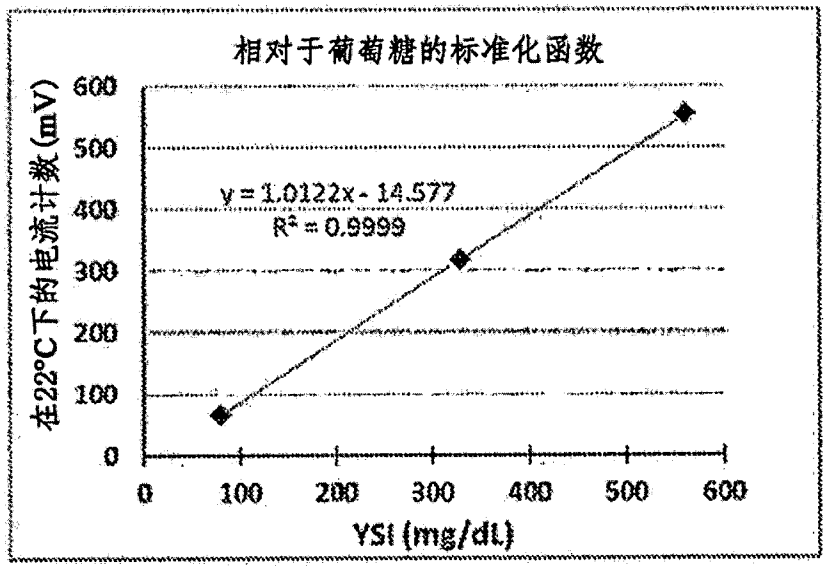
相对于葡萄糖的标准化函数
在22°C下的电流计数(mV)
YSI (mg/dL)
y = 1.0122x - 14.577
R² = 0.9999

图3B

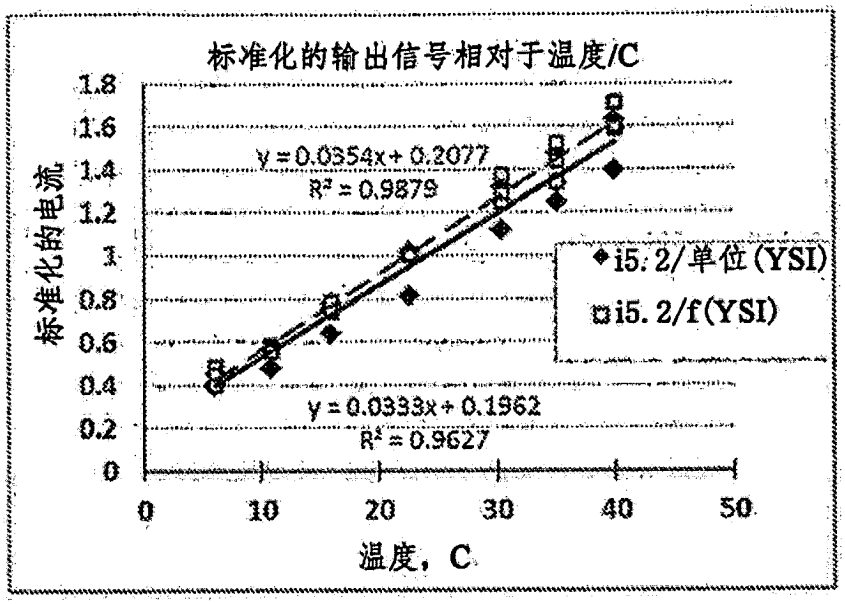

图3C

反向计算的温度的估计准确度		
	$\Delta T = T_{calc} - T_{meas}$	
	方程.(4)(♦)	方程.(5)(□)
平均值，°C	0.0	0.0
SD，°C	2.4	1.3

图3D

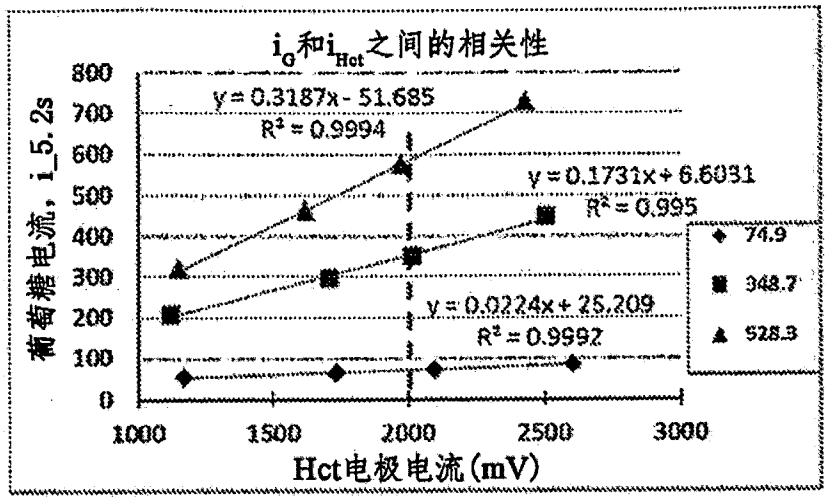
i_G和i_{Hct}之间的相关性
y = 0.3187x - 51.685
R² = 0.9994
y = 0.1731x + 6.6031
R² = 0.995
y = 0.0224x + 25.209
R² = 0.9992
74.9
348.7
528.3
葡萄糖电流，i_5.2s
Hct电极电流(mV)
800
700
600
500
400
300
200
100
0
1000
1500
2000
2500
3000

