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(54) **A METHOD AND DEVICE FOR IMPROVING GLYCEMIC CONTROL BASED ON RESIDUAL INSULIN**

VERFAHREN UND VORRICHTUNG ZUR VERBESSERUNG DER GLYKÄMISCHEN KONTROLLE BASIEREND AUF RESTINSULIN

MÉTHODE ET DISPOSITIF UTILISÉS POUR AMÉLIORER LE CONTRÔLE DE LA GLYCÉMIE D APRÈS L INSULINE RÉSIDUELLE

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Description

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims benefit and priority to U.S. Provisional Patent Application No. 611220,204, filed June 25, 2009, entitled "A Method and Device for Improving Glycemic Control by Adjusting Remaining Insulin to Dose".

FIELD

[0002] A method, a system and a device for sustained medical infusion of therapeutic fluids to patients are described. Some embodiments relate to portable infusion systems and/or devices, and to a method for infusion that includes administering a therapeutic fluid according to patient's parameters. Some embodiments relate to an insulin-dispensing system and/or device configured to sense glucose levels of a patient and to a method for infusing insulin after adjusting the duration of insulin action according to the dose of administered insulin.

BACKGROUND

[0003] Diabetes mellitus is a disease of major global importance, increasing in frequency at almost epidemic rates, such that the worldwide prevalence in 2006 is 170 million people and predicted to at least double over the next 10-15 years. Diabetes is characterized by a chronically raised blood glucose concentration (hyperglycemia), due to a relative or absolute lack of the pancreatic hormone, insulin. Within the healthy pancreas, beta cells, located in the islets of Langerhans, continuously produce and secrete insulin according to the blood glucose levels, maintaining near constant glucose levels in the body.

[0004] Much of the burden of the disease to the user and to health care resources is due to the long-term tissue complications, which affect both small blood vessels (microangiopathy, causing eye, kidney and nerve damage) and large blood vessels (causing accelerated atherosclerosis, with increased rates of coronary heart disease, peripheral vascular disease and stroke). The Diabetes Control and Complications Trial (DCCT) demonstrated that development and progression of the chronic complications of diabetes are greatly related to the degree of altered glycemia as quantified by determinations of glycohemoglobin (HbAlc). [DCCT Trial, N Engl J Med 1993; 329: 977-986, UKPDS Trial, Lancet 1998; 352: 837-853. BMJ 1998; 317, (7160): 703-13 and the EDIC Trial, N Engl J Med 2005; 353, (25): 2643-53]. Thus, maintaining normoglycemia by frequent glucose measurements and adjustment of insulin delivery accordingly can be of utmost importance.

[0005] Insulin pumps have been available which deliver rapid acting insulin (e.g. Lispro, Aspart, etc.) 24 hours a day through a catheter placed under the skin. Rapid acting insulin effect begins in about 10 minutes, peaks at one to one and a half hours and ends in about two to six hours after the administration. The interval between insulin injection and end of its activity is defined as Duration of Insulin Activity (DIA) or Residual/Remaining Insulin time (RI time).

[0006] A simple rule can be applied to calculate the duration of insulin activity, i.e., the DIA. It is often stated that each hour after bolus dose administration, 20% of the dose becomes effective, so that after 5 hours there is no active insulin remaining in the body. FIG. 1 shows the insulin consumption according to the described rule (adapted from Using Insulin © 2003). One of the major advantages of using insulin pumps is the convenience of insulin bolus administration at any desired time. However, boluses may overlap and it can be useful to know the amount of active insulin that is still "working"/effective in the body, i.e. the RI. Accumulation of insulin may lead to life-threatening hypoglycemia. This is especially important at bedtime since users are usually unaware of nocturnal hypoglycemia.

[0007] Conventional insulin pumps can apply the abovementioned rule to calculate the residual insulin and subtract the calculated value from administered bolus. For example, based on FIG. 1, if a desired 5U bolus is administered 2 hours after a 6U bolus, the RI = 3.6U and the actually delivered bolus should be 1.4 U (5U-3.6U). If however an additional bolus of 5U was delivered 4 hours before the desired 5U bolus administration, the total RI is 3.6 (6U minus 40% of 6U) plus 1U(5U minus 80% of 5U). The total RI (i.e. 3.6U+1U = 4.6U) is then subtracted from the desired 5 U bolus to yield a bolus dose of merely 0.4U (5U-4.6U).

[0008] Bolus recommendations provided by portable insulin pumps that include bolus calculators (and other types of bolus determining units) take into consideration the residual insulin. For example, in US patent 6,936,029 assigned to Medtronic Minimed, a pump provided with a bolus calculator and an algorithm for calculating the amount of insulin to be administered is described. The algorithm is based on a formula for calculating a bolus, depending on the user's insulin sensitivity (IS), carbohydrate-to-insulin ration (CIR), target blood glucose (TBG), RI, BG and carbs intake inputted by the user.

[0009] The recommended bolus is calculated as:

$$\text{Recommended bolus} = \underbrace{(TC/CIR)}_{\text{"Food estimate"}} + \underbrace{(CBG-TBG)/IS}_{\text{"Correction estimate"}} - RI$$

where TC - total amount of carbohydrates; CIR - carbohydrate-to-insulin ratio; TBG - target blood sugar; CBG- current blood sugar; IS -insulin sensitivity; and RI -residual insulin.

[0010] The residual insulin is also considered in the bolus recommendation feature described in co-owned/co-pending U.S. publication no. US2008/0234663 and international patent application no. PCT/IL2009/000454. This bolus recommendation feature comprises sets of grids/tables of ranges of carbohydrate and blood glucose level. Each grid corresponds to a different combination of IS, CIR, and TBG. Additional grids correspond to selected bolus doses and residual insulin values. The final recommended dose is related to a value that is substantially equivalent to the selected bolus dose minus the RI.

[0011] Application of the abovementioned rule (as shown in FIG. 1) can lead to over- or under-dosing of insulin due to significant individuality variability of insulin absorption and consumption which varies among different patients. The assumption that the complete bolus absorption time (a state in which there is no residual insulin, RI = 0) is always 5 hours (i.e. assuming 20%/hour), ignores the individual variability, and, as a result, may not be correct. A more accurate, user specific assessment of the RI time is described in co-owned, co-pending international publication no. WO2009/060433

[0012] Generally, the described procedure for assessing residual insulin (RI) time of a patient comprises: allowing the patient to fast during a period of time, determining a known amount of carbohydrates to be administered to the patient, based on the determined amount of carbohydrates, administering an insulin bolus to the patient, administering the determined amount of carbohydrates to the patient, subsequently periodically measuring blood glucose (BG) levels of the patient at predetermined times for indication of at least two successive substantially equal values, or values within a predetermined range, and calculating the RI time based on the time span between the insulin administration to the first measurement of the at least two successive equal values.

[0013] Furthermore, it has been shown that the remaining insulin time is volume dependent. For example, at a certain concentration (e.g., 100U/ml), a smaller insulin volume (e.g., 2U) is absorbed faster than a larger volume (e.g., 20U) (Journal of Diabetes Science and Technology, 2007 Vol. 1 (5), pp. 780-793). FIG. 2 shows an example of a graph of the percentage of insulin remaining at the injection site versus elapsed time after subcutaneous injection. It can be seen that the lower the subcutaneously injected volume, the steeper is the decline of the percentage of insulin remaining at the injection site as a function of time after the injection. In other words, it can be seen that the RI time is a function of the injected dose - the lower the dose, the shorter the RI time.

SUMMARY

[0014] The present disclosure describes embodiments directed to devices, systems and methods for infusing insulin. Some embodiments are directed to devices, systems and methods for adjusting RI time according to at least one bolus dose. In some embodiments, an infusion device comprises a memory device that stores respective RI time values for different insulin doses, and a processor-based device configured to correlate the bolus dose with the respective RI time. In some embodiments, the device includes a glucose monitor (e.g., glucometer) which may be a continuous glucose monitor (CGM). In some embodiments, the device includes a remotely controlled skin adherable dispensing unit that may include a reusable part and a disposable part.

[0015] In some embodiments, the RI time for various insulin doses (e.g., 2U, 5U, and 8U) can be determined based on consecutive glucose level measurements (continuous or periodic) after a meal, and corresponding insulin injection. The RI time is the time elapsed until a glucose level plateau is reached, as described, for example in co-owned, co-pending international publication No. WO2009/060433. RI time for all doses can be determined (e.g., interpolated, extrapolated, rounded, truncated, set to the nearest multiple of some fraction, etc.) based on tested doses.

[0016] For example, the RI time periods for 2U, 5U, and 8U are 3, 3.5, and 5 hours respectively. If the user delivers a bolus dose of 4U, the RI time can be interpolated to yield 3.3 hours (between 3 hours and 3.5 hours). Alternatively, the RI time can be set to the nearest tested bolus dose, which in this case is 3.5 hours (respective RI time of 5U). Similarly, if the user delivers a bolus dose of 9U, the RI time can be extrapolated to 5.1 hours or rounded to 5 hours.

[0017] In some embodiments, calculation of a meal bolus dose is typically based on summation of previous RIs based on the dose adjusted RI time. For example, given a meal that requires absolute value of 7U, occurring 3 hour after an 8U meal and 1 hour after a 3U meal, a recommendation of delivering 1.8U would be effected:

- RI from the 8U meal is 3.2U, i.e., RI = 8U - 8U * (3/RI time) = 8U - 8U* 3/5 = 3.2U.

- RI from the 3U meal is 2U, i.e., RI=3U-3U*(1/RI time) = 3U- 3U* 1/3 = 2U.

Thus, covering the current meal (i.e., the 7U meal) that requites 7U would require 1.8U (i.e., 7U - (3.2U + 2U) = 1.8U).

[0018] According to some embodiments, the RI time for a plurality of doses can be assessed and a graph of bolus dose versus RI time can be generated.

[0019] In some embodiments, a drug delivery system for administration of insulin to a body of a patient is disclosed. The system includes a processor-based device implementing at least a residual insulin (RI) determination unit, the RI determination unit configured to determine a residual insulin in the patient's body at a particular time instance based on one or more bolus doses previously delivered to the body of the patient, each of the one or more bolus doses being associated with at least one dose value and an associated time representative of the time the at least one dose value was delivered to the body of the patient, and based on one or more dose dependent RI time records, each of the one or more dose dependent RI time records includes at least a dose value and an associated at least a duration value representative of dose-dependent duration of therapeutic effectiveness of the associated at least the dose value. The system also includes a pump to controllably dispense the insulin from a reservoir to the body of the patient based on the residual insulin determined by the RI determination unit.

[0020] Embodiments of the system may include any of the features described in the present disclosure, including any of the following features.

[0021] The duration value of at least one of the one or more dose dependent RI records may be based on one or more of, for example, insulin type, site of cannula insertion and insulin delivery, physical activity, body temperature, fluid absorption characteristics, weight, age, gender, CIR, IS, and/or concentration of insulin.

[0022] The RI determination unit may further be configured to determine a bolus amount to be delivered to the patient's body based on determined residual insulin. The pump configured to controllably dispense the insulin may be configured to deliver the determined bolus amount to the patient's body.

[0023] The RI determination unit configured to determine the residual insulin based on the one or more bolus records and the one or more dose dependent RI time records may be configured to determine the residual insulin in the patient's body by performing one or more of, for example, matching, using data tables, a dose value of at least one of the one or more bolus records to data corresponding to the one or more of the dose dependent RI time records arranged in the data tables, and/or determining the residual insulin value for the dose value of the at least one of the one or more bolus doses using relationships, determined based on the data corresponding the one or more dose dependent RI time records, that relate the dose value of the at least one of the one or more bolus records to a corresponding RI time determined using the determined relationship.

[0024] The RI determination unit configured to determine the residual insulin based on the one or more bolus records and the one or more dose dependent RI time records may be configured to determine for a delivered bolus of at least one of the one or more bolus records an associated RI time equivalent to the duration value associated with a dose value from the one or more dose dependent RI time records closest in value to a dose value of the delivered bolus.

