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(54) Benævnelse: **Glucosestyringssystem med automatisk tilpasning af glucosemål**

(56) Fremdragne publikationer:
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US-A1- 2015 018 633
US-A1- 2015 217 052

DESCRIPTION

BACKGROUND

[0001] The present invention is related to the field of medical systems and devices, and more specifically to medical systems and devices for controlling delivery of insulin (including analogs) to a subject to maintain euglycemia.

[0002] US 2015/0217052 A1 discloses a method of operating an infusion device capable of delivering fluid to a user. The method involves identifying a condition of the user that is likely to influence a response to the fluid in the body of the user and classifying the condition as a first type of a plurality of types of conditions. After classifying the condition as the first type, the method continues by adjusting control information for operating the infusion device based on the first type and operating the infusion device to deliver the fluid to the user in accordance with the adjusted control information.

[0003] US 2009/0164239 A1 discloses a system for dynamically displaying glucose information.

[0004] EP 2 537 110 A1 discloses systems for closed-loop glucose control startup. A request for entry of an automatic mode of operation of a glucose monitoring and insulin delivery system for a patient may be detected. An entry of the automatic mode of operation may be controlled based, at least in part, on a detected rate of change of blood glucose concentration of the patient.

SUMMARY

[0005] A sensor-driven glucose control system as recited in the independent claim is provided. The dependent claims define preferred embodiments.

[0006] Techniques are disclosed for adaptation of a glucose target (set-point) control variable in a glucose control system controlling delivery of insulin to a subject to maintain euglycemia, e.g., a blood-glucose control system. In this description the term "insulin" encompasses all forms of insulin-like substances including natural human or animal insulin as well as synthetic insulin in any of a variety of forms (commonly referred to as an "insulin analogs"). Generally, the glucose target adapts based on trends in actual glucose level (e.g., measured blood glucose in the subject), and/or computed doses of a counter-regulatory agent (e.g. glucagon or dextrose). An adaptation region with upper and lower bounds for the glucose target may be imposed. The disclosed techniques can provide for robust and safe glucose level control. In one embodiment, adaptation is based on computed doses of a counter-regulatory agent whether or not such agent is available or actually delivered to the subject, and may be used for

example to adjust operation in a bihormonal control system, including during periods in which the counter-regulatory agent is not available for delivery, or in an insulin-only control system where (hypothetical) doses of a counter-regulatory agent are computed even it is absent. Adaptation is based on trends in glucose level (including emphasis on the extent and/or duration of low glucose levels or trends and/or the mean glucose) or a combination of trends in glucose level and computed doses of a counter-regulatory agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views.

Figure 1 is a block diagram of a blood glucose level control system;

Figure 2 is a block diagram of a blood glucose level controller;

Figure 3 is a block diagram of a corrective insulin controller;

Figure 4 is a flow diagram of high-level operation of the blood glucose level controller with respect to adjusting target glucose level; and

Figures 5 and 6 are plots of results of simulations of the disclosed operation.

DETAILED DESCRIPTION

Overview

[0008] A technique is described for automatically modulating the glucose target (set-point) used in an autonomous glucose-control system, whether employing the delivery of only insulin or the delivery of insulin as well as a counter-regulatory agent (e.g. glucagon or dextrose). The glucose target automatically adapts based on (a) the usage of a counter-regulatory agent, (b) the otherwise intended usage of a counter-regulatory agent had it been available (e.g. in insulin-only systems or in cases where the counter-regulatory agent or its delivery channel are temporarily unavailable), (c) trends in glucose level (including emphasis on the extent and/or duration of low glucose levels or trends and/or the mean glucose), or (d) any combination of these measures. The technique may impose upper and/or lower bounds (static or dynamic) for the range over which the dynamic glucose target varies, and may coexist with an option for a user to set a static target on a temporary (including isolated, recurring, or scheduled) basis.

The technique can be implemented within an autonomous glucose-control system or during periods of autonomous control in a semi-autonomous glucose-control system.

[0009] An implementation example is in an automated insulin delivery system for ambulatory diabetes care. In such a system, the glucose target is set to float dynamically online, between lower and upper bounds, depending on the degree of hypoglycemia or near- hypoglycemia that the system records in a moving receding time window. The degree or rate at which the glucose target adapts either upwards (towards its upper bound) or downwards (towards its lower bound) for a given degree of hypoglycemia or near-hypoglycemia is controlled by a system setting or scaling factor. The higher the setting or scaling factor is, the more the glucose target will automatically rise for a given recorded degree of hypoglycemia or near hypoglycemia, and likewise fall as the degree of hypoglycemia decreases. The glucose target may be set to float dynamically online, between lower and upper bounds, depending on the degree to which the mean glucose level in a moving receding time window is outside a targeted range of mean glucose level values that are desired. For example, the system dynamically raises the glucose target if the mean glucose level is below a certain threshold, below which there is no predicted benefit of additional glucose lowering, even if the target might not otherwise be raised based on the degree of hypoglycemia.

