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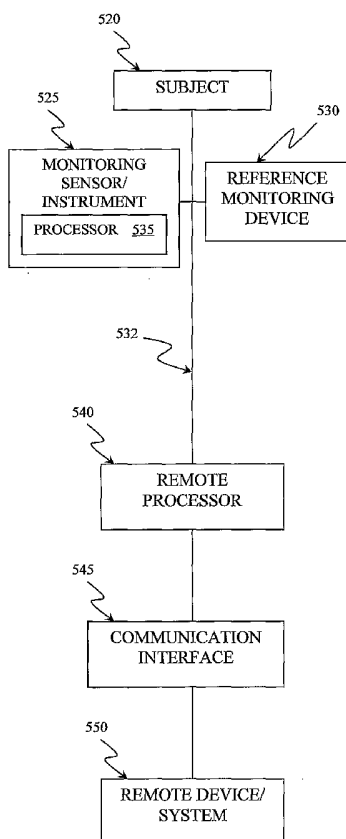
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(54) Title: METHOD, SYSTEM AND COMPUTER PROGRAM PRODUCT FOR EVALUATING THE ACCURACY OF BLOOD GLUCOSE MONITORING SENSORS/DEVICES



(57) Abstract: Continuous Glucose Error-Grid Analysis (CG-EGA) method, system or computer program product designed for evaluation of continuous glucose sensors providing frequent BG readings. The CG-EGA estimates the precision of such sensors/devices in terms of both BG values and temporal characteristics of BG fluctuation. The CG-EPA may account for, among other things, specifics of process characterization (location, speed and direction), and for biological limitations of the observed processes (time lags associated with interstitial sensors).



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Method, System and Computer Program Product for Evaluating the Accuracy of Blood Glucose Monitoring Sensors/Devices

CROSS-REFERENCES TO RELATED APPLICATIONS

The present invention claims priority from U.S. Provisional Patent Application Serial No. 60/564,195, filed April 21, 2004, entitled "Continuous Glucose Error-Grid Analysis (CG-EGA): A Method, System and Computer Program Product for Evaluating the Accuracy of Continuous Blood Glucose Monitoring Sensors," the disclosure of which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to the method and related system for evaluating the accuracy of a glucose monitoring sensors or instruments, in particular continuous or semi-continuous glucose sensors or instruments and related methods.

BACKGROUND OF THE INVENTION

In the Diabetes Control and Complication Trial (DCCT) (1), the risks of microvascular (retinopathy and nephropathy) and neuropathic complications of diabetes were predicted by Hemoglobin A1c (HbA1c) for subjects with Type 1 diabetes (T1DM). Similarly, for those with Type 2 diabetes (T2DM), in the United Kingdom Prospective Diabetes Study (UKPDS) the risks of microvascular complications of diabetes were predicted based on HbA1c (2). However, blood glucose (BG) fluctuations are a process in time and understanding their temporal characteristics is important. Despite the excellent predictive power of HbA1c for chronic diabetes complications, patients commonly experience disturbing symptoms related to rapid blood glucose (BG) swings deviating from their average glycemia. Measures of average glycemia thus may fail to capture important aspects of the temporal patterns of glycemia (3). Recently, it has been reported that extreme fluctuations in glucose values are important markers of diabetes

control in both T1DM and T2DM (4): (i) the Low BG Index (LBGI) (5, 6) predicts the risk and frequency of severe hypoglycemia; (ii) the High BG Index (HBGI) predicts the risk of extremes of hyperglycemia (5,7), and (iii) previously reported symptom-BG associations (8) and recent data (9) suggest that BG rate of change may be linked to the development of negative mood and cognitive symptoms, especially post meals (9). Mounting evidence point to the importance of rapid BG fluctuations for long-term diabetes complications as well. A number of recent studies found that postprandial hyperglycemia is an independent factor contributing to cardiovascular complications and increased mortality, especially in T2DM (10,11,12,13,14,15). The Diabetes Intervention Study, concluded that postprandial, but not fasting BG, was an independent predictor of mortality in T2DM (15). A recent review of studies in this area concluded that there are now comprehensive and consistent data from pathophysiological as well as epidemiologic studies that excessive post-load glucose excursions have acute and chronic harmful effects on the endothelium and vessel wall (16). Thus, an accurate assessment of BG dynamics in peoples' natural environment is a valuable tool for both everyday maintenance of diabetes and long-term effectiveness of glycemic control. This is the premise behind increasing industrial and research efforts concentrated on the development of sensors for continuous, or nearly continuous, monitoring of BG (CGS, 17,18,19). Compared to a few self-monitoring BG (SMBG) readings per day, continuous glucose sensor (CGS) yield detailed time series of BG determinations, e.g. BG samples every 5 minutes for several days. The evaluation of the accuracy of CGS, however, is not straightforward, especially if taken in the context of established accuracy measures, such as statistical correlation or regression, or the clinically based Error-Grid Analysis (EGA) previously introduced (20,21). A problem is that all these accuracy measures are designed to reflect the quality of approximation of reference BG by measurements taken in isolated static points in time, regardless of the temporal structure of the data. As such, these measures work well for evaluation of self-monitoring (SMBG) devices and are accepted by FDA as valid supplements to the review of clinical measurement methods (22,23). However, applying these measures to evaluate the process approximation offered by CGS is questionable. An analogy of CGS vs. SMBG with camcorders vs. still cameras is inevitable, and might be helpful. Still cameras produce highly accurate snapshots of a process in time; camcorders generally offer lower resolution and precision of each separate image, but

capture the dynamics of the action. Thus, it would be inappropriate to gauge the accuracy of still cameras and camcorders using the same static measure--the number of pixels in a single image. Similarly, it is inappropriate to gauge the precision of CGS and SMBG devices using the same measures, especially when these measures ignore the temporal characteristics of the observed process.

The original Error Grid Analysis (EGA) some time ago, which was intended to quantify the clinical significance of the agreement between a BG estimate and reference value (20). While other methods were available to quantify the statistical significance of such agreement, such as correlational and regression analyses, these approaches did not address the important question of the clinical implications of accuracy of BG estimates, i.e., what would be the potential outcome if a patient took some self-treatment action based upon a BG estimate. In its original form, the EGA was used to quantify the accuracy of patient BG estimates, based on physical symptoms and information about time of day, insulin, food and physical activity, compared to BG meter values. Subsequently, the EGA was used to assess the accuracy of BG meters compared to reference laboratory measurements (21). Over time, the EGA became one of the accepted standards for demonstrating acceptable levels of accuracy of BG meters to the FDA (23).

The original EGA plots each BG estimate (from any source) on the Y-axis against its companion reference BG measure on the X-axis, so that each estimate falls into one of 10 zones (upper and lower A – E zones). The upper and lower A zones are clinically accurate, indicating that a BG estimate deviates less than 20% from the reference, or that both the estimate and reference value are < 70 mg/dl. These estimates are considered accurate because they are likely to lead to an appropriate clinical response (e.g., attempting to raise a BG value that is too low or lower a BG value that is too high). Clinically significant errors are those that fall into the upper and lower 1) C zones (possible over-correction when estimated BG indicates treatment may be needed but reference value is in an acceptable range), 2) D zones (failure to detect and possibly treat reference BG levels that are too low or too high, and 3) E zones (erroneous estimates indicating that BG needs to be raised when it is actually too high already, and vice versa). Estimates falling into the remaining area of the Error Grid are B zone errors, indicating benign errors that deviate more than 20% from the reference value but are unlikely to lead to any clinical action or have significant implications if action is taken.

Once the original EGA was published, the scientific community quickly recognized the important unique information provided by this method of evaluating accuracy, and it became a standard component of almost all clinical trials of new BG meters. This was an appropriate use of the EGA since BG meters are designed to provide an accurate estimate of a single static BG value. However, because the EGA only quantifies point accuracy of each single static estimate of BG, and does not take into consideration temporal characteristics of BG fluctuations, its use for determining the accuracy of CGS devices is problematic. In fact, because the EGA does not quantify the accuracy of estimations of temporal changes, such as rate and direction of BG fluctuation, it may even yield misleading results concerning the clinical implications of errors in CGS devices.

Traditional device evaluation methods fail to capture a most important temporal characteristic of the continuous glucose monitoring process.

BRIEF SUMMARY OF INVENTION

Various embodiments of the present invention comprises, but not limited thereto, a Continuous Glucose Error-Grid Analysis (CG-EGA) method, system or computer program product designed for evaluation of continuous glucose sensors providing frequent (e.g., every 5 minutes or desired/required period or frequency) BG readings. CG-EGA estimates the precision of such sensors/devices in terms of both BG values and temporal characteristics of BG fluctuation. The estimates are then combined in a single accuracy assessment that preserves the clinical assumptions of our original EGA (21,24). This "backward compatibility" makes the accuracy evaluation of continuous glucose sensors using the present invention CG-EGA comparable to accuracy evaluation of SMBG devices using the traditional EGA.

The various embodiments of the present invention Continuous Glucose Error-Grid Analysis (CG-EGA) provides, for example, a new method, system, and computer program product for evaluating the accuracy of continuous glucose monitoring sensors in terms of both accurate blood glucose (BG) values, and accurate direction and rate of BG fluctuations. It should be appreciated that continuous glucose sensors allow, for the first time, routine observation of BG fluctuations as a process in time. The various

embodiments of the present invention, account for, among other things, specifics of process characterization (location, speed and direction), and for biological limitations of the observed processes (time lags associated with interstitial sensors).

An embodiment of the present invention CG-EGA includes two interacting components: (1) Rate Error-Grid Analysis assessing sensors' ability to capture the direction and rate of BG fluctuations, and (2) Point Error-Grid Analysis evaluating the sensors' point accuracy in terms of correct presentation of BG values. The CG-EGA then combines rate and point accuracy in a single estimate of sensor precision using a weighed combination of three grids designed specifically for hypoglycemic, euglycemic, and hyperglycemic BG ranges.

An aspect of an embodiment of the present invention is directed to a method for evaluating accuracy of a glucose monitoring sensor. The method comprising: evaluating point accuracy of blood glucose (BG) values received from the monitoring sensor; evaluating accuracy of direction and rate of BG fluctuations received from the monitoring sensor; and combining the point accuracy and rate accuracy in an estimate of sensor precision. The accuracy evaluation of direction and rate of BG fluctuations includes performing rate error-grid analysis (R-EGA), and the accuracy evaluation blood glucose (BG) values includes performing point error-grid analysis (P-EGA) that determines correct presentation of the blood glucose (BG) values. The method may further comprise: splitting the reference BG values received from a reference sensor BG monitoring device into three clinically meaningful regions including hypoglycemia, euglycemia and hyperglycemia regions; and combining results from the rate error-grid analysis (R-EGA) and point error-grid analysis (P-EGA) within each of these regions.

Another aspect of an embodiment of the present invention is directed to a system for evaluating accuracy of a glucose monitoring sensor. The system may comprise a microprocessor or the like programmed to perform the following: evaluate point accuracy of blood glucose (BG) values received from the monitoring sensor; evaluate accuracy of direction and rate of BG fluctuations received from the monitoring sensor; and combine the point accuracy and rate accuracy in an estimate of sensor precision.

Additionally, an aspect of an embodiment of the present invention is directed to a computer program product comprising a computer usable medium having computer program logic for enabling at least one processor in a computer system to evaluate

accuracy of a glucose monitoring sensor. The computer program logic may comprise: evaluating point accuracy of blood glucose (BG) values received from the monitoring sensor; evaluating accuracy of direction and rate of BG fluctuations received from the monitoring sensor; and combining the point accuracy and rate accuracy in an estimate of sensor precision.

Further yet, an aspect of an embodiment of the present invention is directed to a system for evaluating accuracy of a glucose monitoring sensor. The system comprises a glucose monitoring sensor and a microprocessor. The microprocessor may be programmed to perform the following: evaluate point accuracy of blood glucose (BG) values received from the monitoring sensor; evaluate accuracy of direction and rate of BG fluctuations received from the monitoring sensor; and combine the point accuracy and rate accuracy in an estimate of sensor precision.

Further still, an aspect of an embodiment of the present invention is directed to a system for evaluating accuracy of a glucose monitoring sensor. The system comprises a glucose monitoring sensor, a reference device; and a microprocessor. The microprocessor being programmed to perform the following: evaluate point accuracy of blood glucose (BG) values received from the monitoring sensor; evaluate accuracy of direction and rate of BG fluctuations received from the monitoring sensor; and combine the point accuracy and rate accuracy in an estimate of sensor precision.

These and other objects, along with advantages and features of the invention disclosed herein, will be made more apparent from the description, drawings and claims that follow.

BRIEF SUMMARY OF THE DRAWINGS

The foregoing and other objects, features, and advantages of the present invention, as well as the invention itself, will be more fully understood from the following description of the invention, when read together with the accompanying drawings, in which:

FIG. 1 provides a vector presentation of sensor (estimated) vs. reference BG over the grid of the traditional EGA.

FIG. 2 provides the rate error-grid analysis (R-EGA), wherein the sensor (estimated) BG rate of change is plotted against reference BG rate of change.

FIGS. 3(A)-(E) provide a point error-grid analysis (P-EGA), wherein P-EGA is a scatterplot of sensor (estimated) vs. reference BG divided into A_P , B_P , C_P , D_P , and E_P zones.

FIG. 4 provides a grid that combines rate and point error-grid zones with possible R-EGA (rows) and P-EGA (columns) values.

FIGS. 5(A)-(B) are schematic block diagrams of alternative variations of an embodiment of the present invention in communication with related processors, communication interfaces, and systems and/or devices.

FIG. 6 is a functional block diagram for a computer system for implementation of an exemplary embodiment or portion of an embodiment of present invention.

FIGS. 7-8 provide a graphic illustration of an exemplary meter evaluation that may provided in a print out form, computer/PDA monitor form, or data storage medium, for example.

DETAILED DESCRIPTION OF THE INVENTION

BG fluctuations are a continuous process in time $BG(t)$, and each point of that process is characterized by its location, speed, and direction of change. In other words, at any point in time $BG(t)$ is a vector with a specific bearing. Turning to **FIG. 1**, **FIG. 1** presents such vectors depicted over the grid of the traditional EGA. The exemplary vectors are illustrated on the grid with circles having arrow heads.

CGS allows monitoring this process in short (e.g. 5-min) increments, in essence producing a parallel discrete time series that approximates $BG(t)$. It should be appreciated that the increments may be any desired or required time period, interval or frequency. The periods may be equivalent or varied. Thus, CG-EGA has to judge the precision of this process approximation in terms of both accuracy of BG readings, and accuracy of evaluation of the direction of BG change. Consequently, a Point Error-Grid Analysis (P-EGA) and Rate Error-Grid Analysis (R-EGA) is introduced that deal with these two requirements.

In an embodiment, in order to construct R-EGA and P-EGA it is set forth that paired reference-sensor BG readings are available through a sufficiently frequent sampling (e.g. 5-15 minutes) capable of capturing a representative picture of BG fluctuations. It should be appreciated that the frequent sampling period may be less than
 5 five minutes or greater than 15 minutes.

An embodiment of the process of sensor evaluation includes the following three steps: 1) computing Rate Error-Grid zones, 2) computing Point Error-Grid zones, and 3) combining Rate and Point Error-Grid zones in a single sensor accuracy assessment.

10 Rate Error-Grid Analysis (R-EGA)

For each pair of reference BG points $RBG(t_1)$, $RBG(t_2)$ taken at times t_1 and t_2 reference BG rate is estimated as the ratio of the change in BG divided by the length of the elapsed time interval:

$$\text{Reference BG Rate of Change (mg/dl/min)} = (RBG(t_2) - RBG(t_1)) / (t_2 - t_1).$$

15 Similarly, for each pair of sensor reported BG points $SBG(t_1)$, $SBG(t_2)$ taken at times t_1 and t_2 , sensor BG rate is estimated as:

$$\text{Sensor BG Rate of Change (mg/dl/min)} = (SBG(t_2) - SBG(t_1)) / (t_2 - t_1).$$

Turning to **FIG. 2**, the sensor (estimated) BG rate of change is then plotted against reference BG rate of change. The boundaries of the scatterplot are set to $[-4, 4]$
 20 mg/dl/min. This assumption follows from evaluation of the observed BG rate of change in 31,000 CGS data points showing that over 99% of all observed changes have rates between -4 and 4 mg/dl/min.

