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(71) Applicants: **KING ABDULLAH UNIVERSITY OF SCIENCE AND TECHNOLOGY** [SA/SA]; 4700 King Abdullah University of Science and Technology, Thuwal 23955-6900 (SA). **PRINCE SULTAN UNIVERSITY** [SA/SA]; Mansur Ibn Muhammad, Salah Ad Din, Riyadh 12435 (SA).

(72) Inventors: **LALEG, Taous Meriem**; 4700 King Abdullah University of Science and Technology, Thuwal 23955-6900 (SA). **AL-MATOUQ, Ali Ahmed**; Mansur Ibn Muhammad, Salah Ad Din, Riyadh 12435 (SA).

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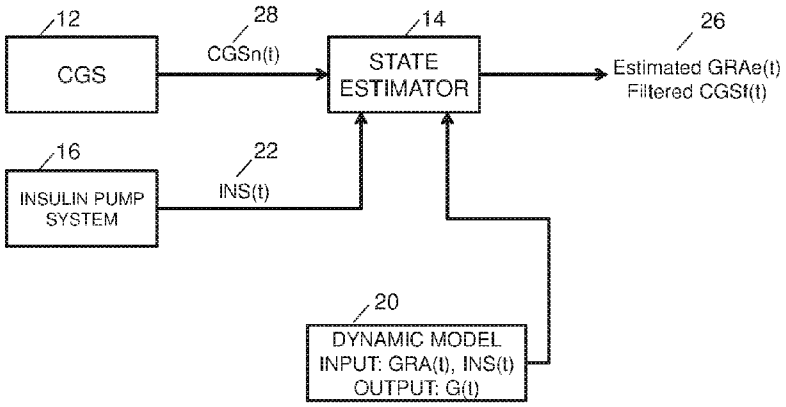

FIG. 1

(57) Abstract: Method and System for providing estimates of Glucose Rate of Appearance from the intestine (GRA) using continuous glucose sensor measurements (CGS) taken from the subcutaneous of a diabetes patient and the amount of insulin administered to the patient.

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ESTIMATION OF GLUCOSE RATE OF APPEARANCE FROM CGS AND SUBCUTANEOUS INSULIN DELIVERY IN TYPE 1 DIABETES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to co-pending U.S. Provisional Application No. 62/300,426, entitled "ESTIMATION OF GLUCOSE RATE OF APPEARANCE FROM CONTINUOUS GLUCOSE SENSORS AND SUBCUTANEOUS INSULIN DELIVERY IN TYPE 1 DIABETES", filed on February 26, 2016 and U.S. Provisional Application No. 62/300,438, entitled "ESTIMATION OF GLUCOSE RATE OF APPEARANCE AND RESPONSIVE CONTROL OF INSULIN DELIVERY", filed on February 26, 2016, the entire disclosures of which are incorporated by reference in their entireties as if fully set forth herein.

TECHNICAL FIELD

The present disclosure relates to medical systems, more specifically, to a system for estimating glucose rate of appearance from the intestine.

BACKGROUND

Continuous Glucose Sensors (hereafter CGS) can provide continuous monitoring of subcutaneous glucose in real time using a small electrode sensor that is implanted on the patient's skin. It is well known that subcutaneous glucose concentration is indicative of plasma glucose concentration after correcting for the delay associated with the diffusion of glucose from the plasma to the interstitial fluid and after filtering out possible measurement noise from the sensor [Breton and Kovatchev, 2008].

Glucose Rate of Appearance from the intestine (hereafter GRA), on the other hand, is a variable that can be measured while a patient is undergoing an oral glucose tolerance test (hereafter OGTT) or a meal tolerance test (hereafter MTT) in a clinical setting.

Measurement of GRA is commonly used for detecting abnormalities in glucose absorption in elderly and diabetic individuals. The methods for measuring GRA, however, are generally complex and require the use of tracers infused intravenously and also intravenous measurements of both glucose and insulin plasma concentrations. There is currently no sensing device that measures GRA continuously in a minimally invasive manner similar to measuring blood glucose using a CGS. To enable more use of this important variable for both diagnosis and treatment, it is desirable to estimate GRA in a continuous manner using minimally invasive techniques by inferring it from CGS measurements. For example, bolus insulin optimal delivery profiles depends on the type of meals consumed as shown in the recent study by [Srinivasan et al., 2014]. This is because of the inherent variations in glucose absorption rates with meal composition. Hence, it is important to determine the glucose rate of appearance for different type of meals so that it can be used in determining the optimal bolus insulin delivery profiles.

A previous attempt was made [Herrero et al., 2012a] to estimate GRA using intravenous measurements of both plasma glucose and plasma insulin concentrations. However, the technique is still invasive as it requires intravenous measurements. Furthermore, the previous study did not take into account possible measurement noise and model uncertainties in calculating the estimations of GRA.

Hence, a method and apparatus for estimating GRA from the intestine continuously throughout the day using minimally invasive sensors such as continuous glucose sensors and subcutaneous insulin infusion devices is needed.

SUMMARY

The present disclosure provides improved systems and methods for estimating GRA in real-time. The estimated GRA can be applied for detecting abnormalities in glucose absorption and/or for insulin dosing. In one or more embodiments, the systems and methods use CGS noisy measurements and amount(s) of insulin delivered to the patient. Hence, they

can make use of simple and accessible CGS measurements that can be taken from the patient easily using a small electrode implanted on the patient's skin and possibly an infusion device for insulin. This enables the estimation of GRA using minimally invasive sensors as compared to estimating GRA using tracers and intravenous measurements of blood glucose and insulin.

Moreover, estimating GRA continuously, as compared to estimating GRA during OGTT and/or MTT only, enables continuous monitoring of this variable which can be useful for diagnosis of metabolism abnormalities, detecting the time of occurrence and extent of certain meals and for developing control algorithms for maintaining euglycemia for people with type 1 diabetes. Specifically, it can enhance the predictability of Model Predictive Controllers and consequently enhance glucose control during meal disturbances.

In one or more aspects, the present disclosure provides for estimating GRA signal in real-time by using (1) a single or a plurality of noisy CGS measurements; (2) a simple glucose-insulin dynamic model of the person; (3) information indicating the time and amount of bolus and basal insulin units injected and (4) a recursive algorithm that calculates an estimated value for glucose rate of appearance GRAe(t) that is indicative of the true GRA. This calculated estimate for GRA using the embodiments of the present disclosure is robust to both model uncertainties and measurement noise. Moreover, the embodiments herein can be readily programmed on a simple micro-controller or digital signal processor for implementation and the recursive solution that it provides allows real time estimates of GRA to be found. The accuracy of these estimates can be enhanced by using a plurality of CGS measurements as exemplified in the disclosed embodiments of the present disclosure.

In one or more aspects, this disclosure makes use of simple and accessible CGS measurements enabling the estimation of GRA using minimally invasive sensors. In an aspect, it employs a simple dynamic model that models the rate of change in glucose when the diabetes patient is subject to glucose disturbances due to meals and injections of subcutaneous bolus insulin. This model can be constructed using standard data available

from OGTT and/or MTT. Alternatively, a model available from the literature may be used; i.e. the Bergman model [Herrero et al., 2012b] or the Della Man model [Dalla Man et al., 2007]. Still other objects and advantages of the disclosure will in part be obvious and will in part be apparent from the specification and drawings. Other variations and modifications can be made without departing from the spirit and scope of the novel concepts of the present disclosure.

In an embodiment a continuous glucose rate of appearance measurement system is provided. The system can comprise a receiver configured to receive subcutaneous glucose concentration data from a continuous glucose sensor that is coupled to a subject, the receiver further configured to receive insulin injection data; processing logic configured to determine a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and processing logic configured to determine an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

In an embodiment a method of estimating a glucose rate of appearance is provided. The method can comprise receiving subcutaneous glucose concentration data from a continuous glucose sensor that is coupled to a subject; receiving insulin injection data; determining a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and determining an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

In an embodiment, a non-transitory computer-readable medium is provided. The non-transitory computer-readable medium can embody a program executable in at least one

computing device, wherein when executed the program causes the at least one computing device to at least: receive insulin injection data of a subject; determine a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and determine an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

In a further embodiment, a system is provided, comprising: at least one computing device; and at least one program executable in the at least one computing device, wherein when executed the at least one program causes the at least one computing device to at least: receive insulin injection data of a subject; determine a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and determine an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

In any one or more aspects of any one or more of the embodiments, the subcutaneous glucose concentration data can be noisy subcutaneous glucose concentration data. Determining an estimated glucose rate of appearance further comprises determining a filtered subcutaneous glucose concentration. The glucose disturbance can be a meal, an injection of insulin, or a combination thereof. Controlling insulin delivery to the subject can be in response at least to a determined estimated glucose rate of appearance.

Other systems, methods, features, and advantages of the present disclosure will be or become apparent to one with skill in the art upon examination of the following drawings and detailed description. It is intended that all such additional systems, methods, features, and advantages be included within this description, be within the scope of the present disclosure, and be protected by the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

For a more complete understanding of the present disclosure, reference is made to the following description and accompanying drawings. The components in the drawings are not necessarily to scale, emphasis instead being placed upon clearly illustrating the principles of the present disclosure. Moreover, in the drawings, like reference numerals designate corresponding parts throughout the several views.

FIG. 1 is a block diagram for a GRA state estimator of the present disclosure.