[0010] The glucose target may additionally float dynamically based on computed counter-regulatory doses over a moving receding time window. The technique may work identically whether the system is functioning in a multi-hormonal configuration, where the counter-regulatory doses are computed and their delivery is performed or at least intended or attempted as part of the system operation, or in an insulin-only configuration, where the counter-regulatory doses are computed only hypothetically (as if a counter-regulatory agent were available) but are not actually delivered. In either case, as online computed glucagon doses increase, the system automatically responds online by dynamically raising the glucose target. Moreover, the degree or rate at which the glucose target floats upwards (departing from its lower bound and towards its upper bound) for a given amount of computed glucagon doses may be controlled by a system setting or scaling factor. For example, the higher the setting or scaling factor is, the more the glucose target will automatically rise for a given computed glucagon dosing amount.

More Detailed Description

[0011] Figure 1 illustrates an automated control system 10 for regulating the blood glucose level of an animal subject (subject) 12, which may be a human. The subject 12 receives doses of insulin from one or more delivery devices 14, for example infusion pump(s) coupled by catheter(s) to a subcutaneous space of the subject 12. As described below, the delivery devices 14 may also deliver a counter-regulatory agent such as glucagon for control of blood glucose level under certain circumstances. For the delivery of both insulin and glucagon, the delivery devices 14 may be mechanically driven infusion mechanisms having dual cartridges for insulin and glucagon respectively. In the present description, reference is made to glucagon

specifically, but it is to be understood that this is for convenience only and that other counter-regulatory agents may be used. Similarly, the term "insulin" herein is to be understood as encompassing all forms of insulin-like substances including natural human or animal insulin as well as synthetic insulin in any of a variety of forms (commonly referred to as an "insulin analogs").

[0012] A glucose sensor 16 is operatively coupled to the subject 12 to continually sample a glucose level of the subject 12. Sensing may be accomplished in a variety of ways. A controller 18 controls operation of the delivery device(s) 14 as a function of a glucose level signal 19 from the glucose sensor 16 and subject to programmed input parameters (PARAMS) 20 which may be provided by the patient/user. One externally provided parameter is a "setpoint" which establishes a target blood glucose level that the system 10 strives to maintain. In the description below the externally provided setpoint is referred to as a "raw" target glucose level signal, and identified as" r_t". Generally the controller 18 operates based on a difference between a glucose level of the subject, as represented by the glucose level signal 19, and a target glucose level signal. As described more below, the raw target glucose level signal r_t is one input to the calculation of a variable target glucose level signal that is used in calculating corrective doses and that represents certain adaptation of the control operation to achieve certain results.

[0013] The controller 18 is an electrical device with control circuitry that provides operating functionality as described herein. In one embodiment, the controller 18 may be realized as a computerized device having computer instruction processing circuitry that executes one or more computer programs each including respective sets of computer instructions. In this case the processing circuitry generally includes one or more processors along with memory and input/output circuitry coupled to the processor(s), where the memory stores computer program instructions and data and the input/output circuitry provides interface(s) to external devices such as the glucose sensor 16 and delivery device(s) 14.

[0014] Figure 2 shows the functional structure of the controller 18. It includes four separate controllers, namely a counter-regulatory (CTR-REG) controller 22, basal insulin controller 24, corrective insulin controller 26. and other controller(s) 28. Each controller may be realized as a computerized device executing respective computer programs (i.e., counter-regulatory program, basal insulin control program, corrective insulin control program, and other program(s) respectively). The counter-regulatory controller 22 generates a counter-regulatory dose control signal 34 provided to a counter-regulatory agent delivery device 14-1. Respective outputs 36 - 40 from the insulin controllers 24 - 28 are combined to form an overall insulin dose control signal 42 provided to insulin delivery device(s) 14-2. The insulin delivery device(s) 14-2 may include devices tailored to deliver different types and/or quantities of insulin, with the exact configuration being known to and under the control of the controllers 24 - 28. For ease of description the collection of one or more insulin delivery devices 14-2 is referred below to in the singular as an insulin delivery device 14-2.

[0015] Also shown in Figure 2 are other input/output signals of the various controllers,

including the glucose level signal 19 and parameters 20 as well as a set of inter-controller signals 44. The inter-controller signals 44 enable communication of information from one controller, where the information is developed or generated, to another controller where the information is used for that controller's control function. Details are provided in the description of the control functions below.

[0016] The corrective insulin controller 26 is the primary dynamic regulator of blood glucose level. It may use any of a variety of control schemes, including for example an MPC cost function in a manner described in US patent publication 2008/0208113 A1. In some embodiments a counter-regulatory agent may not be present or may not be used, in which case the counter-regulatory controller 22 may be absent. However, as described below, in one scheme the counter-regulator controller 22 is still present and still generates values of doses of the counter-regulatory agent as information for use by the corrective insulin controller 26, even though no counter-regulatory agent is actually delivered. This includes situations where the counter-regulatory agent is absent or unavailable or inaccessible for delivery, or the counter-regulatory agent delivery device 14-1 is absent or unavailable or inaccessible for performing the delivery, or both, and whether such situations arise on a temporary, permanent, or intermittent basis.

