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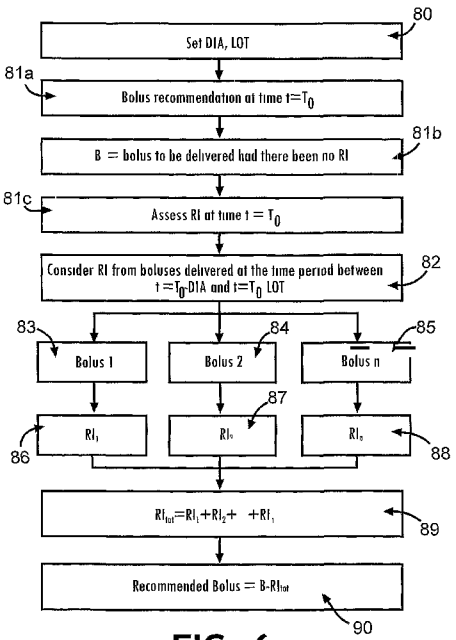

FIG. 6a

(57) Abstract: Embodiments of the present disclosure are directed to systems, devices/apparatuses and methods for assessing a residual insulin value for a user/patient. Such embodiments may be implemented by selecting a first value corresponding to a duration of insulin action; selecting a second value corresponding to a lock out time duration, selecting a first time period beginning at a time point TO minus the first value and ending at the time point TO minus the second value, selecting one or more boluses delivered during the first time period; for each of the one or more boluses selecting a corresponding residual insulin value estimated at the time point TO, computing the cumulative residual insulin value by summation of the corresponding residual insulin values.

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INSULIN DELIVERY SAFETY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to provisional U.S. application Serial No. 61/152,514, entitled "Increasing Safety of Insulin Delivery" filed February 13, 2009, the content of which is hereby incorporated by reference in its entirety.

FIELD

[0001] Embodiments of the subject disclosure are directed to methods, devices and systems for sustained infusion of fluids. Some embodiments are related generally to a portable insulin infusion apparatus and a method for bolus delivery based on the residual insulin computation/determination (each term being used interchangeably throughout the present disclosure).

BACKGROUND

[0002] 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.

[0003] 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 the small blood vessels (microangiopathy, causing eye, kidney and nerve damage) and the 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 (HbAIc). [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 adequate insulin delivery can be of utmost importance.

[0004] Insulin infusion device can deliver rapid acting insulin (e.g. Lispro, Aspart, etc.) 24 hours a day through a cannula placed under the skin. Rapid acting insulin effect begins in about 10 minutes after administration, peaks at 1 to 1.5 hours after administration, and ends in about two to six hours after the administration. The duration of insulin action (DIA) is variable and thus this parameter can be set (programmed) in the pump by the user and/or caregiver.

[0005] A skin-securable insulin infusion device was disclosed in co-owned, U.S. Patent Application No. 11/397,115 (published as US2007/0106218) and International Patent Application No. PCT/IL06/001276 (published as WO2007/052277), and International Patent Application No. PCT/IL09/000388 (published as WO2009/125398) claiming priority to U.S. Provisional Patent Application No. 61/123,509, the disclosures of which are incorporated herein by reference in their entireties.

[0006] Insulin infusion device can be integrated with a continuous glucose monitor allowing open and closed loop systems (patient boluses at meals and automatic administration respectively). Such device integrating insulin delivery and glucose monitoring was disclosed in co-owned, U.S. Patent Application No. 11/706,606 (published as US2007/0191702) and International Patent Application No. PCT/IL07/000163 (published as WO2007/093981), co-owned, U.S. Patent Application No. 11/963,481 (published as US2008/0214916) and International Patent Application No. PCT/IL07/001579 (published as WO2008/078319), and co-owned International Patent Application No. PCT/IL08/001521 (published as the disclosures of which are incorporated herein by reference in their entireties.

[0007] One of the major advantages of insulin pumps is the convenience of insulin bolus administration at any desired time. However, the effect of boluses may overlap, hence the amount of active insulin that is still "working" in the body (hereinafter "residual insulin" or "RI") from previous boluses should be taken into account. Accumulation of insulin in the body, or "insulin stacking", may lead to life-threatening hypoglycemia. Prevention of hypoglycemia can be especially important (but not limited) at bedtime since users are typically unaware of nocturnal hypoglycemia.

[0008] A simple rule can be applied to calculate the RI. It is often stated that after bolus administration 20% of a dose is absorbed each hour, so that after 5 hours there is no active insulin remaining in the body. For example, FIG. 1 shows the insulin consumption according to the described rule (adapted from Using Insulin © 2003). Knowing the RI, can assist in providing the desired bolus dose. For example, if a 5U bolus is planned 2 hours after a 6U bolus [RI= 6U x 0.2 x 2 = 3.6U) the actual administered bolus should be only 1.4U (5U-3.6U = 1.4U).

[0009] Most bolus recommendation tools, provided by different insulin pumps, can take the RI parameter into account. The recommended amount of insulin in the bolus to be delivered can be established, for example, by calculations, as described in U.S. Patent Serial No. 6,936,029 assigned to Medtronic MiniMed, or it can be selected by a method for selection of the desired bolus dose, as described in co-owned, International Application No. PCT/IL2008/000380 (published as WO2008/1 14254) and U.S. Patent Application No. 12/051,400 (published as 2008/0234663), the disclosures of which are incorporated herein by reference in their entireties. Some pumps (e.g., Deltec's, Insulet's) use linear plots to predict the residual insulin, while other pumps (e.g., Animas', MiniMed's) use curvilinear plots which better approximate the pharmacokinetics actions of insulin (Diabetes Technology and Therapeutics, 2008, 10(6), p. 441-44).

[0010] Most available bolus calculators take into account RI from boluses which have been administered during a time interval prior to a current bolus administration. Typically, this time interval does not exceed above the DIA, and the accumulated RI is subtracted from the current bolus dose to be delivered. Although insulin stacking can be prevented, this simple calculation of RI may lead to under - dosing if previous boluses administration times are very close to the current bolus administration time. For example, when a pump user eats a main course, he/she will first have to administer a bolus to balance the main course's carbohydrates. If the user further eats a desert 10 minutes after completing the main course, the pump and/or bolus calculator may indicate a high RI (resulted from the bolus administered prior to the main course to cover the main course) and may not require an additional bolus to cover the carbohydrates of the desert. Such indication can be misleading because the high RI may be sufficient to offset merely the main course but insufficient to offset the desert. The outcome of this miscalculation ;can lead to unbalanced offset of carbohydrates and subsequent hyperglycemia.

SUMMARY

[0011] Embodiments of the present disclosure are directed to systems, devices and methods for estimating residual insulin values. In some embodiments, such methods can be implemented according to one or more (and preferably all) of the following steps: selecting a first value corresponding to a duration of insulin action, selecting a second value corresponding to a lock out time duration, selecting a first time period beginning at a time point T_0 minus the first value and ending at the time point T_0 minus the second value, and selecting one or more boluses delivered during the first time period. The method may further include selecting a corresponding residual insulin value estimated at the time point T_0 for each of the one or more boluses, and computing the cumulative residual insulin value by summation of the corresponding residual insulin values.

[0012] In some embodiments, methods for estimating residual insulin values may include one or more (and preferably all) of the following steps (which may be in addition to the steps described above): selecting an estimated amount of carbohydrates consumed by a user, computing a first insulin bolus corresponding to the estimated amount of carbohydrates without considering a residual insulin parameter, and computing a second insulin bolus by subtracting the cumulative residual insulin from the first insulin bolus. Delivery of the second insulin bolus to a user can also be initiated. The user can also be provided with a recommendation message corresponding to the insulin bolus. In some embodiments, the duration of insulin action and the lock out time duration can be configured by a user. In some embodiments, the lock out time duration can be selected between one and sixty minutes.

[0013] Embodiments of the methods may include any of the features described above in relation to a system, as well as any one of the features set out in the present disclosure.

[0014] Some embodiments of the present disclosure may be implemented using a delivery device and/or system. For example, a delivery device may implement one and/or another of the disclosed methods and may include a delivery mechanism (e.g., a pump) and a tangible machine-readable storage medium: for example, a processor, and/or a memory (e.g., any memory: magnetic disc, optical disc, flash memory, and the like), including instructions for carrying out the one and/or another of the disclosed methods. These features may be enclosed within a housing, for example. The tangible machine-readable storage medium may be enclosed within a housing of a device adapted to communicate wirelessly with the delivery

device (for example), and thus be part of a drug delivery system. The delivery device can comprise a disposable portion and a reusable portion, in which the disposable portion can include a reservoir.

