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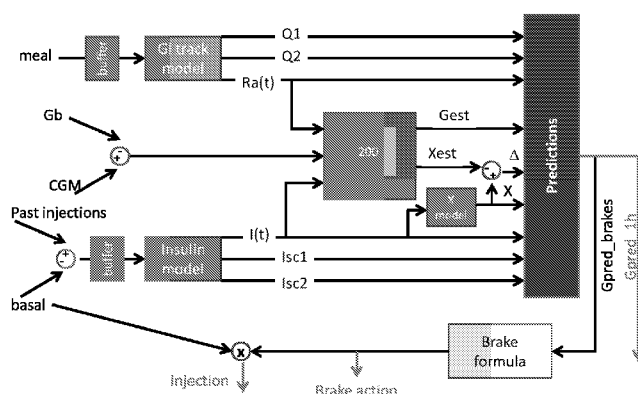


Figure 2

(57) Abstract: An insulin monitoring system includes one or more processors, one or more computer-readable storage devices, and program instructions stored on at least one of the one or more storage devices for execution by at least one of the one or more processors. The program instructions include: first program instructions to track, in real time, the amount of insulin active in a patient; second program instructions to calculate the amount of insulin need of the patient by tracking the patient's metabolic states; third program instructions to compare the insulin active in the patient with the insulin need of the patient; and fourth program instructions to determine an insulin fault level based on the comparison.

INSULIN MONITORING AND DELIVERY SYSTEM AND METHOD FOR CGM
BASED FAULT DETECTION AND MITIGATION VIA METABOLIC STATE
TRACKING

5 **CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims priority under 35 U.S.C. 119(e) to copending U.S. Provisional Application Serial No. 62/173,080, filed June 9, 2015 entitled "CGM BASED FAULT DETECTION AND MITIGATION OF INSULIN DELIVERY/MONITORING SYSTEMS VIA METABOLIC STATE TRACKING," the disclosure of which is incorporated by reference
10 herein in its entirety.

BACKGROUND

Insulin is commonly produced by the human body to help balance blood sugar levels. Some people's bodies, however, do not produce the right amounts of insulin. This can cause medical complications in the body of not addressed properly. Thus, some people may need to
15 deliver insulin to their bodies in order to avoid such medical complications.

A person may choose to deliver insulin to one's body using one of several known systems and methods, including using a syringe, an injection pen, or with an insulin pump. However, existing systems and methods for delivering insulin may not be accurate in delivering the amount of insulin actually needed by a body. Or it may be tedious and time consuming to
20 accurately deliver the actual needed amount of insulin using existing systems and methods. Delivering an inaccurate amount of insulin may result in medical complications.

SUMMARY

An example two-phase 3-tier system, method, and computer readable medium aimed at detecting and potentially remedying inappropriate insulin delivery in diabetic patients (or
25 applicable subjects) is described herein.

In a first phase, the system (and the related method and computer readable medium) detects under-insulinization by tracking in real time the insulin that is active or to be active, in a patient (Insulin on Board or "IOB"), while frequently, but not necessarily regularly, comparing it to the insulin need of the patient (Insulin that Should be On Board or "ISOB"). ISOB is
30 determined by tracking the patient metabolic states. For example, but not limited thereto, ISOB

is determined using measures related to his/her glycemia and/or metabolic states related to glycemic response to insulin such as but not restricted to plasma and capillary insulin concentration, physical activity indicators, e.g. heart rate or movement, and insulin sensitivity modifier such as stress, fever, etc.

5 In a second phase, the system (and related method) determines if a detected lack of active insulin can be remedied with the current insulin delivery/monitoring system, or if a fault exists that requires external intervention on the delivery/monitoring system. In the first case, based on the previous assessment, the system (and related method) can then either (i) alert the patient for the need of additional insulin and advise on a temporary basal rate, or (ii) safely, and over a
10 period of time, replenish the IOB by automatically increasing insulin delivery until ISOB matches IOB. It is noted that the patient's need in insulin may fluctuate during the day based on disturbances to their metabolism and/or different glycemic control goals.

 In one example embodiment, the system alerts the patient of a severe fault with the delivery/monitoring system and guides the patient in identifying and remedying the detected
15 fault.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 illustrates an example IOB based insulin delivery and monitoring system.

FIGURE 2 illustrates an example Kalman filter.

FIGURE 3 illustrates an example ISOB controller.

20 **FIGURE 4** illustrates a graph of an example transformation resulting from the ISOB controller of **FIGURE 3**.

FIGURE 5 illustrates example output of the example ISOB controller of **FIGURE 3**.

FIGURE 6 is a high level functional block diagram of an example glucose monitoring system.

25 **FIGURE 7** illustrates a block diagram of an example computer for implementing the example system of **FIGURE 1**.

FIGURE 8 is an example network system in which embodiments of the example system of **FIGURE 1** can be implemented.

FIGURE 9 is a block diagram that illustrates an example computer system and an example associated Internet connection upon which an embodiment may be implemented.

FIGURE 10 illustrates a system in which one or more embodiments of the invention can be implemented using a network

5

DETAILED DESCRIPTION

Throughout an exemplary, non-limiting embodiment, the system informs the user of the level of fault detection as follows:

- Green: no under delivery of insulin detected
- 10 • Yellow: Under-delivery can be remedied using the current delivery/monitoring device
- Red: Severe under-delivery due to delivery/monitoring system malfunction.

Figure 1 illustrates an example IOB based insulin delivery and monitoring system **100**. The system **100** includes a Fault Detection and Classification module **104** for tracking in real time the insulin that is active or to be active, in a patient (“IOB”) and comparing it to the insulin need of the patient (“ISOB”). The system **100** includes an IOB Estimator module **106** for providing the Fault Detection and Classification module **104** with IOB values. The system **100** further includes a Metabolic Monitoring module **108** for providing the Fault Detection and Classification module **104** with ISOB values. The Fault Detection and Classification module **104** compares the IOB value with the ISOB value to determine and classify the level of fault (green, yellow, or red, for example). In one example, the system **100** includes a notification module **110** to notify a user or patient of the determined fault level. It should be appreciated that the notification module **110** can be any suitable hardware or software module for conveying information to the user, such as a display, an audible alert, and so on. In one example, the system **100** includes a system check module **112** for performing a System Check in the event that
20 (green, yellow, or red, for example). In one example, the system **100** includes a Remediation module **114**, for performing a remediation in the event that a determination is made that the under-delivery can be remedied using the current delivery/monitoring device.

25

INSTANTIATIONS

IOB estimation

It should be appreciated that the IOB Estimator **106** can be configured to compute IOB using different methods. In one example, the IOB Estimator **106** is configured to compute IOB using the estimation of the amount of cleared insulin (insulin that has been degraded by the body or cleared from the central circulation). Removing this quantity from the amount of previously injected insulin one can get an estimate of how much insulin is active and/or will be active in the future. In an aspect of an embodiment of the present invention, IOB is understood as differential from a basal rate: a real (as implemented in an insulin pump) or virtual (e.g. in multiple daily injection therapeutics) insulin infusion rate that is designed to keep a diabetic patient in glycemic range, absent large perturbations (such as meals or exercise). Insulin clearance (the rate at which insulin is cleared at any point in time) can be modulated per patient or representative of a population average. In this instantiation, this is controlled by the INS_A, INS_B, CLEAR_C, and CLEAR_D matrices described below. The present inventors propose a discrete state space model representation of the IOB system. Such an implementation can be run recursively (i.e. X_k is kept in memory until the next estimation which then run from the last estimation) or on-demand (i.e. a large history, such as 6-8h, is fed to the system that retains no initial memory - X_0 is set to a predetermined initial value). Below is one example implementation of an embodiment of an IOB estimator **106**, including variables illustrated in **Table 1** and calculations used.

Name	Description	Units	type																
Inputs																			
J	a vector of past insulin injection in 5min increments	U	1x24 array of floats no empty allowed																
Time	absolute time at execution time	Seconds	UNIX datetime																
basal_hist	a vector of past basal rates in 5min increments	U/hr	1x24 array of floats no empty allowed																
Outputs																			
IOB	insulin on board	U	float																
parameters																			
INS_A	transfer matrix for insulin model	NA	4x4 array of floats fixed at <table border="1"> <tr> <td>0.9048</td><td>6.255e-6</td><td>1.98e-8</td><td>3.994e-8</td></tr> <tr> <td>0</td><td>0.4107</td><td>3.503e-3</td><td>7.104e-3</td></tr> <tr> <td>0</td><td>0</td><td>0.9048</td><td>4.524e-2</td></tr> <tr> <td>0</td><td>0</td><td>0</td><td>0.9048</td></tr> </table>	0.9048	6.255e-6	1.98e-8	3.994e-8	0	0.4107	3.503e-3	7.104e-3	0	0	0.9048	4.524e-2	0	0	0	0.9048
0.9048	6.255e-6	1.98e-8	3.994e-8																
0	0.4107	3.503e-3	7.104e-3																
0	0	0.9048	4.524e-2																
0	0	0	0.9048																

INS_B	input matrix for insulin model	NA	4x1 array of float fixed at <table><tr><td>7.241e-8</td></tr><tr><td>0.0207</td></tr><tr><td>0.117</td></tr><tr><td>4.758</td></tr></table>	7.241e-8	0.0207	0.117	4.758
7.241e-8							
0.0207							
0.117							
4.758							
CLEAR_C	output-state matrix for insulin model	NA	4x4 array of float fixed at <table><tr><td>0</td><td>0</td><td>0.178</td><td>0</td></tr></table>	0	0	0.178	0
0	0	0.178	0				
CLEAR_D	output-input matrix for insulin model	NA	4x1 array of float fixed at <table><tr><td>0</td></tr></table>	0			
0							