Further, the scatterplot is divided into A through E accuracy zones, which have a clinical meaning similar to the clinical meaning of the original EGA (20,21,24). The
 25 assumptions behind the zone definition are as follows:

- (1) Accurate A_R-zone (suffix R stands for rate): The main diagonal in **FIG. 2** signifies a perfect fit. A sensor BG rate of change within 1 mg/dl/min from the main diagonal is considered accurate. The accuracy boundaries are expanded to ± 2 mg/dl/min at extreme BG rates of ± 4 mg/dl/min because such rapid rates of
 30 change is rare, cannot be sustained for prolonged periods, and the correct recognition of their direction is sufficient for an accurate clinical decision.
- (2) C_R-zone (over-correction): Reference rate is within $[-1, 1]$ mg/dl/min showing no

significant BG fluctuation. However, the sensor displays a significant BG fluctuation, which could lead to over-treatment. The C_R -zone is divided into overestimation (uC_R -Upper C_R) and underestimation (lC_R - Lower C_R) of the reference rate of change.

- 5 (3) D_R -zone (failure to detect): Reference BG shows significant change, while the sensor fails to detect that change showing readings within $[-1,1]$ mg/dl/min. An embodiment can distinguish upper uD_R and lower lD_R zones signifying failure to detect rapid BG fall, or rise, respectively.
- (4) E_R -zone (erroneous reading) – the sensor display readings that are opposite to the
10 reference rate of change, upper uE_R – an actual BG decline is estimated as BG rise, lower lE_R – an actual BG rise in interpreted as BG fall.
- (5) B_R -zone (benign errors): sensor errors that do not cause inaccurate clinical interpretation.

15 The computation of the R-EGA zones for each pair of reference-sensor BG rates of change uses the formulas below. The output of this computation is a zone, coded as follows:

1-uE; 2-uD; 3-uC; 4-uB; 5-uA; 6-lA; 7-lB; 8-lC; 9-lD; 10-lE

20 X=REFRATE. (Note: Reference BG rate of change as computed above)
Y=SENSRATE. (Note: Sensor BG rate of change as computed above)
IF (Y ge X) RZONE=5.
IF (Y gt (X+1) and X ge 0-2 and X le 1) RZONE=4.
25 IF (Y gt 0.5 X and X lt 0-2) RZONE=4.
IF (Y gt 2.0 X and X gt 1) RZONE=4.
IF (Y gt (X+2) and X ge 0-1 and X lt 1) RZONE=3.
IF (Y gt (X+2) and X ge 0-3 and X lt 0-1) RZONE=2.
IF (Y gt 0-1 and X lt 0-3) RZONE=2.
30 IF (Y gt 1 and X lt 0-1) RZONE=1.
IF (Y lt X) RZONE=6.
IF (Y lt (X-1) and X ge 0-1 and X le 2) RZONE=7.
IF (Y lt 2.0 X and X lt 0-1) RZONE=7.
IF (Y lt 0.5 X and X gt 2) RZONE=7.
35 IF (Y lt (X-2) and X ge 0-1 and X le 1) RZONE=8.
IF (Y lt (X-2) and X gt 1 and X le 3) RZONE=9.
IF (Y lt 1 and X gt 3) RZONE=9.
IF (Y lt 0-1 and X gt 1) RZONE=10.

40

Point Error-Grid Analysis (P-EGA)

Again this analysis is complimentary with traditional EGA, for example (20,21,24). As presented in **FIG. 3**, P-EGA is a scatterplot of sensor vs. reference BG divided into A_P , B_P , C_P , D_P , and E_P zones (suffix P stands for point, prefix “u” or “l” stands for upper or lower).

In order to account for the specifics of BG fluctuations interpreted as a process in time, not as separate point readings, these zones are defined depending on the reference rate of BG change as follows:

- (1) If the reference BG rate is within [about -1, about 1] mg/dl/min (e.g. no significant change), P-EGA zones are identical to the zones of the traditional EGA, as shown in **FIG. 3(A)**;
- (2) If the reference BG is falling at a rate of [about -2, about -1] mg/dl/min, the upper limits of upper A_P , B_P , and D_P zones are expanded by 10 mg/dl, as shown in **FIG. 3(B)**, wherein the dashed lines are illustrated in A_P , B_P , and D_P zones;
- (3) If the reference BG is falling faster than about -2 mg/dl/min, the upper limits of upper A_P , B_P , and D_P zones are expanded by 20 mg/dl, as shown in **FIG. 3(C)**, wherein the dashed lines are illustrated in A_P , B_P , and D_P zones;
- (4) If the reference BG is rising at a rate of [about 1, about 2] mg/dl/min, the lower limits of lower A_P , B_P , and D_P zones are expanded by 10 mg/dl, as shown in **FIG. 3(D)**, wherein the dashed lines are illustrated in lower A_P , B_P , and D_P zones; and
- (5) If the reference BG is rising faster than about 2 mg/dl/min, the lower limits of lower A_P , B_P , and D_P zones are expanded by 20 mg/dl, as shown in **FIG. 3(E)**, wherein the dashed lines are illustrated in lower A_P , B_P , and D_P zones.

These adjustments are made to equate, in terms of clinical accuracy, the process observation provided by CGS to the point observation provided by SMBG. If BG is rapidly falling and the sensor accurately depicts this descent, then a sensor reading right above the A_P zone will be clinically interpreted as a SMBG reading within the A_P zone. For example, if reference BG is 68mg/dl and the sensor reads 75mg/dl and falling at 2mg/dl/min, the sensor reading will cause a treatment reaction similar to the reference reading. In that sense, the sensor display is clinically accurate (while in the traditional EGA this would be an upper D-zone error). Similarly, when BG is rapidly rising, the lower limits of the lower zones are expanded to accommodate the clinical interpretation

of the display. The zone-expansion constants 10 and 20 mg/dl correspond to rates of change 1-2 mg/dl/min, and faster than 2 mg/dl/min. This means that, on average, the sensor reading will reach the corresponding traditional EGA zone within 7 minutes (1.5 mg/dl/min 7 min, or 3 mg/dl/min 7 min). The constant 7 minutes was selected on the basis of reported average delays between blood and interstitial glucose (*See Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of Changes in Interstitial and Venous Blood Glucose Measured With a Continuous Subcutaneous Glucose Sensor. Diabetes 52: 2790-2794, 2003, of which is hereby incorporated by reference herein in its entirety*). It should be appreciated that a wide variety of sensor periods may be implemented. In that sense, the zone expansion accounts for time lags inherent to interstitial sensor.

The computation of the P-EGA zones for each pair of reference-sensor BG readings uses the formulas below. The output of this computation is a zone, coded as follows:

1-uE; 2-uD; 3-uC; 4-uB; 5-uA; 6-lA; 7-lB; 8-lC; 9-lD; 10-lE

If the BG rate of change is between -1 and 1 mg/dl/min, use the formulas:

U1=REFBG. (Note: Reference BG)

W1=SENBG. (Note: Sensor BG)

IF (W1 ge U1) ZONE0=5.

IF (W1 ge 1.20 U1 and U1 gt 70) ZONE0=4.

IF (W1 ge (1.03 U1+107.9) and U1 gt 70) ZONE0=3.

IF (W1 ge 1.20 U1 and W1 gt 70 and U1 le 70) ZONE0=2.

IF (W1 ge 180 and U1 le 70) ZONE0=1.

IF (W1 lt U1) ZONE0=6.

IF (W1 le 0.8 U1 and U1 gt 70) ZONE0=7.

IF (W1 le (1.4 U1-182) and U1 le 180) ZONE0=8.

IF (U1 ge 240 and W1 gt 70 and W1 lt 180) ZONE0=9.

IF (U1 gt 180 and W1 le 70) ZONE0=10.

IF BG is falling at a rate of -1 to -2 mg/dl/min use the formulas:

U2=REFBG. (Note: Reference BG)

W2=SENBG. (Note: Sensor BG)

IF (W2 ge U2) ZONE2=5.

IF (W2 ge (1.20 U2+10) and U2 gt 70) ZONE2=4.

IF (W2 ge (1.03 U2+117.9) and U2 gt 70) ZONE2=3.

IF (W2 ge (1.20 U2+10) and W2 gt 80 and U2 le 70) ZONE2=2.

IF (W2 ge 190 and U2 le 70) ZONE2=1.

IF (W2 lt U2) ZONE2=6.

IF (W2 le 0.8 U2 and U2 gt 70) ZONE2=7.

IF (W2 le (1.4 U2-182) and U2 le 180) ZONE2=8.

IF (U2 ge 240 and W2 gt 70 and W2 lt 180) ZONE2=9.
 IF (U2 gt 180 and W2 le 70) ZONE2=10.

IF BG is falling faster than -2 mg/dl/min use the formulas:

5

U4=REFBG. (Note: Reference BG)

W4=SENBG. (Note: Sensor BG)

IF (W4 ge U4) ZONE4=5.

IF (W4 ge (1.20 U4+20) and U4 gt 70) ZONE4=4.

10 IF (W4 ge (1.03 U4+127.9) and U4 gt 70) ZONE4=3.

IF (W4 ge (1.20 U4+20) and W4 gt 90 and U4 le 70)
 ZONE4=2.

IF (W4 ge 200 and U4 le 70) ZONE4=1.

IF (W4 lt U4) ZONE4=6.

15 IF (W4 le 0.8 U4 and U4 gt 70) ZONE4=7.

IF (W4 le (1.4 U4-182) and U4 le 180) ZONE4=8.

IF (U4 ge 240 and W4 gt 70 and W4 lt 180) ZONE4=9.

IF (U4 gt 180 and W4 le 70) ZONE4=10.

20

IF BG is rising at a rate of 1 to 2 mg/dl/min use the formulas:

U1=REFBG. (Note: Reference BG)

W1=SENBG. (Note: Sensor BG)

IF (W1 ge U1) ZONE1=5.

25 IF (W1 ge 1.20 U1 and U1 gt 70) ZONE1=4.

IF (W1 ge (1.03 U1+107.9) and U1 gt 70) ZONE1=3.

IF (W1 ge 1.20 U1 and W1 gt 70 and U1 le 70) ZONE1=2.

IF (W1 ge 180 and U1 le 70) ZONE1=1.

IF (W1 lt U1) ZONE1=6.

30 IF (W1 le (0.8 U1-10) and U1 gt 70) ZONE1=7.

IF (W1 le (1.4 U1-192) and U1 le 180) ZONE1=8.

IF (U1 ge 240 and W1 gt 60 and W1 lt 170) ZONE1=9.

IF (U1 gt 180 and W1 le 60) ZONE1=10.

35

IF BG is rising faster than 2 mg/dl/min use the formulas:

U3=REFBG. (Note: Reference BG)

W3=SENBG. (Note: Sensor BG)

IF (W3 ge U3) ZONE3=5.

40 IF (W3 ge 1.20 U3 and U3 gt 70) ZONE3=4.

IF (W3 ge (1.03 U3+107.9) and U3 gt 70) ZONE3=3.

IF (W3 ge 1.20 U3 and W3 gt 70 and U3 le 70) ZONE3=2.

IF (W3 ge 180 and U3 le 70) ZONE3=1.

IF (W3 lt U3) ZONE3=6. U3 gt 70) ZONE3=7.

45 IF (W3 le (1.4 U3-202) and U3 le 180) ZONE3=8.

IF (U3 ge 240 and W3 gt 50 and W3 lt 160) ZONE3=9.

IF (U3 gt 180 and W3 le 50) ZONE3=10.

IF (W3 le (0.8 U3-20) and

50

Combining Rate and Point Error-Grids

The results from R-EGA and P-EGA are combined in a single accuracy assessment depending on the reference BG value of each point. First, reference BG is split into three clinically meaningful regions: hypoglycemia defined as $BG \leq 70 \text{ mg/dl}$ (3.9 mmol/l); euglycemia, and hyperglycemia defined as $BG > 180 \text{ mg/dl}$ (10 mmol/l), as shown in the left portion, middle portion and right portion of the table of **FIG. 4**, respectfully. This division is necessary because different BG levels would require different interpretation of the combination R-EGA+P-EGA. The left portion of the table of **FIG. 4** presents a grid of possible R-EGA (rows) and P-EGA (columns) values of a hypothetical sensor in the hypoglycemic range. A reading will be considered accurate if it falls in the A_P zone of P-EGA and in A_R or B_R zones of R-EGA (white squares). The reading is clinically erroneous if it falls in D_P or E_P zones regardless of R-EGA or if it falls in D_R or E_R regardless of P-EGA (vertical hash squares). The rest of the grid squares are considered benign errors (horizontal hash squares).

In other words, the percentage of a sensor's readings within the combined CG-EGA A-zone during hypoglycemia equals the sum of the percentages readings in the two squares (A_P , A_R) and (A_P , B_R) in left portion of the table of **FIG. 4**. In this particular example, during hypoglycemia the sensor has 70% accurate readings, 6% benign errors, and 24% erroneous readings. Similarly, when reference BG is in euglycemic, or hyperglycemic range, the combined rate-point grids are labeled accurate, benign, and erroneous as presented in middle portion of the table of **FIG. 4** for euglycemia and right portion of the table of **FIG. 4** for hyperglycemia. A premise behind the definition of these combined zones may be for example: to what extent the sensor reading would result in accurate treatment, benign error, or significant error, which includes over-treatment or failure to detect dangerous events. Since the detailed differentiation of C, D, and E-zone errors is usually not utilized in sensor evaluation, in the CG-EGA, these zones are not differentiated.

Finally the results from left, middle and right portions of the table of **FIG. 4** are combined in a single accuracy estimate of a sensor using a linear weighted combination. The formulas combining R_EGA and P-EGA zones are as follows:

$$\begin{aligned} A \text{ (Accurate Readings)} &= w1 \cdot A1 + w2 \cdot A2 + w3 \cdot A3 \\ B \text{ (Benign Errors)} &= w1 \cdot B1 + w2 \cdot B2 + w3 \cdot B3 \end{aligned}$$

$$\text{Err (Erroneous Readings)} = w1*\text{Err}1 + w2*\text{Err}2 + w3*\text{Err}3$$

Where $A1$, $B1$, $\text{Err}1$ are the percentages of accurate readings, benign errors, and erroneous readings during hypoglycemia; $A2$, $B2$, $\text{Err}2$ are the percentages of accurate readings, benign errors, and erroneous readings during euglycemia, and $A3$, $B3$, $\text{Err}3$ are the percentages of accurate readings, benign errors, and erroneous readings during hyperglycemia. The weights assigned to the hypoglycemic, euglycemic, and hyperglycemic BG ranges are 0.07, 0.53, and 0.40 respectively. These weights are based on the frequency of occurrence of hypoglycemia and hyperglycemia in the field, computed from 600,000 SMBG data points of 800 subjects with T1DM and T2DM.

In the example given in **FIG. 4**, the weighted linear combination of all BG ranges results in the following final CG-EGA results:

$$\begin{aligned} A &= 0.07 \ 70\% + 0.53 \ 90\% + 0.4 \ 80\% = 84.6\% \\ B &= 0.07 \ 6\% + 0.53 \ 10\% + 0.4 \ 9\% = 9.3\% \\ \text{Err} &= 0.07 \ 24\% + 0.53 \ 0\% + 0.40 \ 11\% = 6.1\% \end{aligned}$$

Turning to **FIGS. 7 and 8**, there is provided a graphic illustration of exemplary Meter Evaluation Sheets that may be provided for a user to review that includes a standardized CGS evaluation sheet presenting visually the results of CG-EGA and as well as in table format the results of CG-EGA. The illustration may be obtained through a printer or computer monitor such as a personal computer or hand held device.