图3E

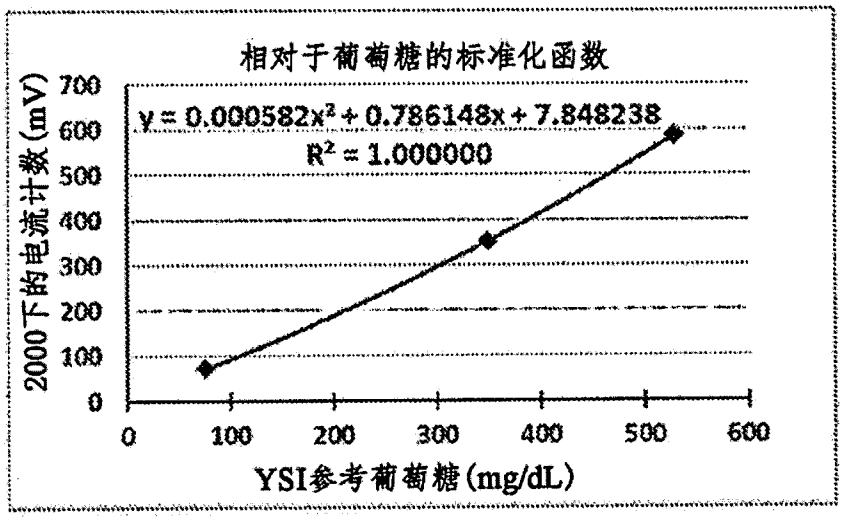
相对于葡萄糖的标准化函数
y = 0.000582x² + 0.786148x + 7.848238
R² = 1.000000
2000下的电流计数(mV)
YSI参考葡萄糖(mg/dL)
700
600
500
400
300
200
100
0
0
100
200
300
400
500
600

图3F

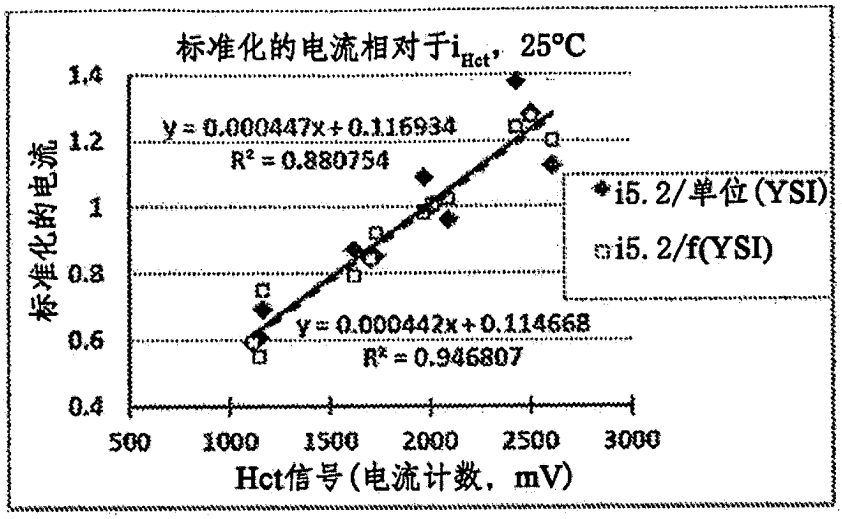
标准化的电流相对于i_{Hct}，25°C
y = 0.000447x + 0.116934
R² = 0.880754
y = 0.000442x + 0.114668
R² = 0.946807
i5.2/单位(YSI)
i5.2/f(YSI)
标准化的电流
Hct信号(电流计数，mV)

图3G

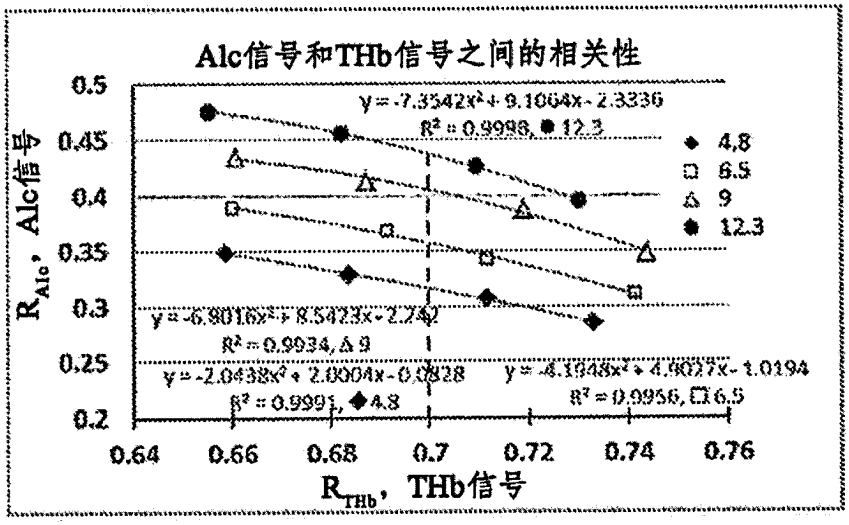
Alc信号和THb信号之间的相关性
y = -7.3542x² + 9.1064x - 2.3336
R² = 0.9998, ● 12.3
y = -6.9016x² + 8.5423x - 2.242
R² = 0.9934, Δ 9
y = -2.0438x² + 2.0004x - 0.0828
R² = 0.9991, ◆ 4.8
y = -4.1948x² + 4.9027x - 1.0194
R² = 0.9956, □ 6.5
4.8
6.5
9
12.3
R_{Alc}，Alc信号
R_{THb}，THb信号