Table 1: Example variables used by the IOB Estimator

Computation:

J is corrected for the basal insulin infusion (**basal_hist**):

$$5 \quad \text{Equ(1)} \quad J_diff_k = J_k - \frac{\text{basal_hist}_k}{12}$$

The IOB estimator **106** computes the IOB by estimating the total (corrected) insulin that is infused so far minus the total insulin that has been cleared from the circulation. To get this estimate, the corrected infusion u_i is transformed in two ways:

1. The total injected is updated every 5 minutes as:

$$10 \quad \text{Equ(2)} \quad \text{total}_{k+1} = \text{total}_k + J_diff_k$$

2. the total cleared insulin is updated every 5 minutes as:

$$\begin{aligned} \text{Equ(3)} \quad & \text{cleared}_k = \text{Clear_C} \times X_k + \text{Clear_D} \times J_diff_k \\ & X_{k+1} = \text{INS_A} \times X_k + \text{INS_A} \times J_diff_k \\ & \text{total_cleared}_{k+1} = \text{total_cleared}_k + \text{cleared}_k \end{aligned}$$

3. IOB is then computed as

$$\text{Equ(4)} \quad \text{IOB}_{k+1} = \text{total}_{k+1} - \text{total_cleared}_k$$

15 Metabolic Monitoring**Metabolic state estimation**

Here the present inventors propose to determine, among other things, the existence of faults in a meal/insulin/continuous glucose monitoring (CGM) informed system in diabetes. One of the key ideas, among others, is that careful monitoring of the capacity of a core Kalman Filter

estimation model to the received data can enable informing the user of the validity/safety of the overall system using the KF estimation.

In particular, in one example, the Metabolic Monitoring module **108** is configured to compute at given intervals (every 5 minutes, for example) an estimate of the patient metabolic status using a Kalman filter **200** as depicted in **Error! Reference source not found.** Contrary to previously proposed systems, Meal CHO appearance and Plasma insulin are treated as feed-forward signals (i.e. they are considered fully known and are derived respectively from the meals and past insulin injections). These two signals are fed into the Kalman filter **200** as inputs, in addition to the CGM values. The Kalman filter then estimates two states: the plasma glucose and the insulin action.

The estimated state is the used to forecast the metabolic state of the patient ahead, assuming no additional disturbance; a forecast that can be used in the ISOB computation.

In addition, the difference between the feed-forward insulin action (X) and the KF estimated insulin action (Xest) can form the basis for the severe fault detection system.

Table 2 illustrates example variables used by the Kalman filter **200** to estimate of the patient metabolic status.

Name	Description	units	type
inputs			
CGM	a vector of the past 2h of CGM values in 5min increments	mg/dl	1x24 array of floats [40-400] empty value:-1
J	a vector of past insulin injection in 5min increments	U	1x24 array of floats no empty allowed

Meal	described the last meal	NA	structure containing the following fields: - time – UNIX datetime - glucose – SMBG meas. - float - CHO - float - type – int 0 (slow) 1 (medium) 2 (fast) - treated – Boolean - active - Boolean if no meal yet set fields to [0;0;0;TRUE;FALSE]
Time	absolute time at execution time	seconds	UNIX datetime
EX	level of exercise	NA	Float [0 1]
basal	basal rate value at execution time	U/hr	float [0-3]
basal_hist	a vector of past basal rates in 5min increments	U/hr	1x24 array of floats no empty allowed
CF	Correction Factor at execution time	mg.dl ⁻¹ .U ⁻¹	float [10-100]
CR	Carbohydrate ration at execution time	U.g ⁻¹	float [5-50]
BW	patient's weight	Kg	float [20-200]
outputs			
Const	Safety System constraint	U.hr ⁻¹	float [0 3]
Gest	plasma glucose level estimation	mg/dl	float [20 400]
Gpred_1h	Plasma glucose 1h prediction	mg/dl	float [20 400]
Gpred_light	Plasma glucose 10min prediction with no insulin assumption for red light	mg/dl	float [20 400]
BrakeAction	reduction amount imposed by the power brakes	NA	Float [0 1]
parameters			
Gop	operation point glucose for kalman filter in KALMAN	mg/dl	float fixed at 90

INS_A	transfer matrix for insulin model	NA	4x4 array of floats fixed at						
			0.9048	6.256e-6	1.498e-6	3.023e-6			
			0	-0.4107	0.2651/BW	0.5376/BW			
			0	0	0.9048	0.0452			
			0	0	0	0.9048			
INS_B	input matrix for insulin model	NA	4x1 array of float fixed at						
			5.47						
			93e-6/BW						
			1.56						
			61/BW						
0.11									
70									
4.75									
81									
INS_C	output-state matrix for insulin model	NA	4x4 array of float fixed at						
			1	0	0	0			
			0	1	0	0			
			0	0	1	0			
			0	0	0	1			
INS_D	output-input matrix for insulin model	NA	4x1 array of float fixed at						
			0						
			0						
			0						
			0						
MEAL_A	transfer matrix for meal model	NA	2x2 array of floats fixed at						
			0.9	0.04					
			048	524					
			0	0.90					
				48					
MEAL_B	input matrix for meal model	NA	2x1 array of float fixed at						
			0.1						
			17						
			4.7						
			58						
MEAL_C	output-state matrix for meal model	NA	3x2 array of float fixed at						
			0.	0.					
			0	0					
			2	1					
			1	0					
0	1								
MEAL_D	output-input matrix for meal model	NA	3x1 array of float fixed at						
			0						
			0						
			0						
			0						
CORE_pred_A	prediction matrix for core model	NA	8x8 array of floats fixed at						
			0.5488	-	-	0.1733/BW	0.1127/BW	-0.0148	-
				1.9972e3	1.4818e3				0.0186/BW
			0	0.9704	0	0	0	0	0
			0	0	0.5488	0	0	6.89e-6	1.75e-5/BW
			0	0	0	0.5488	0.1646	0	0
			0	0	0	0.5488	0	0	0
			0	0	0	0	0	0.0048	0.4315/BW
			0	0	0	0	0	0	0.5488
			0	0	0	0	0	0	0.1646
			0	0	0	0	0	0	0
			0	0	0	0	0	0	0

CORE_pred_C	output matrix for core model	NA	1x8 array of floats fixed at 1 0 0 0 0 0 0 0
LIGHT_pred_A	prediction matrix for red light		8x8 array of floats fixed at 0.8187 -811.5 -736.85 0.08618/BW 0.0474/BW -4.6399e 0 0.99 0 0 0 0 0 0 0.8187 0 0 8.229e-0 0 0 0 0.8187 0.08187 0 0 0 0 0 0.8187 0 0 0 0 0 0 0.16864 0 0 0 0 0 0 0 0 0 0 0 0
LIGHT_pred_B	input matrix for red light model		8x2 array of floats fixed at 0.2457/BW -42499e-3/BW 0 0 0 1.8075e-05/BW 0.4381 0 9.0635 0 0 2.5279/BW 0 9.0635 0 0.4381
LIGHT_pred_C	output matrix for red light model		1x8 array of floats fixed at 1 0 0 0 0 0 0 0
1H_predA	1 hour prediction matrix		8x8 array of floats fixed at 30.119 -3034.3E -1626.4 0.19023/BW 0.1522/BW 0 0.94176 0 0 0 0 0 0.3.0119 0 0 0 0 0 0.30119 0.18072 0 0 0 0 0.30119 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
1H_pred_C			1x8 array of floats fixed at 1 0 0 0 0 0 0 0
KF_A	transfer matrix for kalman filter	NA	4x4 array of floats fixed at 0.006 -407.177 0.0007 0.9048
KF_B	input matrix for kalman filter	NA	4x3 array of float fixed at -0.0021 2.5043/BW 0.8988 9.5163e-6 0 -7.3045e-4
KF_C	output-state matrix for kalman filter	NA	4x4 array of float fixed at 0.3699 0 8.0728e-4 1
KF_D	output-input matrix for meal kalman filter	NA	4x1 array of float fixed at 0 0 0.6301 0 0 -8.0728e-4
BUFF_A	transfer matrix for meal and insulin buffers	NA	2x2 array of float fixed at 0.9512 0.04756 0 0.9512
BUFF_B	transfer matrix for meal and insulin buffers	NA	2x1 array of float fixed at 1.209e-3 4.877e-2
BUFF_C	transfer matrix for meal and insulin buffers	NA	1x2 array of float fixed at 1 0
BUFF_D	transfer matrix for meal and insulin buffers	NA	1x1 array of float fixed at 0

Table 2: Example variables used by the Metabolic Monitoring Module

Computation

1. First, the construction of the feedforward model outputs is performed (green, for example). It should be appreciated that this code is recursive and needs to be run at certain intervals (every 5 minutes, for example). If an execution during an interval is missed, then the code may be run for each interval since the last execution:

GI track system

The calculation for GI track system can be defined as follows:

If Time-Meal.time<300

10 meal_amount_k=1000*Meal.CHO/5

else

meal_amount_k=0;

end

15 Thus,

$$Mbuf = BUFF_A \times Mbuf_k + BUFF_B \times meal_amount_k$$

$$\begin{cases} Mout_k = MEAL_C \times Mstate_k + MEAL_D \times Mbuf_k \\ Mstate_{k+1} = MEAL_A \times Mstate_k + MEAL_B \times Mbuf_k \end{cases}$$

Equ(5)

$$Ra_k = Mout_k(1)$$

$$M_s_out_k = \begin{bmatrix} Mout_k(2) \\ Mout_k(3) \end{bmatrix}$$

Insulin system

The calculation for Insulin system can be defined as follows:

$$Ibuf_k = BUFF_A \times Ibuf_k + BUFF_B \times (J_k - basal_hist_k)$$

$$\begin{cases} Iout_k = INS_C \times Istate_k + INS_D \times Ibuf_k \\ Istate_{k+1} = INS_A \times Istate_k + INS_B \times Ibuf_k \end{cases}$$

Equ(6) $I_k = Iout_k (2)$

$$Xpred_k = Iout_k (1)$$

$$I_s_out_k = \begin{bmatrix} Iout_k (3) \\ Iout_k (4) \end{bmatrix}$$

2. The Kalman Filter estimate is next computed. It should be appreciated that this code is recursive and needs to be run at certain intervals (every 5 minutes, for example). If an execution during an interval is missed, then the code may be run for each interval since the last execution:

Equ(7)
$$\begin{cases} KFout_k = KF_C \times KFstate_k + KF_D \times \begin{bmatrix} I_k \\ Ra_k \\ CGM_k - Gop \end{bmatrix} \\ KFstate_{k+1} = KF_A \times KFstate_k + KF_B \times \begin{bmatrix} I_k \\ Ra_k \\ CGM_k - Gop \end{bmatrix} \end{cases}$$

3. Output variable Gest and Delta are next created:

Equ(8) $Gest = KFout_k(1) + Gop$

10 Equ(9) $Delta = KFout_k(2) - Xpred_k$

4. The predictions are then made:

Equ(10)

$$XI_k = \begin{bmatrix} KFout_k(1) \\ Delta \\ Xpred_k \\ I_k \\ I_s_out_k(1) \\ I_s_out_k(2) \\ M_s_out_k(1) \\ M_s_out_k(2) \end{bmatrix}$$

$$Gpred = CORE_pred_C \times CORE_pred_A \times XI_k + Gop$$

$$Gpred_light = LIGHT_pred_C \times (LIGHT_pred_A \times XI_k + LIGHT_pred_B \times [-basal, 0]) + Gop$$

$$Gpred_1h = 1h_pred_C \times 1h_pred_A \times XI_k + Gop$$

Insulin that should be on board (ISOB) computation

The Metabolic Monitoring module **108** is further configured to compute insulin need of a patient.

- 5 It should be appreciated that the Metabolic Monitoring module **108** may be configured to compute insulin need of a patient, or ISOB, in a multitude of ways: it can be estimated based on past measurements (e.g. glycemia, insulin, heart rate, accelerometry, temperature...), as described herein, or it could even be directly measured (in which case this module would be inactive and it would feed directly in the Advice Rate Computation Module below).

- 10 In one example, the Metabolic Monitoring module **108** includes an ISOB controller **300**, illustrated in **Figure 3**, for computing ISOB. The ISOB computation in this instantiation uses an estimated (or predicted) value of plasma glucose(G) **302** and compares it to a time dependent “glucose ceiling” **304**, which varies based on the time of day **306**. The difference is then transformed, at module **308**, in insulin space using a metric of the patient insulin sensitivity.
- 15 Such metric could be the patient’s own Insulin Sensitivity Factor pattern (ISF, a common insulin pump parameter) or be derived from the past total daily insulin (“1800 rule”: ISF=1800/TDI, or “1500 rule”: ISF=1500/TDI), from the patient 24h basal dose (TDI=2*TDB), and finally the patient’s body weight(TDI=a+b*BW).

- 20 In addition, ISOB can be corrected, at module **310**, for slope (i.e. predicted ahead in a linear fashion) to react faster to increased need or limit the risk of overdose. These corrections do not have to necessarily be symmetric (i.e. one may choose to limit the correction in one

direction more than in the other as below). Similar effect can be achieved by using a predicted glucose instead of an estimated glucose as input. Table 3 illustrates example variables used by the ISOB Controller 300.

Name	Description	units	Type					
Inputs								
Time	absolute time at execution time	seconds	UNIX datetime					
IOB	insulin on board	U	float					
Gest	estimated glucose.	mg/dl	float					
basal	basal rate value at execution time	U/hr	float [0-3]					
CF	Correction Factor at execution time	mg.dl ⁻¹ .U ⁻¹	float [10-100]					
outputs								
du	Differential correction rate	U.min ⁻¹	Float [0 0.1]					
parameters								
DER	FIR filter parameter for short term derivative computation	min ⁻¹	1x5 float array fixed at <table><tr><td>0.04</td><td>0.02</td><td>0</td><td>-0.02</td><td>-0.04</td></tr></table>	0.04	0.02	0	-0.02	-0.04
0.04	0.02	0	-0.02	-0.04				
T2tgt	time to achieve IOB target	min	float fixed at 30					
PredH	prediction horizon for IOB target correction	min	float fixed at 60					

Table 3: Example variables used by the ISOB Controller

5

Computation:

1. The ISOB Controller 300 computes the time of day using:

$$\text{Equ(11)} \quad \text{ToD} = (\text{Time} - 86400 * \text{floor}(\text{Time} / 86400)) / 60$$

10

2. The ISOB Controller 300 computes the glucose target using:

$$\text{Equ(12)} \quad x = \begin{cases} \frac{1 + \text{ToD}}{7} & \text{if } y < 6 \\ 7 - \text{ToD} & \text{if } \text{ToD} \geq 6 \text{ and } \text{ToD} < 7 \\ 0 & \text{if } \text{ToD} \geq 7 \text{ and } \text{ToD} < 23 \\ \frac{\text{ToD} - 23}{7} & \text{if } \text{ToD} > 23 \end{cases}$$

$$\text{Equ(13)} \quad \text{gluc_tgt} = 160 - 45 \times \frac{\left(\frac{x}{0.5}\right)^3}{1 + \left(\frac{x}{0.5}\right)^3}$$

The resulting transformation is illustrated in the graph 400 of **Figure 4**.

5 The amount of insulin required to achieve that target is computed as:

$$\text{Equ(14)} \quad \text{INS}_{\text{Target}} = \frac{\text{Gest} - \text{gluc_tgt}}{\text{CF}}$$

and this variable is extrapolated 1 h ahead ($\text{INS}_{\text{Target_predicted}}$) using its current value and first
 10 derivative as follows: The slope of the $\text{INS}_{\text{Target}}$ is computed with a digital FIR filter using the last 5 values of the (easily accessible by back computing gluc_tgt) $\text{INS}_{\text{TargetSlope}}$. The parameter set for the FIR filter is provided by *der*

$$\text{Equ(15)} \quad \text{INS}_{\text{TargetSlope}_k} = \text{DER} \times \begin{bmatrix} \text{INS}_{\text{Target}_{k-4}} \\ \text{INS}_{\text{Target}_{k-3}} \\ \text{INS}_{\text{Target}_{k-2}} \\ \text{INS}_{\text{Target}_{k-1}} \\ \text{INS}_{\text{Target}_k} \end{bmatrix}$$

15 The variables $\text{INS}_{\text{Target}}$ and $\text{INS}_{\text{TargetSlope}}$ are saturated:

$$\text{Equ(16)} \quad \text{INS}_{\text{TargetSat}} = \begin{cases} \text{INS}_{\text{Target}} & \text{if } \text{INS}_{\text{Target}} < \frac{90}{\text{ctrlr.CF}} \\ \frac{90}{\text{ctrlr.CF}} & \text{otherwise} \end{cases}$$

20

$$\text{Equ(17)} \quad \text{INS}_{\text{TargetSlopeSat}} = \begin{cases} 1/\text{PredH} & \text{if } \text{INS}_{\text{TargetSlope}} > 1/\text{PredH} \\ -10/\text{PredH} & \text{if } \text{INS}_{\text{TargetSlope}} < -10/\text{PredH} \\ \text{INS}_{\text{TargetSlope}} & \text{otherwise} \end{cases}$$

and combined to get a predicted value for INS_{Target} :

Equ(18)

$$INS_{Target_predicted} = INS_{TargetSat} + PredH * INS_{TargetSlopeSat}$$

5

Fault Detection and Classification

Mild/none Fault Detection

This condition is the default of the system. i.e. if no moderate or severe fault are detected then only mild (or no) faults are present.

10

Moderate Fault Detection and Advised Rate Computation

Once an insulin need is identified ($IOB < ISOB$), an aspect of an embodiment of the system 100 (and related method) can compute a rate of insulin needed to remedy this difference within in pre-determined amount of time (τ). It is important to note that (i) this rate is supplemental to the patient's basal rate, and (ii) the rate can (and often should) be saturated so as to limit the risk associated with an error in ISOB determination (here twice the basal rate). Finally, the computed rate can be either sent to an insulin pump for implementation either as (i) a temporary basal rate of t minutes (Open Loop mode), or as the control action of an automated closed loop system (in that case the rate will re computed at every controller step, and therefore is unlikely to be executed in full as ISOB will be re-estimated at each step); or (2) as a display to the patient for manual implementation.