[0017] Figure 3 shows the controller 18 in additional detail, according to one embodiment. It includes the corrective controller 26 as well as target adaptation 48. The corrective controller 26 carries out the dynamic regulation of glucose level based on an input target glucose level shown as r_t'. This dynamic value is generated by the target adaptation 48 partly on the basis of the input (generally fixed) target glucose level signal r_t. In other embodiments, the target adaptation 46 may be in a separate controller (e.g., one of the other controllers 28 of Figure 2). The dynamic target value may be used by only one or by multiple of the controllers within controller 18.

[0018] Figure 4 illustrates certain operation pertaining to the controller 18 at a high level. Generally it continually calculates an insulin dose control signal (e.g., insulin dose control signal 38) in response to (a) a measured glucose level signal (e.g., glucose level signal 19) and (b) a target glucose level signal, a specific example of which is described below. In doing so, at 50 it calculates corrective insulin doses based on the current (latest) target glucose level signal and variations of the measured glucose level signal occurring on the order of seconds to minutes. This is the function of the corrective control 46 of Figure 3. At 52, the corrective insulin controller 26 continually adjusts the target glucose level signal based on a calculated trend over a longer term of at least one of (a) values of the measured glucose level signal over the longer term and (b) values for computed doses of a counter-regulatory agent over the longer term. This is the function of the target adaptation 48 of Figure 3.

Example

[0019] A specific example is provided to illustrate the above.

[0020] Using r_t to represent the input or "raw" target glucose level signal 19, and r_t' to represent the dynamic target glucose level signal that is used by the corrective controller 26 and counter-regulatory controller 22, then one implementation of the target adaptation is:

$$r_t' = r_t + f(G_t) + f(y_t), \quad r_L \le r_t' \le r_H, \qquad (1)$$

where G_t are computed (intended) doses of a counter-regulatory agent (e.g. glucagon or glucose/dextrose), $f(G_t)$ is some function of Gt, $f(y_t)$ is some function of the glucose level y_t, and r_L and r_H are predetermined lower and upper bounds on r_t (which could themselves be dynamic). As an example, $f(G_t)$ could be given by

$$f(G_t) = \sum_{k=t-N}^{t} S_k^{G_k} G_k, \qquad (2)$$

where N defines the length of an interval over which accumulation (summation) of G_t is performed, and

$S_t^{G_t}$

is a scaling or gain factor that defines the magnitudes of the offsets caused on r_t' by each contribution from G_t included in the summation. The scaling or gain factor

S_t^{Gt}

could vary depending only on the magnitude of contributions of G_t (e.g., linearly, non-linearly, piecewise, etc.), i.e.,

$S_t^{Gt} = S^{Gt}$

, or could additionally vary depending on the temporal position of contributions of G_t (e.g., linearly, non-linearly, piecewise, etc.). On the other hand, f(yt) could be given by

$$f(y_t) = \sum_{k=t-N}^{t} S_k^{y_k} y_k, \qquad (3)$$

where, similarly,

$S_t^{y_t}$

is a scaling or gain factor that defines the magnitudes of the offsets caused on r_t' by each contribution from y_t included in the summation. The scaling or gain factor

$S_t^{y_t}$

could take on similar dependencies to those described for

$S_t^{G_t}$

.

$S_t^{y_t}$

is relatively low (or 0) for high values of y_t and progressively higher for lower values of y_t, both assessed relative to r_t and/or a relevant physiological range (e.g. 70-120 mg/dl). Note that although both Eq. (2) and Eq. (3) are formulated in discrete time, counterpart continuous-time integration formulations are an obvious variant for implementing the described technique.

[0021] In one embodiment the computed quantity associated with a counter-regulatory agent may still be present even in systems where the counter-regulatory agent is completely absent, such as in insulin-only systems, by basing the implementation on a signal representing the

intended counter-regulatory delivery had it been possible. This similarly applies when the counter-regulatory agent is temporarily absent in a multi-hormonal system, such as during periods when the counter-regulatory agent or its delivery channel become unavailable or delivery of the counter-regulatory agent via its channel becomes not possible for whatever reasons.

[0022] Figures 5 and 6 present results of simulations demonstrating the described technique. Both plots show 48-hour simulations using the same recurring 24-hour continuous glucose monitoring (CGM) trace. In both simulations, the first 24-hour period uses the same closed-loop algorithm without the implementation of the described technique and using a constant glucose target r_t of 100 mg/dl, whereas the second 24-hour periods use the same algorithm with the implementation of Eq. (1), with r_t = 100 mg/dl, $[r_L; r_H]$ = [100; 150] mg/dl, and N corresponding to one day. Generally, N will cover a longer term than the much shorter term (seconds to minutes) over which corrections could be made by the corrective insulin controller 26. In these plots, the glucose target is plotted as a trace 60 spanning across the upper panel of the graph. Calculated insulin doses are shown at 62 as extending downward, while calculated glucagon doses are shown at 64 as extending upward. Both simulations assume a bihormonal configuration, although the implementation may be the same in the insulin-only configuration where the counter-regulatory agent is absent.

