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(54) **TRACKING CHANGES IN AVERAGE GLYCEMIA IN DIABETICS**

VERFOLGUNG VON ÄNDERUNGEN DER MITTLEREN GLYKÄMIE BEI DIABETIKERN

SUIVI DE MODIFICATIONS DE LA GLYCÉMIE MOYENNE CHEZ DES INDIVIDUS DIABÉTIQUES

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Description

CROSS-REFERENCE TO RELATED APPLICATIONS AND CLAIM OF PRIORITY

[0001] This application claims priority under 35 U.S.C. § 119(e) and PCT Article 8 and Rule 4.10, from copending U.S. Provisional Application Serial No. 61/767,451 filed on 21 February 2013.

BACKGROUND OF THE INVENTION

[0002] Since the discovery of an "unusual hemoglobin in patients with diabetes," over 40 years ago[1], Hemoglobin A1c (HbA1c) has become the established standard clinical measurement used as a marker for glycemic control. HbAlc is formed when hemoglobin joins with glucose in the blood, resulting in a glycosylated hemoglobin molecule. Due to the fact that red blood cells survive for 8-12 weeks before renewal, a patient's HbA1c reflects the average blood glucose levels over the past 3 months.

[0003] The widespread acceptance of this measurement has primarily been driven by two pivotal, large-scale studies in Type 1 (Diabetes Control and Complications Trial; DCCT) and Type 2 (UK Prospective Diabetes Study; UKPDS) diabetes. These prospective, randomized, controlled trials of intensive versus standard glycemic control in patients with relatively recently diagnosed diabetes demonstrated that intensive glucose control, as measured by blood glucose and HbAlc, correlated with a decreased risk of diabetes-related complications[2,3]. The DCCT and UKPDS, along with other clinical studies, also have been used to support the development of hypothetical scenarios and test mathematical calculation models which aim to describe the relationship between HbAlc and blood glucose.

Linear Models for Blood Glucose-HbAlc Relationship

[0004] Based on the UKPDS in type 2 diabetes (T2D) patients a linear regression relationship of HbAlc with fasting plasma glucose (FPG) was observed, where FPG = 1.28 (HbAlc) - 0.66 (r2=0.59).[4] Similarly, using data from the DCCT in type 1 diabetes (T1D) patients, Rohlfing *et al.* analyzed 26,056 values based on 7 mean blood glucose (MPG) measures per day.[5] Using this approach, they established a linear relationship between plasma glucose and HbAlc (MPG (mmol/l) = (1.98 x HbAlc) - 4.29 or MPG (mg/dl) = (35.6 x HbAlc) - 77.3; r = 0.82). This was subsequently used for the American Diabetes Association (ADA) Standards of Medical Care in Diabetes to describe the correlation between HbAlc and mean glucose. However, in the most recent update, it is now considered that this was not optimal, being derived from relatively sparse data (one 7-point profile over 1 day per HbAlc reading) in the primarily Caucasian T1D participants of the DCCT.[6]

[0005] More recently, the ADAG Study Group evaluated data from T1D, T2D and Non-Diabetic patients using self-monitored blood glucose (SMBG).[7] The aim was to define a relationship between HbAlc and average glucose (AG) levels and determine whether HbAlc could be expressed and reported as AG in the same units as used in self-monitoring. Approximately 2,700 glucose values were obtained for each subject during 3 months. Linear regression between the HbAlc and AG values provided the closest correlations, allowing for calculation of an estimated average glucose (eAG) for HbAlc values using the formula AG (mg/dl) = 28.7 * A1c - 46.7; r2 = 0.84; P < 0.0001. Furthermore the authors found that the linear regression equations did not differ significantly across sub-groups based on age, sex, diabetes type, race/ethnicity, or smoking status. This has now been adopted as the current recommended relationship to use according to the ADA 2011 Standards of Medical Care in Diabetes.[6]

[0006] Makris, *et al* have also observed a similar data pattern, with a strong correlation seen between MBG and HbAlc in Type 2 diabetic patients, using the formula MBG (mg/dl) = (34.74 * HbAlc) - 79.21 or MBG (mmol/l) = 1.91 * HbAlc - 4.36; r=0.93. They also found that the linear regression of MBG values vs. HbAlc at 12 weeks was statistically significant; whereas other independent variables of sex, age, body mass index (BMI) and patient status (Type 2 diabetes treated or not) were not.[8] Temsch *et al* also identified issues with a linear mathematical model developed to calculate HbA1c values based on SMBG and past HbA1c levels (HbA1c = 2.6 + 0.03 * G [mg/100 ml] or 2.6 + 0.54 * G [mmol/l]). Overall, the predicted HbAlc values were consistent with measured values and results matched the HbAlc formula in the elevated range. However, the model was found to be too optimistic in the range of better glycemic control. Sub-analysis suggested that bias may have been introduced by use of different glucometers and individual measurement habits.[9]

Factors Influencing the Relationship between Blood Glucose and HbAlc

[0007] A range of factors have been postulated to influence the relationship HbA1c and blood glucose, such as patient's age, body weight (BMI), gender, ethnicity, behavioral characteristics (e.g. time and frequency of blood glucose measurement) and their general status such as duration and type of diabetes, concomitant diseases, etc.[10,11,12,13]. In particular, two critical areas have been identified which appear to have significant impact on this relationship:

1) The time of blood glucose measurement (fasting (FPG), post-prandial etc.) and

2) The frequency and timing of blood glucose measurement.

[0008] Whilst postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated HbAlc levels, its relative contribution is higher at HbAlc levels that are closer to 7%. However, the major outcome studies such as the DCCT and UKPDS, relied overwhelmingly on pre-prandial SMBG. Analysis of DCCT found that among individual time points, the afternoon and evening prandial glucose (post-lunch, pre-dinner, post-dinner, and bedtime) readings showed higher correlations with HbAlc than the morning time points (pre-breakfast, post-breakfast, and pre-lunch), with the best correlation of HbAlc being the area under the glucose profile.[14] Yamamoto-Honda *et al* also showed that FPG and 2-h post-breakfast blood glucose (PBBG) levels exhibited a good sensitivity and specificity for predicting a glycemic control, while the FPG and 3-h PBBG levels only exhibited fair sensitivity and specificity for predicting glycemic control.[15] Similarly chronology and frequency of blood glucose measurements also has influence on the relationship between blood glucose and HbAlc. At any given time, a given blood sample contains erythrocytes of varying ages, with different levels of exposure to hyperglycemia. Whilst the older erythrocytes are likely to have more exposure to hyperglycemia, younger erythrocytes are more numerous. Blood glucose levels from the preceding 30 days contribute approximately 50% to HbAlc, whereas those from the period 90-120 days earlier contribute only approximately 10%.[16] Exploiting further the timing of blood glucose measurements, Trevino challenged the linear model approach as fundamentally flawed and had instead pursued weighted average and nonlinear approaches.[17,18,19]

Development of Non-Linear Models for Blood Glucose-HbAlc Relationship

[0009] Several nonlinear models have been proposed, which aim to address additional key factors that influence the relationship between blood glucose and HbAlc. Zielke *et al* proposed that HbAlc values reflect serum glucose levels of the immediate past much better than levels several weeks ago. Using a biomathematical model that takes into account the chemical reactions during HbAlc formation as well as the life cycle of human erythrocytes, they concluded that in order to ensure some degree of reliability of HbAlc measurements, these readings should not be spaced too far apart.[20] Ollerton et al developed an approach to address the relative contribution of fasting and post-prandial glucose levels to the value of HbAlc, using a mathematical model of hemoglobin glycation. They highlighted that this is based on physiologically reasonable assumptions, to derive a compartmental differential equation model for HbAlc dynamics.[21] Other groups have used data from clinical studies (including DCCT) and hypothetical scenarios, to propose models which incorporate the kinetics of HbAlc formation and removal, in order to better describe the relationship between HbAlc and BGC.[22,23] However, while many of these models may possibly be theoretically sound to some extent, none so far have offered a practically-applicable dynamical approach to tracing the fluctuations of HbAlc over time, an approach that could result in application deployed in an SMBG device ensuring sufficient accuracy by sparse (e.g. fasting glucoses and occasional 7 points profiles) BG measurements.

[0010] WO 2011/084208 A1 discloses a method of estimating HbAlc from blood glucose values. US 2007/010950 A1 discloses a method of calculating parameters related to blood glucose, including a Virtual A1c value which emulates HbAlc.

Risk Analysis of Blood Glucose Data

[0011] The present inventors' group at the University of Virginia has also worked extensively on developing models of the relationship between SMBG and HbAlc. In an early study in T1D patients, we investigated how well the mean of SMBG data describes the actual mean BG.[24] The linear formula HbAlc = 5.21 + 0.39*BGMM (mean SMBG expressed in mmol/liter) resulted in a correlation of 0.7 between mean SMBG and HbAlc. Later, an updated linear relationship was derived: HbAlc = 0.41046 * BGMM + 4.0775. However, due to a number of factors associated with routine SMBG, only about 50% of the variance of the actual BG was accounted for by mean SMBG. Thus, these findings suggested that mean SMBG was far from an ideal descriptor of actual average glycemia.

[0012] To correct for imperfections in SMBG sampling, we have introduced nonlinear corrections for the SMBG-based estimates of HbA1c, which used results from our theory of risk analysis of BG data[25], namely the Low and High BG Indices (LBGI and HBGI). These nonlinear corrections resulted in improved numerical estimation of HbA1c from SMBG data and introduced mean absolute deviation (MAD) and mean absolute relative deviation (MARD) as measures of the accuracy of HbAlc estimation.[26] This simple step was important for the understanding of HbA1c estimation because while correlation alone measures the strength of a linear association, it does not measure any possible offset of the estimates. For example, an estimate having two-fold higher values than actual HbAlc would have perfect correlation with HbA1c.

[0013] Further, based on our risk analysis theory, we introduced a method, system, and computer program, which

was designed to aid the control in both T1 and T2 diabetic patients, by predicting from SMBG readings the long-term exposure to hyperglycemia, as well as the long-term and short-term risks for severe or moderate hypoglycemia.[27] This approach used the HBGI and the LBGI, and later a new algorithm which derived an average daily risk range (ADRR) - a variability measure computed from routine SMBG data. We found that the ADRR provided a superior balance of sensitivity for predicting both hypoglycemia and hyperglycemia.[28]

[0014] Most importantly for this presentation, we have conducted the largest to date study of the effects of offering real-time SMBG-based estimation of HBA1c, LBGI, and ADRR to patients with diabetes in their natural environment. In this study, 120 people with T1D used for 8-9 months a meter and a handheld computer providing these glycemic markers at each SMBG entry. As a result, average glycemic control was significantly improved, the incidence of severe hypoglycemia was reduced, and the patients rated highly the utility of the provided feedback.[29]

SUMMARY OF THE INVENTION

[0015] The above study offered empirical evidence supporting the long-standing belief that providing real-time estimates of HbA1c and risk for hypoglycemia has the desired effect of improving glycemic control. Taking this message forward, we now propose a novel and non-obvious model-based approach (method, system and computer readable medium) to, among other things, track changes in average glycemia from SMBG data. Unlike previously introduced models, this technique (method, system, and computer readable medium) allows for:

- Simple parameterization of the dynamics of average glycemia and thereby HbAlc, with two parameters that can be individually tuned to the physiology an behavior of each person;
- Robust estimation procedure capable of working on sparse readings of fasting BG and occasional (e.g. monthly) 7-point SMBG profiles; and
- Inherent capability for calibration of the algorithm (e.g., method) using SMBG profiles.

[0016] An aspect of an embodiment of the present invention provides a method, system and computer readable medium for tracking changes in average glycemia in diabetes, based on a conceptually new approach (method and technique) to the retrieval of SMBG data. A principal premise of this approach is, among other things, the understanding of HbAlc fluctuation as the measurable effect of the action of an underlying dynamical system. SMBG provides occasional glimpses at the state of this system and, using these measurements, the hidden underlying system trajectory can be reconstructed for each individual.

[0017] Using compartmental modeling - a technique well established in diabetes research[35] - we have constructed a new two-step algorithm (and related method, system and computer readable medium) that includes: (i) real-time estimate of HbAlc from fasting glucose readings, updated with any new incoming fasting SMBG data point, and (ii) initialization and calibration of the estimated HbAlc trace with daily SMBG profiles taken approximately every month. The estimation of these 7-point profiles includes another innovative step - a factorial model capturing daily BG variability into two latent factors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The new method, system and computer-readable medium will become more understood from the following detail description, together with detailed algorithm (e.g., technique) and data requirements for its implementation in a portable SMBG device or other desired or required systems or devices, in conjunction with the accompanying drawings, wherein:

FIG. 1 is a schematic diagram of a system architecture of an HbAlc estimation procedure in accordance with the invention;
FIG. 2 is a diagram showing a one-compartment model of hemoglobin glycation in accordance with the invention;
FIG. 3 is a graph of a Dynamical HbAlc Tracking Procedure in accordance with the invention;
FIG. 4 is a diagram of an HbAlc error-grid for a dynamical HbAlc tracking procedure in accordance with the invention;
FIG. 5 is a diagram of an HbAlc error-grid for a linear estimate of HbAlc in accordance with the invention;
FIG. 6 is a graphical analysis of A1c rate of change in accordance with the invention, wherein the wider bars represent lab values, and the narrow bars represent estimates;
FIG. 7 is a graph showing the effect of missing fasting BG on *eA1c* estimator performances sensitivity to erroneous profiles in accordance with the invention;
FIG. 8 is a graph showing the effect of scrambled profile tags on *eA1c* estimator performances sensitivity to alternate site testing (AST) in accordance with the invention;
FIG. 9 is a high level functional block diagram of an embodiment of the present invention, or an aspect of an

embodiment of the present invention;
FIG. 10A is a block diagram of a computing device usable with the invention;
FIG. 10B is a diagram of a network system in which embodiments of the invention can be implemented;
FIG. 11 is a block diagram of a computer system with Internet connectivity, in which an embodiment of the invention may be implemented; and
FIG. 12 is a diagram of a system embodiment in accordance with the invention.

DETAILED DESCRIPTION OF THE INVENTION

Algorithm Concept: Dynamical Tracking of Changes In Average Glycemia

[0019] Conceptually, a non-limiting embodiment of the estimation procedure for the present invention method, system, and computer readable medium proposed in this disclosure works as follows:

- Fasting SMBG readings are submitted to a *model of HbA1c dynamics,* which tracks the fluctuations of average glycemia over time. This model depends on two individually-adjustable parameters, one of which is fixed to a population value as described below, and the other of which is used to provide inherent ability to individualize (calibrate) the dynamics of HbA1c to a particular person at a particular point in time. For simplification of explanation only, in the exemplary implementation the calibration is fixed for all users.
- Periodically (e.g. once a month) a daily SMBG profile is submitted to a *factorial model,* which reconstructs a person's daily glucose variability via two principal factors (components) that are linear combinations with fixed coefficients of the SMBG values recorded during the day. In this implementation we use standard 7-point profiles;
- The factors are then used to *calibrate* the model for peri-prandial (i.e. pre-prandial and post-prandial) BG deviations from fasting. In other words, the amplitude (variability) of glucose fluctuation is captured using the 7-point profile and is used to adjust the dynamical model to better reflect average glycemia.
- Finally an infrequent (1-3 times a year) reference HbAlc measurement can be used to calibrate the glycation formula (link between HbAlc and glucose exposure).

