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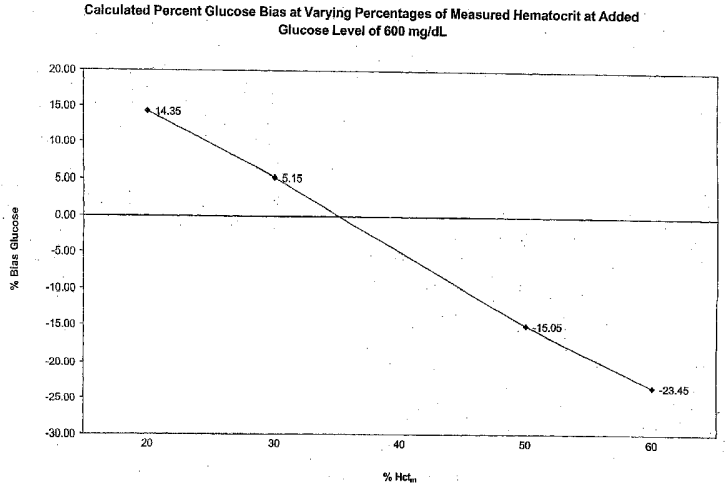

(57) Abstract: Methods and devices for performing *in situ* hematocrit adjustments during glucose testing using glucose-monitoring products and using those adjusted values to estimate the hematocrit value of blood samples to reduce or eliminate the assay bias caused by the different hematocrit levels of blood samples. One method involves measuring the glucose value, Glu_m, of the blood sample; measuring the resistance of the blood sample (R_{cell}) using a biosensor reagent; measuring the resistance of plasma (R_{plasma}) using the biosensor reagent; determining the calculated resistance of red blood cells, R_{RBC},of the blood sample according to the relationship $R_{RBC}=R_{cell}-R_{plasma}$; calculating the percent hematocrit, % Hct_c, of the blood sample; determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and using the percent hematocrit, %. Hct_c, and either the glucose value, Glu_m, or the adjusted glucose value, Glu_{adj}, to adjust for any bias of the biosensor reagent.

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METHODS FOR PERFORMING HEMATOCRIT ADJUSTMENT IN GLUCOSE ASSAYS AND DEVICES FOR SAME

FIELD OF THE INVENTION

The invention relates to methods and devices for correcting the glucose bias in glucose-monitoring products to provide more accurate glucose readings of blood samples. In particular, the invention relates to methods and devices for performing *in situ* hematocrit adjustments during glucose testing using glucose-monitoring products and using those adjusted values to estimate the hematocrit value of blood samples to reduce or eliminate the assay bias caused by the different hematocrit levels of blood samples.

BACKGROUND OF THE INVENTION

Hematocrit is the volume of red blood cells (RBC) expressed as a percentage of the volume of RBC in a whole blood sample. The normal hematocrit range for a typical human being is about 40 Vol.% to about 45 Vol.%. In extreme cases, the hematocrit range for a human beings can range from about 20 Vol.% to about 60 Vol.%.

Prior methods for estimating the hematocrit value of a blood sample have been based upon physical and/or chemical properties of the whole blood sample based upon the amount of red blood cells in the whole blood sample. For example, the hematocrit value of a whole blood sample has been estimated by measuring the RBC volume after centrifugation by conductivity, resistivity, impedance, and/or concentration of markers such as Na^+ cations in red blood cells or heme concentration in hemoglobin and other properties which may be distinguished based on the amount of RBC in whole blood samples. Although hematocrit values of whole blood samples have been measured routinely in the clinical or laboratory setting, hematocrit values are not commonly measured with glucose-monitoring products such as home meters.

One device that may be used to determine the hematocrit value of a whole blood sample in glucose-monitoring products or systems is a biosensor or biosensor reagent. The dependence or sensitivity of a biosensor reagent to hematocrit is one factor used to determine the accuracy and quality of a glucose-monitoring product as the hematocrit level of a blood sample can impact the glucose level of the blood sample being tested.

One problem with using current biosensor reagents to determine the hematocrit value and, consequently, the glucose value of a whole blood sample involves RBC interference. Red blood cells are small particles in blood samples that block a biosensor reagent's ability to measure the glucose level of the blood sample. RBC interference contributes to a bias reading or a glucose bias in the biosensor reagents of glucose-monitoring products.

For a given sample of whole blood, the measurement of the percent glucose in a blood sample should not vary whether the sample is tested at a level of 20 Vol.% hematocrit or a level of 60 Vol.% hematocrit. However, due to RBC interference, there is a percentage bias in the glucose reading that is detected by the biosensor reagent that varies based upon the level of hematocrit in the sample. The bias reading caused by the hematocrit content of a blood sample is commonly referred to as "hematocrit effect."

It is common for glucose biosensor reagents in glucose-monitoring products to exhibit hematocrit effect. For example, in some current glucose-monitoring products, the glucose assay bias for approximately 20 Vol.% RBC in whole blood to approximately 60 Vol.% RBC in whole blood generally ranges from about 15 Vol.% to about 20 Vol.%. In general, the higher the glucose bias, the less accurate the glucose reading and the worse the performance of the glucose-monitoring product. In contrast, the lower the glucose bias, the more accurate the glucose reading and the better the performance of the glucose-monitoring product.

The bias reading caused by the hematocrit content of a blood sample can have an adverse effect on patients. Patients who have low hematocrit levels may misinterpret their glucose value as being too high because of the glucose bias and think they need insulin to bring their high glucose level, down. Because the actual glucose level is not as high as the perceived glucose level, patients may drop their glucose level too low by unnecessarily taking too much insulin. Conversely, patients who have high hematocrit levels may misinterpret their glucose value as being normal when it is actually high because of the glucose bias. Because the actual glucose level is not as low as the perceived glucose level, patients may consistently forego or miss needed treatment, leading to long term medical complications.

One method for determining the glucose bias of a glucose biosensor reagent in a glucose-monitoring product is to measure the glucose value of the blood sample

(Glu_m) using a glucometer and determine the reference value of the glucose content (Glu_{ref}). The value for Glu_m may be measured on a glucose-monitoring product such as a home meter. The value for Clu_{ref} is determined independently of the glucose monitoring product using a reference method and a reference instrument. Glu_{ref} is typically determined in a clinical or laboratory setting. The percentage of glucose bias can be determined according to the relationship set forth in Equation 1:

$$(Glu_m - Glu_{ref}) * 100 / Glu_{ref} \quad \text{(Eq. 1)}$$

Determining the percentage of glucose bias using this method is only practical if the value for Glu_{ref} can be measured for every blood sample, but this is typically not feasible for users of glucose-monitoring products. In addition, this method of determining the percentage of glucose bias is inconvenient as the value for Glu_{ref} is measured in a clinical or laboratory setting.

There is, therefore, a need for methods for correcting and minimizing the glucose bias in glucose-monitoring products which is caused by the hematocrit effect. There is also a need for methods for correcting the glucose bias, if any, in glucose monitoring products such as home meters without the need for patient samples to be brought to a clinical or laboratory setting. There is also a need for devices which cm perform such adjustments without the need for patients to bring blood samples to a clinician or laboratory for determining the glucose bias of the biosensor reagent.