[0023] Figure 5 presents results of a first simulation **A**, with
$S_t^{y_t}$
≡ 0 in Eq. (3) and with
$S_t^{G_t} \equiv S$,
(i.e. a constant relative to time t and values of G_t) in Eq. (2).

[0024] Figure 6 presents results of a second simulation **B,** with
$S_t^{G_t} \equiv 0$
in Eq. (2), and
$S_t^{y_t} = S^{y_t}, \ \forall y_t < 100 \text{ mg/dl},$

$S_t^{y_t} = 0, \ \forall y_t \geq 100 \text{ mg/dl},$
(i.e.
$S_t^{y_t}$
is constant relative to time but with dependence on y_t) in Eq. (3).

[0025] Relevant results from the two simulations are summarized in Table 1. In both simulations, the control system issued 40.90 U of insulin and 0.6775 mg of glucagon in the first 24 hours. In the second 24-hour period in simulation **A** (Figure 5) the issued dosing was reduced to 32.85 U for insulin and 0.53 mg for glucagon, and the dynamic target glucose r_t' floated around a mean of 112 mg/dl. In the second 24- hour period in simulation **B** (Figure 6), the issued dosing was reduced to 33.45 U for insulin and 0.5675 mg for glucagon, and the dynamic target glucose r_t' floated at 111 mg/dl. Thus these simulations demonstrate desirable

reductions in total administered insulin over a period while achieving essentially the same control effect over that period.

Table 1. Relevant results from simulations A and B of Figures 5 and 6.

	Simulation A, Figure 5		Simulation B, Figure 6	
	First 24h	Second 24h	First 24h	Second 24h
Mean Target, mg/dl	100	112	100	111
Insulin, U	40.90	32.85	40.90	33.45
Glucagon, mg	0.6775	0.5300	0.6775	0.5675

[0026] A glucose-control system is disclosed that employs an adaptive (dynamic) glucose target, including when the target is a single glucose level value or when it represents a range or interval of glucose levels. The adaptation of the glucose target may be autonomous in accordance with some mathematical formulation. The adaptive glucose target may be constrained to remain within predefined upper and lower bounds.

[0027] The adaptation of the glucose target may be for the purpose of limiting the frequency, duration, or severity of low or near low glucose levels (such as below or near the low end of normal range) in order to provide safer and/or more stable glucose control.

[0028] The adaptation of the glucose target may be for the purpose of maintaining an achieved mean glucose over a period of time to within a range of mean glucose values in order to minimize the long-term complications of diabetes, preferably avoiding a mean glucose level any lower than what is necessary to reduce long-term complications of diabetes.

[0029] The adaptation of the glucose target may be for the purpose of modulating or limiting the actual delivery of or just computation of (hypothetical) doses of a counter-regulatory agent to insulin in order to provide safer and/or more stable glucose control. It may alternatively be for the purpose of modulating or limiting the delivery of insulin in order to provide safer and/or more stable glucose control.

[0030] The adaptation of the glucose target may be based on the glucose levels in a past and/or receding time horizon, and it may be based on glucose levels that fall below a certain threshold in a past and/or receding time horizon.

[0031] The adaptation of the glucose target may be based on actual delivery of or just computation of (hypothetical) doses of a counter-regulatory agent over a past and/or receding time horizon.

[0032] The adaptation of the glucose target may be part of a glucose-control system that employs the delivery of only insulin, or alternatively employs the delivery of insulin and a counter-regulatory agent or agents. or alternatively that employs the delivery of insulin, a counter-regulatory agent or agents, and potentially other agents.

[0033] The adaptation of the glucose target may coexist with an option for the user to set a static glucose target on a temporary (including isolated, recurring, or scheduled) basis. The glucose control system may be autonomous or semi-autonomous, and the adaptation of the glucose target may be different depending on whether the counter-regulatory agent is actually delivered or is computed but not actually delivered.

[0034] The disclosed adaptation technique may be used in a variety of types of automatic glucose control system. In one example, it may be used in a glucose control system such as disclosed in US Patent 7,806,854 or PCT International Publication No. WO 2012/058694 A2.

[0035] While various embodiments of the invention have been particularly shown and described, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention as defined by the appended claims.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US20150217052A1 **[0002]**
- US20090164239A1 **[0003]**
- EP2537110A1 **[0004]**
- US20080208113A1 **[0016]**
- US7806854B **[0034]**
- WO2012058694A2 **[0034]**