15

20

This value is compared to the available IOB. The difference is divided by a predefined time to target ($T2tgt$) and further limited to be only positive, after which the units are converted:

$$Rate = \frac{INS_{Target_predicted} - IOB}{\tau}$$

25

The output 500 of the module, if use of the IOB controller 300 has been requested, is illustrated in **Figure 5** and defined as:

$$\text{Equ(19)} \quad du = \begin{cases} \delta * \frac{\text{basal}}{\tau} & \text{if } \text{Rate} > \delta * \frac{\text{basal}}{\tau} \\ \text{Rate} & \text{if } 0 < \text{Rate} \leq \delta * \frac{\text{basal}}{\tau} \\ 0 & \text{otherwise} \end{cases}$$

$$\tau = 60; \quad \delta = 2$$

Severe Fault detection

Severe fault detection is handled differently than moderate fault as it uses an internal variable of the Kalman filter metabolic estimate, instead of the predicted output (glucose). This internal variable is the difference between the feed-forward insulin action (X) and the Kalman filtered insulin action ($\hat{X}$). This variable is an indication of how the internal model agrees with the measurements, which can be used to detect changes indicative of faults in the delivery/monitoring system **100** (e.g. drifting CGM or occluded insulin pump).

The detection is made by comparing the behavior of $\square$ the recent past (e.g. one hour) to normative values or its behavior over a longer time period (e.g. 3h); taking into account that some measured disturbances (such as meals) can greatly affect $t \square$. Table 4 illustrates example variables used for severe fault detection.

Name	Description	units	type
inputs			
Meal Flag	a vector of the past 6h of the presence of an announced meal in 5min increments	None	1x72 array of integer [0-1] empty value:0
Delta	a vector of the past 6h of the Delta variable from the Meal informed Kalman filter in 5min increments	min ⁻¹	1x72 array of floats no empty allowed
outputs			
Deviation	Quantification of model deviation	None	float [-1 1]
Detect	Sever fault detection flag	None	boolean
parameters			

W_1	Width of the short term observation window	min	float fixed at 60
W_2	Width of the short term observation window	min	float fixed at 60
ω	Controls how long a meal influences the computation	min	Float fixed at 180
N	Controls how sharply the effect of a meal wanes	none	Float fixed at 7
τ	Detection threshold	none	Float fixed at -0.2

Table 4: Example variables used for severe fault detection

Computation

First, in an aspect of an embodiment, the system **100** (and associated method) averages the Delta variable over the short term and long term windows:

$$5 \quad \text{Equ(20)} \quad \Delta_{short} = \frac{5}{W_1} \sum_i^{\frac{W_1}{5}} \Delta \left(72 + 1 - \frac{W_1}{5}, 72 \right)$$

$$\text{Equ(21)} \quad \Delta_{long} = \frac{5}{W_2} \sum_i^{\frac{W_2}{5}} \Delta \left(72 + 1 - \frac{W_2}{5}, 72 \right)$$

How close a meal is will determine how much an aspect of an embodiment of the system **100** (and associated method) trusts the short term average over the long term one to compute this parameters we construct recursively a Meal factor for each 5 minute interval (k) over the last 6
10 hours (k=1...72)

$$\text{Equ(22)} \quad MealF_0 = 0$$

$$\text{Equ(23)} \quad MealF_{k+1} = \begin{cases} MealF_k + 1 & \text{if } Meal(k+1) = 0 \\ 0 & \text{otherwise} \end{cases}$$

The meal factor is then transformed in a trust factor (from 0 to 1) using a sigmoidal function:

$$\text{Equ(24)} \quad p = \frac{\left(\frac{MealF_{72}}{\omega} \right)^n}{1 + \left(\frac{MealF_{72}}{\omega} \right)^n}$$

15 And finally the model deviation is quantified:

$$\text{Equ(25)} \quad \text{Deviation} = p * \text{Delta}_{\text{short}} + (1 - p) * \text{Delta}_{\text{long}}$$

Detection of a severe fault is done by comparing the deviation to a preset threshold:

$$\text{Equ(26)} \quad \text{Detect} = \begin{cases} \text{FALSE if } \text{Deviation} > \tau \\ \text{TRUE otherwise} \end{cases}$$

Patient Alert Module

5 Regardless of the new insulin delivery rate being automatically sent to an insulin delivery device or displayed to the patient, the system **100** can also alert the patient of the current risk for hyperglycemia. The present inventors, regarding an aspect of an embodiment, propose a three tiers system of alarm (similar to a stoplight):

- Green: no or minimal risk
 - 10 • Yellow: hyperglycemic risk is present, insulin should be increased
 - Red: Serious hyperglycemic risk, cannot be easily mitigated by increase insulin rate.
- Possible system failure (e.g. pump occlusion, severe sensor drift, dramatic change is patient metabolism)

Light colors can be determined by a range of algorithms

15 Threshold based:

- G: $\text{IOB} < \square_{\text{I}}$
- Y: $\square_{\text{I}} < \text{IOB} < \square_{\text{Y}}$
- R: $\text{IOB} > \square_{\text{Y}}$

Glycemic control based:

- 20 • G: $G_{\text{est}} < \square_{\text{G}}$
- Y: $\square_{\text{Y}} < G_{\text{est}} < \square_{\text{Y}}$
- R: $\square_{\text{Y}} > G_{\text{est}}$

System action based

- G: no hyperglycemic mitigation needed: $\text{ISOB} - \text{IOB} < \square_{\text{G}}$
- 25 • Y: Hyperglycemic mitigation active: $\text{ISOB} - \text{IOB} > \square_{\text{Y}}$
- R: Hyperglycemic mitigation saturated: $\text{ISOB} - \text{IOB} > \square * \text{basal} / \square$

Red light based on system fault detection

- G: no fault or mild fault
- Y: moderate fault
- R: Severe fault

5 **Figure 6** is a high level functional block diagram of an example glucose monitoring system. As shown in **Figure 6**, a processor or controller **102** communicates with the glucose monitor or device **101**, and optionally the insulin device **105**. 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 **105** 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 **105** 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 **105**, 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.

Referring to **Figure 7**, 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.

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.

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. As a way of example, **Figure 8** 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 8** 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.

5 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
10 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.

15 **Figure 9** 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
20 processor described herein, may use the computer system configuration and the Internet connection shown in **Figure 9**. 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
25 computing devices, or a combination of any of these devices. Note that while **Figure 9** 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
30 components may also be used. The computer system of **Figure 9** 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
5 dynamic storage device, coupled to bus **137** for storing information and instructions to be executed by processor **138**.

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
10 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
15 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
20 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
25 managing files. Non-limiting examples of operating systems are Microsoft Windows, Mac OS X, and Linux.

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
30 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.

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.

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.

The term "computer-readable medium" (or "machine-readable medium") 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.).

5 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.

10 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
15 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**.

20 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
25 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
30 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
5 entirety for all purposes as if fully set forth herein.

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.

10 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,
15 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.

A received code may be executed by processor **138** as it is received, and/or stored in
20 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.

The concept of detecting and potentially remedying inappropriate insulin delivery in diabetic patients (or applicable subjects) has been developed; and may be implemented and utilized with the related processors, networks, computer systems, internet, and components and
25 functions according to the schemes disclosed herein.

Figure 10 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.

Figure 10 diagrammatically illustrates an exemplary system in which examples of the
30 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 10**, 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 10**. 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.

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.

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 7**.

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 disclosure, including all modifications and equivalents.

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. 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.

5

References

The following patents, applications and publications as listed below and throughout this document are hereby incorporated by reference in their entirety herein. It should be appreciated that various aspects of embodiments of the present method, system, devices, article of
10 manufacture, computer readable medium, and compositions may be implemented with the following methods, systems, devices, article of manufacture, computer readable medium, and compositions disclosed in the following U.S. Patent Applications, U.S. Patents, and PCT International Patent Applications and are hereby incorporated by reference herein and co-owned with the assignee (and which are not admitted to be prior art with respect to the present invention
15 by inclusion in this section):

A. U.S. Patent Application No. 14/419,375 entitled “Computer Simulation for Testing and Monitoring of Treatment Strategies for Stress Hyperglycemia”, filed February 3, 2015.

B. International Patent Application No. PCT/US2013/053664 entitled “Computer
20 Simulation for Testing and Monitoring of Treatment Strategies for Stress Hyperglycemia”, filed August 5, 2013; International Patent Application Publication No. WO 2014/022864, February 6, 2014. International Patent Application No. PCT/US2015/010167 entitled “Central Data Exchange Node For System Monitoring and Control of Blood Glucose Levels in Diabetic Patients”, filed January 5, 2015.

C. International Patent Application No. PCT/US2014/045393 entitled “Simulation of
25 Endogenous and Exogenous Glucose/Insulin/Glucagon Interplay in Type 1 Diabetic Patients”, filed July 3, 2014; International Patent Application Publication No. WO 2015/003124, January 8, 2015.

D. U.S. Patent Application No. 14/266,612 entitled “Method, System and Computer
30 Program Product for Real-Time Detection of Sensitivity Decline in Analyte Sensors”, filed April 30, 2014; U.S. Patent Application Publication No. 2014/0244216, August 28, 2014.