SUMMARY OF THE INVENTION

In general, the invention relates to methods for adjusting glucose bias, any, of a blood sample in a glucose-monitoring product. One method involves measuring the glucose value, Glu_m, of the blood sample; measuring the resistance of the blood sample (R_{cell}) using a biosensor reagent; measuring the resistance of plasma (R_{plasma}) using the biosensor reagent; determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship

$$R_{RBC} = R_{cell} - R_{plasma};$$

calculating the percent hematocrit, % Hct_c, of the blood sample; determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and using the percent hematocrit, % Hct_c, and either the glucose value, Glu_m, or the adjusted glucose value, Glu_{adj}, to adjust for the bias of the biosensor reagent, if any.

The invention further relates to meters that correct the glucose bias of a blood sample in a glucose-monitoring product. One meter includes means for measuring the glucose value, Glu_m, of the blood sample; means for measuring the resistance of the blood sample (R_{plasma}) using a biosensor reagent; means for measuring the resistance of plasma (R_{plasma}) using the biosensor reagent; means for determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship

$$R_{RBC} = R_{cell} - R_{plasma};$$

means for calculating the percent hematocrit, % Hct_c, of the blood sample; means for determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and means for using the percent hematocrit, % Hct_c, and either the glucose value, Glu_m, or the adjusted glucose value, Glu_{adj}, to adjust for the bias of the biosensor reagent, if any.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other advantages of the invention will become apparent upon reading the following detailed description and upon reference to the drawings.

FIG. 1 is a plot showing the percent glucose bias versus the percent hematocrit calculated for a blood sample.

FIG. 2 is a plot of the percent hematocrit calculated (% Hct_c) versus the percent hematocrit measured (% Hct_m) for a series of whole blood samples.

DESCRIPTION OF EMBODIMENTS OF THE INVENTION

Embodiments of the invention are, in part, based on the discovery that the performance of glucose-monitoring products may be improved by lowering the glucose bias, if any, of the biosensor reagent measurement in glucose-monitoring products. It has been discovered that by using the methods and devices described herein, a more accurate glucose reading can be obtained from the biosensor reagent measurement in glucose-monitoring products. By obtaining a more accurate glucose reading, a more accurate assessment of the glycermic stage of a patient can be obtained and readily reported to the patient's physician.

As used herein, the term "glucose bias" is defined as a trend in the collection, analysis, interpretation, or review of glucose data from a glucose assay that leads to

the conclusion that the patient's glucose level of the blood sample is systematically different from the patient's actual glucose level.

The inventive methods and devices generally reduce or eliminate the glucose bias caused by the different hematocrit levels of blood samples. Generally, when a blood sample has a low hematocrit level, the biosensor reagent gives an increasingly positive bias moving from low to high glucose levels. The bias effect is also dependent on the hematocrit level. In other words, the bias effect is noticeably more significant at a 20 vol.% hematocrit level than at a 30 vol.% hematocrit level. Conversely, when a blood sample has a high hematocrit level, the biosensor reagent generally gives increasingly negative bias moving from low to high glucose levels. In other words, the bias effect is more significant at a 60 vol.% hematocrit level than at a 50 vol.% hematocrit level. The methods and devices described herein accommodate the varying degrees of glucose bias which are obtained in blood samples depending on whether the sample has a low or high hematocrit level.

The present invention generally involves determining the glucose level of a blood sample, using the difference in resistivity or resistance between plasma and blood cells to determine the hematocrit level of the blood sample, and then using the calculated percent hematocrit level to adjust for the glucose bias, if one exists. The methods and devices described herein also provide a way of estimating the hematocrit value of blood samples using biosensor reagents.

More specifically, the present invention involves the acts of (1) measuring the glucose value, Glu_m, of the blood sample; (2) measuring the resistance of the blood sample (R_{cell}) using a biosensor reagent; (3) measuring the resistance of plasma (R_{plasma}) using a biosensor reagent; (4) determining the calculated resistance of red blood cells (R_{RBC}) by subtracting the resistance of plasma (R_{plasma}) from the resistance of the blood sample (R_{cell}); (5) calculating the percent hematocrit, % Hct_c, of the blood sample; (6) determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and (7) using the calculated percent hematocrit, % Hct_c, and either the glucose value, Glu_m, or the adjusted glucose value, Glu_{adj}, to adjust for the bias of the biosensor reagent, if any, which is caused by the glucose bias.

In another embodiment, the present invention involves the acts of (1) measuring the glucose value, Glu_m, of the blood sample; (2) measuring the cell

resistance, R_{cell}, of the blood sample using a biosensor reagent; (3) measuring the plasma resistance, R_{plasma} of the blood sample using a biosensor reagent; (4) determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship:

$$R_{RBC} = R_{cell} - R_{plasma};$$

(5) calculating the percent hematocrit, % Hct_c, of the blood sample according to the relationship:

$$\% Hct_c = -k_1 * (R_{RBC})^2 + k_2 * R_{RBC} + k_3$$

where k_1 ranges from about +100 to about –100, k_2 ranges from about +100 to about –100, and k_3 from about +100 to about –100; and (6) determining whether to adjust the glucose value, Glu_m; and (7) adjusting, if necessary, the glucose value, Glu_m, using the percent hematocrit, % Hct_c, and the glucose value Glu_m according to the relationship:

$$Glu_{adj} = Glu_m + k_5.$$

By using the present invention, the glucose level of a blood sample without the hematocrit bias or effect can be obtained and, hence, a more accurate assessment of a patient's glycermic stage may be obtained.

By using the methods and devices described herein, *in situ* hematocrit adjustments may be performed during glucose testing. By programming the equations described herein into software that is used with an electrochemical device or meter, *in situ* hematocrit adjustments may be performed. Alternatively, one or more pieces of data obtained from the equations described herein may be manually calculated and/or entered into the software that is used with the electrochemical device so that *in situ* hematocrit adjustments may be performed.

As the glucose level and hematocrit level can be measured at the same time using the inventive methods and devices, the hematocrit effect can be estimated and adjusted from the glucose value. The adjusted glucose value more accurately reflects the true glucose value and, hence, the true glycermic stage of the patient.

Typical biosensor reagents operate using electrochemical cells. For an electrochemical cell, the potential of the working electrode (WE) is the equilibrium value (E°) at open circuit (I=0). By applying an external voltage, a current is forced through the electrochemical cell and the potential of the working electrode shifts to a new value (E°). Assuming the reference electrode (RE) does not change its potential

at the external current level, the potential difference between the equilibrium and new values (E° and E^{n}) is the potential drop, *i.e.*, iR drop, in the test solution. This potential drop is characteristic of the bulk solution in the electrochemical cell.

As used herein, the term "biosensor reagent" includes any agent that can detect glucose in a blood specimen via an electrochemical reaction or a reaction by changing the optical property of the biosensor. Examples of suitable biosensor reagents for use in embodiments of this invention include, but are not limited to, DEX®, Espirit®, and Elite® biosensor reagents available from Bayer Corporation in Elkhart, Indiana; Precision® biosensor reagents available from MediSense in Abbott Park, Illinois; Accucheck® biosensor reagents available from Roche in Indianapolis, Indiana; and OneTouch® biosensor reagents available from Lifescan in Milpitas, California.