FIG. 2 is a diagram showing blood glucose concentration recorded data of the person G(t) and corresponding noisy measurements CGSn(t) obtained from a simulation experiment using the UV-Padova model [Dalla Man et al., 2006], [Dalla Man et al., 2014].

FIG. 3 is a diagram showing the training data used to develop a simple glucose/insulin dynamic model. Top figure: blood glucose concentration signal G(t). Middle figure: glucose rate of appearance from the intestine signal GRA(t). Bottom figure: bolus insulin injection units INS(t) as explained in the detailed description of the preferred embodiments of the present invention.

FIG. 4 is a diagram showing the step response of the simple glucose/insulin dynamic model obtained in the detailed description of the preferred embodiments of the present invention. Top figure: step response of G(t) with respect to INS(t). Bottom figure: step response of G(t) with respect to GRA(t).

FIG. 5 is a diagram showing a comparison plot between simulated data for G(t) from the UV-Padova model and a predicted signal Gp(t) that is calculated using a simple glucose/insulin model as explained in the detailed description below.

FIG. 6 is a diagram showing an example of a signal G(t), noisy measurements of subcutaneous glucose CGSn(t) and the corresponding filtered signal CGSf(t) that is calculated using a descriptor state estimator as explained in the detailed description below.

FIG. 7 is a diagram showing GRA(t) and an estimated signal GRAe(t) that is calculated using a descriptor state estimator as explained in the detailed description below.

FIG. 8 is a diagram showing an example of a signal G(t), noisy measurements of subcutaneous glucose CGSn(t) and the corresponding filtered signal CGSf(t) that is calculated using a descriptor state estimator as further explained herein.

FIG. 9 is a diagram showing GRA(t) and an estimated signal GRAe(t) that is calculated using a descriptor state estimator as further explained herein.

FIG. 10 is a diagram showing an example of a signal G(t), noisy measurements of subcutaneous glucose CGSn(t) and the corresponding filtered signal CGSf(t) that is calculated using a descriptor moving horizon state estimator as further explained herein.

FIG. 11 is a diagram showing GRA(t) and an estimated signal GRAe(t) that is calculated using a descriptor moving horizon state estimator as further explained herein.

FIG. 12 is a schematic diagram of an apparatus in which embodiments for providing estimation of glucose rate of appearance (GRA) disclosed herein can be implemented.

DETAILED DESCRIPTION

Various embodiments of the present disclosure described herein relate to estimating the GRA of a person using measurements obtained from a CGS coupled to a person in the presence of sensor noise and calibration errors. The various embodiments will be disclosed with reference to specific examples to simplify discussion and should not be interpreted as a limitation to the disclosure.

FIG. 1 depicts a block diagram showing a CGS device 12 which can be used to continuously measure the subcutaneous glucose concentration of the person according to an example of the invention. The CGS can be coupled to a person having diabetes (not shown). The CGS 12 can transmit noisy (unfiltered) measurements of subcutaneous glucose concentration CGSn(t) 28 to a state estimator module 14. The noisy measurements CGSn(t) are interfaced to the state estimator system 14 via a wired or wireless communication link. The state estimator 14 can also take a noisy measurement INS(t) 22 that measures the time and amount of bolus insulin units injected to the person subcutaneously (for example, in

units of *pmole)* which can come from an insulin pump device 16 or directly from the person as user input data to the state estimator. The state estimator can include a dynamic model 20 that can capture the dynamic behaviour of glucose concentration in the blood G(t) subject to meal and subcutaneous bolus insulin disturbances.

FIG. 2 depicts an example of a two-dimensional graph of a plasma glucose concentration signal G(t) and noisy subcutaneous glucose measurement signal CGSn(t) of the person in units of *mg / dL* obtained from a CGS device coupled to a person for three consecutive days. The data was obtained from a simulation experiment conducted using the UVPadova simulator for type 1 diabetes (release 3.2) described in [Dalla Man et al., 2014] which incorporates a first principle model of the glucose/insulin system of a human with parameters based on specific patient data for normal and diabetic individuals.

The simulation experiment used a sample rate of 1 minute and included three meals and 1 snack per day for three consecutive days as input to the model. Bolus subcutaneous insulin injections before 10 minutes of each meal were also used as input to the model with amounts in *pmole* calculated based on patient specific carbohydrate/insulin ratio and a correction factor. The endogenous glucose production rate from the liver was assumed constant at a rate of 2.63 *mg / kg:min* while the balas insulin concentration rate was assumed constant at a rate of 0.8 *Units / hr*. Other specific patient parameters for this simulation experiment can be found in reference to the average adult parameters given in the UVPadova model [Dalla Man et al., 2014]. The noise associated with CGS measurements in the UV-Padova model is modelled using an SU Johnson distribution with partial autocorrelation. This statistical model was used based on a comparison between CGM measurements and Self Monitoring Blood Glucose measurements (hereafter SMBG) as discussed in [Breton and Kovatchev, 2008]. The parameters of the SU Johnson distribution in the present simulation experiment $\gamma = -0.5444$, $\lambda = 15.9574$, $\delta = 1.6898$ $\zeta = -5.47$ with a partial auto-correlation coefficient of 0.7.

As shown in **FIG. 2**, the noisy CGS measurement signal CGSn(t) correlates strongly with the plasma glucose concentration signal G(t) with some differences. The differences between the actual and measured glucose by the CGS is known to be attributed mostly to diffusion delays of glucose from plasma to the interstitial fluid and measurement sensor calibration errors. Other possible random errors could originate, for example, from sensor vibration or change in position, accumulation of fat on the electrode sensor and/or exposure to surrounding electromagnetic interferences.

In an embodiment, the present invention can estimate GRA(t) in real time using (1) a single or a plurality of noisy CGS measurements; (2) a signal INS(t) indicating the amount of subcutaneous bolus insulin injected (e.g., in *pmole*) and (3) a simple model that captures the dynamic behaviour between blood glucose concentration G(t), glucose rate of appearance from the intestine GRA(t) and the signal INS(t). This model can be developed using first principles combined with parameter identification as done for example in the UVPadova model given in [Dalla Man et al., 2006] or using the Bergman model as described in [Herrero et al., 2012b], or by using system identification techniques to develop black box models from experimental data obtained, for example, from a standard meal tolerance test, both of which are incorporated by reference as if fully described herein. In an aspect, this will be exemplified herein by using data collected from simulation experiments from the UV-Padova simulator.

Referring again to **FIG. 1**, in one or more aspects, the system 14 for estimating GRA of a person having diabetes can comprise a recursive unknown input state estimator which can be used to estimate the GRA of the person and filter CGS measurement noise simultaneously. Examples of recursive unknown input state estimators which can be used include Descriptor State Estimator (hereafter DSE) and Descriptor Moving Horizon State Estimator (hereafter DMHE).

Identification of a simple glucose/insulin model

In an embodiment, for the purpose of simplifying the discussion, a simple dynamic model can be developed and employed for glucose concentration in plasma that captures the effect of glucose rate of appearance and subcutaneous insulin only. The inputs to the model are GRA(t) and INS(t) and the single output of the model is G(t). The influences of other important physiological variables, i.e. endogenous glucose production from the liver and glucose utilization (both insulin dependent and insulin independent), will not be directly considered in the model rather their effect will be captured using black box system identification techniques and experimental data collected from either a simulated first principle model or data obtained from a standard OGTT and/or MTT that includes intravenous measurements of glucose and insulin concentrations and estimation of glucose rate of appearance.

This simple model can be a linear time invariant discrete state space model. The model can be expressed as follows:

$$x_{k+1} = Ax_k + B_{ins}INS_{k-\tau} + B_{gra}GRA_k \qquad (1)$$

$$G_k = Cx_k \qquad k = 0, 1, \cdots, T \qquad (2)$$

where k is the discrete time index; T is the simulation time; $x_k \in \mathbb{R}^n$ is the state vector sequence of length n; $INS_{k-\tau}$ and GRA_k are the input vector sequences measuring discrete samples of the signals INS(t) and GRA(t) respectively; Gk is the single output sequence measuring discrete samples of the signal G(t). Matrices $A \in \mathbb{R}^{n\times n}$, B_{ins}, $B_{gra} \in \mathbb{R}^n$ and $C \in \mathbb{R}^{1\times n}$ are the model parameters to be identified. The parameter τ gives the number of discrete time samples reflect the time delay between the onset of injecting subcutaneous bolus insulin and the onset of its effect on plasma glucose concentration.

Referring to **FIG. 3**, the diagram shows simulation data for G(t) (top), GRA(t) (middle) and INS(t) (bottom) generated using the UV-Padova model. The simulation experiment was configured to have three meals and 1 snack per day for seven days using

parameters for an average adult with type 1 diabetes as explained earlier in this disclosure. Both the carbohydrate content of meals and the amount of bolus insulin units injected sub-cutaneously were modified using randomly selected amounts for the purpose of collecting sufficiently excited data for system identification. Also, the timings of the insulin bolus injections relative to the time of meal occurrences has been selected so that some injections occur before the start of a meal and some after. Note that the simulation experiment was conducted within unhealthy glucose ranges only to help capture the dynamics of the system.