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WHAT IS CLAIMED IS:

1. An insulin monitoring system, the system comprising one or more processors, one or
5 more non-transitory computer-readable storage devices, and program instructions stored on at
least one of the one or more storage devices for execution by at least one of the one or more
processors, the program instructions comprising:
 - first program instructions to track, in real time, the amount of insulin active in a patient;
 - second program instructions to calculate the amount of insulin need of the patient by
10 tracking the patient's metabolic states;
 - third program instructions to compare the insulin active in the patient with the insulin
need of the patient; and
 - fourth program instructions to determine an insulin fault level based on the comparison.
2. The system of claim 1, wherein the first program instructions are further configured to
15 track the amount of insulin active in the patient by estimating the total insulin that is infused and
subtracting the total insulin that has been cleared from the circulation.
3. The system of claim 1, wherein the second program instructions are configured to use
Kalman filtering to estimate a plasma glucose state and an insulin action state based on received
data representative of continuous glucose monitoring values, meal CHO, and plasma insulin, and
20 determine the patient's metabolic state based on the estimated plasma glucose state and insulin
action state.
4. The system of claim 3, wherein the second program instructions are configured to
calculate the amount of insulin need of the patient by comparing the estimated value of plasma
glucose with a time-dependent glucose ceiling and transforming the difference using a metric of
25 the patient insulin sensitivity.

5. The system of claim 1, wherein the fourth program instructions are configured to determine one of three fault levels based on the comparison, wherein a first fault level is indicative of little or no hyperglycemic risk, wherein a second fault level is indicative of moderate hyperglycemic risk, and wherein a third fault level is indicative of severe hyperglycemic risk.

6. The system of claim 5, further comprising fifth program instructions for communicating to a patient an alert indicative of a need for additional insulin, responsive to the fourth program instructions determining a second fault level.

7. The system of claim 5, further comprising sixth program instructions for causing an insulin device to automatically increase insulin delivery until the amount of insulin active in a patient matches the amount of insulin need of a patient, responsive to the fourth program instructions determining a second fault level.

8. The system of claim 5, further comprising seventh program instructions for communicating to a patient an alert indicative of a severe hyperglycemic risk, responsive to the fourth program instructions determining a third fault level.

9. The system of claim 8, further comprising eighth program instructions for communicating to the patient instructions for identifying and remedying the third fault.

10. A computer-implemented method for monitoring insulin, comprising:

tracking, by at least one processor in real time, the amount of insulin active in a patient;

calculating, by at least one processor, the amount of insulin need of the patient by tracking the patient's metabolic states;

comparing, by at least one processor, the insulin active in the patient with the insulin need of the patient; and

determining, by at least one processor, an insulin fault level based on the comparison.

11. The computer-implemented method of claim 10, wherein the tracking comprises tracking the amount of insulin active in the patient by estimating the total insulin that is infused and subtracting the total insulin that has been cleared from the circulation.

12. The computer-implemented method of claim 10, wherein the calculating comprises using
5 Kalman filtering to estimate a plasma glucose state and an insulin action state based on received data representative of continuous glucose monitoring values, meal CHO, and plasma insulin, and determining the patient's metabolic state based on the estimated plasma glucose state and insulin action state.

13. The computer-implemented method of claim 12, wherein the calculating further
10 comprises calculating the amount of insulin need of the patient by comparing the estimated value of plasma glucose with a time-dependent glucose ceiling and transforming the difference using a metric of the patient insulin sensitivity.

14. The computer-implemented method of claim 10, wherein the determining comprises
15 determining one of three fault levels based on the comparison, wherein a first fault level is indicative of little or no hyperglycemic risk, wherein a second fault level is indicative of moderate hyperglycemic risk, and wherein a third fault level is indicative of severe hyperglycemic risk.

15. The computer-implemented method of claim 14, further comprising communicating to
20 the patient, by at least one processor, an alert indicative of a need for additional insulin, responsive to determining a second fault level.

16. The computer-implemented method of claim 14, further comprising causing an insulin device to automatically increase insulin delivery until the amount of insulin active in the patient matches the amount of insulin need of the patient, responsive to determining a second fault level.

17. The computer-implemented method of claim 14, further comprising communicating to
25 the patient, by at least one processor, an alert indicative of a severe hyperglycemic risk, responsive to determining a third fault level.

18. The computer-implemented method of claim 17, further comprising communicating to the patient, by at least one processor, instructions for identifying and remedying the third fault.

19. A non-transitory computer-readable storage medium having stored therein computer-executable instructions that when executed cause at least one processor to:

5 track, in real time, the amount of insulin active in a patient;

calculate the amount of insulin need of the patient by tracking at least one metabolic state of the patient;

compare the insulin active in the patient with the calculated insulin need of the patient;
and

10 determine an insulin fault level based on the comparison.

20. The non-transitory computer-readable medium of claim 19, wherein the instructions causing at least one processor to track are further configured to cause said at least one processor to track the amount of insulin active in the patient by estimating the total insulin that is infused and subtracting the total insulin that has been cleared from the circulation.

15 21. The non-transitory computer-readable medium of claim 19, wherein the instructions causing at least one processor to calculate are further configured to cause said at least one processor to use Kalman filtering to estimate a plasma glucose state and an insulin action state based on received data representative of continuous glucose monitoring values, meal CHO, and plasma insulin, and determine the patient's metabolic state based on the estimated plasma
20 glucose state and insulin action state.

22. The non-transitory computer-readable medium of claim 21, wherein the instructions causing at least one processor to calculate are further configured to cause said at least one processor to calculate the amount of insulin need of the patient by comparing the estimated value of plasma glucose with a time-dependent glucose ceiling and transforming the difference using a
25 metric of the patient insulin sensitivity.

23. The non-transitory computer-readable medium of claim 19, wherein the instructions causing at least one processor to determine are further configured to cause said at least one processor to determine one of three fault levels based on the comparison, wherein a first fault level is indicative of little or no hyperglycemic risk, wherein a second fault level is indicative of moderate hyperglycemic risk, and wherein a third fault level is indicative of severe hyperglycemic risk.

24. The non-transitory computer-readable medium of claim 23, wherein the program instructions further comprise instructions for causing at least one processor to communicate to a patient an alert indicative of a need for additional insulin, responsive to the fourth program instructions determining a second fault level.

25. The non-transitory computer-readable medium of claim 23, wherein the program instructions further comprise instructions for causing an insulin device to automatically increase insulin delivery until the amount of insulin active in a patient matches the amount of insulin need of a patient, responsive to the fourth program instructions determining a second fault level.

26. The non-transitory computer-readable medium of claim 23, wherein the program instructions further comprise instructions for causing at least one processor to communicate to a patient an alert indicative of a severe hyperglycemic risk, responsive to the fourth program instructions determining a third fault level.

27. The non-transitory computer-readable medium of claim 26, wherein the program instructions further comprise instructions for causing at least one processor to communicate to the patient instructions for identifying and remedying the third fault.