[0015] Some embodiments include a portable therapeutic fluid delivery apparatus/device (each term used interchangeably throughout), which may also be part of a system. Such an apparatus may comprise a skin securable (e.g., adherable), portable therapeutic fluid delivery apparatus comprising pump, a reservoir, a processer and a memory. At least one of the memory and processer includes a plurality of computer instructions for carrying out operations on the processor for a method for computing a cumulative residual insulin value, according to any of the method embodiments disclosed in the present application. The method may also be performed on a processor of a second device (in addition to it being performed on the processor of the delivery apparatus, or in place thereof). In some embodiments, the apparatus/device or system may include a remote control and/or a sensor for monitoring body analytes (e.g., glucose, ketones).

[0016] Embodiments of the device, apparatus and system may include any of the features a switches/buttons located adjacent the GUI (for example). Other elements of the GUI may include:

- a second input element for selecting a bolus dose without considering RI values; and
- a third input element for selecting of at least one of: an amount of carbohydrates to be consumed by a user, a glycemic index (GI), a glycemic load (GL), type of insulin, and insulin absorption rate.

[0017] In such a GUI, the second output element may be used for visually presenting a first potion of the recommended bolus dose and a second portion of the recommended bolus dose. Moreover, the first input element may include scrolling functionality.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 shows a table of residual insulin (RI) estimation 1-5 hours after bolus administration of 1-lOU of insulin Lispro;

[0019] FIG. 2 illustrates an insulin infusion device for implementing a method for RI assessment according to some embodiments of the present disclosure;

[0020] FIG. 3 illustrates an insulin infusion device configured to recommend a bolus dose in accordance with a method for RI assessment according to some embodiments of the present disclosure;

[0021] FIG. 4 is a time axis illustrating the EDIA;

[0022] FIGs. 5a-b are block diagrams of an RI assessment method and a numerical example of the RI assessment method, respectively, according to some embodiments of the present disclosure; and

[0023] FIGs. 6a-b are block diagrams for bolus recommendation in accordance with an RI assessment method and a numerical example of bolus recommendation in accordance with an RI assessment method, respectively, according to some embodiments of the present disclosure.

DETAILED DESCRIPTION

[0024] Methods, systems and devices are provided herein for assessing a residual insulin (RI) value of a patient/user. Some embodiments can be implemented according to one or more (and preferably all) of the following steps: selecting a first value corresponding to a duration of insulin action, selecting a second value corresponding to a lock out time duration, selecting a first time period beginning at a time point T_0 minus the first value and ending at the time point T_0 minus the second value, selecting one or more boluses delivered during the first time period, for each of the one or more boluses - selecting a corresponding residual insulin value estimated at the time point To, and computing a cumulative residual insulin value by summation of the corresponding residual insulin values.

[0025] In some embodiments, a method for assessing the residual insulin value may be implemented via an infusion device comprises a dispensing patch unit (hereinafter the "patch"). In some embodiments, the patch can include two parts: a disposable part and a reusable part. In some embodiments, the infusion device can include a skin adherable cradle unit (hereinafter the "cradle"). In some embodiments, the infusion device can be part of an infusion system, which can further include a remote control unit (hereinafter the "RC"). The

patch can be disconnected and reconnected from and to the cradle. A connecting lumen can provide fluid communication between the patch and a subcutaneously insertable cannula that can be rigidly connected to the cradle. Fluid delivery can be remotely controlled by the RC or by manual buttons/switches located on the patch.

[0026] Some embodiments provide a device (and corresponding system) that can deliver insulin into the body and can further monitor body (e.g. blood, interstitial fluid (ISF)) glucose levels. Some embodiments provide a method for RI assessment to prevent insulin under¬ dosing, hyperglycemia, and insulin stacking.

[0027] Some embodiments provide a device which is miniature, discreet, economical for users and highly cost effective. Such a device can implement a method for RI assessment to prevent insulin under-dosing, hyperglycemia, and insulin stacking (for example). For example, the device can contain a miniature skin securable (e.g., adherable to the skin) dispensing patch unit that can continuously dispense insulin and a method for RI assessment to prevent insulin under-dosing, hyperglycemia, and insulin stacking. The device can also comprise an insulin dispensing patch unit that can be remotely controlled and a method for RI assessment that can prevent insulin under-dosing, hyperglycemia, and insulin stacking. In some embodiments, the device can include a closed or semi-closed loop system that can sense and monitor glucose levels and dispense insulin according to the sensed glucose levels.

[0028] In some embodiments, the device can comprise a patch. For example, a patch can comprise a pumping mechanism (also referred-to as "pump", which may be any pump capable of conveying a liquid/fluid), reservoir and outlet port. The patch can be configured as a single part including a reservoir, one or more batteries, electronics (e.g., processor, memory, sensors), and a pump. The patch can also be configured as a two-part device, comprising a reusable part (hereinafter "RP") and a disposable part (hereinafter "DP").

[0029] For example, RP can comprise a motor, gear(s), electronics, and other relatively expensive components (e.g., an occlusion sensor). DP can comprise an outlet port, a reservoir, a slidable plunger (for example), a drive screw, and a nut. In some preferred embodiments the DP can contain at least one battery (e.g., Zinc air battery). In another embodiment, the reservoir can have a thin profile (e.g., oval, ellipse, four arches, etc.).

[0030] In some embodiments each one of the RP and DP can comprise a housing (shell, or pocket) and an insert (chassis) and upon RP-DP connection the housings and inserts can be coupled.

[0031] The device (or system) can also include a cradle., A cradle can be implemented as a flat sheet or otherwise structural member, with adhesive layer facing the skin provided with a passageway to a subcutaneously insertable cannula and snaps to secure the cannula and patch.

[0032] Some embodiments of the device (or system) described herein can also include a remote control unit ("RC"). The RC can be a handheld piece for programming fluid flows, controlling the patch, data acquisition, and providing indications (e.g., display, speaker, vibration mechanism). In some embodiments the RC can further comprise a wrist-watch, cellular phone, PDA, smart-phone (e.g., iPhone), media player (e.g., iPod), and laptop (for example). The insulin infusion device can also be integrated with a continuous glucose monitor to allow open or closed loop systems.

[0033] In some embodiments, an assessed RI value can be used for bolus determination (or recommendations). For example, the RI can be calculated in accordance with boluses administered during a defined time period. In some implementations, the defined time period can last from the time of the current bolus administration minus the duration of insulin action "DIA" (e.g., 5 hours) until the time of the current bolus minus the lock-out time "LOT". In some embodiments, the LOT can be 15 minutes (for example). That is, the calculated RI can be derived from previous boluses given during the set DIA up to the lock-out time (e.g., from 5 hours before the current bolus until 15 minutes before the current bolus). The lock out time can prevent insulin under-dosing due to miscalculation of residual insulin which is supposedly remained from very recent administered boluses. Thus, for example, if an unplanned desert is eaten 10 minutes after the main course, the bolus delivered to cover the carbohydrates (or other consumables) of the main course will not be accounted for in the RI calculation.

[0034] According to some embodiments, during the defined time period between the DIA to the lock-out time (hereinafter "Effective Duration of Insulin Action" or "EDIA"), the RI can be calculated according to a linear plot, a curvilinear plot, or any other plot of insulin pharmacokinetics known in the art.

[0035] According to some embodiments, if a bolus is to be delivered, the RI can be subtracted from the bolus dose. In some embodiments, the method for assessing residual insulin values can be incorporated in the insulin infusion device.

[0036] FIG. 2 illustrates an exemplary insulin infusion system (1000), according to some embodiments, that can comprise a dispensing patch unit (1010), which can be adhered to the user's skin (5), and a remote control unit (1008), which can communicate with the dispensing patch unit (1010), allowing programming, user inputs and data acquisition. The remote control unit (1008) can be implemented as a dedicated remote control or in a cell phone, watch, Personal Data Assistant ("PDA"), laptop, iPod or any other device having wire or wireless communication capabilities such as RF, IR, magnetic, etc.

[0037] The patch unit (1010) can be attached to a cradle (20) that is a flat sheet or other structural member adhered to the user's skin (5) and can allow connection/disconnection of the patch unit (1010). During connection of the patch unit (1010) to the cradle (20), a connecting lumen can pierce a self sealed septum (e.g., rubber septum) in the cannula (6) providing fluid communication between the reservoir in the patch unit and subcutaneous tissue through the cannula (6).