图3H

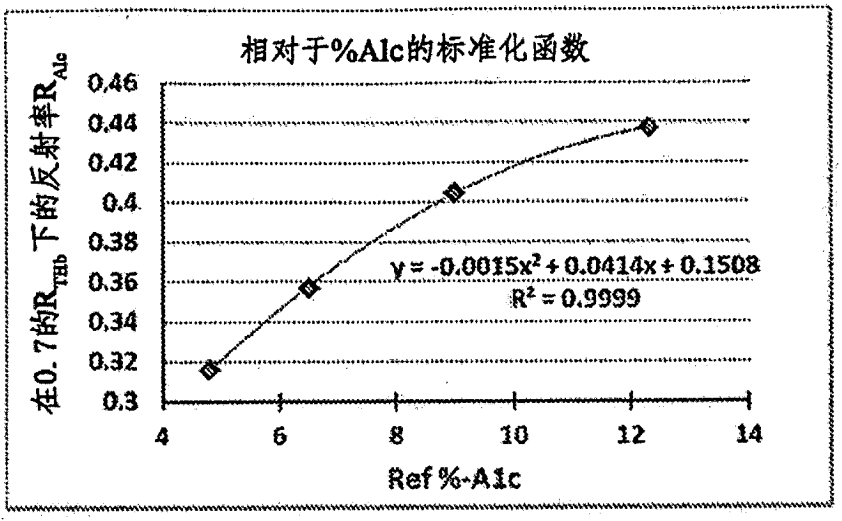
相对于%Alc的标准化函数
在0.7的R_{THb}下的反射率R_{Alc}
0.46
0.44
0.42
0.4
0.38
0.36
0.34
0.32
0.3
y = -0.0015x² + 0.0414x + 0.1508
R² = 0.9999
4
6
8
10
12
14
Ref %-A1c

图3I

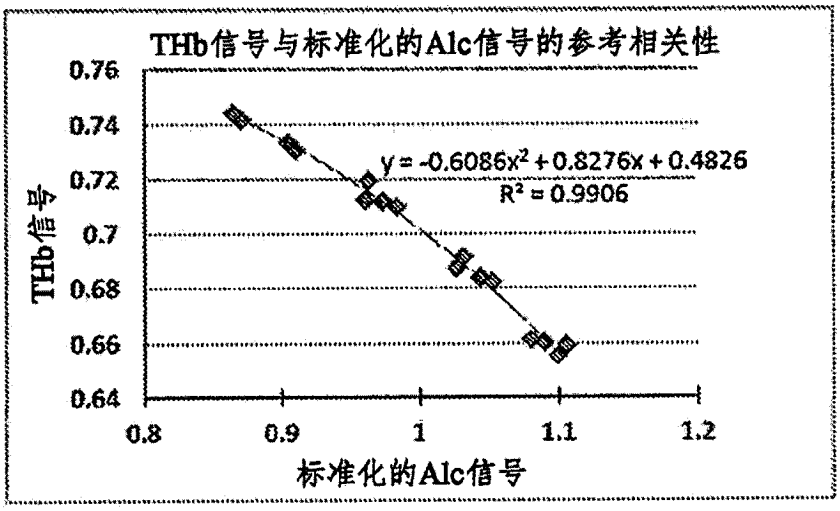
THb信号与标准化的Alc信号的参考相关性
THb信号
0.76
0.74
0.72
0.7
0.68
0.66
0.64
y = -0.6086x² + 0.8276x + 0.4826
R² = 0.9906
0.8
0.9
1
1.1
1.2
标准化的Alc信号

图3J

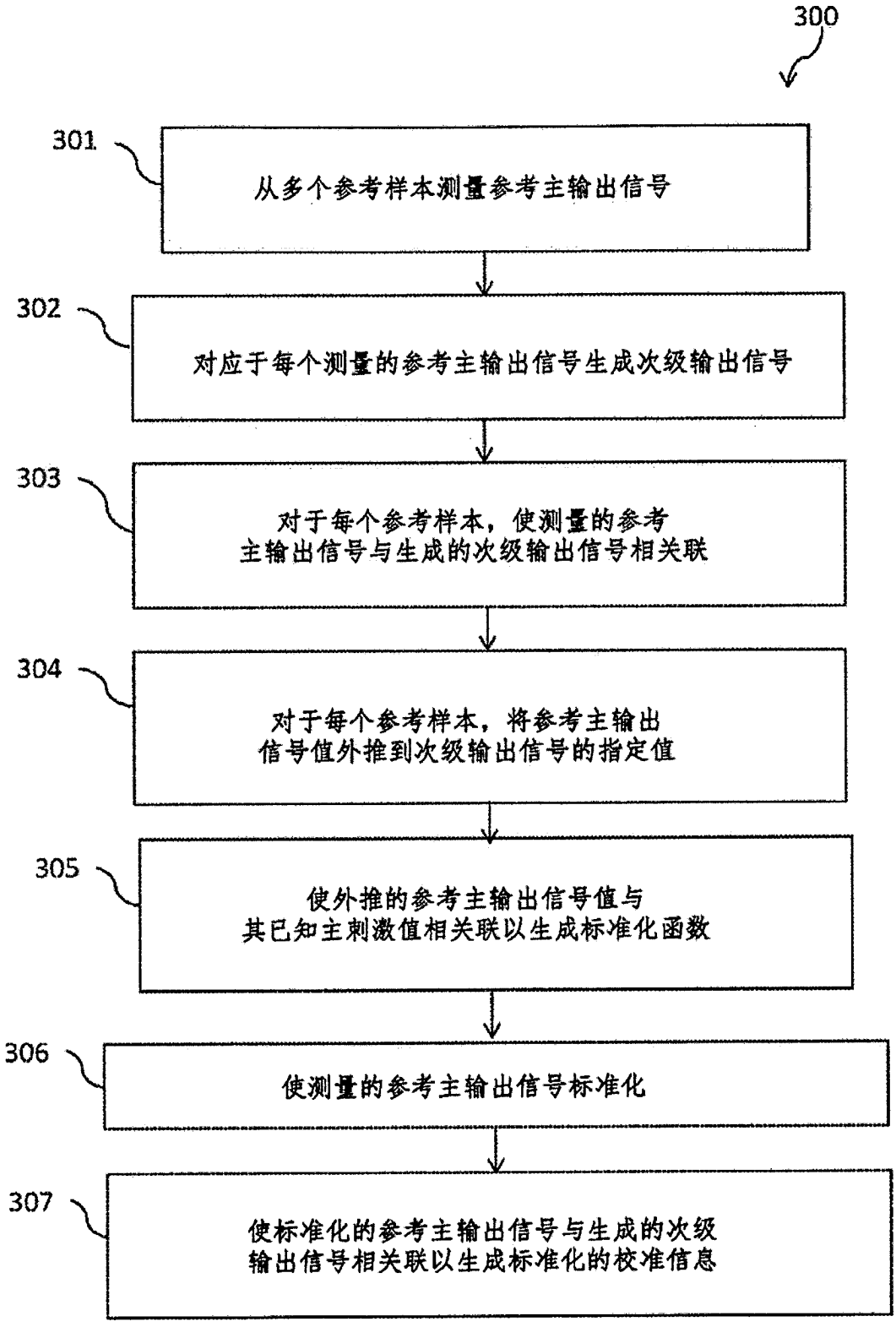
300
301
从多个参考样本测量参考主输出信号
302
对应于每个测量的参考主输出信号生成次级输出信号
303
对于每个参考样本，使测量的参考主输出信号与生成的次级输出信号相关联
304
对于每个参考样本，将参考主输出信号值外推到次级输出信号的指定值
305
使外推的参考主输出信号值与其已知主刺激值相关联以生成标准化函数
306
使测量的参考主输出信号标准化
307
使标准化的参考主输出信号与生成的次级输出信号相关联以生成标准化的校准信息