FIGS. 5(A)-(B) are schematic block diagrams of alternative variations of an embodiment of the present invention in communication with related processors, communication links, and remote systems, processors, and/or devices. For instance, a continuous (or semi-continuous) monitoring sensor **525** and reference monitoring device **530** receives readings from a subject **520** in accordance with the methodology discussed throughout this document. The subject **520** may be a human or any animal. It should be appreciated that an animal may be a variety of any applicable type, including, but not limited thereto, mammal, veterinarian animal, livestock animal or pet type animal, etc. As an example, the animal may be a laboratory animal specifically selected to have blood glucose characteristics similar to human (e.g. rat, dog). It should be appreciated that the subject **520** may any applicable patient, for example. A processor **535** in communication with the monitoring sensor **525** and reference monitoring device **530** is adapted to

evaluate the accuracy of the continuous (or semi-continuous) monitoring sensor **525** in accordance with the methodologies discussed throughout out this document. The monitoring sensor **525** may be separate from or integral with the processor **535**, as shown in **FIGS. 5(A)-(B)**, respectively. Similarly, although not shown, any one or all of the monitoring sensor **525**, reference device **530**, processor **535** may be separate or integral with one another. Moreover, it should be appreciated that the monitoring sensor **525** and reference device **530** may be in hard-wire or wireless communication with the processor **535**. Moreover, any one or all of the monitoring sensor **525**, reference device **530**, processor **535**, may be in communication with (hard wire or wireless) a remote processor **540** communication device **545** and/or remote device **550** via communication path or channel **532**. Any part of the communications paths/channels **532** (i.e., communication among the various modules illustrated in **FIG. 5** as well as remote modules not specifically illustrated) and related may be implemented using wire or cable, fiber optics, a phone line, a cellular phone link, an RF link, an infrared link, and other physical or wireless communications channels, for example. Additionally, any one or all of the monitoring sensor **525**, reference device **530**, processor **535**, remote processor **540**, communication device **545** and/or remote device **550** may be portable such as a PDA, hand held device or lap top or embodied at a work station such at a personal computer or the like. It should be appreciated that any readings received by the subject **520** (or patient) and data handled by the monitoring sensor **525** and reference device **530** may be uploaded via the internet for processing or as desired and sent back to monitoring sensor **525** and reference device **530** or any other location (local or remote) for use, processing or data storage for example.

An example of a remote device **550** may be, for example, a display interface that forwards and provides graphics, text, and other data. Another example of a remote device **550** may be memory, storage drive, or storage medium, such as a floppy disk drive, a magnetic tape drive, an optical disk drive, a flash memory, etc. Examples of a communications interface **545** may include a modem, a network interface (such as an Ethernet card), a communications port (e.g., serial or parallel, etc.), a PCMCIA slot and card, a modem, etc. It should be appreciated that software and data transferred via communications interface or any portion of communication path or channel **532** or the

like may be in the form of signals which may be electronic, electromagnetic, optical or other signals capable of being received by communications interface 545 as well as the monitoring sensor 525, reference device 530, processor 535, remote processor 540, communication device 545, and/or remote device/system 550. Other examples of a remote device/system 550 may include at least one of the following: personal computer, processor, keyboard, input device, mouse device, PDA, hand-held device, monitor, printer, work station, remote laboratory, remote medical facility, inpatient facility or system, outpatient facility or system, remote clinic, remote subject or patient site, internet system and intranet system.

It should be appreciated that any or all of the monitoring sensor 525, reference device 530, processor 535, a remote processor 540, communication device 545, remote device/system 550, and communication path or channel 532 may be separately or integrally formed with one another. Moreover, any of these modules/components may be detachable, replaceable, stationary and portable.

Examples of the continuous (or semi-continuous) monitoring sensor 525 and related systems/devices may include, but not limited thereto, the following technologies as discussed in the following U.S. patents and of which are hereby incorporated by reference herein in their entirety:

U.S. Patent 6,865,408 B1 to Abbink et al., entitled "System for Non-Invasive Measurement of Glucose in Humans;"

U.S. Patent 6,853,854 B1 to Proniewicz et al., entitled "Noninvasive Measurement System;"

U.S. Patent 6,675,030 B2 to Ciurczak et al., entitled "Near Infrared Blood Glucose Monitoring System;"

U.S. Patent 6,654,620 B2 to Wu et al., entitled "Method for Improving Non-Invasive Determination of the Concentration of Analytes in a Biological Sample;"

U.S. Patent 6,574,501 B2 to Lambert et al., entitled "Assessing Blood Brain Barrier Dynamics or Identifying or Measuring Selected Substances or Toxins in a Subject by Analyzing Raman Spectrum Signals of Selected Regions in the Eye;"

U.S. Patent 6,574,490 B2 to Abbink et al., entitled "System for Non-Invasive Measurement of Glucose in Humans;"

U.S. Patent 6,477,393 B1 to Chou, entitled "Non-Invasive Blood Glucose

Measurement Techniques;"

U.S. Patent 6,424,850 B1 to Lambert et al., entitled "Non-Invasive Glucose Monitor;"

U.S. Patent 6,181,957 B1 to Lambert et al., entitled "Non-Invasive Glucose
5 Monitor;"

U.S. Patent 6,097,975 to Petrovsky et al., entitled "Apparatus and Method for Noninvasive Glucose Measurement;" and

U.S. Patent 5,077,476 to Rosenthal, entitled "Instrument for Non-Invasive Measurement of Blood Glucose."

10 Additional examples of the continuous (or semi-continuous) monitoring sensor
525 and related systems/devices may include, but not limited thereto, the following technologies:

CGMS® (CONTINUOUS GLUCOSE MONITORING SYSTEM) by MINIMED
MEDTRONIC, Inc.;

15 GLUCOWATCH® G2™ BIOGRAPHER by CYGNUS/SANKYO PHARMA,
Inc.;

GLUCODAY® CONTINUOUS GLUCOSE MONITORING by A. MENARINI
DIAGNOSTICS, Inc.;

CONTINUOUS GLUCOSE SENSOR by ANIMAS, Inc.;

20 FREESTYLE NAVIGATOR CONTINUOUS GLUCOSE MONITOR by
THERASENSE, Inc.;

CONTINUOUS GLUCOSE METER by SPECTRX, Inc.;

NIMOS SENSOR by INSTITUT FÜR CHEMO- UND BIOSENSORIK, Inc.;

SYMPHONY™ DIABETES MANAGEMENT SYSTEM by SONTRA

25 MEDICAL:

GLUCONIR by NIR DIAGNOSTICS, Inc.;

SMSI™ GLUCOSE SENSOR by SENSORS FOR MEDICINE AND SCIENCE,
Inc.; and

CONTINUOUS GLUCOSE MONITORING SYSTEM by DEXCOM, Inc.

30 Still yet, other examples of the continuous monitoring sensors and related
systems/devices may include, but not limited thereto, the following technologies as

discussed in the following references, of which are hereby incorporated by reference herein in their entirety:

1. Diabetes Technol Ther. 2003;5(4):609-14, "Continuous Glucose Monitoring: Reliable Measurements for Up to 4 Days with the SCGM1 System," Kapitza C, Lodwig V, Obermaier K, Wientjes KJ, Hoogenberg K, Jungheim K, Heinemann L; Glucose Monitoring Study Group;
2. Diabetes Technol Ther. 2003;5(4):572-86, "Continuous Glucose Monitoring with Glucose Sensors: Calibration and Assessment Criteria," Lodwig V, Heinemann L; Glucose Monitoring Study Group; and
3. Diabetes Metab. 2003 Apr; 29(2 Pt 1): 159-62, "Accuracy of the Continuous Glucose Monitoring System in Inpatient and Outpatient Conditions," Djakoure-Platonoff C, Radermercker R, Reach G, Slama G, Selam JI.

Next, examples of reference monitoring devices **530** and related systems/devices may include, but not limited thereto, the following technologies as discussed in the following U.S. patents, U.S. Applications, or PCT publications and of which are hereby incorporated by reference herein in their entirety:

1. International Patent Application No. PCT/US01/09884, filed March 29, 2001, entitled "Method, System, and Computer Program Product for the Evaluation of Glycemic Control in Diabetes from Self-monitoring Data," and corresponding U.S. Patent Application Serial No.:10/240,228, filed September 26, 2002, entitled "Method, System, and Computer Program Product for the Evaluation of Glycemic Control in Diabetes from Self-monitoring Data," and are commonly owned with the present Assignee; and
2. International Patent Application No. PCT/US2003/025053, filed August 8, 2003, entitled "Method, System, and Computer Program Product for the Processing of Self-monitoring Glucose (SMBG) Data to Enhance Diabetic Self-management," and corresponding U.S. Patent Application Serial No.:10/524,094, filed February 9, 2005, entitled "Managing and Processing of Self-monitoring Glucose (SMBG) Data to Enhance Diabetic Self-management." and are commonly owned with the present Assignee.

Additional examples of reference monitoring devices **530** and related systems/devices may include, but not limited thereto, the following technologies: Beckman glucose analyzers; glucose oxidase method, YSI Instruments, Yellow Springs, Ohio, and finger stick glucose meters used by professional personnel, as well as patients

for example.

Turning to **FIG. 6**, **FIG. 6** is a functional block diagram for a computer system for implementation of an exemplary embodiment or portion of an embodiment of present invention. For example, a method of an embodiment of the present invention may be implemented using hardware, software or a combination thereof and may be implemented in one or more computer systems or other processing systems, such as personal digit assistants (PDAs), or directly in a continuous (or semi-continuous) blood glucose monitor or reference glucose monitor. In an example embodiment, an embodiment of the invention was implemented in software running on a general purpose computer **600** as illustrated in **FIG. 6**. Computer system **600** includes one or more processors, such as processor **604**. Processor **604** is connected to a communication infrastructure **606** (e.g., a communications bus, cross-over bar, or network). Computer system **600** may include a display interface **602** that forwards graphics, text, and other data from the communication infrastructure **606** (or from a frame buffer not shown) for display on the display unit **630**.

Computer system **600** also includes a main memory **608**, preferably random access memory (RAM), and may also include a secondary memory **610**. The secondary memory **610** may include, for example, a hard disk drive **612** and/or a removable storage drive **614**, representing a floppy disk drive, a magnetic tape drive, an optical disk drive, a flash memory, etc. The removable storage drive **614** reads from and/or writes to a removable storage unit **618** in a well known manner. Removable storage unit **618**, represents a floppy disk, magnetic tape, optical disk, etc. which is read by and written to by removable storage drive **614**. As will be appreciated, the removable storage unit **618** includes a computer usable storage medium having stored therein computer software and/or data.

In alternative embodiments, secondary memory **610** may include other means for allowing computer programs or other instructions to be loaded into computer system **600**. Such means may include, for example, a removable storage unit **622** and an interface **620**. Examples of such removable storage units/interfaces include a program cartridge and cartridge interface (such as that found in video game devices), a removable memory chip (such as a ROM, PROM, EPROM or EEPROM) and associated socket, and other removable storage units **622** and interfaces **620** which allow software and data to be transferred from the removable storage unit **622** to computer system **600**.

Computer system **600** may also include a communications interface **624**. Communications interface **624** allows software and data to be transferred between computer system **600** and external devices. Examples of communications interface **624** may include a modem, a network interface (such as an Ethernet card), a communications port (e.g., serial or parallel, etc.), a PCMCIA slot and card, a modem, etc. Software and data transferred via communications interface **624** are in the form of signals **628** which may be electronic, electromagnetic, optical or other signals capable of being received by communications interface **624**. Signals **628** are provided to communications interface **624** via a communications path (i.e., channel) **626**. Channel **626** carries signals **628** and may be implemented using wire or cable, fiber optics, a phone line, a cellular phone link, an RF link, an infrared link, and other communications channels.

In this document, the terms “computer program medium” and “computer usable medium” are used to generally refer to media such as removable storage drive **614**, a hard disk installed in hard disk drive **612**, and signals **628**. These computer program products are means for providing software to computer system **600**. The invention includes such computer program products.

Computer programs (also called computer control logic) are stored in main memory **608** and/or secondary memory **610**. Computer programs may also be received via communications interface **624**. Such computer programs, when executed, enable computer system **600** to perform the features of the present invention as discussed herein. In particular, the computer programs, when executed, enable processor **604** to perform the functions of the present invention. Accordingly, such computer programs represent controllers of computer system **600**.

In an embodiment where the invention is implemented using software, the software may be stored in a computer program product and loaded into computer system **600** using removable storage drive **614**, hard drive **612** or communications interface **624**. The control logic (software), when executed by the processor **604**, causes the processor **604** to perform the functions of the invention as described herein.

In another embodiment, the invention is implemented primarily in hardware using, for example, hardware components such as application specific integrated circuits (ASICs). Implementation of the hardware state machine to perform the functions described herein will be apparent to persons skilled in the relevant art(s).

In yet another embodiment, the invention is implemented using a combination of both hardware and software.

In an example software embodiment of the invention, the methods described above were implemented in SPSS control language, but could be implemented in other programs such as, but not limited to, C++ programming language or other programs available to those skilled in the art.

In summary, an advantage associated with some of the various embodiments of the present invention includes, but not limited thereto, that this is the first method of evaluation of the clinical accuracy of continuous glucose sensors in terms of both point and rate precision. It should be appreciated that there is rapidly growing number of companies manufacturing devices, including major companies in the diabetes home monitoring market. Each new device, or each device modification, would require numerous evaluations prior to its submission to FDA. Additional evaluations will be required by FDA during their approval process. Typically, after approval a number of research studies and clinical trials involve device accuracy assessment in various patient subgroups or subject patient groups.

Thus, for example, the present invention CG-EGA can become a standard for, among other things, evaluation of the new CGS devices. Moreover, the request for service computing CG-EGA would be significant, and growing. Still yet, the software associate with the present invention may be distributed, or the computation could be provided on-line, such as on-line for-fee service for example.

Still other embodiments will become readily apparent to those skilled in this art from reading the above-recited detailed description and drawings of certain exemplary embodiments. It should be understood that numerous variations, modifications, and additional embodiments are possible, and accordingly, all such variations, modifications, and embodiments are to be regarded as being within the spirit and scope of the appended claims. For example, regardless of the content of any portion (e.g., title, section, abstract, drawing figure, etc.) of this application, unless clearly specified to the contrary, there is no requirement for any particular described or illustrated activity or element, any particular sequence of such activities, any particular size, speed, material, dimension, time period, or frequency, or any particular interrelationship of such elements. Moreover, any activity can be repeated, any activity can be performed by multiple entities, and/or any element

can be duplicated. Further, any activity or element can be excluded, the sequence of activities can vary, and/or the interrelationship of elements can vary. Accordingly, the descriptions and drawings are to be regarded as illustrative in nature, and not as restrictive.

5 The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting of the invention described herein.

10 References

The following references as cited throughout this document are hereby incorporated by reference herein in their entirety:

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Understanding error grid analysis. *Diabetes Care* 20: 911-912, 1997.

CLAIMS

We claim:

1. A method for evaluating accuracy of a glucose monitoring sensor, said method comprising:
 - 5 evaluating point accuracy of blood glucose (BG) values received from said monitoring sensor;
 - evaluating accuracy of direction and rate of BG fluctuations received from said monitoring sensor; and
 - combining said point accuracy and rate accuracy in an estimate of sensor
- 10 precision.
2. The method of claim 1, wherein said estimate of sensor precision comprises:
 - performing a combination of three grids adapted specifically for hypoglycemic,
- 15 euglycemic, and hyperglycemic BG ranges.
3. The method of claim 2, wherein said estimate of sensor precision includes solely a single estimate using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.
- 20
4. The method of claim 2, wherein said estimate of sensor precision includes a plurality of estimates using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.
- 25
5. The method of claim 1, wherein said method is for use with a subject, wherein said subject is a human or an animal.
6. The method of claim 1, wherein said sensor comprises a continuous glucose monitor or semi-continuous glucose monitor or combination of both.
- 30
7. The method of claim 1, wherein:
 - said accuracy evaluation of direction and rate of BG fluctuations includes

performing rate error-grid analysis (R-EGA), and
said accuracy evaluation blood glucose (BG) values includes performing
point error-grid analysis (P-EGA) that determines correct presentation of said
blood glucose (BG) values.