[0020] Fig. 1 shows a system for the estimation procedure flow. In essence, SMBG measurements are divided in two groups, (i) fasting glucose measurements (1) and (ii) profile glucose measurements (2). Fasting glucose readings are expected once in a couple of days and are the main driving function of the model, while profile measurements are scarce (e.g. monthly) and allow for calibration of the glucose exposure function to the patient's glucose variability. The final result is an estimate of Hba1c (4) that is updated with any incoming fasting SMBG data point (1) and is calibrated with any incoming 7-point profile (2). The SMBG-only system can function as such or be enhanced by reference HbAlc (3) calibration of the calibration formula; in the absence of HbAlc reference (3), the system uses a fixed glycation formula.

Datasets:

[0021] The data for training and test data set were provided by Sanofi-Deutschland GmbH originating from the phase IIIb study: Target Glycemic Control and the Incidence of Symptomatic Nocturnal Hypoglycemia in Insulin Naive Subjects with Type 2 Diabetes on Oral Hypoglycemic Agent(s) and Treated with Insulin Glargine or NPH Human Insulin, HOE901, 4002.

[0022] This study was conducted in Type 2 DM patients between 7 January 2000 and 22 October 2001 in 80 study centers in USA and Canada.

[0023] The demographics of the ITT study population can be found in Table 1.

[0024] Training data set: All formulas were developed using a training data set provided by Sanofi-Aventis Deutschland GmbH, which contained 17,863 fasting SMBG readings and approximately monthly 7-point profiles for 379 individuals with type 2 diabetes (see Table 1 for details.)

[0025] On average, each individual contributed 47 days of data. After using the training data, *all formulas were fixed* and then applied without modification to a test and to an external-validation dataset.

[0026] Test data set provided by Sanofi-Aventis Deutschland GmbH was used to validate the formulas developed on the training data. The test data set contained 17,925 fasting SMBG readings and approximately monthly 7-point profiles for 375 individuals with type2 diabetes (see Table 1 for details). On average, each individual contributed 48 days of data.

Table 1: Demographics/summary table for training and testing data sets

	Female	**Men**
Age Average	54 years	56 years

(continued)

	Female	Men
Age Standard deviation	9,2	9,2
Age Min	29 years	30 years
Age Max	74 years	75 years
BMI Average	33,4 kg/m2	31,5 kg/m2
Duration Diabetes	8,6 years	8,7 years
Height Average	162,9 cm	177,3 cm
Race	White: 263	White: 369
	Black: 59	Black: 34
	Multi: 3	Multi: 6
	Asian: 10	Asian: 12
Sex (754 participants)	44,31%	55,69%
Weight Average	88,9 kg	99,5 kg
Pregnancy test (712 participants)	Not applicable: 657	
	Negative: 47	
	Error Entry: 8	
HbA1c (4351 datapoints)	SD: 1,1	
	Avg: 7,6%	
	Min: 5,2%	
	Max: 12,2%	

Variables:

[0027] The variable names were unified across the data sets and are as follows:

- SUBNO - subject ID number;
- PGDT - time (day) of glucose measurement;
- PG1 - fasting BG measured pre-breakfast every day;
- PG2 to PG8 - BG measurements forming a 7-point profile:
    - PG2: first meal preprandial
    - PG3: first meal postprandial
    - PG4: second meal preprandial
    - PG5: second meal postprandial
    - PG6: third meal preprandial
    - PG7: third meal postprandial
    - PG8: before bedtime

Modeling of Fasting BG: Dynamics of HBAlc

[0028] First, a dynamic model of hemoglobin glycation and clearance is constructed, as shown in Fig. 2. Being mindful that the final goal of the resulting algorithm (method and related system) may be deployment in a portable device with limited computing power, we limit this model to a one-compartment representation.
This model corresponds to a first order differential equation:

$$\frac{\partial \widehat{HbA1c}}{\partial t} = -\frac{1}{\tau}\left(\widehat{HbA1c} - f(SMBG_t)\right) \quad (1)$$

where the function $f(SMBG_t)$ is a function using self-monitoring data to track glycemia exposure over time.

Modeling 7-point profiles: Factorial Model of Daily Glucose Variability

[0029] Using the training data, a linear model is constructed of the primary factors determining a 7-point profile of SMBG. The reason that we have opted for factors (or principal components) of this profile instead of individual data are the following:

- Statistically, latent factors tend to be more stable and reproducible across diverse data sets;
- Collapsing the entire profile into two factors allows for easy handling of missing data: a missing value in a 7-point profile can be simply imputed in the factorial representation.

With this understanding, the factors are computed as follows:

$$\theta_1 = .4006*PG2 + .4645*PG3 + .3753*PG4 + .2411*PG5 - .1805*PG6 - .2528*PG7 + .0481*PG8 \quad (2)$$

$$\theta_2 = -.1557*PG2 - .2077*PG3 - .1177*PG4 + .0341*PG5 + .5255*PG6 + .6014*PG7 + .2543*PG8 \quad (3)$$

Computational Algorithm:

[0030] The implementation of the dynamical model and of factorial models of HbA1c includes initial estimation of Hbalc, tracking of HbA1c fluctuations over time, and occasional (e.g. monthly) calibrations of the tracking value. The initial and the calibration values of HbAlc are obtained using the same formula. The tracking procedure uses the dynamical model of HbA1c setting its parameter values at $\gamma=0.99$ and $\tau=20$. These two parameters are kept fixed throughout the estimation procedure. The end result is an *estimated value of HbA1c, eA1c,* given by the formulas below:

Step 1 **(optional)- Calibration of HbAlc** is derived from the factorial model of 7-point profiles presented in the previous section.. Calibration values for HbAlc are computed using the formula:

$$CalA1c = \frac{6.507}{1000} * \theta_1 + \frac{4.353}{1000} * \theta_2 \quad (4)$$

Where: *CalA1c* is the calibration value for HbAlc derived from the most recent profile;
θ_1 and θ_2 are the factors defined in the Factorial Model presented above. In the absence of a profile to calibrate, θ1 and θ2 are fixed (e.g. 180).

Step 2 - Initial Estimate, and Tracking Changes in Average Glycemia:
The glycation function is given by the formula:

$$f(SMBG_t) = MAX\left(\gamma * \left(4.7561 + \frac{4.854}{1000} * mP_0(t) + CalA1c\right), 5\right) \quad (5)$$

Where:

- $mP_0(t)$ is the average fasting glucose over the past 5 days and is updated every time a new fasting glucose is measured,
- CalA1c is the calibration offset as computed at the previous step.

- γ is the glycation efficacy parameter and is fixed by default at 0.99 (unless modified by step 3)

Initial Estimate:

[0031] To compute an initial estimate (when the device is first used or if a re-initialization is required (see Data Requirements section below) the tracking function is used directly:

$$eA1c(t_0) = f(SMBG_{t_0}) \quad (6)$$

Runtime Estimate

[0032] The HbAlc estimate is updated using the dynamic model presented in Figure 2.

[0033] For example, the glycation function can be fed into a discretized version (1 day time step) of the dynamic equation above to produce the updated HbAlc estimate *eA1c(t):* at any time t after initialization of the algorithm:

$$eA1c(t) = 0.95 * eA1c(t - 1\ day) + 0.05 * f(SMBG_t) \quad (7)$$

[0034] In addition, the output of the *eA1c* algorithm is saturated: instead of providing numerical estimates, values below 6% or above 10% are reported as *Low* and *High* respectively. This is done for the following three reasons:

(i) First, clinically, values below 6% are equivalent to values observed in non-diabetics and do not require any action, while values above 10 require significant clinical action regardless of the exact number;
(ii) Second, any estimation procedure would be less robust at the extremes of the HbAlc range and therefore including extreme values would lower unnecessarily its accuracy. This is valid for any estimation, not for this method alone;
(iii) Third, in these data sets, values below 6% and above 10% include less than 5% of all HbAlc records (2.8% below 6 and 1.4% above 10); thus, focusing on the clinically-relevant range of 6-10% HbAlc is also statistically justified.

Step 3 (optional) - Glycation formula calibration:

[0035] Equation (5) can be modified using a reference HbAlc calibration:
y is set in equation (5) so that the eA1c value corresponding to the reference HbAlc measurement. This calibration can occur at anytime in the functioning of the algorithm (e.g., method and related system) but is most efficient after at least a month of data collection.

RESULTS

[0036] An Example: (Patient 291039): Figure 3 illustrates the procedure tracking changes in average glycemia during normal operation of the method using fasting glucose and 7-point profiles assessed approximately once a month (Fasting and Profiles); with no 7-point profile available (Fasting data only); and enhanced by a 1 point reference HbAlc calibration (Fasting and Profiles with 1 Point Calibration).

Accuracy of the model-based *eA1c* compared to model-free linear formula:

[0037] In the tables below, the accuracy of estimation of HbAlc (*eA1c*) using the dynamical method detailed above omitting step 3 (first line of the table) is presented. For comparison with prior established methods, the second line of the table includes the same results for the widely accepted Nathan's linear formula[7] applied on the last 2 weeks of data. In addition to correlations, we use Mean Absolute Deviation (MAD) and Mean Absolute Relative Deviation (MARD) as standard approaches to accuracy evaluation:

Table 2: Training data: in the training data set, the method produced the following results:

Type of Algorithm Operation	Correlation with reference HbA1c	MAD	**MARD**
***eA1c* - Dynamic HbA1c Tracking (steps 1-3):** tracking fasting glucose; calibration with 7-point profiles approximately once a month and one reference HbA1c	0.85	0.39	**5.2%**
***eA1c* - Dynamic HbA1c Tracking (steps 1-2):** tracking fasting glucose; calibration with 7-point profiles approximately once a month	0.76	0.48	**6.6%**
Established linear formula (Nathan et al[7])	0.73	0.96	**12.8%**

[0038] While the table above presents a comparison of our dynamical HbA1c tracking procedure in the training data initially used for algorithm development, the table below presents the same comparisons in a data set that was *not* used for algorithm development. Thus, Table 3 below should be viewed as the "true test" of algorithm performance as compared to well-established contemporary methods:

Table 3: Test data: in the test data set, the method produced the following results:

Mode of Algorithm Operation	Correlation with reference HbA1c	MAD	**MARD**
***eA1c* - Dynamic HbA1c Tracking (steps 1-3):** tracking fasting glucose; calibration with 7-point profiles approximately once a month and one reference HbA1c	0.87	0.40	**5.3%**
***eA1c* - Dynamic A1c Tracking (steps 1-2)::** tracking fasting glucose; calibration with 7-point profiles approximately once a month	0.76	0.51	**6.8%**
Established linear formula (Nathan et al[7])	0.73	0.98	**13.1%**

[0039] It is considered that the most important result above may be MARD - the metric that is typically used to assess accuracy of any direct measurement or other assessment of unknown analyte. Achieving MARD well below 10% signifies that the method is capable of providing accurate and precise tracking of changes in average glycemia over time.

[0040] These results indicate that the dynamical estimation procedure proposed herein produces substantially more

accurate estimates of HbAlc than the latest widely accepted linear methods. Better accuracy is evident in all data sets used for the testing of the procedure.

[0041] Using the dynamical *eA1c* over other established procedures is particularly adapted to sparse data, e.g. where only fasting glucose is available together with occasional 7-point profiles and simple averages are likely to be biased. In this particular situation (which is common in Type 2 diabetes), having an underlying model has *clear robustness advantages* over a model-free linear procedure, which is heavily influenced by missing data and tends to produce biased results when limited data is available.

Distribution of *eA1c* Errors and Trends

[0042] This section focuses only on the SMBG-only based A1c estimation (steps 1-2)

HbAlc Error-Grid Analysis

[0043] Looking at the distribution of estimation error in the test data set (Table 2), we can make the following statements:

- more than 95% of *eA1c* values fall within ±17% of a standard lab reference measurement; corresponding to 95% of the eAlc values within ±1.17 HbAlc units (%) of the laboratory value.
- more than 61% of *eA1c* values fall within ± 7% of a standard lab reference measurement; corresponding to 61% of the eA1c values within ±0.52 HbAlc units (%) of the laboratory value.
- more than 53% *eA1c* values fall within ± 6% of a standard lab reference measurement.; corresponding to 53% of the eA1c values within ±0.44 HbAlc units (%) of the laboratory value.

A detailed look at the accuracy of HbA1c estimation is presented in the following pages, beginning with an error-grid type presentation of *eA1c* values vs. reference HbAlc. The Hbalc error-grid plot below is inspired by graphical error analyses presented in the past for the assessment of the accuracy of SMBG devices, e.g. Clarke Error-Grid[30] or Parkes (also known as Consensus) Error-. Constructing the HbAlc Error Grid we have relied in our extensive expertise Grid[31] analyses with this type of analyses which includes, but is not limited to, the introduction of the Continuous Error Grid now used for evaluation of the accuracy of continuous glucose monitors[32] and recommended by the Clinical and Laboratory Standardization Institute (CLSI) for this purpose[33].

[0044] Following the tradition of these Error-Grid plots, we define **A-zone** for *eA1c* accuracy as follows:

- *eA1c* is within 10% from reference HbAlc value, or
- Both reference HbAlc and *eA1c* are below 6% Hbalc, or
- Both reference HbAlc and *eA1c* are above 10% Hbalc.

[0045] B-zone is defined as *eA1c* that is within 20% from reference HbAlc value (note that in the established Clarke and Parkes error-grids, the A-zone is 20%; thus our analysis is *substantially more demanding*). Typically, A-zone is referred to as "Accurate" while B-Zone is referred to as "Benign errors"[30,31] which are generally acceptable in the evaluation of SMBG devices i.e. the cumulative percentage of A+B zone data pairs is used as a metric of device accuracy. Pairs outside of the A+B zones are generally considered erroneous.

HbAlc Error-Grid Analysis for *eA1c* in the Test Data Set

[0046] With the above in mind, Figure 4 presents the HbAlc Error-Grid plot for *eA1c* computed by the formulas above in the Test data set provided by Sanofi-Aventis (Table 2). The data is stratified by reference HbAlc values below 6% (green or hollow circles at the left-hand side of the grid), 6-10% (solid or blue circles) and above 10% (red or hollow circles at the right-hand side of the grid).

[0047] In Figure 4, 76.2% of the all data pairs fall within Zone A of the grid and 97.5% fall within Zones A+B of the grid. If limited to the reportable HbAlc range (6-10%), the accuracy increases to *78.3%* A-zone and 98.6% A+B zone, which is comparable to the accuracy of SMBG devices used for BG measurement in the clinical practice. Thus, the estimate of HbAlc derived from SMBG is comparable to the accuracy of the original SMBG readings[34]. This means that the model-based estimation procedure does not introduce further bias in the estimate, beyond the errors inherent with the input SMBG data.

HbAlc Error-Grid Analysis for the Linear Formula in the Test Data Set

[0048] Further, to compare the performance of the model-based *eA1c* to model-free linear estimators of HbAlc we

use the same Test data set and plot the HbAlc Error-Grid for the established linear model introduced by Nathan et al[7].