[0038] In some embodiments, manual inputs can be carried out by one or more buttons/switches (1011) located on the dispensing patch unit (1010). The dispensing patch unit (1010) can be composed of two parts: a reusable part (1) and a disposable part (2) residing in one or two housings respectively.

[0039] According to some embodiments, the remote control unit (1008) can include an RI calculator (2000) for assessing the RI value, a processor (2010), a memory (2020), and a display/screen (2040). The display can communicate messages to the user, e.g., messages corresponding to bolus recommendation or RI values. Input means (2030) (e.g., buttons, switches, keys, keypad, icons, areas of a touch-sensitive screen, voice command, and the like) may also be provided. In some embodiments, communication with the user can be via a visual, audible or vibrational notification.

[0040] According to some embodiments, means (2000) for assessing the RI value (which may be a software application program run on a processor), and/or processor (2010), and/or memory (2020), and/or display (2040), and/or input means (2030) can be located in or on the dispensing patch unit (1010), particularly in the reusable part (1) of the dispensing patch unit

(1010). According to some embodiments, the device/system (1000) can also comprise a blood glucose monitor and/or a continuous glucose monitor (CGM).

[0041] FIG.3 illustrates one example of the insulin infusion device which includes a bolus recommendation device (2200) that provides a recommended bolus dose based on the RI value provided by the RI calculator (2000). The bolus recommendation device (2200) and RI calculator (2000) can be located in the remote control unit (1008).

[0042] According to some embodiments, the bolus recommendation device and/or the RI calculator can be located in the reusable part (1) of the dispensing patch unit (1010) or shared between the dispensing patch unit (1010) and the RC (1008).

[0043] In some embodiments, the assessed RI value can be used for bolus recommendations. For example, the RI can be calculated in accordance with boluses administered and or delivered during a defined time period. FIG 4 shows a time axis (t) illustrating the EDIA (Effective Duration of Insulin Action). At the time of current bolus administration, $t = T_0$, the RI can be calculated. The boluses that account for the RI value can be those administered and/or delivered during the EDIA; the time period that falls between T_{DIA} and T_{LOT}, i-e-, EDIA = DIA - LOT. The time period between T_{DIA} and T_0 is the duration of insulin action "DIA". The duration of insulin action is the period of time during which insulin dose is "active" in the body, i.e., offsets carbohydrates (for example) effect. In some embodiments, the DIA varies between 2hrs and 8hrs. The DIA may vary based on several factors, for example the type of insulin (e.g., Lispro, Aspart), physiological parameters of the user/patient (e.g., insulin absorption rate) and location (or site) of insulin administration. The time period that lasts between T_{LOT} and T_0 is the lock-out time, or "LOT". The lock-out time period is the period of time prior to the current bolus administration and food intake (e.g., carbohydrates intake) during which the delivered insulin does not affect/offset the consumed carbohydrates. Typically, a delay may be present between administration of the bolus to the subcutaneous tissue and its effect in the blood tissue, e.g., due to insulin absorption kinetics. Various meal characteristics, such as the glycemic index (GI) of the meal and fat percentage of the meal, may also influence the period of time during which the insulin does not affect/offset the consumed carbohydrates. The absorption of carbohydrates of the ingested food can also lag behind the absorption of the insulin. Thus, the "free" insulin, or "residual" insulin may counteract/offset the carbohydrates that may not have been absorbed yet. In some embodiments, the LOT varies between 0 and 60 minutes. Thus, boluses administered during

the LOT may not be taken into account in assessing the current RI value (but may be taken into account for future assessments). That is, the calculated RI can be derived from previous boluses given during the EDIA.

[0044] According to some embodiments, during the defined time period between the DIA to the lock-out time (hereinafter "Effective Duration of Insulin Action" or "EDIA"), the RI can be calculated according to a linear plot, a curvilinear plot, or any other plot of insulin pharmacokinetics known in the art.

[0045] In some embodiments, the DIA can be assessed by the user/caregiver based on the method and device described in co-owned, International Patent Application No. PCT/IL08/001444 (published as WO2009/060433), entitled "Assessing Residual Insulin Time", the disclosure of which is incorporated herein by reference in its entirety.

[0046] FIG. 5a is a block diagram illustrating a method for assessing an RI value that can be implemented by the RI calculator according to some embodiments. At (60), the user/caregiver can set (or determine) at least one of the duration of insulin action (DIA), and the lock-out time period (LOT). The DIA can relate to the duration over which the insulin is being depreciated in the body. According to some embodiments, the user can set the DIA in the range of 2hr to 8hr with a 10-30 minutes step. According to some embodiments, a default DIA may be set (and stored in a memory), for example to 5 hrs. The LOT can relate to the most recent time period prior to the current RI assessment. Boluses that are being delivered during the LOT can be disregarded in the current RI value assessment (however data related to these boluses can be stored in a memory and retrieved in future occurrences). According to some embodiments, the user can set the LOT in the range of 0 to 60 minutes with a 1-30 minutes step. According to some embodiments, a default LOT may be set (and stored in a memory), for example to 10 - 60 minutes. Step (60) does not necessarily have to be performed in close proximity to the RI assessment. For example, DIA and LOT can be set once, and then being used every time that an RI is being assessed.

[0047] The RI value assessment can be initiated (61) at time $t = T_0$. At (62), the boluses delivered between time T_{DIA} until time T_{LOT} can be considered. In some embodiments, boluses delivered before T_{DIA} and all boluses delivered after T_{LOT}, may not be considered for assessing the current RI value.

[0048] At (66)-(68), the RI can be calculated for boluses indexed as T - 'n1 (63)-(65), respectively (V representing an integer equal or higher than 1), wherein for boluses which were not administered/delivered during the EDIA, the corresponding RI would be zero. The RI can be calculated according to a linear plot, a curvilinear plot, or any other plot known in the art that reflects insulin pharmacokinetics. At (69), the separate RI values (RI_1, RI_2,..., RI_n) calculated in (66)-(68) can be summated to yield the final total RI value (RI_{tot}), also referred-to as "cumulative RI value".

[0049] The RI can be assessed based on at least one of a normal bolus (i.e., bolus delivered at the shortest time possible), long bolus (i.e., bolus delivered over an extended period of time), combination bolus (i.e., a combination of normal and long boluses), food bolus (i.e., a bolus that serves to cover a certain amount of carbohydrates in a meal), a correction bolus (i.e., a bolus that serves to bring the user from hyperglycemia back to target blood glucose levels), or a combination of any of the foregoing.

[0050] In some embodiments, a bolus may last longer than the DIA. In such a case, only the portion of the delivered bolus that falls within the EDIA will be considered in assessing the RI. For example, assessing an RI value at time 17:00 with a DIA of 3hrs, LOT of 10 minutes, and considering a long bolus which was administered at time 12:00 and lasts 3 hours. The portion of this long bolus taken into account when assessing the current RI would be based on the amount of insulin delivered between 14:00 and 15:00, for example. In other embodiments, the long bolus can be administered during the EDIA and last even after the current bolus administered at T_0. For example, assessing an RI value at time 17:00 with a DIA of 3hrs, LOT of 10 minutes, and considering a long bolus which was administered at time 16:00 and lasts 3 hours. The portion of this long bolus taken into account when assessing the RI would be based on the amount of insulin delivered between 16:00 and 16:50. In such cases, wherein a portion of the bolus is considered, the remained bolus portion can be recorded in memory for future use, for example, to be considered in assessing the RI value for a subsequent bolus administration.

[0051] FIG. 5b illustrates a numerical example of the RI assessment method depicted in FIG. 5a. At (70) the user sets a DIA of 5 hours and a LOT of 1 hour. At (71) the RI is to be assessed at time 17:00. At (73) and (74) boluses delivered between 12:00 (17:00 minus DIA) and 16:00 (17:00 minus LOT) are depicted; a bolus of 5U was delivered at time 13:00 (73) and a bolus of 3U was delivered at time 15:00 (741 At (73) and (74). the underlined boluses

(8.6U and 7.2U respectively) represent the boluses that would have been delivered had there been no RI. The computations/determinations in brackets ([6-0.2*2*6] and [(5-0.2*2*5)+(6-0.2*4*6)] respectively) represent the RI calculations performed according to a decaying linear curve in which 20% of the dose is consumed every hour (DIA of 5 hours), according to some embodiments.