The inventive methods involve measuring the solution resistance or cell resistance (R_{cell}) of the blood sample between the reference electrode and the working electrode in a biosensor reagent such as a DEX® biosensor reagent. This is accomplished by applying a potential pulse, such as a 50 mV pulse. The current is measured at two time points after the pulse, and the initial current is calculated by exponential extrapolation to the time at which the pulse is applied. R_{cell} is the blood resistance contributed by plasma and blood cells. Due to the differences in the physical properties of plasma and blood cells, plasma and blood cells exhibit differences in resistivity. When the blood cells increase (and the plasma decreases), the value of R_{cell} increases. When the blood cells decrease (and the plasma increases), the value of R_{cell} decreases.

The inventive methods further involve measuring the plasma resistance (R_{plasma}) between the reference electrode and the working electrode in a biosensor reagent. This is accomplished by applying a potential pulse such as 50 mV. This current is measured at two time points after the pulse, and the initial current is calculated by exponential extrapolation to the time at which the pulse is applied. R_{cell} is calculated from the initial current and pulse amplitude using Ohm's law. R_{plasma} depends on the components of the plasma (*i.e.*, protein and electrolytes). R_{plasma} does not vary with changing levels of hematocrit in a blood sample as there are no cells in plasma. Minor variations in the value of R_{plasma} occur with different lots of reagents.

The value of R_{plasma} can be electronically programmed into the software that is used with the electrochemical device or meter. The value of R_{plasma} can also be included on a calibration chip provided with the biosensor reagent or included on a label located on the biosensor reagent. Alternatively, the value of R_{plasma} can be predetermined for each lot of reagent during manufacturing and provided to the user or patient to be manually input by the user or patient into the electrochemical device or commercially available optical strip.

Electrochemical devices are instruments which read biosensor reagents. Examples of suitable electrochemical devices which may be used for reading biosensor reagents according to the present invention include, but are not limited to, the BAS 100B Analyzer available from BAS Instruments in West Lafayette, Indiana; the CH Instrument Analyzer available from CH Instruments in Austin, Texas; the Cypress Electrochemical Workstation available from Cypress Systems in Lawrence, Kansas; and the EG&G Electrochemical Instrument available from Princeton Research Instruments in Princeton, New Jersey.

The inventive methods further involve determining the calculated resistance of the red blood cells, R_{RBC}, of a biosensor reagent according to the relationship set forth in Equation 2:

$$R_{RBC} = R_{cell} - R_{plasma} \qquad \text{(Eq. 2)}$$

R_{RBC} is the resistance difference between whole blood and plasma. A typical value of R_{RBC} is approximately 1000 and may range from approximately 0 to approximately 500,000. Equation 2 can be electronically programmed into the software that is used with the electrochemical device or meter so that the value of R_{RBC} may be calculated by the software. Alternatively, the value of R_{RBC} may be calculated by the user or patient and may be manually input into the electrochemical device or commercially available optical strip.

The inventive methods further involve calculating the percent hematocrit, % Hct_c, of the blood sample according to the relationship set forth in Equation 3:

$$\% Hct_c = -k_1 * (R_{RBC})^2 + k_2 * R_{RBC} + k_3 \qquad \text{(Eq. 3)}$$

It has been discovered that the hematocrit of whole blood has a polynomial relationship with the calculated percent hematocrit, % Hct_c. Specifically, the % Hct_c is equal to a first constant, k_1, multiplied by the square of R_{RBC} derived from Equation 2 plus a second constant, k_2, multiplied by R_{RBC} plus a third constant, k_3.

First, second, and third constants, k_1, k_2, and k_3, may range from about +100 to about –100. In some embodiments, k_1, ranges from about +5 to about –5. In some embodiments, k_2 ranges from about +10 to about –10. In some embodiments, k_3 ranges from about +50 to about –50. First, second and third constants, k_1, k_2, and k_3, may be determined for each lot of biosensor reagent. The values for k_1, k_2, and k_3 can be determined using standard curve-fitting software. Specifically, the values of R_{RBC} and % Hct_c, can be curve-fitted using a second order polynomial math conversation to determine the values for k_1, k_2, and k_3.

The values for k_1, k_2, and k_3 can be predetermined for each lot of reagent during manufacturing. The values for k_1, k_2, and k_3 can be electronically programmed into the software that is used with the electrochemical device. The values for k_1, k_2, and k_3 can also be provided to the user or patient who can manually input the values for k_1, k_2, and k_3 into the electrochemical device.

Equation 3 can be electronically programmed into the software that is used with the electrochemical device so that the value of % Hct_c may be calculated by the software. Alternatively, the value of % Hct_c may be calculated by the user or patient by using the values for k_1, k_2, and k_3 that are provided to the user or patient and manually input into the electrochemical device.

Ideally, the biosensor reagent exhibits no hematocrit effect and, consequently, no glucose bias. In an ideal situation where the biosensor reagent exhibits no hematocrit effect and no glucose bias, a plot of the percent of glucose bias versus the percent hematocrit calculated, % Hct_c, would produce a flat line with a slope equal to 0 and data points with are close to the line. Generally, however, due to RBC interference, a plot of the percent of glucose bias versus the percent hematocrit calculated, % Hct_c, for a typical biosensor reagent measurement produces a curve which is nonlinear.

The inventive methods further involve measuring the glucose level, Glu_m, of the whole blood sample. The measured glucose level, Glu_m, may be determined by art-recognized, conventional methods such as using glucose analyzers, for example a YSI 2300 Glucose and Lactate Analyzer or a STAT Plus Glucose & Lactate Analyzer available from YSI Incorporated in Yellow Springs, Ohio.

The inventive methods further involve determining whether to adjust the measured glucose value, Glum, and correcting the hematocrit bias of the measured

glucose value to adjust for the hematocrit effect and, consequently, the glucose bias, if one exists. Using the value of % Hct_c, which is obtained from Equation 3 and the measured glucose level, Glu_m, which is determined by art-recognized, conventional methods, an adjustment or correction factor is determined.

Specifically, a correspondent adjustment may be made to Glu_m, if necessary, to adjust for the glucose bias of the biosensor reagent. The adjustment is performed using the relationship set forth in Equation 4:

$$Glu_{adj} = Glu_m + k_5 \quad \text{(Eq. 4)}$$

where Glum is obtained using art-recognized, conventional methods and k_5 is an adjustment factor. The values for k_5 may be included on a calibration chip provided with the biosensor reagent or included on a label located on the biosensor reagent. Alternatively, the values for k_5 may be provided to the user for programming into a home glucose monitor. The adjustment factor which is used to adjust for the glucose bias of the biosensor reagent may range from about -50% to about 50%. An adjustment is made to Glu_m to adjust for the glucose bias of the biosensor reagent only if the calculated percent hematocrit, % Hct_c, level does not equal 40%. The normal hematocrit range for humans generally ranges from about 20% to about 60% and is centered around 40%. As a result, glucose sensors are calibrated at 40% whole blood and the slope and intercept at 40% hematocrit are used to calculate the glucose concentration. Thus, an adjustment is made to Glu_m for the glucose bias of the biosensor reagent where the calculated percent hematocrit, % Hct_c, level does not equal 40%.