Patentkrav

1. Sensordrevet glucosestyringssystem, omfattende:
en glucosesensor (16), der kan arbejde kontinuerligt for at generere et målt glucoseniveausignal, der indikerer et målt glucoseniveau i et individ;
en insulinafgivelsesindretning (14-2), der kan arbejde som reaktion på et insulindoseringsstyresignal for at afgive doser af insulin til indsprøjtning i individet; og
en styreenhed (18), der kan arbejde i henhold til et kontrolskema for at generere insulindoseringsstyresignalet som reaktion på (a) det målte glucoseniveausignal og (b) et targetglucoseniveausignal ved at:
(1) beregne korrigerende insulindoser på basis af targetglucoseniveausignalet og variationer af det målte glucoseniveausignal, der opstår i størrelsesordenen af sekunder til minutter; og
(2) kontinuerligt at indstille targetglucoseniveausignalet på basis af en beregnet langtidstrend, der er repræsenteret af i det mindste værdier af det målte glucoseniveausignal over det længere tidsrum,
hvor den kontinuerlige indstilling af targetglucoseniveausignalet er baseret på en funktion af målte glucoseniveauer over et nyligt tidsrum,
kendetegnet ved, at
funktionen er en vægtet sum, der er beregnet under anvendelse af en skaleringsfaktor, med hvilken målte glucoseniveauer multipliceres for at bestemme forskydninger på targetglucoseniveausignalet, der er forårsaget af respektive bidrag fra målte glucoseniveauer,
hvor skaleringsfaktoren varierer afhængigt af de respektive målte glucoseniveauer, hvor skaleringsfaktoren er en relativt lav værdi for høje værdier af målt glucoseniveau og progressivt højere for lavere værdier af målt glucoseniveau.

2. Sensordrevet glucosestyringssystem ifølge krav 1, hvor den kontinuerlige indstilling af targetglucoseniveausignalet indbefatter at beregne targetglucoseniveausignalet ud fra et statisk targetglucoseniveausignal, der er tilvejebragt som en inputparameter til styreenheden (18).

3. Sensordrevet glucosestyringssystem ifølge krav 1, yderligere indbefattende en modregulerende middelafgivelsesindretning (14-1), der kan arbejde som reaktion på et modregulerende doseringsstyresignal for at afgive doser af et

modregulerende middel til indsprøjtning i individet, og hvor styreenheden (18) yderligere kan arbejde i henhold til kontrolskemaet for at generere det modregulerende middeldoseringsstyresignal som reaktion på (a) det målte glucoseniveausignal og (b) targetglucoseniveausignalet for at opretholde euglykæmier af individet.

4. Sensordrevet glucosestyringssystem ifølge krav 1, hvor skaleringsfaktoren varierer afhængigt af en midlertidig position af bidrag af de respektive målte glucoseniveauer.

5. Sensordrevet glucosestyringssystem ifølge krav 1, yderligere indbefattende en modregulerende middelafgivelsesindretning (14-1), der kan arbejde som reaktion på et modregulerende doseringsstyresignal for at afgive doser af et modregulerende middel for insulin til indsprøjtning i individet, hvor den kontinuerlige indstilling af targetglucoseniveauet er yderligere baseret på en kalkuleret langtidstrend, der er repræsenteret af værdier for beregnede doser af et modregulerende middel over det længere tidsrum, og den kontinuerlige indstilling af targetglucoseniveauet er baseret på en funktion af de beregnede doser af det modregulerende middel over et nyligt tidsrum.

6. Sensordrevet glucosestyringssystem ifølge krav 5, hvor funktionen af de beregnede doser af det modregulerende middel er en vægtet sum under anvendelse af en yderligere skaleringsfaktor, som definerer en størrelse af forskydninger på targetglucoseniveausignalet, der er forårsaget af respektive bidrag fra de beregnede doser af det modregulerende middel.

7. Sensordrevet glucosestyringssystem ifølge krav 6, hvor den yderligere skaleringsfaktor varierer afhængigt af en midlertidig position af bidrag af de respektive beregnede doser af det modregulerende middel.

8. Sensordrevet glucosestyringssystem ifølge krav 6, hvor den yderligere skaleringsfaktor varierer afhængigt af en størrelse af bidrag af de respektive beregnede doser af det modregulerende middel.

9. Sensordrevet glucosestyringssystem ifølge krav 6, hvor styreenheden (18) er konfigureret således, at når det modregulerende middel er fraværende eller

ikke er til rådighed eller er utilgængeligt for afgivelse, beregner styreenheden (18) doserne af det modregulerende middel til anvendelse ved generering af insulindoseringsstyresignalet.