[0049] The grid in Figure 5 shows that the linear formula tends to overestimate significantly HbAlc, particularly readings above 8% HbAlc, and to underestimate HbAlc readings below 6%. This results in *only 43.8%* of the all data pairs within

[0050] Zone A of the grid and *only* 78.6% within Zones A+B of the grid (slightly lower - 42.5% and 78% - if the analysis is limited to reference HbAlc of 6-10%). Thus, the linear model has higher error estimating HbAlc than the SMBG data it uses as input. It follows that in this case the *linear model tends to amplify the SMBG errors of its input.*

[0051] The 20-percent difference in A+B zone hits observed between the model-based *eA1c* and Nathan's linear formula is not only very substantial, but also highlights a basic requirement for any estimation procedure: besides the errors inherent in the data, a good estimator should not introduce additional errors due to the estimation procedure itself.

Distribution of HbAlc rate of change

[0052] Looking at the distributions of the HbAlc daily rate of change observed in reference HbAlc values and in the dynamical estimate *eA1c,* we see that these two distributions are very similar (Figure 6, wide bars for laboratory values). The data shows that there is no difference in the rate of change distributions in laboratory and estimated HbAlc. Thus, accurate trend arrows can be displayed using *eA1.* The proposed trending system displays down/flat/up arrows, based on the **absolute change in eA1c,** conditions for arrow display is as follows:

- arrow up: *eA1c* is increasing faster than 0.01% per day (corresponding to an approximately 0.3% eA1c increase in a month);
- arrow down: *eA1c* is decreasing faster than 0.01% per day (corresponding to an approximately 0.3% *eA1c* decrease in a month);
- arrow flat: absolute *eA1c* changes are less or equal to 0.01% per day.

Figure 6 is a bar chart showing analysis of the A1c rate of change (wider bars: lab values; narrow bars: estimate).

Robustness Analysis

Stratification of the estimation error by reference HbAlc levels

[0053] By breaking down the accuracy of the HbAlc estimate by HbAlc values, we can determine how precise the *eA1c* estimate is given a laboratory HbAlc value. We stratify the testing data set by reference HbA1c and observe that the estimation procedure is most accurate in the 7% to 8% range with no bias and 4.5% MARD, which compares favorably to the Nathan's formula[7] (-0.81% bias and MARD 14.4%). Performance degrades on both side of the optimal range. It is to be noted that the *eA1c* algorithm is designed to not report values below 6% and above 10% (Lo and Hi displays). Within the HbAlc range of 6-10% the bias of *eA1c* is always less than 1% HbAlc and MARD is below 10%. Complete results are provided in the tables below:

Table 4: Bias stratified by laboratory HbA1c levels

	HbA1c<6	6≤HbA1c <7	7≤HbA1c <8	8≤HbA1c <9	9≤HbA1c≤10	HbA1c >10
***eA1c* algorithm**	1.02 n=40	0.49 n=516	-0.03 n=608	-0.37 n=265	-0.83 n=113	-1.46 n=19
Nathan's formula	0.09 n=43	-0.53 n=518	-0.81 n=616	-0.26 n=268	0.3 n=115	0.53 n=23
		Reportable HbA1c Range				

Table 5: MARD stratified by laboratory HbA1c levels

	HbA1c<6	6≤HbA1c <7	7≤HbA1c <8	8≤HbA1c <9	9≤HbA1c≤10	HbA1c >10
***eA1c* algorithm**	17.89 n=40	8.01 n=516	4.48 n=608	6.51 n=265	9.49 n=113	14.16 n=19
Nathan's formula	10.81 n=43	11.19 n=518	14.44 n=616	14.19 n=268	12.32 n=115	15.06 n=23
		Reportable HbA1c Range				

Stratification of the estimation error by estimated HbAlc levels

[0054] To answer the question "how much trust should one have, given an *eA1c* reading?" we offer another type of analysis: stratification of accuracy along estimated, not the reference HbA1c. First note that *eA1c* should not be used to report any values below 6% or above 10% by design. Within these confines, the *eA1c* algorithm is very stable, resulting in HbA1c biases between -0.23% and 0.19% and MARDs between 6.74% and 7.24%. In contrast, Nathan's formula shows a clear negative bias at low values and positive bias at high values, likely resulting from heavier weighting of fasting BG in the calculation of the mean. MARD for the Nathan's formula is always higher than for *eA1c,* with large values (18.3% and 22.5%) at the extremes. In addition, note that the Nathan's formula often predicts low HbAlc (<6%): 527 data points, compared to only 43 true HbAlc values below 6%. Complete results are presented below; see also Figure 4 and Figure 5:

Table 6: Bias and MARD for *eA1c* stratified by *eA1c* levels

	eA1c<6	6≤ *eA1c* <7	7≤ *eA1c* <8	8≤ *eA1c* <9	9≤ *eA1c* ≤10	*eA1c* >10
***eA1c* algorithm**	NA n=0	0.11 n=397	0.07 n=870	-0.23 n=243	0.19 n=51	NA n=7
	NA n=0	6.74 n=397	6.80 n=870	6.9 n=243	7.24 n=51	NA n=7
		Reportable *eA1c* Range				

Table 7: Bias and MARD for Nathan's formula stratified by the levels of Nathan's formula

	estimate <6	6≤ est. <7	7≤ est. <8	8≤ est. <9	9≤ est. ≤10	est. >10
Nathan's formula	-1.29 n=527	-0.69 n=497	-0.23 n=237	0.19 n=134	0.73 n=95	2.00 n=92
	18.34 n=527	10.27 n=497	7.68 n=237	7.56 n=135	10.95 n=95	22.51 n=92
		Reportable *eA1c* Range				

Analysis of Initial Estimation Errors

[0055] To determine if initialization creates larger initial errors compared to overall algorithm functioning, we contrast *eA1c* performance for the earliest available HbA1c/*eA1c* pairs for each subject of the testing data set (374 pairs) to the previously reported overall errors.
shows that performance in the early phases on *eA1c* computation is very similar to overall performance. It is to be noted that, due to the progression of the treatment in this study, the first laboratory HbAlc values across the subjects are significantly larger than the subsequent HbAlc values - 8.49% vs 7.43%, p<0.01 - which explains the slightly larger MAD, while MARD stays stable.

Table 8: Performance of *eA1c* estimation at initialisation vs. overall performance

	First pairs	Overall
MARD	7.0	6.8
MAD	0.61	0.51

Sensitivity Analysis

Sensitivity to missing fasting measurements

[0056] To perform this analysis we randomly dropped a fixed percentage of fasting BG measurement from the database. The percentage was increased from 0% to 90%. In addition we did not apply the Data Requirements (see below) to explore the limits of the "unprotected" algorithm.

[0057] The experiment is repeated 10 times and MARD results are presented in Figure 7. The *eA1c* algorithm proves extremely resilient to missing data with overall MARD rising only to 7% from 6.8% when 90% of fasting measurements are eliminated from the data base. Correlation does decrease more rapidly - from 0.76 to 0.68 - but remains high.

[0058] This analysis assesses degradation in *eA1c* performance if the user accidentally mixes the tags of a 7 point profiles (e.g. post breakfast is identified as fasting, or post-lunch is confused with pre dinner).

[0059] To perform this analysis we randomly identify a fixed percentage of profiles to be scrambled, then for each selected profile we randomly identify 3 pairs of BG measurement (6 values out of the 7 available) and for each pair we transpose the measurements in the profiles. The percentage of scrambled profiles was increased from 0% to 100%.

[0060] The experiment is repeated 10 times and MARD results are presented in Figure 8. Again the *eA1c* algorithm (and related method, system and computer readable medium) is robust to profile scrambling: MARD rises from 6.81 to 7.14% when all profiles are scrambled, and correlation goes from 0.76 to 0.74. This robustness is attributed to the use of factors (principal components) to quantify the profiles, as discussed above.

[0061] Alternate site testing is simulated by adding random noise to each SMBG measurements in the testing data set. The simulated error is normally distributed with zero mean SD=10% (meaning that 95% of the simulated 'AST' measurements are within 20% of the original SMBG value). We repeated the simulation 10 times and for each computed MARD, MAD and correlation between *eA1c* and lab HbAlc. Results are presented in Table 9. Some of the 10 simulations resulted in marginally degraded performance (far right column in Table 9), but overall the performance using AST was virtually identical to regular SMBG. Again this robustness can be attributed to the use of factors (instead of raw SMBG readings) and to the use of average fasting over 5 days in the tracking formula, which diminished the influence of SMBG errors approximately 2.24-fold (square root of 5).

Table 9: Performance of HbA1c estimation using simulated AST glucose measurements

	Original analysis	Mean performance across all AST simulations	Worst performance across all AST simulations
MARD	6.81	6.84	6.93
MAD	0.51	0.51	0.51
Correlation	0.76	0.755	0.750

Data Requirements

[0062] The estimation algorithm (and related method, system and computer readable medium) is built to be robust to missing profiles and occasional missing fasting values. The following minimum requirements and conditions determine

when reliable HbAlc estimate can be displayed to the user:

- no fasting values for less than 32 days
    - ◦ A1c estimate cannot be computed or displayed. Estimate will be reinitialized upon fasting BG condition being met again
    - ◦ user should be advised to measure fasting glucose
- number of fasting glucose in last 2 weeks is less than 7 or no fasting glucose in the last 5 days
    - ◦ Estimate is computed but possibly estimate value should not be displayed
    - ◦ user should be advised to measure fasting glucose
- time since last profile equal to or is more than 32 days but less than 64 days
    - ◦ Estimate is computed but possibly estimate value should not be displayed
    - ◦ user should be advised to provide profiles
- time since last profile is equal to or more than 64 days or no profile at all
    - ◦ A1c estimate cannot be computed and displayed. Estimate will be reinitialized upon profile BG condition being met again
    - ◦ User should be advised to provide profiles
- time since last profile is less than 32 days, number of fasting glucose in last 2 weeks is greater or equal to 7, and at least one fasting BG in last 5 days
    - ◦ A1c estimate can be computed and displayed
    - ◦ user should be encouraged to measure fasting BG daily

SUMMARIZATION AND IMPLEMENTATION EXAMPLES

[0063] In diabetes, the struggle for tight glycemic control results in large blood glucose fluctuations over time. This process is influenced by many external factors, including the timing and amount of insulin injected, food eaten, physical activity, etc. In other words, BG fluctuations are the measurable result of the action of a complex dynamical system, influenced by many internal and external factors. The macro (human)-level optimization of this system depends on self-treatment behavior. Thus, such an optimization has to be based on feedback utilizing readily available data, such as SMBG.

[0064] Although HbAlc is confirmed as the gold standard marker for average glycemia in both type 1 and type 2 diabetes,[2,3] HbAlc assays typically require a laboratory and are routinely done only every few months. On the other hand, we have shown that providing real-time estimates of HbAlc increases patient motivation and results in improved diabetes control.[29] Thus, tracking of changes in average glycemia is needed that is independent from laboratory HbAlc assays. SMBG offers this possibility, provided that appropriate algorithms (e.g., method, system, and computer readable medium) are employed to retrieve SMBG data.

[0065] An aspect of an embodiment of the present invention provides a method, system and computer readable medium for tracking changes in average glycemia in diabetes, based on a conceptually new approach (method and technique) to the retrieval of SMBG data. A principal premise of this approach is, among other things, the understanding of HbAlc fluctuation as the measurable effect of the action of an underlying dynamical system. SMBG provides occasional glimpses at the state of this system and, using these measurements, the hidden underlying system trajectory can be reconstructed for each individual.

[0066] Using compartmental modeling - a technique well established in diabetes research[35] - we have constructed a new two-step algorithm (and related method, system and computer readable medium) that includes: (i) real-time estimate of HbAlc from fasting glucose readings, updated with any new incoming fasting SMBG data point, and (ii) initialization and calibration of the estimated HbAlc trace with daily SMBG profiles taken approximately every month. The estimation of these 7-point profiles includes another innovative step - a factorial model capturing daily BG variability into two latent factors.

[0067] The development of our method and system followed a robust approach using a training data set to estimate all model parameters. After the initial estimation, all parameters were fixed and the algorithm was run prospectively on

an independent test data set. As evident from Tables 1 and 2 above, the results held, which confirms the robustness of the proposed procedure.

[0068] Further, we introduce and use HbAlc Error-Grid analysis inspired by the now classic Clarke[30] or Parkes[31] Error-Grids, which permits the graphical representation of accuracy results and the classification of accuracy into A- and B-zones signifying "Accurate" readings or "Benign" errors. This analysis resulted in 98.6% readings in the A+B zones - a result comparable to the accuracy of contemporary SMBG devices[34] (see also Figure 4).

[0069] At every step, we have compared the accuracy of our HbAlc estimator to a well-established linear formula (Nathan et al[7]), showing that our results are superior according to all analyses. Most striking is the accuracy comparison presented by the HbAlc Error-Grid (Figure 5), which shows 20% poorer performance by Nathan's formula in the A+B zones. The reason for this difference is in the nature of the data - it is evident that with sparse SMBG readings that include fasting glucose and occasional 7-point profiles, the mean does not represent well the true underlying average of blood glucose fluctuations. As a result, linear formulas based on mean SMBG tend to be significantly biased.

[0070] We can therefore conclude that a conceptually new, clinically viable, procedure has been developed for real-time estimation of HBA1c from self-monitoring data. As seen from the algorithm requirements, the procedure is readily applicable into devices, systems and networks with limited processing power, such as for example, but not limited thereto, home SMBG meters.

[0071] Example systems for implementation of the present invention will now be described with reference to Figs. 9 - 12. **Figure 9** is a high level functional block diagram of an embodiment of the present invention, or an aspect of an embodiment of the present invention.

[0072] As shown in **Figure 9,** a processor or controller **102** communicates with the glucose monitor or device **101,** and optionally the insulin device **100.** The glucose monitor or device **101** communicates with the subject **103** to monitor glucose levels of the subject **103.** The processor or controller **102** is configured to perform the required calculations. Optionally, the insulin device **100** communicates with the subject **103** to deliver insulin to the subject **103.** The processor or controller **102** is configured to perform the required calculations. The glucose monitor **101** and the insulin device **100** may be implemented as a separate device or as a single device. The processor **102** can be implemented locally in the glucose monitor **101,** the insulin device **100,** or a standalone device (or in any combination of two or more of the glucose monitor, insulin device, or a stand along device). The processor **102** or a portion of the system can be located remotely such that the device is operated as a telemedicine device.

[0073] Referring to **Figure 10A,** in its most basic configuration, computing device **144** typically includes at least one processing unit **150** and memory **146.** Depending on the exact configuration and type of computing device, memory **146** can be volatile (such as RAM), non-volatile (such as ROM, flash memory, etc.) or some combination of the two.

[0074] Additionally, device **144** may also have other features and/or functionality. For example, the device could also include additional removable and/or non-removable storage including, but not limited to, magnetic or optical disks or tape, as well as writable electrical storage media. Such additional storage is the figure by removable storage **152** and non-removable storage **148.** Computer storage media includes volatile and nonvolatile, removable and non-removable media implemented in any method or technology for storage of information such as computer readable instructions, data structures, program modules or other data. The memory, the removable storage and the non-removable storage are all examples of computer storage media. Computer storage media includes, but is not limited to, RAM, ROM, EEPROM, flash memory or other memory technology CDROM, digital versatile disks (DVD) or other optical storage, magnetic cassettes, magnetic tape, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to store the desired information and which can accessed by the device. Any such computer storage media may be part of, or used in conjunction with, the device. The device may also contain one or more communications connections **154** that allow the device to communicate with other devices (e.g. other computing devices). The communications connections carry information in a communication media. Communication media typically embodies computer readable instructions, data structures, program modules or other data in a modulated data signal such as a carrier wave or other transport mechanism and includes any information delivery media. The term "modulated data signal" means a signal that has one or more of its characteristics set or changed in such a manner as to encode, execute, or process information in the signal. By way of example, and not limitation, communication medium includes wired media such as a wired network or direct-wired connection, and wireless media such as radio, RF, infrared and other wireless media. As discussed above, the term computer readable media as used herein includes both storage media and communication media.

[0075] In addition to a stand-alone computing machine, embodiments of the invention can also be implemented on a network system comprising a plurality of computing devices that are in communication with a networking means, such as a network with an infrastructure or an ad hoc network. The network connection can be wired connections or wireless connections. By way of example, **Figure 10B** illustrates a network system in which embodiments of the invention can be implemented. In this example, the network system comprises computer **156** (e.g. a network server), network connection means **158** (e.g. wired and/or wireless connections), computer terminal **160,** and PDA (e.g. a smart-phone) **162** (or other handheld or portable device, such as a cell phone, laptop computer, tablet computer, GPS receiver, mp3 player, handheld video player, pocket projector, etc. or handheld devices (or non portable devices) with combinations of such features).

In an embodiment, it should be appreciated that the module listed as **156** may be glucose monitor device. In an embodiment, it should be appreciated that the module listed as **156** may be a glucose monitor device and/or an insulin device. Any of the components shown or discussed with **Figure 10B** may be multiple in number. The embodiments of the invention can be implemented in anyone of the devices of the system. For example, execution of the instructions or other desired processing can be performed on the same computing device that is anyone of **156, 160,** and **162.** Alternatively, an embodiment of the invention can be performed on different computing devices of the network system. For example, certain desired or required processing or execution can be performed on one of the computing devices of the network (e.g. server **156** and/or glucose monitor device), whereas other processing and execution of the instruction can be performed at another computing device (e.g. terminal **160**) of the network system, or vice versa. In fact, certain processing or execution can be performed at one computing device (e.g. server **156** and/or glucose monitor device); and the other processing or execution of the instructions can be performed at different computing devices that may or may not be networked. For example, the certain processing can be performed at terminal **160,** while the other processing or instructions are passed to device **162** where the instructions are executed. This scenario may be of particular value especially when the PDA **162** device, for example, accesses to the network through computer terminal **160** (or an access point in an ad hoc network). For another example, software to be protected can be executed, encoded or processed with one or more embodiments of the invention. The processed, encoded or executed software can then be distributed to customers. The distribution can be in a form of storage media (e.g. disk) or electronic copy.

[0076] **Figure 11** is a block diagram that illustrates a system **130** including a computer system **140** and the associated Internet **11** connection upon which an embodiment may be implemented. Such configuration is typically used for computers (hosts) connected to the Internet **11** and executing a server or a client (or a combination) software. A source computer such as laptop, an ultimate destination computer and relay servers, for example, as well as any computer or processor described herein, may use the computer system configuration and the Internet connection shown in **Figure 11**. The system **140** may be used as a portable electronic device such as a notebook/laptop computer, a media player (e.g., MP3 based or video player), a cellular phone, a Personal Digital Assistant (PDA), a glucose monitor device, an insulin delivery device, an image processing device (e.g., a digital camera or video recorder), and/or any other handheld computing devices, or a combination of any of these devices. Note that while **Figure 11** illustrates various components of a computer system, it is not intended to represent any particular architecture or manner of interconnecting the components; as such details are not germane to the present invention. It will also be appreciated that network computers, handheld computers, cell phones and other data processing systems which have fewer components or perhaps more components may also be used. The computer system of **Figure 11** may, for example, be an Apple Macintosh computer or Power Book, or an IBM compatible PC. Computer system **140** includes a bus **137,** an interconnect, or other communication mechanism for communicating information, and a processor **138,** commonly in the form of an integrated circuit, coupled with bus **137** for processing information and for executing the computer executable instructions. Computer system **140** also includes a main memory **134,** such as a Random Access Memory (RAM) or other dynamic storage device, coupled to bus **137** for storing information and instructions to be executed by processor **138.**

[0077] Main memory **134** also may be used for storing temporary variables or other intermediate information during execution of instructions to be executed by processor **138.** Computer system **140** further includes a Read Only Memory (ROM) **136** (or other non-volatile memory) or other static storage device coupled to bus **137** for storing static information and instructions for processor **138.** A storage device **135,** such as a magnetic disk or optical disk, a hard disk drive for reading from and writing to a hard disk, a magnetic disk drive for reading from and writing to a magnetic disk, and/or an optical disk drive (such as DVD) for reading from and writing to a removable optical disk, is coupled to bus **137** for storing information and instructions. The hard disk drive, magnetic disk drive, and optical disk drive may be connected to the system bus by a hard disk drive interface, a magnetic disk drive interface, and an optical disk drive interface, respectively. The drives and their associated computer-readable media provide non-volatile storage of computer readable instructions, data structures, program modules and other data for the general purpose computing devices. Typically computer system **140** includes an Operating System (OS) stored in a non-volatile storage for managing the computer resources and provides the applications and programs with an access to the computer resources and interfaces. An operating system commonly processes system data and user input, and responds by allocating and managing tasks and internal system resources, such as controlling and allocating memory, prioritizing system requests, controlling input and output devices, facilitating networking and managing files. Non-limiting examples of operating systems are Microsoft Windows, Mac OS X, and Linux.

[0078] The term "processor" is meant to include any integrated circuit or other electronic device (or collection of devices) capable of performing an operation on at least one instruction including, without limitation, Reduced Instruction Set Core (RISC) processors, CISC microprocessors, Microcontroller Units (MCUs), CISC-based Central Processing Units (CPUs), and Digital Signal Processors (DSPs). The hardware of such devices may be integrated onto a single substrate (e.g., silicon "die"), or distributed among two or more substrates. Furthermore, various functional aspects of the processor may be implemented solely as software or firmware associated with the processor.

[0079] Computer system **140** may be coupled via bus **137** to a display **131,** such as a Cathode Ray Tube (CRT), a

Liquid Crystal Display (LCD), a flat screen monitor, a touch screen monitor or similar means for displaying text and graphical data to a user. The display may be connected via a video adapter for supporting the display. The display allows a user to view, enter, and/or edit information that is relevant to the operation of the system. An input device **132,** including alphanumeric and other keys, is coupled to bus **137** for communicating information and command selections to processor **138.** Another type of user input device is cursor control **133,** such as a mouse, a trackball, or cursor direction keys for communicating direction information and command selections to processor **138** and for controlling cursor movement on display **131.** This input device typically has two degrees of freedom in two axes, a first axis (e.g., x) and a second axis (e.g., y), that allows the device to specify positions in a plane.

[0080] The computer system **140** may be used for implementing the methods and techniques described herein. According to one embodiment, those methods and techniques are performed by computer system **140** in response to processor **138** executing one or more sequences of one or more instructions contained in main memory **134.** Such instructions may be read into main memory **134** from another computer-readable medium, such as storage device **135.** Execution of the sequences of instructions contained in main memory **134** causes processor **138** to perform the process steps described herein. In alternative embodiments, hard-wired circuitry may be used in place of or in combination with software instructions to implement the arrangement. Thus, embodiments of the invention are not limited to any specific combination of hardware circuitry and software.

[0081] The terms "computer-readable medium," "machine-readable medium," or other analogous term as used herein is an extensible term that refers to any medium or any memory, that participates in providing instructions to a processor, (such as processor **138**) for execution, or any mechanism for storing or transmitting information in a form readable by a machine (e.g., a computer). Such a medium may store computer-executable instructions to be executed by a processing element and/or control logic, and data which is manipulated by a processing element and/or control logic, and may take many forms, including but not limited to, non-volatile medium, volatile medium, and transmission medium. Transmission media includes coaxial cables, copper wire and fiber optics, including the wires that comprise bus **137.** Transmission media can also take the form of acoustic or light waves, such as those generated during radio-wave and infrared data communications, or other form of propagated signals (e.g., carrier waves, infrared signals, digital signals, etc.). Common forms of computer-readable media include, for example, a floppy disk, a flexible disk, hard disk, magnetic tape, or any other magnetic medium, a CD-ROM, any other optical medium, punch-cards, paper-tape, any other physical medium with patterns of holes, a RAM, a PROM, and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave as described hereinafter, or any other medium from which a computer can read.

[0082] Various forms of computer-readable media may be involved in carrying one or more sequences of one or more instructions to processor **138** for execution. For example, the instructions may initially be carried on a magnetic disk of a remote computer. The remote computer can load the instructions into its dynamic memory and send the instructions over a telephone line using a modem. A modem local to computer system **140** can receive the data on the telephone line and use an infra-red transmitter to convert the data to an infra-red signal. An infra-red detector can receive the data carried in the infra-red signal and appropriate circuitry can place the data on bus **137.** Bus **137** carries the data to main memory **134,** from which processor **138** retrieves and executes the instructions. The instructions received by main memory **134** may optionally be stored on storage device **135** either before or after execution by processor **138.**

[0083] Computer system **140** also includes a communication interface **141** coupled to bus **137.** Communication interface **141** provides a two-way data communication coupling to a network link **139** that is connected to a local network **111.** For example, communication interface **141** may be an Integrated Services Digital Network (ISDN) card or a modem to provide a data communication connection to a corresponding type of telephone line. As another non-limiting example, communication interface **141** may be a local area network (LAN) card to provide a data communication connection to a compatible LAN. For example, Ethernet based connection based on IEEE802.3 standard may be used such as 10/100BaseT, 1000BaseT (gigabit Ethernet), 10 gigabit Ethernet (10 GE or 10 GbE or 10 GigE per IEEE Std 802.3ae-2002 as standard), 40 Gigabit Ethernet (40 GbE), or 100 Gigabit Ethernet (100 GbE as per Ethernet standard IEEE P802.3ba), as described in Cisco Systems, Inc. Publication number 1-587005-001-3 (6/99), "Internetworking Technologies Handbook", Chapter 7: "Ethernet Technologies", pages 7-1 to 7-38, which is incorporated in its entirety for all purposes as if fully set forth herein. In such a case, the communication interface **141** typically include a LAN transceiver or a modem, such as Standard Microsystems Corporation (SMSC) LAN91C111 10/100 Ethernet transceiver described in the Standard Microsystems Corporation (SMSC) data-sheet "LAN91C111 10/100 Non-PCI Ethernet Single Chip MAC+PHY" Data-Sheet, Rev. 15 (02-20-04), which is incorporated in its entirety for all purposes as if fully set forth herein.

[0084] Wireless links may also be implemented. In any such implementation, communication interface **141** sends and receives electrical, electromagnetic or optical signals that carry digital data streams representing various types of information. Network link **139** typically provides data communication through one or more networks to other data devices. For example, network link **139** may provide a connection through local network **111** to a host computer or to data equipment operated by an Internet Service Provider (ISP) 142. ISP **142** in turn provides data communication services through the world wide packet data communication network Internet **11.** Local network **111** and Internet **11** both use electrical, electromagnetic or optical signals that carry digital data streams. The signals through the various networks

and the signals on the network link **139** and through the communication interface **141,** which carry the digital data to and from computer system **140,** are exemplary forms of carrier waves transporting the information.

[0085] A received code may be executed by processor **138** as it is received, and/or stored in storage device **135,** or other non-volatile storage for later execution. In this manner, computer system **140** may obtain application code in the form of a carrier wave.

[0086] The concept of real-time estimation of HbA1c from self-monitoring data has been developed. As seen from the algorithm and methodology requirements discussed herein, the procedure is readily applicable into devices with limited processing power, such as hoe SMBG meters, and may be implemented and utilized with the related processors, networks, computer systems, internet, and components and functions according to the schemes disclosed herein.

[0087] **Figure 12** illustrates a system in which one or more embodiments of the invention can be implemented using a network, or portions of a network or computers. Although the present invention glucose device may be practiced without a network.

[0088] **Figure 12** diagrammatically illustrates an exemplary system in which examples of the invention can be implemented. In an embodiment the glucose monitor may be implemented by the subject (or patient) locally at home or other desired location. However, in an alternative embodiment it may be implemented in a clinic setting or assistance setting. For instance, referring to **Figure 12,** a clinic setup **158** provides a place for doctors (e.g. **164**) or clinician/assistant to diagnose patients (e.g. **159**) with diseases related with glucose and related diseases and conditions. A glucose monitoring device **10** can be used to monitor and/or test the glucose levels of the patient-as a standalone device. It should be appreciated that while only glucose monitor device **10** is shown in the figure, the system of the invention and any component thereof may be used in the manner depicted by **Figure 12.** The system or component may be affixed to the patient or in communication with the patient as desired or required. For example the system or combination of components thereof - including a glucose monitor device **10** (or other related devices or systems such as a controller, and/or an insulin pump, or any other desired or required devices or components) - may be in contact, communication or affixed to the patient through tape or tubing (or other medical instruments or components) or may be in communication through wired or wireless connections. Such monitor and/or test can be short term (e.g. clinical visit) or long term (e.g. clinical stay or family). The glucose monitoring device outputs can be used by the doctor (clinician or assistant) for appropriate actions, such as insulin injection or food feeding for the patient, or other appropriate actions or modeling. Alternatively, the glucose monitoring device output can be delivered to computer terminal **168** for instant or future analyses. The delivery can be through cable or wireless or any other suitable medium. The glucose monitoring device output from the patient can also be delivered to a portable device, such as PDA **166.** The glucose monitoring device outputs with improved accuracy can be delivered to a glucose monitoring center **172** for processing and/or analyzing. Such delivery can be accomplished in many ways, such as network connection **170,** which can be wired or wireless.

[0089] In addition to the glucose monitoring device outputs, errors, parameters for accuracy improvements, and any accuracy related information can be delivered, such as to computer **168,** and / or glucose monitoring center **172** for performing error analyses. This can provide a centralized accuracy monitoring, modeling and/or accuracy enhancement for glucose centers, due to the importance of the glucose sensors.

[0090] Examples of the invention can also be implemented in a standalone computing device associated with the target glucose monitoring device. An exemplary computing device (or portions thereof) in which examples of the invention can be implemented is schematically illustrated in **Figure 10A**.

REFERENCES

[0091] The following patents, applications and publications as listed below and throughout this document are hereby incorporated by reference in their entirety herein, and which are not admitted to be prior art with respect to the present invention by inclusion in this section.

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[0092] The devices, systems, computer readable medium, algorithms, models, and methods of various embodiments of the invention disclosed herein may utilize aspects disclosed in the following references, applications, publications and patents and which are hereby incorporated by reference herein in their entirety (and which are not admitted to be prior art with respect to the present invention by inclusion in this section):

A. U.S. Patent Application Serial No. 13/637,359, entitled "Method, System, and Computer Program Product for Improving the Accuracy of Glucose Sensors Using Insulin Delivery Observation in Diabetes", filed September 25, 2012;
B. U.S. Patent Application Serial No. 13/634,040, entitled "Method and System for the Safety, Analysis, and Supervision of Insulin Pump Action and Other Modes of Insulin Delivery in Diabetes", filed September 11, 2012.
C. International Patent Application Serial No. PCT/US2012/052422, entitled "Method, System and Computer Readable Medium for Adaptive Advisory Control of Diabetes", filed 8/26/2012;
D. International Patent Application Serial No. PCT/US2012/043910, entitled "Unified Platform For Monitoring and Control of Blood Glucose Levels in Diabetic Patients" filed 6/23/2012;
E. International Patent Application Serial No. PCT/US2012/043883, entitled "Methods and Apparatus for Modular Power Management and Protection of Critical Services in Ambulatory Medical Devices", filed 6/22/2012;
F. US Patent Application No. 13/394,091, entitled "Tracking the Probability for Imminent Hypoglycemia in Diabetes from Self-Monitoring Blood Glucose (SMBG) Data filed 3/2/12;
G. US Patent Application No. 13/393,647 filed 3/1/12, National Stage of PCT/US2010/047386, entitled "System, Method and Computer Program Product for Adjustment of Insulin Delivery (AID) in Diabetes Using Nominal Open-Loop Profiles" filed August 31, 2010;
H. US Patent Application No. 13/380,839 filed February 10, 2012, National Stage of PCT/US2010/040097, entitled "System, Method and Computer Stimulation Environment for In Silico Trials in Prediabetes and Type 2 Diabetes" filed June 25, 2010;
I. International Patent Application Serial No. PCT/US2011/029793, entitled "Method, System and Computer Program Product for Improving the Accuracy of Continuous Glucose Sensors Using Insulin Delivery Observation in Diabetes" filed March 24, 2011;
J. International Patent Application Serial No. PCT/US2011/028163, entitled "Method and System for the Safety, Analysis, and Supervision of Insulin Pump Action and Other Modes of Insulin Delivery in Diabetes" filed March 11, 2011;
K. U.S. Patent Application Serial No. 12/975,580, entitled "System, Method and Computer Program Product for Adjustment of Insulin Delivery (AID) in Diabetes Using Nominal Open-Loop Profiles", filed December 22, 2010;
L. International Patent Application Serial No. PCT/US2010/047711, entitled "Tracking the Probability for Hypoglycemia in Diabetes from Self-Monitoring Blood Glucose (SMBG) Data, filed September 2, 2010;
M. International Patent Application Serial No. PCT/US2010/047386, entitled "System Coordinator and Modular Architecture for Open-Loop and Closed-Loop Control of Diabetes", August 31, 2010;
N. International Patent Application Serial No. PCT/US2010/036629, entitled "System Coordinator and Modular Architecture for Open-Loop and Closed-Loop Control of Diabetes", filed May 28, 2010;
O. International Patent Application Serial No. PCT/US2010/025405, entitled "Method, System and Computer Program Product for CGM-Based Prevention of Hypoglycemia via Hypoglycemia Risk Assessment and Smooth Reduction Insulin Delivery," filed February 25, 2010;
P. International Patent Application Serial No. PCT/US2009/065725, entitled "Method, System, and Computer Program Product for Tracking of Blood Glucose Variability in Diabetes from Data," filed November 24, 2009;
Q. International Patent Application Serial No. PCT/US2008/082063, entitled "Model Predictive Control Based Method for Closed-Loop Control of Insulin Delivery in Diabetes Using Continuous Glucose Sensing", filed October 31, 2008;
R. PCT/US2008/069416, entitled "Method, System and Computer Program Product for Evaluation of Insulin Sensitivity, Insulin/Carbohydrate Ratio, and Insulin Correction Factors in Diabetes from Self-Monitoring Data", filed July

8, 2008;
S. PCT/US2008/067725, entitled "Method, System and Computer Simulation Environment for Testing of Monitoring and Control Strategies in Diabetes," filed June 20, 2008;
T. PCT/US2008/067723, entitled "LQG Artificial Pancreas Control System and Related Method", filed on 6/20/2008;
U. U.S. Patent Application Serial No. 12/516,044, entitled "Method, System, and Computer Program Product for the Detection of Physical Activity by Changes in Heart Rate, Assessment of Fast Changing Metabolic States, and Applications of Closed and Open Control Loop in Diabetes", filed May 22, 2009;
V. PCT/US2007/085588, entitled "Method, System, and Computer Program Product for the Detection of Physical Activity by Changes in Heart Rate, Assessment of Fast Changing Metabolic States, and Applications of Closed and Open Control Loop in Diabetes", filed November 27, 2007;
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X. U.S. Patent Application No. 11/578,831, entitled "Method, System and Computer Program Product for Evaluating the Accuracy of Blood Glucose Monitoring Sensors/Devices", filed October 18, 2006;
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AA. U.S. Patent No. 7,025,425 B2 issued April 11, 2006, entitled "Method, System, and Computer Program Product for the Evaluation of Glycemic Control in Diabetes from Self-Monitoring Data";
BB. U.S. Patent Application No. 11/305,946 filed December 19, 2005 entitled "Method, System, and Computer Program Product for the Evaluation of Glycemic Control in Diabetes from Self-Monitoring Data" (Publication No. 2006/0094947);
CC. PCT International Application Serial No. PCT/US2003/025053, filed August 8, 2003, entitled "Method, System, and Computer Program Product for the Processing of Self-Monitoring Blood Glucose (SMBG) Data to Enhance Diabetic Self-Management;"
DD. U.S. Patent Application No. 10/524,094 filed February 9, 2005 entitled "Managing and Processing Self-Monitoring Blood Glucose" (Publication No. 2005/214892);
EE. U.S. Serial No. 12/065,257, filed August 29, 2008, entitled "Accuracy of Continuous Glucose Sensors;"
FF. PCT International Application Serial No PCT/US2006/033724, filed August 29, 2006, entitled "Method for Improvising Accuracy of Continuous Glucose Sensors and a Continuous Glucose Sensor Using the Same";
GG. U.S. Serial No. 12/159,891, filed July 2, 2008, entitled "Method, System and Computer Program Product for Evaluation of Blood Glucose Variability in Diabetes from Self-Monitoring Data";
HH. PCT International Application No. PCT/US2007/000370, filed January 5, 2007, entitled "Method, System and Computer Program Product for Evaluation of Blood Glucose Variability in Diabetes from Self-Monitoring Data";
II. U.S. Patent Application No. 11/925,689 and PCT International Patent Application No. PCT/US2007/082744, both filed October 26, 2007, entitled "For Method, System and Computer Program Product for Real-Time Detection of Sensitivity Decline in Analyte Sensors";
JJ. U.S. Serial No. 10/069,674, filed February 22, 2002, entitled "Method and Apparatus for Predicting the Risk of Hypoglycemia";
KK. PCT International Application No. PCT/US00/22886, filed August 21, 2000, entitled "Method and Apparatus for Predicting the Risk of Hypoglycemia"; and
LL. U.S. Patent No. 6,923,763 B1, issued August 2, 2005, entitled "Method and Apparatus for Predicting the Risk of Hypoglycemia".

[0093] In summary, while the present invention has been described with respect to specific embodiments, many modifications, variations, alterations, substitutions, and equivalents will be apparent to those skilled in the art. The present invention is not to be limited in scope by the specific embodiment described herein. Indeed, various modifications of the present invention, in addition to those described herein, will be apparent to those of skill in the art from the foregoing description and accompanying drawings. Accordingly, the invention is to be considered as limited only by the spirit and scope of the following disclosure, including all modifications and equivalents.

[0094] 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 this application. For example, regardless of the content of any portion (e.g., title, field, background, summary, abstract, drawing figure, etc.) of this application, unless clearly specified to the contrary, there is no requirement for the inclusion in any claim herein or of any application claiming

priority hereto of any particular described or illustrated activity or element, any particular sequence of such activities, 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.

[0095] Unless clearly specified to the contrary, there is no requirement for any particular described or illustrated activity or element, any particular sequence or such activities, any particular size, speed, material, dimension or frequency, or any particularly interrelationship of such elements. Accordingly, the descriptions and drawings are to be regarded as illustrative in nature, and not as restrictive. Moreover, when any number or range is described herein, unless clearly stated otherwise, that number or range is approximate. When any range is described herein, unless clearly stated otherwise, that range includes all values therein and all sub ranges therein. Any information in any material (e.g., a United States/foreign patent, United States/foreign patent application, book, article, etc.) that has been incorporated by reference herein, is only incorporated by reference to the extent that no conflict exists between such information and the other statements and drawings set forth herein. In the event of such conflict, including a conflict that would render invalid any claim herein or seeking priority hereto, then any such conflicting information in such incorporated by reference material is specifically not incorporated by reference herein.

Claims

1. A computer-implemented method for providing a real-time estimate of glycosylated hemoglobin (HbAlc) of a patient (103, 159) from a self-monitoring blood glucose (SMBG) measurement, and tracking changes in average glycemia of said patient over time, said method comprising:

   Receiving, by a processor (102, 138, 150), a fasting SMBG measurement (1) from said patient;
   computing, by a processor (102, 138, 150), a glycation value using said fasting SMBG measurement in a predetermined glycation equation;
   outputting, by a processor (102, 138, 150), said glycation value as an initial estimate of HbAlc (4) upon initialization of tracking of said patient's average glycemia;
   characterised in that the method further comprises:

      updating, by a processor (102, 138, 150), said glycation value by using an updated SMBG value in said predetermined glycation equation, said updated SMBG value being based on a subsequent fasting SMBG measurement from said patient;
      computing, by a processor (102, 138, 150), an updated estimate of HbAlcusing said initial estimate of HbAlc and said updated glycation value in a predetermined HbAlc estimation equation; and
      outputting, by a processor (102, 138, 150), said updated estimate of HbAlc to a user.

2. The computer-implemented method of claim 1, further comprising:
   updating, by a processor (102, 138, 150), said updated estimate of HbAlc by:

      using a subsequent updated SMBG value in said predetermined glycation equation based on a further subsequent fasting SMBG measurement from said patient to compute a further updated glycation value; and
      computing, by a processor (102, 138, 150), a further updated estimate of HbAlc using a last updated estimate of HbAlc and said further updated glycation value in a predetermined HbAlc estimation equation; and
      outputting, by a processor (102, 138, 150), said further updated estimate of HbAlc to a user.

3. The computer-implemented method of claim 1 or 2, wherein said predetermined glycation equation is given by:

$$f(SMBG_t) = MAX\left(\gamma * \left(4.7561 + \frac{4.854}{1000} * mP_0(t) + CalA1c\right), 5\right)$$

   where

   mP_0(t) is the average fasting glucose over a predetermined period of time and is updated every time a new fasting glucose measurement is obtained from said patient,
   CalA1c is a calibration offset, and

y is a glycation efficacy parameter;

the initial estimate of HbA1c is given by

$$eA1c(t_0) = f\left(SMBG_{t_0}\right);$$

and
the updated estimate of HbA1c is given by

$$eA1c(t) = 0.95 * eA1c(t - 1\ day) + 0.05 * f(SMBG_t)$$

.

4. The computer-implemented method of claim 3, wherein said predetermined period of time is 5 days.

5. The computer-implemented method of claim 3, wherein y is fixed at 0.99.

6. The computer-implemented method of claim 3, wherein y is set so that the last updated estimate of HbAlc, *eA1c(t),* is set to correspond to a reference HbAlc measurement obtained from said patient.

7. The computer-implemented method of claim 3, wherein

$$CalA1c = \frac{6.507}{1000} * \theta_1 + \frac{4.353}{1000} * \theta_2$$

,

θ_1 and θ_2 are predefined factors in a SMBG profile (2) of said patient.

8. The computer-implemented method of claim 7, wherein said SMBG profile is a multipoint peri-prandial profile.

9. The computer-implemented method of claim 8, wherein said multipoint peri-prandial profile is a seven point profile including the following SMBG measurements:

PG2: first meal preprandial
PG3: first meal postprandial
PG4: second meal preprandial
PG5: second meal postprandial
PG6: third meal preprandial
PG7: third meal postprandial
PG8: before bedtime.

10. The computer-implemented method of claim 9, wherein

θ_1= .4006*PG2 + .4645*PG3 + .3753*PG4 + .2411*PG5 -.1805*PG6 - .2528*PG7 + .0481*PG8,

and

θ_2= -.1557*PG2 - .2077*PG3 .1177*PG4 + .0341*PG5 + .5255*PG6 + .6014*PG7 + .2543*PG8.

11. A system for providing a real-time estimate of glycosylated hemoglobin (HbA1c) of a patient (103, 159) from a self-

monitoring blood glucose (SMBG) measurement, and tracking changes in average glycemia of said patient over time, comprising:

a processor (102, 138, 150); and
a processor-readable memory (146, 134) including processor-executable instructions for performing the method of any of claims 1 to 10.

Patentansprüche

1. Computerimplementiertes Verfahren zum Bereitstellen einer Echtzeitschätzung von glykolisiertem Hämoglobin (HbA1c) eines Patienten (103, 159) von einer Messung im Rahmen der Blutzuckerselbstkontrolle (SMBG) und Verfolgen von Änderungen bei der mittleren Glykämie des Patienten, das Verfahren umfassend:

Empfangen, durch einen Prozessor (102, 138, 150), einer Nüchtern-SMBG-Messung (1) vom Patienten;
Berechnen, durch einen Prozessor (102, 138, 150), einer Glykierung unter Verwendung der Nüchtern-SMBG-Messung in einer vorbestimmten Glykierungsgleichung;
Ausgeben, durch einen Prozessor (102, 138, 150), des Glykierungswertes als eine erste Schätzung des HbA1c (4) bei der Initialisierung der Verfolgung der mittleren Glykämie des Patienten;
dadurch gekennzeichnet, dass das Verfahren ferner Folgendes umfasst:

Aktualisieren, durch einen Prozessor (102, 138, 150), des Glykierungswertes unter Verwendung eines aktualisierten SMBG-Wertes in der vorbestimmten Glykierungsgleichung, wobei der aktualisierte SMBG-Wert auf einer nachfolgenden Nüchtern-SMBG-Messung des Patienten basiert;
Berechnen, durch einen Prozessor (102, 138, 150), einer aktualisierten Schätzung des HbA1c unter Verwendung der ersten Schätzung des HbA1c und des aktualisierten Glykierungswertes in einer vorbestimmten HbA1c-Gleichung; und
Ausgeben, durch einen Prozessor (102, 138, 150), der aktualisierten Schätzung des HbA1c an einen Benutzer.

2. Computerimplementiertes Verfahren nach Anspruch 1, ferner umfassend:
Aktualisieren, durch einen Prozessor (102, 138, 150), der aktualisierten Schätzung des HbA1c durch:

Verwenden eines nachfolgenden aktualisierten SMBG-Wertes in der vorbestimmten Glykierungsgleichung basierend auf einer weiteren nachfolgenden Nüchtern-SMBG-Messung vom Patienten zum Berechnen eines weiteren aktualisierten Glykierungswertes; und
Berechnen, durch einen Prozessor (102, 138, 150), einer weiteren aktualisierten Schätzung des HbA1c unter Verwendung einer letzten Schätzung des HbA1c und des weiteren aktualisierten Glykierungswertes in einer vorbestimmten HbA1c-Schätzgleichung; und
Ausgeben, durch einen Prozessor (102, 138, 150), der weiteren aktualisierten Schätzung des HbA1c an einen Benutzer.

3. Computerimplementiertes Verfahren nach Anspruch 1 oder 2, wobei die vorbestimmte Glykierungsgleichung gegeben ist durch:

$$f(SMBG_t) = MAX\left(\gamma * \left(4.7561 + \frac{4.854}{1000} * mP_0(t) + CalA1c\right), 5\right)$$

wobei

$mP_0(t)$ der durchschnittlichen Nüchternglukose über eine vorbestimmte Zeitdauer entspricht, und jedes Mal aktualisiert wird, wenn eine neue Nüchternglukosemessung vom Patienten erhalten wird,
CalA1c einem Kalibrierungs-Offset entspricht, und
γ einem Glykierungswirksamkeitsparameter entspricht;
die erste Schätzung des HbA1c gegeben ist durch

$$eA1c(t_0) = f\left(SMBG_{t_0}\right) \ ;$$

und
die aktualisierte Schätzung des HbA1c gegeben ist durch

$$eA1c(t) = 0.95 * eA1c(t - 1\ day) + 0.05 * f(SMBG_t)$$

4. Computerimplementiertes Verfahren nach Anspruch 3, wobei die vorbestimmte Zeitdauer 5 Tage beträgt.

5. Computerimplementiertes Verfahren nach Anspruch 3, wobei γ auf 0,99 festgelegt wird.

6. Computerimplementiertes Verfahren nach Anspruch 3, wobei y so eingestellt wird, dass die letzte aktualisierte Schätzung des HbA1c, *eA1c(t),* eingestellt wird, um einer vom Patienten erhaltenen Referenz-HbA1c-Messung zu entsprechen.

7. Computerimplementiertes Verfahren nach Anspruch 3, wobei

$$CalA1c = \frac{6.507}{1000} * \theta_1 + \frac{4.353}{1000} * \theta_2$$

θ_1 und θ_2 vordefinierte Faktoren in einem SMBG-Profil (2) des Patienten sind.

8. Computerimplementiertes Verfahren nach Anspruch 7, wobei das SMBG-Profil ein periprandiales Mehrpunktprofil ist.

9. Computerimplementiertes Verfahren nach Anspruch 8, wobei das periprandiale Mehrpunktprofil ein Sieben-Punkte-Profil ist, das folgende SMBG-Messungen enthält:

PG2: erste Mahlzeit präprandial
PG3: erste Mahlzeit postprandial
PG4: zweite Mahlzeit präprandial
PG5: zweite Mahlzeit postprandial
PG6: dritte Mahlzeit präprandial
PG7: dritte Mahlzeit postprandial
PG8: vor dem Schlafengehen.

10. Computerimplementiertes Verfahren nach Anspruch 9, wobei

$$\theta_1 = ,4006*PG2 + ,4645 *PG3 + ,3753*PG4 + ,2411*PG5 - ,1805*PG6 - ,2528*PG7 + ,0481*PG8,$$

und

$$\theta_2 = -,1557*PG2 - ,2077*PG3a ,1177*PG4 + ,0341 *PG5 + ,5255*PG6 + ,6014*PG7 + ,2543*PG8.$$

11. System zum Bereitstellen einer Echtzeitschätzung des glycosylierten Hämoglobins (HbA1c) eines Patienten (103, 159) von einer Messung im Rahmen einer Blutzuckerselbstkontrolle (SMBG) und zeitlichen Verfolgen von Änderungen der mittleren Glykämie des Patienten, umfassend:

einen Prozessor (102, 138, 150); und
einen prozessorlesbaren Speicher (146, 134), der prozessorausführbare Anweisungen zum Durchführen des Verfahrens nach einem der Ansprüche 1 bis 10 beinhaltet.

Revendications

1. Procédé mis en oeuvre par ordinateur pour fournir une estimation en temps réel de l'hémoglobine glyquée (HbAlc) d'un patient (103, 159) à partir d'une mesure de l'autosurveillance glycémique (ASG), et pour suivre les variations de la glycémie moyenne dudit patient au fil du temps, ledit procédé comprenant :

   la réception, par un processeur (102, 138, 150), d'une mesure de l'ASG à jeun (1) à partir dudit patient ;
   le calcul, par un processeur (102, 138, 150), d'une valeur de glycation utilisant ladite mesure de l'ASG à jeun dans une équation de glycation prédéterminée ;
   la délivrance, par un processeur (102, 138, 150), de ladite valeur de glycation comme estimation initiale de l'HbA1c (4) lors de l'initialisation du suivi de la glycémie moyenne dudit patient ;
   caractérisé en ce que le procédé comprend en outre :

      la mise à jour, par un processeur (102, 138, 150), de ladite valeur de glycation en utilisant une valeur ASG actualisée dans ladite équation de glycation prédéterminée, ladite valeur ASG actualisée étant basée sur une mesure de l'ASG à jeun ultérieure dudit patient ;
      le calcul, par un processeur (102, 138, 150), d'une estimation mise à jour de l'HbA1c en utilisant l'estimation initiale de l'HbA1c et ladite valeur de glycation actualisée dans une équation d'estimation prédéterminée d'HbA1c ; et
      la délivrance, par un processeur (102, 138, 150), de ladite estimation mise à jour de l'HbA1c à un utilisateur.

2. Procédé mis en oeuvre par ordinateur selon la revendication 1, comprenant en outre :
   la mise à jour, par un processeur (102, 138, 150), de ladite estimation de l'HbA1c par :

      l'utilisation d'une valeur ASG actualisée ultérieure dans ladite équation de glycation prédéterminée basée sur une mesure supplémentaire ultérieure de l'ASG à jeun dudit patient pour calculer une valeur de glycation supplémentaire mise à jour ; et
      le calcul, par un processeur (102, 138, 150), d'une estimation supplémentaire mise à jour de l'HbA1c à l'aide d'une dernière estimation mise à jour de l'HbA1c et d'une valeur supplémentaire de glycation actualisée dans une équation d'estimation prédéterminée d'HbA1c ; et
      la délivrance, par un processeur (102, 138, 150), de ladite estimation supplémentaire de l'HbA1c à un utilisateur.

3. Procédé mis en oeuvre par ordinateur selon la revendication 1 ou selon la revendication 2, dans lequel ladite équation de glycation prédéterminée est donnée par :

$$f(SMBG_t) = MAX\left(\gamma * \left(4.7561 + \frac{4.854}{1000} * mP_0(t) + CalA1c\right), 5\right)$$

   où

   $mP_0(t)$ est la glycémie à jeun moyenne sur une période de temps prédéterminée et est mis à jour chaque fois qu'une nouvelle mesure de glycémie à jeun est obtenue à partir dudit patient,
   CalA1c est un décalage de calibrage, et
   γ est un paramètre d'efficacité de glycation ;
   l'estimation initiale de l'HbA1c est donnée par

$$eA1c(t_0) = f\left(SMBG_{t_0}\right) \ ;$$

   et
   l'estimation mise à jour de l'HbA1c est donnée par

$$eA1c(t) = 0.95 * eA1c(t - 1\ day) + 0.05 * f(SMBG_t)$$

4. Procédé mis en oeuvre par ordinateur selon la revendication 3, dans lequel ladite période prédéterminée de temps est de 5 jours.

5. Procédé mis en oeuvre par ordinateur selon la revendication 3, dans lequel γ est fixé à 0,99.

6. Procédé mis en oeuvre par ordinateur selon la revendication 3, dans lequel y est défini de sorte que la dernière estimation mise à jour de l'HbA1c, *eAlc(t),* est définie pour correspondre à une mesure de référence d'HbA1c obtenue auprès dudit patient.

7. Procédé mis en oeuvre par ordinateur selon la revendication 3, dans lequel

$$CalA1c = \frac{6.507}{1000} * \theta_1 + \frac{4.353}{1000} * \theta_2$$

θ_1 et θ_2 sont des facteurs prédéfinis dans un profil ASG (2) dudit patient.

8. Procédé mis en oeuvre par ordinateur selon la revendication 7, dans lequel ledit profil ASG est un profil péri-prandial à points multiples.

9. Procédé mis en oeuvre par ordinateur selon la revendication 8, dans lequel ledit profil péri-prandial à points multiples est un profil à sept points, y compris les mesures d'ASG suivantes :

PG2 : premier repas préprandial
PG3 : premier repas postprandial
PG4 : deuxième repas préprandial
PG5 : deuxième repas postprandial
PG6 : troisième repas préprandial
PG7 : troisième repas postprandial
PG8 : avant le coucher.

10. Procédé mis en oeuvre par ordinateur selon la revendication 9, dans lequel

$$\theta_1 = 0,4006*PG2 + 0,4645 *PG3 + 0,3753*PG4 + 0,2411*PG5 - 0.1805*PG6 - 0,2528*PG7 + 0,0481*PG8,$$

et

$$\theta_2 = -0.1557*PG2 - 0,2077*PG3a\ 0,1177*PG4 + 0,0341 *PG5 + 0,5255*PG6 + 0,6014*PG7 + 0,2543*PG8.$$

11. Système permettant de fournir une estimation en temps réel de l'hémoglobine glyquée (HbAlc) d'un patient (103, 159) à partir d'une mesure de l'autosurveillance glycémique (ASG), et de suivre les variations de la glycémie moyenne dudit patient au fil du temps, comprenant :

un processeur (102, 138, 150) ; et
une mémoire lisible par un processeur (146, 134), y compris des instructions exécutables par le processeur pour exécuter le procédé selon l'une quelconque des revendications 1 à 10.

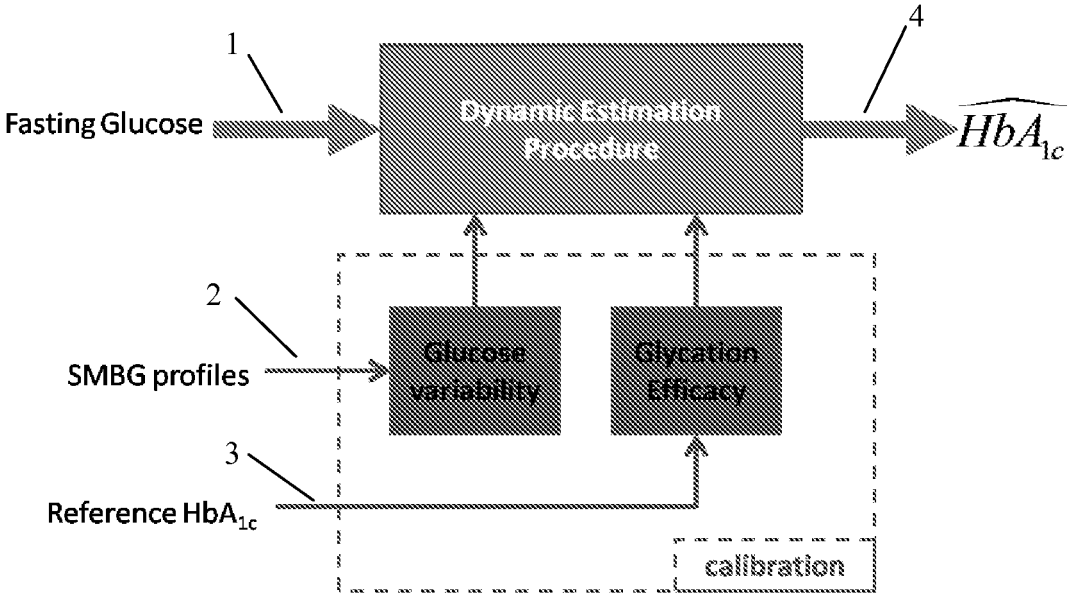
1
4
Fasting Glucose
Dynamic Estimation Procedure
$\widehat{HbA_{1c}}$
2
SMBG profiles
Glucose variability
Glycation Efficacy
3
Reference HbA1c
calibration

Fig. 1

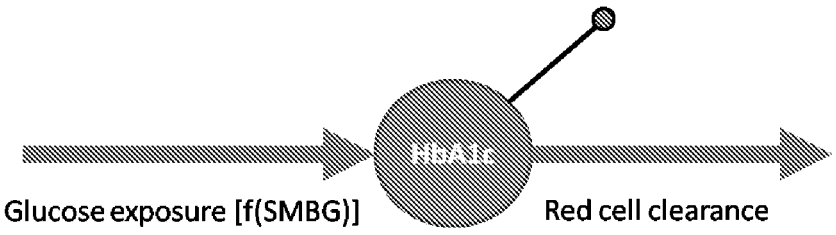
HbA1c
Glucose exposure [f(SMBG)]
Red cell clearance

Fig. 2

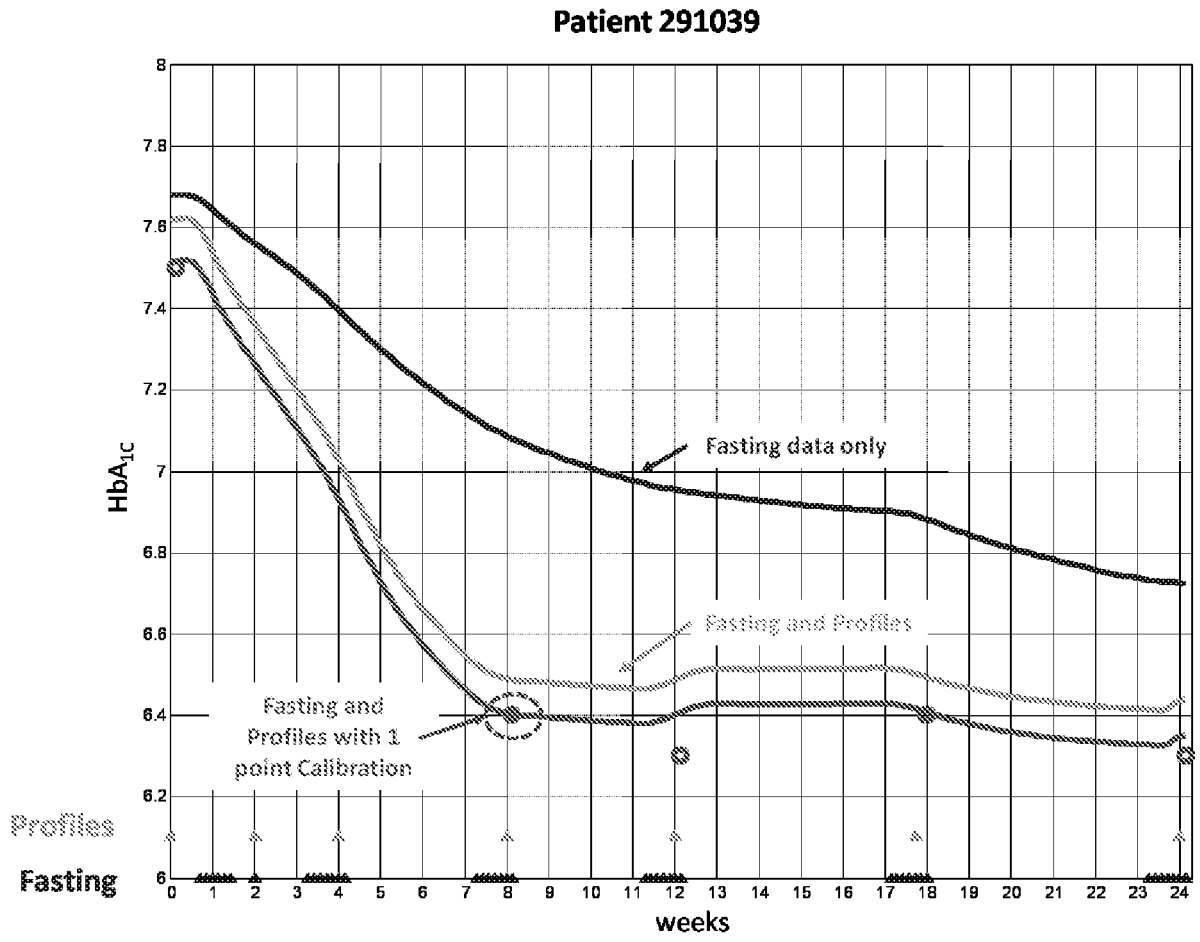
Patient 291039
HbA1C
Fasting data only
Fasting and Profiles
Fasting and Profiles with 1 point Calibration
Profiles
Fasting
weeks

Fig. 3

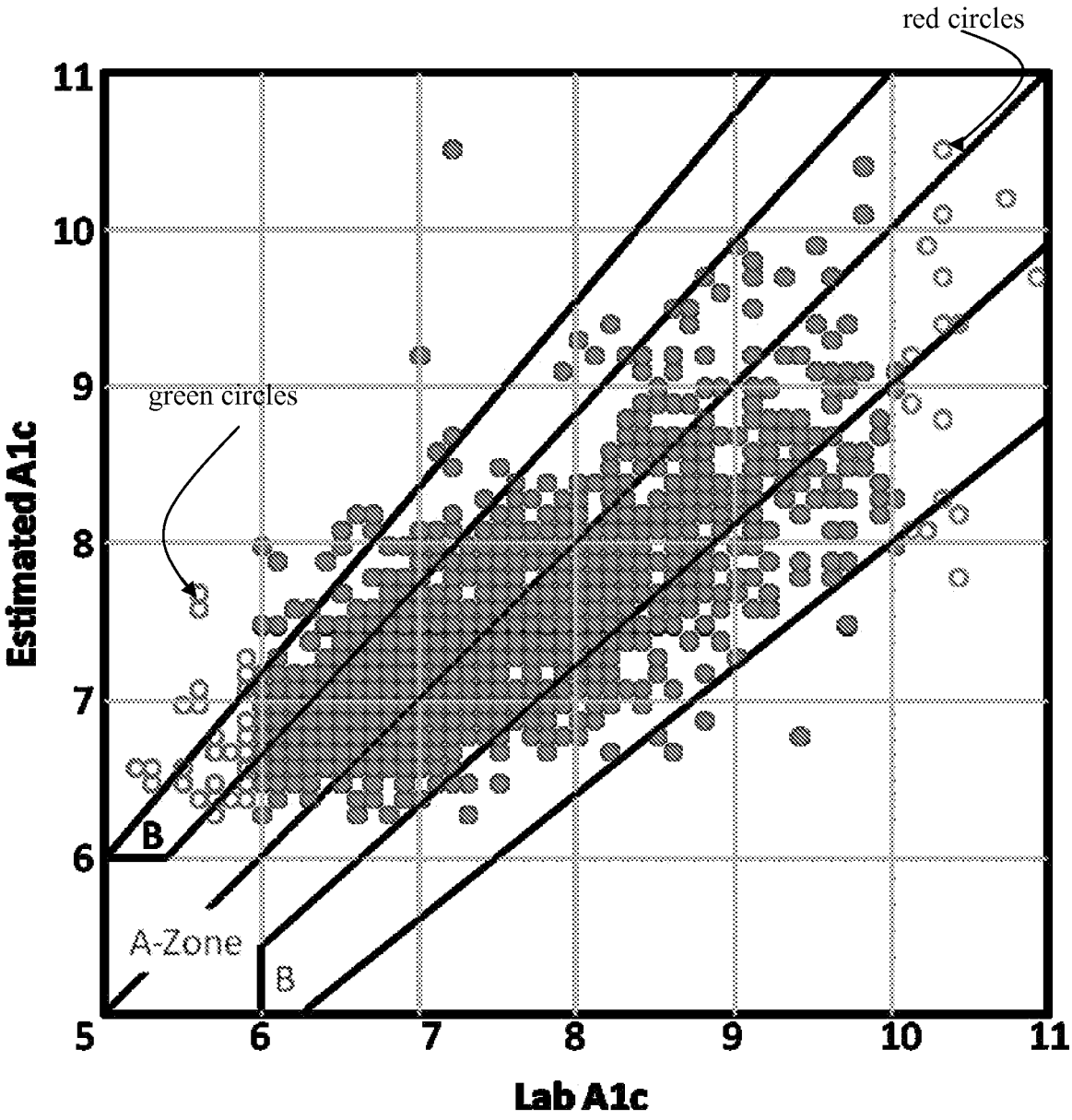
red circles
green circles
A-Zone
B
B
Estimated A1c
Lab A1c
11
10
9
8
7
6
5
6
7
8
9
10
11

Fig. 4

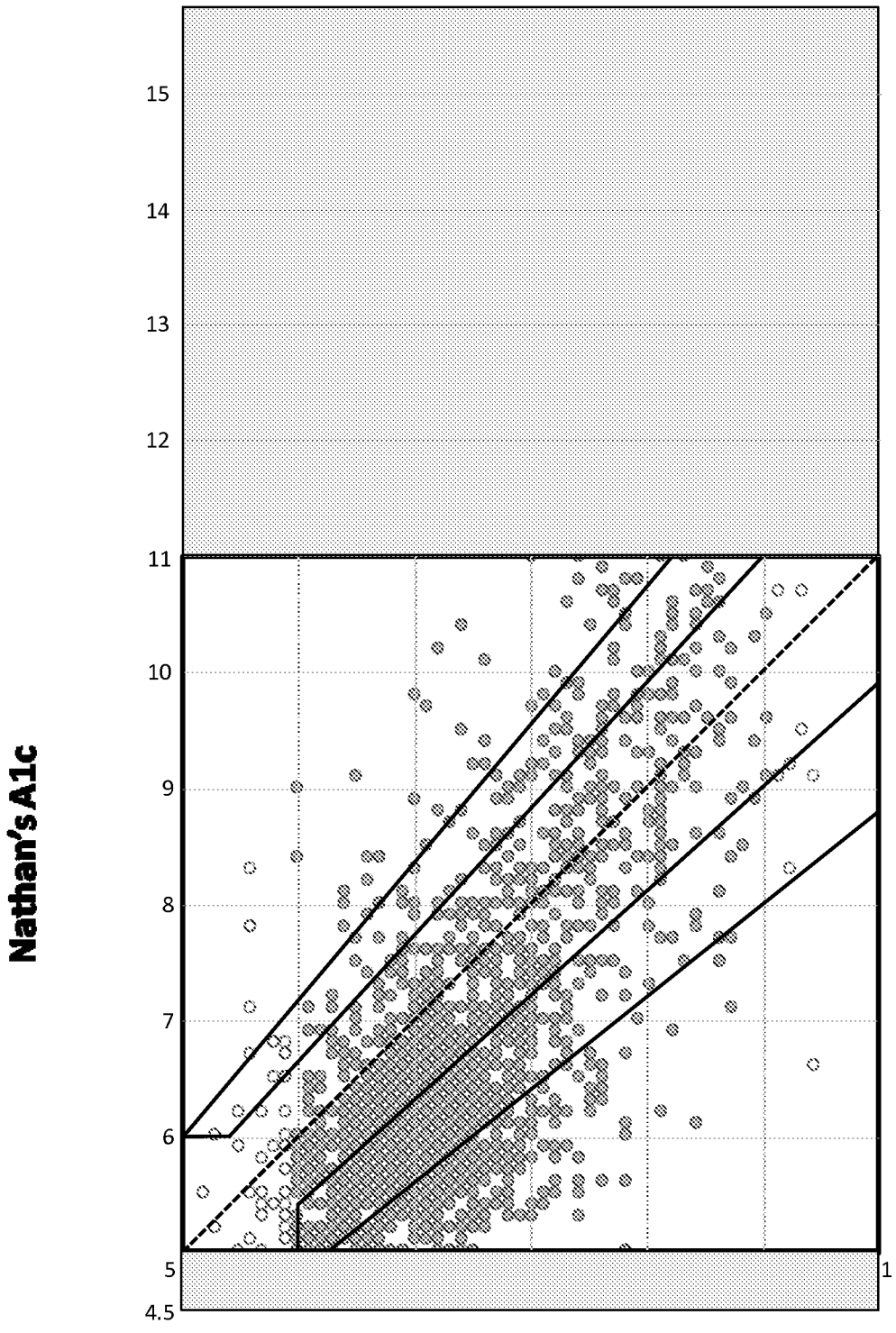

Fig. 5

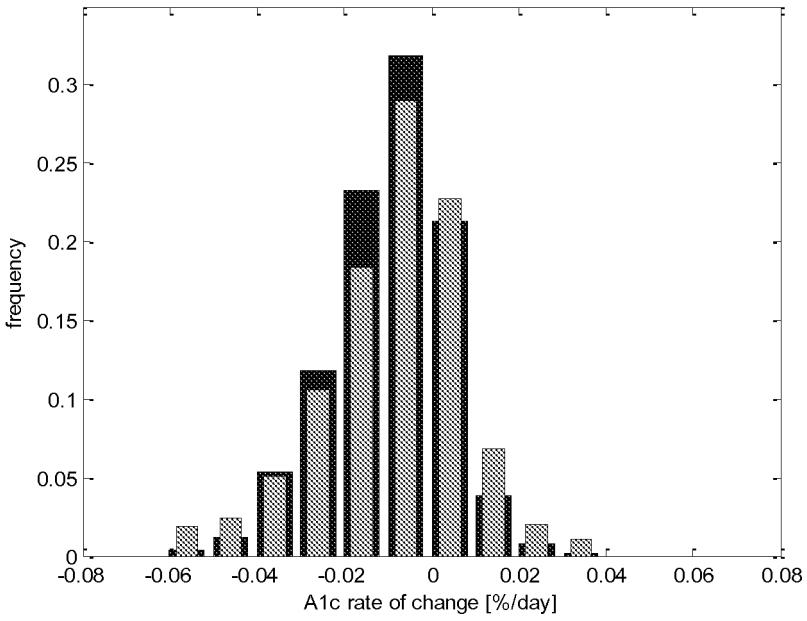
frequency
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.08
-0.06
-0.04
-0.02
0
0.02
0.04
0.06
0.08
A1c rate of change [%/day]

Fig. 6

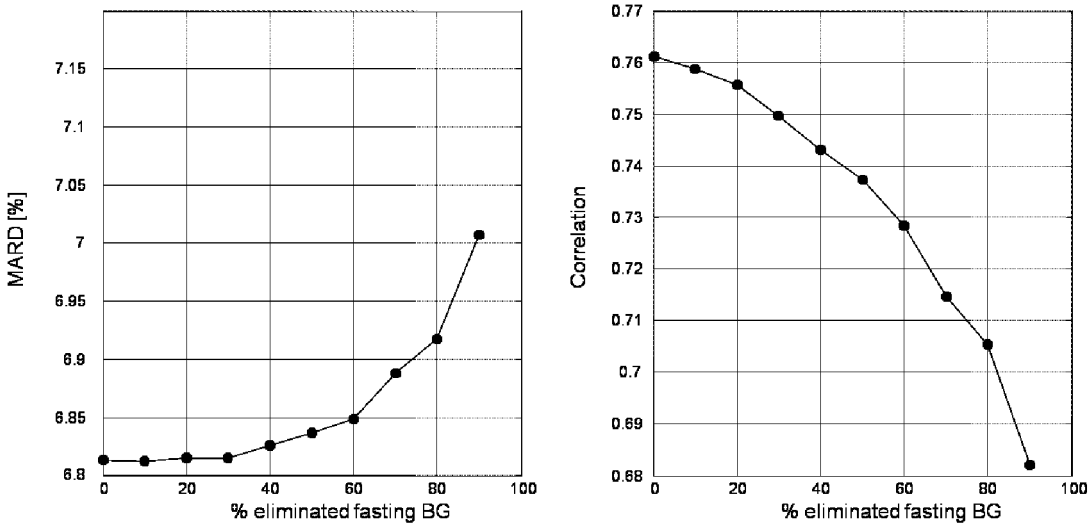
MARD [%]
7.15
7.1
7.05
7
6.95
6.9
6.85
6.8
0
20
40
60
80
100
% eliminated fasting BG
Correlation
0.77
0.76
0.75
0.74
0.73
0.72
0.71
0.7
0.69
0.68
0
20
40
60
80
100
% eliminated fasting BG

Fig. 7

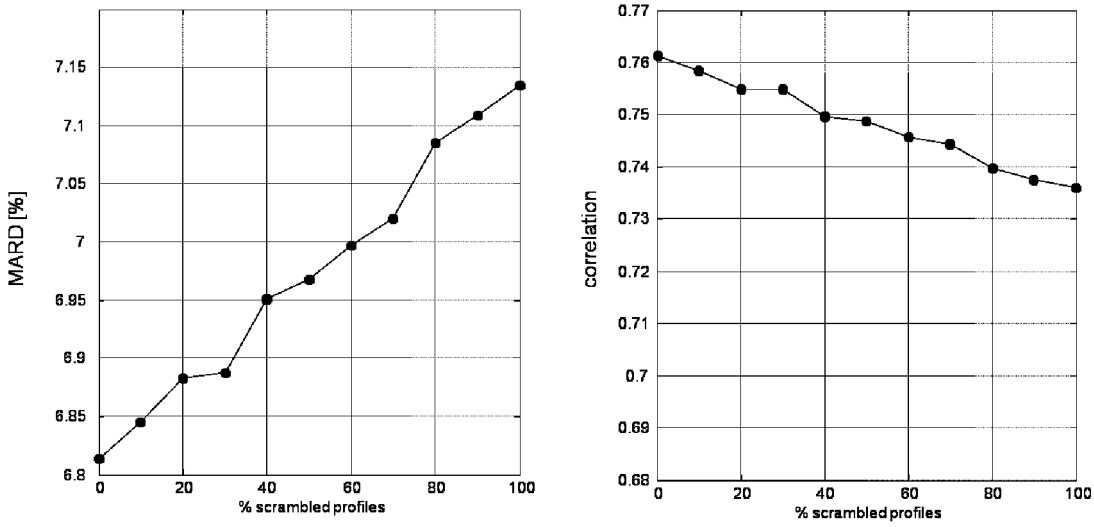
MARD [%]
7.15
7.1
7.05
7
6.95
6.9
6.85
6.8
0
20
40
60
80
100
% scrambled profiles
correlation
0.77
0.76
0.75
0.74
0.73
0.72
0.71
0.7
0.69
0.68
0
20
40
60
80
100
% scrambled profiles

Fig. 8

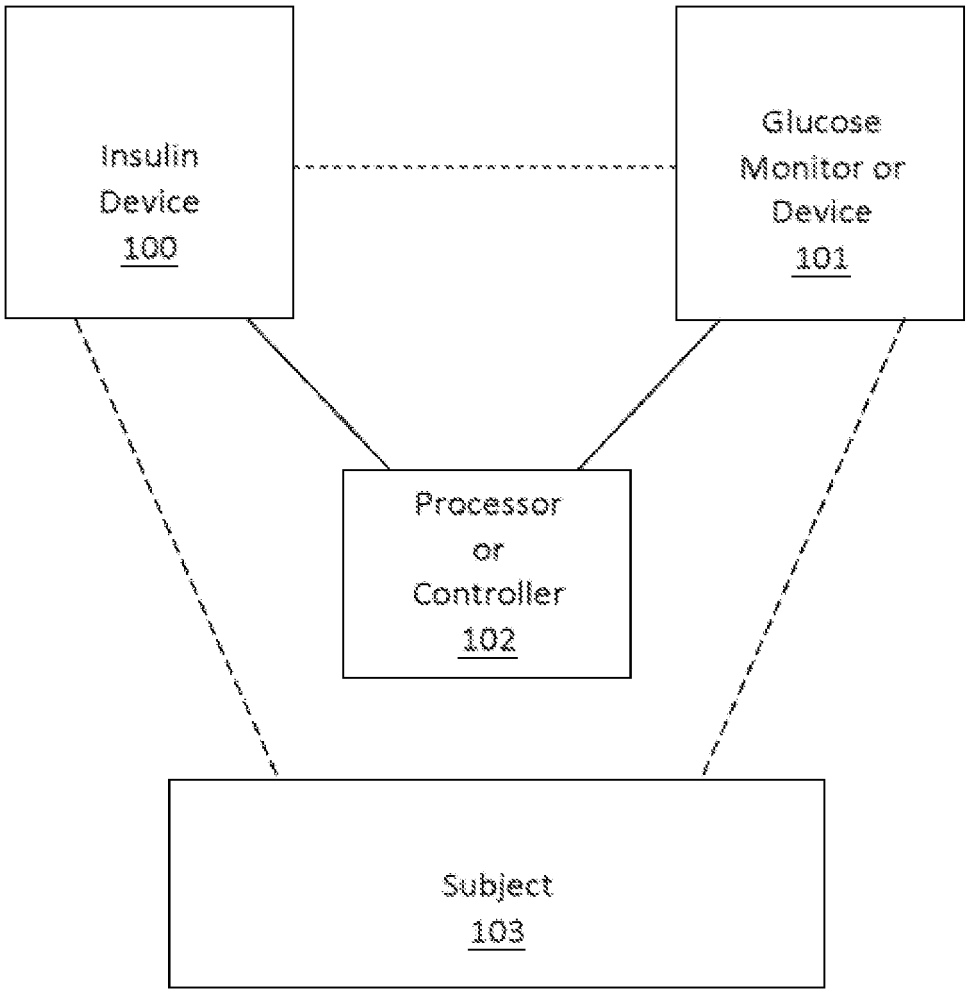
Insulin
Device
100
Glucose
Monitor or
Device
101
Processor
or
Controller
102
Subject
103

Fig. 9

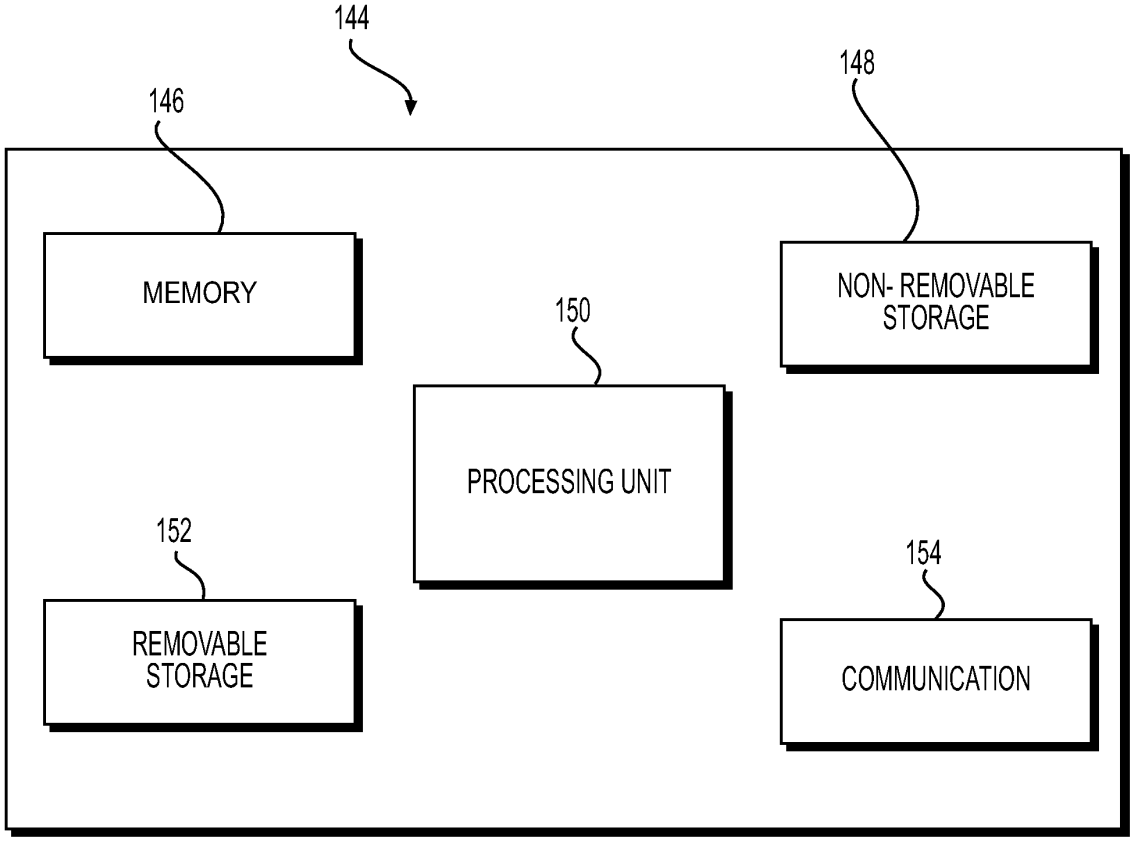

FIG. 10A

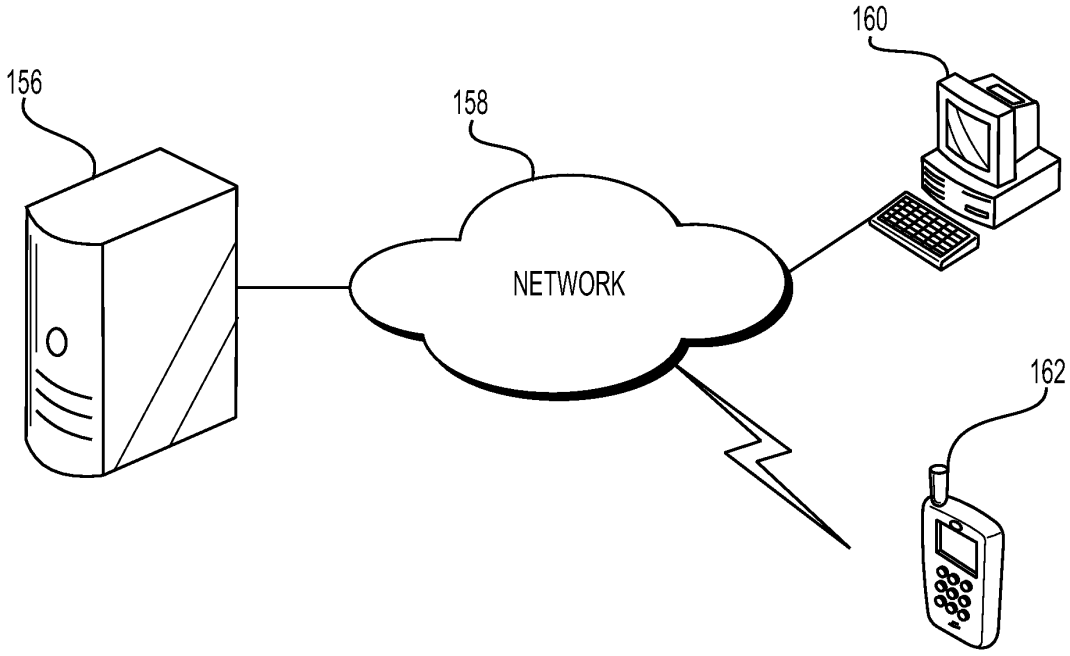

FIG. 10B

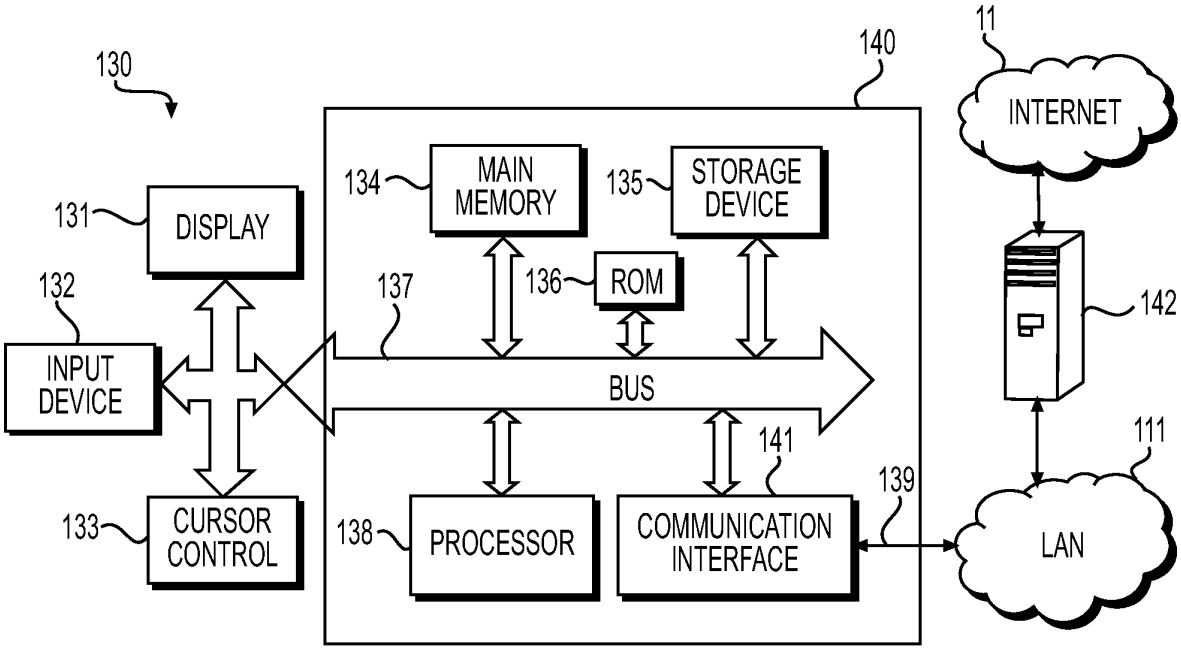
130
140
11
INTERNET
134
MAIN MEMORY
135
STORAGE DEVICE
131
DISPLAY
137
136
ROM
142
132
INPUT DEVICE
BUS
141
111
139
133
CURSOR CONTROL
138
PROCESSOR
COMMUNICATION INTERFACE
LAN

FIG. 11

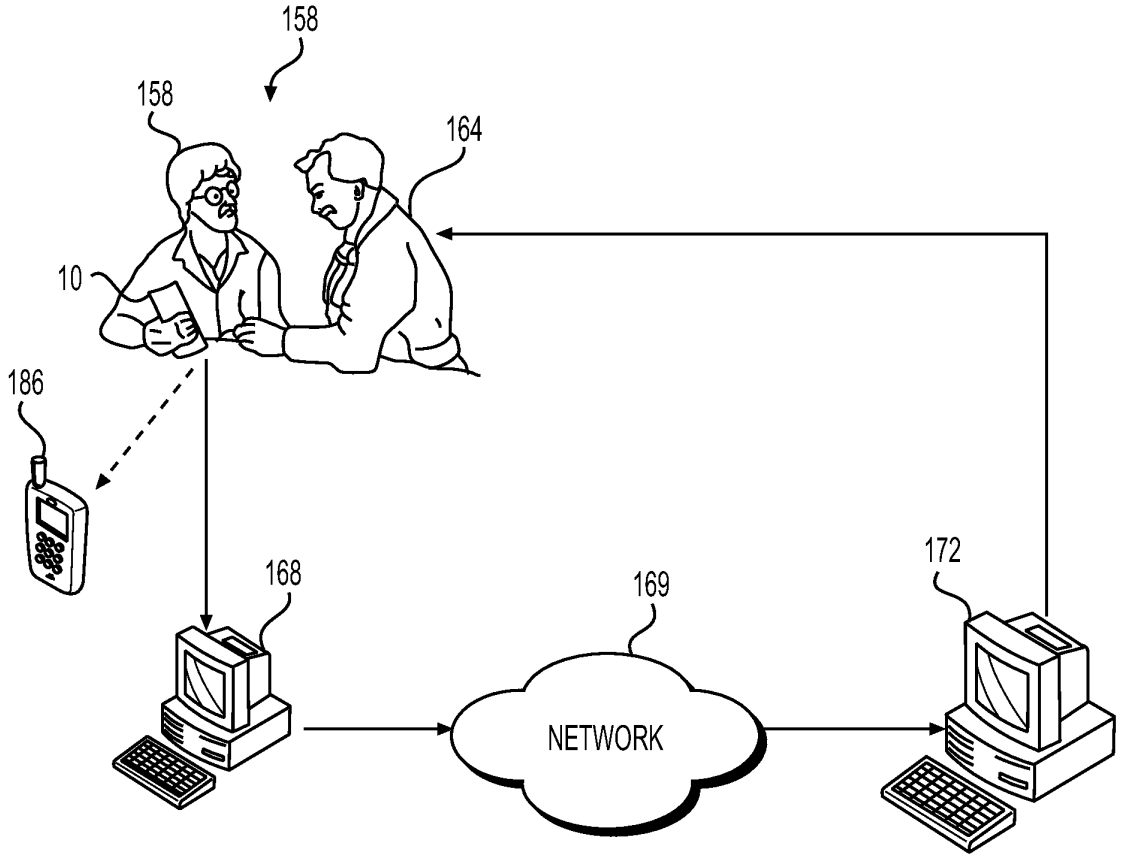
158
158
164
10
186
168
169
172
NETWORK

FIG. 12

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摘要(译)

用于跟踪糖尿病中平均血糖变化的方法，系统和计算机可读介质基于概念上用于检索SMBG数据的新方法。利用对HbA1c波动的理解作为潜在动力系统作用的可测量效应，SMBG偶尔会对该系统的状态进行一瞥，并且使用这些测量结果，可以为个体糖尿病患者重建隐藏的基础系统轨迹。使用隔室建模，提供了一种新的两步算法，其包括：（i）从空腹葡萄糖读数实时估计HbA1c，用任何新的进入空腹SMBG数据点更新，以及（ii）初始化和校准估计HbA1c追踪与每日SMBG概况定期获得。这些概况的估计包括在两个潜在因子内捕获每日BG变异性的因子模型。