Glu_{adj} represents the adjusted or corrected glucose value which is obtained upon performing the adjustment. The adjusted glucose value, Glu_{adj}, is a more accurate reflection of the patient's true glucose value and, hence, the patient's glycermic stage. Equation 4 can be electronically programmed into the software that is used with the electrochemical device.

By the methods and devices described herein, the measured glucose and hematocrit levels can be determined at the same time. Specifically, the computer can be programmed to calculate the values for R_{cell} and Glu_m. The computer may be programmed to simultaneously calculate the values for R_{cell} and Glu_m. From these values, the adjusted glucose value, Glu_{adj}, may be calculated.

By the methods and devices described herein, the calculated percent hematocrit, % Hct_c, and the glucose value, Glu_m, and/or the adjusted glucose value, Glu_{adj}, are used to adjust for the bias of the biosensor reagent, if any, which is caused by the glucose bias.

The methods and devices described herein also allow end users of glucometers to determine the true glucose value of blood samples conveniently and easily outside of the clinical or laboratory setting and without using clinical or laboratory equipment. The methods and devices described herein obviate the need to measure the percent hematocrit of the blood sample in a clinical or laboratory setting. The end users of the inventive methods and devices may be patients, physicians, or other health care professionals. Because the methods described herein allow a patient to determine the adjusted glucose value from home without waiting on test results from a laboratory or clinic, the patient can immediately relay his or her true glucose value to a physician.

It is contemplated that the methods described herein may be used with any system that uses electrochemical devices or cells for measuring the glucose level of a blood sample. For example, it is contemplated that the methods of the present invention may be used with home glucose-monitoring products, glucose -monitoring products used in a laboratory setting, or any other devices which employ electrochemical circuitry.

Also contemplated by the invention described herein are systems for use in practicing the subject invention. The subject systems are composed of biosensor reagents and meters. The meters typically include (a) means for measuring the glucose value, Glu_m, of the blood sample; (b) means for measuring the resistance of the blood sample ($R_{cel}l$) using a biosensor reagent; (c) means for measuring the resistance of plasma (R_{plasma}) using a biosensor reagent; (d) means for determining the calculated resistance of red blood cells (R_{RBC}) by subtracting the resistance of plasma (R_{plasma}) from the resistance of the blood sample (R_{cell}); (e) means for calculating the percent hematocrit, % Hct_c, of the blood sample; (f) means for determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and (g) means for using the calculated percent hematocrit, % Hct_c, and the glucose value, Glu_m, or the adjusted glucose value, Glu_{adj}, to adjust for the bias of the biosensor reagent, if any, which is caused by the glucose bias.

The meters may also include (a) means for measuring the glucose value, Glu_m, of the blood sample; (b) means for measuring the cell resistance, R_{cell}, of the blood sample using a biosensor reagent; (c) means for measuring the plasma resistance, R_{plasma}, of the blood sample using a biosensor reagent; (d) means for determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship:

$$R_{RBC} = R_{cell} - R_{plasma};$$

(e) means for calculating the percent hematocrit, % Hct_c, of the blood sample according to the relationship:

$$\% Hct_c = k_1 * (R_{RBC})^2 + k_2 * R_{RBC} + k_3$$

where k_1 ranges from about +100 to about –100, k_2 ranges from about +100 to about –100, and k_3 from about +100 to about –100; (f) means for determining whether to adjust the glucose value, Glu_m; and (g) means for adjusting, if necessary, the glucose value, Glu_m, using the percent hematocrit, % Hct_c, and the glucose value Glu_m according to the relationship:

$$Glu_{adj} = Glu_m + k_5$$

The following examples are given to exemplify embodiments of the invention. These examples should not be construed to limit the invention as otherwise described and claimed herein.

EXPERIMENTAL

EXAMPLE 1: HEMATOCRIT EFFECT ON GLUCOSE MEASUREMENT

This example illustrates the hematocrit effect (*i.e.*, the bias reading derived from hematocrit content) that is observed in glucose biosensor reagents. To illustrate the variation in the measured glucose level that is obtained with whole blood samples having different hematocrit content, four aliquots of whole blood (Samples 1-4) were obtained and pooled together.

The hematocrit content of Samples 1-4 was adjusted to 20 vol.%, 30 vol.%, 50 vol.%, and 60 vol.% Hct, respectively, using the hematocrit adjustment protocol described below. The volume of plasma to be added to each of the four aliquots of whole blood (*i.e.*, Samples 1-4) to achieve the target hematocrit contents (*i.e.*, 20

vol.%, 30 vol.%, 50 vol.%, and 60 vol.% Hct) was calculated using the relationship set forth in Equation 5:

$$P = \left(\frac{Hct_o}{Hct_t}\right) - 1 \times V \qquad \text{(Eq. 5)}$$

where

P = Volume of plasma to be added or subtracted from the volume of the whole blood sample (V)

V = Volume of the whole blood sample

Hct_o = Observed hematocrit of the whole blood sample

Hct_t = Target hematocrit of the whole blood sample

To adjust the hematocrit content of Samples 1-4 to 20 vol.%, 30 vol.%, 50 vol.%, and 60 vol.% Hct_t, respectively, the values of P, V, Hct_t listed in Table A below were used. The final volume for all levels was 15 mL.

TABLE A

Determination of Plasma Levels to be Added to Achieve Target Hematocrit Levels				
Sample No.	Hct_o	Hct_t	V (mL)	P (mL)
1	40	20	7.5	+7.5
2	40	30	10	+5.0
3	40	50	18	-3.0
4	40	60	20	-5.0

Therefore, 7.5 mL of plasma had to be added to Sample 1 to achieve a target hematocrit level of 20 Vol.%; 5.0 mL of plasma had to be added to Sample 2 to achieve a target hematocrit level of 30 Vol.%; 3.0 mL of plasma had to be removed from to Sample 3 to achieve a target hematocrit level of 50 Vol.%; and 5.0 mL of plasma had to be removed from Sample 4 to achieve a target hematocrit level of 60 Vol.%.

Glucose was also added to each of the four aliquots of whole blood (Samples 1-4) using the glucose addition or fortification protocol described below. For each of Samples 1-4, target whole blood glucose concentrations were set at 20 mg/dL, 50 mg/dL, 100 mg/dL, 200 mg/dL, and 600 mg/dL. Each of Samples 1-4 was divided into aliquots which were each adjusted to blood glucose concentrations of 20 mg/dL, 50 mg/dL, 100 mg/dL, 200 mg/dL, and 600 mg/dL.

To determine the appropriate volume of 25% glucose stock to add to obtain the desired blood glucose concentration, the following equation (Equation 6) was used:

$$D = A (Glu_t - Glu_i) / Glu_{stock} \quad \text{(Eq. 6)}$$

where

A = Volume of blood sample to be fortified or spiked with glucose (mL)

Glu_t = Target blood glucose concentration (mg/dL) to be achieved through addition of glucose stock solution

Glu_i = Initial blood glucose concentration (mg/dL)

Glu_{stock} = Blood glucose concentration of stock solution (25 g/dL)

D = Volume of 25% glucose stock solution (μL) to add to sample to obtain target blood glucose concentration

The values for A, Glu_t, Glu_i, Glu_{stock}, and D at each of the target whole blood glucose concentrations are set forth in Table B below.