Using the above mentioned set of input/output data, a 4th order state space model can be identified using the prediction error method [Ljung, 1999]. Using the system identification toolbox of Matlab [MATLAB, 2012], the following identified system matrices for the model in (1) can be found:

$$A = \begin{bmatrix} 1.005 & 0.01759 & -0.0218 & 0.03179 \\ 0.01446 & 1.016 & -0.03014 & 0.01648 \\ 0.0136 & 0.02143 & 0.9673 & 0.03532 \\ -0.02645 & -0.01307 & 0.02794 & 0.9608 \end{bmatrix}$$

$$B_{ins} = \begin{bmatrix} 0.0003896 \\ -0.0004393 \\ 0 \\ 0.0001885 \end{bmatrix} \quad B_{gra} = \begin{bmatrix} 0.0424 \\ 0.0418 \\ 0.0507 \\ -0.01917 \end{bmatrix}$$

$$C = \begin{bmatrix} 5.521 & 5.512 & 0.3844 & 0.3909 \end{bmatrix} \qquad (3)$$

The input delay τ between the onset of subcutaneous bolus insulin injections and the onset of its effect on plasma glucose concentration was identified to be 11 minutes using the "delayest" function available in Matlab also [MATLAB, 2012].

The step response of the identified model is shown in **FIG. 4**. The diagram shows the effect of a step change in the insulin signal from INS(0)=0 to INS(t)=1*pmole / min*

on blood glucose trajectory G(t) in $mg\ /\ dL$ (top diagram) and the effect of having a step change in GRA from GRA(0)=0 to GRA(t) = 1*mg / kg.min* on blood glucose (bottom diagram). The model step responses reflect that a step change in subcutaneous bolus insulin will have a delayed effect in reducing blood glucose concentration while a step change in GRA will have an immediate effect in increasing blood glucose concentration as expected. Insulin has the dual effect of suppressing endogenous glucose production and promoting glucose absorption by muscle and fat tissues. The slopes of these step responses can depend on specific patient parameters including insulin sensitivity, rate constant of intestinal absorption, body weight etc. [Dalla Man and Cobelli, 2007]. The identified state space model can capture the effect of these specific patient parameters and influences indirectly through the identification of state space model parameters.

Model Validation

To validate the accuracy of the identified model, a comparison was made between simulation data obtained the UVPadova model and model predictions obtained from simulating the identified model (1) given by the model parameters in (3). The sum of root mean square errors RMSE (given by $\sum_{k=0}^{T}\sqrt{\frac{1}{d}(G_k - G_{pk})^2}$, where d is the number of data samples) was calculated to be 526. **FIG. 5** shows a validation plot comparing glucose concentration data from the simulation of the UV-Padova model and a plot of predicted glucose concentration Gp(t) obtained by simulating the identified state space model given by (1) and (3). The validation plot shows that the predicted glucose concentration Gp(t) obtained by simulating the identified state space model (using the same input signals GRA(t) and INS(t) in both models) matches closely with the simulated glucose signal G(t) with some deviation at low glucose concentrations.

To enhance estimation accuracy in the state estimator (that will follow), it can desired to include information about the nature of the signal GRA(t). A simple auto-regressive model can be identified from the data shown in **FIG. 3** for GRA(t) as follows:

$$x_{k+1}^{GRA} = A_{gra} x_k^{gra} + K_{gra} e_k \quad (4)$$

$$GRA_k = C_{gra} x_k^{gra} + e_k \qquad k = 0, 1, \cdots, T \quad (5)$$

where e_k is a random sequence with a normal distribution of mean 0 and variance 1. The model parameters identified are $Agra = 0{:}99, Kgra = 0{:}006 \; and \; Cgra = 265$. The RMSE for the identified model is 0.006 with a fit to estimation data of 96%.

Unknown Input Descriptor State Estimation

It can be desired to design the state estimator such that it can estimate the GRA given CGS noisy measurements. In one embodiment, the unknown input GRA can be estimated by transforming it to a state variable and forming a descriptor system [Darouach et al., 1995]. Descriptor Moving Horizon Estimation (hereafter DMHE) can be used to overcome errors due to quantization and impose positivity constraints to the state estimator. However, it will be appreciated for those who are skilled in the art that the following discussion is for demonstration purposes only and the state estimation method is not limited to the ones discussed herein.

All possible disturbances, including disturbances arising from model uncertainties, can be modelled using a normally distributed iid random sequence with zero mean and covariance matrix Q denoted by $\mathbf{w}_k \sim \mathcal{N}(0, Q)$ added to the state space model given in (1). Measurement noise, on the other hand, can also be modelled as a random sequence with zero mean and covariance matrix R denoted by $\mathbf{v}_k \sim \mathcal{N}(0, R)$. The process noise sequence and the measurement noise sequence are assumed independent. The following stochastic linear model for the glucose/insulin system can be used:

$$\mathbf{E}\mathbf{x}_{k+1} = \mathbf{A}\mathbf{x}_k + \mathbf{B}\mathbf{u}_k + \mathbf{w}_k \quad (6a)$$

$$\mathbf{y}_k = \mathbf{C}\mathbf{x}_k + \mathbf{v}_k \quad (6b)$$

where,

$$\mathbf{E}=\begin{bmatrix} I & 0 & -B_{gra} \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix},\ \mathbf{A}=\begin{bmatrix} A & 0 & 0 \\ 0 & A_{gra} & 0 \\ 0 & 0 & C_{gra} \end{bmatrix},\ \mathbf{C}=\begin{bmatrix} C & 0 & 0 \end{bmatrix},\ \mathbf{B}=B_{ins}$$

$$\mathbf{y}_k=CGSn_k,\ \mathbf{x}_k=\begin{bmatrix} x_k & x_k^{gra} & GRA_{k-1} \end{bmatrix}^T,\ \mathbf{u}_k=INS_{k-\tau} \qquad (6c)$$

Here the measurement vector y_k are noisy sample measurements of subcutaneous glucose CGSn(t). The matrix $I \in \mathbb{R}^{4\times4}$ is the 4 x 4 identity matrix. The stochastic model composed of (6a) and (6b) is called a stochastic linear descriptor system [Nikoukhah et al., 1992]. Note that the augmented state vector contains the unknown input GRA_{k-1} at time $k-1$ and hence our estimates will be estimated with an additional lag of one sample.

Consequently, a state estimation problem can be formally stated as follows: Given the noisy measurement $y_k = CGSn_k$ for $k = 0, 1, \ldots, t$, an a priori estimate of the initial state as a random variable with mean $\bar{x}_0$ and covariance matrix P_0 denoted as $\mathbf{x}_0 \sim \mathcal{N}(\bar{x}_0, P_0)$ and the stochastic model (6a) and (6b), find an estimate of the augmented state vector sequence $\mathbf{x}_k$ for $k = 0, 1, \cdots, T$.

The descriptor state estimation recursions can be found in [Nikoukhah et al., 1999] and are briefly presented here. The maximum likelihood (or the maximum a posterior [Al-Matouq et al., 2012]) objective function to be minimized can be stated as:

$$J(\mathbf{x}_k)=\frac{1}{2}\left(\left\|\mathbf{E}\mathbf{x}_1-\mathbf{A}\bar{x}_0-\mathbf{B}u_0\right\|^2_{P_0^{(-)}}+\sum_{k=1}^{T-1}\left\|\mathbf{w}_k\right\|^2_Q+\sum_{k=0}^{T-1}\left\|\mathbf{v}_k\right\|^2_R\right), \qquad (7)$$

subject to (6a) and (6b)

State Estimation for Descriptor Systems

Input Data: $\mathbf{E}, \mathbf{A}, \mathbf{B}, \mathbf{C}, \bar{x}_0, P_0$ and $\mathbf{y}_k, \mathbf{u}_k$ for $k = 0, 1, \cdots, T$

Initialization: $P_0^{(-)} = Q + \mathbf{A} P_0 \mathbf{A}^T$

Output Data: Filtered estimates $\hat{x}_k^{(+)}$ for $k = 0, 1, \cdots, T$

$$\begin{aligned} \hat{\mathbf{x}}_k^{(+)} &= P_k^{(+)} \mathbf{C}^T R^{-1} \mathbf{y}_k + P_k^{(+)} \mathbf{E}^T (P_{k-1}^{(-)})^{-1} (\mathbf{A} \hat{\mathbf{x}}_{k-1}^{(+)} + \mathbf{B} \mathbf{u}_{k-1}) \\ P_k^{(+)} &= (\mathbf{E}^T (P_{k-1}^{(-)})^{-1} \mathbf{E} + \mathbf{C}^T R^{-1} \mathbf{C})^{-1} \\ P_k^{(-)} &= \mathbf{A} P_k^{(+)} \mathbf{A}^T + Q \end{aligned} \tag{8}$$

where $P_0^{(-)} = Q + \mathbf{A} P_0 \mathbf{A}^T$ and the decision variables for minimization are the unknown state vectors $x_1, x_2, \ldots, x_T$. Here, the quadratic form symbol $\|z\|_A^2 = z^T A^{-1} z$ is used. A recursive solution to this objective function using dynamic programming was derived in [AlMatouq et al., 2013] and is shown in Algorithm I.

Descriptor Moving Horizon State Estimation with ℓ_1 trend filtering

Additional prior knowledge in the form of known linear inequality constraints on the state vector x_k can be incorporated in the estimation problem as follows:

$$F \mathbf{x}_k \leq d \tag{9}$$

where $\leq$ is used for element wise $\leq$ comparison. For example, the CGS sensor minimum and maximum values in the UV-Padova simulation module are 32 *mg / dL* and 600 *mg / dL* which can be represented by (9) by specifying $F = C$ and vector $d = [32\ 600]^T$. Also, positivity constraints can be incorporated for estimating GRA since this variable can not be negative.

Additionally, since CGS measurements are quantized to integer values between samples, quantization errors need to be filtered. To suppress quantization errors, ℓ_1 trend filtering can be used [Kim et al., 2009] which imposes an ℓ_1 norm penalty on the numerical second derivative of GRA e_k.

Consequently, the estimation problem is to estimate x_k for $k = t - N, \ldots, t$ by solving the following minimization problem:

$$\hat{J}_t^{mh} = \min_{\{\mathbf{x}_k\}_{t-N}} \Gamma_{t-N}^{mh}(\mathbf{x}_{t-N}) + \sum_{k=t-N}^{t-1} \|\mathbf{w}_k\|_Q^2 + \sum_{k=t-N}^{t-1} \left(\|\mathbf{v}_k\|_R^2 + \lambda_{gra}\|\mathbf{M}.\mathbf{GRA}_t\|_1\right) \quad (10)$$

$$\text{subject to } F\mathbf{x}_k \preceq d, \text{ and (6a), (6b)} \quad (11)$$

where N is the horizon length that specifies the size of the sliding window in the past; $\mathbf{GRA}_t = [GRA_{t-N}, GRA_{t-N-1}, \cdots, GRA_t]^T$ and λ_{gra} is a weighting parameter that should be properly selected for adequate ℓ_1 trend filtering as studied in [Kim et al., 2009]. The matrix $\mathbf{M} \in \mathbb{R}^{(n-2)\times n}$ is the second-order Toeplitz difference matrix given for $n = 4$ by:

$$\mathbf{M} = \begin{bmatrix} 1 & -2 & 1 & & \\ & 1 & -2 & 1 & \\ & & \ddots & \ddots & \ddots \\ & & & 1 & -2 & 1 \\ & & & & 1 & -2 & 1 \end{bmatrix} \quad (12)$$

This matrix can be used to approximate the second derivative of GRA_k using three points in time. However, other second derivative approximations can be used.

The weighting function $\Gamma_{t-N}^{mh}(\mathbf{x}_{t-N})$ is called the arrival cost function. This cost function can be used so that the obtained estimates account for past measurements and input sequences while ensuring stability of the estimator as discussed in [Rawlings and Mayne, 2009]. A suitable arrival cost function can be found based on the arrival cost of the unconstrained minimization problem given by(7):

$$\Gamma_{t-N}^{mh}(\mathbf{x}_{t-N}) = \frac{1}{2}\|\mathbf{E}\mathbf{x}_{t-N} - \mathbf{A}\hat{\mathbf{x}}_{t-N-1}^{(+)} - \mathbf{B}\mathbf{u}_{t-N-1}\|_{P_{t-N-1}^{(-)}}^2 \quad (13)$$

where $\hat{\mathbf{x}}_{t-N-1}^{(+)}$ and $P_{t-N-1}^{(-)}$ are found from the recursions given in (8).

Algorithm II: Descriptor Moving Horizon Estimation

Input Data: $\mathbf{E}, \mathbf{A}, \mathbf{B}, \mathbf{C}, \bar{x}_0, P_0$ and $\mathbf{y}_k, \mathbf{u}_k$ for $k = 0, 1, \cdots, T$

Initialization: $P_0^- = Q + \mathbf{A}P_0\mathbf{A}^T$

Output Data: Filtered estimates $\hat{x}_k^{mh}$ for $k = 0, 1, \cdots, T$

Minimization Problem at time $k = t$:

$$\min_{(\mathbf{x}_k)_{t-N}^{t}} \Gamma_{t-N}^{mh}(\mathbf{x}_{t-N}) + \sum_{k=t-N}^{t-1} \|\mathbf{w}_k\|_Q^2 + \sum_{k=t-N}^{t-1} \|\mathbf{v}_k\|_R^2 + \lambda_{R_e} \|\mathbf{M}.\mathbf{GRA}_t\|_1$$

subject to $F\mathbf{x}_k \preceq d$, and (6a), (6b)

where $\Gamma_{t-N}^{mh}(\mathbf{x}_{t-N})$ is given by (13).

Algorithm II summarizes the DMHE method that is used as an example for this invention for estimating GRA. The minimization problem can be solved using the convex program solver CVX [Grant and Boyd, 2012] in Matlab [MATLAB, 2012].

Simulation Experiments

For the state estimation experiments discussed in the present invention, simulation data for CGS noisy measurements discussed earlier and shown in **FIG. 2** can be used for the purpose of estimating GRA in conjunction with the algorithms for DSE and DMHE. The noise parameters are as given earlier. The descriptor system model given by (6a) and (6b) with model parameters given in (3) and earlier herein are used. For implementing the DSE algorithm (8) and DMHE algorithm (11), a computer program written in Matlab [MATLAB, 2012] is used.

DSE using a one CGS

The first state estimation experiment used quantized and noisy glucose sensor measurements $CGMn_k$ shown in **FIG. 2** obtained from the UV-Padova simulation model as explained earlier. The estimator parameters used are $R = 100$, $Q = 0.001 \times I_4$, $P_0 = 10^{-3} I_5$ and $\bar{x}_0 = 0$. **FIG. 6** and **FIG. 7** show the results of this simulation experiment. **FIG. 6** combines the signals G(t), CGSn(t) and the filtered measurements CGSf(t) as a result of estimating the states of the model (6a). **FIG. 7** shows a diagram for GRA(t) and the estimated signal GRAe(t) that was found from this simulation experiment. The calculated

RMSE for estimating GRA is 74.4 and the condition number of the error covariance matrix is in the order of 10^4. The estimation errors can be attributed to unfiltered measurement noise as evident from **FIG. 6** where the filtered signal CGSf(t) matches the noisy signal CGSn(t). Also, model uncertainties are evident in **FIG. 7** when estimates are calculated as negative numbers.

DSE using a plurality of CGS devices

To overcome these estimation errors a second experiment was conducted using the same DSE in the first experiment but with additional 2 CGS noisy measurements that may be placed on the patient. The CGS devices are assumed to have identical noise characteristics as given before. The experiment was conducted using the same parameters for the state estimator explained earlier for the first experiment except that the measurement matrix becomes $\mathrm{C} \leftarrow [\mathrm{C}\,\mathrm{C}\,\mathrm{C}]^{\mathrm{T}}$. **FIG. 8** depicts one of the noisy measurements used CGSn(t) together with the signal G(t) and the calculated filtered measurements CGSf(t) for comparison. **FIG. 9** shows a diagram for GRA(t) and the estimated signal GRAe(t) for this experiment. The calculated RMSE for GRA is 59 and the condition number of the error covariance matrix is reduced by approximately 30% signifying improvement over the previous experiment. This experiment shows that estimation accuracy is enhanced using a plurality of CGS measurements.

DMHE using a plurality of CGS devices

A third simulation experiment can be conducted using MHE with ℓ_1 trend filtering as given in Algorithm II. The horizon length selected in this example is N = 10 with $\lambda_{gra} = 1000$. The estimator parameters used were similar to that of the previous experiments with three noisy measurements used as in the second experiment. **FIG. 10** and **FIG. 11** show the results of this simulation experiment using disciplined convex programming software CVX [Grant and Boyd, 2012]. The ℓ_1 trend filtering penalty helped to suppress the effect of quantization noise while positivity constraints helped to ensure positive values of GRAe_k.

The calculated RMSE value is 57 which shows improvement over DSE methods.

Referring next to **FIG. 12**, shown is one example of a system that performs various functions for continuous glucose rate of appearance measurements in accordance with various embodiments as set forth above. As shown, a processor system 700 is provided that includes a processor 703 and a memory 706, both of which are coupled to a local interface 709. The local interface 709 may be, for example, a data bus with an accompanying control/address bus as can be appreciated by those with ordinary skill in the art. The processor system 700 may comprise, for example, a computer system such as a server, desktop computer, laptop, mobile device (e.g., smart phone, tablet, personal digital assistant, etc.) or other system with like capability.

Coupled to the processor system 700 are various peripheral devices such as, for example, a continuous glucose sensor (CGS) 713, an insulin pump system (IPS) 716, and/or other devices as can be appreciated. The CGS 713 and insulin pump system 716 can communicate with the processor system 700 via a transceiver 719 (or transmitter and/or receiver). The communications can be wired or wireless (e.g., Bluetooth, WiFi, etc.).

Stored in the memory 706 and executed by the processor 703 are various components that provide various functionality according to the various embodiments of the present invention. In the example embodiment shown, stored in the memory 706 is an operating system 723, a state estimator application 726, various dynamic models 729, and potentially other information associated with the glucose rate of appearance.

The state estimator application 726 and dynamic models 129 can be executed by the processor 703 in order to determine the glucose rate of appearance as previously described. A number of software components are stored in the memory 706 and are executable by the processor 703. In this respect, the term "executable" means a program file that is in a form that can ultimately be run by the processor 703. Examples of executable programs may be, for example, a compiled program that can be translated into machine code in a format that can be loaded into a random access portion of the memory 706 and run by the processor

703, or source code that may be expressed in proper format such as object code that is capable of being loaded into a of random access portion of the memory 706 and executed by the processor 703, *etc.* An executable program may be stored in any portion or component of the memory 506 including, for example, random access memory, read-only memory, a hard drive, compact disk (CD), floppy disk, or other memory components.