DRAWINGS

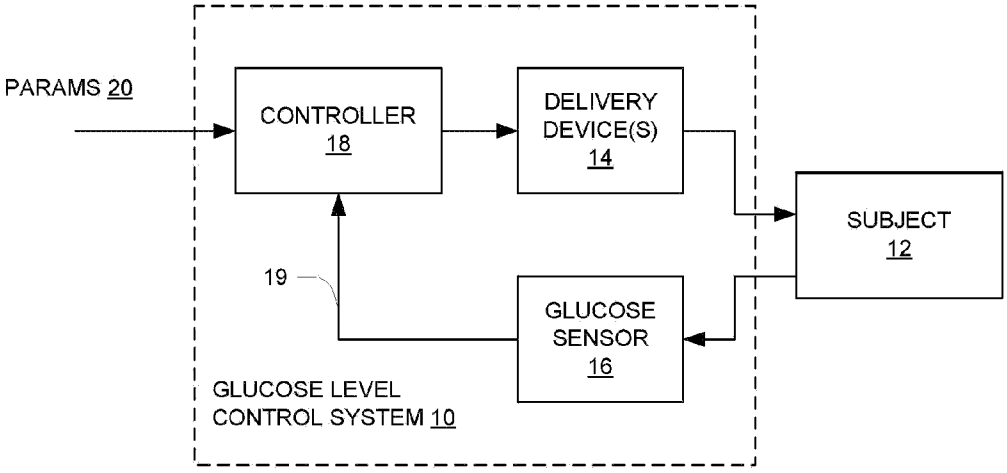

Fig. 1

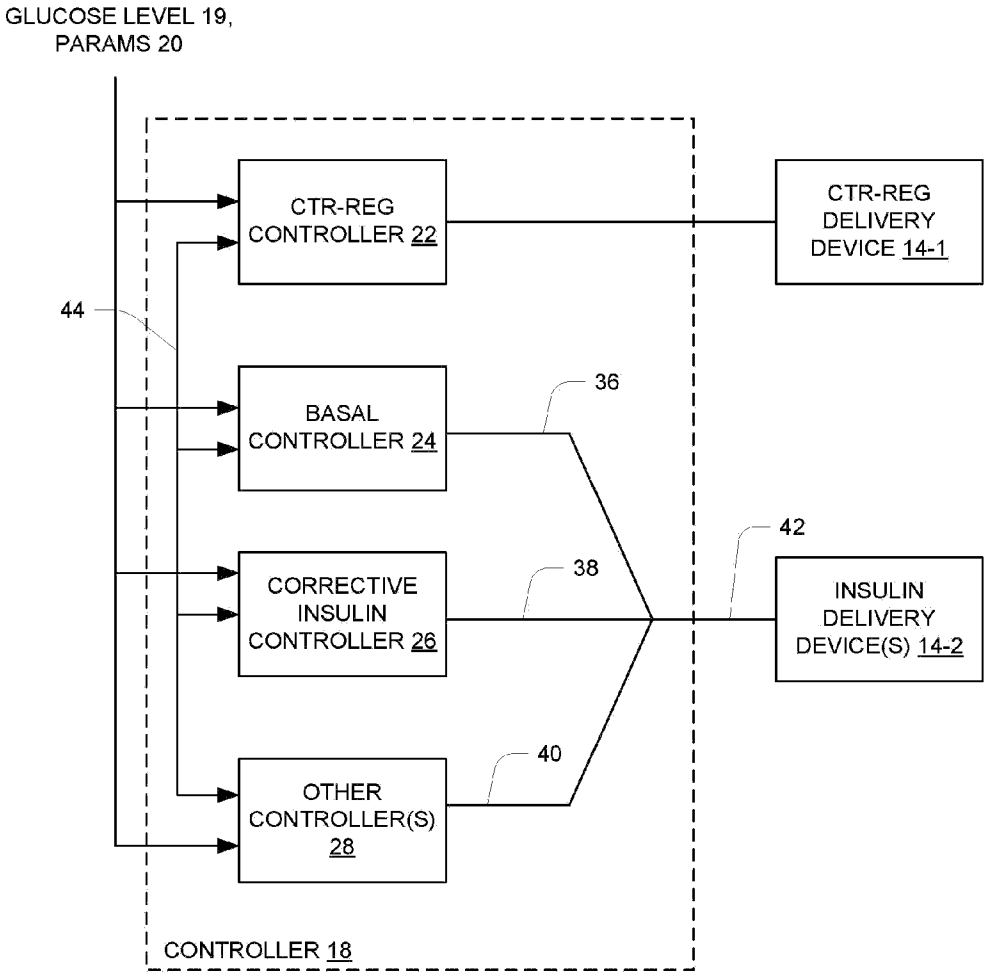
GLUCOSE LEVEL 19,
PARAMS 20
CTR-REG CONTROLLER 22
CTR-REG DELIVERY DEVICE 14-1
44
BASAL CONTROLLER 24
36
42
CORRECTIVE INSULIN CONTROLLER 26
38
INSULIN DELIVERY DEVICE(S) 14-2
40
OTHER CONTROLLER(S) 28
CONTROLLER 18

Fig. 2

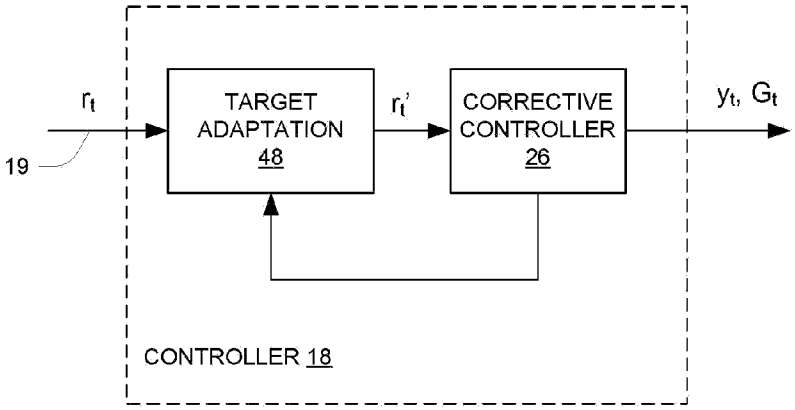
r_t
19
TARGET ADAPTATION 48
r_t'
CORRECTIVE CONTROLLER 26
y_t, G_t
CONTROLLER 18

Fig. 3

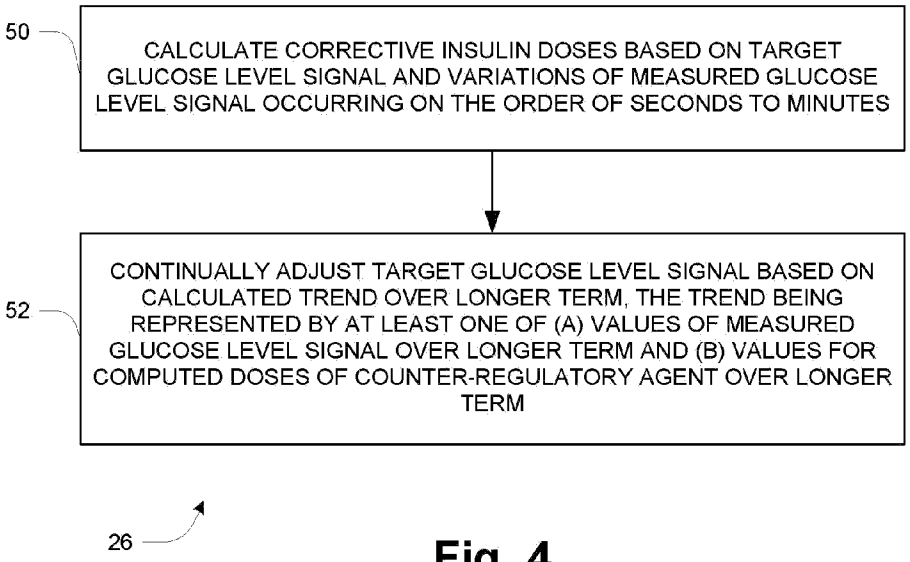
50
CALCULATE CORRECTIVE INSULIN DOSES BASED ON TARGET GLUCOSE LEVEL SIGNAL AND VARIATIONS OF MEASURED GLUCOSE LEVEL SIGNAL OCCURRING ON THE ORDER OF SECONDS TO MINUTES
52
CONTINUALLY ADJUST TARGET GLUCOSE LEVEL SIGNAL BASED ON CALCULATED TREND OVER LONGER TERM, THE TREND BEING REPRESENTED BY AT LEAST ONE OF (A) VALUES OF MEASURED GLUCOSE LEVEL SIGNAL OVER LONGER TERM AND (B) VALUES FOR COMPUTED DOSES OF COUNTER-REGULATORY AGENT OVER LONGER TERM
26

Fig. 4

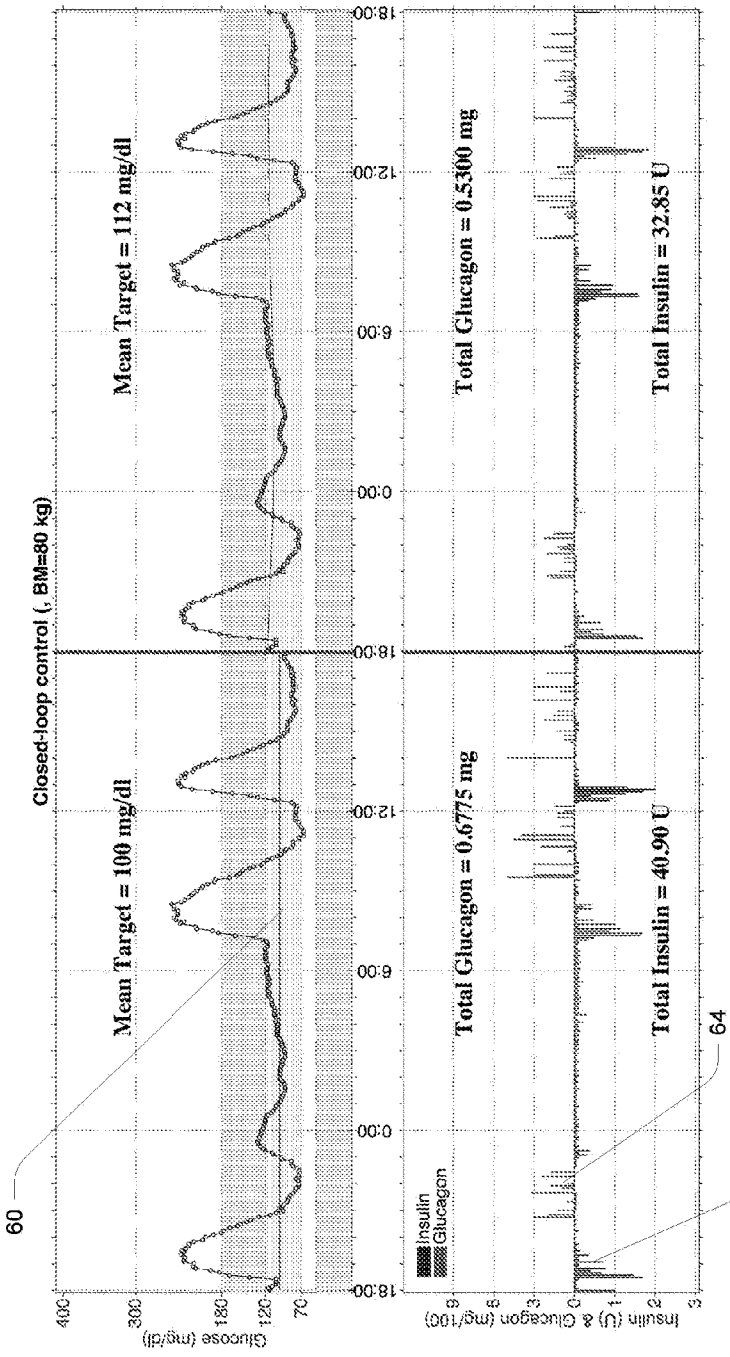
Closed-loop control (, BM=80 kg)
Mean Target = 100 mg/dl
Mean Target = 112 mg/dl
Glucose (mg/dl)
400
300
180
120
70
18:00
0:00
6:00
12:00
18:00
Total Glucagon = 0.6775 mg
Total Glucagon = 0.5300 mg
Total Insulin = 40.90 U
Total Insulin = 32.85 U
Insulin
Glucagon
Insulin (U) & Glucagon (mg/100g)
0
1
2
3
4
5
6
60
62
64

Fig. 5

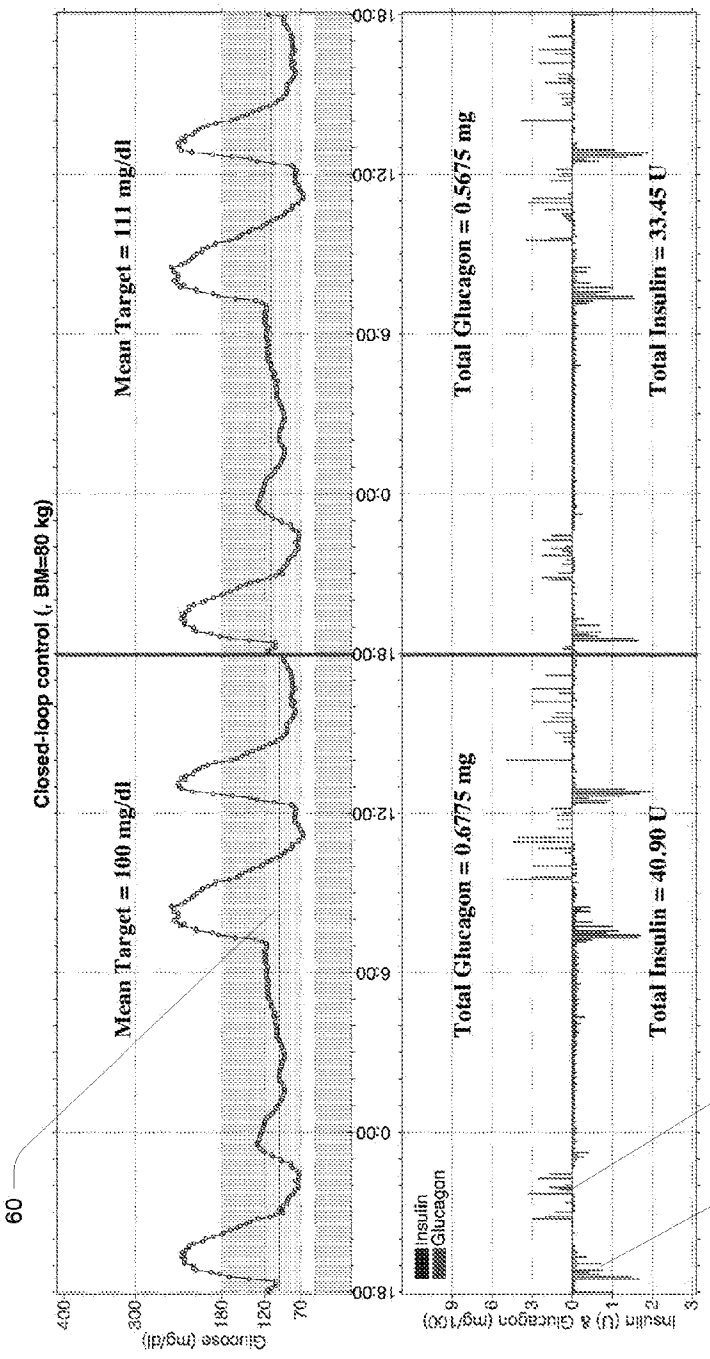
Closed-loop control (, BM=80 kg)
Mean Target = 100 mg/dl
Mean Target = 111 mg/dl
Total Glucagon = 0.6775 mg
Total Glucagon = 0.5675 mg
Total Insulin = 40.90 U
Total Insulin = 33.45 U
Glucose (mg/dl)
Insulin (U) & Glucagon (mg*100)
Insulin
Glucagon
18:00
0:00
6:00
12:00
60
62
64

Fig. 6