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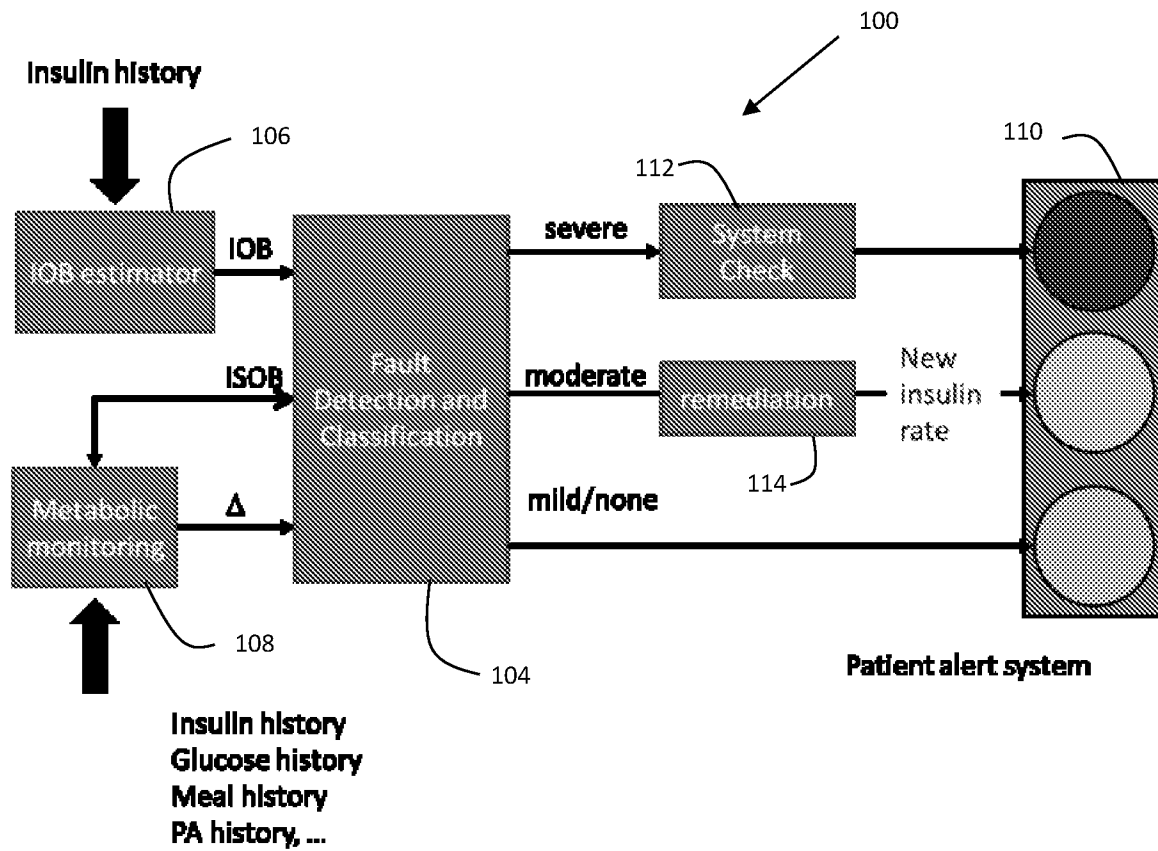
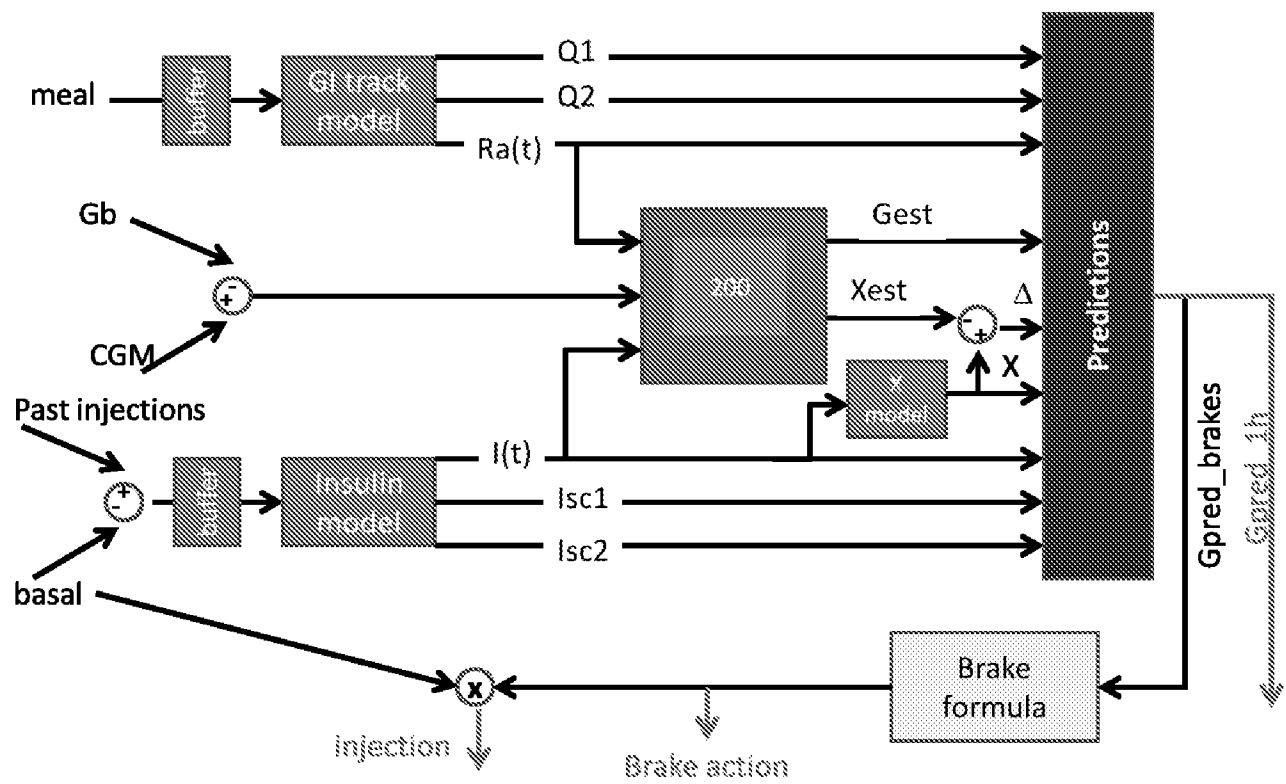


Figure 1

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**Figure 2**

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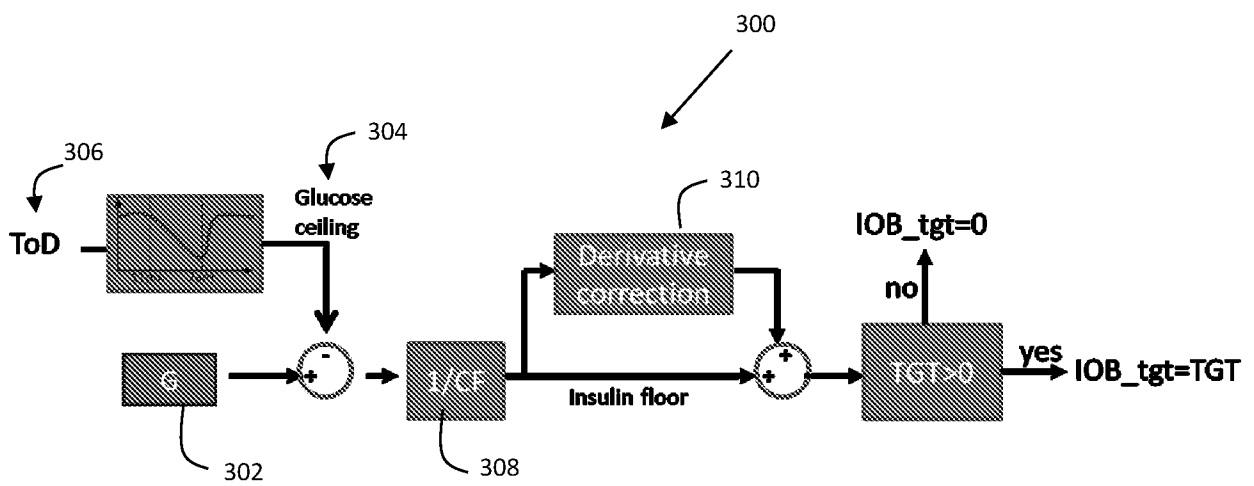