图3K

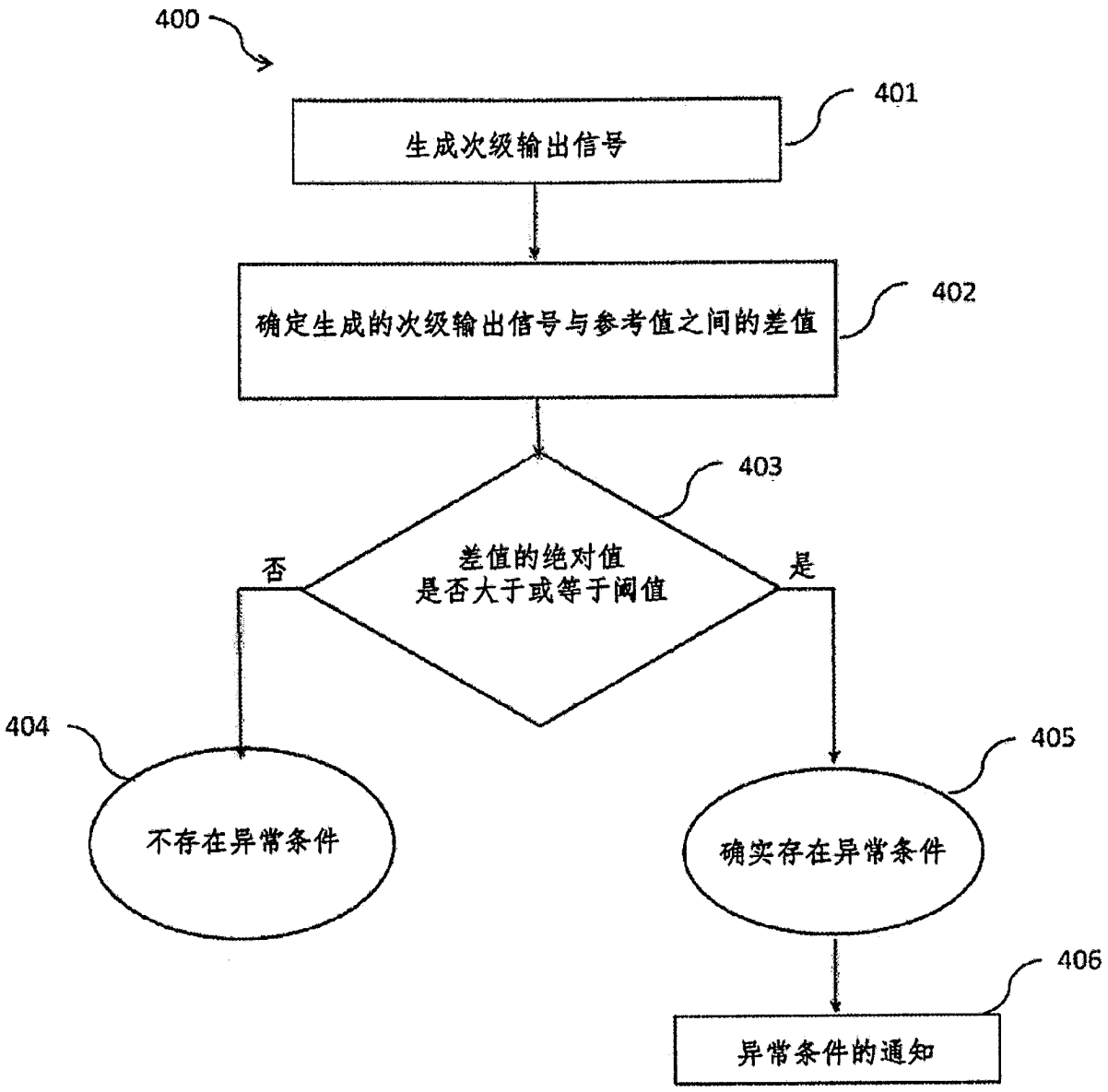
400
401
生成次级输出信号
402
确定生成的次级输出信号与参考值之间的差值
403
差值的绝对值
是否大于或等于阈值
否
是
404
不存在异常条件
405
确实存在异常条件
406
异常条件的通知

图4A

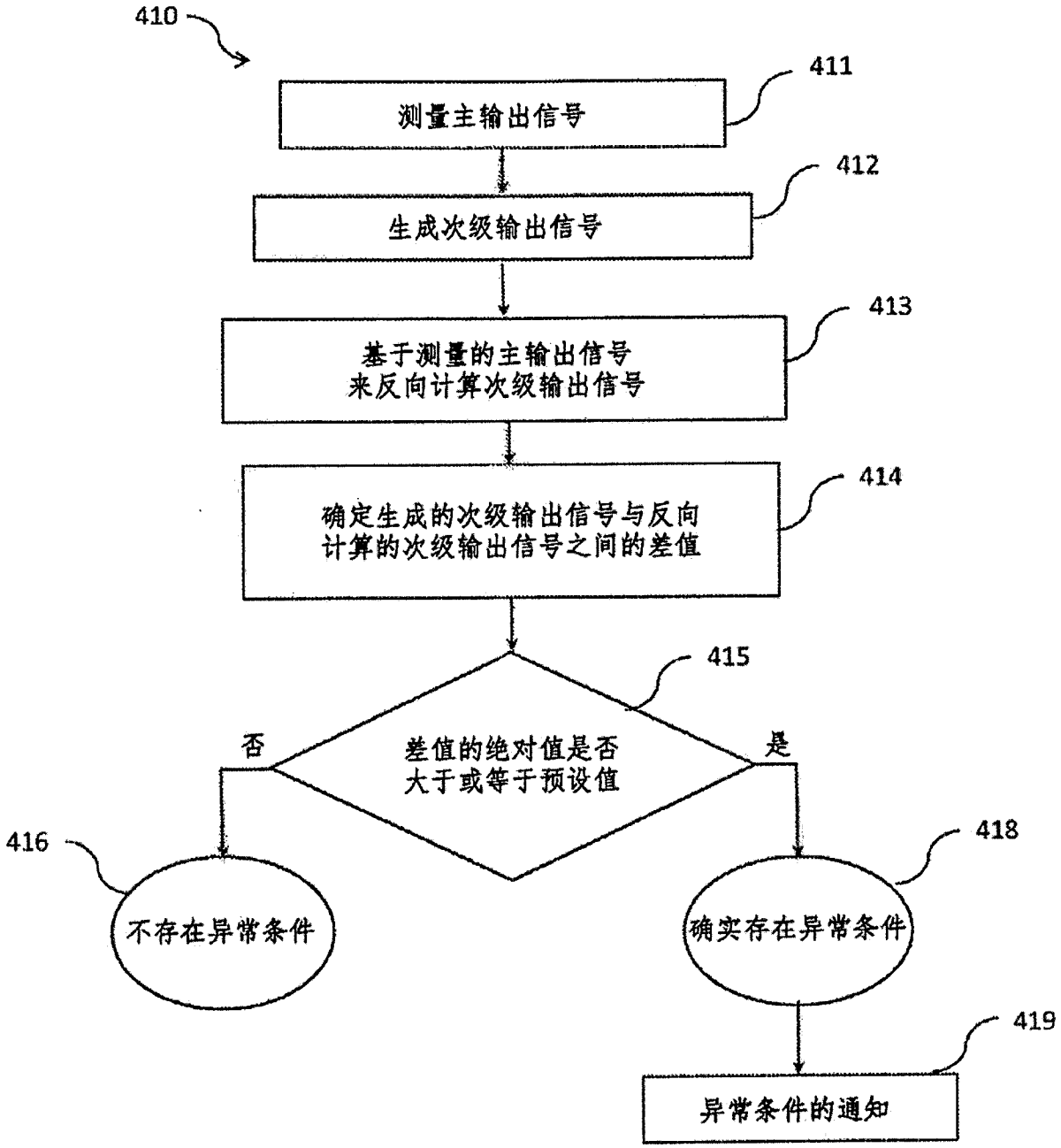
410
411
测量主输出信号
412
生成次级输出信号
413
基于测量的主输出信号
来反向计算次级输出信号
414
确定生成的次级输出信号与反向
计算的次级输出信号之间的差值
415
差值的绝对值是否
大于或等于预设值
否
是
416
不存在异常条件
418
确实存在异常条件
419
异常条件的通知

图4B

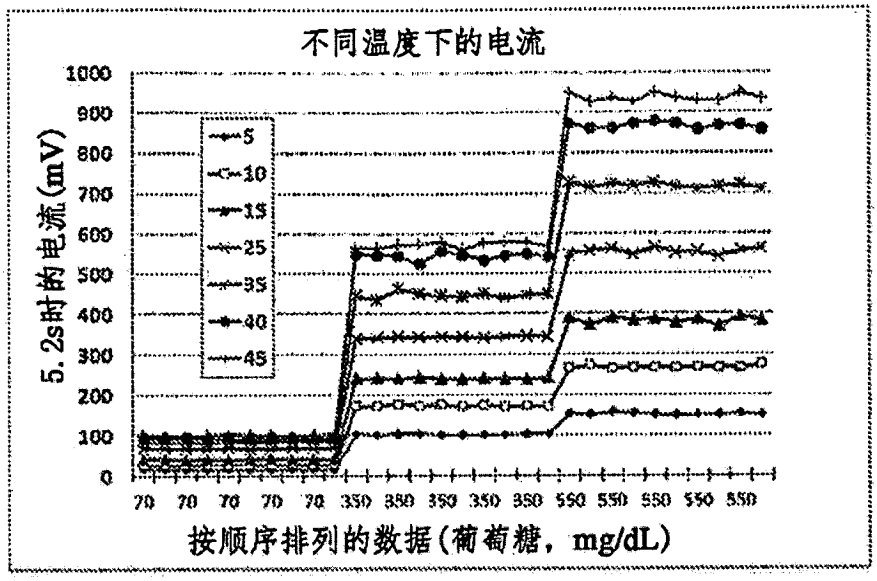
不同温度下的电流
5.2s时的电流(mV)
1000
900
800
700
600
500
400
300
200
100
0
5
10
15
25
35
40
45
70 70 70 70 70 350 350 350 350 350 550 550 550 550 550
按顺序排列的数据(葡萄糖，mg/dL)

图5A

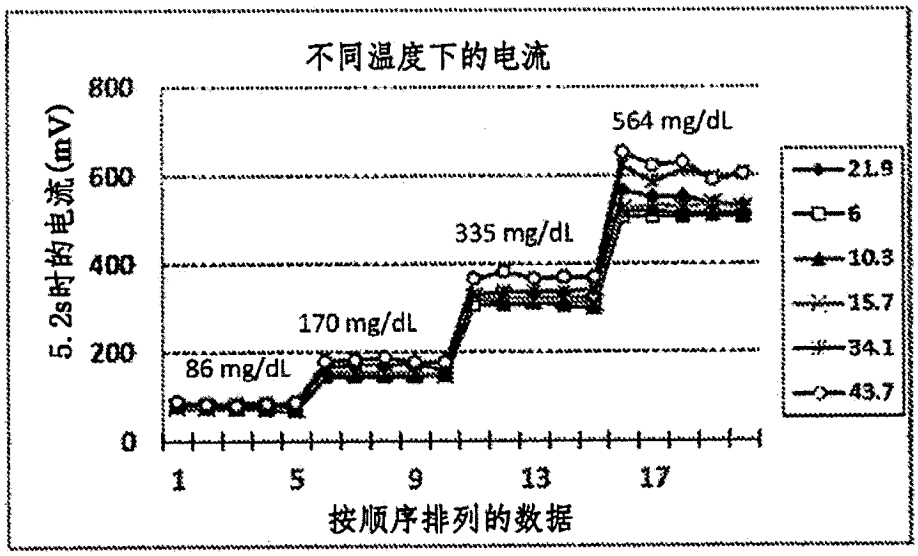
不同温度下的电流
5.2s时的电流(mV)
800
600
400
200
0
564 mg/dL
335 mg/dL
170 mg/dL
86 mg/dL
21.9
6
10.3
15.7
34.1
43.7
1
5
9
13
17
按顺序排列的数据

图5B

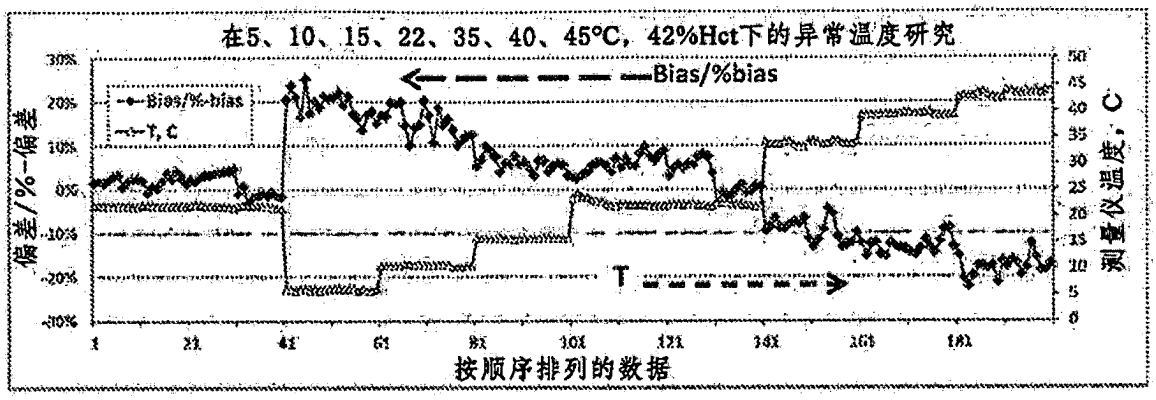
在5、10、15、22、35、40、45°C，42%Hct下的异常温度研究
Bias/%bias
T, C
偏差/%-偏差
测量仪温度，C
按顺序排列的数据

图5C

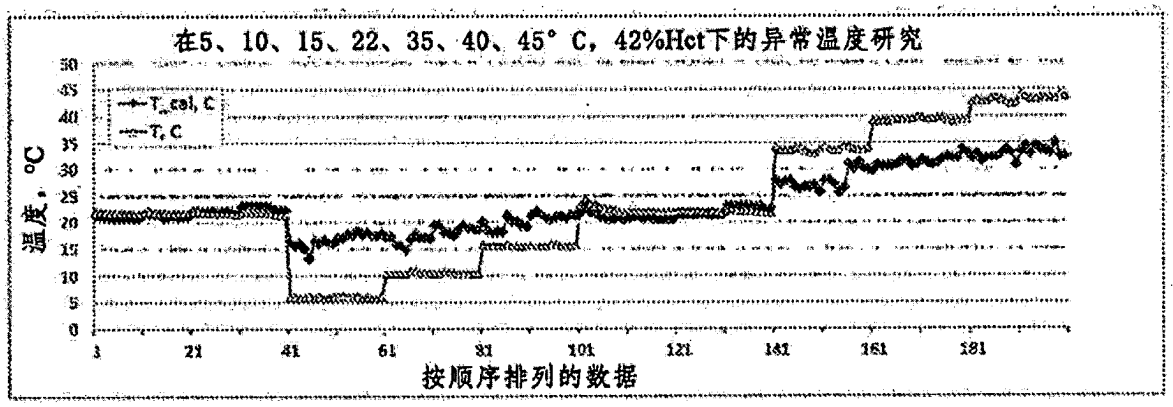
在5、10、15、22、35、40、45° C，42%Hct下的异常温度研究
T_cal, C
T, C
温度，°C
按顺序排列的数据

图6A

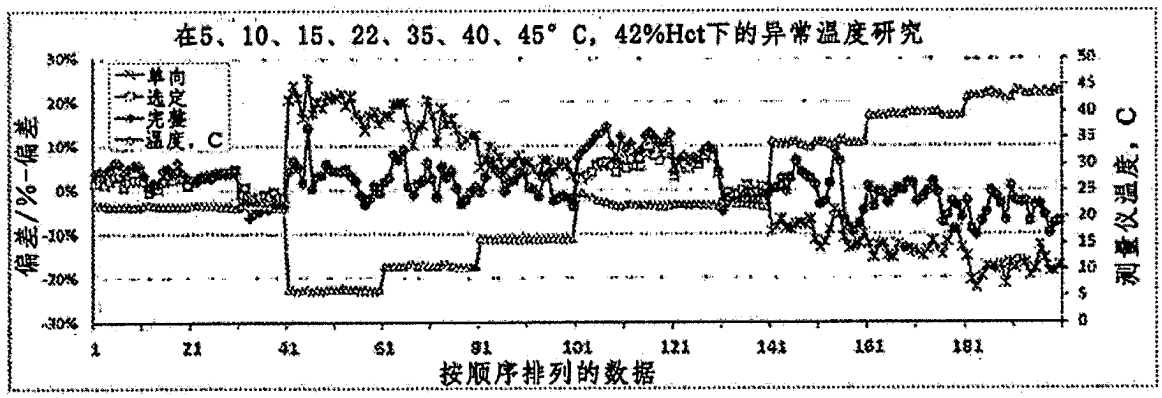
在5、10、15、22、35、40、45° C，42%Hct下的异常温度研究
单向
选定
无偏
温度，C
偏差/%-偏差
测量仪温度，C
按顺序排列的数据

图6B

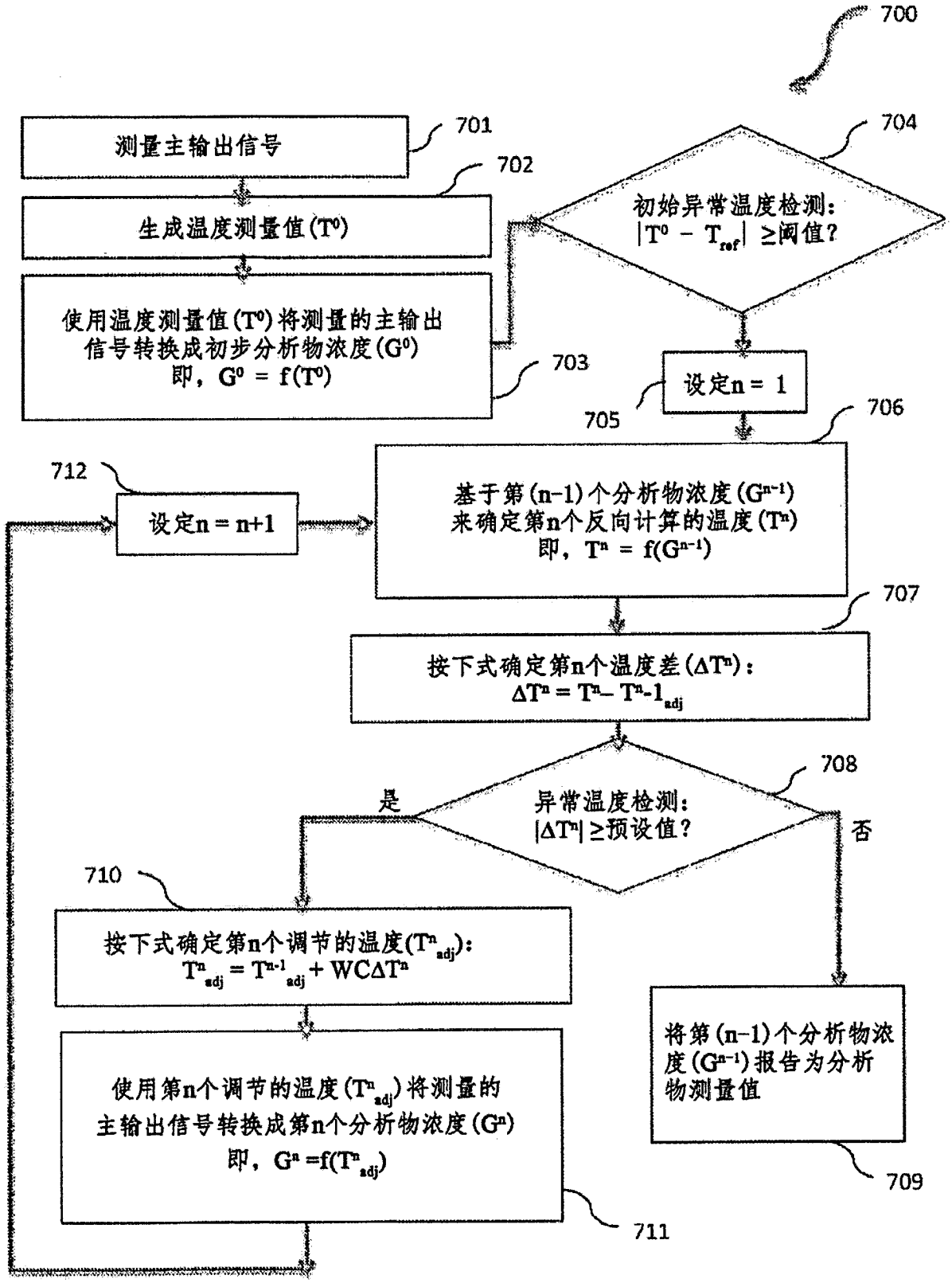
700
测量主输出信号
701
生成温度测量值(T^0)
702
使用温度测量值(T^0)将测量的主输出信号转换成初步分析物浓度(G^0)
即，$G^0 = f(T^0)$
703
初始异常温度检测：
$|T^0 - T_{ref}| \geq$阈值?
704
设定n = 1
705
706
基于第(n-1)个分析物浓度(G^{n-1})来确定第n个反向计算的温度(T^n)
即，$T^n = f(G^{n-1})$
707
按下式确定第n个温度差(ΔT^n)：
$\Delta T^n = T^n - T^n\text{-}1_{adj}$
708
异常温度检测：
$|\Delta T^n| \geq$预设值?
是
否
710
按下式确定第n个调节的温度(T^n_{adj})：
$T^n_{adj} = T^{n-1}_{adj} + WC\Delta T^n$
使用第n个调节的温度(T^n_{adj})将测量的主输出信号转换成第n个分析物浓度(G^n)
即，$G^n = f(T^n_{adj})$
711
将第(n-1)个分析物浓度(G^{n-1})报告为分析物测量值
709
712
设定n = n+1