[0052] At (76) and (77), the RI values of IU and 1.8U may be calculated for the boluses at (73) and (74) respectively, according to a decaying linear curve in which 20 % (i.e., 100/DIA) of the dose is consumed every hour (as depicted in FIG. 2). At (78), the total RI value, also referred-to as "cumulative RI value", is received by summation of the RI values calculated separately for each bolus, i.e., RIl and RI2, calculated in (76) and (77), respectively. Boluses delivered before 13:00 (72) and after 16:00 (75) are not considered for the current RI value assessment (for example).

[0053] FIG. 6a is a block diagram for bolus recommendation in accordance with the RI assessment method, according to some embodiments. For example, at (80), the user/caregiver sets the duration of insulin action (DIA), and the lock-out time (LOT) period. At (81a), a bolus calculation/recommendation is to be performed at time $t=T_0$. At (81b) a bolus (B) dose may be assessed, in some embodiments according to at least the user's current glucose level. The bolus (B) at this stage may be assessed without consideration of the RI value. The bolus can be directly estimated by the user or caregiver, calculated by a bolus calculator, or provided by a bolus recommendation tool such as the one described in co-owned, U.S. Patent Application No. 12/051,400 (published as US2008/0234663) and International Patent Application No. PCT/IL08/000380 (published as WO2008/1 14254), and International Patent Application No. PCT/IL09/000454 (published as WO2009/133558) claiming priority to U.S. Provisional Patent Application No. 61/048,856, the disclosures of which are incorporated herein by reference in their entireties. At (81c), an RI value assessment may be performed at time $t = T_0$. At (82), the boluses delivered between time t = To-DIA = T_{DIA} until time $t = T_0$-LOT = T_Loτ may be considered. All boluses delivered before T_{DIA} and after T_{LOT} may not be considered for assessing the current RI value, i.e., their respective RI is set to zero for this assessment, but can be recorded in memory for calculation of future RI values (for example). At (86)-(88) the RI may then be calculated for boluses indexed as T - 'n' (83)-(85), whereas 'n' represents an integer equal or higher than 1. At (89), the separate RI values are summated to yield the final total RI value (RItot), also referred-to as

"cumulative RI value". At (90), the final bolus recommendation may be provided as the bolus (B) as provided at (81a) minus the total RI (i.e., RW) as provided at (89). In some embodiments, the final bolus recommendation, as provided at (90), can be administered to a user, for example via a pump.

[0054] FIG. 6b shows a numerical example of bolus recommendation in accordance with the method depicted in FIG. 6a. At (90a) the user sets a DIA of 5 hours and a LOT of 1 hour. At (91a) a bolus is to be delivered at 17:00 to cover a planned meal. At (91c) the RI at the same time (designated as T_0) is to be assessed. At (91b) a bolus (B) dose of 6U is determined (e.g., directly by the user, or by a bolus calculator). At (93) and (94) bolus doses (i.e., bolus doses after subtraction of RI) delivered between 12:00 (17:00 minus DIA) and 16:00 (17:00 minus LOT) are depicted; a bolus of 5U was delivered at 13:00 (93) and a bolus of 3U was delivered at 15:00 (94). At (96) - (97), corresponding RI values of IU and 1.8U are calculated for the boluses at (93) and (94) respectively. The RI values can be calculated according to a decaying linear curve in which 20 % (i.e., 100/DIA) of the dose is consumed every hour. At (98), the total RI value is received by summation of the RI values calculated separately for each bolus. Boluses delivered before 13:00 (92) and after 16:00 (95) are not considered for the current RI value assessment. At (99), a final bolus dose of 3.2U is recommended based on the bolus (B = 6U) as provided at (91a) minus the total RI (2.8U) as provided at (98). In some embodiments, the recommended bolus can be presented to a user via a screen (for example) and can be recorded in a memory. Then, the recommended bolus can be administered to a user, for example by using a pump.

[0055] In some embodiments, the LOT can relate to other parameters such as glycemic index (GI) or glycemic load (GL). A meal can correspond to a GI value which may be classified as ranges for example Low, Medium or High (e.g., GI value of yogurt, banana, and white bread respectively). The GI and LOT can obtain an inverse correlation, i.e., High GI (e.g., of white bread) may correlate with Low LOT (e.g., 10 minutes), and Low GI (e.g., of yogurt) may correlate with High LOT (e.g., 60 minutes). According to some embodiments, the GI values can be inputted by the user or retrieved from a memory or from a food database. The correlation can be based on a mathematical model or retrieved from a predetermined schedule which correlates GI values with LOT values.

[0056] In some embodiments, the LOT and/or RI values can be assessed based on a insulin pharmacokinetic model (e.g., model described by Trajanoski et al. *(Computer Methods and*

Progr-ams in Biomedics; 62 (2000), 249-257), herein incorporated by reference) which considers the insulin absorption in the subcutaneous tissue.

[0057] Various implementations of the subject matter described herein, such as the RI calculator and/or the bolus recommendation device, may 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 implementations may include implementation in one or more computer programs that are executable and/or interpretable on a programmable system including at least one programmable processor, which may 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, for example.

[0058] Such computer programs (also known as programs, software, software applications or code) include machine instructions for operation on a processor, and may 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" or "tangible medium" refers to any computer program product, apparatus, system and/or device (e.g., magnetic discs, optical disks, memory, Programmable Logic Devices (PLDs), flash memory, and the like) used to provide machine instructions and/or data to a processor (e.g., a programmable processor), including a machine-readable 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.

[0059] To provide for interaction with a user, the subject matter described herein may be implemented on a computer having a display device (e.g., a CRT (cathode ray tube) or LCD (liquid crystal display) monitor and the like) 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 may be used to provide for interaction with a user as well; for example, feedback provided to the user may be any form of sensory feedback (e.g., visual feedback, auditory feedback, or tabtile feedback); and input from the user may be received in any form, including acoustic, speech, or tactile input.

[0060] The subject matter described herein may also 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 may 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.

[0061] Any and all references to publications or other documents, including but not limited to patents, patent applications, articles, webpages, books', etc presented and referenced in this specification are hereby incorporated by reference herein in their entireties. Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, which follow.

[0062] It will thus be seen that many of the embodiments of the present disclosure attain objects made apparent from the preceding description. Since certain changes may be made without departing from the scope of the present disclosure, it is intended that all matter contained in the above description or shown in the accompanying drawings be interpreted as illustrative and not in a literal sense (and thus, not limiting). Practitioners of the art will realize that the method, device and system configurations depicted and described herein are examples of multiple possible system configurations that fall within the scope of the current disclosure.

[0063] While the disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the disclosure. All such modifications are intended to be within the scope of the claims appended hereto, as well as other claims which may be subsequently included in this or subsequent related filing. Other aspects, advantages, and modifications are also considered to be within the scope of the following claims.

What is claimed is:

1. A drug delivery system for dispensing insulin to a body of a user, the device comprising:

a drug deliver device, the device comprising:

at least one housing containing a pump, the pump is configured for dispensing the insulin from a reservoir into a body of a user;

input means for receiving input corresponding to at least one of: a duration of insulin action and a lock out time duration for the user;

a processor having a residual insulin (RI) calculator operating thereon configured for determining a cumulative RI value by summation of RI values estimated at a time point T_0 and corresponding to one or more boluses delivered during a first time period, wherein the first time period beginning at the time point T_0 minus a first value corresponding to the duration of insulin action and ending at the time point T_0 minus a second value corresponding to the lock out time duration; and

a memory for storing the duration of insulin action, the lock out time duration, and the RI values.

2. The system of claim 1, wherein the processor further comprises a bolus recommendation application operating thereon configured for determining an insulin bolus dose associated with the cumulative RI value.

3. The system of claim 2, wherein the input also optionally includes an estimated amount of carbohydrates consumed by the user, and wherein the bolus recommendation application determines:

a first insulin bolus dose corresponding to the estimated amount of carbohydrates, without considering a residual insulin value, and

a second insulin bolus dose established by subtracting the cumulative residual insulin from the first insulin bolus.

4. The system of claim 2, wherein the pump dispenses the determined insulin bolus dose.

5. The system of claim 1, further comprising a remote control, the remote control including at least one of: the processor, the input means, and the memory.

6. The system of claim 1, wherein the at least one housing includes a reusable part housing and a disposable part housing, the disposable part housing includes the reservoir and the reusable part housing includes the processor and the memory.