Figure 3

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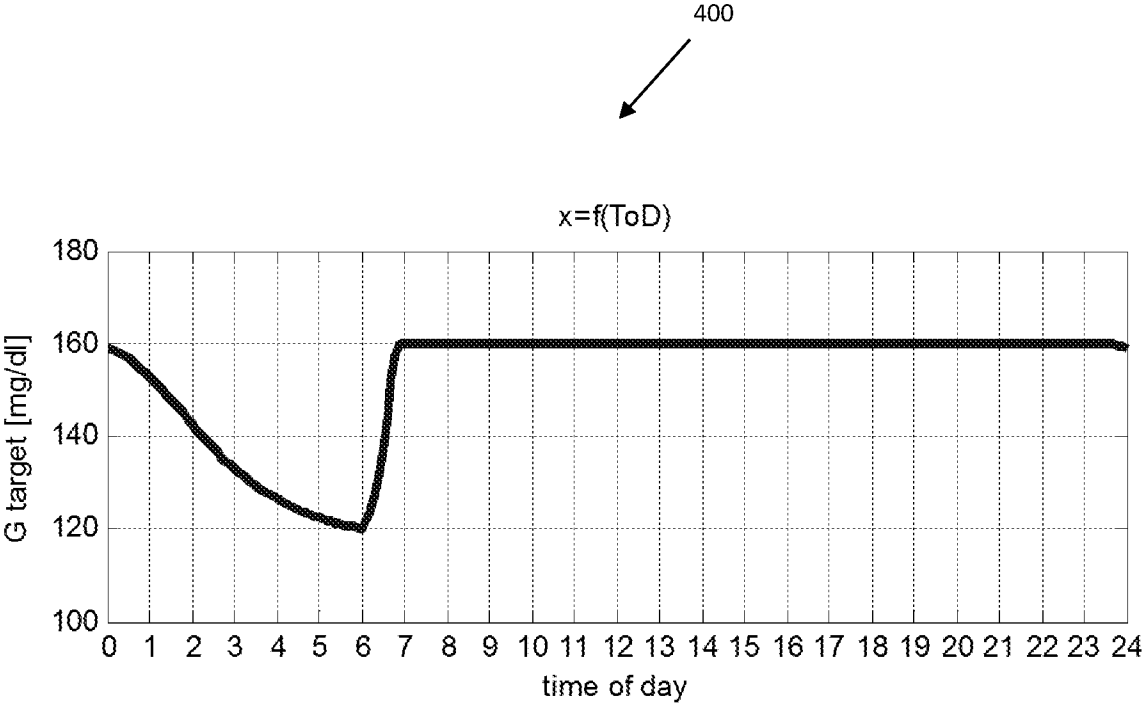
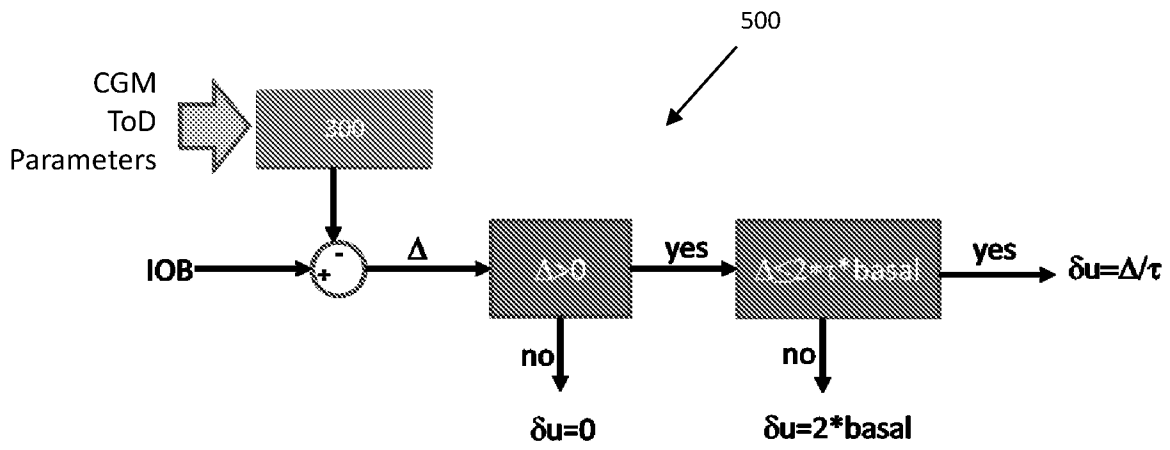
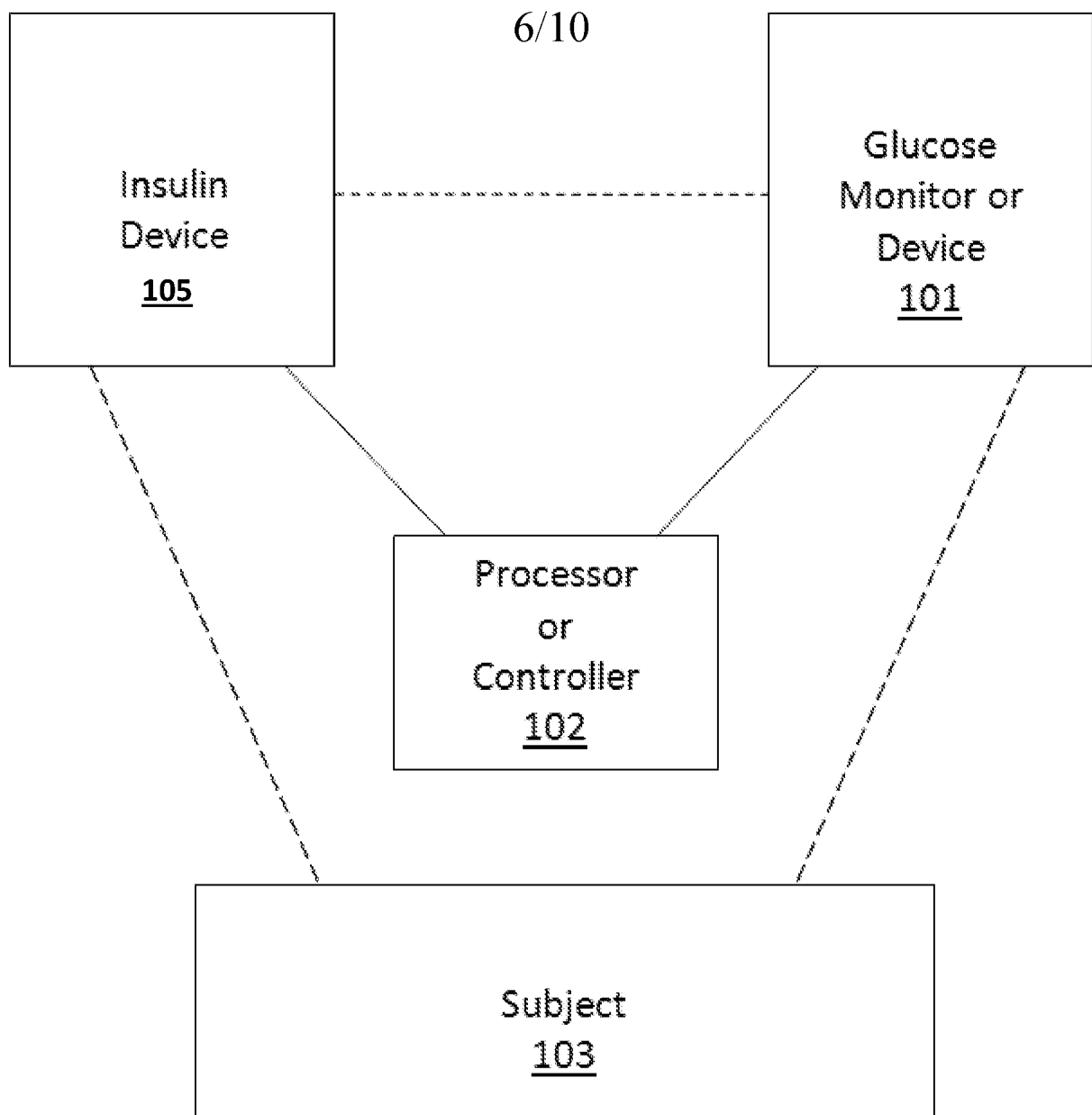