TABLE B

Calculation of Percent Glucose Stock Solution to Add to Obtain Target Glucose Concentration				
A (mL)	Glu_t (mg/dL)	Glu_i (mg/dL)	Glu_{stock} (g/dL)	D (μL)
2.5	20	8	25	1.2
2.5	50	8	25	4.2
2.5	100	8	25	10.0
2.5	200	8	25	19.2
2.5	600	8	25	59.2

The appropriate volume of 25% glucose stock solution was pipetted into each of Samples 1-4 to obtain the target blood glucose concentrations. Therefore, 1.2 μL of 25% glucose stock solution had to be added to Sample A to achieve a target blood glucose concentration of 20 mg/dL; 4.2 μL of 25% glucose stock solution had to be added to Sample B to achieve a target blood glucose concentration of 50 mg/dL; 10.0 μL of 25% glucose stock solution had to be added to Sample C to achieve a target blood glucose concentration of 100 mg/dL; 19.2 μL of 25% glucose stock solution had to be added to Sample D to achieve a target blood glucose concentration of 200 mg/dL; and 59.2 μL of 25% glucose stock solution had to be added to Sample E to achieve a target blood glucose concentration of 600 mg/dL.

The glucose levels (in mg/dL) of Samples 1-4 at each of the target whole blood glucose concentrations (i.e., the target glucose levels (Glu_t) of 20 mg/dL, 50 mg/dL, 100 mg/dL, 200 mg/dL, and 600 mg/dL achieved through the glucose addition protocol described above) were measured using two lots of DEX® biosensor reagents, Lots A and B. The target whole blood glucose concentrations (Glu_t) obtained using the glucose addition protocol described above are set forth in Table C below. The measured glucose values (Glu_m) of Samples 1-4 obtained from DEX® biosensor reagents lots A and B at varying measured percent hematocrit levels (% Hct_m) are also set forth in Table C below. The value of % Hct_m may be calculated by the software or by the user or patient and manually input into the electrochemical device.

The DEX® biosensor reagent lots were programmed using a standard curve adjusted to 40 vol.% Hct because it is the expected percent hematocrit (vol.% Hct) for human blood samples.

TABLE C

GU_t(mg/dL)	GLu_m(mg/dL) at Varying % Hct_m Levels			
DEX® BIOSENSOR REAGENT, LOT A RESULTS				
	Sample 1: 20 vol.% Hct_m	Sample 2: 30 Vol.% Hct_m	Sample 3: 50 Vol.% Hct_m	Sample 4: 60 vol.% Hct_m
20	21.1	15.3	14.2	26.1
50	50.6	45.3	48.3	59.0
100	99.65	98.59	94.29	91.67
200	204.81	99.81	86.7	187.5
600	615.1	605.3	585.4	577.2
DEX® BIOSENSOR REAGENT, LOT B RESULTS				
	Sample 1: 20 vol.% Hct_m	Sample 2: 30 Vol.% Hct_m	Sample 3: 50 Vol.% Hct_m	Sample 4: 60 vol.% Hct_m
20	19.8	14.0	14.6	30.5
50	47.8	48.3	47.7	45.4
100	102.1	99.1	95.6	96.8
200	206.8	201.1	186.4	190.7
600	613.6	605.0	584.5	575.9

Although the measured glucose levels, Glu_m, theoretically should be the same as the target added glucose levels, Glu_t obtained using the glucose addition protocol, the measured glucose levels, Glu_m, varied as shown in Table C depending upon the

measured hematocrit level, % Hct_m, of a given sample. The percent glucose bias readings (*i.e.*, the difference between the measured glucose values levels, Glu_m, and the target added glucose levels, Glu_t) that were obtained at varying measured percent hematocrit (% Hct_m) levels from Lots A and B for Samples 1-4 are set forth in Table D below:

TABLE D

GU_t (mg/dL)	Calculated Percent Glucose Bias Obtained at Varying % Hct_m Levels			
DEX® BIOSENSOR REAGENT, LOT A RESULTS				
	Sample 1: 20 vol.% Hct_m	Sample 2: 30 Vol.% Hct_m	Sample 3: 50 Vol.% Hct_m	Sample 4: 60 vol.% Hct_m
20	1.1	-4.7	-5.8	6.1
50	0.6	-4.7	-1.7	9.0
100	-0.35	-1.41	-5.71	-8.33
200	4.8	-0.2	-13.3	-12.5
600	15.1	5.3	-14.6	-22.8
DEX® BIOSENSOR REAGENT, LOT B RESULTS				
	Sample 1: 20 vol.% Hct_m	Sample 2: 30 Vol.% Hct_m	Sample 3: 50 Vol.% Hct_m	Sample 4: 60 vol.% Hct_m
20	-0.2	-6.0	-5.4	10.5
50	-2.2	-1.7	-2.3	4.6
100	2.1	-0.9	-4.4	-3.2
200	6.8	1.1	-13.6	-9.3
600	13.6	5.0	-15.5	24.1

As shown in Tables C and D, the samples containing lower hematocrit levels generally provided an increasingly positive bias as the level of added glucose increased. This effect, for example, was more significant at 20 vol.% Hct than at 30 vol.% Hct. Also as shown in Tables C and D, the samples containing higher hematocrit levels generally provided an increasingly negative glucose bias as the level of added glucose increased. This effect, for example, was more significant at 60 vol.% Hct than at 50 vol.% Hct.

The percent glucose bias was plotted versus the average measured percent hematocrit, % Hct_m, at the 600 mg/dL glucose concentration at the averaged

hematocrit levels from Table D above. In other words, the values shown in Table E were plotted in FIG. 1:

TABLE E

GU_t (mg/dL)	Average Calculated Percent Glucose Bias Obtained at Varying % Hct_m Levels from Lots A and B			
	Sample 1: 20 vol.% Hct_m	Sample 2: 30 Vol.% Hct_m	Sample 3: 50 Vol.% Hct_m	Sample 4: 60 vol.% Hct_m
600	14.35	5.15	-15.05	-23.45

EXAMPLE 2: DERIVATION OF HEMATOCRIT ADJUSTMENT FACTOR FOR GLUCOSE

This example explains the derivation process for one embodiment of Equation 3 described above. Six whole blood samples were obtained and were divided into Samples 5-10. Using the hematocrit adjustment protocol set forth in Example I above, the hematocrit contents of Samples 5-10 were adjusted to 20 vol.%, 30 vol.%, 40 Vol.%, 45 Vol.%, 50 Vol.%, and 60 Vol.% Hct respectively (*i.e.*, the measured percent hematocrit, % Hct_m, levels). The measured percent hematocrit, % Hct_m, levels (*i.e.*, the 20 Vol.%, 30 Vol.%, 40 Vol.%, 45 Vol.%, 50 Vol.%, and 60 Vol.% Hct_m levels) were obtained by measurement on a Compur M1100 micro-centrifuge.

Using three lots of DEX® biosensor reagents (Lots C, D, and E) and a BAS 100B Analyzer electrochemical device, the resistance of the blood sample (R_{cell}) and the resistance of plasma (R_{plasma}) of Samples 5-10 were measured. The test potential of the working electrode was 400 mV, and the glucose concentration was about zero for each run. The values for R_{cell} for Lots C-E at varying measured percent hematocrit (% Hct_m) levels are set forth in Table F below:

TABLE F

DEX® Biosens or Reagent Lot	R_{cell} of Whole Blood at Varying Measured Percent Hematocrit (% Hct_m) Levels					
	Sample 5: 20 vol.% Hct_m	Sample 6: 30 vol.% Hct_m	Sample 7: 40 vol.% Hct_m	Sample 8: 45 Vol.% Hct_m	Sample 9: 50 Vol.% Hct_m	Sample 10: 60 vol.% Hct_m
C	1046	989	1091	1055	1079	1286
D	983	1036	1076	1111	1111	1219
E	984	1013	10890	1077	1132	1297

The values for R_{plasma} for four replicates of Lots C-E are set forth in Table G below. The values for R_{plasma} did not vary with varying- measured percent hematocrit (% Hct_m) levels as observed with the values for R_{cell}.

TABLE G

DEX® Biosensor Reagent Lot	R_{plasma} of Whole Blood			
	Replicate 1	Replicate 2	Replicate 3	Replicate 4
C	948	976	913	924
D	894	993	901	912
E	981	950	953	926

The average value for Rplasma for each of the four replicates for each of Lots C-E was calculated at 939.

Using the values of R_{cell} from Table F and the average R_{plasma} value of 939 from the replicates in Table G, the values of R_{RBC} for Samples 5-10 for Lots C-E were calculated using Equation 2:

$$R_{RBC}=R_{cell}-R_{plasma} \quad \text{(Eq. 2)}$$

The values for R_{RBC} at varying measured percent hematocrit (% Hct_m) levels which were obtained from the calculations of Equation 2 are set forth in Table H below:

TABLE H

DEX® Biosensor Reagent Lot	R_{RBC} of Whole Blood at Varying Measured Percent Hematocrit (% Hct_m) Levels					
	Sample 5: 20 vol.% Hct_m	Sample 6: 30 vol.% Hct_m	Sample 7: 40 vol.% Hct_m	Sample 8: 45 Vol.% Hct_m	Sample 9: 50 Vol.% Hct_m	Sample 10: 60 vol.% Hct_m
C	1076	50	152	116	140	347
D	44	97	137	172	172	280
E	45	74	150	138	193	358

Using the values of R_{RBC}, the measured percent hematocrit (% Hct_m) levels (*i.e.*, 20 vol.%, 30 vol.%, 40 vol.%, 45 vol.%, 50 vol.%, and 60 vol.% Hct respectively), and curve-fitting software, the values of k_1, k_2, and k_3 in Equation 3 were determined. Specifically, the values of R_{RBC} and % Hct_m were curve-fitted using

a second order polynomial math conversion via Slide Write Pro software manufactured by Advances Graphics Software, Inc. The values of R_{RBC} were plotted on the x axis while the values of % Hct_m were plotted on the y axis. The values of k_1, k_2, and k_3 that were obtained through the curve-fitting software are set forth in Table I below:

TABLE I

Constant in Equation 3	Value Determined From Curve-Fitting Software
k1	-0.000397
k2	0.285
k3	9.63

The calculated percent hematocrit, % Hct_c, levels for Samples 5-10 for Lots C-E were then calculated using Equation 7:

$$\% Hct_c = -0\text{-}000397 \cdot (R_{RBC})^2 + 0.285 \cdot R_{RBC} + 9.63 \quad \text{(Eq. 7)}$$

The calculated percent hematocrit, % Hct, levels which were obtained at the varying measured percent hematocrit levels using Equation 7 are set forth in Table J below-

TABLE J

DEX® Biosensor Reagent Lot	Calculated Percent Hematocrit (% Hct_c) Levels at Varying Measured Percent Hematocrit Levels (% Hct_m)					
	Sample 5: 20 vol.% Hct_m	Sample 6: 30 vol.% Hct_m	Sample 7: 40 vol.% Hct_m	Sample 8: 45 Vol.% Hct_m	Sample 9: 50 Vol.% Hct_m	Sample 10: 60 vol.% Hct_m
C	35.58	22.83	43.74	37.30	41.71	60.72
D	21.34	33.49	41.18	46.87	46.87	58.29
E	21.59	28.49	43.41	41.36	49.81	60.78

A correlation curve between the measured percent hematocrit level (% Hct_m) and the calculated hematocrit level (% Hct_c)) was prepared and is shown in FIG. 2. As shown in FIG. 2, the slope was 1.72 with an intercept of 26.3 while R^2 was 0.08311. R^2 is a correlation coefficient that reflects the degree of linearity of the plotted curve.

EXAMPLE 3: DETERMINATION OF ADJUSTMENT FACTOR

This example explains the process involved in determining the need for hematocrit correction, in determining the hematocrit correction factor, and in performing the hematocrit correction. The process begins by having a home glucose monitor user apply blood to an electrochemical sensor. The home glucose monitor will electrochemically determine the resistance of the blood sample, R_{cell}, using a biosensor reagent. The resistance of plasma, R_{plasma}, for the particular sensor lot will be electrochemically determined using a biosensor reagent by the manufacturer prior to shipment of the home glucose monitor. The value of R_{plasma} will be stored in the calibration chip or label or will be provided to the user for programming into the home glucose monitor.

Using the values of R_{cell} and R_{plasma}, the calculated resistance of red blood cells, R_{RBC}, is mathematically determined within the home glucose monitor. Once the R_{RBC} has been determined, the percent hematocrit, % Hct_c, of the blood sample is determined within the home glucose monitor using Equation 3 set forth above. The values for k_1, k_2, and k_3 will be determined by the manufacturer using standard curve-fitting software. The values for k_1, k_2, and k_3 will be electronically programmed by the manufacturer into the software that is used with the home glucose monitor or will be provided to the user for programming or manually inputting into the home glucose monitor.

The measured glucose level, Glu_m, is determined by art.-recognized, conventional methods such as using a glucose analyzer. Once the % Hct_c is determined, the value of k_5 can be determined from the graph in FIG. 1. The values from FIG. 1 may be stored on a calibration chip provided with the biosensor reagent or stored on a label located on the biosensor reagent or may be provided for the user for programming into the home glucose monitor.

The calculated percent glucose bias is also predetermined and programmed into the calibration chip or label. An example of this percent glucose bias is graphed and shown in FIG. 1. The following is an example of the calculations:

R_{cell}	984	1040	1297		
R_{RBC}	45	101	358	(R_{RBC}=R_{cell}-R_{plasma})	
% Hct_c	20%	40%	60%		
Glu_m	134	120	96.6		
k_5	-14	0	23.4		
Glu_{adj}	120	120	120	(Glu_{adj} = Glu_m+k_5	

The values for R_{RBC} were obtained from Equation 2 while the values for Glu_{adj} were obtained from Equation 4 discussed above. This will be determined within the laboratory by determining the percent glucose bias at various glucose- levels and hematocrit levels. An example of this determination is shown in Table C (the actual glucose, Glu_m, values) and Table D (percent glucose bias from expected value). These percent glucose bias values are plotted as shown in Figure 1. These values, which need to be added for higher hematocrits or subtracted for lower hematocrits generated from Figure 1, will be electronically stored within the calibration chip or label for each reagent lot.

Once the calculated percent hematocrit, % Hct_c, levels have been determined and if the calculated percent hematocrit, % Hct_c, level does not equal 40%, the stored percent glucose bias value (from FIG. 1) is electronically retrieved and is used to display the correct glucose value on the display screen of the home glucose monitor. The process involved in determining the need for hematocrit correction, in' determining the hematocrit correction factor, and in performing the hematocrit correction is invisible to the user of the home glucose meter.

While the invention has been described with a number of embodiments, the scope of the invention is not intended to be limited by the specific embodiments. Various modifications, changes, and variations may be apparent from the foregoing descriptions without departing from the spirit and scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method for adjusting glucose bias, if any, of a blood sample in a glucose-monitoring product comprising the acts of:

(a) measuring the glucose value, Glu_m, of the blood sample;

(b) measuring the resistance of the blood sample (R_{cell}) using a biosensor reagent;

(c) measuring the resistance of plasma (R_{plasma}) using the biosensor reagent;

(d) determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship:

$$R_{RBC} = R_{cell} - R_{plasma};$$

(e) calculating the percent hematocrit, % Hct_c, of the blood sample;

(f) determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and

(g) using the percent hematocrit, % Hct_c, and the glucose value from either act (a) or act (f) to adjust for the bias of the biosensor reagent, if any.

2. The method of claim 1, wherein the act of measuring the glucose value, Glu_m, of the blood sample involves using a laboratory glucose analyzer.

3. The method of claim 1, wherein the values of R_{RBC} and % Hct_c are manually calculated.

4. The method of claim 1, wherein the values of R_{RBC} and % Hct_c are determined by software used with the glucose-monitoring product.

5. The method of claim 1, wherein the act of measuring R_{cell} involves measuring the cell resistance of the blood sample between the reference electrode and the working electrode in the biosensor reagent.

6. The method of claim 1, wherein the value of R_{plasma} is electronically programmed into software used with the glucose-monitoring product.

7. The method of claim 1, wherein the value of R_{plasma} is included on a calibration chip provided with the biosensor reagent.

8. The method of claim 1, wherein the value of R_{plasma} is included on a label located on the biosensor reagent.

9. The method of claim 1, wherein the act of measuring R_{plasma} involves inputting a predetermined value by a user into the glucose-monitoring product.

10. The method of claim 1, wherein the value of R_{RBC} is calculated by software used with the glucose-monitoring product.

11. The method of claim 1, wherein the value of R_{RBC} is calculated manually and input into the glucose-monitoring product.

12. The method of claim 1, wherein the value of % Hct_c is calculated by software used with the glucose-monitoring product.

13. The method of claim 1, wherein the value of % Hct_c is calculated manually and input into the glucose-monitoring product.

14. The method of claim 1, wherein the sample is a whole blood sample.

15. A method for adjusting glucose bias, if any, of a blood sample in a glucose-monitoring product, the method comprising the acts of:

measuring the glucose value, Glu_m, of the blood sample;

measuring the cell resistance, R_{cell}, of the blood sample using a biosensor reagent;

measuring the plasma resistance, R_{plasma}, of the blood sample using a biosensor reagent;

determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship:

$$R_{RBC} = R_{cell} - R_{plasma};$$

calculating the percent hematocrit, % Hct, of the blood sample according to the relationship:

$$\% Hct_c = -k_1 * (R_{RBC})^2 + k_2 * R_{RBC} + k_3$$

where k_1 ranges from about +100 to about -100, k_2 ranges from about +100 to about -100, and k_3 from about +100 to about -100;

determining whether to adjust the glucose value, Glu_m; and

adjusting, if necessary, the glucose value, Glu_m, using the percent hematocrit, % Hct_c, and the glucose value Glu_m according to the relationship:

$$Glu_{adj} = Glu_m + k_5.$$

16. The method of claim 15, wherein the act of measuring the glucose value, Glu_m, of the blood sample involves using a laboratory glucose analyzer.

17. The method of claim 15, wherein the values of R_{RBC} and % Hct_c, are manually calculated.

18. The method of claim 15, wherein the values of R_{RBC} and % Hct_c are determined by software used with the glucose-monitoring product.

19. The method of claim 15, wherein the act of measuring R_{cell} involves measuring the cell resistance of the blood sample between the reference electrode and the working electrode in the biosensor reagent.

20. The method of claim 15, wherein the value of R_{plasma} is electronically programmed into software used with the glucose-monitoring product.

21. The method of claim 15, wherein the value of R_{plasma} is included on a calibration chip provided with the biosensor reagent.

22. The method of claim 15, wherein the value of R_{plasma} is included on a label located on the biosensor reagent.

23. The method of claim 15, wherein the act of measuring R_{plasma} involves inputting a predetermined value by a user into the glucose-monitoring product.

24. The method of claim 15, wherein the value of R_{RBC} is calculated by software used with the glucose-monitoring product.

25. The method of claim 15, wherein the value of R_{RBC} is calculated manually and input into the glucose-monitoring product.

26. The method of claim 15, wherein the value of % Hct_c is calculated by software used with the glucose-monitoring product.

27. The method of claim 15, wherein. the value of % Hct_c is calculated manually and input into the glucose-monitoring product.

28. The method of claim 15, wherein the sample is a whole blood sample.

29. A meter for correcting glucose bias of a blood sample in a glucose-monitoring product, the meter comprising:

means for measuring the glucose value, Glu_m, of the blood sample;

means for measuring the resistance of the blood sample (R_{cell}) using a biosensor reagent;

means for measuring the resistance of plasma (R_{plasma}) using the biosensor reagent;

means for determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship

$$R_{RBC} = R_{cell} - R_{plasma};$$

means for calculating the percent hematocrit, % Hct_c, of the blood sample;

means for determining whether to adjust the glucose value, Glu_m, to an adjusted glucose value, Glu_{adj}; and

means for using the percent hematocrit, % Hct_c, and either the glucose value, Glu_m, or the adjusted glucose value, Glu_{adj}, to adjust for the bias of the biosensor reagent, if any.

30. A meter for correcting glucose bias of a blood sample in a glucose-monitoring product, the meter comprising:

means for measuring the glucose value, Glu_m, of the blood sample;

means for measuring the cell resistance, R_{cell}, of the blood sample using a biosensor reagent;

means for measuring the plasma resistance, R_{plasma}, of the blood sample using a biosensor reagent;

means for determining the calculated resistance of red blood cells, R_{RBC}, of the blood sample according to the relationship:

$$R_{RBC} = R_{cell} - R_{plasma};$$

means for calculating the percent hematocrit, % Hct_c, of the blood sample according to the relationship:

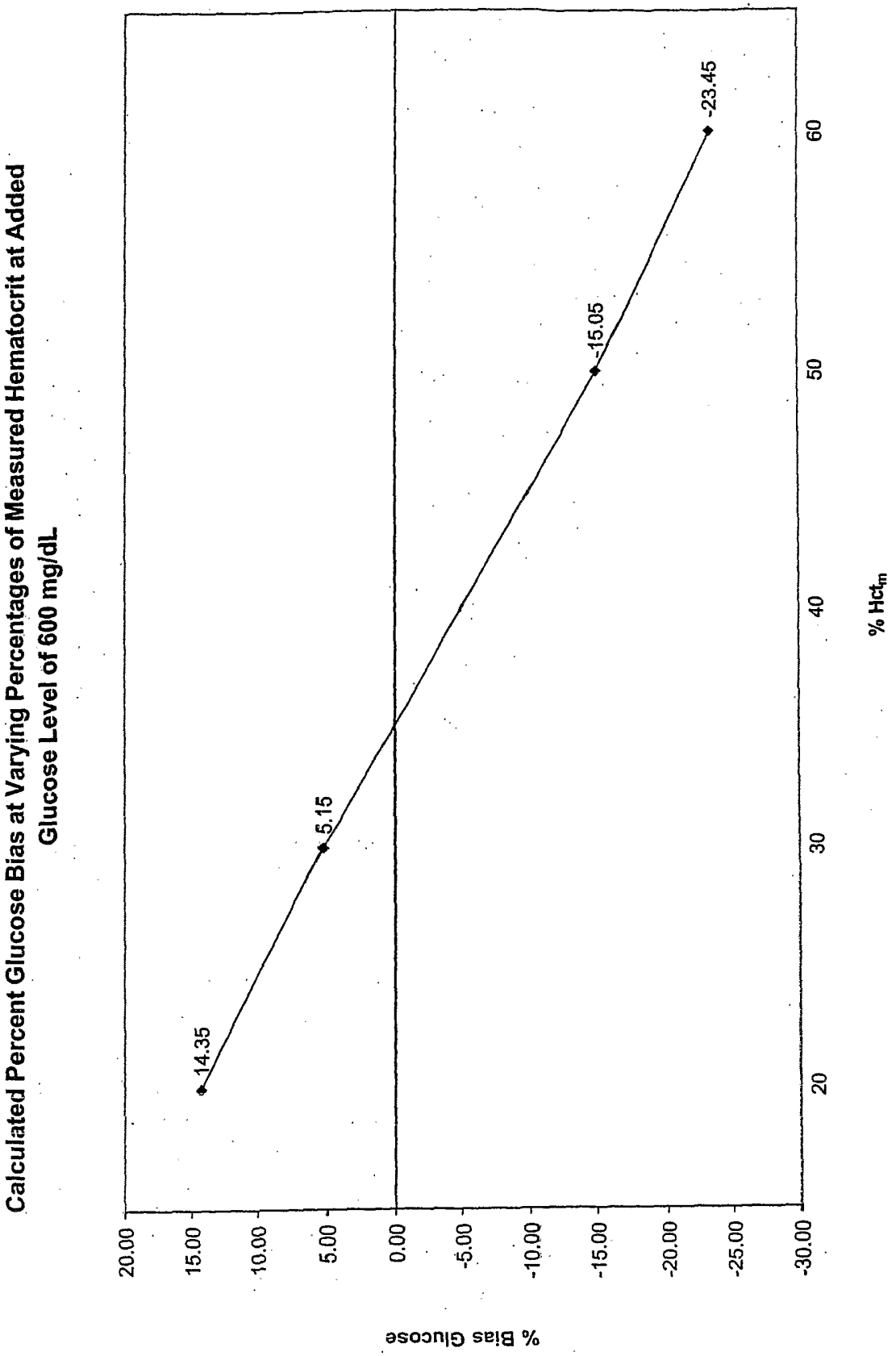
$$\% Hct_c = -k_1 * (R_{RBC})^2 + k2 * R_{RBC} + k_3$$

where k_1 ranges from about +100 to about -100, k_2 ranges from about +100 to about -100, and k_3 from about + 100 to about -100;

means for determining whether to adjust the glucose value, Glu_m; and

means for adjusting, if necessary, the glucose value, Glu_m, using the percent hematocrit, % Hct_c, and the glucose value Glu_m according to the relationship:

$$Glu_{adj} = Glu_m + k_5.$$


Calculated Percent Glucose Bias at Varying Percentages of Measured Hematocrit at Added Glucose Level of 600 mg/dL
% Bias Glucose
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
20
30
40
50
60
% Hct$_m$
14.35
5.15
-15.05
-23.45

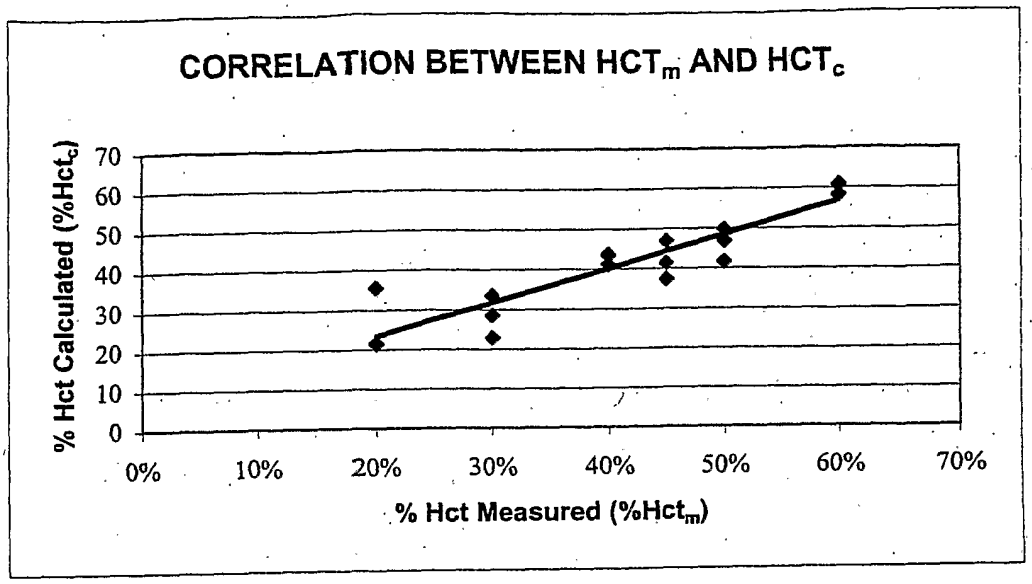

CORRELATION BETWEEN HCTm AND HCTc
% Hct Calculated (%Hctc)
70
60
50
40
30
20
10
0
0%
10%
20%
30%
40%
50%
60%
70%
% Hct Measured (%Hctm)

FIG 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/017014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N27/416 G01N33/487

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)
IPC 7 G01N C12Q A61B

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 411 348 A (ARKRAY, INC) 21 April 2004 (2004-04-21) paragraphs '0028! - '0057!	1,2,4, 12, 14-16, 18,24, 26,28-30
Y	US 2004/021469 A1 (BLOMBERG SCOTT EVERETT ET AL) 5 February 2004 (2004-02-05) paragraphs '0046! - '0048!	1,2,4, 12, 14-16, 18,24, 26,28-30
A	EP 1 394 545 A (BAYER HEALTHCARE, LLC) 3 March 2004 (2004-03-03) claim 1	1,5

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

[X] Patent family members are listed in 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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"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
7 September 2005	22/09/2005

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Duchatellier, M

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/064525 A1 (LIESS MARTIN DIETER ET AL) 3 April 2003 (2003-04-03) paragraphs '0019! - '0022!	1
A	EP 0 928 967 A (KYOTO DAIICHI KAGAKU CO., LTD) 14 July 1999 (1999-07-14) claim 1	1
A	US 2003/096420 A1 (HELLER ZINDEL HERBERT) 22 May 2003 (2003-05-22) claim 1	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/017014

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