5

8. The method of claim 7, wherein said estimate of sensor precision
comprises:

performing a combination of three grids adapted specifically for hypoglycemic,
euglycemic, and hyperglycemic BG ranges.

10

9. The method of claim 8, wherein said estimate of sensor precision includes
solely a single estimate using a weighted combination of hypoglycemic, euglycemic,
hyperglycemic BG ranges.

15

10. The method of claim 8, wherein said estimate of sensor precision includes
a plurality of estimates using a weighted combination of hypoglycemic, euglycemic,
hyperglycemic BG ranges.

11. The method of claim 7, wherein said method is for use with a subject,
wherein said subject is a human or an animal.

20

12. The method of claim 7, wherein said sensor comprises a continuous
glucose monitor or semi-continuous glucose monitor or combination of both.

13. The method of claim 7, wherein said rate error-grid analysis (R-EGA)
includes:

25

for each pair of reference BG points, $RBG(t_1)$ and $RBG(t_2)$, received from a
reference blood glucose monitoring device, taken at times t_1 and t_2 , a reference BG rate is
estimated as the ratio of the change in the BG points divided by the length of the elapsed
time interval as follows:

30

reference BG rate of change (mg/dl/min) = $(RBG(t_2) - RBG(t_1)) / (t_2 - t_1)$.

14. The method of claim 13, wherein said rate said error-grid analysis (R-EGA) further includes:

for each pair of sensor reported BG points, SBG(t₁) and SBG(t₂), received from said glucose monitoring sensor, taken at times t₁ and t₂, a sensor BG rate is estimated as:

5 sensor BG rate of change (mg/dl/min) = (SBG(t₂)-SBG(t₁))/(t₂-t₁).

15. The method of claim 14, wherein said rate said error-grid analysis (R-EGA) further includes:

10 scatter plotting said sensor BG rate of change against said reference BG rate of change.

16. The method of claim 15, wherein said rate said error-grid analysis (R-EGA) further includes dividing said scatter plot into accuracy zones.

15 17. The method of claim 16, wherein said accuracy zones comprise A through E accuracy zones, which have a clinical meaning similar to the clinical meaning of the conventional Error Grid Analysis (EGA).

18. The method of claim 17, wherein said clinical meanings are defined as
20 follows:

- (a) AR-zone (accurate);
 - (b) CR-zone (over-correction);
 - (c) DR-zone (failure to detect);
 - (d) ER-zone (erroneous reading); and
 - 25 (e) BR-zone (benign errors),
- wherein suffix R stands for rate.

19. The method of claim 18, wherein said rate error-grid analysis (R-EGA) further includes:
30 computing said R-EGA zones for each pair of said reference-sensor BG rates of change using the formulas below, wherein X is abbreviated for said reference BG rate of change and wherein Y is abbreviated for said sensor BG rate of change:

IF (Y $\geq$ X) RZONE=5,
 IF (Y $\geq$ (X+1) and X $\geq$ 0-2 and X $\leq$ 1) RZONE=4,
 IF (Y $\geq$ 0.5 X and X $\leq$ 0-2) RZONE=4,
 IF (Y $\geq$ 2.0 X and X $\geq$ 1) RZONE=4,
 5 IF (Y $\geq$ (X+2) and X $\geq$ 0-1 and X $\leq$ 1) RZONE=3,
 IF (Y $\geq$ (X+2) and X $\geq$ 0-3 and X $\leq$ 0-1) RZONE=2,
 IF (Y $\geq$ 0-1 and X $\leq$ 0-3) RZONE=2,
 IF (Y $\geq$ 1 and X $\leq$ 0-1) RZONE=1,
 IF (Y $\leq$ X) RZONE=6,
 10 IF (Y $\leq$ (X-1) and X $\geq$ 0-1 and X $\leq$ 2) RZONE=7,
 IF (Y $\leq$ 2.0 X and X $\leq$ 0-1) RZONE=7,
 IF (Y $\leq$ 0.5 X and X $\geq$ 2) RZONE=7,
 IF (Y $\leq$ (X-2) and X $\geq$ 0-1 and X $\leq$ 1) RZONE=8,
 IF (Y $\leq$ (X-2) and X $\geq$ 1 and X $\leq$ 3) RZONE=9,
 15 IF (Y $\leq$ 1 and X $\geq$ 3) RZONE=9, and
 IF (Y $\leq$ 0-1 and X $\geq$ 1) RZONE=10,

wherein the output of this computation is a zone, coded as follows:

1-uE 2-uD 3-uC 4-uB 5-uA 6-lA 7-lB 8-lC 9-lD 10-lE.

20 20. The method of claim 13, wherein said glucose monitoring sensor comprises at least one of Beckman glucose analyzer, glucose oxidase analyzer, YSI Instruments analyzer and finger stick glucose meters, or any combination thereof.

25 21. The method of claim 7, wherein said point error-grid analysis (P-EGA) includes:

scatter plotting said point error-grid analysis (P-EGA) for said sensor BG rate against a reference BG rate computed from the data of a reference monitoring device, wherein said scatter plot is divided into A_P, B_P, C_P, D_P, and E_P zones, wherein suffix "P" stands for point.

30

22. The method of claim 21, wherein said B_P zone is divided into upper B_P zone and lower B_P zone;

said C_P zone is divided into upper C_P zone and lower C_P zone;
said D_P zone is divided into upper D_P zone and lower D_P zone; and
said E_P zone is divided into upper E_P zone and lower E_P zone.

5 23. The method of claim 22, wherein said point error-grid analysis (P-EGA) includes:

said zones are defined depending on the reference rate of BG change classified as follows:

- (a) slow change range;
- 10 (b) moderate decrease range;
- (c) moderate increase range;
- (d) rapid decrease range; and
- (e) rapid increase range.

15 24. The method of claim 23, wherein said classification of reference BG change comprises:

- (a) said slow change range being about -1 and about 1 mg/dl/min;
- (b) moderate decrease range being about -2 and about -1 mg/dl/min;
- (c) moderate increase range being about 1 and about 2 mg/dl/min;
- 20 (d) rapid decrease range being less than about -2 mg/dl/min; and
- (e) rapid increase range being greater than about 2mg/dl/min.

 25. The method of claim 24, wherein said point error-grid analysis (P-EGA) includes:

25 said zones are defined depending on the reference rate of BG change as follows:

- (a) if the reference BG rate is within said slow change range, said P-EGA zones are identical to the zones of the conventional EGA;
- (b) if the reference BG is falling at a rate within said moderate increase range, the upper limits of upper said A_P, B_P, and D_P zones are expanded by about 10
- 30 mg/dl,

 and if the reference BG is falling faster than said rapid decrease range, the upper limits of upper A_P, B_P, and D_P zones are expanded by about 20 mg/dl; and

- (c) if the reference BG is rising at a rate within said moderate increase, the lower limits of lower A_P , B_P , and D_P zones are expanded by about 10 mg/dl, and if the reference BG is rising faster than said rapid increase range, the lower limits of lower said A_P , B_P , and D_P zones are expanded by about 20 mg/dl.

5

26. The method of claim 23, wherein said point error-grid analysis (P-EGA) further includes:

computing said P-EGA zones for each pair of said reference-sensor BG readings using the formulas below:

- 10 a) if the BG rate of change is in said slow change range, apply the formulas: wherein $U1$ is abbreviated for said Reference BG, wherein $W1$ is abbreviated for said Sensor BG,

IF ($W1 \geq U1$) $ZONE0=5$,

IF ($W1 \geq 1.20 U1$ and $U1 > 70$) $ZONE0=4$,

15 IF ($W1 \geq (1.03 U1 + 107.9)$ and $U1 > 70$) $ZONE0=3$,

IF ($W1 \geq 1.20 U1$ and $W1 > 70$ and $U1 \leq 70$) $ZONE0=2$,

IF ($W1 \geq 180$ and $U1 \leq 70$) $ZONE0=1$,

IF ($W1 < U1$) $ZONE0=6$,

IF ($W1 \leq 0.8 U1$ and $U1 > 70$) $ZONE0=7$,

20 IF ($W1 \leq (1.4 U1 - 182)$ and $U1 \leq 180$) $ZONE0=8$,

IF ($U1 \geq 240$ and $W1 > 70$ and $W1 < 180$) $ZONE0=9$, and

IF ($U1 > 180$ and $W1 \leq 70$) $ZONE0=10$;

- b) if BG is falling at said moderate rate apply the formulas:

wherein $U2$ is abbreviated for said Reference BG,

25 wherein $W2$ is abbreviated for said Sensor BG,

IF ($W2 \geq U2$) $ZONE2=5$,

IF ($W2 \geq (1.20 U2 + 10)$ and $U2 > 70$) $ZONE2=4$,

IF ($W2 \geq (1.03 U2 + 117.9)$ and $U2 > 70$) $ZONE2=3$,

IF ($W2 \geq (1.20 U2 + 10)$ and $W2 > 80$ and $U2 \leq 70$) $ZONE2=2$,

30 IF ($W2 \geq 190$ and $U2 \leq 70$) $ZONE2=1$,

IF ($W2 < U2$) $ZONE2=6$,

IF ($W2 \leq 0.8 U2$ and $U2 > 70$) $ZONE2=7$,

IF (W2 $\leq$ (1.4 U2-182) and U2 $\leq$ 180) ZONE2=8,
 IF (U2 $\geq$ 240 and W2 $\geq$ 70 and W2 $\leq$ 180) ZONE2=9, and
 IF (U2 $\geq$ 180 and W2 $\leq$ 70) ZONE2=10;

c) if BG is falling at said rapid rate use the formulas:

5 wherein U4 is abbreviated for said Reference BG,
 wherein W4 is abbreviated for said Sensor BG,
 IF (W4 $\geq$ U4) ZONE4=5,
 IF (W4 $\geq$ (1.20 U4+20) and U4 $\geq$ 70) ZONE4=4,
 IF (W4 $\geq$ (1.03 U4+127.9) and U4 $\geq$ 70) ZONE4=3,
 10 IF (W4 $\geq$ (1.20 U4+20) and W4 $\geq$ 90 and U4 $\leq$ 70) ZONE4=2,
 IF (W4 $\geq$ 200 and U4 $\leq$ 70) ZONE4=1,
 IF (W4 $\leq$ U4) ZONE4=6,
 IF (W4 $\leq$ 0.8 U4 and U4 $\geq$ 70) ZONE4=7,
 IF (W4 $\leq$ (1.4 U4-182) and U4 $\leq$ 180) ZONE4=8,
 15 IF (U4 $\geq$ 240 and W4 $\geq$ 70 and W4 $\leq$ 180) ZONE4=9, and
 IF (U4 $\geq$ 180 and W4 $\leq$ 70) ZONE4=10;

d) if BG is rising at said moderate rate use the formulas:

wherein U1 is abbreviated for said Reference BG,
 wherein SENBG is abbreviated for said Sensor BG,
 20 IF (W1 $\geq$ U1) ZONE1=5,
 IF (W1 $\geq$ 1.20 U1 and U1 $\geq$ 70) ZONE1=4,
 IF (W1 $\geq$ (1.03 U1+107.9) and U1 $\geq$ 70) ZONE1=3,
 IF (W1 $\geq$ 1.20 U1 and W1 $\geq$ 70 and U1 $\leq$ 70) ZONE1=2,
 IF (W1 $\geq$ 180 and U1 $\leq$ 70) ZONE1=1,
 25 IF (W1 $\leq$ U1) ZONE1=6,
 IF (W1 $\leq$ (0.8 U1-10) and U1 $\geq$ 70) ZONE1=7,
 IF (W1 $\leq$ (1.4 U1-192) and U1 $\leq$ 180) ZONE1=8,
 IF (U1 $\geq$ 240 and W1 $\geq$ 60 and W1 $\leq$ 170) ZONE1=9, and
 IF (U1 $\geq$ 180 and W1 $\leq$ 60) ZONE1=10; and

30 e) if BG is rising at said rapid rate use the formulas:

wherein U3 is abbreviated for said Reference BG,
 wherein W3 is abbreviated for said Sensor BG,

IF (W3 ge U3) ZONE3=5,
 IF (W3 ge 1.20 U3 and U3 gt 70) ZONE3=4,
 IF (W3 ge (1.03 U3+107.9) and U3 gt 70) ZONE3=3,
 IF (W3 ge 1.20 U3 and W3 gt 70 and U3 le 70) ZONE3=2,
 5 IF (W3 ge 180 and U3 le 70) ZONE3=1,
 IF (W3 lt U3) ZONE3=6. U3 gt 70) ZONE3=7,
 IF (W3 le (1.4 U3-202) and U3 le 180) ZONE3=8,
 IF (U3 ge 240 and W3 gt 50 and W3 lt 160) ZONE3=9,
 IF (U3 gt 180 and W3 le 50) ZONE3=10, and
 10 IF (W3 le (0.8 U3-20),

wherein the output of this computation is a zone, coded as follows:

1-uE, 2-uD, 3-uC, 4-uB, 5-uA, 6-1A, 7-1B, 8-1C, 9-1D, 10-1E.

27. The method of claim 7, comprises:
 15 splitting reference BG values received from a reference BG monitoring device into
 three clinically meaningful regions including hypoglycemia, euglycemia and
 hyperglycemia regions; and
 combining results from the rate error-grid analysis (R-EGA) and point error-grid
 analysis (P-EGA) within each of these regions.

20 28. The method of claim 27, wherein:
 said hypoglycemia region is defined as $BG \leq 70 \text{ mg/dl}$ (3.9 mmol/l);
 said euglycemia region is defined as 70 mg/dl (3.9 mmol/l) $< BG < 180 \text{ mg/dl}$ (10
 mmol/l), and
 25 said hyperglycemia region defined as $BG > 180 \text{ mg/dl}$ (10 mmol/l).

29. The method of claim 28, further comprising :
 as presented in table below:

Point Error-Grid Zones				
Hypoglycemia BG < 70 mg/dl				
Rate Error- Grid Zones		A	D	E
	A	60%	10%	3%
	B	10%	5%	2%
	uC	3%	1%	0%
	lC	2%	1%	0%
	uD	1%	1%	0%
	lD	1%	0%	0%
	uE	0%	0%	0%
	lE	0%	0%	0%

providing a relationship of said R-EGA and P-EGA values of said sensor in a hypoglycemic range according to a table including rows of said R-EGA values and columns of P-EGA values.

5

30. The method of claim 29, wherein said R-EGA and P-EGA values will be considered accurate if a value falls in the A_P zone of the P-EGA column of the table and said same value falls in the A_R or B_R zones of the R-EGA rows of the table, as denoted by the white section of the table of claim 28.

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31. The method of claim 29, wherein said R-EGA and P-EGA values will be considered clinically erroneous if a value falls in the

D_P zone or E_P zone of the P-EGA column of the table, or

15 A_P zone of the P-EGA column of the table and said same value falls in the u_D or u_E zones of the R-EGA rows of the table, as denoted by the shaded section of the table in claim 28.

20 32. The method of claim 29, wherein said R-EGA and P-EGA values will be considered benign errors if a value falls A_P zone of the P-EGA column of the table and said same value falls in the u_C , l_C , l_D , or l_E zones of the R-EGA rows of the table, as denoted by the horizontal hash section of the table in claim 28.

33. The method of claim 29, further comprising :
as presented in table below:

Point Error-Grid Zones				
Euglycemia 70<BG<180mg/dl				
Rate Error- Grid Zones		A	B	C
	A	60%	13%	0%
	B	12%	5%	0%
	uC	4%	1%	0%
	lC	1%	1%	0%
	uD	1%	0%	0%
	lD	1%	1%	0%
	uE	0%	0%	0%
	lE	0%	0%	0%

providing a relationship of said R-EGA and P-EGA values of said sensor in a
5 euglycemia range according to a table including rows of said R-EGA values and columns
of P-EGA values.