The memory 706 is defined herein as both volatile and nonvolatile memory and data storage components. Volatile components are those that do not retain data values upon loss of power. Nonvolatile components are those that retain data upon a loss of power. Thus, the memory 706 may comprise, for example, random access memory (RAM), read-only memory (ROM), hard disk drives, floppy disks accessed via an associated floppy disk drive, compact discs accessed via a compact disc drive, magnetic tapes accessed via an appropriate tape drive, and/or other memory components, or a combination of any two or more of these memory components. In addition, the RAM may comprise, for example, static random access memory (SRAM), dynamic random access memory (DRAM), or magnetic random access memory (MRAM) and other such devices. The ROM may comprise, for example, a programmable read-only memory (PROM), an erasable programmable read-only memory (EPROM), an electrically erasable programmable read-only memory (EEPROM), or other like memory device.

The processor 703 may represent multiple processors and the memory 706 may represent multiple memories that operate in parallel. In such a case, the local interface 709 may be an appropriate network that facilitates communication between any two of the multiple processors, between any processor and any one of the memories, or between any two of the memories *etc.* The processor 703 may be of electrical, optical, or molecular construction, or of some other construction as can be appreciated by those with ordinary skill in the art.

The operating system 723 is executed to control the allocation and usage of hardware resources such as the memory, processing time and peripheral devices in the

processor system 700. In this manner, the operating system 723 serves as the foundation on which applications depend as is generally known by those with ordinary skill in the art. Although the state estimation application 726 and dynamic models are described as being embodied in software or code executed by general purpose hardware as discussed above, as an alternative the same may also be embodied in dedicated hardware or a combination of software/general purpose hardware and dedicated hardware. If embodied in dedicated hardware, each of the state estimation application 726 and dynamic models can be implemented as a circuit or state machine that employs any one of or a combination of a number of technologies. These technologies may include, but are not limited to, discrete logic circuits having logic gates for implementing various logic functions upon an application of one or more data signals, application specific integrated circuits having appropriate logic gates, programmable gate arrays (PGA), field programmable gate arrays (FPGA), or other components, *etc.* Such technologies are generally well known by those skilled in the art and, consequently, are not described in detail herein.

Also, where the state estimation application 726 and dynamic models may comprise software or code, each can be embodied in any computer-readable medium for use by or in connection with an instruction execution system such as, for example, a processor in a computer system or other system. In this sense, the logic may comprise, for example, statements including instructions and declarations that can be fetched from the computer-readable medium and executed by the instruction execution system. In the context of the present invention, a "computer-readable medium" can be any medium that can contain, store, or maintain the state estimation application 726 and dynamic models for use by or in connection with the instruction execution system. The computer readable medium can comprise any one of many physical media such as, for example, electronic, magnetic, optical, electromagnetic, infrared, or semiconductor media. More specific examples of a suitable computer-readable medium would include, but are not limited to, magnetic tapes, magnetic floppy diskettes, magnetic hard drives, or compact discs. Also, the computer-

readable medium may be a random access memory (RAM) including, for example, static random access memory (SRAM) and dynamic random access memory (DRAM), or magnetic random access memory (MRAM). In addition, the computer-readable medium may be a read-only memory (ROM), a programmable read-only memory (PROM), an erasable programmable read-only memory (EPROM), an electrically erasable programmable read-only memory (EEPROM), or other type of memory device.

References

The subject Matter of the Following Publications and the US Provisional Applications are Incorporated herein by reference in their entirety

[Al-Matouq et al., 2012] "Derivation of the maximum a posterori estimate for discrete time descriptor systems" (Ali Al-Matouq and Tyrone Vincent and Luis Tenorio).

[AlMatouq et al., 2013] AlMatouq, A., Vincent, T., and Tenorio, L. (2013) Reduced complexity kalman filtering of discrete time descriptor systemsIn Proceedings of the American Control Conference.

[Breton and Kovatchev, 2008] "Analysis, modeling, and simulation of the accuracy of continuous glucose sensors" (Breton, Marc and Kovatchev, Boris).

[Dalla Man et al., 2006] "A system model of oral glucose absorption: validation on gold standard data" (Dalla Man, CD and Camilleri, Michael and Cobelli, Claudio).

[Dalla Man et al., 2014] "The uva/padova type 1 diabetes simulator new features" (Dalla Man, Chiara and Micheletto, Francesco and Lv, Dayu and Breton, Marc and Kovatchev, Boris and Cobelli, Claudio).

[Dalla Man et al., 2007] "Gim, simulation software of meal glucose?insulin model" (Dalla Man, Chiara and Raimondo, DavideMand Rizza, Robert A and Cobelli, Claudio).

[Dalla Man and Cobelli, 2007] "Meal simulation model of the glucose-insulin system" (Dalla Man, Rizza, Robert A and Cobelli, Claudio).

[Darouach et al., 1995] "Kalman filtering with unknown inputs via optimal state estimation of singular systems" (Darouach, M. and Zasadzinski, M. and Onana, A. Bassong and Nowakwski, S.).

[Grant and Boyd, 2012] Grant, M. and Boyd, S. (2012) CVX: Matlab software for disciplined convex programming, version 2.0 betahttp://cvxr.com/cvx.

[Herrero et al., 2012a] "A simple robust method for estimating the glucose rate of appearance from mixed meals" (Herrero, Pau and Bondia, Jorge and Palerm, Cesar C and Vehí, Josep and Georgiou, Pantelis and Oliver, Nick and Toumazou, Christofer).

[Herrero et al., 2012b] "Robust fault detection system for insulin pump therapy using continuous glucose monitoring" (Herrero, Pau and Calm, Remei and Vehí, Josep and Armengol, Joaquim and Georgiou, Pantelis and Oliver, Nick and Tomazou, Christofer).

[Kim et al., 2009] "nell_1 trend filtering" (Kim, Seung-Jean and Koh, Kwangmoo and Boyd, Stephen and Gorinevsky, Dimitry).

[Ljung, 1999] Ljung, L. (1999)System identificationWiley Online Library.

[MATLAB, 2012] MATLAB (2012)version 8.0.0.783 (R2012b)The MathWorks Inc.Natick, Massachusetts.

[Nikoukhah et al., 1999] "Kalman filtering for general discrete-time linear systems" (Nikoukhah, R. and Campbell, S.L. and Delebecque, F.).

[Nikoukhah et al., 1992] "Kalman Filtering and Riccati equations for descriptor systems" (Nikoukhah, R. and Willsky, A.S. and Levy, B.C.).

[Rawlings and Mayne, 2009] Rawlings, J. and Mayne, D. (2009)Model Predictive Control Theory and DesignNob Hill Pub, Llc.

[Srinivasan et al., 2014] "Novel insulin delivery profiles for mixed meals for sensoraugmented pump and closed-loop artificial pancreas therapy for type 1 diabetes mellitus" (Srinivasan, Asavari and Lee, Joon Bok and Dassau, Eyal and Doyle, Francis J).

Claims:

1. A continuous glucose rate of appearance measurement system comprising:

a receiver configured to receive subcutaneous glucose concentration data from a continuous glucose sensor that is coupled to a subject, the receiver further configured to receive insulin injection data;

processing logic configured to determine a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and

processing logic configured to determine an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

2. The continuous glucose rate of appearance measurement system of claim 1, wherein the subcutaneous glucose concentration data is noisy subcutaneous glucose concentration data.

3. The continuous glucose rate of appearance measurement system of claim 2, wherein the processing logic configured to determine an estimated glucose rate of appearance is further configured to determine a filtered subcutaneous glucose concentration.

4. The continuous glucose rate of appearance measurement system of any one of claims 1-3, wherein the glucose disturbance is a meal, an injection of insulin, or a combination thereof.

5. The continuous glucose rate of appearance measurement system of any one of claims 1-4, further comprising processing logic configured to control insulin delivery to the

subject in response at least to the estimated glucose rate of appearance.

6. A method of estimating a glucose rate of appearance, the method comprising:

receiving subcutaneous glucose concentration data from a continuous glucose sensor that is coupled to a subject;

receiving insulin injection data;

determining a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and

determining an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

7. The method of estimating a glucose rate of appearance of claim 6, wherein the subcutaneous glucose concentration data is noisy subcutaneous glucose concentration data.

8. The method of estimating a glucose rate of appearance of claim 7, wherein the step of determining an estimated glucose rate of appearance further comprises determining a filtered subcutaneous glucose concentration.

9. The method of estimating a glucose rate of appearance of any one of claims 6-8, wherein the glucose disturbance is a meal, an injection of insulin, or a combination thereof.

10. The method of estimating a glucose rate of appearance of any one of claims 6-9, further comprising the step of controlling insulin delivery to the subject in response at least to a determined estimated glucose rate of appearance.

11. A non-transitory computer-readable medium embodying a program executable in at least one computing device, wherein when executed the program causes the at least one computing device to at least:

receive insulin injection data of a subject;

determine a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and

determine an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

12. The non-transitory computer-readable medium of claim 11, wherein the subcutaneous glucose concentration data is noisy subcutaneous glucose concentration data.

13. The non-transitory computer-readable medium of claim 12, wherein when executed the program further causes the at least one computing device to determine an estimated glucose rate of appearance is further configured to determine a filtered subcutaneous glucose concentration.

14. The non-transitory computer-readable medium of any one of claims 11-13, wherein the glucose disturbance is a meal, an injection of insulin, or a combination thereof.