[0025] The RI determination unit configured to determine the residual insulin based on the one or more bolus records and the one or more dose dependent RI time records may be configured to generate a graph of RI time versus bolus dose based, at least in part, on the one or more dose dependent RI time records, and determine an RI time for a given delivered bolus value from one of the one or more bolus records in accordance with the generated graph.

[0026] The RI determination unit configured to determine the residual insulin based on the one or more bolus records and the one or more dose dependent RI time records may be configured to determine for each of the one or more bolus records an associated individual residual insulin at the particular time instance based, at least in part, on the one or more dose dependent RI time records, and determine a sum of the determined individual residual insulin for each of the one or more bolus records.

[0027] The RI determination unit configured to determine the sum of the determined individual residual insulin may be configured to determine a weighted sum of the determined individual residual insulin according to the relationship $\sum_{j=1}^{n} \alpha_j RI_j$, where RI_j is the determined individual residual insulin for the j^{th} bolus record from the one or more bolus records, and α_j is an associated weight to apply to the determined residual insulin.

[0028] The RI determination unit configured to determine the residual insulin based on the one or more bolus records and the one or more dose dependent RI time records may be configured to tailor the residual insulin to the patient based on patient-specific characteristics. The RI determination unit configured to tailor the residual insulin may be configured to tailor the residual insulin using at least one of, for example, linear curve fitting, non-linear curve fitting, Bayesian models, neural network, fuzzy logic, genetic algorithms, linear regression, machine learning procedures, and/or statistical

learning procedures.

[0029] A duration value of one of the one or more dose dependent RI time records for a bolus used to cover a meal with a low glycemic index (GI) or glycemic load (GL) is lower than another duration value of another of the one or more dose dependent RI time records used to cover a meal with high glycemic index.

[0030] The RI determination unit may be located in a remote control.

[0031] The system may further include a screen to display at least the residual insulin determined by the RI determination unit.

[0032] The system may further include a user interface for receiving at least one of, for example, a dose value associated with at least one of the one or more bolus doses previously delivered to the body of the patient, an associated time representative of the time the dose value was delivered to the body of the patient, a dose value of at least one of the one or more dose dependent RI time records, a duration value associated with the dose value of the at least one of the one or more dose dependent RI time records, and/or a confirmation of the user.

[0033] The user interface may include at least one of, for example, buttons, switches, keys, a keyboard, a touch-sensitive screen, and/or a voice command interface.

[0034] The system may further include a transceiver configured to receive and/or transmit data related to operation of the RI determination unit.

[0035] In some embodiments, a method for determining residual insulin (RI) for use with an insulin delivery device is disclosed. The method includes receiving one or more bolus records, each bolus record includes at least one dose value and an associated time representative of the time the at least one dose value was delivered to a patient, and receiving one or more dose dependent RI time records, each of the one or more RI time records includes at least a dose value and an associated at least a duration value representative of dose-dependent duration of therapeutic effectiveness of the associated at least the dose value. The method also includes determining based on the one or more bolus records and the one or more dose dependent RI time records a residual insulin in the patient's body at a particular time instance.

[0036] Embodiments of the method include any of the features described in the present disclosure, including any of the features described above in relation to the system and any of the following features.

[0037] The method may further include determining a bolus amount to be delivered to the patient's body based on determined residual insulin. The method may further include delivering the determined bolus amount to the patient's body.

[0038] Determining based on the one or more bolus records and the one or more dose dependent RI time records the residual insulin in the patient's body at the particular time instance may include determining the residual insulin in the patient's body by performing one or more of, for example, matching, using data tables, a dose value of at least one of the one or more bolus records to data corresponding to the one or more of the dose dependent RI time records arranged in the data tables, and/or determining the residual insulin value for the dose value of the at least one of the one or more bolus doses using relationships, determined based on the data corresponding the one or more dose dependent RI time records, that relate the dose value of the at least one of the one or more bolus records to a corresponding RI time determined using the determined relationship.

[0039] Determining based on the one or more bolus records and the one or more dose dependent RI time records the residual insulin in the patient's body at the particular time instance may include determining for a delivered bolus of at least one of the one or more bolus records an associated RI time equivalent to the duration value associated with a dose value from the one or more dose dependent RI time records closest in value to a dose value of the delivered bolus.

[0040] Determining based on the one or more bolus records and the one or more dose dependent RI time records the residual insulin in the patient's body at the particular time instance may include generating a graph of RI time versus bolus dose based, at least in part, on the one or more dose dependent RI time records, and determining an RI time for a given delivered bolus value from one of the one or more bolus records in accordance with the generated graph.

[0041] Determining based on the one or more bolus records and the one or more dose dependent RI time records the residual insulin in the patient's body at the particular time instance may include determining for each of the one or more bolus records an associated individual residual insulin at the particular time instance based, at least in part, on the one or more dose dependent RI time records, and determining a sum of the determined individual residual insulin for each of the one or more bolus records.

[0042] Determining the sum of the determined individual residual insulin may include determining a weighted sum of the determined individual residual insulin according to the relationship $\sum_{j=1}^{n} \alpha_j RI_j$, where RI_j is the determined individual residual insulin for the j^{th} bolus record from the one or more bolus records, and α_j is an associated weight to apply to the determined residual insulin.

[0043] Determining based on the one or more bolus records and the one or more dose dependent RI time records the residual insulin in the patient's body at the particular time instance may include tailoring the residual insulin to the patient based on patient-specific characteristics.

[0044] Tailoring the residual insulin may be performed using at least one of, for example, linear curve fitting, non-linear curve fitting, Bayesian models, neural network, fuzzy logic, genetic algorithms, linear regression, machine learning procedures, and/or statistical learning procedures.

[0045] In some embodiments, a computer program product comprising computer instructions stored on a non-transitory computer readable storage device is disclosed. The computer instructions, when executed on one or more processor-based devices, cause the one or more processor-based devices to receive one or more bolus records, each bolus record includes at least one dose value and an associated time representative of the time the at least one dose value was delivered to a patient, and to receive one or more dose dependent RI time records, each of the one or more RI time records includes at least a dose value and an associated at least a duration value representative of dose-dependent duration of therapeutic effectiveness of the associated at least the dose value. The computer instructions also cause the one or more processor-based devices to determine based on the one or more bolus records and the one or more dose dependent RI time records a residual insulin in the patient's body at a particular time instance.

[0046] Embodiments of the computer program product may include any of the features described in the present disclosure, including the above-described features of the system and method.

[0047] In some embodiments, a system to determine residual insulin (RI) for use with an insulin delivery device is disclosed. The system includes means for receiving one or more bolus records, each bolus record includes at least one dose value and an associated time representative of the time the at least one dose value was delivered to a patient, and means for receiving one or more dose dependent RI time records, each of the one or more RI time records includes at least a dose value and an associated at least a duration value representative of dose-dependent duration of therapeutic effectiveness of the associated at least the dose value. The system also includes means for determining based on the one or more bolus records and the one or more dose dependent RI time records a residual insulin in the patient's body at a particular time instance.

[0048] Embodiments of the computer program product may include any of the features described in the present disclosure, including the above-described features of the system, the method, and the computer program product.

[0049] Details of one or more implementations are set forth in the accompanying drawings and in the description below. Further features, aspects, and advantages will become apparent from the description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050]

FIG. 1 is a chart of residual insulin of RI time of 5 hours after insulin Lispro bolus administration (dose independent RI time).

FIG. 2 is a graph of RI vs. time for various bolus doses (dose dependent RI time).

FIGS. 3a-c are schematic diagrams of an example fluid delivery device that includes an insulin dispensing unit and a remote control unit, and which may include a dose dependent RI time feature.

FIG. 4 is a flowchart of an example procedure for RI determination.

FIG. 5 is a flowchart of an example procedure for bolus determination implementing a bolus dependent RI time feature.

FIG. 6 is a flowchart of a further example procedure for bolus determination implementing a bolus dependent RI time feature.

FIG. 7 is a flowchart of another example method for bolus determination implementing a bolus dependent RI time feature.

DETAILED DESCRIPTION

[0051] FIG. 1 is a chart of residual insulin at different hours (1-5) after insulin Lispro bolus administration. It can be seen that, based on this chart, a constant percentage (20%) of the given bolus is consumed every hour regardless of the bolus dose (i.e., volume). That is, all doses have a RI time of 5 hours. Therefore, with this methodology of residual insulin calculation, the residual insulin calculation is dose-independent.

[0052] FIG. 2 is a graph of the percentage of insulin remaining (at an injection site) versus time after subcutaneous injection (graph adapted from the Journal of Diabetes Science and Technology, 2007 Vol. 1 (5), 780-793). It can be seen, for example, that 0.4U of insulin is substantially entirely depleted within 2 hours while 4U is substantially entirely

depleted within 2.8 hours. In other words, the smaller the subcutaneously injected volume, the steeper the decline in the percentage of insulin remaining at the injection site as a function of time. Thus, here the residual insulin is shown to be dose-dependent.

[0053] FIGS. 3a-c illustrate embodiments of a system 1000 according to some embodiments. The system 1000 can be used for dispensing therapeutic fluids (e.g., insulin) to the body of the patient. In some implementations, the system includes a dispensing unit 1010, a remote control unit 1008, and a blood glucose (BG) monitor 90. In some embodiments, the dispensing unit is connected to a cannula 6 that penetrates a patient's skin 5 to deliver insulin to the subcutaneous tissue. The dispensing unit may include a single part having a single housing 1003, as shown in FIGS. 3a-b, or may include two parts having two separate connectable housings 1001, 1002. In some embodiments, a first part can be a reusable part 1 and a second part can be disposable (disposable part 2), as shown in FIG. 3c. Flow programming and data acquisition can be done by the remote control unit 1008 or directly by one or more operating buttons/switches 1004 located on the dispensing unit housing. A BG monitor or a continuous glucose monitor (CGM) may be located at the remote control unit and/or the dispensing unit. In some embodiments, the remote control unit may be implemented in one of a Personal Data Assistance (PDA), a cellular phone, a watch, an iPod (i.e., a media player), an iPhone, a laptop, a PC, some other processor-based device, etc.

[0054] In some embodiments, an RI feature 10 for dose dependent RI time adjustment and RI determination/calculation may be located in the dispensing unit 1010 (see FIG. 3a), in the remote control unit 1008 (as shown in FIGS. 3b-c) and/or implemented using the two units 1010 and 1008. Such a dispensing unit and/or remote control device/system is disclosed in co-owned co-pending U.S. publication no. US2007/106218 and in co-owned, co-pending international application no. PCT/IL09/000388.

[0055] In some embodiments, the remote control unit 1008 and/or dispensing unit 1010 containing the RI feature 10 (also referred-to as RI calculator, RI module, and/or RI determination unit) for dose-dependent RI time adjustment and RI determination may include a memory device, a user interface such as a keypad and/or any other input mechanisms (e.g., buttons, switches, keys, touch-screen, voice command interface, etc.), a display/screen and/or other notification (or output) devices such as audible output device (e.g., buzzer) and/or vibration output devices (e.g., a vibrator) to notify/alert the user. The keypad and/or input devices can be used for programming and commanding the dispensing patch unit 1010 and/or the RI feature 10 for dose dependent RI time adjustment and RI calculation. In some embodiments, the dispensing unit (which may include a pump) may controllably dispense insulin based, at least in part, on the determined residual insulin. In some embodiments, the remote control unit 1008 and/or dispensing unit 1010 may also include a transceiver to enable transmission and receipt (wirelessly and/or through wired-connections) of data and/or commands relating to the operation of the RI feature (RI determination unit). In some embodiments, the user interface is configured to receive at least one of, for example, a dose value associated with at least one of the one or more bolus doses previously delivered to the body of the patient, an associated time representative of the time the dose value was delivered to the body of the patient, a dose value of at least one of the one or more dose dependent RI time records, an associated duration value of the at least one of the one or more dose dependent RI time records, and a confirmation of the user regarding the data (e.g., confirmation of the accuracy of the bolus doses).

[0056] According to some embodiments, continuous glucose readings may be transmitted to the remote control and/or patch unit from a stand-alone sensing apparatus (e.g., CGM). Alternatively and/or additionally, a sensing apparatus can be contained or integrated within the patch unit. This sensing apparatus may be included in the reusable part, may be included in the disposable part, or may be shared between the reusable part and the disposable part. The dispensing apparatus (i.e., the mechanism responsible of dispensing the fluid to the user's body) may be coupled to a cannula and the sensing apparatus may be coupled to a separate probe/sensor. In some embodiments, both apparatus (dispensing and sensing) may be connected to a single cannula/probe as described in greater detail in, for example, co-owned/co-pending US publication US2007/0191702 and in international publications nos. WO2008/078319 and WO2009/066288. In some embodiments, the sensing apparatus can include a separate unit and/or incorporated within the dispensing unit, and the RI feature for dose dependent RI time adjustment and RI determination can be included in the remote control unit.

[0057] In some embodiments, the therapeutic fluid (e.g.,'insulin) can be dispensed based on analyte (e.g., glucose) sensing (e.g., CGM readings) using a closed loop mode/system implementation or in a semi-closed loop mode/system, according to analyte readings (comprising analyte concentration) and/or based on additional inputs (e.g., pre-meal bolus). For example, the dose dependent RI determination in a semi-closed loop system can be used for bolus calculation.

[0058] FIG. 4 is a flowchart of an example procedure for RI determination, implementing the bolus dependent RI time, according to some embodiments of the present disclosure. Briefly, in performing the procedure, at least one of the operations depicted in FIG. 4 may be performed. In some embodiments, a plurality of the depicted operations of FIG. 4 may be performed, and in some embodiments, all of the depicted operations may be performed. As shown, an RI value (also referred-to as "Current Effective RI") may be determined 400 based on a relationship (e.g., mathematical, empirical, approximation, etc.) between one or more boluses and an RI time. A Bolus History may then be retrieved 402, and an RI Database may also be retrieved 404. Then, by correlating 406 the data of the Bolus History and the RI Database, a

Current Effective RI can be determined (e.g., calculated). In some embodiments, correlating the data of bolus history and the RI database includes determining from dose-dependent data obtained from the RI database an estimate or approximation of the RIs for the administered bolus schedule (obtained from the bolus history) at a particular time. These determined approximations of the effective RI in a body of a patient at a particular time thus enable determining the bolus dosage required for a particular meal that is to be consumed by the patient at that particular time.

[0059] In some embodiments, the RI time Database can be a database stored in one or more memory storage devices (which may be distributed across a network connecting the memory storage devices) which store doses and corresponding RI times. In some embodiments, the RI Database can include formulations, scripts, expressions, functions, operators (e.g., analytic, numeric, empiric) that can be used to determine correlations between a bolus dose and an RI time. The dose dependent RI time can be further associated or dependent (e.g., be a function of) on one or more of the following parameters: insulin type (e.g., rapid acting insulin, regular insulin), site of cannula insertion and insulin delivery, physical activity, body temperature, fluid absorption characteristics, weight, age, gender, CIR, IS, concentration of insulin and other known health related parameters of the user. According to some embodiments, the RI Database can be created/generated via a window/screen of the user interface of the device where the user or caregiver can enter/input at least one dose dependent RI time, by implementing an RI time determination test as described, for example, in co-owned, co-pending international publication no. WO2009/060433, or by performing other suitable RI database generation procedures. In some embodiments, the RI time Database can include one or more tables (e.g., schedules, look-up tables) receivable or downloadable from a remote source (e.g., from the web or a PC, wirelessly or through an appropriate connector).

[0060] As noted, in performing the procedure of FIG. 4, the bolus history may be retrieved 402. The Bolus History, in some embodiments, includes one or more records specifying an amount of therapeutic fluid ("dose") and time of its administration ("t"). In some embodiments, the bolus history may further include the type of bolus, e.g., "normal bolus" where the entire bolus dose is delivered at the highest delivery rate enabled by the delivery device (e.g., pump), "extended bolus" where the entire bolus dose is delivered over a relatively long period of time at a constant rate, "combined bolus" where a portion of the bolus dose is delivered as an immediate bolus at a first rate and another portion (e.g., the rest of the bolus dose) delivered as an extended bolus employing a second rate, etc. The Bolus History can be stored in a memory storage device located in the delivery device and/or on one or more external devices (e.g., cellular phone, PC, web-based application, and the like).

[0061] After retrieving data from the Bolus History and from the RI Database, the data from the Bolus History may be processed (e.g., correlated, matched, etc.) 406 with the data of RI Database (also referred-to as "RI time Database") to determine the corresponding RI value for each bolus dose. The processing can be done via matching tables or matrices, performing computation/correlation procedures (which may be represented, at least partly, as mathematical formulations), etc. In some embodiments, the mathematical formulations representative of the correlation techniques/behavior employed can be obtained by implementing curve fitting of data specific for the patient (i.e., tailored), by implementing other types of optimization and/or regression procedures, etc.

[0062] As further shown in FIG. 4, a majority, or substantially all, or in some embodiments, all the bolus dependent RI values, may be taken into account to determine the Current Effective RI. According to some embodiments, the Current Effective RI can include a simple summation of all RI's (e.g., $RI_1+RI_2...+RI_n$). Alternatively, the Current Effective RI can include a weighted summation $(\text{e.g.,} \sum_{j=1}^{n} \alpha_i RI_j)$, i.e., a particular RI may have more or less influence. For example, the RI from a bolus used to cover a meal with a low glycemic index (GI) or glycemic load (GL) may have less influence on the Current Effective RI than the RI from a bolus used to cover a meal with high glycemic index. The GI can be expressed as a ranking/indexed schedule for carbohydrates contained in food according to how they affect the blood glucose levels. For example, in some embodiments, the fastest-acting carbohydrate, glucose, is given a value of 100, and the other carbs are ranked relative to that value. A low GI food will release glucose more slowly and steadily than food containing high GI (high GI food causes a more rapid rise in blood glucose).

[0063] In some embodiments, procedure of FIG. 4 can further include the generation of a dose-dependent RI time Database associated with different values of bolus doses and/or the generation of the Bolus History.

[0064] FIG. 5 is a flow chart of an example procedure for bolus determination according to the bolus dependent RI time. As shown, dose dependent RI times are presented (e.g., retrieved, determined, or otherwise obtained) 501. For example, the RI times of 0.5, 2, 6, and 10 insulin units, are 2, 3, ,4 , and 5 hours, respectively. As noted above, The RI times can be determined for example by the method described in, for example, co-owned, co-pending international publication no. WO2009/060433. Additionally, an exemplary bolus schedule may be obtained 502. In the example illustrated in FIG. 5, Boluses comprising 2, 6, 10, and 0.5 units have been delivered at 8:00, 9:00, 10:00, and 11:00 o'clock respectively. If a linear consumption of the bolus is assumed (i.e., the graph of residual insulin versus DIA is linear), the RI determined (e.g., computed/calculated) 503 at 12:00 o'clock is 7.75 units, which is the sum of 0 units of

insulin contributed by bolus 1 (because its RI time has elapsed), 1.5 units of insulin contributed by bolus 2, 6 units of remaining effective insulin contributed by bolus 3, and 0.25 units of remaining effective insulin contributed by bolus 4. In some embodiments, other behavioral profiles (or regimens), such as exponential or polynomial behaviors, may be used to determine the RI.

[0065] With continued reference to FIG. 5, in the illustrated example, a meal covered by 10 units is to be consumed at 12:00 o'clock. Since the calculated RI at 12:00 is 7.75, the recommended bolus dose is determined 504 to be 2.25 U (10-7.75).

[0066] By contrast, the calculated RI when using dose independent RI time determination (computation) methodology (as shown for example in FIG. 1) may be (according to some embodiments):

- Assumption: RI time = 20%/hour = 5 hours
- RI of bolus 1 = 2U * 20% = 0.4U (4 h passed from a 2U bolus)
- RI of bolus 2 = 6U * 40% = 2.4U (3 h passed from a 6U bolus)
- RI of bolus 3 = 10U * 60% = 6U (2 h passed from a 10U bolus)
- RI of bolus 4 = 0.5 * 80% = 0.4U (1 h passed from a 0.5 U bolus)
- Total RI at 12:00 = 0.4U + 2.4U + 6U + 0.4U = 9.2U

Thus, using the dose-independent determination methodology, for a meal consumed at 12:00 pm (for example) that should be covered by 10 units, the recommended bolus dose would be determined as 10U - 9.2U = 0.8U.

[0067] FIG. 6 depicts a block diagram of another example procedure for bolus determination according to the bolus dependent RI time according to some embodiments of the disclosure. As shown, dose dependent RI times of tested boluses are obtained 601. For example, the RI time of 0.5, 2, 6, and 10 insulin units are 2, 3, 4, and 5 hours, respectively. Additionally, an example bolus schedule is obtained (presented) 602. The boluses in the schedule include boluses of 3, 7, 12, and 1 units, delivered, in the example depicted in FIG. 6, at 8:00, 9:00, 10:00, and 11:00 am, respectively. In the given example, the RI time of the exact boluses delivered have not been tested. According to some embodiments, the RI time of the delivered bolus may thus be determined by selecting the RI time of the nearest tested bolus dose (as noted herein, RI times for bolus schedule may be determined based on other techniques/procedures that use the RI data of the test boluses, including such techniques/procedures as extrapolation, interpolation, curve fitting, linear regression, etc.) In the given example, the RI time of bolus 1, which includes 3 units, is determined to be 3 hours because the closest available tested bolus RI (obtained at 601) is for a bolus dose of 2 units. In the same manner, the RI time of bolus 2, which comprises 7 U would be 4 hours (since the A dose is 6 U). So, based on an assumed linear consumption of the bolus (in this particular example), the RI determined 603 at 12:00 o'clock for the given bolus schedule, is 9.45 units, determined as 0 units of insulin contributed by bolus 1 (since the RI time has passed), 1.75 units of insulin contributed by bolus 2, 7.2 units of insulin contributed by bolus 3, and 0.5 units of insulin contributed by bolus 4. As further illustrated in the example of FIG, 6, a meal covered by 10 units is to be consumed at 12:00 o'clock. Because the determined RI at 12:00 is 9.45U, the recommended bolus dose is determined 604 to be 0.55 U (10U - 9.45U).

[0068] FIG. 7 is a block diagram of another depicted example procedure for bolus determination based on bolus dependent RI time, according to some embodiments of the present disclosure. As shown, dose dependent RI times of tested boluses are obtained 701. For example, the RI times of 1, 2, 4, and 8 insulin units, are 1, 2, 4, and 8 hours, respectively. A relationship representing the RI time versus bolus dose is determined or otherwise obtained 702. In this example, such a relationship is represented by a generated graph plotting the RI time versus the bolus dose. As shown in the graph, a linear curve is plotted. Yet, in some embodiments, other behaviors (e.g., exponential) may be used. As further shown in FIG. 7, a bolus schedule is obtained (e.g., retrieved and/or presented) 703. In this example, the boluses in the schedule include boluses of 2, 6, 3, and 0.5 units, delivered, in the example of FIG. 7, at 8:00, 9:00, 10:00, and 11:00 o'clock, respectively. In some embodiments, the RI times of the delivered boluses can be determined by obtaining from the RI time versus bolus dose graph (determined or generated at 702) the RI times for the delivered doses. In the given example, because a linear curve has been assumed and computed, the RI time of bolus 1, which includes 2 units, is determined to be 2 hours, the RI time of bolus 2, which includes 6 units, is determined to be 6 hours, the RI time of bolus 3, which comprises 3 U, is determined to be 3 hours, and the RI time of bolus 4, which comprises 0.5 U, is determined to be 0.5 hours. Thus, if a linear consumption of the bolus is assumed, the RI determined 704 at 12:00 o'clock for the given bolus schedule, is 4 units, determined as 0 units of insulin contributed by bolus 1 (since the RI time has elapsed), 3 units of insulin contributed by bolus 2, 1 units of insulin contributed by bolus 3, and 0 units of insulin contributed by bolus 4. As further illustrated in the example of FIG, 7, a meal covered by 10 units is to be consumed at

12:00. Because the determined RI in this example at 12:00 is 4 units, the recommended bolus dose will be 6U (10-4).

[0069] In some embodiments, the above-mentioned RI determination unit (e.g., an RI. calculator) and procedures can be implemented to tailor the RI to a specific user based, for example, on user-specific characteristics (e.g., age, weight, overall health, etc.) Deriving the user-specific behavior can be implemented in a self-learning system employing conventional procedures/techniques that include linear or non-linear curve fitting, Bayesian models, neural network, fuzzy logic, genetic algorithms, and the like. Adjusting the RI calculator parameters (or the parameters of the implemented RI determination unit) enables an improved RI determination for each user, thus resulting in improved diabetic care.

[0070] Assessing an RI time can be implemented according to implementations described in co-owned, co-pending international publication no. WO2009/060433. The determined RI times can subsequently be used to accurately determine the dose dependent RI's.

[0071] Various embodiments of the subject matter described herein can be realized in digital electronic circuitry, integrated circuitry, specially designed ASICs (application specific integrated circuits), computer hardware, firmware, software, and/or combinations thereof. These various embodiments may include implementations in one or more computer programs, stored on non-transitory media, that are executable and/or interpretable on a processor-based systems including, for example, at least one programmable processor, which can be special or general purpose, coupled to receive data and instructions from, and to transmit data and instructions to, a storage system, at least one input device, and at least one output device.

[0072] These computer programs (also known as programs, software, software applications or code) include machine instructions for a programmable processor, and can be implemented in a high-level procedural and/or object-oriented programming language, and/or in assembly/machine language. As used herein, the term "machine-readable medium" refers to any computer program product, apparatus and/or device (e.g., magnetic discs, optical disks, memory, Programmable Logic Devices (PLDs)) used to provide machine instructions and/or data to a programmable processor, including a non-transitory machine-readable storage medium that receives machine instructions as a machine-readable signal. The term "machine-readable signal" refers to any signal used to provide machine instructions and/or data to a programmable processor.

[0073] To provide for interaction with a user, the subject matter described herein can be implemented on a computer having a display device, e.g., a CRT (cathode ray tube) or LCD (liquid crystal display) monitor, or some other display device, for displaying information to the user, and a keyboard and a pointing device, e.g., a mouse or a trackball, by which the user may provide input to the computer. Other kinds of devices can be used to provide for interaction with a user as well; for example, feedback provided to the user can be any form of sensory feedback (e.g., visual feedback, auditory feedback, or tactile feedback); and input from the user can be received in any form, including acoustic, speech, or tactile input.

[0074] The subject matter described herein can be implemented in a computing system that includes a back-end component (e.g., as a data server), or that includes a middleware component (e.g., an application server), or that includes a front-end component (e.g., a client computer having a graphical user interface or a Web browser through which a user may interact with an implementation of the subject matter described herein), or any combination of such back-end, middleware, or front-end components, The components of the system can be interconnected by any form or medium of digital data communication (e.g., a communication network). Examples of communication networks include a local area network ("LAN"), a wide area network ("WAN"), and the Internet.

[0075] The computing system may include clients and servers. A client and server are generally remote from each other and typically interact through a communication network. The relationship of client and server arises by virtue of computer programs running on the respective computers and having a client-server relationship to each other.

[0076] Some embodiments of the present disclosure preferably implement the RI determination unit (e.g., RI calculator) via software operated on a processor contained in a remote control device of an insulin dispensing system and/or a processor contained in a insulin dispensing device being part of an insulin dispensing system.

[0077] Any and all references to publications or other documents, including but not limited to, patents, patent applications, articles, webpages, books, etc., presented in the present application, are herein incorporated by reference in their entirety.

[0078] Although a few variations have been described in detail above, other modifications are possible. For example, the logic flow depicted in the accompanying figures and described herein does not require the particular order shown, or sequential order, to achieve desirable results. Other embodiments can be within the scope of the following claims.

Claims

1. A method for determining residual insulin (RI) for use with an insulin delivery device, the method comprising:

receiving one or more bolus records (502),(602),(703), each bolus record includes at least one bolus dose value

and an associated time representative of the time the at least one_bolus dose value was delivered to a patient;
receiving one or more dose dependent RI time records (501),(601),(701), each of the one or more RI time records includes at least a dose value and an associated at least a duration value representative of dose-dependent duration of therapeutic effectiveness of the associated at least the dose value; and
determining based on the one or more bolus records (502),(602),(703) and the one or more dose dependent RI time records (501),(601),(701), a residual insulin (503),(603),(704) in the patient's body at a particular time instance.

2. The method of claim 1, wherein the associated duration value of at least one of the one or more dose dependent RI records (501),(601),(701) is based on one or more of: insulin type, site of cannula insertion and insulin delivery, physical activity, body temperature, fluid absorption characteristics, weight, age, gender, CIR,1S, and concentration of insulin.

3. The method of claim 1, further comprising: determining a bolus amount (504),(604),(705) to be delivered to the patient's body based on the determined residual insulin.

4. The method of claim 1, wherein the step of determining based on the one or more bolus records (502),(602),(703) and the one or more dose dependent RI time records (501),(601),(701) the residual insulin in the patient's body at the particular time instance comprises: determining the residual insulin in the patient's body by performing one or more of: matching, using data tables, a first dose value of at least one of the one or more bolus records to data corresponding to the one or more of the dose dependent RI time records arranged in the data tables, and determining the residual insulin value for the dose value of the at least one of the one or more bolus doses using relationships, determined based on the data corresponding the one or more dose dependent RI time records, that relate the dose value of the at least one of the one or more bolus records to a corresponding RI time determined using the determined relationship.

5. The method of claim 1, wherein the step of determining the residual insulin in the patient's body at the particular time instance comprises: determining for a delivered bolus of at least one of the one or more bolus records (602) an associated RI time equivalent to the duration value associated with a dose value from the one or more dose dependent RI time records (601) closest in value to a dose value of the delivered bolus.

6. The method of claim 1, wherein the step of determining the residual insulin in the patient's body at the particular time instance comprises: generating a graph (702) of RI time versus bolus dose based, at least in part, on the one or more dose dependent RI time records (701); and determining an RI time for a given delivered bolus value from one of the one or more bolus records (703) in accordance with the generated graph.

7. The method of claim 1, wherein the step of determining the residual insulin in the patient's body at the particular time instance comprises: determining for each of the one or more bolus records an associated individual residual insulin at the particular time instance based, at least in part, on the one or more dose dependent RI time records; and determining a sum of the determined individual residual insulin for each of the one or more bolus records.

8. The method of claim 7, wherein determining the sum of the determined individual residual insulin comprises: determining a weighted sum of the determined individual residual insulin according to the relationship $\sum_{j=1}^{n} \alpha_j RI_j$ where RI_j is the determined individual residual insulin for the j^{th} bolus record from the one or more bolus records, and α_j is an associated weight to apply to the determined residual insulin.

9. The method of claim 1, wherein the step of determining the residual insulin in the patient's body at the particular time instance comprises: tailoring the residual insulin to the patient based on patient-specific characteristics.

10. The method of claim 9, wherein the step of tailoring the residual insulin is performed by using at least one of: linear curve fitting, non-linear curve fitting, Bayesian models, neural network, fuzzy logic, genetic algorithms, linear regression, machine learning procedures, and statistical learning procedures.

11. The method of claim 1, wherein a duration value of one of the one or more dose dependent RI time records for a bolus used to cover a meal with a low glycemic index (GI) or glycemic load (GL) is lower than another duration value of another of the one or more dose dependent RI time records used to cover a meal with high glycemic index.

12. A drug delivery system for administration of insulin to a body of a patient, the system comprising:

a processor-based device implementing at least a residual insulin (RI) determination unit, the RI determination unit configured to determine a residual insulin in the patient's body at a particular time instance based on one or more bolus doses previously delivered to the body of the patient, each of the one or more bolus doses being associated with at least one bolus dose value and an associated time representative of the time the at least one dose value was delivered to the body of the patient, and based on one or more dose dependent RI time records, each of the one or more dose dependent RI time records includes at least a dose value and an associated at least a duration value representative of dose-dependent duration of therapeutic effectiveness of the associated at least the dose value; and
a pump to controllably dispense the insulin from a reservoir to the body of the patient based on the residual insulin determined by the RI determination unit.

13. The system of claim 12, further including a user interface for receiving at least one of: a dose value associated with at least one of the one or more bolus doses previously delivered to the body of the patient, an associated time representative of the time the dose value was delivered to the body of the patient, a dose value of at least one of the one or more dose dependent RI time records, a duration value associated with the dose value of the at least one of the one or more dose dependent RI time records, and a confirmation of the user.

14. A computer program comprising computer-executable instructions, which when executed on a suitable computer device, perform the method of claim 1.

15. A non-transitory computer readable medium comprising computer-executable instructions recorded thereon for performing the method of claim 1.

Patentansprüche

1. Verfahren zum Ermitteln von Restinsulin (RI) zur Verwendung mit einer Insulinabgabevorrichtung, wobei das Verfahren Folgendes beinhaltet:

Empfangen von einem oder mehreren Bolusdatensätzen (502), (602), (703), wobei jeder Bolusdatensatz wenigstens einen Bolusdosiswert und eine assoziierte Zeit beinhaltet, die die Zeit repräsentiert, zu der der wenigstens eine Bolusdosiswert einem Patienten gegeben wurde;
Empfangen von einem oder mehreren dosisabhängigen RI-Zeitdatensätzen (501), (601), (701), wobei jeder der ein oder mehreren RI-Zeitdatensätze wenigstens einen Dosiswert und einen assoziierten wenigstens einen Dauerwert beinhaltet, der eine dosisabhängige Dauer der therapeutischen Wirksamkeit wenigstens des assoziierten Dosiswertes repräsentiert; und
Ermitteln von Restinsulin (503), (603), (704) im Körper des Patienten zu einem bestimmten Zeitpunkt auf der Basis der ein oder mehreren Bolusdatensätze (502), (602), (703) und der ein oder mehreren dosisabhängigen RI-Zeitdatensätze (501), (601), (701).

2. Verfahren nach Anspruch 1, wobei der assoziierte Dauerwert von wenigstens einem der ein oder mehreren dosisabhängigen RI-Datensätze (501), (601), (701) auf einem oder mehreren der Folgenden basiert: Insulintyp, Ort der Kanüleneinführung und Insulinabgabe, körperliche Aktivität, Körpertemperatur, Fluidabsorptionscharakteristiken, Gewicht, Alter, Geschlecht, CIR, IS und Insulinkonzentration.

3. Verfahren nach Anspruch 1, das ferner das Ermitteln einer dem Körper des Patienten zu gebenden Bolusmenge (504), (604), (705) auf der Basis des ermittelten Restinsulins beinhaltet.

4. Verfahren nach Anspruch 1, wobei der Schritt des Ermittelns, auf der Basis der ein oder mehreren Bolusdatensätze (502), (602), (703) und der ein oder mehreren dosisabhängigen RI-Zeitdatensätze (501), (601), (701), des Restinsulins im Körper des Patienten zu dem bestimmten Zeitpunkt Folgendes beinhaltet: Ermitteln des Restinsulins im Körper des Patienten durch Ausführen von einem oder mehreren der Folgenden: Vergleichen, anhand von Datentabellen, eines ersten Dosiswertes von wenigstens einem der ein oder mehreren Bolusdatensätze mit Daten, die den in den Datentabellen angeordneten ein oder mehreren der dosisabhängigen RI-Zeitdatensätzen entsprechen, und Ermitteln des Restinsulinwertes für den Dosiswert der wenigstens einen der ein oder mehreren Bolusdosen anhand von Beziehungen, ermittelt auf der Basis der Daten, die den ein oder mehreren dosisabhängigen RI-Zeit-

datensätzen entsprechen, die den Dosiswert des wenigstens einen der ein oder mehreren Bolusdatensätze auf eine entsprechende, mit der ermittelten Beziehung ermittelte RI-Zeit bezieht.

5. Verfahren nach Anspruch 1, wobei der Schritt des Ermittelns des Restinsulins im Körper des Patienten zu dem bestimmten Zeitpunkt Folgendes beinhaltet: Ermitteln, für einen zugeführten Bolus von wenigstens einem der ein oder mehreren Bolusdatensätze (602), einer assoziierten RI-Zeit, die mit dem Dauerwert äquivalent ist, der mit einem Dosiswert von den ein oder mehreren dosisabhängigen RI-Zeitdatensätzen (601) assoziiert ist, der einem Dosiswert des zugeführten Bolus am nächsten liegt.

6. Verfahren nach Anspruch 1, wobei der Schritt des Ermittelns des Restinsulins im Körper des Patienten zu dem bestimmten Zeitpunkt Folgendes beinhaltet: Erzeugen einer Kurve (702) von RI-Zeit gegenüber Bolusdosis wenigstens teilweise auf der Basis der ein oder mehreren dosisabhängigen RI-Zeitdatensätze (701); und Ermitteln einer RI-Zeit für einen bestimmten gegebenen Boluswert anhand von einem der ein oder mehreren Bolusdatensätze (703) gemäß der erzeugten Kurve.

7. Verfahren nach Anspruch 1, wobei der Schritt des Ermittelns des Restinsulins im Körper des Patienten zu dem bestimmten Zeitpunkt Folgendes beinhaltet: Ermitteln, für jeden der ein oder mehreren Bolusdatensätze, eines assoziierten individuellen Restinsulins zu dem bestimmten Zeitpunkt wenigstens teilweise auf der Basis der ein oder mehreren dosisabhängigen RI-Zeitdatensätze; und Ermitteln einer Summe des ermittelten individuellen Restinsulins für jeden der ein oder mehreren Bolusdatensätze.

8. Verfahren nach Anspruch 7, wobei das Ermitteln der Summe des ermittelten individuellen Restinsulins Folgendes beinhaltet: Ermitteln einer gewichteten Summe des ermittelten individuellen Restinsulins gemäß der Beziehung $\sum_{j=1}^{n} \alpha_j \, RI_j$, wobei RI_j das ermittelte individuelle Restinsulin für den j-ten Bolusdatensatz von den ein oder mehreren Bolusdatensätzen ist und α_j eine assoziierte Gewichtung zum Anwenden auf das ermittelte Restinsulin ist.

9. Verfahren nach Anspruch 1, wobei der Schritt des Ermittelns des Restinsulins im Körper des Patienten zu dem bestimmten Zeitpunkt Folgendes beinhaltet: Anpassen des Restinsulins an den Patienten auf der Basis von patientenspezifischen Charakteristiken.

10. Verfahren nach Anspruch 9, wobei der Schritt des Anpassens des Restinsulins anhand von wenigstens einem der Folgenden erfolgt: lineare Kurvenanpassung, nichtlineare Kurvenanpassung, Bayesian-Modelle, neuronales Netzwerk, Fuzzy Logic, genetische Algorithmen, lineare Regression, Maschinenlernprozeduren und statistische Lernprozeduren.

11. Verfahren nach Anspruch 1, wobei ein Dauerwert von einem der ein oder mehreren dosisabhängigen RI-Zeitdatensätze für einen Bolus, der zum Ausgleichen einer Mahlzeit mit einem niedrigen glykämischen Index (GI) bzw. glykämischen Last (GL) benutzt wird, niedriger ist als ein anderer Dauerwert eines anderen der ein oder mehreren dosisabhängigen RI-Zeitdatensätze, die zum Ausgleichen einer Mahlzeit mit hohem glykämischen Index verwendet werden.

12. Arzneimittelabgabesystem zur Verabreichung von Insulin an den Körper eines Patienten, wobei das System Folgendes umfasst:

ein prozessorbasiertes Gerät, das wenigstens eine Restinsulin-(RI)-Ermittlungseinheit implementiert, wobei die RI-Ermittlungseinheit zum Ermitteln von Restinsulin im Körper eines Patienten zu einem bestimmten Zeitpunkt auf der Basis von einer oder mehreren zuvor dem Körper des Patienten gegebenen Bolusdosen konfiguriert ist, wobei jede der ein oder mehreren Bolusdosen mit wenigstens einem Bolusdosiswert und einer assoziierten Zeit assoziiert ist, die die Zeit repräsentiert, zu der wenigstens ein Dosiswert dem Körper des Patienten gegeben wurde, und auf der Basis von einem oder mehreren dosisabhängigen RI-Zeitdatensätzen, wobei jeder der ein oder mehreren dosisabhängigen RI-Zeitdatensätze wenigstens einen Dosiswert und einen assoziierten wenigstens einen Dauerwert beinhaltet, der eine dosisabhängige Dauer der therapeutischen Wirksamkeit wenigstens des assoziierten Dosiswerts repräsentiert; und
eine Pumpe zum steuerbaren Abgeben des Insulins aus einem Reservoir an den Körper des Patienten auf der Basis des von der RI-Ermittlungseinheit ermittelten Restinsulins.

13. System nach Anspruch 12, das ferner eine Benutzeroberfläche zum Empfangen von wenigstens einem der Folgenden beinhaltet: einem Dosiswert, der mit wenigstens einer der ein oder mehreren Bolusdosen assoziiert ist, die zuvor dem Körper des Patienten gegeben wurden, einer assoziierten Zeit, die die Zeit repräsentiert, zu der der Dosiswert dem Körper des Patienten gegeben wurde, einem Dosiswert von wenigstens einem der ein oder mehreren dosisabhängigen RI-Zeitdatensätze, einem Dauerwert, der mit dem Dosiswert des wenigstens einen der ein oder mehreren dosisabhängigen RI-Zeitdatensätze assoziiert ist, und einer Bestätigung des Benutzers.

14. Computerprogrammprodukt, das computerausführbare Befehle umfasst, die bei Ausführung auf einem geeigneten Computergerät das Verfahren nach Anspruch 1 ausführen.

15. Nichttransitorisches computerlesbares Medium, auf dem vom Computer ausführbare Befehle zum Ausführen des Verfahrens nach Anspruch 1 aufgezeichnet sind.

Revendications

1. Méthode de détermination de l'insuline résiduelle (IR) conçue pour être utilisée en conjonction avec un dispositif d'administration d'insuline, la méthode comprenant :

   la réception de un ou plusieurs schémas de bolus (502),(602),(703), chacun du ou des plusieurs schémas comportant au moins une valeur de dose du bolus et un temps associé représentatif du moment auquel la au moins une valeur de dose du bolus a été administrée à un patient ;
   la réception de un ou plusieurs relevés dans le temps de l'IR en fonction de la dose (501),(601),(701), chacun du ou des plusieurs relevés dans le temps de l'IR comprenant au moins une valeur de dose et au moins une valeur de durée associée représentative de la durée, en fonction de la dose, de l'efficacité thérapeutique de la au moins une valeur de dose associée ; et
   la détermination, sur la base du ou des plusieurs schémas de bolus (502),(602), (703) et du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose (501),(601),(701), de l'insuline résiduelle (503),(603),(704) dans l'organisme du patient à un point temporel particulier.

2. Méthode de la revendication 1, dans laquelle la valeur de durée associée à un au moins du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose (501),(601),(701) repose sur un ou plusieurs des critères suivants: type d'insuline, site d'insertion de la canule et d'administration de l'insuline, niveau d'activité physique, température corporelle, caractéristiques en matière d'absorption de fluides, poids, âge, sexe, rapport hydrates de carbone/insuline (RCI), sensibilité à l'insuline (SI) et concentration de l'insuline,

3. Méthode de la revendication 1, qui comprend également : l'évaluation de la dose de bolus (504),(604),(705) à administrer dans l'organisme du patient sur la base de l'insuline résiduelle déterminée.

4. Méthode de la revendication 1, dans laquelle l'étape de détermination, sur la base du ou des plusieurs schémas de bolus (502),(602),(703) et du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose (501),(601),(701), de l'insuline résiduelle dans l'organisme du patient au point temporel particulier comprend : la détermination de l'insuline résiduelle dans l'organisme du patient par le biais de un ou plusieurs des moyens suivants : l'appariement, à l'aide de tableaux de données, entre une première valeur de dose de un au moins du ou des plusieurs schémas de bolus et les données correspondantes du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose consignées dans les tableaux de données, et la détermination de la valeur d'insuline résiduelle pour la valeur de dose de un au moins du ou des plusieurs schémas de bolus au moyen de corrélations établies sur la base des données correspondantes du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose, qui lient la valeur de dose du au moins un du ou des plusieurs schémas de bolus à une durée d'action de l'IR correspondante évaluée en utilisant la relation déterminée.

5. Méthode de la revendication 1, dans laquelle l'étape de détermination de l'insuline résiduelle dans l'organisme du patient au point temporel particulier comprend : la détermination, pour un bolus administré selon un au moins du ou des plusieurs schémas de bolus (602), de la durée d'action de l'IR associée équivalente à la valeur de durée associée à la valeur de dose du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose (601) qui est la plus proche en valeur de la valeur de dose du bolus administré.

6. Méthode de la revendication 1, dans laquelle l'étape de détermination de l'insuline résiduelle dans l'organisme du

patient au point temporel particulier comprend : la production d'un diagramme (702) de la durée d'action de l'IR en fonction de la dose de bolus sur la base, tout au moins en partie, du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose (701) ; et la détermination de la durée d'action de l'IR pour une valeur de bolus donnée administrée selon un du ou des plusieurs schémas de bolus (703) conformément au diagramme généré.

7. Méthode de la revendication 1, dans laquelle l'étape de détermination de l'insuline résiduelle dans l'organisme du patient au point temporel particulier comprend : la détermination, pour chacun du ou des plusieurs schémas de bolus, de l'insuline résiduelle associée individuelle au point temporel particulier sur la base, tout au moins en partie, du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose ; et le calcul d'une somme des insulines résiduelles individuelles déterminées pour chacun du ou des plusieurs schémas de bolus.

8. Méthode de la revendication 7, dans laquelle le calcul de la somme des insulines résiduelles individuelles déterminées comprend : la détermination d'une somme pondérée des insulines résiduelles individuelles déterminées conformément à la relation $\sum_{j=1}^{n} \alpha_j IR_j$, où IR_j est l'insuline résiduelle individuelle déterminée pour le $j^{ème}$ schéma de bolus du ou des plusieurs schémas de bolus et α_j est un poids associé à appliquer à l'insuline résiduelle déterminée.

9. Méthode de la revendication 1, dans laquelle l'étape de détermination de l'insuline résiduelle dans l'organisme du patient au point temporel particulier comprend : l'adaptation de l'insuline résiduelle au patient sur la base de caractéristiques spécifiques au patient.

10. Méthode de la revendication 9, dans laquelle l'étape d'adaptation de l'insuline résiduelle est effectuée par le biais d'au moins un des moyens suivants : ajustement de courbe linéaire, ajustement de courbe non linéaire, modèles bayésiens, réseau de neurones, logique floue, algorithmes génétiques, régression linéaire, procédures d'apprentissage automatique et procédures d'apprentissage statistique.

11. Méthode de la revendication 1, dans laquelle une valeur de durée de un du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose pour un bolus utilisé pour couvrir un repas à charge glycémique (IG) ou index glycémique (CG) faible est plus basse qu'une autre valeur de durée du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose utilisée pour couvrir un repas à index glycémique élevé.

12. Dispositif d'administration de médicaments utilisé pour administrer une insuline dans l'organisme d'un patient, le dispositif comprenant :

un dispositif à base de processeur comportant au moins une unité de détermination de l'insuline résiduelle (IR), l'unité de détermination de l'insuline résiduelle étant configurée pour déterminer l'insuline résiduelle dans l'organisme d'un patient à un point temporel particulier sur la base de une ou plusieurs doses de bolus administrées antérieurement dans l'organisme du patient, chacune de la ou des plusieurs doses de bolus étant associées à au moins une valeur de dose de bolus et à un temps associé représentatif du temps auquel la au moins une valeur de dose a été administrée dans l'organisme du patient et sur la base de un ou plusieurs relevés dans le temps de l'IR en fonction de la dose, chacun du ou des plusieurs relevés dans le temps de l'IR en fonction de la dose comprenant au moins une valeur de dose et au moins une valeur de durée associée représentative de la durée, en fonction de la dose, de l'efficacité thérapeutique de la au moins une valeur de dose associée ; et une pompe permettant de délivrer d'une manière contrôlable l'insuline d'un réservoir à l'organisme du patient sur la base de l'insuline résiduelle évaluée par l'unité de détermination de l'IR.

13. Dispositif de la revendication 12, qui comprend également une interface utilisateur pour recevoir une au moins des informations suivantes : une valeur de dose associée à au moins une de la ou des plusieurs doses de bolus administrées antérieurement dans l'organisme du patient, un temps associé représentatif du temps auquel la valeur de dose a été administrée dans l'organisme du patient, une valeur de dose du ou des plusieurs relevés dans le temps de l'IR en fonction la dose, une valeur de durée associée à la valeur de dose de un au moins du ou des plusieurs relevés dans le temps de l'IR en fonction la dose et une confirmation de l'utilisateur.

14. Programme informatique comprenant des instructions exécutables par un ordinateur qui, lors d'être exécutées dans un dispositif informatique approprié, effectuent la méthode de la revendication 1.

15. Support non transitoire pouvant être lu par un ordinateur dans lequel des instructions exécutables par un ordinateur sont mémorisées pour effectuer la méthode de la revendication 1.

Dose Given [IU]	Units left to work after:				
	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
1	0.8	0.6	0.4	0.2	0
2	1.6	1.2	0.8	0.4	0
3	2.4	1.8	1.2	0.6	0
4	3.2	2.4	1.6	0.8	0
5	4.0	3.0	2.0	1.0	0
6	4.8	3.6	2.4	1.2	0
7	5.6	4.2	2.8	1.4	0
8	6.4	4.8	3.2	1.6	0
9	7.2	5.4	3.6	1.8	0
10	8.0	6.0	4.0	2.0	0

Fig. 1

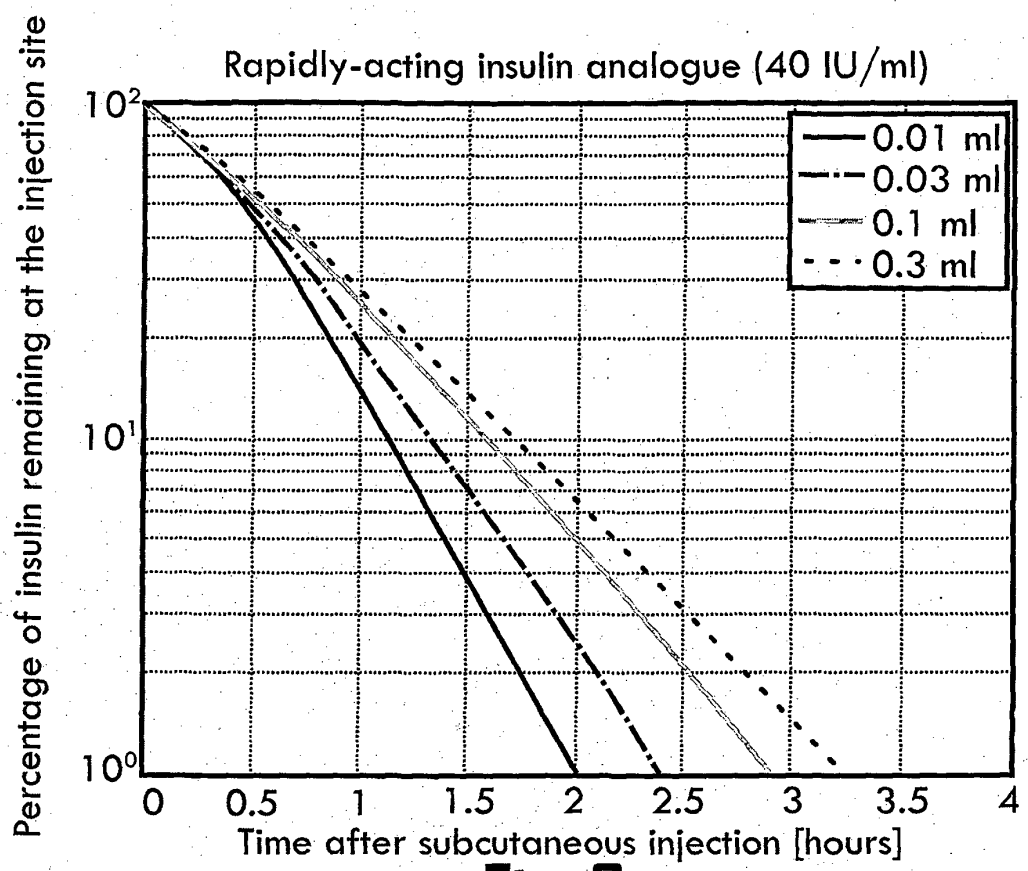
Rapidly-acting insulin analogue (40 IU/ml)
Percentage of insulin remaining at the injection site
10^2
10^1
10^0
0.01 ml
0.03 ml
0.1 ml
0.3 ml
0
0.5
1
1.5
2
2.5
3
3.5
4
Time after subcutaneous injection [hours]

Fig. 2

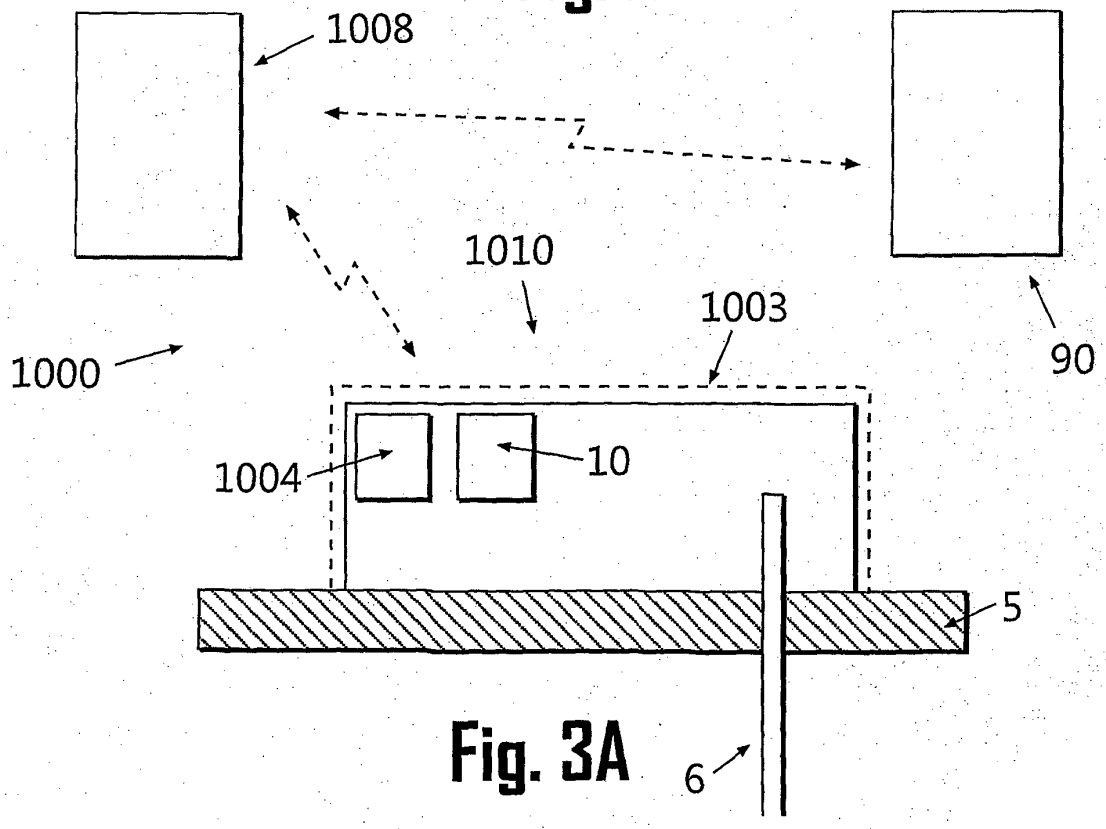
1008
1010
1003
1000
90
1004
10
5
6

Fig. 3A

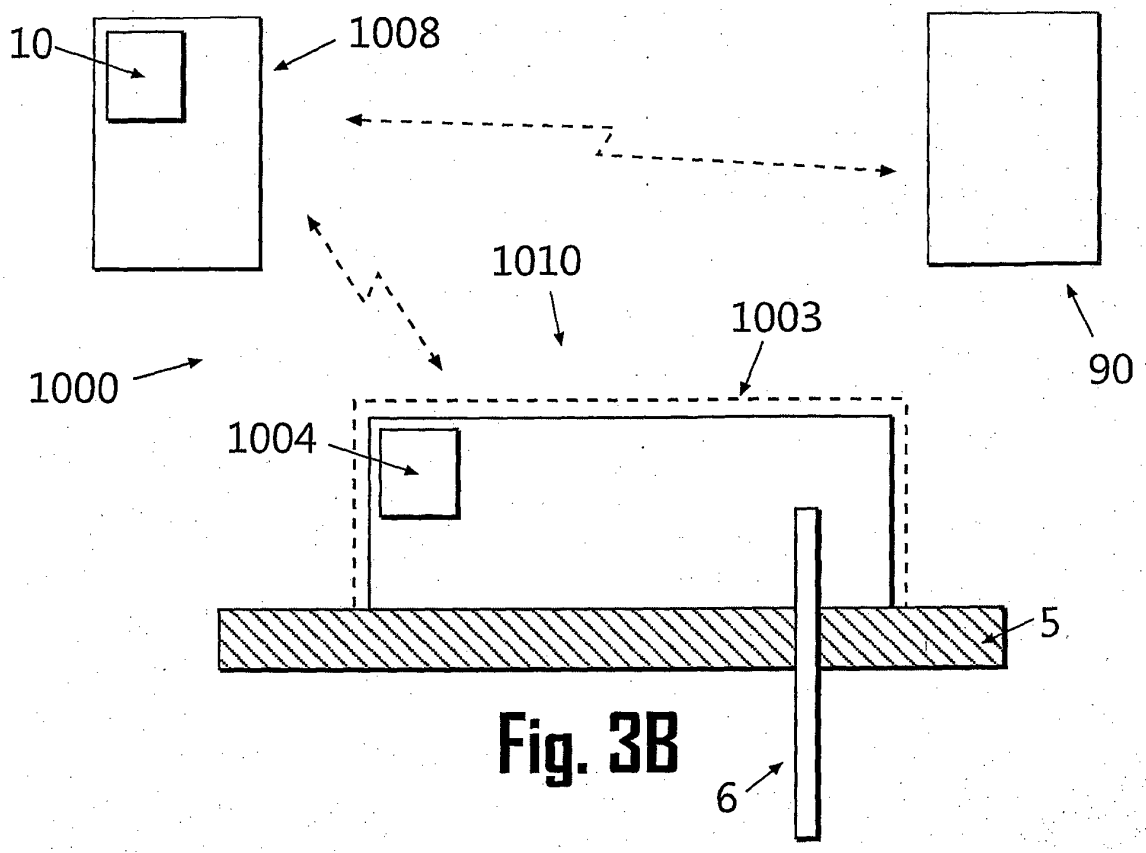
10
1008
1010
1003
90
1000
1004
5
6

Fig. 3B

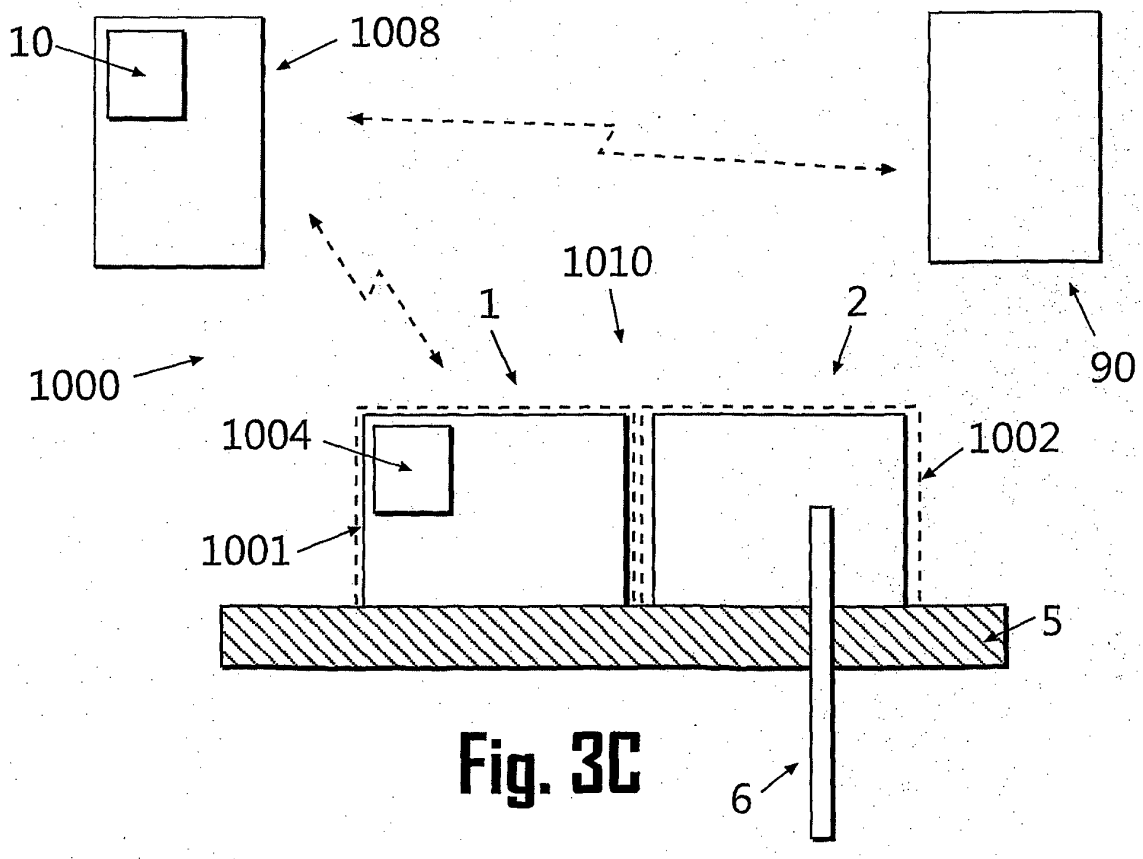
10
1008
1010
1
2
90
1000
1004
1002
1001
5
6

Fig. 3C

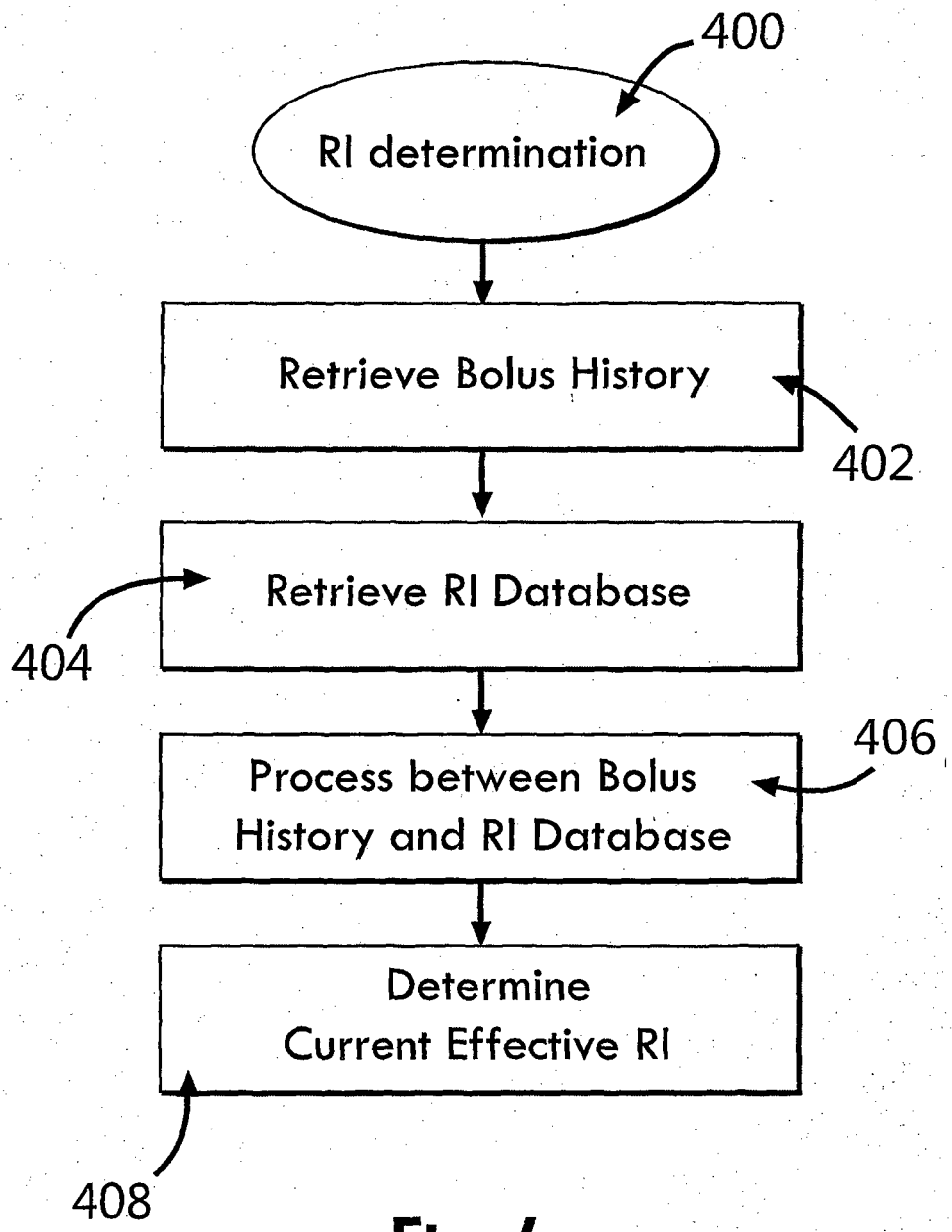
400
RI determination
Retrieve Bolus History
402
Retrieve RI Database
404
406
Process between Bolus History and RI Database
Determine Current Effective RI
408

Fig. 4

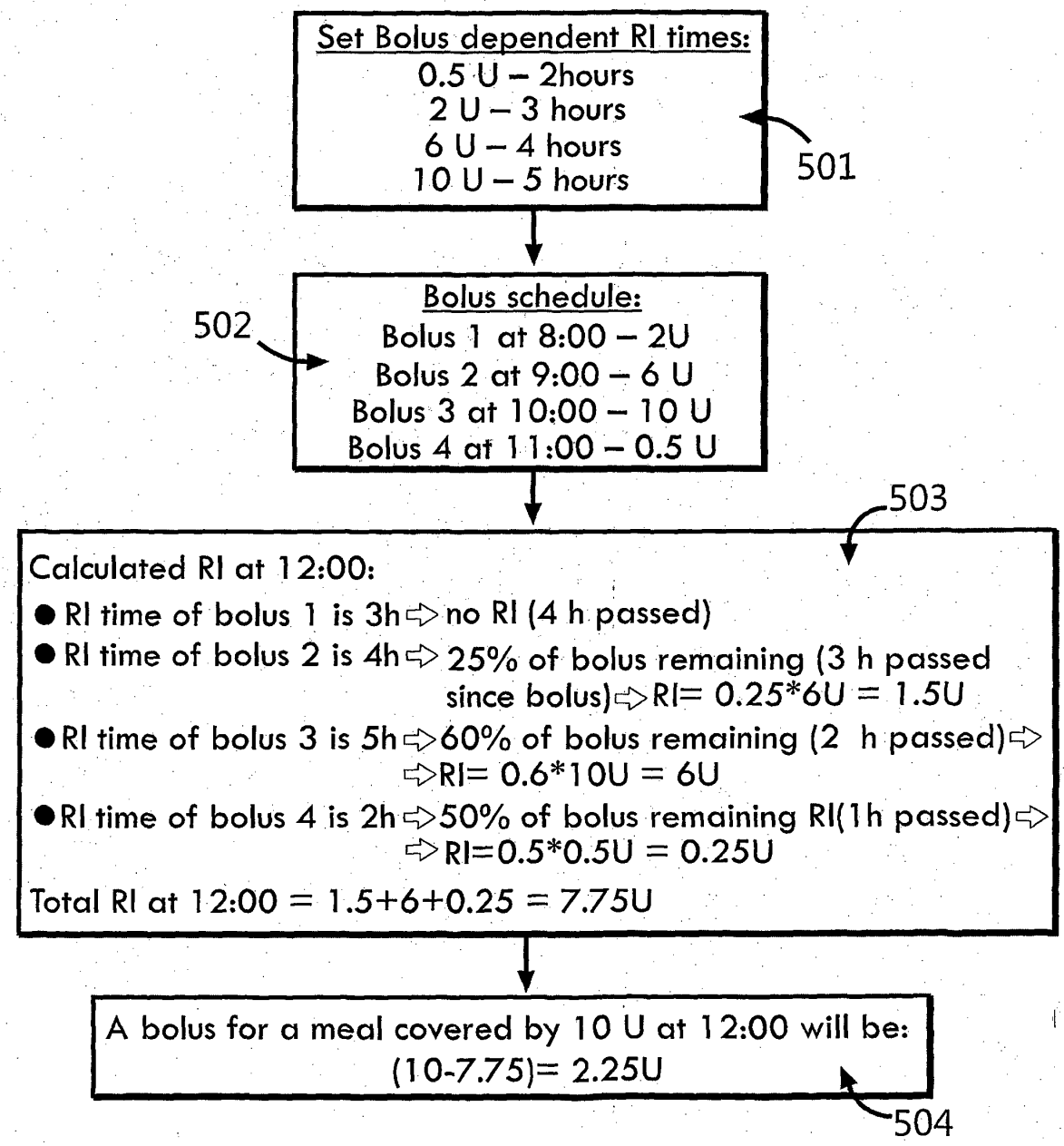
Set Bolus dependent RI times:
0.5 U – 2hours
2 U – 3 hours
6 U – 4 hours
10 U – 5 hours
501
Bolus schedule:
Bolus 1 at 8:00 – 2U
Bolus 2 at 9:00 – 6 U
Bolus 3 at 10:00 – 10 U
Bolus 4 at 11:00 – 0.5 U
502
503
Calculated RI at 12:00:
● RI time of bolus 1 is 3h ⇨ no RI (4 h passed)
● RI time of bolus 2 is 4h ⇨ 25% of bolus remaining (3 h passed since bolus) ⇨ RI= 0.25*6U = 1.5U
● RI time of bolus 3 is 5h ⇨ 60% of bolus remaining (2 h passed) ⇨ ⇨ RI= 0.6*10U = 6U
● RI time of bolus 4 is 2h ⇨ 50% of bolus remaining RI(1h passed) ⇨ ⇨ RI=0.5*0.5U = 0.25U
Total RI at 12:00 = 1.5+6+0.25 = 7.75U
A bolus for a meal covered by 10 U at 12:00 will be:
(10-7.75)= 2.25U
504

Fig. 5

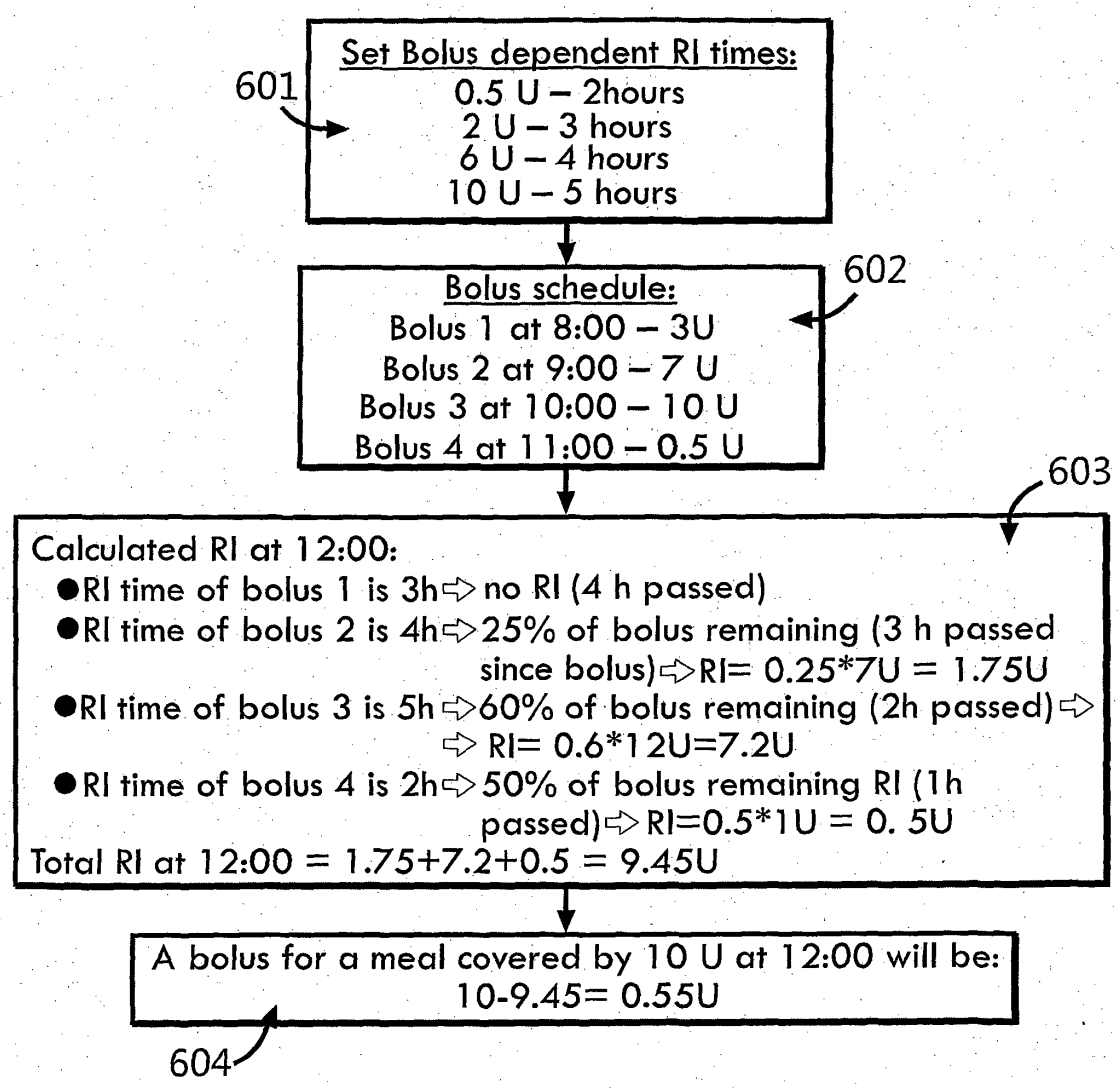
601
Set Bolus dependent RI times:
0.5 U – 2hours
2 U – 3 hours
6 U – 4 hours
10 U – 5 hours
602
Bolus schedule:
Bolus 1 at 8:00 – 3U
Bolus 2 at 9:00 – 7 U
Bolus 3 at 10:00 – 10 U
Bolus 4 at 11:00 – 0.5 U
603
Calculated RI at 12:00:
●RI time of bolus 1 is 3h⇨no RI (4 h passed)
●RI time of bolus 2 is 4h⇨25% of bolus remaining (3 h passed since bolus)⇨RI= 0.25*7U = 1.75U
●RI time of bolus 3 is 5h⇨60% of bolus remaining (2h passed)⇨⇨ RI= 0.6*12U=7.2U
●RI time of bolus 4 is 2h⇨50% of bolus remaining RI (1h passed)⇨RI=0.5*1U = 0. 5U
Total RI at 12:00 = 1.75+7.2+0.5 = 9.45U
A bolus for a meal covered by 10 U at 12:00 will be:
10-9.45= 0.55U
604

Fig. 6

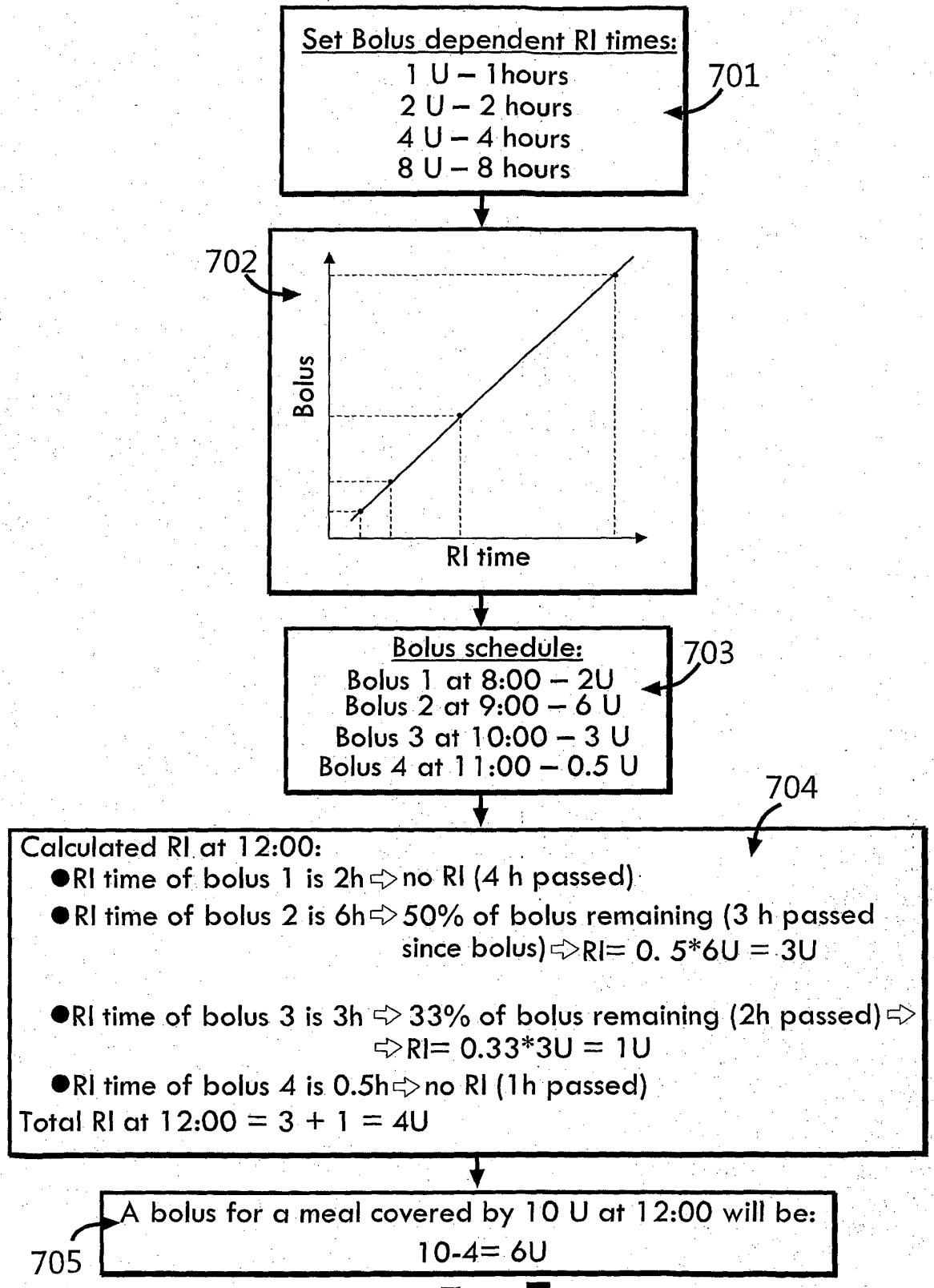
Set Bolus dependent RI times:
1 U – 1hours
2 U – 2 hours
4 U – 4 hours
8 U – 8 hours
701
702
Bolus
RI time
Bolus schedule:
Bolus 1 at 8:00 – 2U
Bolus 2 at 9:00 – 6 U
Bolus 3 at 10:00 – 3 U
Bolus 4 at 11:00 – 0.5 U
703
704
Calculated RI at 12:00:
●RI time of bolus 1 is 2h ⇨ no RI (4 h passed)
●RI time of bolus 2 is 6h ⇨ 50% of bolus remaining (3 h passed since bolus) ⇨ RI= 0. 5*6U = 3U
●RI time of bolus 3 is 3h ⇨ 33% of bolus remaining (2h passed) ⇨ ⇨ RI= 0.33*3U = 1U
●RI time of bolus 4 is 0.5h ⇨ no RI (1h passed)
Total RI at 12:00 = 3 + 1 = 4U
A bolus for a meal covered by 10 U at 12:00 will be:
10-4= 6U
705

Fig. 7

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	一种基于残余胰岛素改善血糖控制的方法和装置		
公开(公告)号	EP2445407A4	公开(公告)日	2013-08-28
申请号	EP2010791740	申请日	2010-06-23
[标]申请(专利权)人(译)	梅丁格有限公司		
申请(专利权)人(译)	MEDINGO LTD.		
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[标]发明人	YODFAT OFER GESCHEIT IDDO M SHAPIRA GALI		
发明人	YODFAT, OFER GESCHEIT, IDDO M. SHAPIRA, GALI		
IPC分类号	A61B5/1468 A61B5/00 A61B5/145 A61K38/28 A61M5/168 A61M5/172		
CPC分类号	A61M5/168 A61B5/14532 A61B5/4839 A61K38/28 A61M5/1723		
优先权	61/220204 2009-06-25 US		
其他公开文献	EP2445407A2 EP2445407B1		
外部链接	Espacenet		

摘要(译)

公开了包括系统的系统，设备和方法，所述系统包括基于处理器的设备，所述基于处理器的设备实现至少残余胰岛素（RI）确定单元，所述残留胰岛素（RI）确定单元被配置成基于先前的推注剂量在特定时间点确定患者体内的残留胰岛素。递送至患者的身体，每个推注剂量与至少一个剂量值和表示剂量值被递送至患者身体的时间的时间相关联，并且基于剂量依赖性RI时间记录，每个包括至少一个剂量值和相关的持续时间值表示相关联的至少剂量值的剂量依赖性治疗有效性持续时间。该系统还包括泵，用于基于由RI确定单元确定的残留胰岛素将胰岛素从储存器可控制地分配到患者身体。