34. The method of claim 33, wherein said R-EGA and P-EGA values will be
considered accurate if a value falls in the A_P zone or B_P zone of the P-EGA columns of
10 the table and said same value falls in the A_R or B_R zones of the R-EGA rows of the table,
as denoted by the white section of the table of claim 32.

35. The method of claim 33, wherein said R-EGA and P-EGA values will be
considered clinically erroneous if a value falls in the
15 A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in
the uE or lE of the R-EGA rows of the table; or
C_P zone of the P-EGA column of the table, as denoted by the shaded section of the
table in claim 32.

20 36. The method of claim 33, wherein said R-EGA and P-EGA values will be
considered benign errors if a value falls in the
A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in

the uC, IC, uD or ID of the R-EGA rows of the table, as denoted by the horizontal hash section of the table in claim 32.

37. The method of claim 33, further comprising :

as presented in table below:

Point Error-Grid Zones						
Hyperglycemia BG > 180 mg/dl						
Rate Error- Grid Zones		A	B	C	D	E
	A	60%	8%	3%	3%	0%
	B	7%	5%	2%	2%	0%
	uC	2%	1%	0%	0%	0%
	IC	3%	1%	0%	0%	0%
	uD	1%	1%	0%	0%	0%
	ID	1%	0%	0%	0%	0%
	uE	0%	0%	0%	0%	0%
	IE	0%	0%	0%	0%	0%

providing a relationship of said R-EGA and P-EGA values of said sensor in a hyperglycemia range according to a table including rows of said R-EGA values and columns of P-EGA values.

38. The method of claim 37, wherein said R-EGA and P-EGA values will be considered accurate if a value falls in the A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the A_R or B_R zones of the R-EGA rows of the table, as denoted by the white section of the table of claim 36.

39. The method of claim 37, wherein said R-EGA and P-EGA values will be considered clinically erroneous if a value falls in the

A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the ID, uE or IE of the R-EGA rows of the table; or

C_P zone, D_P zone or E_P zone of the P-EGA column of the table, as denoted by the shaded section of the table of claim 36.

40. The method of claim 37, wherein said R-EGA and P-EGA values will be considered benign errors if a value falls in the

A_p zone or B_p zone of the P-EGA columns of the table and said same value falls in
5 the uC, IC or uD of the R-EGA rows of the table, as denoted by the horizontal hash section of the table of claim 36.

41. The method of claim 37, comprising:
combining the results from tables of claims 28, 32 and 36 into a single accuracy
10 estimate of a sensor using a linear weighted combination.

42. The method of claim 41, said combining of the R-EGA and P-EGA zone as according to the following formulas:

A (Accurate Readings) = $w_1 * A_1 + w_2 * A_2 + w_3 * A_3$,

15 B (Benign Errors) = $w_1 * B_1 + w_2 * B_2 + w_3 * B_3$,

Err (Erroneous Readings) = $w_1 * Err_1 + w_2 * Err_2 + w_3 * Err_3$, wherein:

A_1 , B_1 , Err_1 are percentages of accurate readings, benign errors, and erroneous readings during hypoglycemia;

A_2 , B_2 , Err_2 are the percentages of accurate readings, benign errors, and
20 erroneous readings during euglycemia, and

A_3 , B_3 , Err_3 are the percentages of accurate readings, benign errors, and erroneous readings during hyperglycemia, and wherein the weights w_1 , w_2 , w_3 are assigned to the hypoglycemic, euglycemic, and hyperglycemic BG ranges.

25 43. The method of claim 42, wherein said weights are about 0.07, about 0.53, and about 0.40 for hypoglycemic, euglycemic, and hyperglycemic ranges, respectively.

44. A system for evaluating accuracy of a glucose monitoring sensor, said system comprising a microprocessor programmed to perform the following:

30 evaluate point accuracy of blood glucose (BG) values received from said monitoring sensor;

evaluate accuracy of direction and rate of BG fluctuations received from said

monitoring sensor; and

combining said point accuracy and rate accuracy in an estimate of sensor precision.

5 45. The system of claim 44, wherein said estimate of sensor precision comprises:

performing a combination of three grids adapted specifically for hypoglycemic, euglycemic, and hyperglycemic BG ranges.

10 46. The system of claim 45, wherein said estimate of sensor precision includes solely a single estimate using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

15 47. The system of claim 45, wherein said estimate of sensor precision includes a plurality of estimates using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

 48. The system of claim 44, wherein said system is for use with a subject, wherein said subject is a human or an animal.

20 49. The system of claim 44, wherein said sensor comprises a continuous glucose monitor or semi-continuous glucose monitor or combination of both.

 50. The system of claim 44, wherein:
25 said accuracy evaluation of direction and rate of BG fluctuations includes performing rate error-grid analysis (R-EGA), and
 said accuracy evaluation blood glucose (BG) values includes performing point error-grid analysis (P-EGA) that determines correct presentation of said blood glucose (BG) values.

30 51. The system of claim 50, wherein said estimate of sensor precision comprises:

performing a combination of three grids adapted specifically for hypoglycemic, euglycemic, and hyperglycemic BG ranges.

52. The system of claim 51, wherein said estimate of sensor precision includes
5 solely a single estimate using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

53. The system of claim 51, wherein said estimate of sensor precision includes
a plurality of estimates using a weighted combination of hypoglycemic, euglycemic,
10 hyperglycemic BG ranges.

54. The system of claim 50, wherein system is for use with a subject, wherein
said subject is a human or an animal.

55. The system of claim 50, wherein said sensor comprises a continuous
15 glucose monitor or semi-continuous glucose monitor or combination of both.

56. The system of claim 50, wherein said rate error-grid analysis (R-EGA)
includes:
20 for each pair of reference BG points, $RBG(t_1)$ and $RBG(t_2)$ received from a
reference blood glucose monitoring device, taken at times t_1 and t_2 , a reference BG rate is
estimated as the ratio of the change in the BG points divided by the length of the elapsed
time interval as follows:

$$\text{reference BG rate of change (mg/dl/min)} = (RBG(t_2) - RBG(t_1)) / (t_2 - t_1).$$

25 57. The system of claim 56, wherein said rate said error-grid analysis (R-EGA)
further includes:

for each pair of sensor reported BG points, $SBG(t_1)$ and $SBG(t_2)$,) received from
said glucose monitoring sensor, taken at times t_1 and t_2 , a sensor BG rate is estimated as:
30 sensor BG rate of change (mg/dl/min) = $(SBG(t_2) - SBG(t_1)) / (t_2 - t_1)$.

58. The system of claim 57, wherein said rate said error-grid analysis (R-EGA)

further includes:

scatter plotting said sensor BG rate of change against said reference BG rate of change.

5 59. The system of claim 58, wherein said rate said error-grid analysis (R-EGA) further includes dividing said scatter plot into accuracy zones.

60. The system of claim 59, wherein said accuracy zones comprise A through E accuracy zones, which have a clinical meaning similar to the clinical meaning of the
10 conventional Error Grid Analysis (EGA).

61. The system of claim 60, wherein said clinical meanings are defined as follows:

- (a) AR-zone (accurate);
 - 15 (b) CR-zone (over-correction);
 - (c) DR-zone (failure to detect);
 - (d) ER-zone (erroneous reading); and
 - (e) BR-zone (benign errors),
- wherein suffix R stands for rate.

20

62. The system of claim 61, wherein said rate error-grid analysis (R-EGA) further includes:

computing said R-EGA zones for each pair of said reference-sensor BG rates of change using the formulas below, wherein X is abbreviated for said reference BG rate of change and wherein Y is abbreviated for said sensor BG rate of change:
25

- IF (Y $\geq$ X) RZONE=5,
- IF (Y $\geq$ (X+1) and X $\geq$ 0-2 and X $\leq$ 1) RZONE=4,
- IF (Y $\geq$ 0.5 X and X $\leq$ 0-2) RZONE=4,
- IF (Y $\geq$ 2.0 X and X $\geq$ 1) RZONE=4,
- 30 IF (Y $\geq$ (X+2) and X $\geq$ 0-1 and X $\leq$ 1) RZONE=3,
- IF (Y $\geq$ (X+2) and X $\geq$ 0-3 and X $\leq$ 0-1) RZONE=2,
- IF (Y $\geq$ 0-1 and X $\leq$ 0-3) RZONE=2,

IF (Y $\geq$ 1 and X $\leq$ 0.1) RZONE=1,
 IF (Y $\leq$ X) RZONE=6,
 IF (Y $\leq$ (X-1) and X $\geq$ 0.1 and X $\leq$ 2) RZONE=7,
 IF (Y $\leq$ 2.0 X and X $\leq$ 0.1) RZONE=7,
 5 IF (Y $\leq$ 0.5 X and X $\geq$ 2) RZONE=7,
 IF (Y $\leq$ (X-2) and X $\geq$ 0.1 and X $\leq$ 1) RZONE=8,
 IF (Y $\leq$ (X-2) and X $\geq$ 1 and X $\leq$ 3) RZONE=9,
 IF (Y $\leq$ 1 and X $\geq$ 3) RZONE=9, and
 IF (Y $\leq$ 0.1 and X $\geq$ 1) RZONE=10,
 10 wherein the output of this computation is a zone, coded as follows:
 1-uE 2-uD 3-uC 4-uB 5-uA 6-lA 7-lB 8-lC 9-lD 10-lE.

63. The system of claim 56, wherein said glucose monitoring sensor comprises
 at least one of Beckman glucose analyzers, glucose oxidase analyzer, YSI Instruments
 15 analyzer and finger stick glucose meters, or any combination thereof.

64. The system of claim 50, wherein said point error-grid analysis (P-EGA)
 includes:
 scatter plotting said point error-grid analysis (P-EGA) for said sensor BG rate
 20 against a reference BG rate computed from the data of a reference monitoring device,
 wherein said scatter plot is divided into A_P , B_P , C_P , D_P , and E_P zones, wherein suffix "P"
 stands for point.

65. The system of claim 64, wherein
 25 said B_P zone is divided into upper B_P zone and lower B_P zone;
 said C_P zone is divided into upper C_P zone and lower C_P zone;
 said D_P zone is divided into upper D_P zone and lower D_P zone; and
 said E_P zone is divided into upper E_P zone and lower E_P zone.

66. The system of claim 65, wherein said point error-grid analysis (P-EGA)
 includes:
 said zones are defined depending on the reference rate of BG change classified as

follows:

- (a) slow change range;
- (b) moderate decrease range;
- (c) moderate increase range;
- 5 (d) rapid decrease range; and
- (e) rapid increase range.

67. The system of claim 66, wherein said classification of reference BG change comprises:

- 10 (a) said slow change range being about -1 and about 1 mg/dl/min;
- (b) moderate decrease range being about -2 and about -1 mg/dl/min;
- (c) moderate increase range being about 1 and about 2 mg/dl/min;
- (d) rapid decrease range being less than about -2 mg/dl/min; and
- (e) rapid increase range being greater than about 2 mg/dl/min.

15

68. The system of claim 67, wherein said point error-grid analysis (P-EGA) includes:

said zones are defined depending on the reference rate of BG change as follows:

- (a) if the reference BG rate is within said slow change range, said P-EGA
20 zones are identical to the zones of the conventional EGA;
- (b) if the reference BG is falling at a rate within said moderate increase range,
the upper limits of upper said A_P , B_P , and D_P zones are expanded by about 10
mg/dl,
and if the reference BG is falling faster than said rapid decrease range, the
25 upper limits of upper A_P , B_P , and D_P zones are expanded by about 20 mg/dl; and
- (c) if the reference BG is rising at a rate within said moderate increase, the
lower limits of lower A_P , B_P , and D_P zones are expanded by about 10 mg/dl,
and if the reference BG is rising faster than said rapid increase range, the
lower limits of lower said A_P , B_P , and D_P zones are expanded by about 20 mg/dl.

30

69. The system of claim 66, wherein said point error-grid analysis (P-EGA) further includes:

computing said P-EGA zones for each pair of said reference-sensor BG readings using the formulas below:

a) if the BG rate of change is in said slow change rate, apply the formulas:

wherein U1 is abbreviated for said Reference BG,

wherein W1 is abbreviated for said Sensor BG,

IF (W1 $\geq$ U1) ZONE0=5,

IF (W1 $\geq$ 1.20 U1 and U1 $>$ 70) ZONE0=4,

IF (W1 $\geq$ (1.03 U1+107.9) and U1 $>$ 70) ZONE0=3,

IF (W1 $\geq$ 1.20 U1 and W1 $>$ 70 and U1 $\leq$ 70) ZONE0=2,

IF (W1 $\geq$ 180 and U1 $\leq$ 70) ZONE0=1,

IF (W1 $<$ U1) ZONE0=6,

IF (W1 $\leq$ 0.8 U1 and U1 $>$ 70) ZONE0=7,

IF (W1 $\leq$ (1.4 U1-182) and U1 $\leq$ 180) ZONE0=8,

IF (U1 $\geq$ 240 and W1 $>$ 70 and W1 $<$ 180) ZONE0=9, and

IF (U1 $>$ 180 and W1 $\leq$ 70) ZONE0=10;

b) if BG is falling said moderate rate apply the formulas:

wherein U2 is abbreviated for said Reference BG,

wherein W2 is abbreviated for said Sensor BG,

IF (W2 $\geq$ U2) ZONE2=5,

IF (W2 $\geq$ (1.20 U2+10) and U2 $>$ 70) ZONE2=4,

IF (W2 $\geq$ (1.03 U2+117.9) and U2 $>$ 70) ZONE2=3,

IF (W2 $\geq$ (1.20 U2+10) and W2 $>$ 80 and U2 $\leq$ 70) ZONE2=2,

IF (W2 $\geq$ 190 and U2 $\leq$ 70) ZONE2=1,

IF (W2 $<$ U2) ZONE2=6,

IF (W2 $\leq$ 0.8 U2 and U2 $>$ 70) ZONE2=7,

IF (W2 $\leq$ (1.4 U2-182) and U2 $\leq$ 180) ZONE2=8,

IF (U2 $\geq$ 240 and W2 $>$ 70 and W2 $<$ 180) ZONE2=9, and

IF (U2 $>$ 180 and W2 $\leq$ 70) ZONE2=10;

c) if BG is falling at said rapid rate use the formulas:

wherein U4 is abbreviated for said Reference BG,

wherein W4 is abbreviated for said Sensor BG,

IF (W4 $\geq$ U4) ZONE4=5,

- IF (W4 ge (1.20 U4+20) and U4 gt 70) ZONE4=4,
 IF (W4 ge (1.03 U4+127.9) and U4 gt 70) ZONE4=3,
 IF (W4 ge (1.20 U4+20) and W4 gt 90 and U4 le 70) ZONE4=2,
 IF (W4 ge 200 and U4 le 70) ZONE4=1,
 5 IF (W4 lt U4) ZONE4=6,
 IF (W4 le 0.8 U4 and U4 gt 70) ZONE4=7,
 IF (W4 le (1.4 U4-182) and U4 le 180) ZONE4=8,
 IF (U4 ge 240 and W4 gt 70 and W4 lt 180) ZONE4=9, and
 IF (U4 gt 180 and W4 le 70) ZONE4=10;
- 10 d) if BG is rising at said moderate rate of use the formulas:
 wherein U1 is abbreviated for said Reference BG,
 wherein SENBG is abbreviated for said Sensor BG,
 IF (W1 ge U1) ZONE1=5,
 IF (W1 ge 1.20 U1 and U1 gt 70) ZONE1=4,
 15 IF (W1 ge (1.03 U1+107.9) and U1 gt 70) ZONE1=3,
 IF (W1 ge 1.20 U1 and W1 gt 70 and U1 le 70) ZONE1=2,
 IF (W1 ge 180 and U1 le 70) ZONE1=1,
 IF (W1 lt U1) ZONE1=6,
 IF (W1 le (0.8 U1-10) and U1 gt 70) ZONE1=7,
 20 IF (W1 le (1.4 U1-192) and U1 le 180) ZONE1=8,
 IF (U1 ge 240 and W1 gt 60 and W1 lt 170) ZONE1=9, and
 IF (U1 gt 180 and W1 le 60) ZONE1=10; and
- e) if BG is rising at said rapid rate use the formulas:
 wherein U3 is abbreviated for said Reference BG,
 25 wherein W3 is abbreviated for said Sensor BG,
 IF (W3 ge U3) ZONE3=5,
 IF (W3 ge 1.20 U3 and U3 gt 70) ZONE3=4,
 IF (W3 ge (1.03 U3+107.9) and U3 gt 70) ZONE3=3,
 IF (W3 ge 1.20 U3 and W3 gt 70 and U3 le 70) ZONE3=2,
 30 IF (W3 ge 180 and U3 le 70) ZONE3=1,
 IF (W3 lt U3) ZONE3=6. U3 gt 70) ZONE3=7,
 IF (W3 le (1.4 U3-202) and U3 le 180) ZONE3=8,

IF (U3 ge 240 and W3 gt 50 and W3 lt 160) ZONE3=9,

IF (U3 gt 180 and W3 le 50) ZONE3=10, and

IF (W3 le (0.8 U3-20),

wherein the output of this computation is a zone, coded as follows:

5 1-uE, 2-uD, 3-uC, 4-uB, 5-uA, 6-1A, 7-1B, 8-1C, 9-1D, 10-1E.