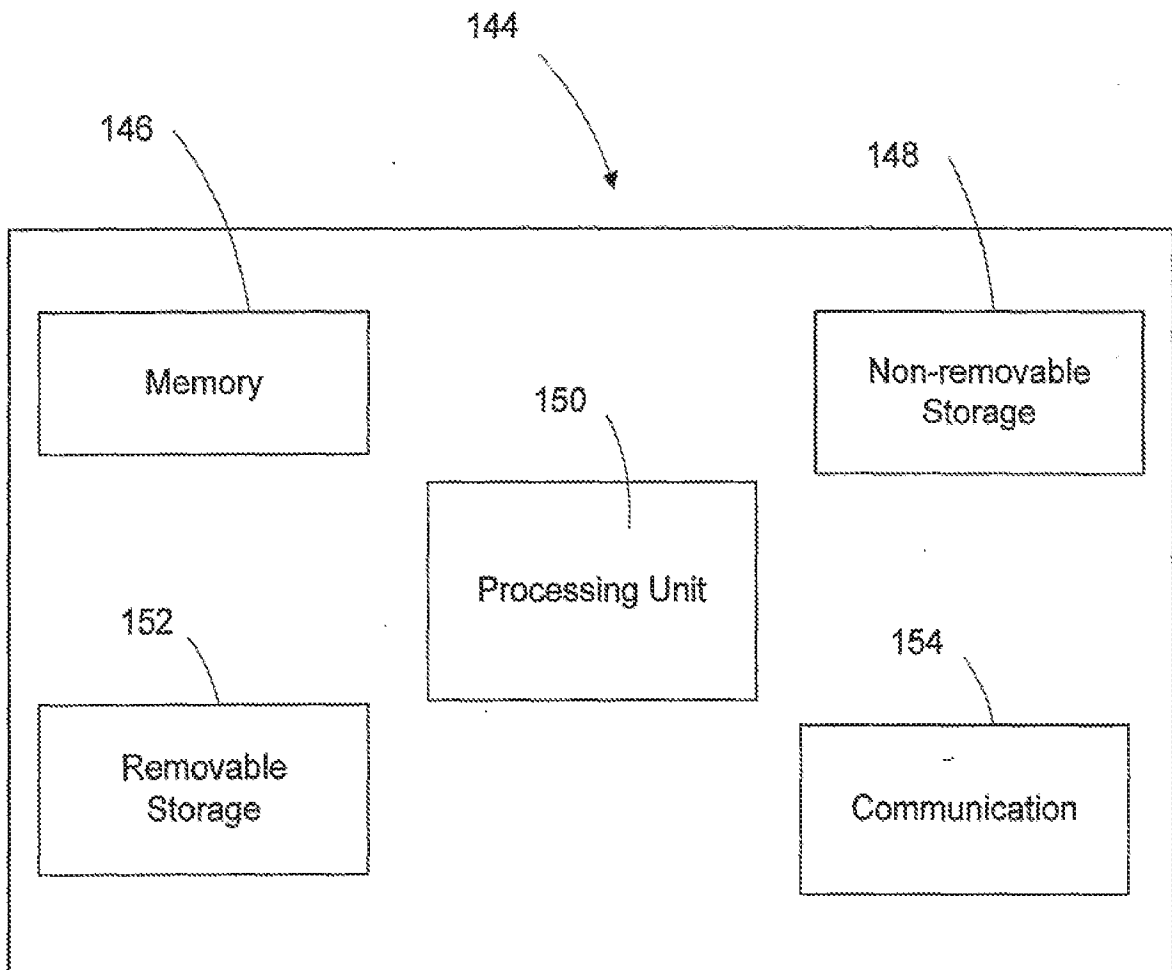
Figure 4

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**Figure 5**

**Figure 6**

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**Figure 7**

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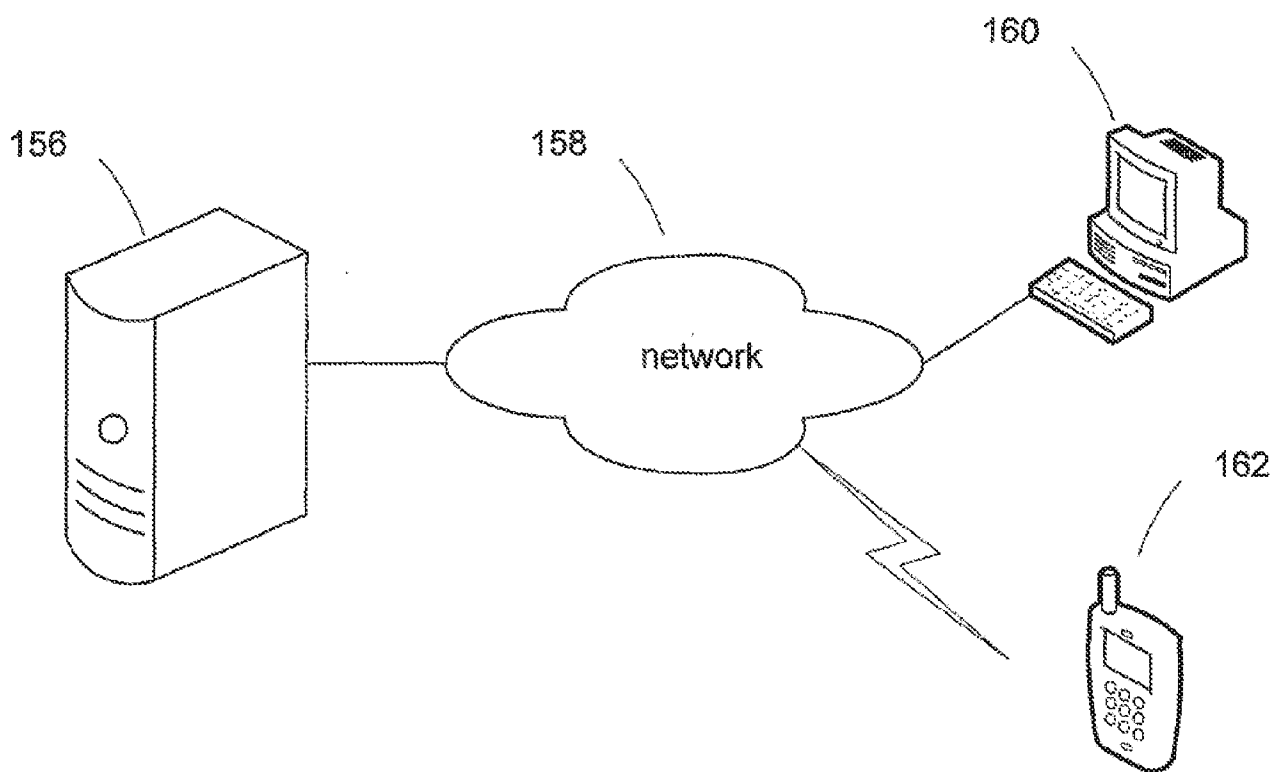
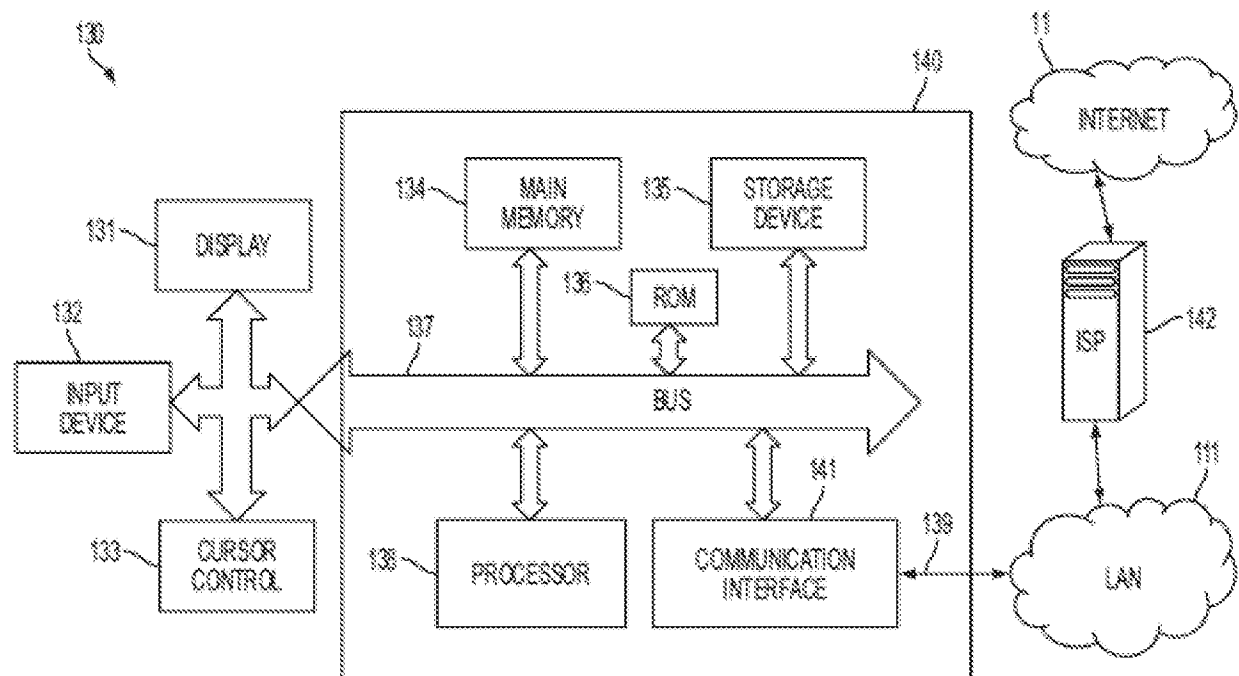
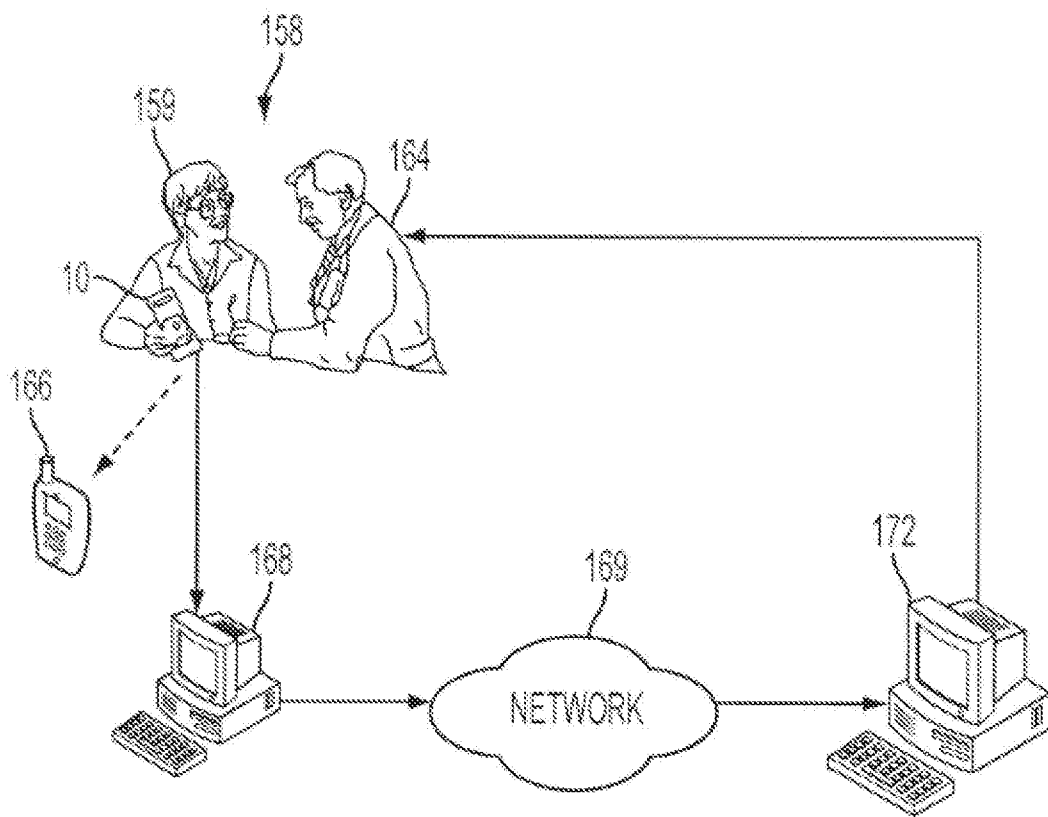


Figure 8

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**Figure 9**

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**Figure 10**

A. CLASSIFICATION OF SUBJECT MATTER**G06F 19/00(2011.01)I, A61B 5/145(2006.01)I, A61M 5/172(2006.01)I, A61M 5/142(2006.01)I**

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)

G06F 19/00; A61M 5/142; A61B 5/145; A61M 5/172; G01N 33/50; A61B 5/00

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & keywords: amount of insulin, need, insulin on board, compare, fault level, glucose, metabolic state, hyperglycemic risk**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009-0209938 A1 (MATTI AALTO-SETALA) 20 August 2009 See paragraphs [0009]-[0107], [0116]-[0121]; claims 24, 26-28; and figures 2-4.	1-27
Y	US 2015-0018633 A1 (BORIS P. KOVACHEV et al.) 15 January 2015 See paragraphs [0039]-[0087]; claim 1; and figures 3-5.	1-27
A	WO 2015-021441 A1 (ALERE SAN DIEGO, INC.) 12 February 2015 See paragraphs [0027]-[0055], [0069]; and figure 19.	1-27
A	US 2012-0041415 A1 (MARK C. ESTES et al.) 16 February 2012 See paragraphs [0008]-[0009], [0013], [0027]-[0052]; and figures 1-2.	1-27
A	US 2011-0046895 A1 (PIET MOERMAN) 24 February 2011 See paragraphs [0092]-[0145]; and figures 6-11.	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

22 September 2016 (22.09.2016)

Date of mailing of the international search report

23 September 2016 (23.09.2016)

Name and mailing address of the ISA/KR

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International application No.

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