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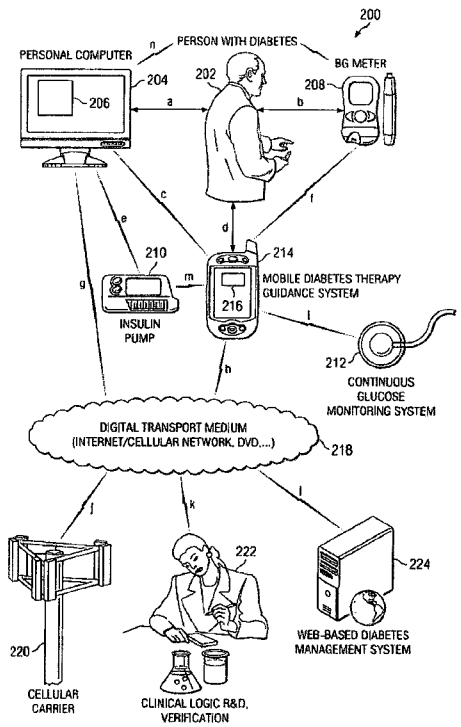

Fig. 4

(57) Abstract: A system (200) which is designed to determine an optimal insulin infusion profile useful as a postprandial blood glucose control for a patient/meal combination is disclosed. The system comprises: a) an input device configured to receive information about a pre-meal measurement of blood glucose concentration, and size and composition of a meal to be consumed; b) a memory which contains additional information about a pre-meal insulin infusion history, a chosen insulin pattern for the postprandial blood glucose control, and a dynamical minimal model having model parameters which are predetermined for the patient/meal combination; c) a processor programmed to use the received information and the additional information to compute automatically the optimal insulin infusion profile by minimizing an objective function, wherein said minimizing of the objective function results in the optimal insulin infusion profile; and d) a display configured to display the optimal insulin infusion profile. Furthermore, a method for the determination of an optimal insulin infusion profile useful as a postprandial blood glucose control for a patient/meal combination is disclosed.

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SYSTEM AND METHOD FOR DETERMINING TIME VARYING OPTIMAL INSULIN PROFILES

FIELD OF THE INVENTION

The present invention relates to a system which is designed to determine an optimal insulin infusion profile useful as a postprandial blood glucose control as well as to a method for determining such a profile.

BACKGROUND OF THE INVENTION

Insulin pumps are thought to improve glucose metabolic control and reduce long-term complications compared to conventional therapy or even compared to Multiple Daily Injections (MDI) therapy. While both Continuous Subcutaneous Insulin Infusion (CSII) and MDI fail to reproduce the physiological delivery of insulin exactly because insulin is disposed into the subcutaneous tissue instead of the hepatic portal vein, CSII allows one to program changes in basal insulin dosage according to anticipated need and thereby reduce blood glucose variability. This is one of the major advantages of CSII. As such, CSII is increasingly used as a means of insulin delivery for those with Type 1 diabetes and in some cases for those with Type 2 diabetes as CSII improves glycemic control compared to other intensified insulin regimens.

Indeed, with both MDI and CSII, controlling blood glucose excursions after meals is the main challenge for the otherwise more controlled metabolism of a person with diabetes. Classical therapy methods based on insulin administration use a single-shot bolus to correct for the meals. This bolus is calculated on the basis of the meal carbohydrate contents.

As alternative to a single-shot bolus, some modern insulin pumps additionally allow the infusion of boli which are distributed over an extended period of time. This is widely considered as favorable for some meals because it allows taking into account the dependency of the carbohydrate absorption speed on the type and size of a meal. However, the appropriate usage of such bolus types is found to be tricky by many persons with diabetes. Furthermore, it is sometimes unclear which of the offered distributions, if any, is appropriate in a specific case. Therefore, the postprandial blood glucose excursion is not

satisfying in many cases, resulting in long-term complications and in some cases in potentially dangerous short-term complications.

It is against the above background that the present invention provides a number of advantages and features over the prior art.

SUMMARY OF THE INVENTION

The present invention is based on the basic insight that, for a specific meal to be eaten by a specific person with diabetes, the optimal insulin infusion profile is dependent on a number of factors, in particular the meal size and composition as well as the person. The disclosed system and method provide an optimal insulin infusion profile that is automatically computed by minimizing an objective function. In this way, an improved control of the postprandial blood glucose is obtained in particular for meals having complex absorption characteristics.

In one aspect, a system is disclosed which is designed to determine an optimal insulin infusion profile tat is useful as a postprandial blood glucose control for a patient/meal combination. The system includes:

a) an input device configured to receive information about a pre-meal measurement of blood glucose concentration, and size and composition of a meal to be consumed;

b) a memory which contains additional information about a pre-meal insulin infusion history, a chosen insulin pattern for the postprandial blood glucose control, and a dynamical minimal model having model parameters which are predetermined for the patient/meal combination;

c) a processor programmed to use the received information and the additional information to compute automatically the optimal insulin infusion profile by minimizing an objective function, wherein said minimizing of the objective function results in the optimal insulin infusion profile; and

d) a display configured to display the optimal insulin infusion profile.

According to the disclosure, which accounts for meal composition and not only meal carbohydrate content, the dosing amount (dosage) and timing sequence of the optimal insulin infusion profile results in a shape or pattern specific to the patient and to the meal

by which insulin may be infused in order to reach a predefined postprandial blood glucose profile.

The system may for example, include a computer desktop tool for a health care provider (HCP) for parameter identification purposes and a handled device for the person with diabetes to implement the insulin profile optimization.

In some embodiments, the system comprises a portable electronic device which is configured to record data concerning the pre-meal insulin infusion history, to measure the pre-meal measurement of blood glucose concentration, to provide the size and composition of a meal to be consumed, and to provide the data to a computing device.

In some embodiments, the system comprises a portable electronic device which is configured to compute automatically the optimized insulin infusion profile by minimizing the objective function. This portable electronic device may, fully or partly, be integral with the portable electronic device as described in the previous paragraph.

In some embodiments, the system includes an insulin pump which is configured to record and provide for pre-meal insulin infusion history and to infuse insulin in accordance with the optimal insulin infusion profile. Besides some aspects and features which will become more readily apparent as the description proceeds, the insulin infusion pump may be designed in a similar way and to further include the same or similar features and capabilities as present state-of-the-art devices, such as the insulin pump which is commercially available from Roche Diagnostics.

In some embodiments, the dynamical minimal model is implemented as a set of linear or nonlinear ordinary differential equations, a set of linear or nonlinear partial differential equations, a set of linear or nonlinear ordinary difference equations, a set of linear or nonlinear partial difference equations, a set of linear or nonlinear stochastic ordinary differential equations, a set of linear or nonlinear stochastic partial differential equations, a set of linear or nonlinear stochastic ordinary difference equations, a set of linear or nonlinear stochastic partial difference equations, an autoregressive moving average model, or a neural network model.

In some embodiments, the dynamical minimal model is implemented as an augmented minimal model, the augmented minimal model comprising a merged insulin absorption and insulin action model.

In a further aspect of the invention a method is provided for the determination of an optimal insulin infusion profile useful as a postprandial blood glucose control for a patient/meal combination. The method includes:

a) measuring and providing a pre-meal measurement of blood glucose concentration;
b) providing size and composition of a meal to be consumed;
c) recording and providing pre-meal insulin infusion history,
d) providing a chosen insulin pattern for the postprandial blood glucose control;
e) providing a dynamic minimal model having model parameters which are predetermined for the patient/meal combination;
f) computing automatically the optimal insulin infusion profile by minimizing an objective function which is defined such that if two different insulin profiles are candidates to compensate for a patient/meal combination, the value of the objective function will be lower for the insulin profile which represents the best postprandial blood glucose control for this patient/meal combination, and said minimizing resulting in the optimal insulin infusion profile; and
g) displaying the optimal insulin infusion profile on an output device.

The method of the present invention builds upon a dynamical model describing the relationship between infused insulin, meal intake rate and blood glucose concentration. The model parameter values are specific for each patient and meal type. They are determined from measured data and a process which minimizes the differences between measurements and model predictions. This process of determining the model parameters is referred as parameters identification in what follows. The optimal insulin infusion profile for each patient and meal is determined using the model, the determined model parameters for this combination meal/patient, pre-meal measurement, meal size, and insulin infusion history before meal time. This process of computing the optimal insulin profile for a patient/meal couple is referred as optimal insulin profile computation in what follows.

In some embodiments, the method includes using a portable electronic device to compute automatically the optimized insulin infusion profile by minimizing the objective function.

In some embodiments, the method includes providing information concerning the absorption speed and carbohydrate content of the meal to be consumed.

In some embodiments, the method includes using an insulin pump to record the pre-meal insulin infusion history.

In some embodiments, the method includes using a portable electronic device for recording data concerning the pre-meal insulin infusion history, for taking the pre-meal measurement of blood glucose concentration, for providing the size and composition of a meal to be consumed, and for providing the data to a computing device.

In some embodiments, the method comprises using a portable electronic device to compute automatically the optimized insulin infusion profile by minimizing an objective function.

In some embodiments, the dynamical minimal model is selected from a set of linear or nonlinear ordinary differential equations, a set of linear or nonlinear partial differential equations, a set of linear or nonlinear ordinary difference equations, a set of linear or nonlinear partial difference equations, a set of linear or nonlinear stochastic ordinary differential equations, a set of linear or nonlinear stochastic partial differential equations, a set of linear or nonlinear stochastic ordinary difference equations, a set of linear or nonlinear stochastic partial difference equations, an autoregressive moving average model, or a neural network model.

In some embodiment the dynamic minimal model is provided as an augmented minimal model, the augmented minimal model comprising a merged insulin absorption and insulin action model.

In some embodiments, the method includes computing a meal-related glucose absorption from a meal related carbohydrate intake rate for use in the objective function.

In some embodiments, the method comprises providing the optimal insulin infusion profile to an insulin pump of the patient.

In some embodiments, the method comprises permitting acceptance of the displayed optimal insulin profile before providing it to the insulin pump.

A method according to the invention may especially be implemented on a system according to the invention. In an analogue way, a system according to the invention may especially be designed to carry out a method according to the invention. For a person skilled in the art, further aspects of a system according to the invention are therefore implicitly disclosed by a method according to the invention, and vice versa.

In the following, exemplary and favorable embodiments are described in more detail with reference to the figures. It should further be noted that while the following description of the invention is mainly made with reference to the method for determining an optimal insulin infusion profile, corresponding embodiments of a system are implicitly disclosed for a person skilled in the art.

EXEMPLARY EMBODIMENTS

In the following, exemplary embodiments of the present invention are described in more detail with reference to the figures. It is in no way intended to limit the invention or its application or uses.

FIG. 1 is a block diagram of an embodiment showing a process according to the present invention which optimize postprandial blood glucose excursions for persons with diabetes via computation of time-varying optimal insulin profiles.

FIG. 2 is a graph of target blood glucose traces for slow and fast meal absorptions.

FIG. 3 is a graph illustrating a discretization of an insulin infusion profile.

FIG. 4 is a diagram of an embodiment showing a therapy delivery system for optimizing therapy for a diabetic individual according to the present invention.

FIG. 5 is a block diagram of a use embodiment illustrating steps to optimize postprandial blood glucose excursions for persons with diabetes via computation of time-varying optimal insulin profiles according to the present invention.

FIG. 6 is a graphical representation of a traditional one-shot bolus compared to distributed bolus therapy according to the present invention for a fast absorbing meal in a clinical trial.

FIG. 7 is a graphical representation of a traditional one-shot bolus compared to distributed bolus therapy according to the present invention for a slow absorbing meal in a clinical trial.

FIG. 8 is a graphical representation of a traditional one-shot bolus therapy compared to an optimized one-shot bolus therapy for a fast absorbing meal according to the present invention in a clinical trial.

FIG. 9 is a graphical representation of a traditional one-shot bolus compared to optimized one-shot bolus therapy according to the present invention for a slow absorbing meal in a clinical trial.

Optimal insulin profile determination for prandial blood glucose excursion optimization

With reference to FIG. 1, an optimal prandial insulin infusion determination method according to one embodiment of the present invention is disclosed. The method helps to determine a time-varying, optimal prandial insulin infusion profile 102 by accounting not only for a patient's pre-meal glucose measurement (i.e., measurements) 130, pre-meal insulin infusion history 126 and meal size and time 124, but also model parameters 116 which are specific to a patient/meal couple. These model parameters for a given patient/meal couple are computed using data collected in the past for the same patient/meal couple. This data collection can be repeated several times (referred as learning 1 to N in FIG. 1) for the same patient/meal couple and contains glucose measurements around the meal 104, insulin infusion history 106 and meal intake history 108. Through use of the present invention, greater control over a patient's blood glucose can be maintained with meal-specific customization of both the insulin dosage and timing sequence (i.e., shape or pattern) of the time-varying, optimal insulin infusion profile 102.

The determination of the optimal insulin infusion profile 102, thus providing optimal distributed boli, includes two main steps: parameters identification 110 based on a predefined model 114, and insulin profile optimization 112. The predefined model 114 is used to describe the relationship between infused insulin, meal intake, and plasma glucose concentrations. Although the structure of the model 114 is similar for all of the patient/meal combinations, the values of the model parameters 116 generally differ for every patient/meal combination. These model parameters 116 for every patient/meal combination are computed for a given patient and meal owing to the procedure of the parameters identification 110.

For example, for a given meal, a given patient is asked by its health care provider (HCP) or decides alone to follow a protocol 118. This protocol 118 describes very precisely what kind of measurements should be performed to make sure that the parameters identification 110 will be successful. The implementation of the protocol 118 can take the shape of an

electronic reminder which makes sure that the patient does not forget a measurement such as, for example, a series of pre-defined alarms on a blood glucose monitor which when activated reminds the patient to comply with the predefined protocol 118.

In another embodiment, for example, the protocol 118 requests that the patient measures his/her blood glucose concentration two times before the meal, at meal time, and six times after the meal. In other embodiments, the number and timing of measurements may be provided which vary greatly, such as once before the meal, and eight times after the meal over a 24 hour period or even continously. Therefore, it is to be appreciated that the predefined protocol 118 is to be used to measure pre-prandial and exactly timed post-prandial situations, to log the associated insulin delivery history, and to analyze basal and bolus needs. Additionally, diary relevant facts like sport, stress, illness, menses, and the size and timing of the meal in question is optionally logged, for example, in an electronic logbook 128 as requested by the protocol 118. In one embodiment, the logbook 128 is used by the HCP to help assess effectiveness of the therapy and relevance of a particular meal as discussed hereafter in a later section.

The predefined protocol 118 is optimized to extract the maximum of information on the status and behavior of the metabolism of the patient out of the additional measurements in combination to an analysis of the available metabolic history from data in the components of the system, e.g. blood glucose meter, diabetes management component, and insulin pump. Accordingly, different protocols may be predefined for this purpose, whereby a proposed protocol in one embodiment may be provided from a diabetes management software component and/or system. In such an embodiment, final selection of the protocol 118 is done by the patient and/or HCP dependant on the seriousness of the meal-related problem, general quality of metabolic control of the patient, and knowledge or estimation of the compliance level of the patient.

After the patient has completed the protocol 118 for a given meal, the previously mentioned glucose measurements as well as the profile of infused insulin over a period (e.g., meal time -l0h, meal time + 6h, or other such periods determined by the HCP) and the information regarding the meal (e.g., meal unique identifier, size, composition, absorption rate, amount of carbohydrates, etc.) are saved, for example, in memory of a blood glucose meter 208 and/or a mobile diabetes therapy guidance system 214 (FIG. 4). In another

embodiment, additional glucose intakes for compensating low BG values are also included in the previously mentioned information. In still other embodiment, the information (i.e., input data) also includes, but is not limited to, blood glucose values coming from spot or continuous measurements performed by the patient during its routine therapy, the insulin infusion history information about meal including, but not limited to, size and composition, and patient demographic data.

The protocol 118 in one embodiment is applied several times for the same meal and/or for different meals between two subsequent visits at the HCP's practice. When visiting the HCP the next time, the HCP will download the saved data and will perform the parameters identification 110 for all meals for which the patient has followed the protocol 118. In this manner, a value set of model parameter 116 is computed for each meal by the parameter identification 110.

The structure of the model 114 in one embodiment is a set of ordinary differential equations (linear or nonlinear). In other embodiments, the model 114 may be a model defined by a set of linear or nonlinear partial differential equations, a set of linear or nonlinear ordinary difference equations, a set of linear or nonlinear partial difference equations, a set of linear or nonlinear stochastic ordinary differential equations, a set of linear or nonlinear stochastic partial differential equations, a set of linear or nonlinear stochastic ordinary difference equations, a set of linear or nonlinear stochastic partial difference equations, an autoregressive moving average model, and/or a neural network model. As those skilled in the art understand how to use the above mentioned questions to model the behavior of a complex system, such as diabetes therapy, no further discussion is provided.

The process of parameter identification 110 computes the model parameters 116. For example, one process suitable for parameter identification 110 is the Maximum A Posteriori Identification Strategy (MAP). In statistics, the method of maximum a posteriori (MAP, or posterior mode) estimation can be used to obtain a point estimate of an unobserved quantity on the basis of empirical data. It is closely related to Fisher's method of maximum likelihood (ML), but employs an augmented optimization objective which incorporates a prior distribution over the quantity one wants to estimate. MAP estimation can therefore be seen as a regularization of ML estimation. (See, e.g., Harold W. Sorenson, *Parameter Estimation: Principles and Problems*, Marcel Dekker Inc., 1980.) In other

embodiments, other methods, which may be used for parameter identification 110, include maximum likelihood estimation, maximum a posteriori estimation with Bayesian priors, least squares fitting, and nonlinear least squares fitting. As parameter identification is well understood by one skilled in the art, no further discussion is provided herein.

Once the model parameters 116 for a patient/meal couple have been computed, these model parameters 116 together with the structure of the model 114 is used to give a predictor of the glucose metabolism again for the given coupled patient/meal. Accordingly, if a patient has followed the protocol 118 for a given meal, and if the parameters identification 110 for the meal has been performed, then it is possible to predict in advance the glucose excursion for this patient and this meal for any given insulin profile, for any given meal size (the meal should be the same but the size can change) and for any given insulin on board.

In one embodiment, the optimal insulin profile computation 112 consists in adjusting the decision variables of the chosen insulin pattern 120 for a particular forecasted meal 124 in order to have a predicted post prandial glucose excursion as close as possible to the chosen postprandial glucose excursion target 112. An objective function is defined to quantify the distance between the predicted postprandial glucose excursion and the target one 112.

By the method, the value of the objective function is minimized by an optimization algorithm using the profiles 120, 122 and the forecasted meal 124 with the model 114, which results in the calculation of optimal insulin profile 102. For example, this insulin pattern could be a piecewise constant function starting one hour before the meal and ending six hours after the meal. The time period of this piecewise constant function can for example be 10 minutes as can be seen in FIG. 3. In this case, the decision variable are the 42 (7 hour pattern horizon times 6 periods per hour) levels of the piecewise constant function at each of its intervals.

It is to be appreciated that the calculation of the optimal insulin infusion profile 102 for the corresponding meal is also dependent on the actual meal size, the pre-prandial measured blood glucose value and insulin dose history, and therefore in each instance a new optimization of the insulin infusion profile for the corresponding meal is done. Further factors e.g. sport, stress, conditions like illness or menses will influence the metabolic process may additionally be taken into account.

The calculated optimal insulin infusion profile 102 is then displayed to the patient such as, for example, on device 208 or 214, or computer 204 (FIG. 4), and if accepted, transferred to an insulin pump e.g., insulin pump 210 (FIG. 4), such that insulin is delivered to the patient according to the dosages and timing aspects of the profile 102 as well as documented in a patient record such as provided on computer 204 of the HCP. Further details concerning the model 114 of the present invention is also provided hereafter.

Augmented Minimal Model

The model 114, which may be represented by a number of different types of mathematical equations as mentioned previously above, is derived from an augmentation to a conventionally known minimal model. One suitable overview of the minimal model can be found in Richard N. Bergman and Jennifer C. Lovejoy, editors, *The Minimal Model Approach and Determinants of Glucose Tolerance*, Louisiana State University Press, 1997. As the minimal model is well understood by those skilled in the art no further details are provided.

In the minimal model, an equation may be used to describe the behavior of the insulin action. The input of this equation is the insulin plasma concentration as the minimal model in most cases has in the prior art been used in conjunction with intra venous glucose tolerance tests (IVGTT). Thus, it was originally thought that to the minimal model, an independent sub-model could be added to account for insulin absorption. In such an arrangement, two systems would be serially connected, one for the insulin absorption part and one for the insulin action, whereby the plasma insulin concentration compartment would then be linked between these two subsystems. However, in such an arrangement the inventors noted that without plasma insulin concentrations measurements, using only the available glucose measurements would not suffice to identify two such independent sub-models. Accordingly, in an embodiment according to the present invention, the two sub-models (insulin absorption and insulin action) are merged resulting in the augmented minimal model 114 according to the present invention. In the augmented minimal model 114 there is no explicit state variable representing the insulin plasma concentration anymore. Instead, in this illustrative embodiment, a linear second order model accounts for

both insulin absorption and insulin action parts of the insulin dependent compartment. Still further details of the augmented minimal model 114 are provided hereafter.

Model Inputs

The list of inputs to the augmented minimal model 114 in one embodiment is given as follows: the term $U_{i;sq}$ is the insulin injected subcutaneously in [mU/min]; and the term $U_{cho,mt}$ is normal carbohydrate intakes (meals) in [g/min]. The subscript *mt* stands for "meal type" such that there are as many inputs as the meal types considered. For purposes of illustration, for example, three meal types *mt* are considered: Fast, Medium and Slow. There are thus, in this example, three corresponding inputs: $U_{cho,fm}$, $U_{cho,mm}$ and $U_{cho,sm}$, respectively.

Model states variables

With the above-given exemplary model inputs, there are nine state variables. The state variables are given as follows: the term Q_{ga} is the glucose amount in the accessible compartment [mmol/kg]; the term X is the insulin action [min^{-1}]; the term X_1 is the first compartment insulin action [min^{-1}]; the term $U_{g,gut,fm}$ is the fast carbohydrate intake rate [g/min]; the term $\acute{U}_{g,gut,fm}$ is the fast carbohydrate intake rate time derivative [g/min/min]; the term $U_{g,gut,mm}$ is the medium carbohydrate intake rate [g/min]; the term $\acute{U}_{g,gut,mm}$ is the medium carbohydrate intake rate time derivative [g/min/min]; the term $U_{g,gut,sm}$ is the slow carbohydrate intake rate [g/min]; and the term $\acute{U}_{g;gut;sm}$ is the slow carbohydrate intake rate time derivative [g/min/min]. However, if six of them characterize the three meal types considered and given the fact that only one meal is considered at a time, it can be stated that the model 114 in this illustrative embodiment is of dimension five.

The model 114 can be decomposed into three sub-models: meal absorption, glucose, and insulin absorption/action. The sub-models are described in what follows in the above given order.

Meal absorption sub-model

The two equations describing the meal absorption sub-model are given by the following Equations 1 and 2:

$$dU_{g,gut,mt}/dt = \acute{U}_{g;gut;mt} \quad (1); \text{ and}$$

$$d\acute{U}g,gut,mt/dt = -2a_{mt}\acute{U}_{g,gut,mt} - a^2_{mt}U_{g,gut,mt} + K_{g,mt}a^2_{mt}U_{cho,mt} \quad (2),$$

wherein $K_{g,mt}$ is the bioavailability for the meal *mt* (either *fm*, *mm*, or *sm* for fast, medium and slow meals respectively), and a_{mt} the inverse of the time-of-maximum appearance rate of glucose in the accessible compartment for the considered meal. $U_{cho,mt}$ is the rate of ingested carbohydrates in [g/min]. There are two linear ordinary differential equations for each meal type in the provided illustrative embodiment. Thus, for the three meal types considered, six equations are provided.

Glucose sub-model

Equation 3 hereafter describes the behavior of the glucose amount in the accessible compartment, which is given as follows:

$$dQ_{ga}/dt = -XQ_{ga} - S_{g,zero}Q_{ga} + U_{endo} + U_{g,gut}(K_{g\rightarrow mmol}/M) \quad (3).$$

The term on the left-hand side of Equation 3 gives the glucose amount variation in [mmol/kg/min] in the accessible compartment. The first term on the right-hand side deals with the insulin dependent glucose uptake. The transport rate is dependent on the glucose concentration in the accessible compartment Q_{ga} and also on the state variable *X* representing the insulin action. The term $S_{g,zero}Q_{ga}$ determines the insulin independent glucose uptake, and the term $S_{g,zero}$ is known as the glucose effectiveness at zero insulin. The term U_{endo} determines the insulin independent endogenous production.

The glucose concentration in [mmol/L] Cga is given by Equation 4:

$$Cga = Q_{ga}/V_{ga} \quad (4),$$

wherein V_{ga} is the accessible volume per body mass.

Insulin absorption/action sub-model

As already mentioned above in a previous section, the insulin absorption sub-model and the insulin action sub-model have been merged into a single sub-model which is used to account for both. In one embodiment, a Laplace representation of the considered linear model (i.e., insulin subsystem) is represented by Equation 5:

$$X/U_{i,sq} = (K_x/M) / (1 + s(1/a_x))^2 \quad (5),$$

wherein X is the insulin action in [min^{-1}], and $U_{i,sq}$ is the insulin infusion rate in [mU/min]. The term K_x/M is the gain of this transfer function and is called the insulin sensitivity in what follows. It must be noticed that it does not correspond to the sensitivity of the original version of the minimal model. The sensitivity in the minimal model defines a relationship between the plasma insulin concentration and the insulin action. This newly defined sensitivity defines a relationship between the insulin action and the subcutaneous insulin infusion rate. The term M is the patient body mass in [kg]. The term a_x is the inverse of the time constant of the insulin absorption/action.

The above Laplace transfer function is equivalent to the two following differential equations:

$$dX/dt = a_x(X_1 - X) \quad (6); \text{and}$$

$$dX_1/dt = a_x(K_x (U_{i,sq}/M) - X_1) \quad (7).$$

In one embodiment, equations 6 and 7 are integrated to determine the initial values for the insulin dependent compartments.

Model parameters

The model parameters are listed and described in what follows: the term M is the body weight in kilograms [kg]; the term V_{ga} is the volume of the accessible compartment per body mass [L/kg]; the term $K_{g,fm}$ is the bioavailability for fast meals [-]; the term $a_{g,fm}$ is an inverse of time constant for fast meals absorption [min^{-1}]; the term $K_{g,mm}$ is the bioavailability for medium meals [-]; the term $a_{g,mm}$ is an inverse of time constant for medium meals absorption [min^{-1}]; the term $K_{g,sm}$ is the bioavailability for slow meals [-];

the term $a_{g,sm}$ is an inverse of time constant for slow meals absorption [min^{-1}]; the term K_x is an insulin sensitivity [kg/mU]; the term $S_{g,zero}$ is glucose effectiveness at zero insulin [min^{-1}]; the term a_x is an inverse of the time constant of the insulin absorption/action [min^{-1}]; and the term *Uendo* is the insulin independent endogenous production [mmol/kg/min]. The terms M and V_{ga} are supposed to be known, the terms $K_{g,mt}$ and $a_{g,mt}$ characterize only the meal absorption part, and remaining parameters are related only to the patient.

The next sections describe the optimization method according to embodiments of the present invention.

Preliminary conditions

In the following example, the parameters of the augmented minimal model 114 are identified for the specific patient/meal combination for which the optimization 112 of the prandial insulin infusion is to be carried out. It is to be appreciated that the parameters in the system implementation embodiment which follows are made available to the software facilitating the optimization performed by the system.

Input data

The input data needed for the optimization 112 are the following: the infused insulin over a pre-defined time interval before the start of the optimized infusion; at least one pre-meal spot measurement of blood glucose concentration provided in the glucose measurements; at least the size and composition of the meal to be consumed provided in the meal information; and the previously identified set of model parameters.

Timing

Before the optimization can take place, it is assumed that the patient has inputted the information regarding the meal that he/she plans to eat. If the patient inputs this information some time before the meal intake, the optimization start time can be some time before the meal intake allowing meal insulin to be infused before the meal. It is well known that for fast absorbing meal, meal insulin should be infused before the meal to avoid high glucose values after the meal. Such an anticipation is possible with the current embodiment as soon as the patient inputs the information before the meal. However, if for some practical or

safety reasons, the patient does not want meal insulin to be infused before meal time, the optimization start time is simply the meal intake time.

Initial conditions

To carry out the optimization 112, the states of the model at the optimization start time have to be computed. This process is often referred as initial conditions computation. These initial conditions are derived from the input data as follows: the initial blood glucose value is given by the measured pre-meal value (i.e., pre-meal glucose measurement 130); the initial values for the insulin dependent compartments are computed by integration of the insulin sub-model equations (i.e., Equations 6 and 7) up to the optimization start time point with the pre-meal insulin infusion as input (i.e., infused insulin 126). In addition, all initial values for the meal related compartments are set to zero as it is assumed that the previous meal has been absorbed completely at the intake time of the meal of interest. In other words, the glucose coming from the meal is set to zero at t=0. Accordingly, a meal related carbohydrate intake rate starts at t=0, and the meal related glucose absorption is computed from this rate.

Objective function

The insulin infusion profile 102, which corresponds to optimal postprandial blood glucose control, is obtained by minimization of the following objective function (Equation 8) with respect to the insulin infusion:

$$F(u(t)) = \int_{t_{sstart}}^{t_{end}} dt\left\{\left[G_M(t,\Theta,u(t)) - G_T(t)\right]^2\right\} + \alpha\left\{\int_{t_{start}}^{t_{end}} dt\left[u(t) - u_{init}(t)\right]\right\}^2 \qquad (8)$$

The above symbols of equation 8 have the following meaning: t_{start} start time point for optimization (referred as optimization start point in what precedes); t_{end} end time point for optimization; θ is the set of model parameters; u(t) insulin infusion; $G_M(t, \Theta, u(t))$ blood glucose trace predicted by the model; $G_T(t)$ target blood glucose trace 122; α weight factor; $u_{init}(t)$ insulin amount infused to achieve postprandial blood glucose control during the last level. t_{start} can be 1 hour before the meal for which the patient would like to optimize the

prandial glucose excursion. Such a t_{start} allows meal insulin to be infused before the meal intake. t_{end} can be 6 hours after the meal.

Target blood glucose traces

From a mathematical point of view, it is highly unlikely to optimize such a continuous profile, as the dimension of the problem is infinite. Instead the insulin infusion profile 102 is characterized in one embodiment by a piecewise constant function, whereby each level of the function is a decision variable, i.e., a variable that is determined and/or modified during the optionmization. Accordingly, the piecewise constant function can be as close as possible to a continuous function as soon as the sampling period of this function is small enough. The target blood glucose profile (i.e., profile 122) mentioned above depends on the meal type. The reason therefore is the fact that, given specific meal absorption characteristics, the same target profile cannot be expected to be targeted for all meals. To account for such differences, two target blood glucose profiles, representing fast and slow absorbing meals for postprandial blood glucose control for type 1 diabetics, are show graphically by FIG. 2. The corresponding numeric values for these target blood glucose profiles are indicated in Table 1.

Table 1 - Numeric values for the target blood glucose profiles.

t[min]	BG_fast[mmol/l]	t[min]	BG_slow[mmol/l]
-180	5.5	-180	5.5
-150	5.5	-150	5.5
-120	5.5	-120	5.5
-90	5.5	-90	5.5
-60	5.5	-60	5.5
-30	5.5	-30	5.5
0	5.5	0	5.5
30	8	30	6.9
60	10	60	8.22
90	9.7	90	9.4
120	9	120	10
150	8.2	150	9.35
180	7.3	180	8.2
210	6.2	210	6.75
240	5.5	240	5.5
270	5.5	270	5.5
300	5.5	300	5.5

330	5.5	330	5.5
360	5.5	360	5.5
390	5.5	390	5.5
420	5.5	420	5.5

It is to be appreciated that the maximum blood glucose values for fast and slow absorbing meals can be different as well as blood glucose target profiles being multimodal. Therefore, according to an alternative embodiment, the invention may be modified such that during an adaptive learning phase, the average blood glucose profile observed while the patient follows the protocol 118 could be used as the departure point for the definition of the target profile.

Insulin infusion profile discretization

A generic insulin infusion profile to be optimized is defined as a discrete profile $u(t_i)$ with the following parameters: resolution, $\Delta t_i = t_i - t_{i-1}$; duration of infusion, $\Delta T = t_{final} - t_{start}$; and anticipation of infusion with respect to meal intake. The anticipation with respect to meal intake is needed due to the discrepancy between the delay in the insulin action and the increase of blood glucose concentration after meal intake. Every element $u_i = u(t_i)$ represents an insulin bolus delivered during the time interval $[t_{i-1}, t_i]$. The amounts of the boli u_i are varied during the optimization process. FIG. 3 illustrates the discretization of one embodiment of an insulin infusion profile. In this illustrated example, the infusion duration is 420 minutes and there is an anticipation of 1 hour of the insulin infusion with respect to meal intake. The infusion resolution is 10 minutes in the illustrated embodiment, but in other embodiments, other resolutions and durations may be used.

Optimization Method

The problem described by Equation 8 is solved by constrained nonlinear optimizations in one embodiment. The optimization is carried out using the sequential quadratic programming described in the reference entitled *Optimization Toolbox, For Use with Matlab, User's Guide, Version 2*, The MathWorks, Inc., 2000. Constrained nonlinear optimization problems are composed of nonlinear objective functions and may be subject to linear and nonlinear constraints. Active-set sequential quadratic programming (SQP) is

used for general nonlinear optimization. Quadratic programming problems involve minimizing a multivariate quadratic function subject to linear equality and inequality constraints. Active set minimizes the objective at each iteration over the active set (a subset of the constraints that are locally active) until it reaches a solution. In other embodiments, other software packages in addition to Matlab, such as for example, NPSOL, NLPQL, OPSYC, and OPTIMA, may also be used to solve the problem described by Equation 8 using SQP. A system embodiment employing a method in accordance with the invention is now described hereafter. In addition, the objective function may also be minimized in other embodiments using means such as, for example, global optimization, genetic algorithms, simulated annealing, linear programming, stochastic optimization, and calculus of variations. As such minimizing means are well known to those skilled in the art, no further discussion is provided thereon.

FIG. 4 illustrates an exemplary system 200 in accordance with the invention which may be used to implement a method according to the present invention. Typically, a person with diabetes (PWD) 202 will have multiple devices and software to help with the management of their disease. For example, it is assumed that the PWD 202 or the health care provider (HCP) will have a personal computer 204 running software 206 for tracking health status which includes blood glucose (BG) measurements and insulin dosing, a blood glucose (BG) meter 208 (spot measuring type) for intermittent measurements, an insulin pump 210 for delivering insulin subcutaneously, and optionally a continuous glucose monitoring system 212 for monitoring blood glucose frequently, which may be subcutaneous and/or cutaneous, and/or a mobile diabetes therapy guidance system 214 running therapy guidance software 216, such as implemented on a mobile phone, a personal digital assistance, a notebook computer, and the like. As shown by FIG. 4 and in one embodiment, the PWD 202 (and/or HCP) interacts (arrows a, b, d) with the personal computer 204, the bG meter 208, and optionally, the therapy guidance system 214.

For the purpose of this system example and in other embodiments, the insulin pump 210 and the continuous monitoring system 212 is also used by the PWD 202 and configured through the software 206 of the personal computer 204, therapy guidance software 216 of the therapy guidance system 214, and/or the BG meter 208. For this system example and in other embodiments, devices 204, 208, 210, 212, and 214 contain operating

software/firmware that embodies logic to facilitate the PWD 202 to manage his or her diabetes care therapy. It is also to be appreciated that the devices 204, 208, 210, 212, and 214 communicate (arrows e, c, f, and i) with each other in one form or another via wired or wireless data communications (infrared, Blue tooth, RF, etc.) as is known.

In another embodiment of the invention, the therapy guidance system 214 contains logic, for example, embodied in the software 216 which advises the PWD 202 on proper insulin dosing, such as, for example as computed by a method in accordance with the present invnetion. In such an embodiment, the method 100 embodied in the software 216 optimizes the insulin infusion profile 102 (FIG. 1) wherein insulin pump 210 is instructed (arrow m) by the therapy guidance system 214 to infuse insulin according to the profile 102. Additionally, the therapy guidance software 216 may offer diary and documentation functions (e.g., via the electronic logbook 128), which can implement and manage a list of supported meals, and which can implement the therapy protocol 118 to ensure compliance and successful results of the method in accordance with the present invention.

Optionally, data to and from devices 204, 214 may be provided (arrows g, h) to a web-based diabetes management system 224 via a digital transport medium 218 (arrow l), such as provided in one embodiment as a public network (i.e., the Internet), or via a cellular carrier 220 (arrow J). Such an embodiment is useful in providing updates to and from clinicians and medical health care providers 222 concerning the health condition of the PWD 202, therapy actions and/or recommendations, and/or updates to the software implementing the method 100, such as changes/refinement to the equations used to compute the optimized insulin infusion profile 102. It is to be appreciated that other embodiments of this invention in the environment of FIG. 4 are possible, which is by no means exhaustive. A use case example is now provided hereafter.

Use Case Example

With reference made to FIGS. 1, 4 and 5, a use case example according to an embodiment of the present invention is disclosed. In this use case example, the PWD 202 uses portions of the system 200, which in one embodiment comprises the insulin pump 210, the blood glucose meter 208, and one of the devices 204, 214 implementing the method of the present invention, via software application 206, 216, respectively. As illustrated and in one

embodiment, data concerning the amount of infused insulin 106 taken over a period of time is provided from the insulin pump 112 to one of the diabetes management devices 204, 214, running software 206, 216 providing the method 100. In this embodiment, reference hereafter is made to device 204, however, it is understood that this example applies equally to device 214. Also as illustrated and in one embodiment, data concerning the glucose measurements 104 taken over a period of time is also provided from the blood glucose meter 208 to device 204.

Data concerning the meal information 110 in one embodiment is inputted directed to the device 204 via an input interface such as a keyboard, stylus, touch screen, touchpad, track ball, voice recognition, etc., or in another embodiment captured via the insulin pump 112 and/or the blood glucose meter 116, or combinations thereof, and then inputted to device 204 and stored thereon in memory as data. Such data is then used by the method, implemented on the device 204, to analyze meal dependant absorption speed for the corresponding meal, identify corresponding model parameters 116 of the predefined mathematical model 114 based on current knowledge about human physiology, and calculates an optimized insulin infusion profile 102 for the corresponding meal as detailed previously above. In other embodiments the data may be downloaded to device 204 or device 214, whereby method is performed thereon resulting in the optimized insulin infusion profile 102 being displayed thereon.

With the above described system embodiment, the following steps are then carried at in this use case example with reference mainly to FIG. 5. In step 150, during a first visit once the above-mentioned tools are available, the PWD 202 together with a health care provider (HCP) 155 identify a list of meals whose control have been noticed to be bad in the last months. The HCP 155 then recommends that the PWD 202 follow a learning phase for one or more times for these identified meals. The HCP 155 then uploads a protocol 118 from the diabetes management software 206 running on the device 204 to the therapy guidance system 214, which is used by the software 216.

Next in step 160, the PWD 202 goes on with life following the protocol 118, and at the appropriate times will indicate to the software 216 of the guidance system 214 that he/she is about to eat a meal 165 which has been previously been identified as problematic. The PWD 202 at this point will apply the classical therapy for this meal but will tell the

software 216 to learn about the meal 165 using an adaptive learning phase 168. The software 216 implements a reminder, such as previously described above, that helps the PWD 202 follow the measuring protocol 118. The patient follows the protocol 118 and the measurements together with meal information about history of infused insulin are saved in memory of the device 204 by the software 216. The PWD 202 may repeat the learning phase 168 for the same meal or for any other meals that he/she was told by the HCP that are problematic or also for new meals believed that could be problematic such that a number of data points concerning the meal is available for analysis.

Next in step 170, the PWD 202 again visits the HCP 155. During this second (or latter) visit, the HCP 155 downloads the data 175 saved after all of the learning phases 168 that the PWD 202 has gone through since the last visit. In one embodiment, the data 175 contains information concerning the glucose measurements 104, the infused insulin 106, the meal information 108, and optionally information contained in the logbook 128 (FIG. 1). The HCP 155 then uses the software 206 to perform the parameters identification 110 for all of the meals concerned. The HCP 155 optionally runs a validation to make sure that the identified parameters 110 will compute reasonable boli, such as in a simulation running on device 204. The identified and optionally validated model parameters 110 are then uploaded to the device 214 for use by the software 216.

Next, in step 180, the PWD 202 goes on with his/her life, and if it happens that he/she is again confronted with a meal for which the PWD 202 has gone through the learning phase 168 in the past, the PWD 202 is now given the opportunity to compute the optimized insulin infusion profile 102 in accordance with the present invention which provides an optimal distributed bolus for that meal. It is to be appreciated that the PWD 202 still has the freedom to apply the classical therapy. If the PWD 202 decides to have an optimal distributed bolus controlled by the optimized insulin infusion profile 102, then the insulin profile optimization 112 is carried out using the identified model parameters 110 on the device 214.

The computed optimal boli is then displayed on a display to the PWD 202. In one embodiment, the PWD 202 is given the option to modify manually this profile 202 and asks for validation. Once the profile 202 has been accepted, it is then sent to the insulin pump

210 to be infused in step 190. Experimental results obtained with the method 100 are exemplified by the data shown in FIGS. 6 and 7.

It should be noted that in this exemplary use case some steps, in particular those steps which are required for the parameter identification, are carried out on the device 204 which typically is a computer, such as a PC, used by the HCP. Other steps, in particular those steps which are required for the optimization of the insulin infusion profile 102, are carried out on device 214 which is a portable guidance system used by the PwD. This allows the PwD to carry out the optimization each time he or she wants to eat a meal for which a corresponding parameter set has been identified, thus determining an optimal infusion profile for the specific situation, considering factors such as the insulin infusion history, the glucose history, and the meal size which may be different each time.

Experimental Results

FIG. 6 shows the comparison of glucose traces and insulin infusions obtained with the traditional one-shot bolus versus that obtained when using distributed insulin infusions according to a computed insulin infusion profile 102 in conjunction with the intake of a fast meal. For comparison purposes, the predicted glucose trace is shown as well as the targeted glucose profile. When using the optimized insulin distribution it is obvious that no hypoglycemic episode occurs around five hours after meal intake as this was the case when the data used for identification were measured.

FIG. 7 shows the corresponding data for a slow absorbing meal. Based on the model, a more aggressive insulin therapy is recommended, thus trying to catch up with the large glucose values, which still show up in the curve used for the model identification. A hypoglycemic episode occurred at 4.5h after meal intake in this case. Although the shape of the measured bolus profile 3, obtained when using the optimized insulin distribution, matches the shapes of the predicted and targeted profiles very well it is shifted towards lower glucose values. As for the previous example, the different factors which are currently not taken into consideration as well as the model limitations should explain the observed differences between measurement and prediction. Accordingly, a conservative approach should be adopted in such cases which will minimize the risk for patients by targeting bolus patterns which are dose to current therapy practices.

It is to be appreciated that the optimized insulin infusion profile 102 is not restricted to a particular bolus shape. The optimized insulin infusion profile 102 can be of arbitrary shape; in particular, the method 100 can be applied to the optimization of one-shot, dual or multi-wave boluses, too. Examples for applications to the optimization of one-shot boluses are shown in FIGS. 8 and 9. The identification step is not modified by this constraint while the bolus shape has to be constrained to a single bolus during the optimization step. Only the amount of insulin to be infused is optimized in this particular solution.

While discussed here with reference to insulin pumps, the invention may be used in a syringe and pen therapy too in a natural way. For such therapy approaches the bolus shape is given by a series of single shot boluses. In order to apply the method, different insulin absorption models for long-acting insulin used for basal needs and short-acting insulin used for meal boluses have to be taken into consideration. Dedicated data are needed for the parameter identification describing the absorption for these particular insulin preparations. Once this has been achieved, the optimization step has to be modified to take into account the particular shape of the insulin infusion. In this embodiment, insulin infusions are restrained to series of pulses whose dosing amounts as well as timing sequence are optimized.

Finally, it is to be appreciated that in terms of activity, insulins are distinguished by their onset, peak, and duration and come in very rapid-acting (e.g., insulin lispro, insulin aspart), rapid-acting (e.g., regular, velosulin), intermediate-acting (e.g., NPH, lente, ultralente), long-acting (e.g., ultralente, insulin glargine), and pre-mixed (e.g., 70/30, 50/50, 75/25) varieties. In order to take into account what insulin is being used, the insulin absorption characteristics are determined from available knowledge and measured data. Once these are known and expressed as corresponding model parameters, optimized doses and the infusion timing sequences for any such or arbitrary insulin formulations can be determined in accordance with the present invention.

Finally, although this application relates to an insulin profile, it is contemplated that the principles disclosed herein may be used for any medication including oral medications in still further embodiments of the present invention.

It is noted that terms like "preferably", "commonly", and "typically" are not utilized herein to limit the scope of the claimed invention or to imply that certain features are critical,

essential, or even important to the structure or function of the claimed invention. Rather, these terms are merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the present invention.

Having described the invention in detail and by reference to specific embodiments thereof, it will be apparent that modification and variations are possible without departing from the scope of the invention defined in the appended claims. More specifically, although some aspects of the present invention are identified herein as preferred or particularly advantageous, it is contemplated that the present invention is not necessarily limited to these preferred aspects of the invention.

Claims

1. A system (200) which is designed to determine an optimal insulin infusion profile useful as a postprandial blood glucose control for a patient/meal combination, said system comprising:
   e) an input device configured to receive information about a pre-meal measurement of blood glucose concentration, and size and composition of a meal to be consumed;
   f) a memory which contains additional information about a pre-meal insulin infusion history, a chosen insulin pattern for the postprandial blood glucose control, and a dynamical minimal model having model parameters which are predetermined for the patient/meal combination;
   g) a processor programmed to use the received information and the additional information to compute automatically the optimal insulin infusion profile by minimizing an objective function, wherein said minimizing of the objective function results in the optimal insulin infusion profile; and
   h) a display configured to display the optimal insulin infusion profile.

2. The system (200) according Claim 1, comprising a portable electronic device (214) which is configured to record data concerning the pre-meal insulin infusion history, measuring the pre-meal measurement of blood glucose concentration, providing the size and composition of a meal to be consumed, and providing the data to a computing device.

3. The system according either of the preceding claims, comprising a portable electronic device (214) which is configured to compute automatically the optimized insulin infusion profile by minimizing the objective function.

4. The system (200) according either of the preceding claims, comprising an insulin pump (210) which is configured to record and provide for pre-meal insulin infusion history and to infuse insulin in accordance with the optimal insulin infusion profile.

5. The system (200) according either of the preceding claims, wherein the dynamical minimal model is implemented as an augmented minimal model, the augmented minimal model comprising a merged insulin absorption and insulin action model.

6. A method for the determination of an optimal insulin infusion profile useful as a postprandial blood glucose control for a patient/meal combination, said method comprising:

h) measuring and providing a pre-meal measurement of blood glucose concentration;

i) providing size and composition of a meal to be consumed;

j) recording and providing pre-meal insulin infusion history,

k) providing a chosen insulin pattern for the postprandial blood glucose control;

l) providing a dynamical minimal model having model parameters which are predetermined for the patient/meal combination;

m) computing automatically the optimal insulin infusion profile by minimizing an objective function which is defined such that if two different insulin profiles are candidates to compensate for a patient/meal combination, the value of the objective function will be lower for the insulin profile which represents the best postprandial blood glucose control for this patient/meal combination, and said minimizing resulting in the optimal insulin infusion profile; and

n) displaying the optimal insulin infusion profile on an output device (214).

7. The method of claim 6, further comprising using a portable electronic device (214) to compute automatically the optimized insulin infusion profile by minimizing the objective function.

8. The method of claim 6 or claim 7, further comprising providing information concerning the absorption speed and carbohydrate content of the meal to be consumed.

9. The method of either of claim 6 to claim 8, further comprising using an insulin pump (210) to record the pre-meal insulin infusion history.

10. The method of either of claim 6 to claim 9, further comprising using a portable electronic device (214) for recording data concerning the pre-meal insulin infusion history, measuring the pre-meal measurement of blood glucose concentration, providing the size and composition of a meal to be consumed, and providing the data to a computing device.

11. The method of either of claim 6 to claim 10, further comprising using a portable electronic device (214) to compute automatically the optimized insulin infusion profile by minimizing the objective function.

12. The method of claim 6 to claim 11, wherein the dynamic minimal model is provided as an augmented minimal model, the augmented minimal model comprising a merged insulin absorption and insulin action model.

13. The method of either of claim 6 to 12, wherein a meal-related glucose absorption is computed from a meal related carbohydrate intake rate for use in the objective function.

14. The method of either of the claim 6 to 13, wherein the optimal insulin infusion profile is provided to an insulin pump (210) of the patient.

15. The method of claim 14, comprising permitting acceptance of the displayed optimal insulin profile before providing it to the insulin pump (210).

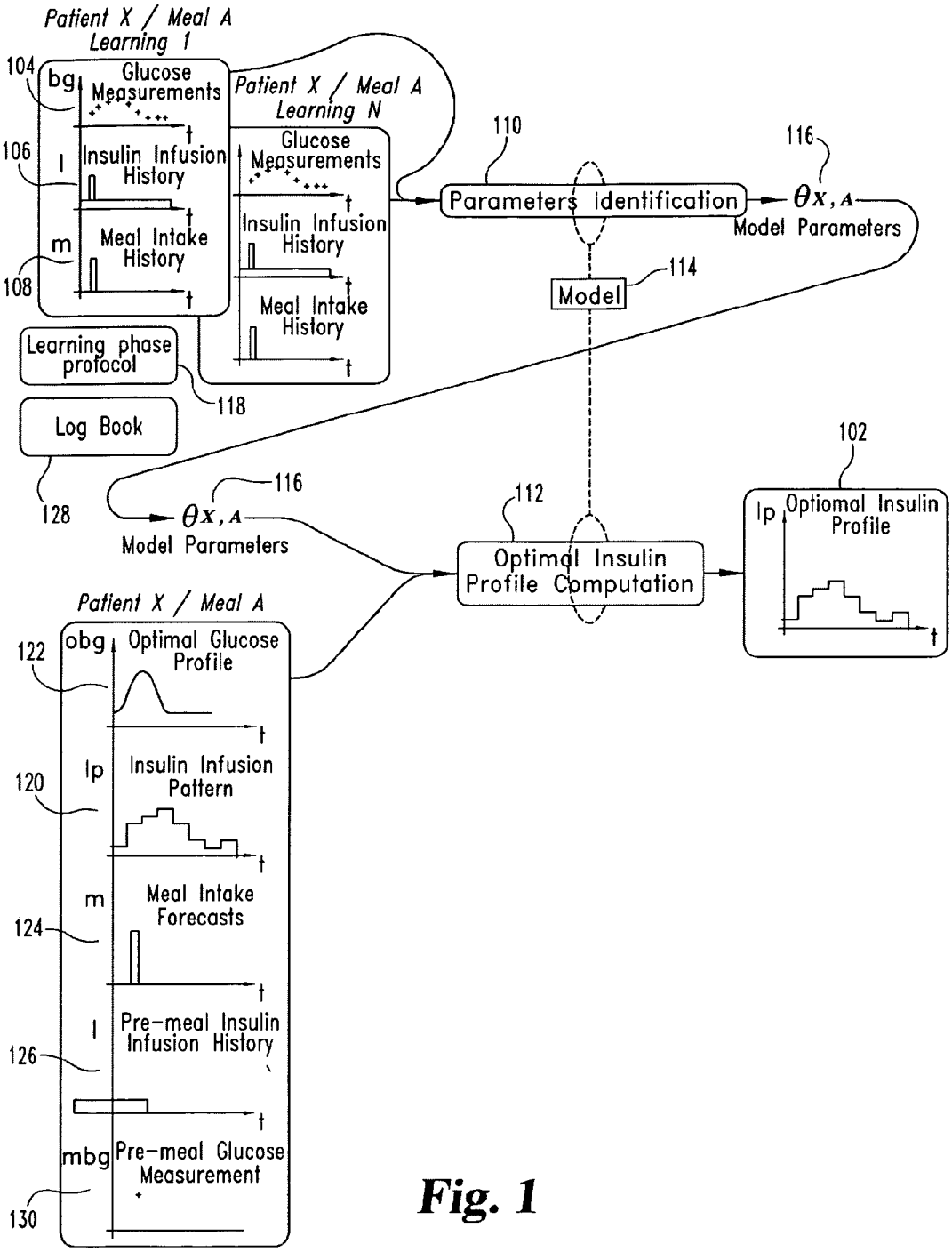
Patient X / Meal A
Learning 1
104
bg
Glucose Measurements
106
I
Insulin Infusion History
m
Meal Intake History
108
Patient X / Meal A
Learning N
Glucose Measurements
Insulin Infusion History
Meal Intake History
110
Parameters Identification
116
$\theta_{X,A}$
Model Parameters
114
Model
Learning phase protocol
118
Log Book
128
102
Ip
Optiomal Insulin Profile
116
$\theta_{X,A}$
Model Parameters
112
Optimal Insulin Profile Computation
Patient X / Meal A
122
obg
Optimal Glucose Profile
120
Ip
Insulin Infusion Pattern
m
Meal Intake Forecasts
124
I
Pre-meal Insulin Infusion History
126
mbg
Pre-meal Glucose Measurement
130

Fig. 1

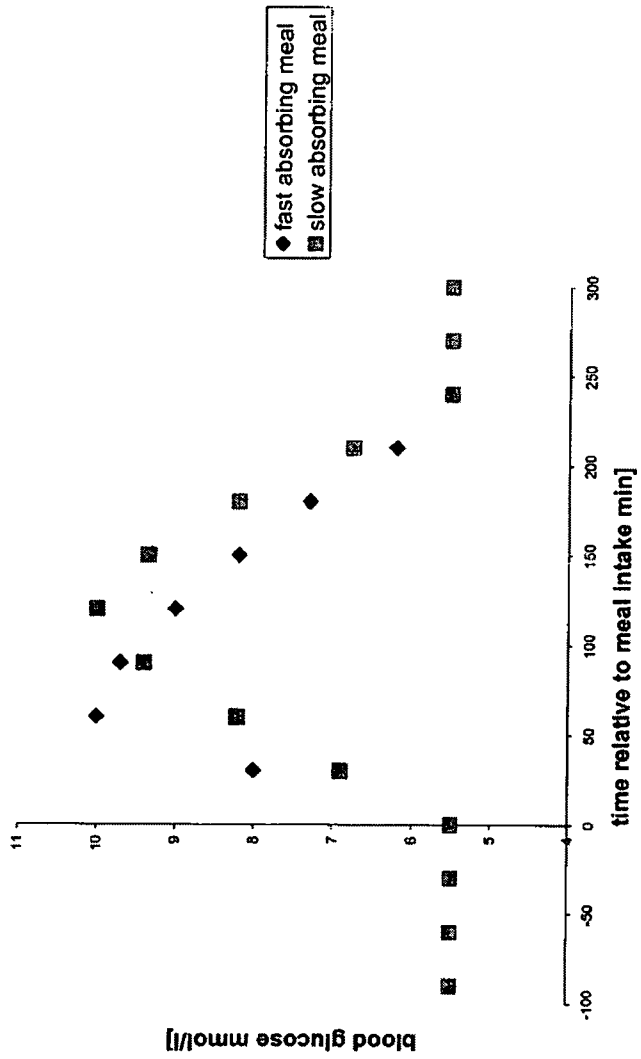
fast absorbing meal
slow absorbing meal
blood glucose mmol/l]
time relative to meal intake min]
11
10
9
8
7
6
5
-100
-50
0
50
100
150
200
250
300

FIG. 2

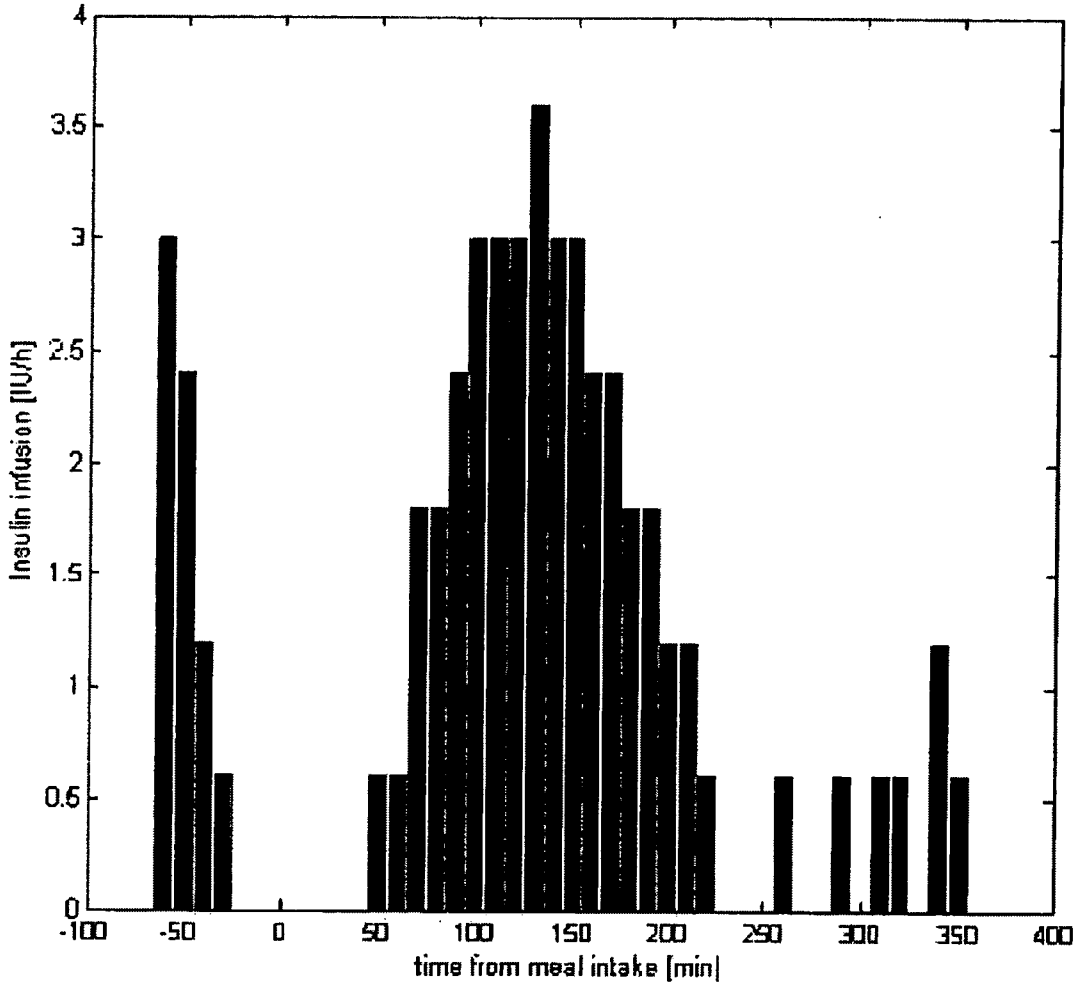
Insulin infusion [IU/h]
time from meal intake [min]
4
3.5
3
2.5
2
1.5
1
0.5
0
-100
-50
0
50
100
150
200
250
300
350
400

FIG. 3

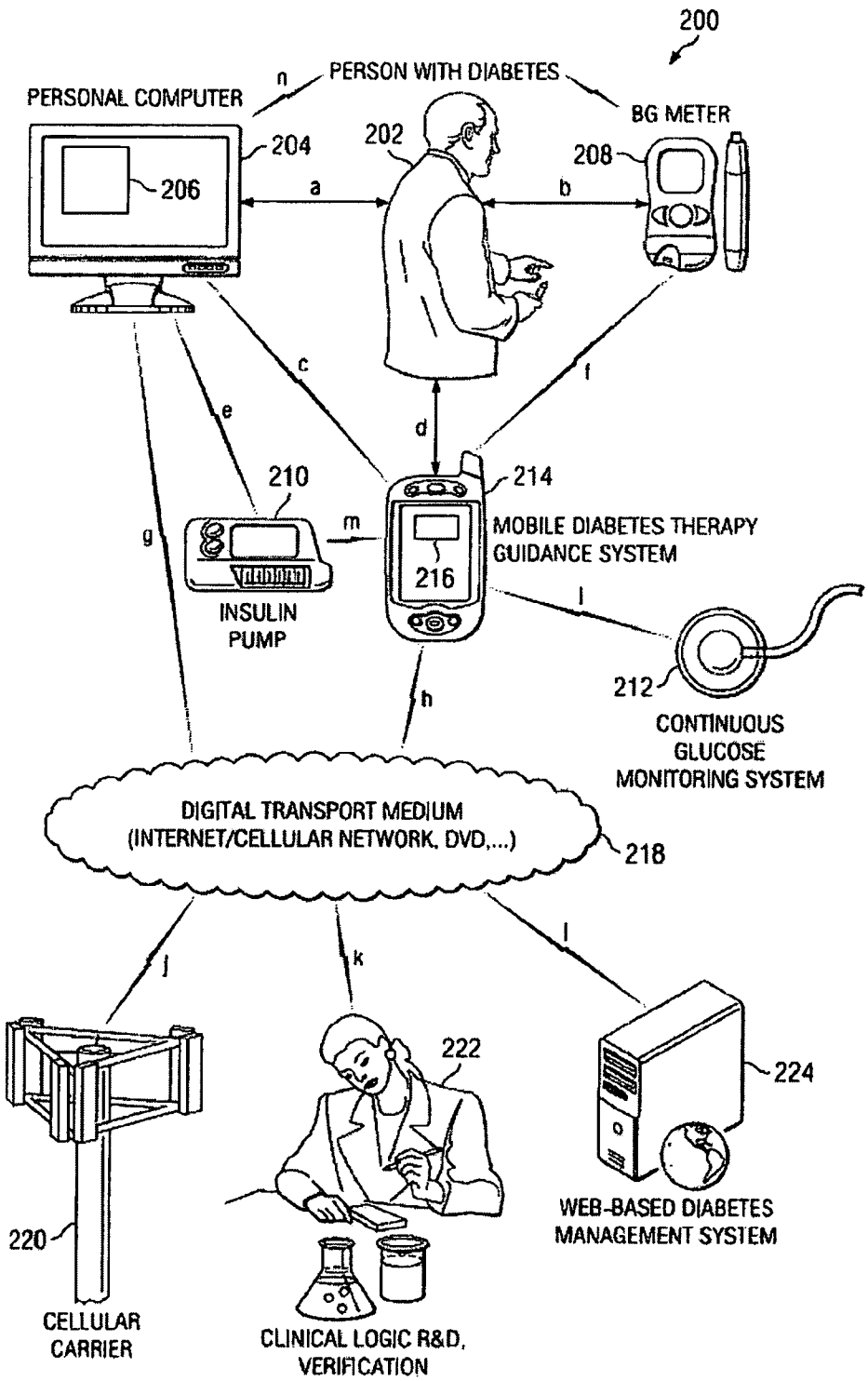
200
PERSON WITH DIABETES
n
PERSONAL COMPUTER
204
206
202
BG METER
208
a
b
c
d
e
f
210
214
INSULIN PUMP
m
g
216
MOBILE DIABETES THERAPY GUIDANCE SYSTEM
l
212
CONTINUOUS GLUCOSE MONITORING SYSTEM
h
DIGITAL TRANSPORT MEDIUM (INTERNET/CELLULAR NETWORK, DVD,...)
218
j
k
l
220
CELLULAR CARRIER
222
CLINICAL LOGIC R&D, VERIFICATION
224
WEB-BASED DIABETES MANAGEMENT SYSTEM

Fig. 4

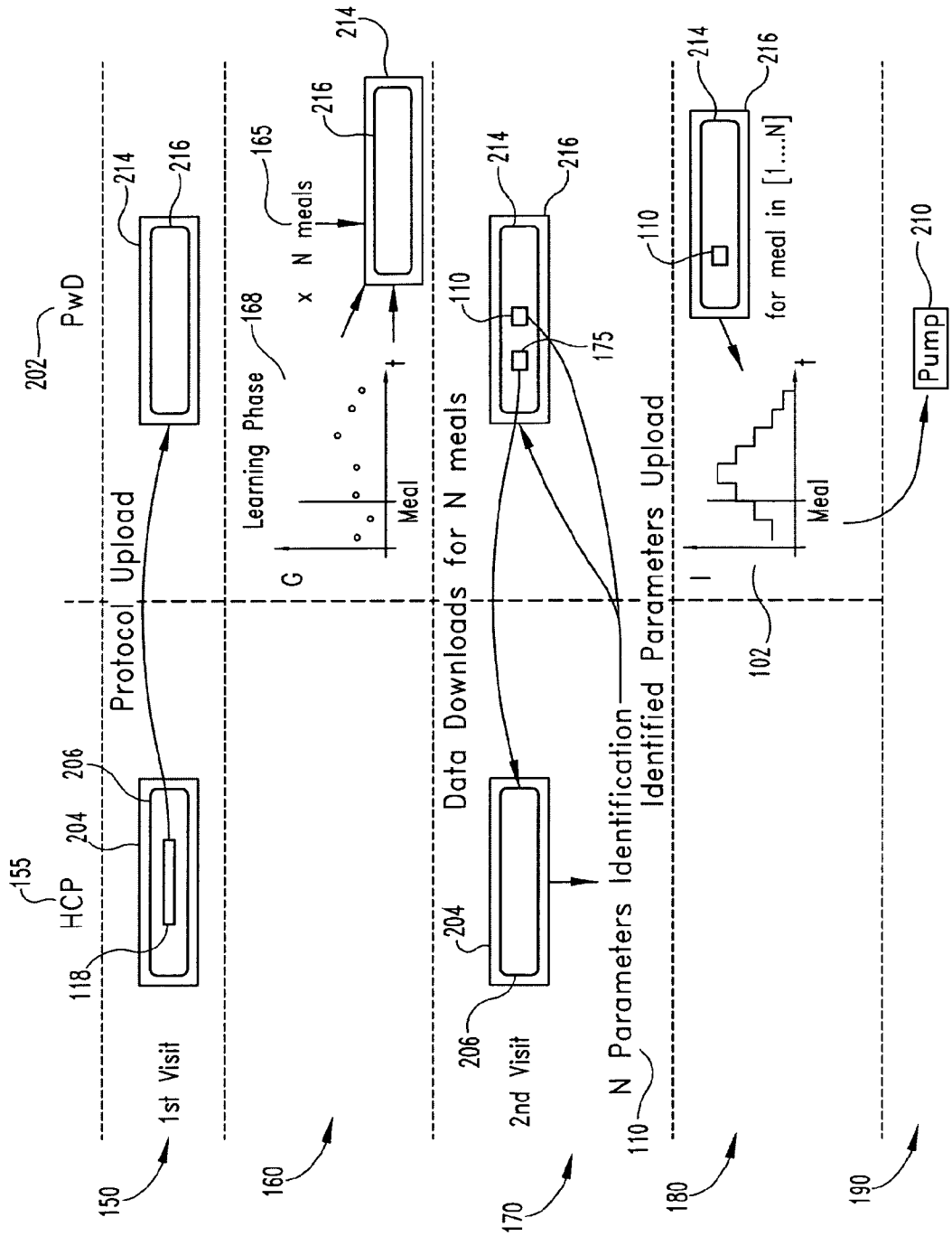
155
HCP
118
204
206
1st Visit
150
Protocol Upload
202
PwD
214
216
160
Learning Phase
168
165
x N meals
G
t
Meal
Data Downloads for N meals
110
175
2nd Visit
170
N Parameters Identification
110
Identified Parameters Upload
180
for meal in [1...N]
I
102
Meal
Pump
210
190

Fig. 5

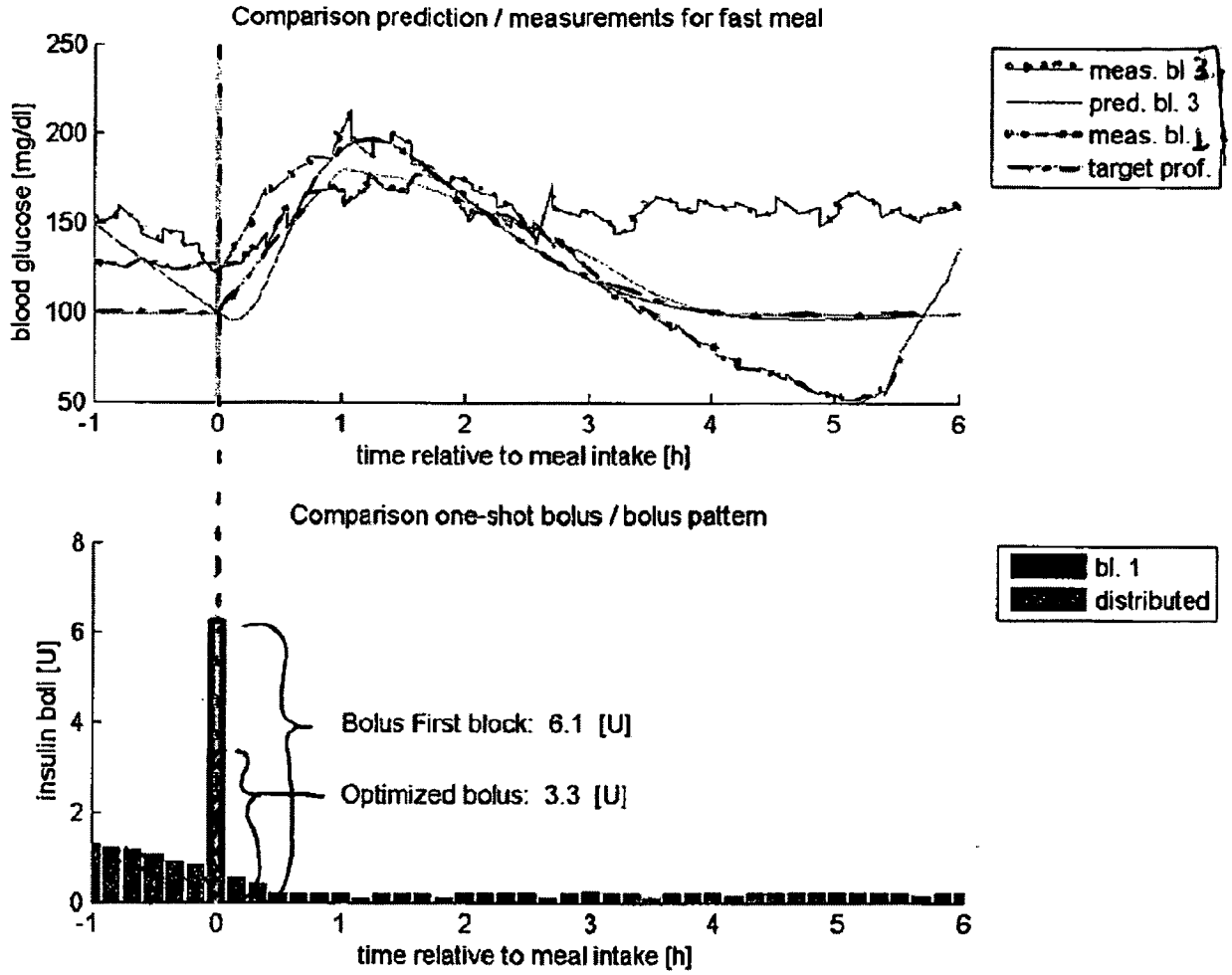
Comparison prediction / measurements for fast meal
blood glucose [mg/dl]
250
200
150
100
50
-1
0
1
2
3
4
5
6
time relative to meal intake [h]
meas. bl 3
pred. bl. 3
meas. bl. 1
target prof.
Comparison one-shot bolus / bolus pattern
insulin bol [U]
8
6
4
2
0
Bolus First block: 6.1 [U]
Optimized bolus: 3.3 [U]
time relative to meal intake [h]
bl. 1
distributed

FIG. 6

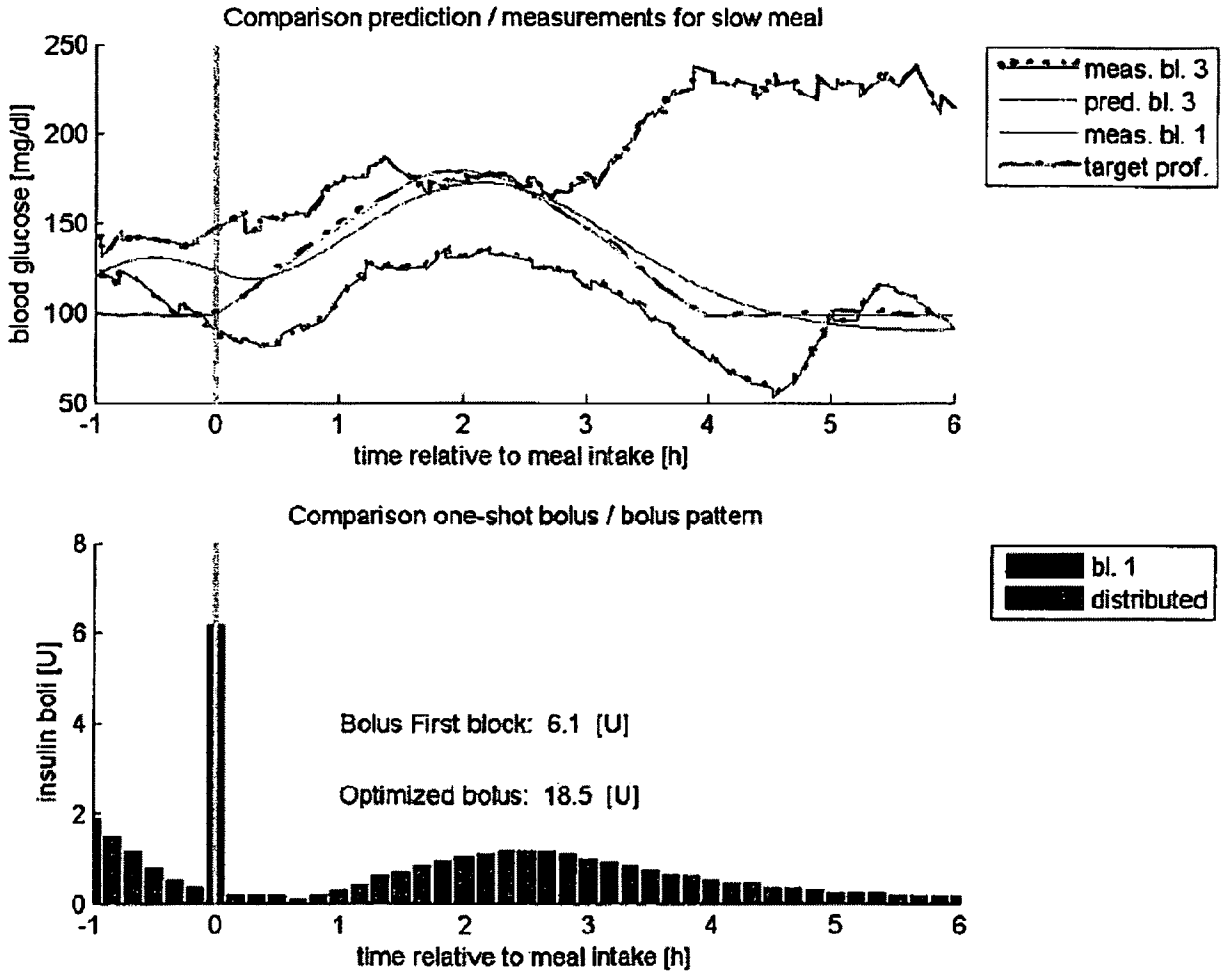
Comparison prediction / measurements for slow meal
blood glucose [mg/dl]
250
200
150
100
50
-1
0
1
2
3
4
5
6
time relative to meal intake [h]
meas. bl. 3
pred. bl. 3
meas. bl. 1
target prof.
Comparison one-shot bolus / bolus pattern
insulin boli [U]
8
6
4
2
0
Bolus First block: 6.1 [U]
Optimized bolus: 18.5 [U]
time relative to meal intake [h]
bl. 1
distributed

FIG. 7

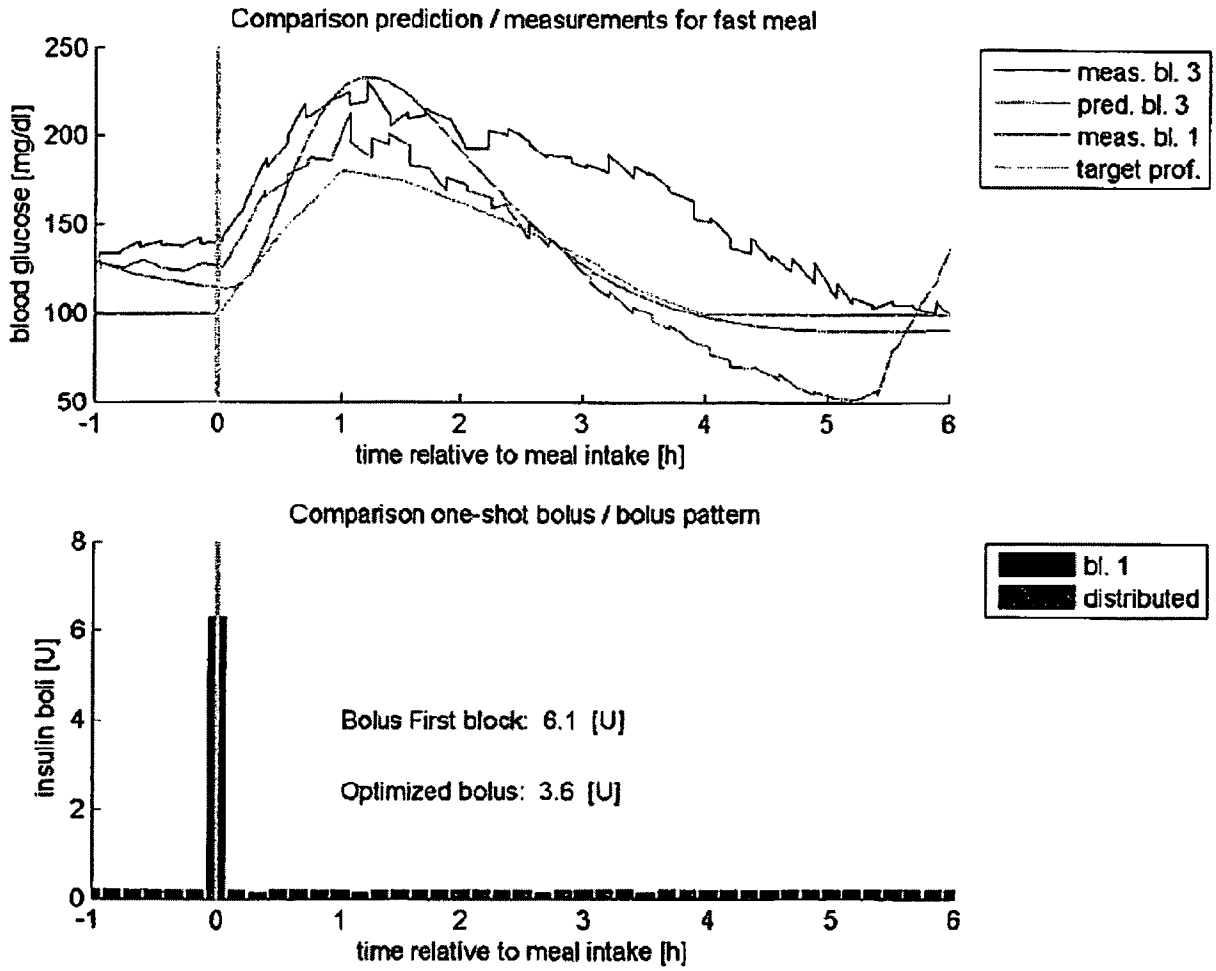
Comparison prediction / measurements for fast meal
blood glucose [mg/dl]
250
200
150
100
50
-1
0
1
2
3
4
5
6
time relative to meal intake [h]
meas. bl. 3
pred. bl. 3
meas. bl. 1
target prof.
Comparison one-shot bolus / bolus pattern
insulin boli [U]
8
6
4
2
0
Bolus First block: 6.1 [U]
Optimized bolus: 3.6 [U]
time relative to meal intake [h]
bl. 1
distributed

FIG. 8

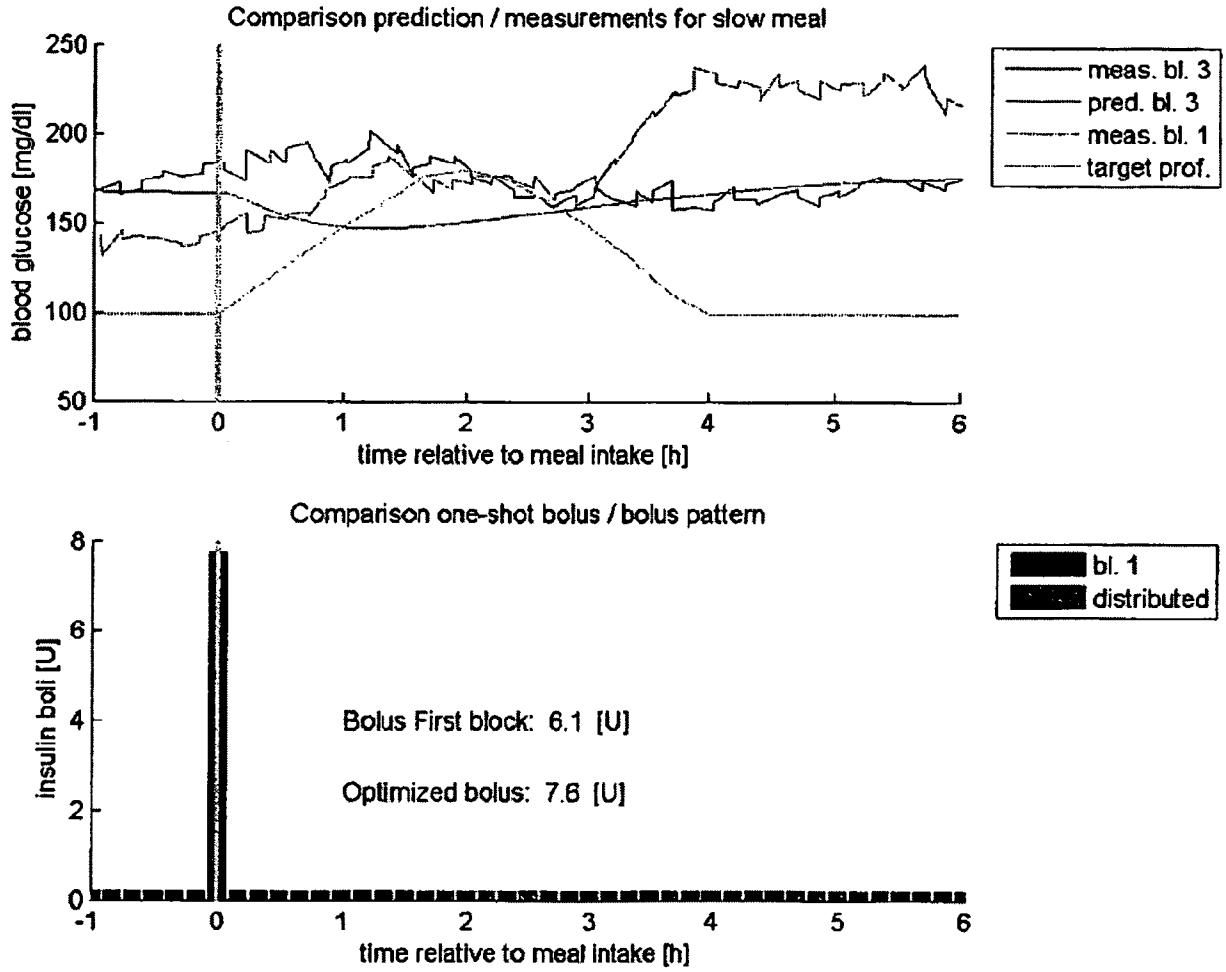
Comparison prediction / measurements for slow meal
blood glucose [mg/dl]
250
200
150
100
50
-1
0
1
2
3
4
5
6
time relative to meal intake [h]
meas. bl. 3
pred. bl. 3
meas. bl. 1
target prof.
Comparison one-shot bolus / bolus pattern
insulin boli [U]
8
6
4
2
0
Bolus First block: 6.1 [U]
Optimized bolus: 7.6 [U]
time relative to meal intake [h]
bl. 1
distributed

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/007951

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

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2005/093629 A2 (NOVO NORDISK AS [DK]; RANDLOEV JETTE [DK]; THODBERG HANS HENRIK [DK];) 6 October 2005 (2005-10-06) the whole document	1-15
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X	US 2003/055570 A1 (RIBEIRO JOSE CARLOS [US] RIBEIRO JR JOSE CARLOS [US]) 20 March 2003 (2003-03-20) the whole document	1-15

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2010	31/08/2010

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/007951

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No
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