70. The system of claim 50, comprises:

splitting reference BG values received from a reference BG monitoring device into three clinically meaningful regions including hypoglycemia, euglycemia and

10 hyperglycemia regions; and

combining results from the rate error-grid analysis (R-EGA) and point error-grid analysis (P-EGA) within each of these regions.

71. The system of claim 70, wherein:

15 said hypoglycemia region is defined as $BG \leq 70 \text{ mg/dl}$ (3.9 mmol/l);

said euglycemia region is defined as 70 mg/dl (3.9 mmol/l) $< BG < 180 \text{ mg/dl}$ (10 mmol/l), and

said hyperglycemia region defined as $BG > 180 \text{ mg/dl}$ (10 mmol/l).

20 72. The system of claim 71, further comprising :

as presented in table below:

Point Error-Grid Zones				
Hypoglycemia BG < 70 mg/dl				
Rate Error- Grid Zones		A	D	E
	A	60%	10%	3%
	B	10%	5%	2%
	uC	3%	1%	0%
	1C	2%	1%	0%
	uD	1%	1%	0%
	1D	1%	0%	0%
	uE	0%	0%	0%
	1E	0%	0%	0%

providing a relationship of said R-EGA and P-EGA values of said sensor in a hypoglycemic range according to a table including rows of said R-EGA values and columns of P-EGA values.

5 73. The system of claim 72, wherein said R-EGA and P-EGA values will be considered accurate if a value falls in the A_P zone of the P-EGA column of the table and said same value falls in the A_R or B_R zones of the R-EGA rows of the table, as denoted by the white section of the table of claim 69.

10 74. The system of claim 72, wherein said R-EGA and P-EGA values will be considered clinically erroneous if a value falls in the
 D_P zone or E_P zone of the P-EGA column of the table, or
 A_P zone of the P-EGA column of the table and said same value falls in the uD or uE zones of the R-EGA rows of the table, as denoted by the shaded section of the table of
15 claim 69.

 75. The system of claim 72, wherein said R-EGA and P-EGA values will be considered benign errors if a value falls A_P zone of the P-EGA column of the table and said same value falls in the uC , IC , ID , or IE zones of the R-EGA rows of the table, as
20 denoted by the horizontal hash section of the table of claim 69.

 76. The system of claim 72, further comprising :
 as presented in table below:

Point Error-Grid Zones				
Euglycemia 70<BG<180mg/dl				
Rate Error- Grid Zones		A	B	C
	A	60%	13%	0%
	B	12%	5%	0%
	uC	4%	1%	0%
	IC	1%	1%	0%
	uD	1%	0%	0%
	ID	1%	1%	0%
	uE	0%	0%	0%
	IE	0%	0%	0%

providing a relationship of said R-EGA and P-EGA values of said sensor in a euglycemia range according to a table including rows of said R-EGA values and columns
 5 of P-EGA values.

77. The system of claim 76, wherein said R-EGA and P-EGA values will be considered accurate if a value falls in the A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the A_R or B_R zones of the R-EGA rows of the table,
 10 as denoted by the white section of the table of claim 73.

78. The system of claim 76, wherein said R-EGA and P-EGA values will be considered clinically erroneous if a value falls in the
 A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in
 15 the uE or IE of the R-EGA rows of the table; or
 C_P zone of the P-EGA column of the table, as denoted by the shaded section of the table of claim 73.

79. The system of claim 76, wherein said R-EGA and P-EGA values will be
 20 considered benign errors if a value falls in the
 A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the uC, IC, uD or ID of the R-EGA rows of the table, as denoted by the horizontal hash

section of the table of claim 73.

80. The system of claim 76, further comprising :
as presented in table below:

Point Error-Grid Zones						
Hyperglycemia BG > 180 mg/dl						
Rate Error- Grid Zones		A	B	C	D	E
	A	60%	8%	3%	3%	0%
	B	7%	5%	2%	2%	0%
	uC	2%	1%	0%	0%	0%
	lC	3%	1%	0%	0%	0%
	uD	1%	1%	0%	0%	0%
	ID	1%	0%	0%	0%	0%
	uE	0%	0%	0%	0%	0%
	IE	0%	0%	0%	0%	0%

5

providing a relationship of said R-EGA and P-EGA values of said sensor in a hyperglycemia range according to a table including rows of said R-EGA values and columns of P-EGA values.

10 81. The system of claim 80, wherein said R-EGA and P-EGA values will be considered accurate if a value falls in the A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the A_R or B_R zones of the R-EGA rows of the table, as denoted by the white section of the table of claim 77.

15 82. The system of claim 80, wherein said R-EGA and P-EGA values will be considered clinically erroneous if a value falls in the
A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the ID, uE or IE of the R-EGA rows of the table; or
C_P zone, D_P zone or E_P zone of the P-EGA column of the table, as denoted by the
20 shaded section of the table of claim 77.

83. The system of claim 80, wherein said R-EGA and P-EGA values will be considered benign errors if a value falls in the

A_P zone or B_P zone of the P-EGA columns of the table and said same value falls in the u_C , $1C$ or u_D of the R-EGA rows of the table, as denoted by the horizontal hash
5 section of the table of claim 77.

84. The system of claim 80, comprising:

combining the results from tables of claims 69, 73 and 77 into a single accuracy estimate of a sensor using a linear weighted combination.

10

85. The system of claim 84, said combining of the R-EGA and P-EGA zone as according to the following formulas:

A (Accurate Readings) = $w_1 * A_1 + w_2 * A_2 + w_3 * A_3$,

B (Benign Errors) = $w_1 * B_1 + w_2 * B_2 + w_3 * B_3$,

15 Err (Erroneous Readings) = $w_1 * Err_1 + w_2 * Err_2 + w_3 * Err_3$, wherein:

A_1 , B_1 , Err_1 are percentages of accurate readings, benign errors, and erroneous readings during hypoglycemia;

A_2 , B_2 , Err_2 are the percentages of accurate readings, benign errors, and erroneous readings during euglycemia, and

20 A_3 , B_3 , Err_3 are the percentages of accurate readings, benign errors, and erroneous readings during hyperglycemia, and wherein the weights w_1 , w_2 , w_3 are assigned to the hypoglycemic, euglycemic, and hyperglycemic BG ranges.

86. The method of claim 85, wherein said weights are about 0.07, about 0.53,
25 and about 0.40 for hypoglycemic, euglycemic, and hyperglycemic ranges, respectively.

87. A computer program product comprising a computer usable medium having computer program logic for enabling at least one processor in a computer system to evaluate accuracy of a glucose monitoring sensor, said computer program logic
30 comprising:

evaluating point accuracy of blood glucose (BG) values received from said monitoring sensor;

evaluating accuracy of direction and rate of BG fluctuations received from said monitoring sensor; and

combining said point accuracy and rate accuracy in an estimate of sensor precision.

5

88. The computer program product of claim 87, wherein said estimate of sensor precision comprises:

performing a combination of three grids adapted specifically for hypoglycemic, euglycemic, and hyperglycemic BG ranges.

10

89. The computer program product of claim 88, wherein said estimate of sensor precision includes solely a single estimate using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

15

90. The computer program product of claim 88, wherein said estimate of sensor precision includes a plurality of estimates using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

20

91. The computer program product of claim 87, wherein said computer program product is for use with a subject, wherein said subject is a human or an animal.

92. The computer program product of claim 87, wherein said sensor comprises a continuous glucose monitor or semi-continuous glucose monitor or combination of both.

25

93. The computer program product of claim 87, wherein:

said accuracy evaluation of direction and rate of BG fluctuations includes performing rate error-grid analysis (R-EGA), and

said accuracy evaluation blood glucose (BG) values includes performing point error-grid analysis (P-EGA) that determines correct presentation of said blood glucose (BG) values.

30

94. The computer program product of claim 93, wherein said estimate of sensor precision comprises:

performing a combination of three grids adapted specifically for hypoglycemic, euglycemic, and hyperglycemic BG ranges.

5

95. The computer program product of claim 94, wherein said estimate of sensor precision includes solely a single estimate using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

10

96. The computer program product of claim 94, wherein said estimate of sensor precision includes a plurality of estimates using a weighted combination of hypoglycemic, euglycemic, hyperglycemic BG ranges.

15

97. The computer program product of claim 93, wherein said computer program product is for use with a subject, wherein said subject is a human or an animal.

20

98. The computer program product of claim 93, wherein said sensor comprises a continuous glucose monitor or semi-continuous glucose monitor or combination of both.

99. A system for evaluating accuracy of a glucose monitoring sensor, said system comprising:

said glucose monitoring sensor; and

a microprocessor programmed to perform the following:

25

evaluate point accuracy of blood glucose (BG) values received from said monitoring sensor;

evaluate accuracy of direction and rate of BG fluctuations received from said monitoring sensor; and

30

combine said point accuracy and rate accuracy in an estimate of sensor precision.

100. A system for evaluating accuracy of a glucose monitoring sensor, said

system comprising:

said glucose monitoring sensor;

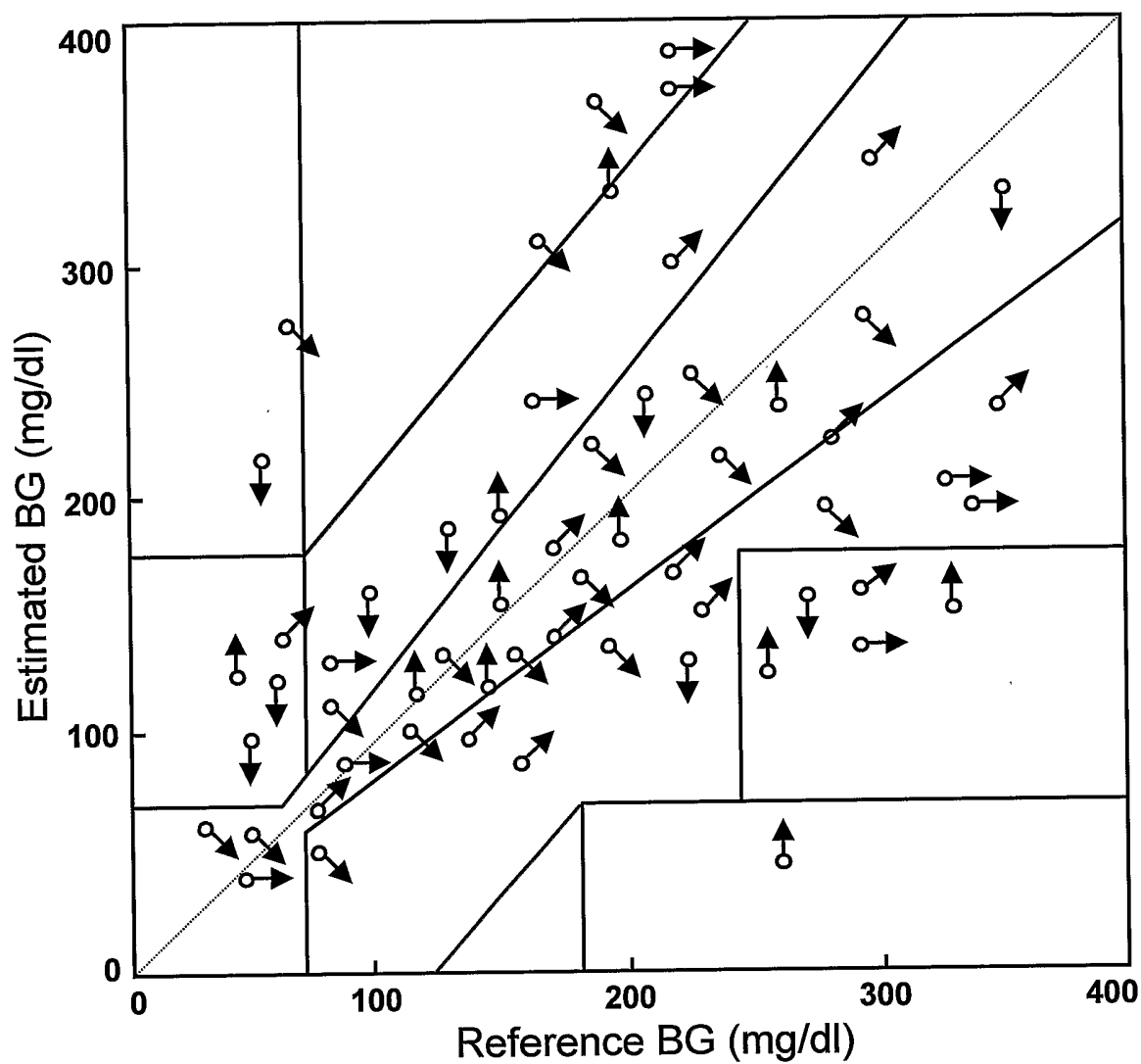
a reference device; and

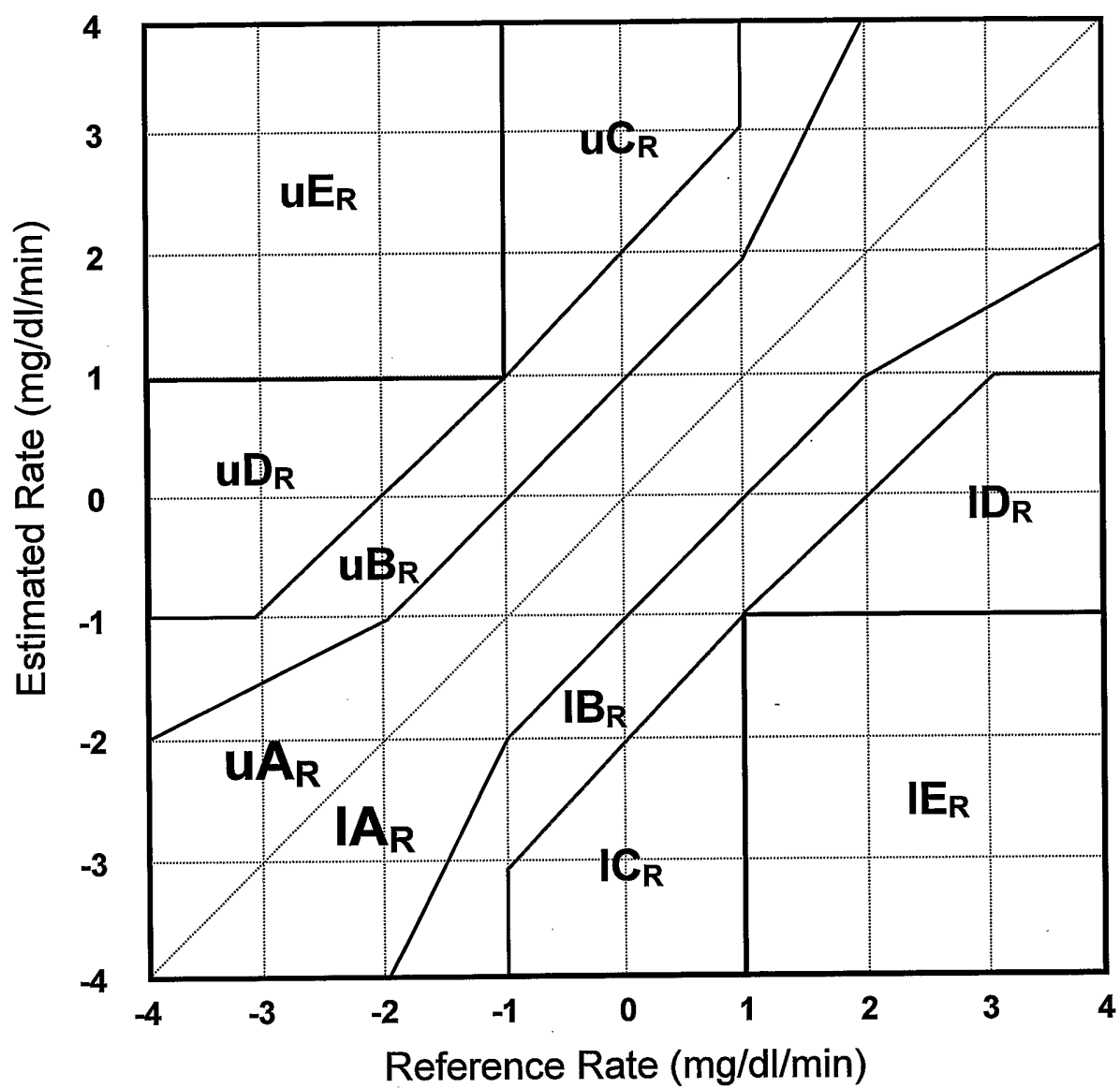
a microprocessor programmed to perform the following:

5 evaluate point accuracy of blood glucose (BG) values received from said
monitoring sensor;

 evaluate accuracy of direction and rate of BG fluctuations received from
said monitoring sensor; and

 combine said point accuracy and rate accuracy in an estimate of sensor
10 precision.

**FIG. 1**

**FIG. 2**

**Point Error-Grid – Minimal BG Fluctuation
Reference Rate of $[-1,+1]$ mg/dl/min:**

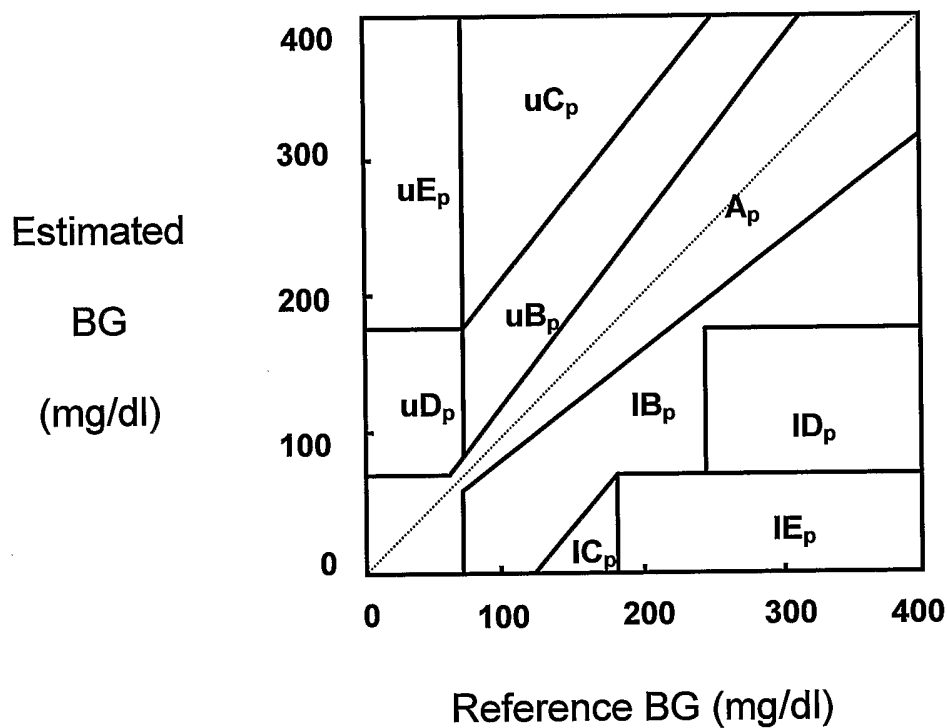


FIG. 3A

Reference Rate of $[-2,-1]$ mg/dl/min:

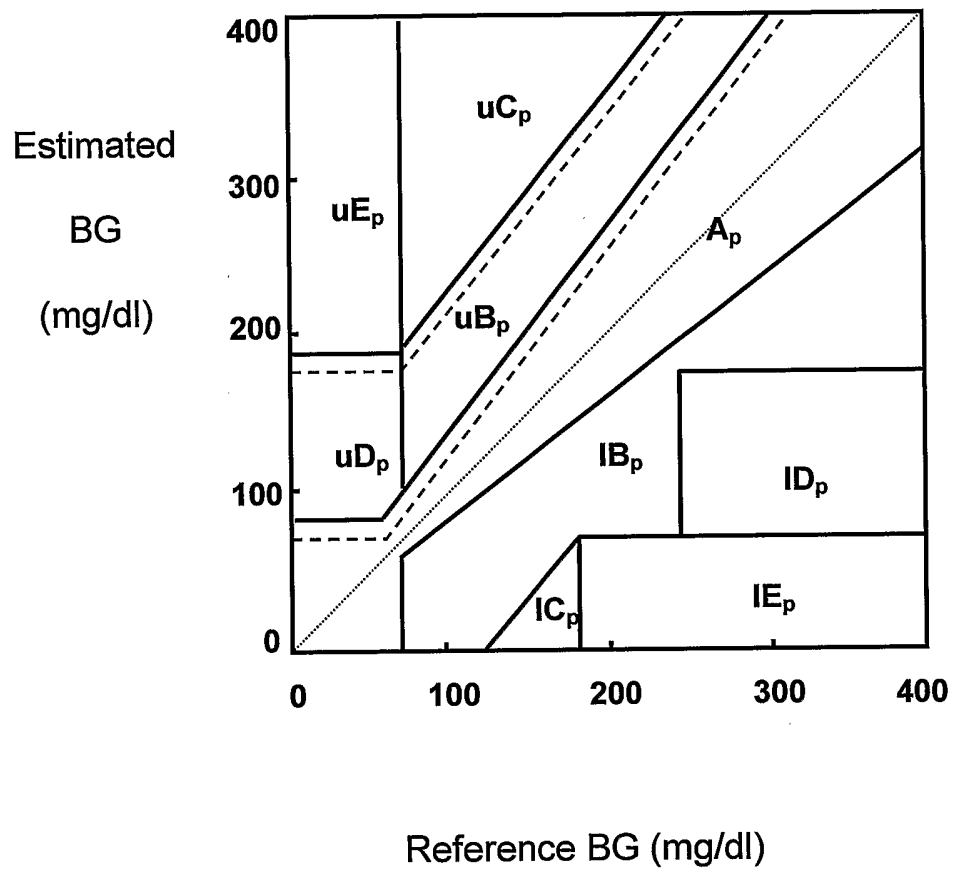


FIG. 3B

BG falls faster than -2 mg/dl/min:

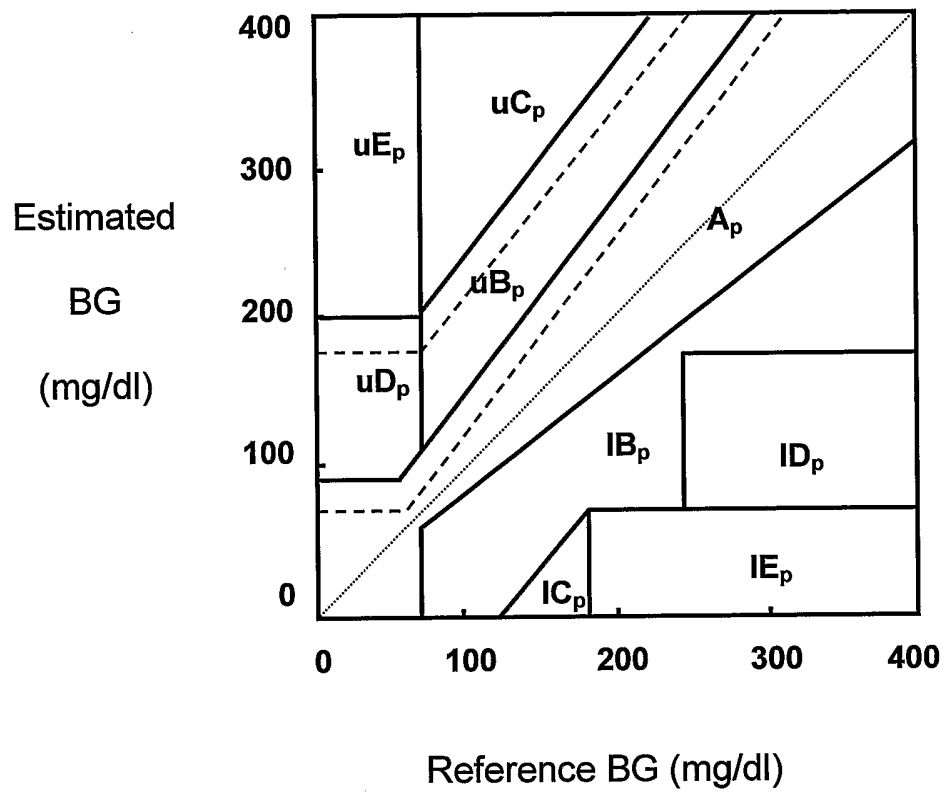


FIG. 3C

Reference Rate of [1,2] mg/dl/min:

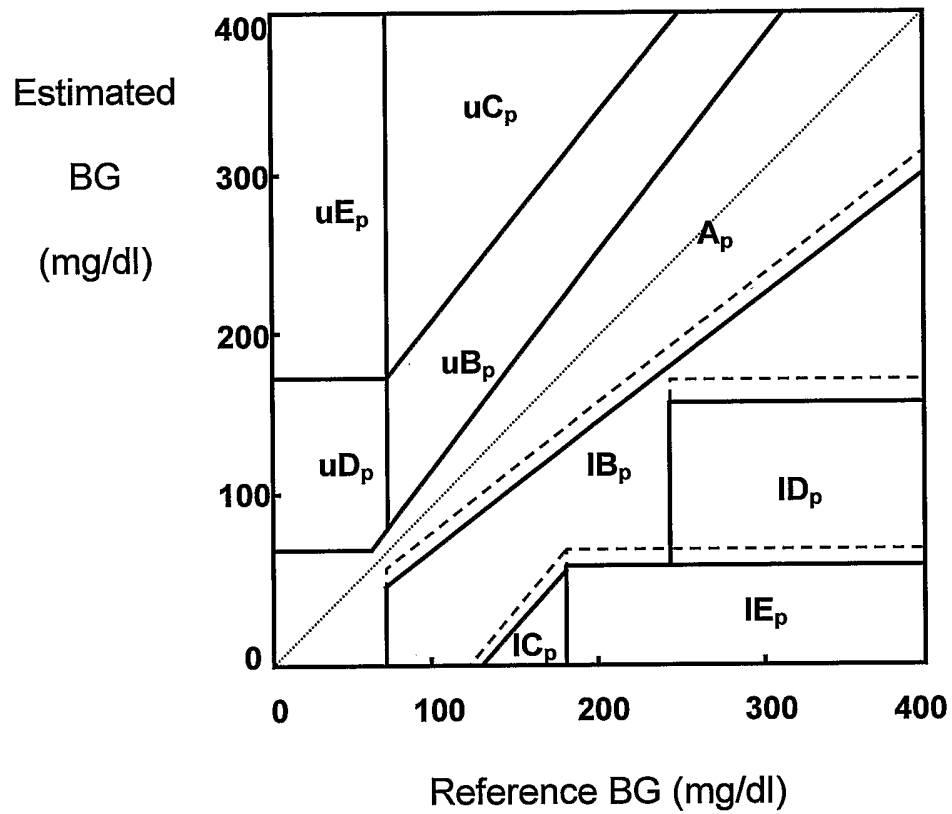


FIG. 3D

BG rises faster than 2 mg/dl/min:

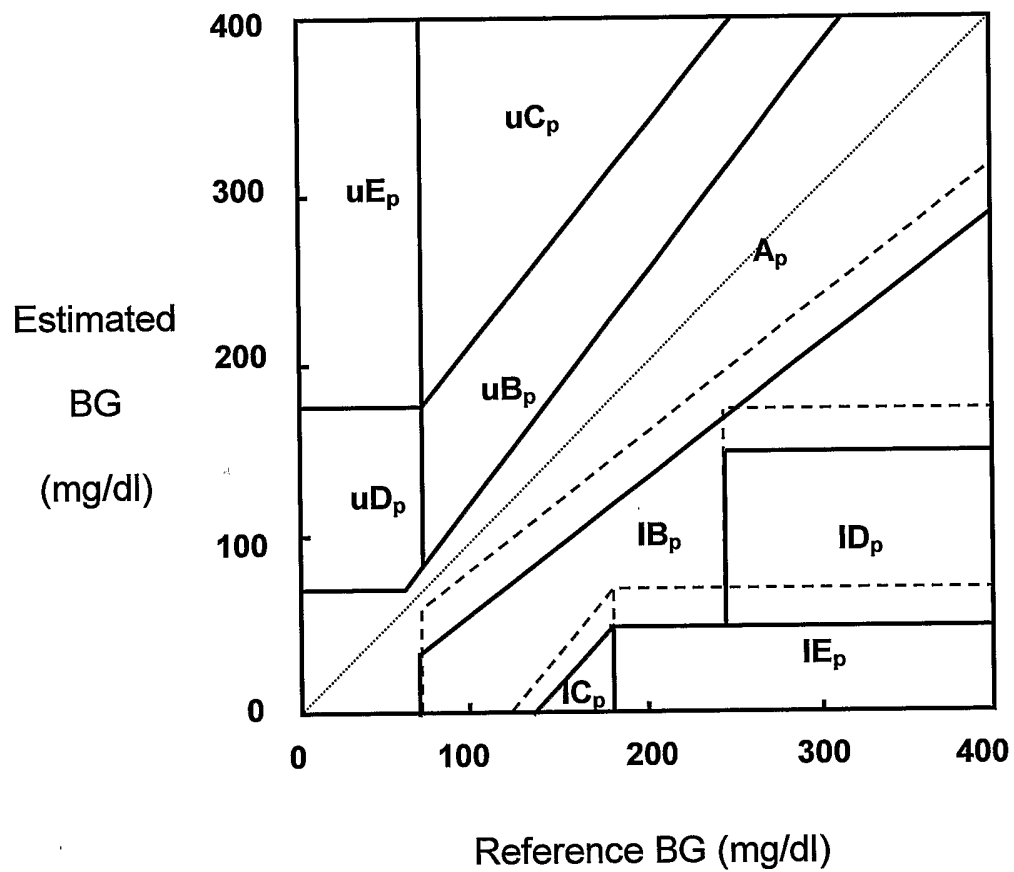


FIG. 3E

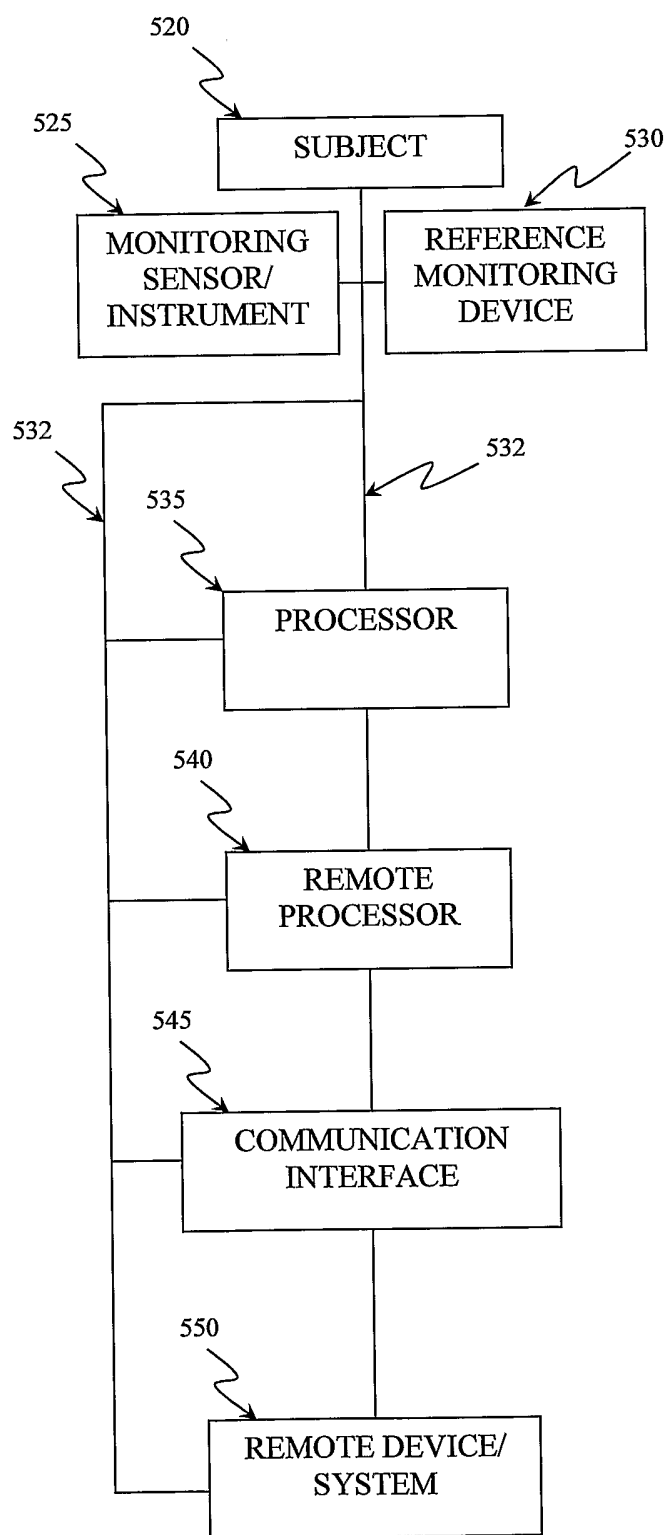
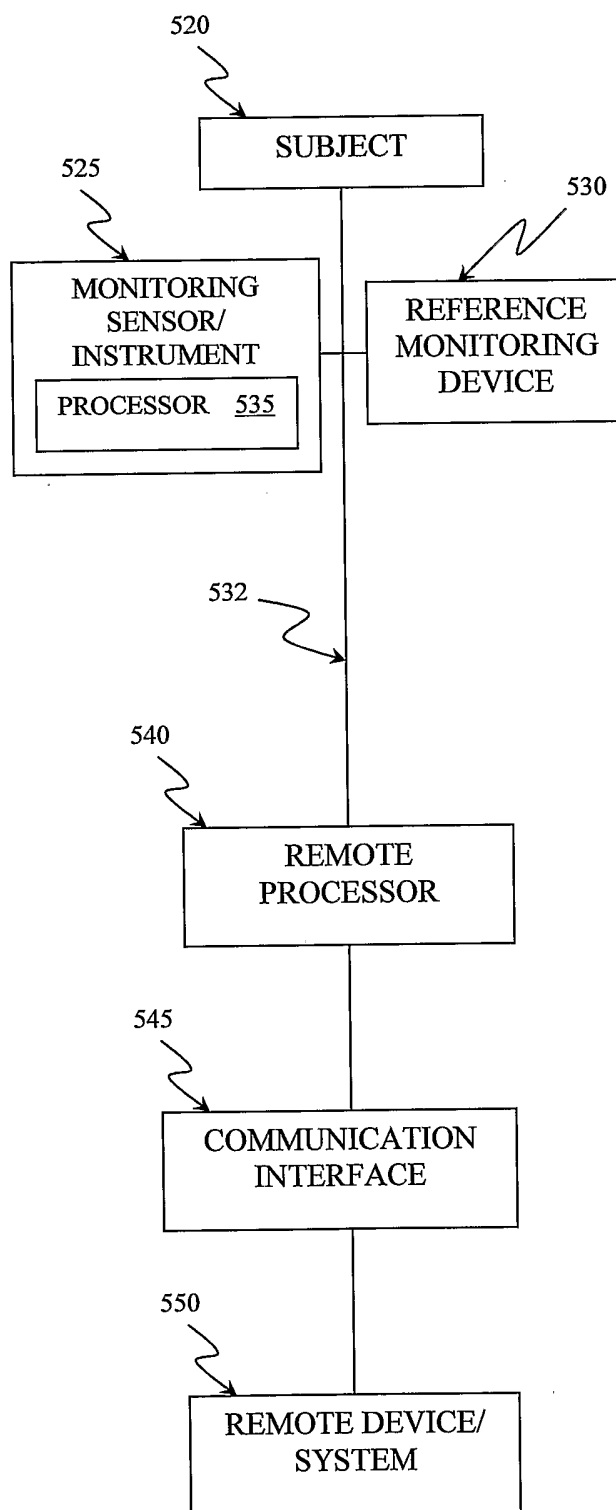
Point Error-Grid Zones																			
Hypoglycemia BG < 70 mg/dl					Euglycemia 70<BG<180mg/dl					Hyperglycemia BG > 180 mg/dl									
					A	D	E	A			B	C	A			B	C	D	E
Rate	A				60%	10%	3%	60%			13%	0%	60%			8%	3%	3%	0%
	B				10%	5%	2%	12%			5%	0%	7%			5%	2%	2%	0%
	uC				3%	1%	0%	4%			1%	0%	2%			1%	0%	0%	0%
Error-Grid	IC				2%	1%	0%	1%			1%	0%	3%			1%	0%	0%	0%
	uD				1%	1%	0%	1%			0%	0%	1%			1%	0%	0%	0%
Zones	ID				1%	0%	0%	1%			1%	0%	1%			0%	0%	0%	0%
	uE				0%	0%	0%	0%			0%	0%	1%			0%	0%	0%	0%
	IE				0%	0%	0%	0%			0%	0%	0%			0%	0%	0%	0%

 Accurate Readings

 Benign Errors

 Erroneous Readings

FIG. 4

**FIG. 5A****FIG. 5B**

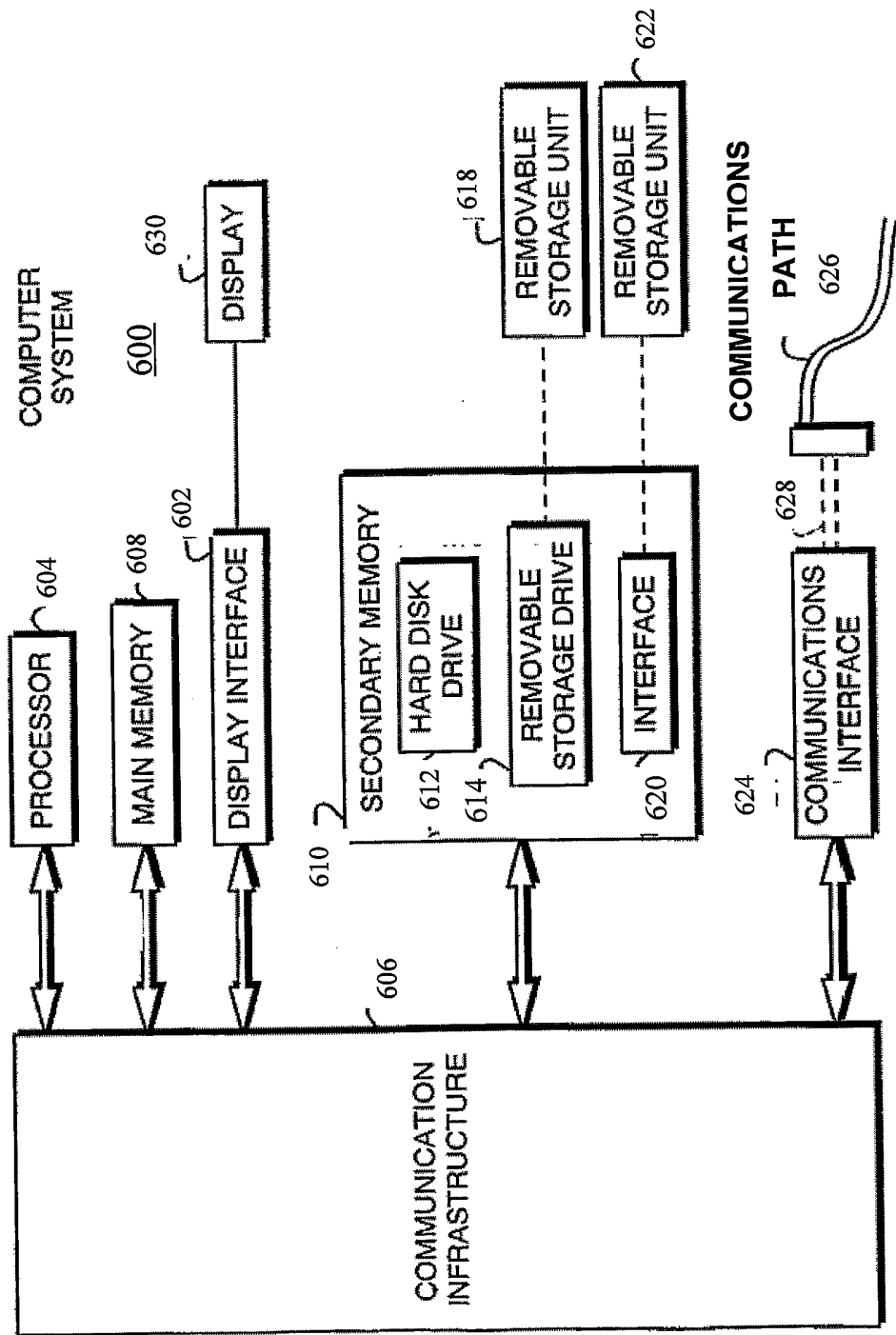


FIG. 6

Continuous Glucose Error-Grid Analysis (CG-EGA)

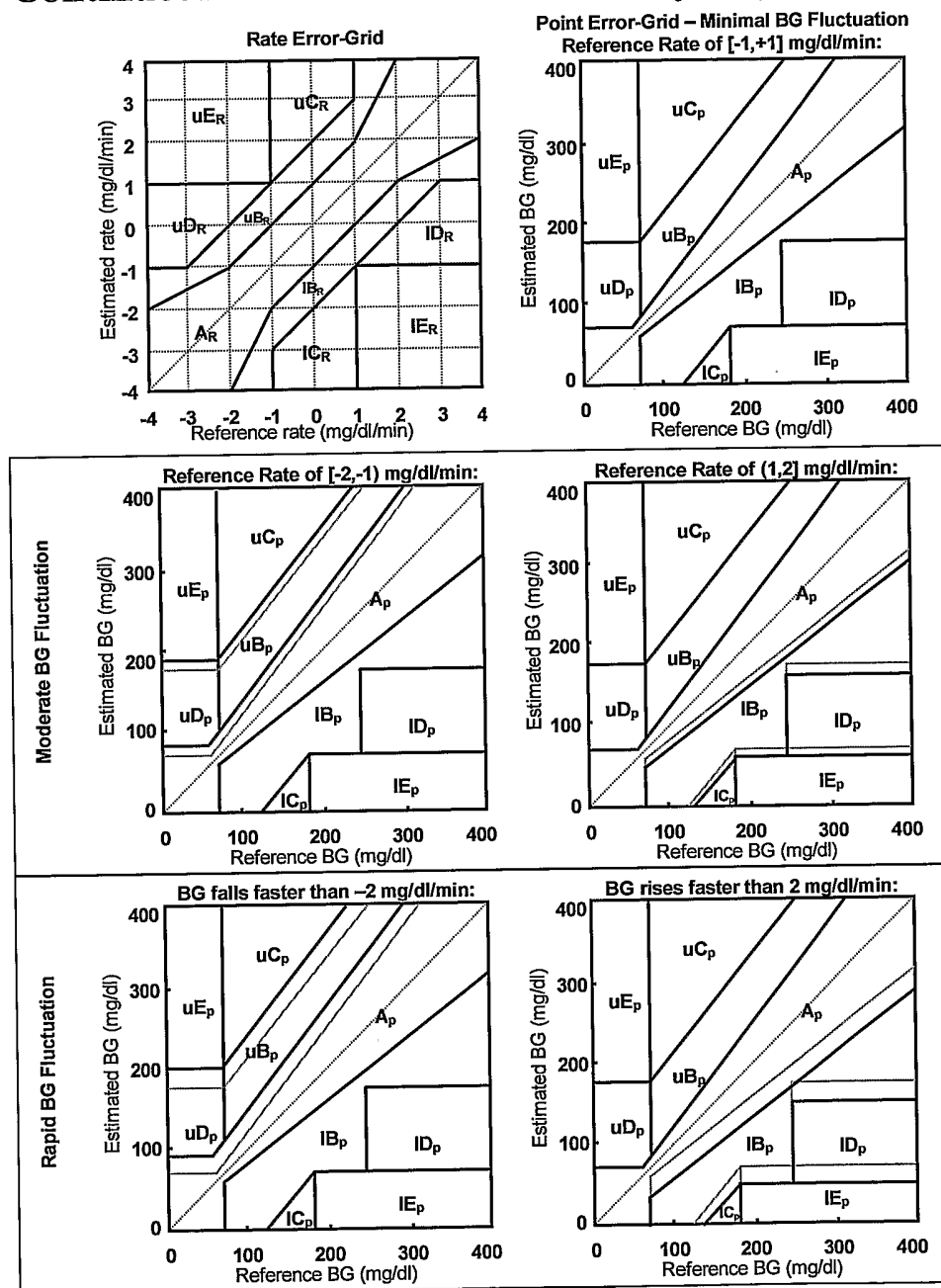


FIG. 7

CG-EGA Summary

Combined weighted accuracy across the entire blood glucose range with fixed weights of 0.07, 0.53, and 0.4 for hypoglycemia, euglycemia, and hyperglycemia, respectively:

A = 84.6%

B = 9.3%

Err = 6.1%

Euglycemia ($70 < BG \leq 180$ mg/dl)

Accuracy = 90%

Point Error-Grid Zones

	A	B	C
A	60%	13%	0%
B	12%	5%	0%
uC	4%	1%	0%
IC	1%	1%	0%
uD	1%	0%	0%
ID	1%	1%	0%
uE	0%	0%	0%
IE	0%	0%	0%

This range contains 53% of the data

Hypoglycemia ($BG \leq 70$ mg/dl)

Accuracy = 70%

Point Error-Grid Zones

	A	D	E
A	60%	10%	3%
B	10%	5%	2%
uC	3%	1%	0%
IC	2%	1%	0%
uD	1%	1%	0%
ID	1%	0%	0%
uE	0%	0%	0%
IE	0%	0%	0%

This range contains 7% of the data

Hyperglycemia ($BG > 180$ mg/dl)

Accuracy = 80%

Point Error-Grid Zones

	A	B	C	D	E
A	60%	8%	3%	3%	0%
B	7%	5%	2%	2%	0%
uC	2%	1%	0%	0%	0%
IC	3%	1%	0%	0%	0%
uD	1%	1%	0%	0%	0%
ID	1%	0%	0%	0%	0%
uE	0%	0%	0%	0%	0%
IE	0%	0%	0%	0%	0%

This range contains 40% of the data

LEGEND

Zone A – Clinically accurate;
Zone B – Benign Rx;

Zone C – Over corrective Rx;
Zone D – Failure to Detect;
Zone E – Erroneous Rx.

FIG. 8