7. The system of claim 1, wherein the lock out time duration corresponds to at least one of a glycemic index (GI), glycemic load (GL), type of insulin and insulin absorption rate.

8. The system of claim 1, wherein the residual insulin value estimated at the time point T_0 corresponds to a first portion of the one or more boluses, and wherein the memory stores a second portion of the one or more boluses.

9. The system of claim 1, further comprising a skin adherable cradle enabling connection and disconnection of the at least one housing.

10. The system as in any of the preceding claims, comprising a screen for displaying at least one of: the RI values, the cumulative RI value, the duration of insulin action, the lock out time duration, the GI, the GL, the type of insulin, the insulin absorption rate, the recommended bolus dose, the first potion of the one or more boluses and the second portion of the one or more boluses.

11. A device comprising a tangible machine-readable storage medium embodying instructions that when performed by one or more machines result in computing a cumulative residual insulin value by operations comprising:

selecting a first value corresponding to a duration of insulin action;

selecting a second value corresponding to a lock out time duration;

selecting a first time period beginning at a time point T_0 minus the first value and ending at the time point T_0 minus the second value;

selecting one or more boluses delivered during the first time period;

selecting a corresponding residual insulin value estimated at the time point To for each of the one or more boluses; and

computing a cumulative residual insulin value by summation of the corresponding residual insulin values.

12. The device of claim 11, wherein the tangible machine-readable storage medium further embodies instructions that when performed by the one or more machines result in operations comprising:

selecting an estimated amount of carbohydrates consumed by a user;

computing a first insulin bolus corresponding to the estimated amount of carbohydrates, without considering a residual insulin value; and

computing a second insulin bolus by subtracting the cumulative residual insulin from the first insulin bolus.

13. The device of claim 12, wherein the tangible machine-readable storage medium further embodies instructions that when performed by the one or more machines result in operations comprising initiating a delivery of the second insulin bolus to a user.

14. The device of claim 12, wherein the tangible machine-readable storage medium further embodies instructions that when performed by the one or more machines result in operations comprising recommending the second insulin bolus.

15. The device of claim 11, wherein the duration of insulin action and the lock out time duration are configurable by a user.

16. The device of claim 11, wherein the lock out time duration is selected between about one and about sixty minutes.

17. The device of claim 11, further comprising a delivery apparatus for delivering insulin to a user.

18. The device of claim 17, wherein the delivery apparatus and the tangible machine-readable storage medium are enclosed within a housing.

19. The device of claim 17, wherein the tangible machine-readable storage medium is enclosed within a housing of a device adapted to communicate wirelessly with the delivery apparatus.

20. The device of claim 17, wherein the delivery apparatus comprises at least one disposable portion and at least one reusable portion.

21. The device of claim 20, wherein the at least one disposable portion includes a reservoir.

22. The device of claim 11, wherein the lock out time duration corresponds to at least one of a glycemic index (GI), glycemic load (GL), type of insulin and insulin absorption rate.

23. The device of claim 11, wherein selecting the residual insulin value estimated at the time point T_0 corresponds to a first portion of the one or more boluses, and

wherein the tangible machine-readable storage medium further embodies instructions that when performed by the one or more machines result in operations comprising recording a second portion of the one or more boluses in a memory.

24. A method for delivering an adjusted insulin bolus into a body of a patient comprising:

selecting a first value corresponding to a duration of insulin action;

selecting a second value corresponding to a lock out time duration;

selecting a first time period beginning at a time point To minus the first value and ending at the time point T_0 minus the second value;

selecting one or more boluses delivered during the first time period;

selecting a corresponding residual insulin value estimated at the time point T_0 for each of the one or more boluses;

computing a cumulative residual insulin value by summation of the corresponding residual insulin values; and

computing the adjusted insulin bolus based on the cumulative residual insulin value.

25. The method of claim 24, further comprising delivering the adjusted insulin bolus into the body of the patient.

26. The method of claim 24, wherein the method further comprises notifying the patient that the adjusted insulin bolus is about to be delivered.

27. The method of claim 26, wherein notifying comprises sending a notification using a wireless device.

28. The method of claim 24, wherein the delivery of the adjusted insulin bolus is initiated by a wireless signal.

29. The method of claim 24, wherein the lock out time corresponds to at least one of a glycemic index (GI), glycemic load (GL), type of insulin and absorption rate.

30. The method of claim 24, wherein selecting the residual insulin value estimated at the time point T_0 corresponds to a first portion of the one or more boluses, and wherein the method further comprising recording a second portion of the one or more boluses in a memory.

31. A therapeutic fluid delivery system comprising:

a skin securable, portable therapeutic fluid delivery apparatus comprising pump, a reservoir, a processer and a memory, wherein at least one of the memory and processer includes a plurality of computer instructions for carrying out operations on at least one of the processor for a method for computing a cumulative residual insulin value, the method comprising:

selecting a first value corresponding to a duration of insulin action;

selecting a second value corresponding to a lock out time duration;

selecting a first time period beginning at a time point T_0 minus the first value and ending at the time point T_0 minus the second value;

selecting one or more boluses delivered during the first time period;

selecting a corresponding residual insulin value estimated at the time point To for each of the one or more boluses; and

computing a cumulative residual insulin value by summation of the corresponding residual insulin values.

32. The system according to claim 31, the second device comprises a remote control unit.

33. The system of claim 31, wherein the instructions further include instructions for carrying out operations in the method for:

selecting an estimated amount of carbohydrates consumed by a user;

computing a first insulin bolus corresponding to the estimated amount of carbohydrates, without considering a residual insulin value; and

computing a second insulin bolus by subtracting the cumulative residual insulin from the first insulin bolus.

34. The system of claim 33, wherein the instructions further include instructions for carrying out operations in the method for initiating a delivery of the second insulin bolus to a user.

35. The system of claim 33, wherein the instructions further include instructions for carrying out operations in the method for recommending the second insulin bolus.

36. The system of claim 31, wherein the duration of insulin action and the lock out time are configurable by a user.

37. The system of claim 31, wherein the lock out time is selected between about one and about sixty minutes.

38. The system of claim 31, wherein the delivery apparatus comprises a disposable portion and a reusable portion.

39. The system of claim 38, wherein the disposable portion includes a reservoir.

40. The system of claim 31, wherein the lock out time corresponds to at least one of a glycemic index (GI), glycemic load (GL), type of insulin and absorption rate.

41. The system of claim 31, wherein selecting the residual insulin value estimated at the time point T_0 corresponds to a first portion of the one or more boluses, and

wherein the tangible machine-readable storage medium further embodies instructions that when performed by the one or more machines results in operations comprising recording a second portion of the one or more boluses in a memory.

42. A graphic user interface of an insulin infusion device, the graphic user interface comprising:

a first input element for selecting at least one of: a duration of insulin action and a lock out time duration; and

a first output element for visually presenting a cumulative RI value, the cumulative RI value comprising a summation of RI values estimated at the time point To and corresponding to one or more boluses delivered during a first time period, wherein the first time period beginning at the time point To minus a first value corresponding to the duration of insulin action and ending at the time point T_0 minus a second value corresponding to the lock out time duration; and

a second output element for visually presenting a recommended bolus dose corresponding to the cumulative RI value.

43. The graphic user interface of claim 42, comprising a second input element for selecting a bolus dose without considering RI values.

44. The graphic user interface of claim 42, further comprising a third input element for selecting at least one of: an amount of carbohydrates to be consumed by a user, a glycemic index (GI), a glycemic load (GL), type of insulin, and insulin absorption rate.

45. The graphic user interface of claim 42, wherein the second output element for visually presenting a first potion of the recommended bolus dose and a second portion of the recommended bolus dose.

46. The graphic user interface of claims 42, wherein the first input element includes scrolling functionality.

47. The graphic user interface of claims 42 to 46, wherein at least one of the input and output elements has a touch sensitive functionality.