15. The non-transitory computer-readable medium of any one of claims 11-14, wherein when executed the program further causes the at least one computing device to control insulin delivery to the subject in response at least to the estimated glucose rate of appearance.

16. A system, comprising:

at least one computing device; and

at least one program executable in the at least one computing device, wherein when executed the at least one program causes the at least one computing device to at least:

receive insulin injection data of a subject;

determine a blood glucose concentration in the subject in response to a glucose disturbance and a rate of glucose appearance from the intestine of the subject; and

determine an estimated glucose rate of appearance in response to received subcutaneous glucose concentration data and a determined blood glucose concentration in the subject in response to the glucose disturbance and the a rate of glucose appearance from the intestine of the subject.

17. The system of claim 16, wherein the subcutaneous glucose concentration data is noisy subcutaneous glucose concentration data.

18. The system of claim 17, wherein when executed the program further causes the at least one computing device to determine an estimated glucose rate of appearance is further configured to determine a filtered subcutaneous glucose concentration.

19. The system of any one of claims 16-18, wherein the glucose disturbance is a meal, an injection of insulin, or a combination thereof.

20. The system of any one of claims 16-19, wherein when executed the program further causes the at least one computing device to control insulin delivery to the subject in response at least to the estimated glucose rate of appearance.

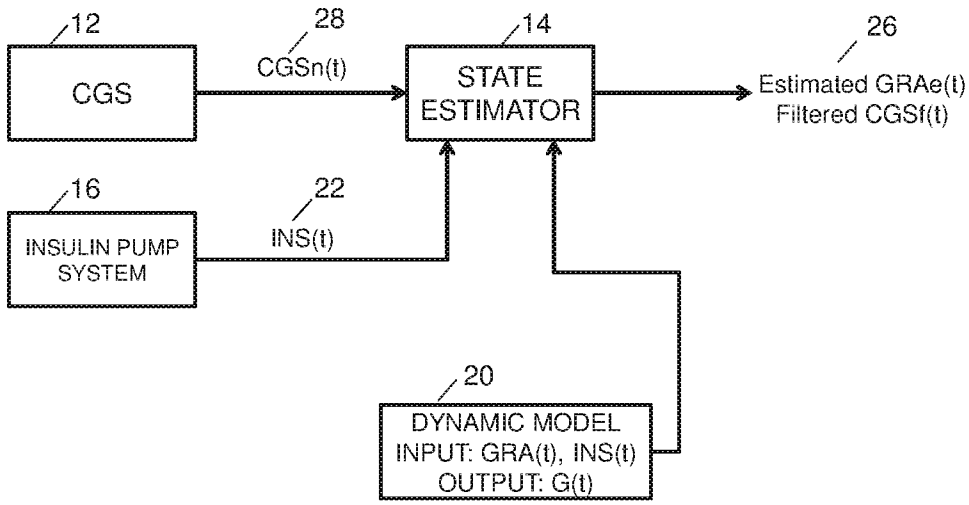
12
CGS
28
CGSn(t)
14
STATE ESTIMATOR
26
Estimated GRAe(t)
Filtered CGSf(t)
16
INSULIN PUMP SYSTEM
22
INS(t)
20
DYNAMIC MODEL
INPUT: GRA(t), INS(t)
OUTPUT: G(t)

FIG. 1

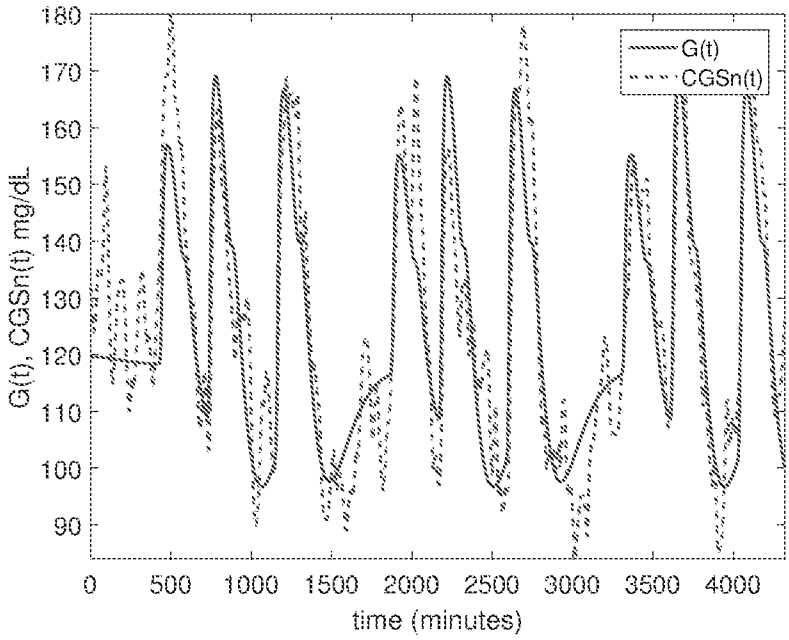
G(t)
CGSn(t)
G(t), CGSn(t) mg/dL
time (minutes)
180
170
160
150
140
130
120
110
100
90
0
500
1000
1500
2000
2500
3000
3500
4000

FIG. 2

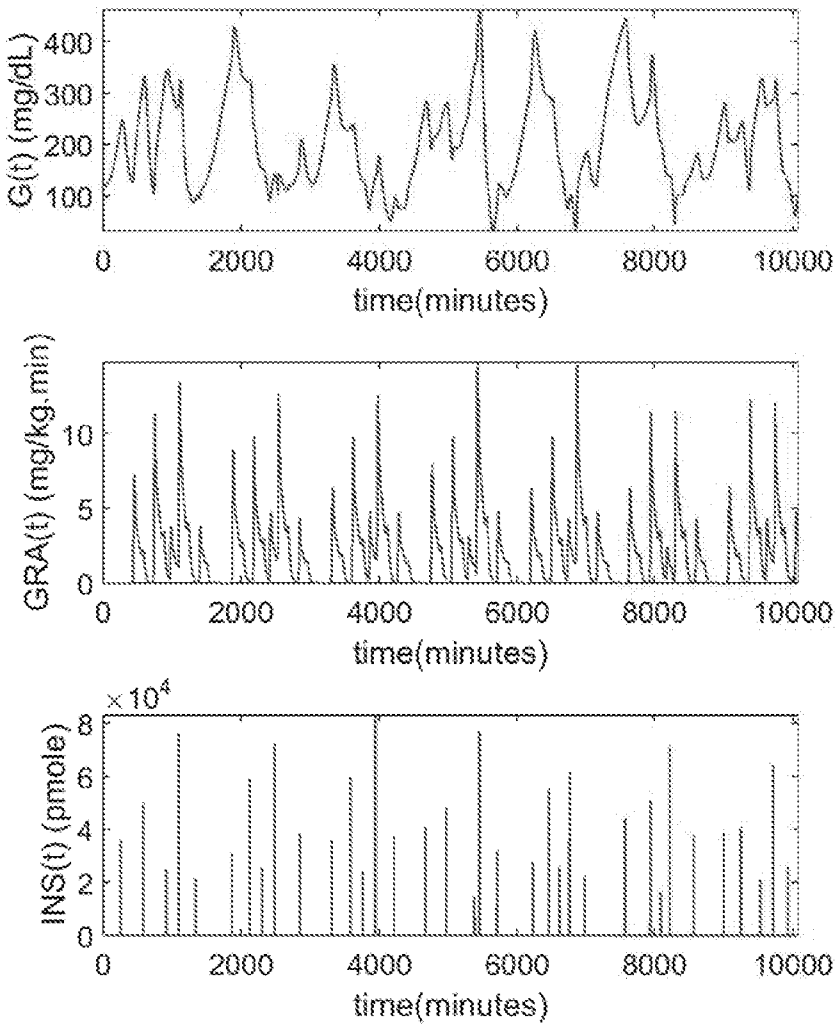
G(t) (mg/dL)
400
300
200
100
0
2000
4000
6000
8000
10000
time(minutes)
GRA(t) (mg/kg.min)
10
5
0
0
2000
4000
6000
8000
10000
time(minutes)
×10^4
INS(t) (pmole)
8
6
4
2
0
0
2000
4000
6000
8000
10000
time(minutes)

FIG. 3

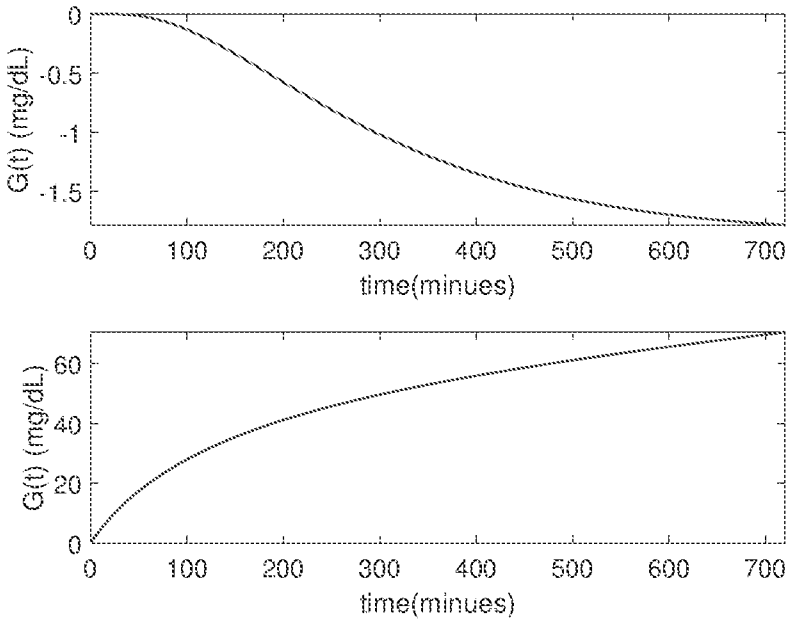
0
-0.5
-1
-1.5
G(t) (mg/dL)
0
100
200
300
400
500
600
700
time(minues)
60
40
20
0
G(t) (mg/dL)
0
100
200
300
400
500
600
700
time(minues)