图7A

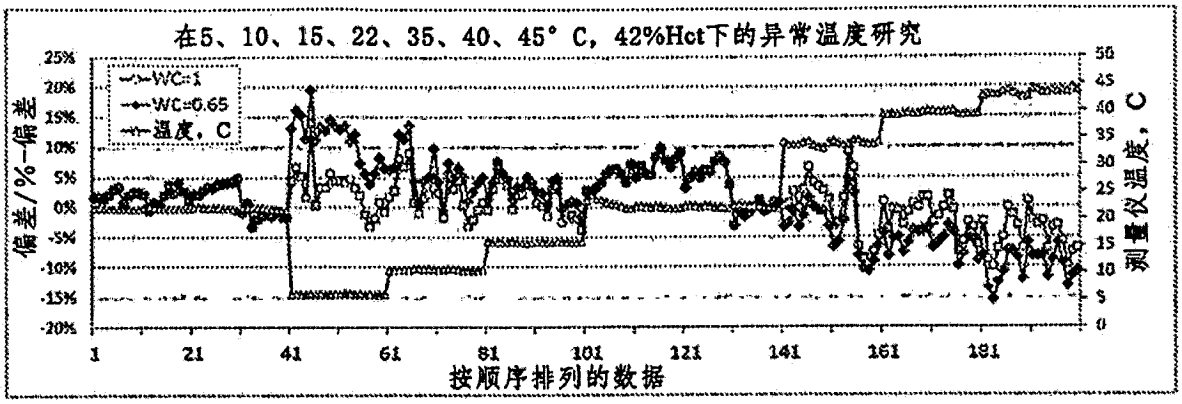
在5、10、15、22、35、40、45° C，42%Hct下的异常温度研究
WC=1
WC=0.65
温度，C
偏差/%-偏差
测量仪温度，C
按顺序排列的数据

图7B

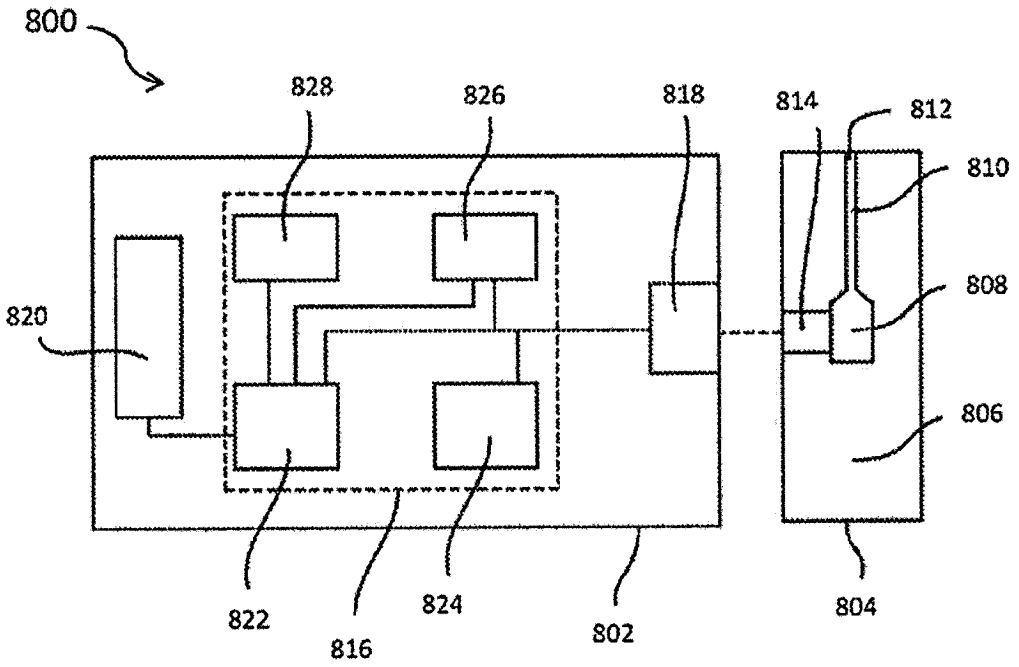
800
828
826
818
814
812
810
808
820
806
822
816
824
802
804

图8

Our Ref：18HKI016-101

說明書摘要

發明名稱：改進的生物傳感器系統分析物測量

本發明提供了用于補償分析物測量的方法和生物傳感器系統。該方法和系統基于測量的主輸出信號來確定次級輸出信號，以便更好地接近在實際測量條件下外來刺激對主輸出信號的影響。根據本公開的方法和系統可以提供更准確的分析物測量，并且在异常條件期間檢測和補償分析物測量時可以特別有用。

ABSTRACT

Title of Invention : IMPROVED BIOSENSOR SYSTEM ANALYTE MEASUREMENT

Methods and biosensor systems for compensating an analyte measurement are provided. The methods and systems determine a secondary output signal based on the measured primary output signal in order to better approximate the effects of an extraneous stimulus on the primary output signal under actual measurement conditions. The methods and systems according to the present disclosure may provide a more accurate analyte measurement, and may be particularly useful in detecting and compensating an analyte measurement during an off-condition.