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

PRIOR ART

FIG. 1

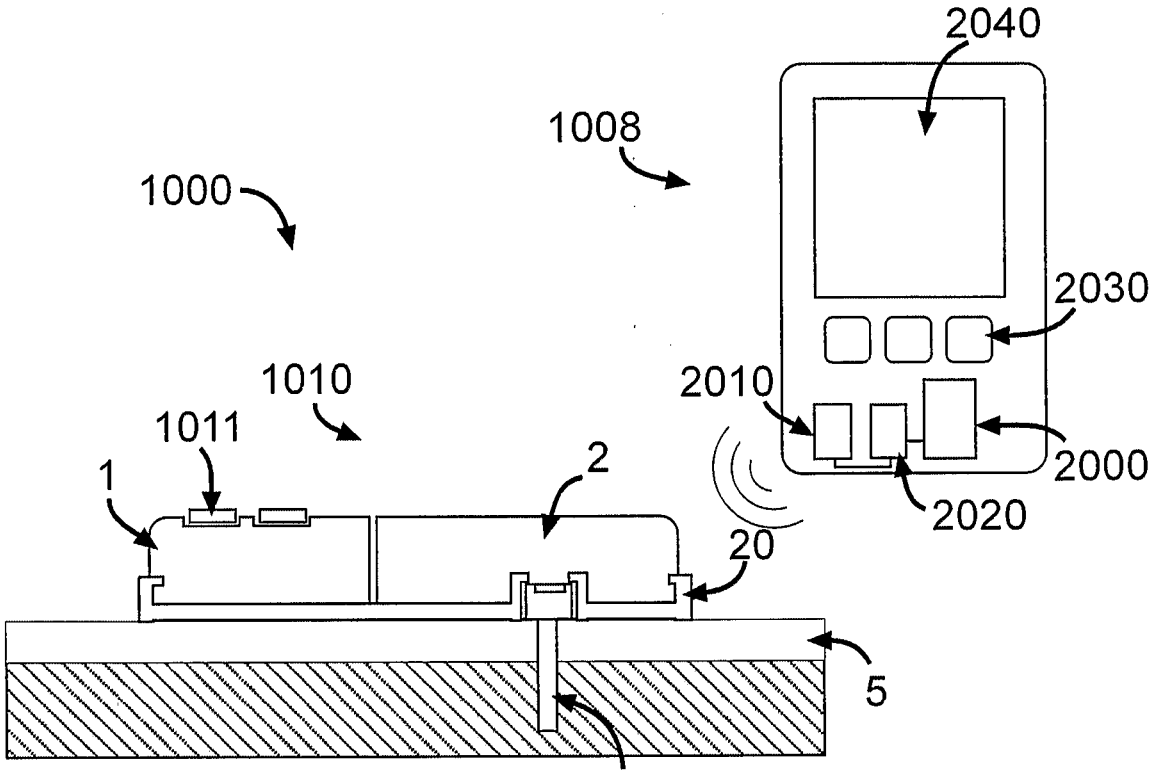
2040
1008
1000
2030
1010
2010
1011
2000
1
2
2020
20
5
6

FIG. 2

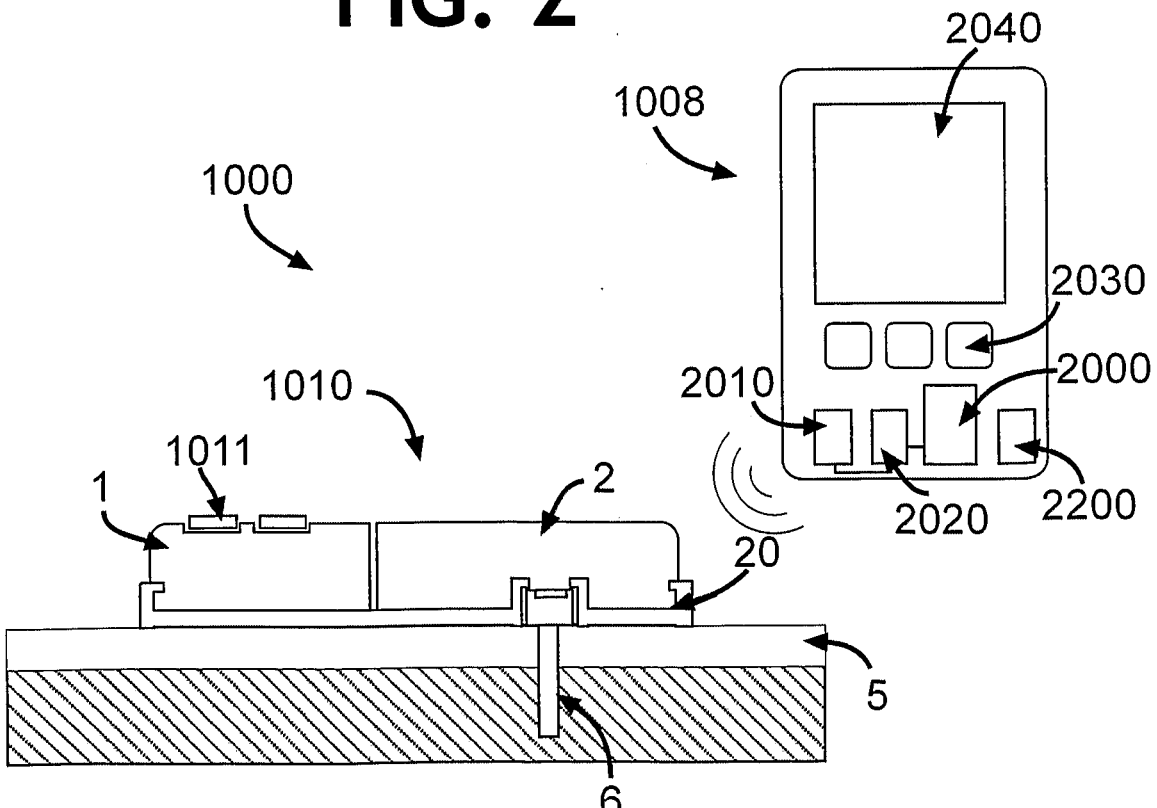
2040
1008
1000
2030
2000
1010
2010
1011
1
2
2200
2020
20
5
6