FIG. 4

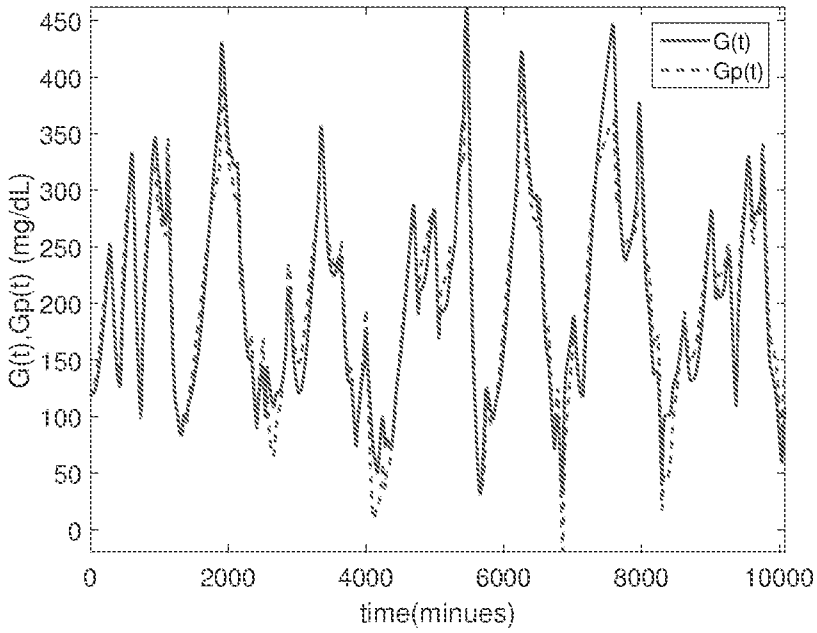
G(t)
Gp(t)
G(t),Gp(t) (mg/dL)
time(minues)
0
50
100
150
200
250
300
350
400
450
0
2000
4000
6000
8000
10000

FIG. 5

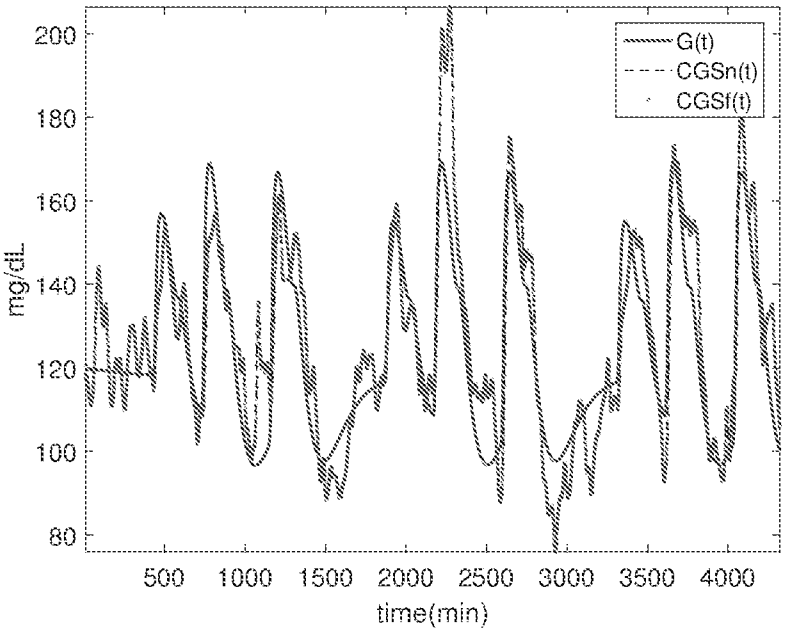
G(t)
CGSn(t)
CGSf(t)
200
180
160
140
120
100
80
mg/dL
500
1000
1500
2000
2500
3000
3500
4000
time(min)

FIG. 6

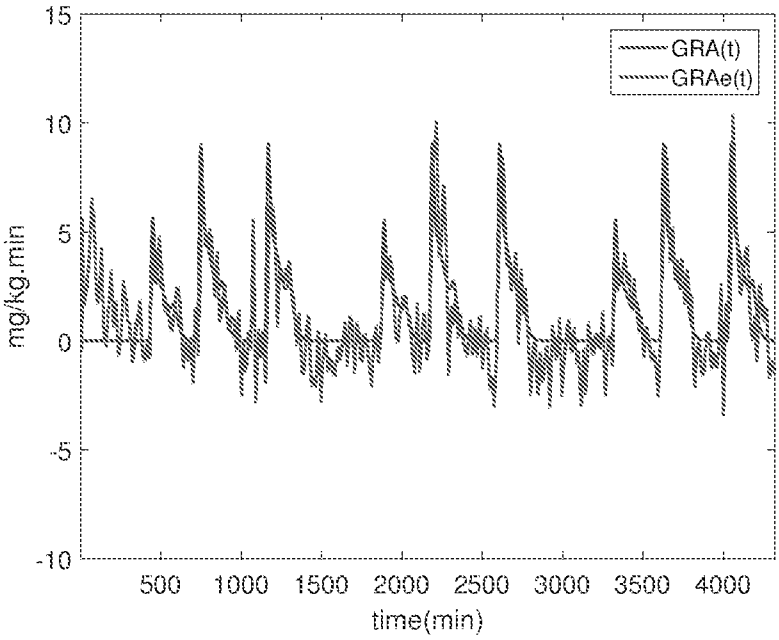
15
10
5
0
-5
-10
mg/kg.min
500
1000
1500
2000
2500
3000
3500
4000
time(min)
GRA(t)
GRAe(t)

FIG. 7

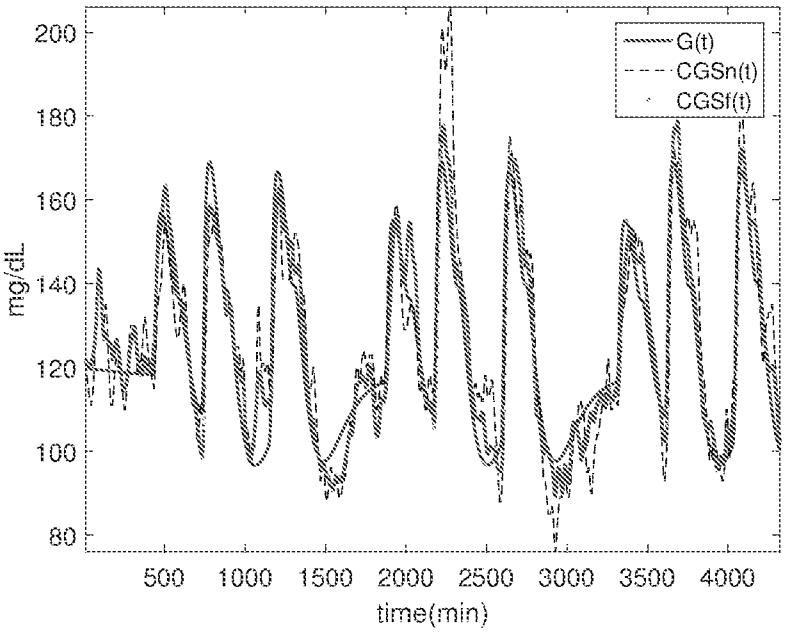
G(t)
CGSn(t)
CGSf(t)
mg/dL
200
180
160
140
120
100
80
500
1000
1500
2000
2500
3000
3500
4000
time(min)

FIG. 8

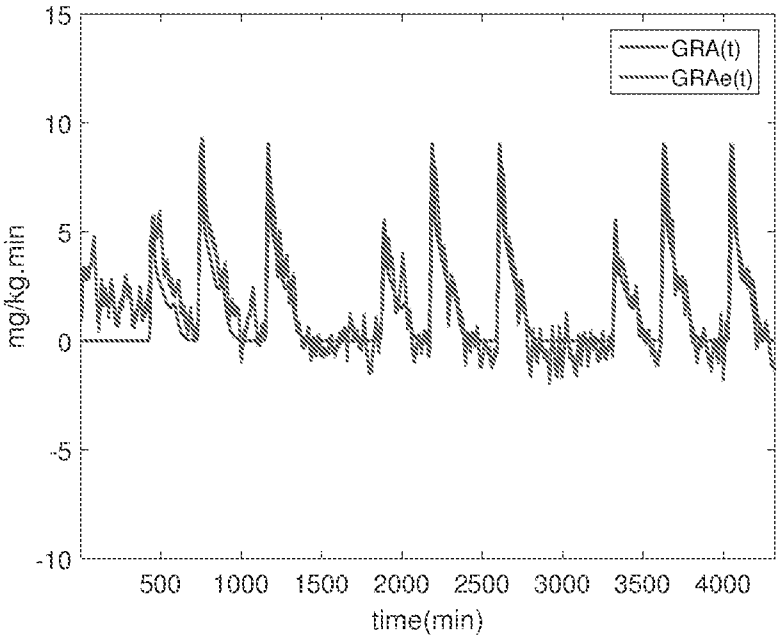
15
10
5
0
-5
-10
mg/kg.min
500
1000
1500
2000
2500
3000
3500
4000
time(min)
GRA(t)
GRAe(t)