FIG. 3

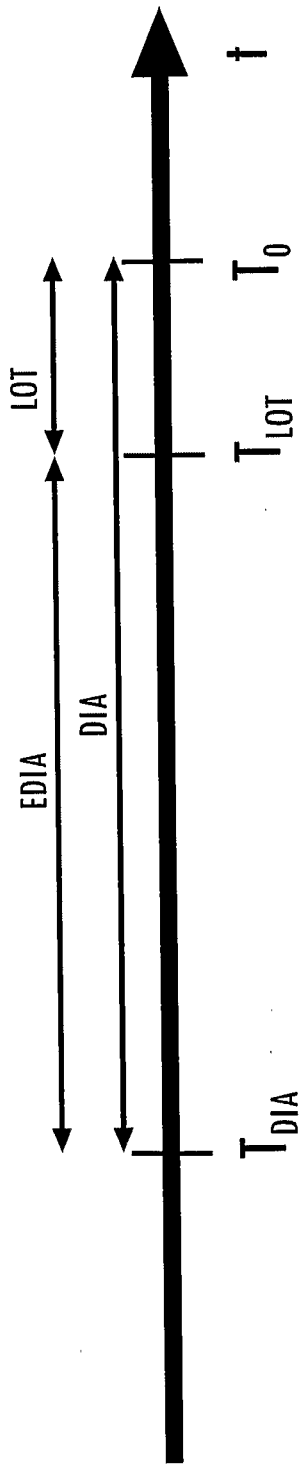

FIG. 4

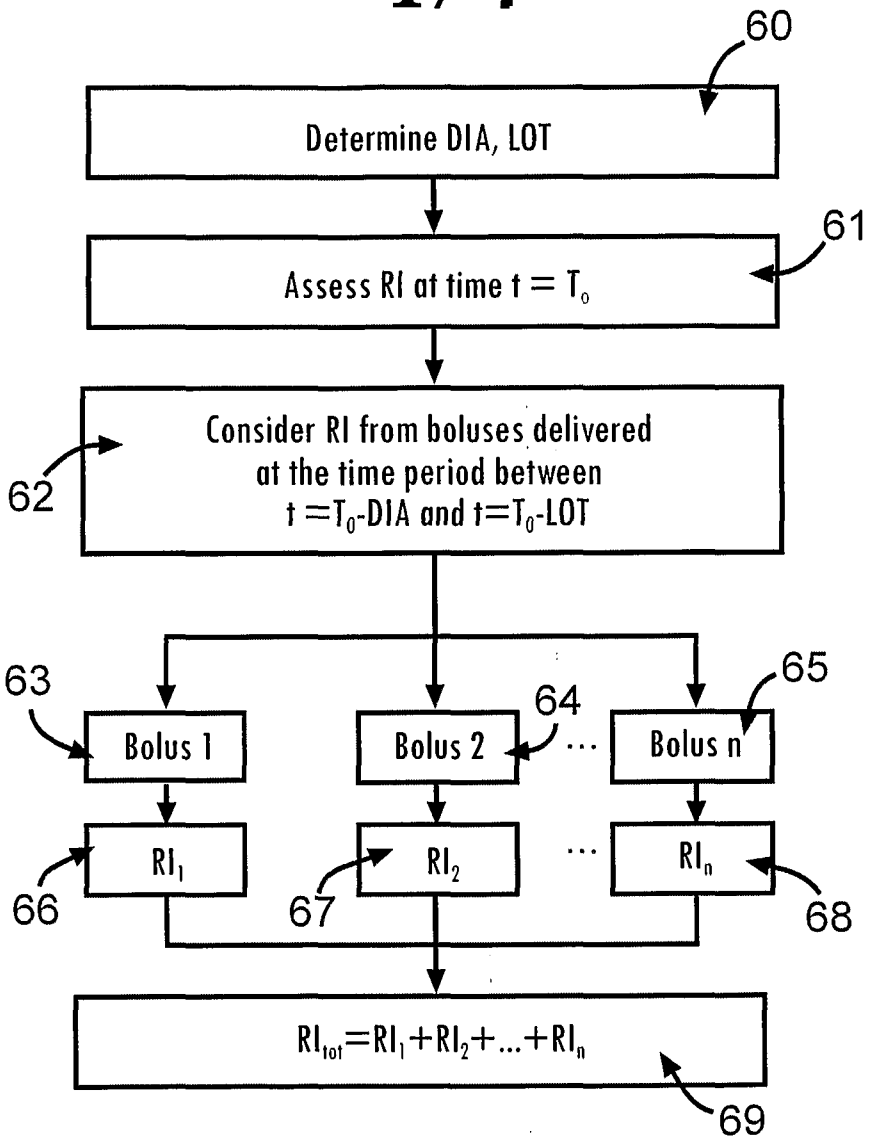
60
Determine DIA, LOT
61
Assess RI at time t = T0
62
Consider RI from boluses delivered at the time period between t =T0-DIA and t=T0-LOT
63
Bolus 1
64
Bolus 2
65
Bolus n
RI1
RI2
RIn
66
67
68
RItot=RI1+RI2+...+RIn
69

FIG. 5a

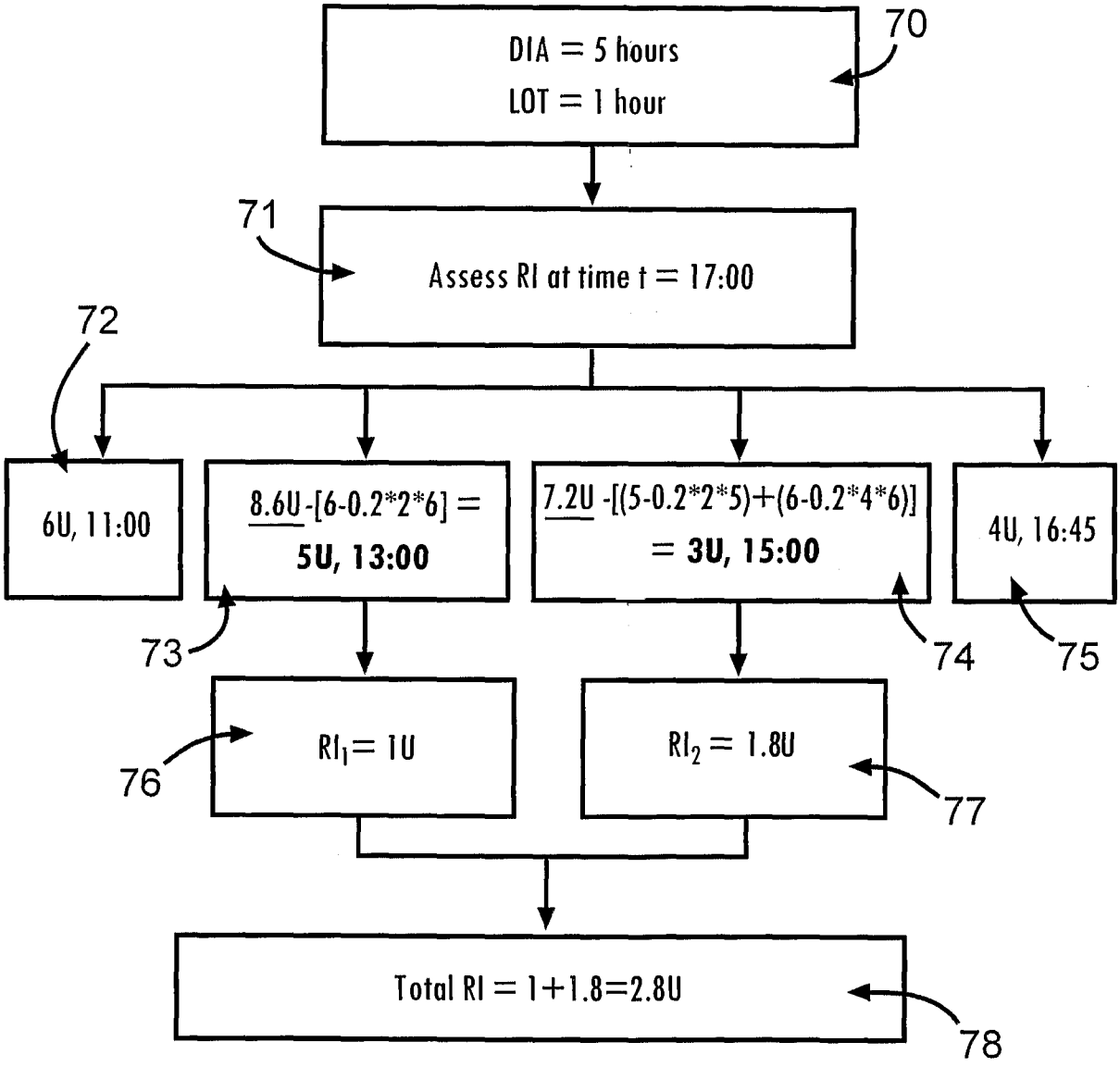
DIA = 5 hours
LOT = 1 hour
70
71
Assess RI at time t = 17:00
72
6U, 11:00
8.6U -[6-0.2*2*6] =
5U, 13:00
7.2U -[(5-0.2*2*5)+(6-0.2*4*6)]
= 3U, 15:00
4U, 16:45
73
74
75
RI1 = 1U
RI2 = 1.8U
76
77
Total RI = 1+1.8=2.8U
78