FIG. 9

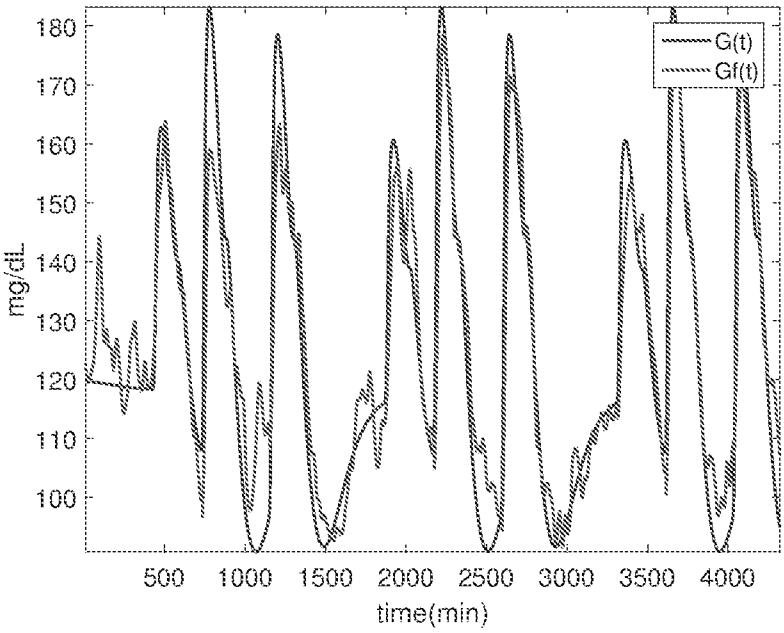
G(t)
Gf(t)
mg/dL
180
170
160
150
140
130
120
110
100
500
1000
1500
2000
2500
3000
3500
4000
time(min)

FIG. 10

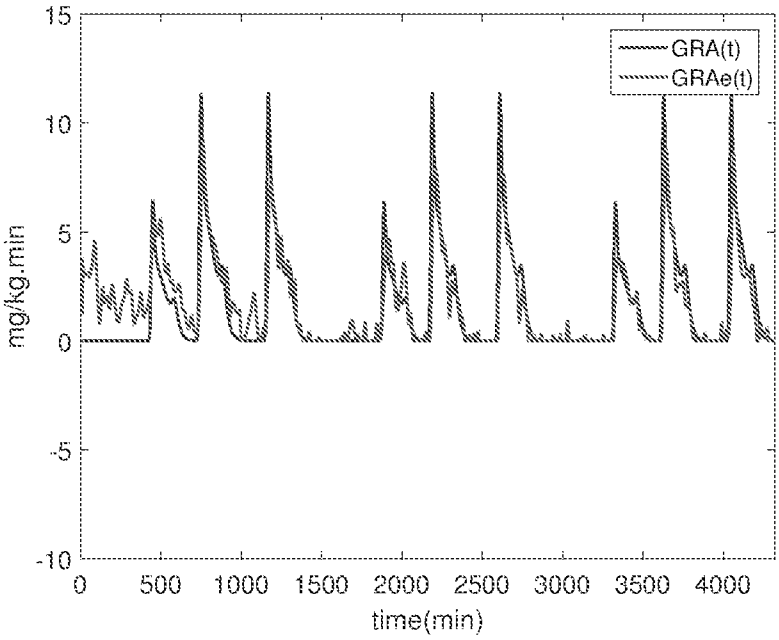
15
10
5
0
-5
-10
mg/kg.min
0
500
1000
1500
2000
2500
3000
3500
4000
time(min)
GRA(t)
GRAe(t)

FIG. 11

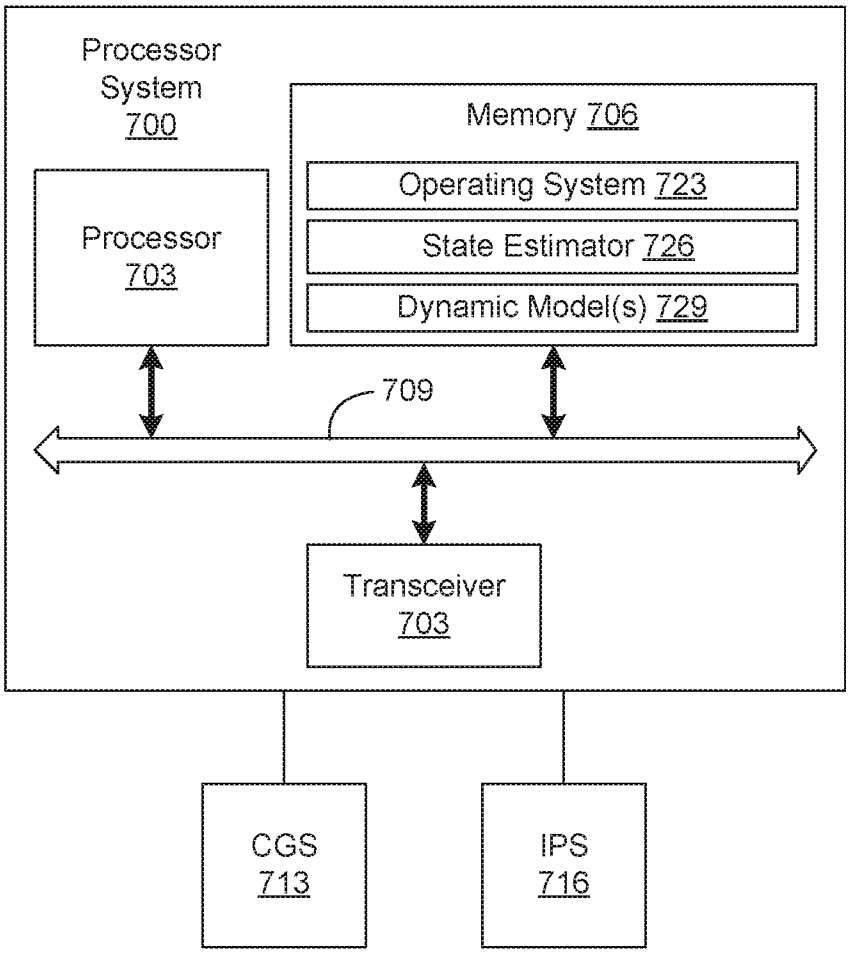
Processor System 700
Memory 706
Operating System 723
State Estimator 726
Dynamic Model(s) 729
Processor 703
709
Transceiver 703
CGS 713
IPS 716

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/051100

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/145
ADD. G06F19/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61M G06F

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRASER CAMERON ET AL: "Probabilistic Evolving Meal Detection and Estimation of Meal Total Glucose Appearance Author Affiliations", JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY VOLUME DIABETES TECHNOLOGY SOCIETY, vol. 3, no. 5, 1 September 2009 (2009-09-01), pages 1022-1030, XP055311666, DOI: 10.1177/193229680900300505 page 1023 - page 1029 ----- -/--	1-9, 11-20

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2017	08/06/2017

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

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/051100

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TURKSOY KAMURAN ET AL: "Meal Detection in Patients With Type 1 Diabetes: A New Module for the Multivariable Adaptive Artificial Pancreas Control System", IEEE JOURNAL OF BIOMEDICAL AND HEALTH INFORMATICS, IEEE, PISCATAWAY, NJ, USA, vol. 20, no. 1, 1 January 2016 (2016-01-01), pages 47-54, XP011596601, ISSN: 2168-2194, DOI: 10.1109/JBHI.2015.2446413 [retrieved on 2015-12-31] page 48 - page 52	1-9, 11-20
X	ZECCHIN C ET AL: "Neural Network Incorporating Meal Information Improves Accuracy of Short-Time Prediction of Glucose Concentration", IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, IEEE SERVICE CENTER, PISCATAWAY, NJ, USA, vol. 59, no. 6, 1 June 2012 (2012-06-01), pages 1550-1560, XP011490085, ISSN: 0018-9294, DOI: 10.1109/TBME.2012.2188893 page 1552 - page 1559	1-9, 11-20
X	US 2010/295686 A1 (SLOAN MARK [US] ET AL) 25 November 2010 (2010-11-25) paragraphs [0049] - [0056], [0058] - [0113]	1-9, 11-20

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/051100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010295686 A1	25-11-2010	EP 2432377 A1	28-03-2012
		US 2010295686 A1	25-11-2010
		US 2014066890 A1	06-03-2014
		US 2017035969 A1	09-02-2017
		WO 2010135646 A1	25-11-2010

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 10

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy This International Search Authority considers method claims which comprise the step of invasively administering an active pharmaceutical ingredient to a tissue portion of a mammal as treatment methods. Therefore, the method step "... of controlling insulin delivery to the subject in response at least to a determined estimated glucose rate of appearance" of claim 10 refers to a method of treatment of a human or animal living body by therapy, which is subject matter on which this Authority is not required to carry out international search (Rules 39.1(iv)).