FIG. 5b

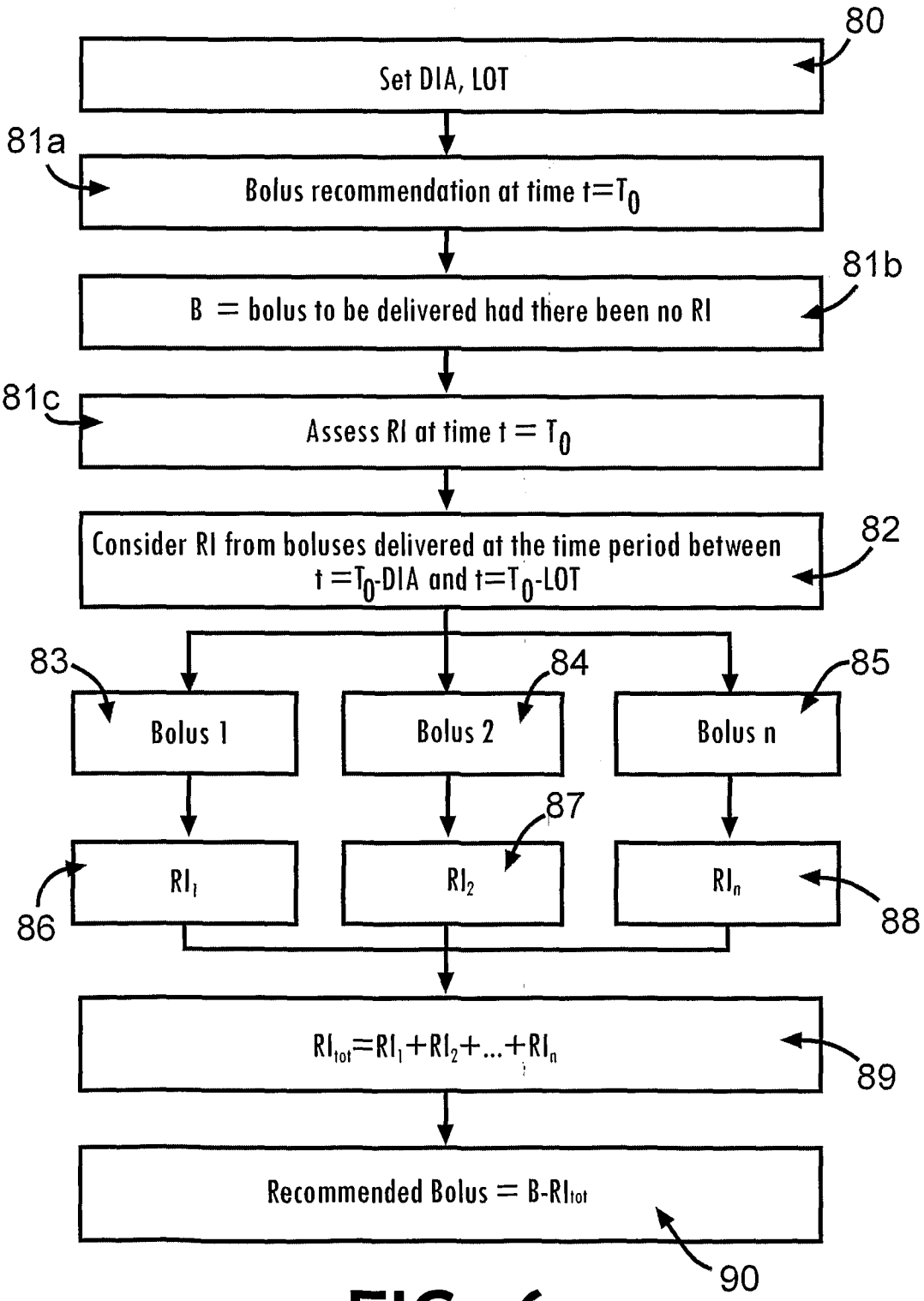
80
Set DIA, LOT
81a
Bolus recommendation at time t=T0
81b
B = bolus to be delivered had there been no RI
81c
Assess RI at time t = T0
82
Consider RI from boluses delivered at the time period between t =T0-DIA and t=T0-LOT
83
84
85
Bolus 1
Bolus 2
Bolus n
87
RI1
RI2
RIn
86
88
RItot=RI1+RI2+...+RIn
89
Recommended Bolus = B-RItot
90

FIG. 6a

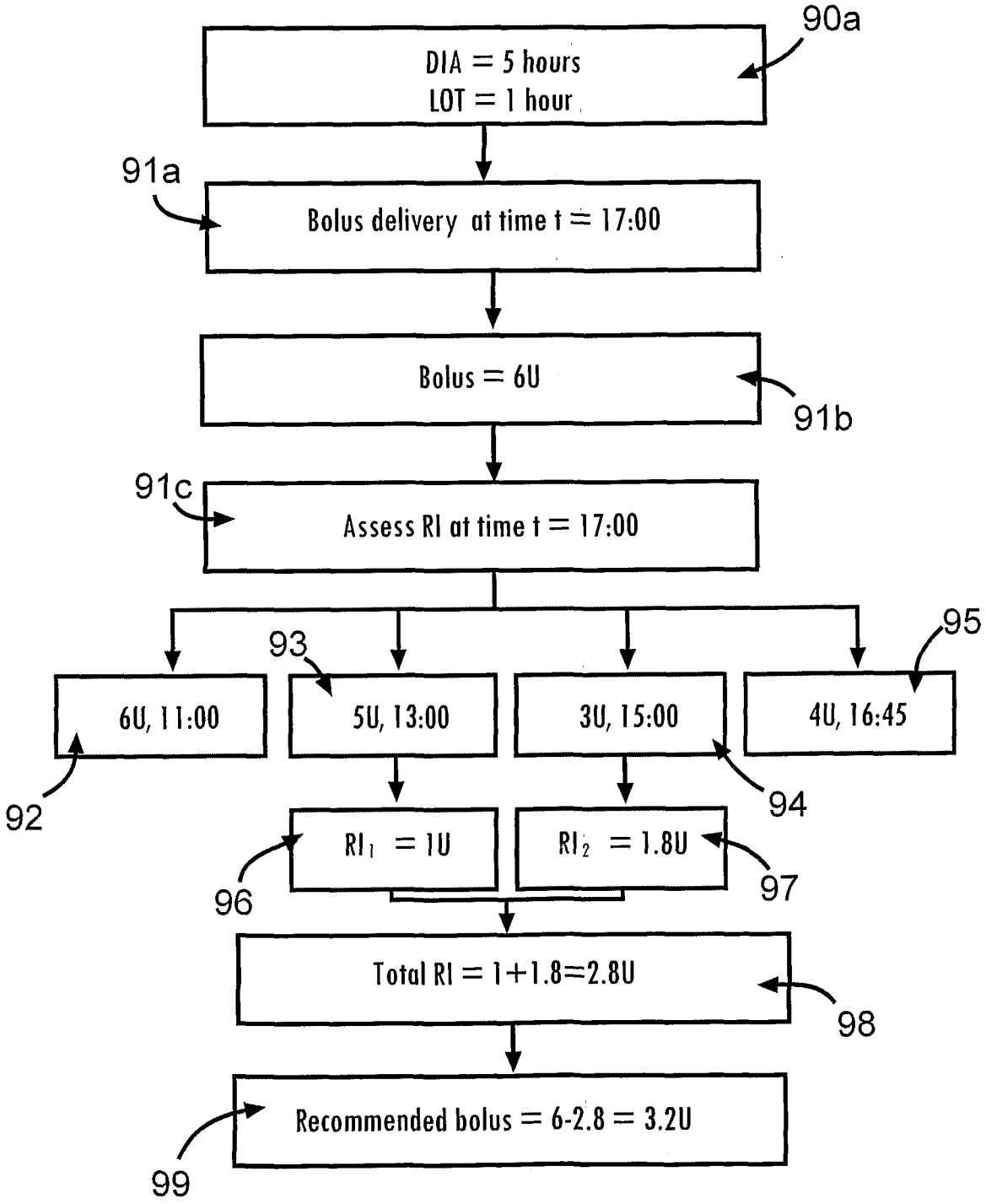
90a
DIA = 5 hours
LOT = 1 hour
91a
Bolus delivery at time t = 17:00
Bolus = 6U
91b
91c
Assess RI at time t = 17:00
93
95
6U, 11:00
5U, 13:00
3U, 15:00
4U, 16:45
92
94
RI1 = 1U
RI2 = 1.8U
96
97
Total RI = 1+1.8=2.8U
98
Recommended bolus = 6-2.8 = 3.2U
99

FIG. 6b

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 10/001 18

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61 M 5/1 72 (201 0.01)
USPC - 604/246
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
604/246

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
A61M5/00, 5/14, 5/142, 5/168 (2010.01)
604/19, 48, 65, 67, 93.01, 131, 151, 174

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Residual insulin, drug, delivery, bolus, pump, Processor, carbohydrates, dose, remote control, wireless, skin adherable cradle, monitor, screen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	US 2008/0172031 A1 (Blomquist) 17 July 2008 (17.07.2008), abstract, para [0004]-[0006], [0027], [0029], [0078], [0133], [0138], [0146]-[0148], [0218], [0274].	1-46
Y	US 2003/0163088 A1 (Blomquist) 28 August 2003 (28.08.2003), para [0162], [0165].	1-46
Y	US 2008/0319384 A1 (Yodfat et al.) 25 December 2008 (25.12.2008), [0019], [0027], [0045], [0064], [0121], [0131]	5-6, 9, 10/(5-6, 9), 20-21, 31-41

J I Further documents are listed in the continuation of Box C |__|

*	Special categories of cited documents	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent but published on or after the international filing date	"Y"	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2010 (21.05.2010)	**08 JUN 2010**

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP- 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL **10/001 18**

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

This international search report has not been established in respect of certain claims under Article I7(2)(a) for the following reasons

1 ☐ Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely

2 **D** Claims Nos
because they relate to parts of the international application that do not comply with the prescnbed requirements to such an extent that no meaningful international search can be carried out, specifically

3 ☒ Claims Nos 47
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees