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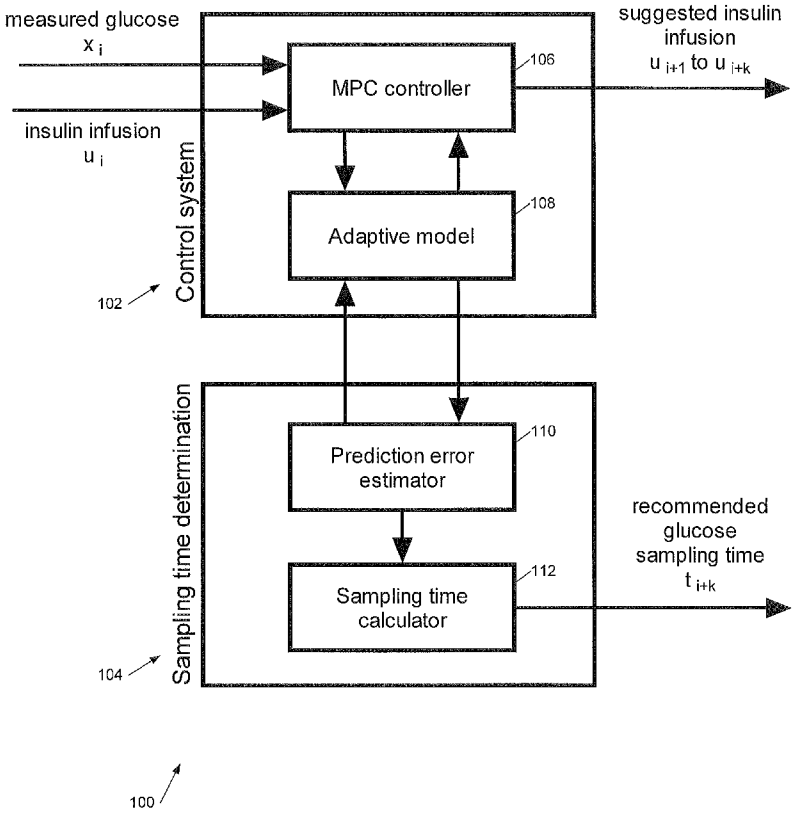
(54) Title: BLOOD GLUCOSE MONITORING SYSTEMS



(57) Abstract: This invention relates to apparatus, methods and computer program code for blood glucose monitoring, more particularly for determining times of blood glucose measurement. An apparatus for determining times of blood glucose measurement of a subject for use in controlling a level of said blood glucose, the apparatus comprising: an input to receive blood glucose measurement data for a series of blood glucose measurements; an adaptive model responsive to said blood glucose measurement data to represent the glucoregulation of said subject; an estimator of a prediction error in said adaptive model as a function of time; and a system to determine a time of a glucose measurement based on a comparison of said time-dependent prediction error with a range of acceptable blood glucose level for said subject.

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Blood Glucose Monitoring Systems

This invention relates to apparatus, methods and computer program code for blood glucose monitoring, more particularly for determining times of blood glucose measurement.

Figure 1, which is taken from WO 03/080157, shows the principle of an automated model-based insulin controller. This general approach can be used for automated control of insulin dosing for intensive care patients. In the system of Figure 1 glycaemia is measured by a glucose sensor that uses blood in an arterial line; many conventional glucose measuring devices are mentioned in WO'157. The automated insulin dosing device is typically a programmable insulin pump which delivers insulin by continuous intravenous infusion through a venous line. A control system is also described in WO'157; the "disturbances" indicated in the figure include external factors such as a history of diabetes, a reason for ICU (Intensive Care Unit) admission, caloric intake and the like.

Such a system has a number of drawbacks, in particular that insulin can kill so that closed-loop continuous monitoring systems are heavily regulated, generally being licensed only for research, and are not a commercial proposition. However, repeated sampling of blood glucose level by intensive care unit nurses is an onerous task and it is generally desirable to be able to reduce the sampling intervals. We describe a system which addresses this general need.

In more detail, a recent study in adult critically ill subjects demonstrated that glucose control below 6.1mmol/l is associated with reduced mortality by 43%, overall inhospital mortality by 34%, newly developed kidney failure requiring dialysis by 41%, bacteremia by 46%, the number of red blood cell transfusions by 50%, and critical illness polyneuropathy by 44% (Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R:

Intensive insulin therapy in the surgical intensive care unit. *N Engl J Med* 345:1359-1367, 2001). Tight glucose control is also beneficial in other intensive care settings such as in diabetic subjects following acute myocardial infarction (Malmberg K: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *Br Med J* 314:1512-1515, 1997).

Based on this evidence, efforts are being made to maintain strict glycaemic control in critically ill patients. In order to achieve this goal, complex insulin titration paper-based guidelines are being developed and tested in intensive care units (Van den BG: Beyond diabetes: saving lives with insulin in the ICU. *Int J Obes Relat Metab Disord* 26 Suppl 3:S3-S8, 2002; Goldberg PA, Sakharova OV, Barrett PW, Falko LN, Roussel MG, Bak L, Blake-Holmes D, Marieb NJ, Sherwin RS, Inzucchi SE: Implementation of a safe, effective insulin infusion protocol (IIP) in the cardiothoracic (CT) intensive care unit (ICU) (Abstract). *Diabetes* 53 (Suppl 2):A109, 2004; Goldberg PA, Siegel MD, Sherwin RS, Halickman JI, Lee M, Bailey VA, Lee SL, Dziura JD, Inzucchi SE: Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care* 27:461-467, 2004). These guidelines require hourly to four-hourly glucose sampling. Most of these guidelines still require user intervention and intuitive decision making of intensive care unit staff. Some uses of a blood glucose regulator are described in WO 01/85256.

To improve further the glucose control and to provide means to achieve consistent and reliable normoglycaemia, closed-loop algorithm-driven insulin delivery systems are being developed (Chee F, Fernando T, van Heerden PV: Closed-loop glucose control in critically ill patients using continuous glucose monitoring system (CGMS) in real time. *IEEE Trans Inf Technol Biomed* 7:43-53, 2003; Hovorka R: Continuous glucose monitoring and closed-loop systems. *Diabetic Med* (in press): 2005). Normally, closed-loop control relies on continuous glucose measurement taken every 15min or more frequently (Clemens AH, Chang PH, Myers RW: The development of Biostator, a

Glucose Controlled Insulin Infusion System (GCIIS). *Horm Metab Res* Suppl 7:23-33, 1977).

Insulin titration in the critically ill is determined by numerous factors. These include the underlying insulin resistance, parenteral nutrition, and enteral nutrition. While the latter two nutritional factors can be ascertained from the medical records, the insulin resistance cannot be directly measured and, furthermore, is subject to temporal variations induced by, for example, pain, trauma, or drugs such as glucocorticoids. Background prior art can be found in US2004/0193205, US2003/0130616, US2002/0107178, EP1487518A, WO 03/080157, US 5840020, WO 01/83007, WO 2006/011869, US2004/0152622, EP0881495 and US6017318.

Model predictive control is at the forefront of the recent research in the area of closed-loop insulin titration with contributions, for example, by Parker *et al* (Parker RS, Doyle FJ, III, Peppas NA: A model-based algorithm for blood glucose control in type I diabetic patients. *IEEE Trans Biomed Eng* 46:148-157, 1999), Lynch and Bequette (Lynch SM, Bequette BW: Estimation-based model predictive control of blood glucose in type I diabetics: A simulation study. *Proc of the IEEE 27th Annual Northeast Bioengineering Conference*79-80, 2001), Trajanoski *at al* (Trajanoski Z, Wach P: Neural predictive controller for insulin delivery using the subcutaneous route. *IEEE Trans Biomed Eng* 45:1122-1134, 1998), and Hovorka *et al* (Hovorka R, Canonico V, Chassin LJ, Haueter U, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller H, Schaupp L, Vering T, Wilinska M: Non-linear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas* 25:905-920, 2004). The MPC approach is most suitable for systems with long delays and open-loop characteristics (Camacho EF, Bordons C: *Model Predictive Control*. Springer-Verlag, 1999).

Model predictive control has a model linking insulin infusion and nutritional input to glucose excursions. This can be, for example, a physiological model representing fundamental glucoregulatory processes or a "black-box" model disregarding the physiological insights but learning the insulin-glucose relationships using pattern

recognition techniques. Both approaches can benefit from a wide range of models of the glucoregulatory system (Cobelli C, Federspil G, Pacini G, Salvan A, Scandellari C: An integrated mathematical model of the dynamics of blood glucose and its hormonal control. *Math Biosc* 58:27-60, 1982; Salzsieder E, Albrecht G, Fischer U, Freyse EJ: Kinetic modeling of the glucoregulatory system to improve insulin therapy. *IEEE Trans Biomed Eng* 32:846-856, 1985; Berger M, Rodbard D: Computer-simulation of plasma-insulin and glucose dynamics after subcutaneous insulin injection. *Diabetes Care* 12:725-736, 1989; Hovorka R, Andreassen S, Benn JJ, Olessen KG, Carson ER: Causal probabilistic network modelling - An illustration of its role in the management of chronic diseases. *IBM Syst J* 31:635-648, 1992). Development of an MPC controller involves selecting a suitable model, obtaining model parameters, and deciding on other elements such as the length of the prediction window and the form of the target trajectory. Adaptive techniques allow model parameters to be individualised.

An alternative to a fully automated, autonomous closed-loop approach is a decision-support system, which provides an advice on insulin infusion at intervals comparable to the current clinical practice at the intensive care units, i.e. hourly to four-hourly. The advantages are the involvement and responsibility of the medical staff in making the decision on insulin titration reducing the demands on safety-critical features of the system. The decision support is based on discrete glucose measurements taken at hourly to four-hourly intervals although a parallel use of continuous glucose monitor could provide real-time alarms about impeding low or high glucose. The ability to work without the use of a continuous glucose monitor is beneficial as a reliable and accurate continuous glucose sensor applicable to health and disease has yet to be developed.

A fully-algorithmic decision-support system has been developed and piloted (Hovorka R, Agbaje OF, Amegah-Sakotnik A, Anderlova K, Blaha J, Chassin LJ, Cordingley J, Ellmerer M, Haluzik M, Jahodova J, Kremen J, Plank J, Plasnik A, Rigler B, Schaupp L, Toller W, Wilinska ME, Morgan CJ, Pieber TR, Svacina S: Glucose control at surgical ICU: Multicentre clinical trial results in patients controlled with model predictive controller and by standard protocols (Abstract). *(submitted)* 2005). Post-cardiac surgery subjects (N = 33 in algorithm and N = 38 in control group) were studied

over 24 hours in a prospective, controlled, randomized study. In the algorithm group, model predictive controller (MPC) running on a PC computer advised hourly on intravenous (iv) insulin titration based on hourly glucose measurements and carbohydrate content of parenteral and enteral intake. In the control group, hourly to four-hourly glucose measurements were used by nursing staff to adjust iv insulin according to paper-based institutional guidelines.

Starting glucose was similar (7.9(7.2-9.1) vs 8.1(7.2-9.3)) mmol/l; algorithm vs control group; median (IQ range); NS) with a tendency of higher glucose levels in the algorithm group during 2-5 h due to more aggressive initial insulin dosing in control group, see Figure 2 shows. In the control group, three hypoglycaemia events (< 3.3 mmol/l) were observed compared to one in algorithm group. Following achievement of the target, algorithm group demonstrated better control as measured by percentage time spend in target glucose range (75(69-92) vs 34(7-46)%; $P < 0.001$) and hyperglycaemic index (0.1 (0.0 - 0.3) vs 0.8 (0.5 - 1.7)mmol/l; $P < 0.001$) during the period 9 to 24h. The target range was 4.4.-6.1 mmol/l

The conclusion from this clinical study was that following initial slower normalization period, algorithm-based control achieves safe and tight glucose control demonstrating feasibility of automated glucose control with hourly sampling at surgical ICU.

Figure 2 shows glucose control in subjects treated by the algorithm with hourly sampling (open circle; N = 33) and in control subjects (closed circle; N = 38). In order to align the decision-support system with existing clinical practise and to reduce the workload, the means to extend the hourly sampling interval, where appropriate, up to two-hourly, three-hourly, or four-hourly are needed. This need is addressed by the present invention.

Summary of the Invention

We will describe a system for determining discrete sampling times of blood glucose measurements during intensive insulin therapy in critically ill subjects and other insulin-treated subjects in the hospital environment. The system determines timing of irregular,

discrete glucose measurements, which may be used by model predictive controller to titrate insulin delivery with the aim to achieve tight glucose control. The model-based sampling time determination exploits (i) an adaptive model assessing the prediction error, and preferably (ii) other characteristics of the input (e.g. nutrition provision and insulin infusion) and the output, i.e. glucose excursions. In embodiments this determination of sampling times reduces the number of conventional glucose samples needed to achieve and maintain tight glucose control with intensive insulin therapy and thus reduces workload at the ICU and increases convenience of system use.

According to the invention there is therefore provided an apparatus for determining times of blood glucose measurement of a subject for use in controlling a level of said blood glucose, the apparatus comprising: an input to receive blood glucose measurement data for a series of blood glucose measurements; an adaptive model responsive to said blood glucose measurement data to represent the glucoregulation of said subject; an estimator of a prediction error in said adaptive model as a function of time; and a system to determine a time of a glucose measurement based on a comparison of said time-dependent prediction error with a range of acceptable blood glucose level for said subject.

Preferably the acceptable range of blood glucose level comprises a range defined by upper and lower bands of a desired blood glucose level. Thus in embodiments the system determines that a glucose measurement should be made when the prediction error goes outside an acceptable range. The acceptable range of blood glucose level may be substantially constant over time or it may be time-dependent. For example the acceptable range of blood glucose level may be determined responsive to the blood glucose measurement data. In embodiments the insulin infusion rate and the time of the next measurement may be determined without a concomitant glucose measurement.

Broadly speaking in embodiments the system looks at the difference between a predicted glucose level and an actually measured glucose level for one or more preceding measurements and uses this to determine a likely spread of future predicted values, in effect a future prediction error. This future prediction error may be used to determine a next measurement time. More particularly a desired blood glucose

trajectory +/- an allowed error may be defined, for example by a desired end point or the trajectory in itself may be a treatment goal. When the model prediction for glucose level, taking into account the model prediction error, goes outside the allowed latitude (based on the desired trajectory plus error), this defines a point in time at which a next measurement should be taken. In embodiments an actual measurement defines a start point for a predicted trajectory with error which increases over time, the limits of this error defining a widening funnel away from the measurement point (in the forward time direction). The boundaries of this funnel (error latitude) may be defined by a predetermined confidence level, for example a 95% confidence level. Where the funnel intersects the desired glucose level trajectory, more precisely a band defined by allowed error to either side of the desired trajectory, two measurement points may be defined, one where the lower limit of the model prediction error intersects the outer lower part of the desired trajectory band, one where the upper band of the model prediction error intersects the upper part of the desired trajectory band. In this case preferably the earliest of the two intersection points is used to determine the time of the glucose measurement. Typically a doctor may enter a blood glucose trajectory and/or target for the subject/patient.

The adaptive model can be run either off-line or on-line. For example in an off-line configuration the model may be based upon a set of patients using historically gathered data. Thus the model may be adapted periodically in response to sets of blood glucose measurement data. In an on-line mode, the model may be adapted in substantially real time responsive to blood glucose measurement data from the subject.

The apparatus may produce an audible or visible alert to indicate the time of a glucose measurement and/or a printout or display of a next measurement time. The apparatus may also include a glucose controller to determine a level of insulin infusion or dose to administer to the subject, using the adaptive model. This may be displayed, printed or otherwise output for a doctor or nurse to manually administer the insulin. Alternatively the apparatus may include a programmable insulin pump automatically controlled by the apparatus. Such devices are known in the art (see, for example, US 4,704,029; US 4,436,094; US 5,665,065; US 5,383,865; and US 5,176,644). The skilled person

will appreciate that the blood glucose measurements may be made using any of a wide range of conventional techniques.

In some preferred embodiments the system to determine the time of a glucose measurement also includes one or more overriding rules. These can be used to implement clinically relevant constraints on the glucose measurement times. For example a rule may specify a particular timing of glucose measurement, for example hourly, if a glucose level is above or below a predetermined threshold. Other examples of rules which may be implemented are described later. These rules may define a timing or timing constraint based upon one or more of a number of glucose measurements, a coefficient of variation and/or standard deviation of a suggested insulin infusion rate, a relative or absolute change between a previous insulin infusion rate and a suggested or current infusion rate, a most recent glucose measurement, a timing of a most recent meal, and a short or long term trend in glucose measurements.

The invention further provides a method of determining times of blood glucose measurement of a subject for use in controlling a level of said blood glucose, the method comprising: receiving blood glucose measurement data for a series of blood glucose measurements; adaptively modelling the glucoregulation of said subject responsive to said blood glucose measurement data; estimating a prediction error in said adaptive model as a function of time; determining a time of a glucose measurement based on a comparison of said time-dependent prediction error with a range of acceptable blood glucose level for said subject.

The invention further provides processor control code to implement aspects and embodiments of the invention, for example on a general purpose computer system or on a digital signal processor (DSP). The code may be provided on a carrier such as a disk, CD- or DVD-ROM, programmed memory such as read-only memory (Firmware), or on a data carrier such as an optical or electrical signal carrier. Code (and/or data) to implement embodiments of the invention may comprise source, object or executable code in a conventional programming language (interpreted or compiled) such as C, or a lower level language such as assembly code. As the skilled person will appreciate such

code and/or data may be distributed between a plurality of coupled components in communication with one another.

In another aspect the invention provides an apparatus configured to reduce the number of samples needed to achieve normoglycaemia in critically ill subject and other subjects treated in hospital consisting of: an adaptive model representing the glucoregulation of said subject, a glucose controller determining the control action needed to achieve normoglycaemia in said subject, an estimator of the prediction error in said subject, and a system to determine the time of the next glucose measurement based on the prediction error and other factors in said subject, the glucose controller and the estimator of the prediction error using the adaptive model.

Preferably the insulin infusion rate and the time of the next measurement is determined without a concomitant glucose measurement. The apparatus may include an attached spot glucose meter measuring the glucose level and a pump delivering a blood glucose regulator. The apparatus may additionally or alternatively include an attached continuous glucose monitor to supervising the performance of the apparatus and raising alarm if the monitored glucose exceeds or drops below predefined thresholds.

The determination of the maximum time of the next measurement time may comprise one or more of the following: the number of glucose measurements, the coefficient of variation and the standard deviation of the suggested insulin infusion rates, the relative change and the absolute change between previous insulin infusion and the suggested infusion rate, the most recent glucose measurement, the most recent meal digestion, the trend in glucose measurements, and the rate of suggested insulin infusion.

The apparatus may be used in treatment with a blood glucose regulator of a subject under a condition of insulin resistance or under a condition of increased glucose turnover in a hospital environment, or with a blood glucose regulator of a critically ill subject. The blood glucose regulator may comprise insulin, an insulin analogue or an active derivative of insulin, or a monomeric human insulin analogue, or a glucagon like peptide 1 (a GLP-1), GLP-1 analogues, GLP-1 derivatives or pharmaceutically

acceptable salts thereof. The blood glucose regulator may also be a compound of the group consisting of somotostatin, gastric inhibitor polypeptide, glucose-dependent insulinotropic peptide, bombesin, calcitonin gene-related peptide, gastrin-releasing peptide, cholinergic agonists, isoproterenol, and bethanechol.

The apparatus may be used to reduce hyperglycaemia to stable normoglycaemia in in-hospital subject under a condition of insulin resistance or under a condition of increased glucose turnover without causing hypoglycaemia in an initial phase of less than 24 hours and to maintain normoglycaemia under changing conditions of said subject (e.g., decreasing insulin resistance, other route of feeding, change in medication,...) or complications of said subject (e.g., concomitant infection). The apparatus may also be used to reduce hyperglycaemia to stable normoglycaemia in a critically ill subject without causing hypoglycaemia in an initial phase of less than 24 hours and to maintain normoglycaemia under changing conditions of said subject (e.g. decreasing insulin resistance, other route of feeding, change in medication, and the like) or complications of said subject (e.g., concomitant infection). The apparatus may further to be used to maintain blood glucose below 6.1 mmol/l in a critically ill subject, to maintain blood glucose between 3.3 and 7.2 mmol/l in a critically ill subject, to maintain blood glucose between 3.9 and 6.7 mmol/l in a critically ill subject, to maintain blood glucose between 4.4 and 6.1 mmol/l in a critically ill subject, or to reach normoglycaemia in a critically ill patent within 24 hours after admission in the ICU (initial phase) and to maintain normoglycaemia thereafter.

These and other aspects of the invention will now be further described, by way of example only, with reference to the accompanying figures in which:

Figure 1 shows an automated model-based insulin controller;

Figure 2 shows glucose control with hourly sampling;

Figure 3 shows an embodiment of a system according to the present invention;

Figure 4 shows an adaptive model of a glucoregulatory system for the system of Figure 3;

Figure 5 shows determination of model prediction error according to an embodiment of the invention;

Figure 6 shows determination of a sampling interval according to an embodiment of the invention; and

Figure 7 shows a flow diagram of a computer program to implement an embodiment of the invention.

Broadly speaking, we will describe a system to determine sampling times of blood glucose during intensive insulin therapy in critically ill subjects, in particular for determining timing of discrete glucose measurements, which are used by model predictive controller to titrate insulin delivery to achieve tight glucose control. This determination of sampling times significantly reduces the number of conventional glucose samples needed to achieve and maintain tight glucose control with intensive insulin therapy and thus reduces workload at the ICU and increase convenience. Model-based control of glucose by the means of infusing insulin is particularly applicable to critically ill subjects and other subjects treated in hospitals requiring insulin administration. We describe means to determine the frequency of discrete glucose measurements with the aim to reduce workload and increase convenience while achieving tight glucose control.

Where applicable, we adopt the following definitions:

The term “blood glucose regulator” refers to any substance, which is able to regulate the blood glucose levels. Examples of blood glucose regulator are insulin, insulin analogues, glucagons like peptide 1 and other biologically active substances having effect on insulin release or insulin action. The term "Glucagon like peptide 1 (GLP-1) "as used herein is a incretin hormone. The term “insulin”, as used herein refers to

insulin from any species such as porcine insulin, bovine insulin, and human insulin and salts thereof such as zinc salts, and protamine salts. The term "active derivatives of insulin" as used herein are what a skilled worker generally considers derivates, see general textbooks, for example, insulin having a substituent not present in the parent molecule.

The term "insulin analogue", as used herein refers to insulin wherein one or more of the amino acid residues have been changed with another amino acid residue and/or from which one or more amino acid residue has been deleted and/or from which one or more amino acid residue has been added with the proviso that said insulin analogue has a sufficient insulin activity. Using results from the so-called free fat cell assay, any skilled art worker, for example, a physician, knows when and which dosages to administer of insulin analogue. The terms "monomeric human insulin analog" "monomeric insulin analog" and "human insulin analog" are well-known in the art, and refer generally to fast-acting analogs of human insulin, which include human insulin, wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and wherein position B29 is Lys or is substituted with Pro; AlaB26-human insulin des (B28-B30) human insulin ; and des (B27) human insulin. The term "critically ill subject", as used herein refers to a patient who has sustained or is at risk of sustaining acutely life-threatening single or multiple organ system failure due to disease or injury, a patient who is being operated and where complications supervene, and a patient who has been operated in a vital organ within the last week or has been subject to major surgery within the last week. A critically ill subject can be a patient who needs vital organ support (either mechanically such as with mechanical ventilation or dialysis etc or pharmacologically such as with inotropes or vasopressors) without which they would not survive. The term "hyperglycaemia" means a greater than normal concentration of glucose in the blood. The term "normoglycaemia" as used herein means a blood glucose between 3.3 and 7.2mmol/l, more preferably between 3.9 and 6.7mmol/l and most preferably between 4.4 to 6.1 mmol/l. The term "insulin resistance" as used herein, refers to reduced biological response to a given concentration of insulin. Insulin resistance is generally characterised by the requirement of inappropriately high levels of insulin for maintaining glucose homeostasis. The term "increased glucose turnover" is a disproportionate increase in glucose turnover. Injury increases whole-body glucose

turnover and whole-body glucose recycling. The term "insulin regulating" as used herein, refers to an ability to control the release of insulin into circulation, in relation to blood glucose and fatty acid levels. The term "intensive care unit", as used herein refers to the part of a hospital where critically ill patients are treated. This may vary from country to country and from hospital to hospital and said part of the hospital may not necessary, officially, bear the name "Intensive Care Unit" or a translation or derivation thereof. The term "Intensive Care Unit" also covers a nursing home, a clinic, for example a private clinic, or the like if the same or similar activities are performed there.

The embodiment of the present invention we describe allows the number of glucose measurement to be minimised while achieving tight glucose control in critically ill subjects. This reduces workload and increases the convenience of system use.

Model-based approaches provide means for the quantification of the underlying insulin resistance by either estimating insulin sensitivity or by estimating a surrogate measure such as the amount of insulin to maintain euglycaemia. Once estimated, the insulin sensitivity or its surrogate marker can be used by the model of the glucoregulatory to predict fluctuations of glucose excursions given the nutritional provision and insulin treatment.

The model representation enables simulation of "what if" scenarios. In particular, the prediction can be made of future glucose excursions resulting from projected insulin infusion rates. These prediction capabilities enable the construction of insulin infusion rates leading to a predefined "target" glucose excursion. The insulin infusion rate is obtained by minimising the difference between the model-predicted glucose concentration and the target glucose trajectory although the minimisation may include other components such as the minimisation of the change in the insulin infusion rate.

The validity of the suggested insulin infusion rate is limited by the accuracy of model-based predictions and other factors such as changes in nutritional input. We extend the capability of the model-predictive controller by assessing the accuracy of model-based predictions and using this information to determine the sampling times.

The following steps are used to determine the next measurement time:

1. The model within the model-predictive controller is adapted to a particular subject

2. A procedure assesses the prediction error associated with the adapted model

3. The extent of the prediction error determines the next measurement time. Other factors apart from the prediction error can be used in the determination of the measurement time such as the ambient glucose level and the rate of change of glucose level.

A schematic diagram of an embodiment of the system is shown in Figure 3, which depicts a model predictive controller extended by a system determining the glucose sampling time.

The system 100 has two main components, a control system module 102 and a sampling time determination module 104. The control system module includes a model predictive controller (MPC) 106 coupled to an adaptive model 108 of the glucoregulatory system. The controller 106 may comprise any of a number of known controllers, as mentioned in the introduction to this specification. A particularly preferred controller is that described by Hovorka *et al.* (*ibid*). However other MPC controllers may also be employed.

The MPC controller 106 receives first and second inputs defining a measured glucose level and an insulin infusion level at a control time denoted by index i and outputs data defining a suggested insulin infusion rate at one or more subsequent control times $i + 1$ to $i + K$. The MPC controller is closely coupled to glucoregulatory model 108 (also described in Hovorka *et al.* an example of which is shown in Figure 4. Again, a range of different known models may be employed.

The glucoregulatory model represents input-output relationship between intravenous insulin infusion as input and intravenous glucose concentration as output. Enteral and parenteral glucose infusions represent optional additional inputs.

Figure 4 shows an example of a compartment model of a glucose-insulin system. In the Figure, Q_1 and Q_2 represent masses in accessible (plasma) and non accessible compartments, I represents plasma insulin, x_i represent insulin action on glucose transport, disposal, and endogenous glucose production.

The model has a glucose subsystem (glucose absorption, distribution, and disposal), an insulin subsystem (insulin distribution, disposal), and an insulin action subsystem (insulin action on glucose transport, disposal, and endogenous production). The model builds on experimental and modelling work, which employed glucose tracers to determine structure and parameter values of glucose kinetics in normal subjects during basal conditions and during the intravenous glucose tolerance test (Hovorka R, Shojaee-Moradie F, Carroll PV, Chassin LJ, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH: Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Am J Physiol* 282:E992-1007, 2002).

Model quantities were divided into model constants and model parameters with the objective of reducing the number of parameters (and thus computational speed) while retaining the ability to represent the wide range of glucose excursions seen in critically ill subjects.

The model parameters are preferably estimated using a Bayesian approach to avoid problems with posterior identifiability.

The objective function at time *t* includes a weighted sum of squares of residuals and a penalty due to the distance from prior parameter distributions (the latter collapses into the sum of squares of standardized parameter values due to standardization of random variables)

$$\arg\min_{p_1 \cdots p_{N_P}} \left\{ \sum_{i=0}^{N_W - 1} w_{t-i} \left[\hat{y}(t-i \mid p_1 \ldots p_{N_P}) - y(t-i) \right]^2 + \sum_{k=1}^{N_P} {p_k}^2 \right\}$$

where w_i is the weight reciprocal to the square of the measurement error, $y(t-i)$ is the measured glucose concentration at time $t-i$, $\hat{y}(i \mid p_1 \ldots p_{N_P})$ is model predicted glucose concentration at time i given standardized parameters $p_1 \ldots p_{Np}$, N_W is the length of the learning window, and N_P is the number of model parameters.

In one embodiment the parameters are estimated at each control time; in another a prior regression model is used to determine initial parameter values for determining initial parameter values for the system.

The model predictive controller is based on that described by Hovorka *et al* (12). Other model-predictive controllers could be used with the present invention.

The MPC controller used this non-linear model and preferably includes following components: parameter optimizer, target projector, dose optimizer, and safety schemes.

Parameters of glucoregulatory system differ considerably between subjects (Bergman RN, Hope ID, Yang YJ, Watanabe RM, Meador MA, Youn JH, Ader M: Assessment of insulin sensitivity in vivo: a critical review. *Diabetes/Metabolism Rev* 5:411-429, 1989) and also exhibit diurnal variations (Lee A, Ader M, Bray GA, Bergman RN: Diurnal-variation in glucose-tolerance - cyclic suppression of insulin action and insulin), (Van Cauter EV, Shapiro ET, Tillil H, Polonsky KS: Circadian modulation of glucose and insulin responses to meals - relationship to cortisol rhythm. *Am J Physiol* 262:E467-E475, 1992) although exact quantification of within subject variation (amplitude and frequency) is yet to be determined. Preferably therefore, in recognition of the between and within subject variation, the controller adapts itself to the changing environment. This is carried out by re-estimating parameters at each control step, as mentioned above.

The parameter optimizer estimates model parameters employing glucose measurements from a "learning window", i.e. a time period immediately preceding the control time.

The target projector calculates target trajectory, i.e. the desired glucose profile.

The dose optimizer calculates a sequence of insulin infusion rates, which gives best fit to the target trajectory. The dose optimizer adopts non-linear function minimization as the underlying model is non-linear.

Preferably control systems are included to cope with exceptional circumstance (Goriya Y, Ueda N, Nao K, Yamasaki Y, Kawamori R, Shichiri M, Kamada T: Fail-safe systems for the wearable artificial endocrine pancreas. *Int J Artif Organs* 11:482-486, 1988). Preferably safety schemes protect against system failures and minimize the risk of insulin overdosing and subsequent hypoglycaemia.

In embodiments, the controller receives glucose measurements every 1 – 4 hours and calculates the insulin infusion rate also every 1 – 4 hours although, in principle, other sampling/control frequencies, equidistant or non-equidistant, are also possible. The calculated insulin infusion rate is in embodiments administered as a constant insulin infusion over the 1 – 4 hour window.

In one embodiment the MPC was implemented in Microsoft Visual C++ using object oriented programming and runs both on a PC (MS Windows NT/98/2000,XP) and a PDA (MS PocketPC). The parameter estimation adopts a Marquardt minimisation procedure (Marquardt DW: An algorithm for least squares estimation of nonlinear parameters, *J Soc Ind Appl Math* 2:431-441, 1963).

Referring again to Figure 3, the sampling time determination module 104 includes a model prediction error estimation module 110, coupled to control system 102, and providing an output to a sampling time calculation module 112, which is used to calculate the next measurement time from the prediction error. Preferably, although now shown in Figure 3, the system also includes a module for modifying a next measurement time based upon one or more additional factors, as described further later.

The output of the sampling time calculation module 112 is a recommended glucose sampling time which determines the time of the next glucose measurement in the monitored subject/patient.

We next describe the operation of the prediction error estimation module 110 with reference to figure 5. In preferred embodiments the estimation of the prediction error has two stages. In some preferred embodiments an adaption step is formed, typically to minimise the difference between past measurements and model fit and then after this adaption step a separate step is executed to estimate the prediction error, which may include the evaluation of point-to-point predictions.

Thus, first, the model of glucose excursions is identified (adapted) using glucose measurements. The identification may or may not use system inputs, e.g. insulin administration and nutritional intake and may or may not use glucose concentration at the control time t_i. Second, the individually identified model is used to predict the glucose concentration at the control time t_i using the preceding glucose measurement at time t_{i-1} as the initial condition. The difference between the model prediction and the actual glucose measurement represents the prediction error (see the inset of Figure 5) expressed in, for example, mmol/l per unit time. The illustrative example uses glucose measurements prior to and including time t_{i-1} during the model identification. The glucose measurement at t_i or any suitable subset of glucose measurements can also be used for the identification. Similarly, other approaches and different initial conditions can be used to estimate the prediction error.

We next describe operation of the sampling time calculation module 112 to calculate a next measurement time from the prediction error, with reference to Figure 6.

Commencing at time t_i of the most recent glucose measurement, the adapted model predicts a glucose trajectory based on advised insulin infusion and administered parenteral and enteral nutrition. For example a doctor may aim to define an insulin plan at, say, hourly intervals, using the model, to define a desired glucose trajectory. In

Figure 6, the desired trajectory and model prediction coincide. The acceptable bounds define a tolerance band to either side of the desired trajectory. Thus the acceptable bounds 600 a, b show the user-selected (e.g. doctor-defined) region of acceptable deviations from a predicted glucose trajectory. In the illustrated example, the acceptable bounds are parallel with the predicted glucose trajectory although other arrangements are possible. A prediction funnel 602 a, b is constructed from the prediction error using, for example, a time-proportional increase in the funnel spread. The crossing of the prediction funnel with the acceptable bounds determines the time at which the subsequent glucose measurement should be taken.

In a preferred embodiment the sampling time calculation module 116 implements logic to define one of a plurality of (predetermined) sampling time intervals according to which (if any) of a plurality of prediction error thresholds is exceeded. In one embodiment the following logic was employed:

- If the prediction error is greater than 0.7mmol/l per hour then the time-to-the-next-glucose-measurement is 1 hour otherwise
- If the prediction error is greater than 0.4mmol/l per hour then the time-to-the-next-glucose-measurement is 2 hours otherwise
- If the prediction error is greater than 0.25mmol/l per hour then the time-to-the-next-glucose-measurement is 3 hours otherwise
- If the prediction error is less or equal to 0.25mmol/l per hour then the time-to-the-next-glucose-measurement is 4 hours

In a variant, the system as described of Figure 3 can be used at a given control time t_i without a concomitant glucose measurement provided that the control time t_i is less than the recommended glucose sampling time determined at the control time t_{i-1}.

In another variant, the prediction error estimator also assesses the plausibility of the glucose measurement (for example from the model) and can suggest re-measurement of the glucose level if the prediction error is too high or too low in effect if the measurement is outside a plausibility threshold.

Figure 7 shows a block diagram of a procedure to determine a next sampling time according to an embodiment of the invention, implemented in a computer program. The procedure initiates in Step 1 and in Step 2, the prediction error PE is estimated. The time-to-next-measurement TnM is initialised to 2 hours in Step 3.

In Step 4, the Boolean function f(TnP, PE) is evaluated. This function evaluates whether for a given measurement error PE and a given time-to-next-measurement TnM, the prediction funnel is within the acceptance bounds. If the result is FALSE, the time-to-next-measurement is reduced by 1 hour in Step 6 and the result is returned in Step 9. If the result is TRUE, the time-to-next measurement is tested whether it is less than 4 hours in Step 7. If FALSE, the time-to-next-measurement is returned in Step 9 otherwise it is incremented by 1 hour in Step 8 and the execution moves to Step 4.

We now describe some additional rules which may be implemented in preferred embodiments of the system in order to provide additional safety precautions. This is because other factors have been identified as playing a role in determining the next measurement time. More particularly the factors we mentioned below shorten the interval to the next measurement time.

The identified factors include:

Other factors have been identified to play role in determining the next measurement time. These include:

- The number of glucose measurements
- The coefficient of variation and the standard deviation of the suggested insulin infusion rates u_i to u_{i+k}
- The relative change and the absolute change between previous insulin infusion u_{I-1} and the suggested infusion rate u_i
- The most recent glucose measurement

- The most recent meal digestion
- The trend in glucose measurements
- The rate of suggested insulin infusion.

We describe, below, some preferred rules to take account of these factors.

The number of glucose measurements. In initial stages of the use of the glucose controller, the following logic applies:

- If the number of glucose measurement is less than 3, then the maximum time-to-next-glucose-measurement is 1hour otherwise
- If the number of glucose measurement is less than 4, then the maximum time-to-next-glucose-measurement is 2hours otherwise
- If the number of glucose measurement is less than 6, then the maximum time-to-next-glucose-measurement is 3hours otherwise
- The maximum time-to-next-glucose-measurement is 4hours.

Coefficient of variation (CV) and standard deviation (SD) of the suggested insulin infusion rates u_i to u_{i+k}. The following logic applies:

- If the CV is less or equal than 15% or the SD is less or equal than 0.3 U/h, then the maximum time-to-next-glucose-measurement is 4hours otherwise
- If the CV is less or equal than 20% or the SD is less or equal than 0.4 U/h, then the maximum time-to-next-glucose-measurement is 3hours otherwise
- If the CV is less or equal than 15% or the SD is less or equal than 0.5 U/h, then the maximum time-to-next-glucose-measurement is 2hours otherwise
- The maximum time-to-next-glucose-measurement is 1hour.

The relative change (RE) and the absolute change (ABS) between previous insulin infusion u_{I-1} and the suggested infusion rate u_i. The following logic applies:

- If the RE is less or equal than 15% or the ABS is less or equal than 0.3 U/h, then the maximum time-to-next-glucose-measurement is 4hours otherwise
- If the RE is less or equal than 20% or the ABS is less or equal than 0.4 U/h, then the maximum time-to-next-glucose-measurement is 3hours otherwise

- If the RE is less or equal than 15% or the ABS is less or equal than 0.5 U/h, then the maximum time-to-next-glucose-measurement is 2hours otherwise
- The maximum time-to-next-glucose-measurement is 1hour.

The most recent glucose measurement (G_i). The following logic applies:

- If G_i is less or equal to 3.5 mmol/l, then the maximum time-to-next-glucose-measurement is 30min otherwise
- If G_i is less or equal to 4.1 mmol/l, then the maximum time-to-next-glucose-measurement is 1hour otherwise
- If G_i is less or equal to 4.3 mmol/l, then the maximum time-to-next-glucose-measurement is 2hours otherwise
- If G_i is less or equal to 4.6 mmol/l, then the maximum time-to-next-glucose-measurement is 4hours otherwise
- The maximum time-to-next-glucose-measurement is 4hours.

The most recent meal digestion. The following logic applies:

- If there was a meal of at least 10g carbohydrate content digested within 120min prior to the control time t_i, then the maximum time-to-next-glucose-measurement is 1hour otherwise
- If there was a meal of at least 10g carbohydrate content digested within 180min prior to the control time t_i, then the maximum time-to-next-glucose-measurement is 2hours otherwise
- The maximum time-to-next-glucose-measurement is 4hours.

The trend in glucose measurements. Two trends are recognised, a short term trend (STT) evaluated by assessing by the linear regression the glucose measurements within 90min prior to the control time t_i, and long term trend (LTT) evaluated by assessing by the linear regression the glucose measurements within 4 hours prior to the control time t_i. The following logic applies:

- If LTT is less than –0.625 mmol/l per hour and the most recent glucose measurement is less than 7.5 mmol/l, then the maximum time-to-next-glucose-measurement is 1hour

- If STT is less than –0.8 mmol/l per hour and the most recent glucose measurement is less than 6mmol/l, then the maximum time-to-next-glucose-measurement is 1hour otherwise
- If STT is less than –0.6 mmol/l per hour and the most recent glucose measurement is less than 6mmol/l, then the maximum time-to-next-glucose-measurement is 2hours otherwise
- The maximum time-to-next-glucose-measurement is 4 hours.

No doubt many other effective alternatives will occur to the skilled person. It will be understood that the invention is not limited to the described embodiments and encompasses modifications apparent to those skilled in the art lying within the spirit and scope of the claims appended hereto.

CLAIMS:

1. An apparatus for determining times of blood glucose measurement of a subject for use in controlling a level of said blood glucose, the apparatus comprising:

an input to receive blood glucose measurement data for a series of blood glucose measurements;

an adaptive model responsive to said blood glucose measurement data to represent the glucoregulation of said subject;

an estimator of a prediction error in said adaptive model as a function of time; and

a system to determine a time of a glucose measurement based on a comparison of said time-dependent prediction error with a range of acceptable blood glucose level for said subject.

2. An apparatus as claimed in claim 1 wherein said acceptable range of blood glucose level comprises a range defined by upper and lower bands of a desired blood glucose level.

3. An apparatus as claimed in claim 1 or 2 wherein said acceptable range of blood glucose level is time dependent.

4. An apparatus as claimed in claim 2 or 3 wherein said acceptable range of blood glucose level is determined responsive to said blood glucose measurement data.

5. An apparatus as claimed in claim 1 or 2 wherein said acceptable range of blood glucose level is substantially constant over time.

6. An apparatus as claimed in any one of claim 1 to 5 wherein said adaptive model is adapted periodically in response to a plurality of sets of said blood glucose measurement data from a plurality of said subjects.

7. An apparatus as claimed in any one of claims 1 to 5 wherein said adaptive model is adapted in substantially real time responsive to said blood glucose measurement data from said subject.

8. An apparatus as claimed in any one of claims 1 to 7 further comprising a glucose controller to determine a level of insulin infusion or dose to administer to said subject using said adaptive model.

9. A method of determining times of blood glucose measurement of a subject for use in controlling a level of said blood glucose, the method comprising:

receiving blood glucose measurement data for a series of blood glucose measurements;

adaptively modelling the glucoregulation of said subject responsive to said blood glucose measurement data;

estimating a prediction error in said adaptive model as a function of time;

determining a time of a glucose measurement based on a comparison of said time-dependent prediction error with a range of acceptable blood glucose level for said subject.

10. A carrier carrying computer program code to implement the method of claim 9.

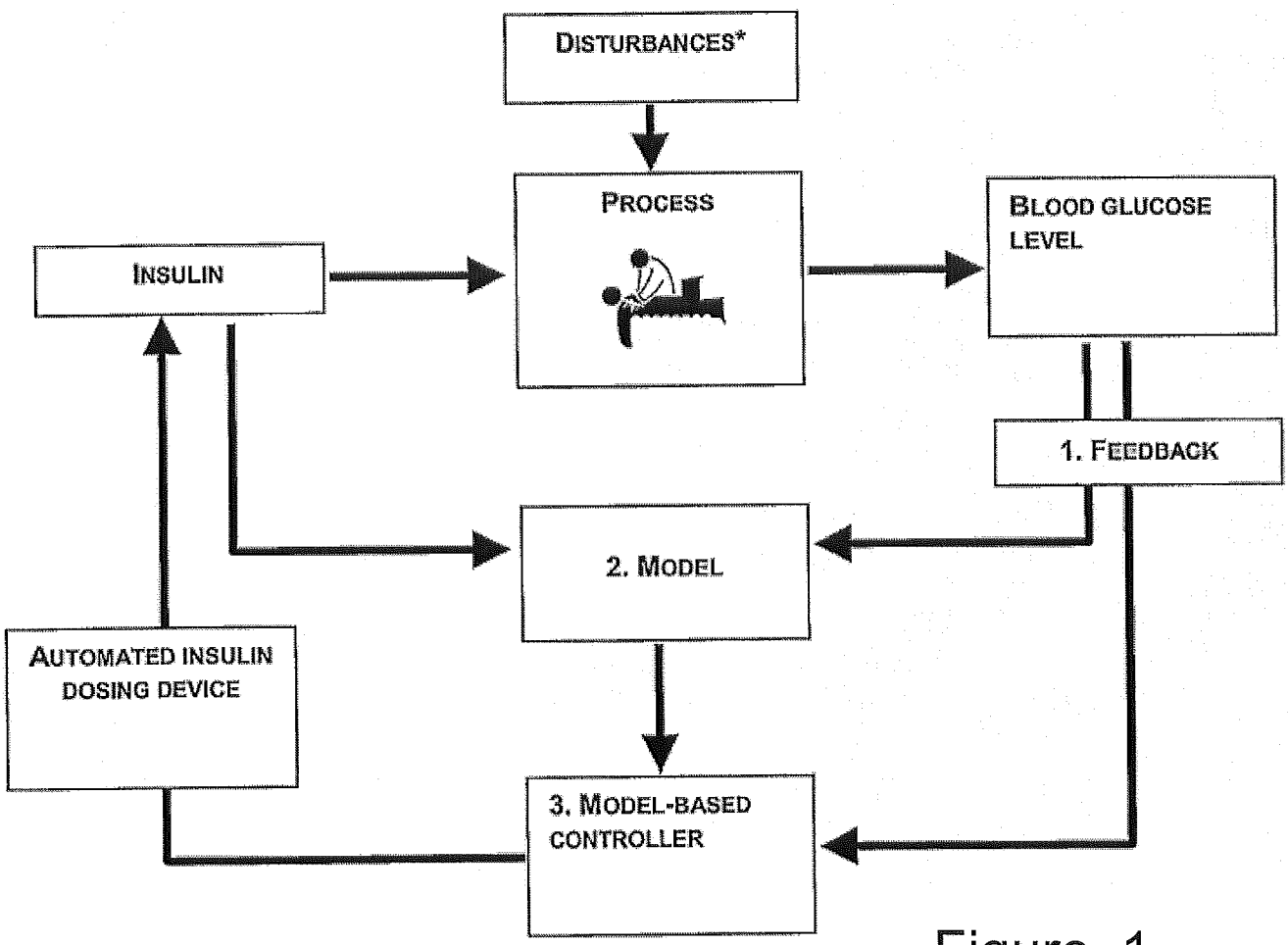

Figure 1

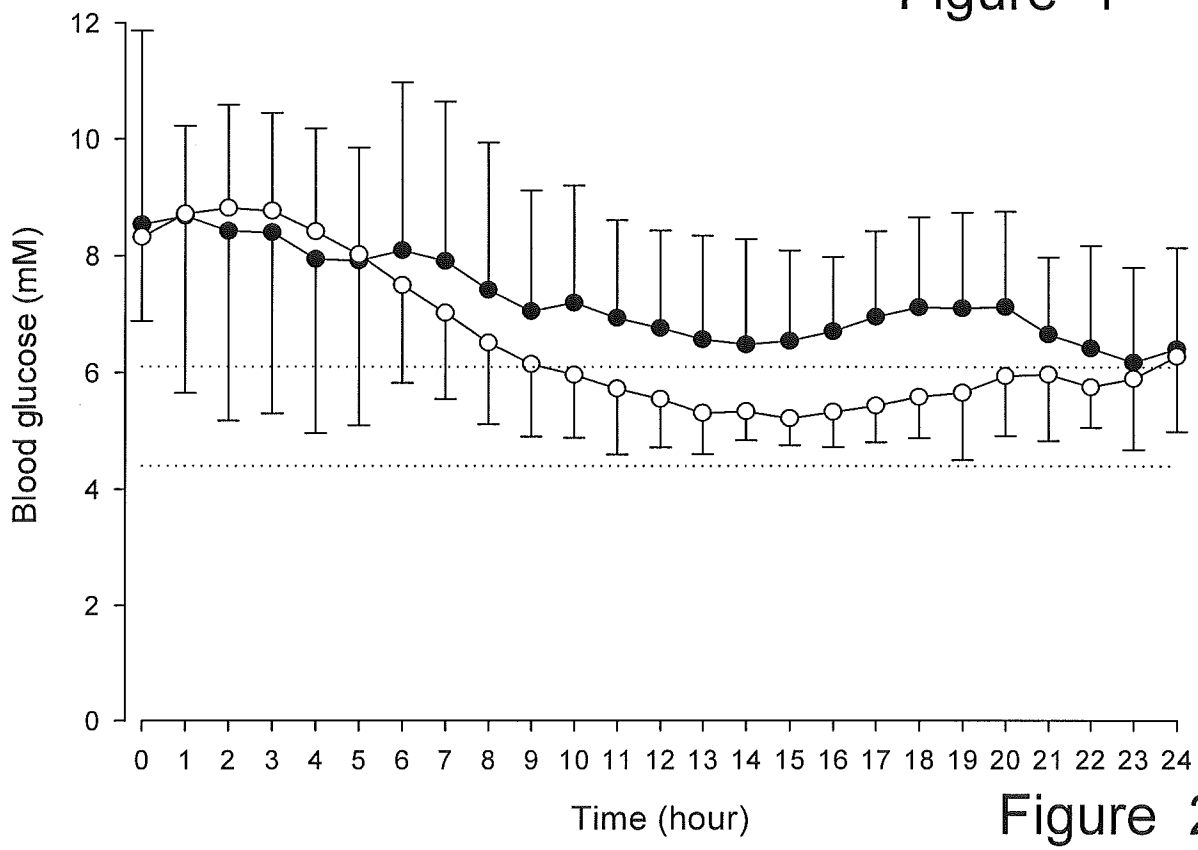

Figure 2

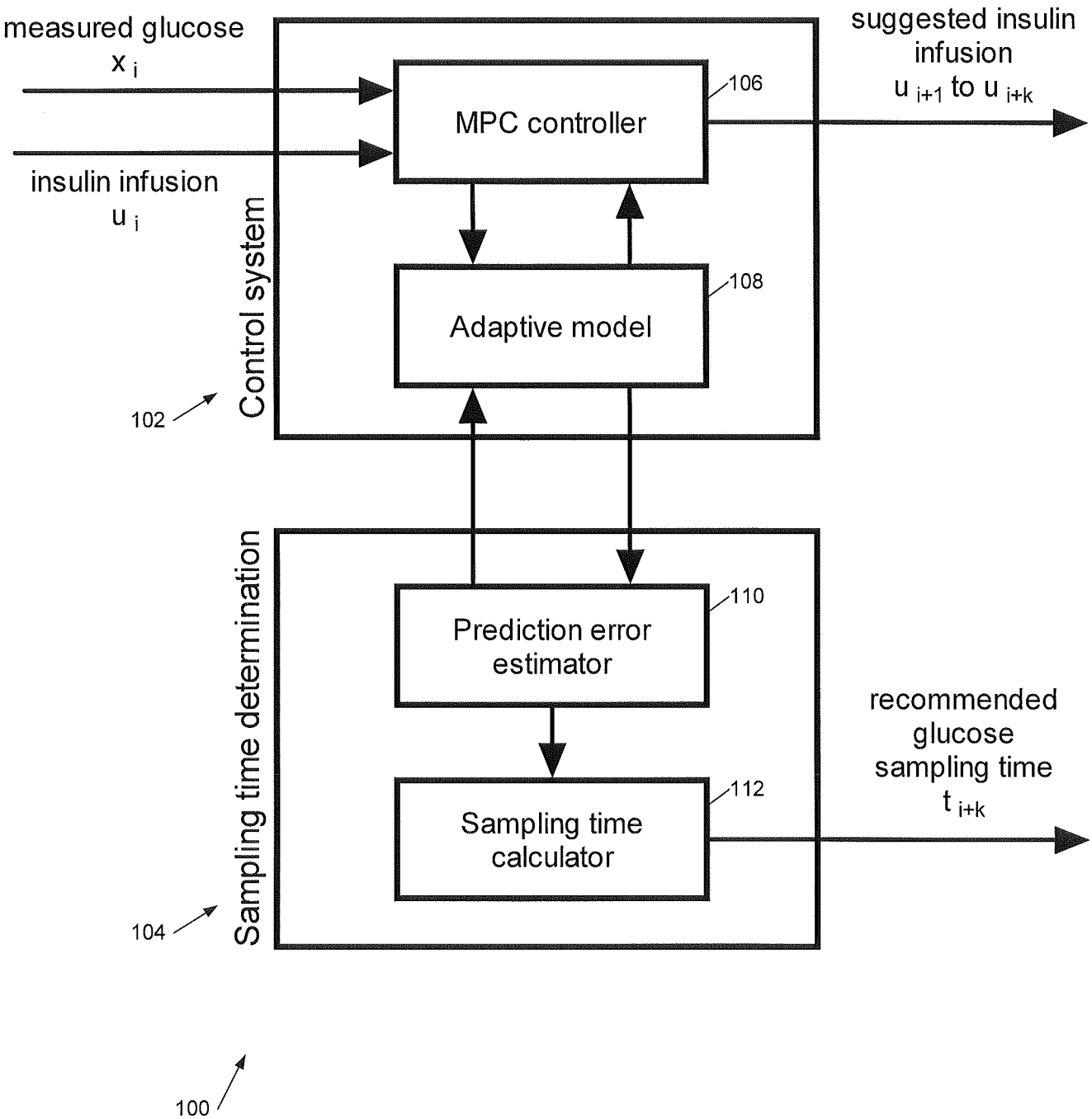
measured glucose
x_i
insulin infusion
u_i
suggested insulin infusion
u_{i+1} to u_{i+k}
MPC controller
106
Adaptive model
108
Control system
102
Prediction error estimator
110
Sampling time calculator
112
Sampling time determination
104
recommended glucose sampling time
t_{i+k}
100

Figure 3

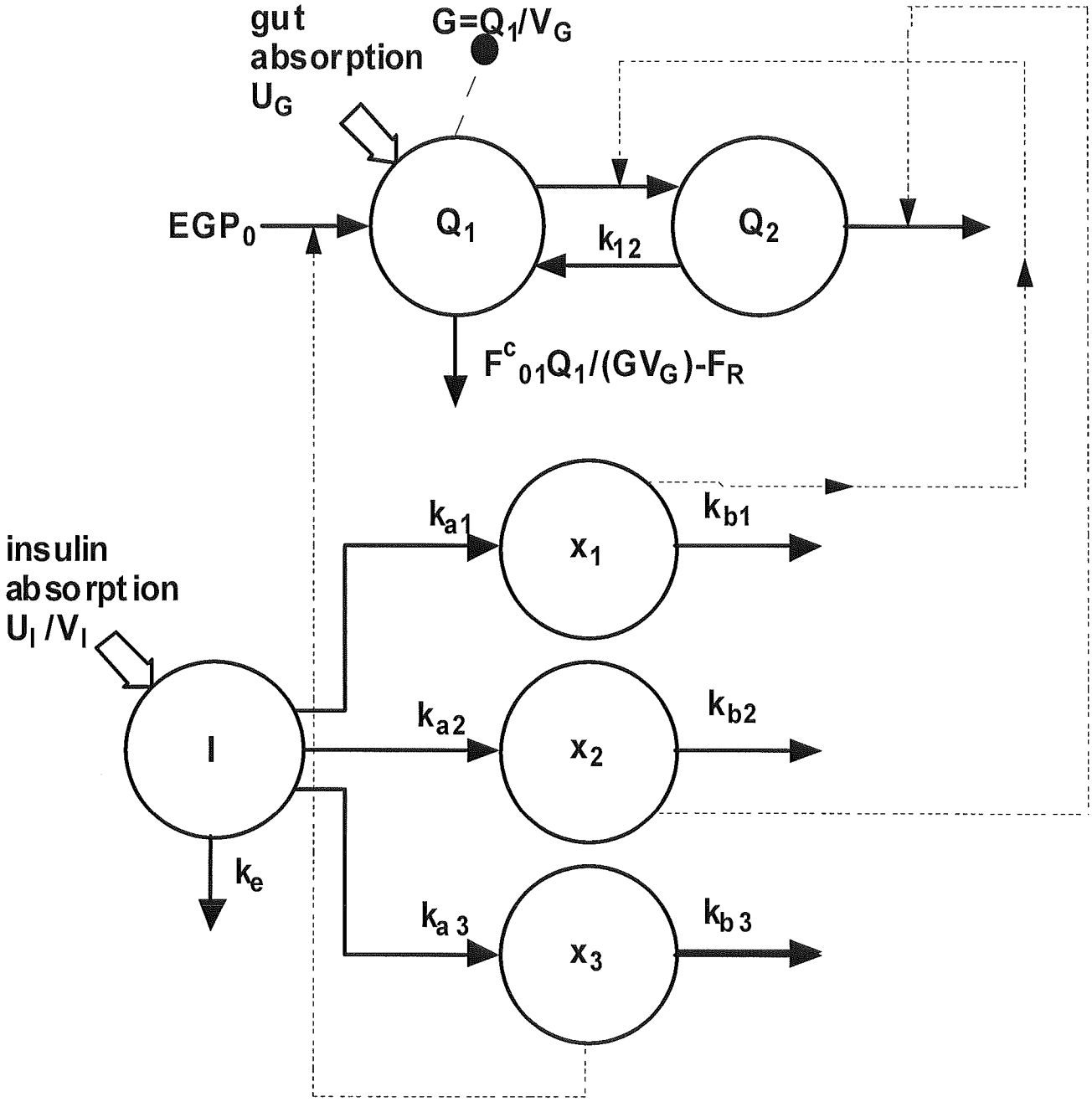
gut
absorption
U_G
$G=Q_1/V_G$
EGP_0
Q_1
k_{12}
Q_2
$F^c_{01}Q_1/(GV_G)-F_R$
insulin
absorption
U_I/V_I
I
k_e
k_{a1}
x_1
k_{b1}
k_{a2}
x_2
k_{b2}
k_{a3}
x_3
k_{b3}

Figure 4

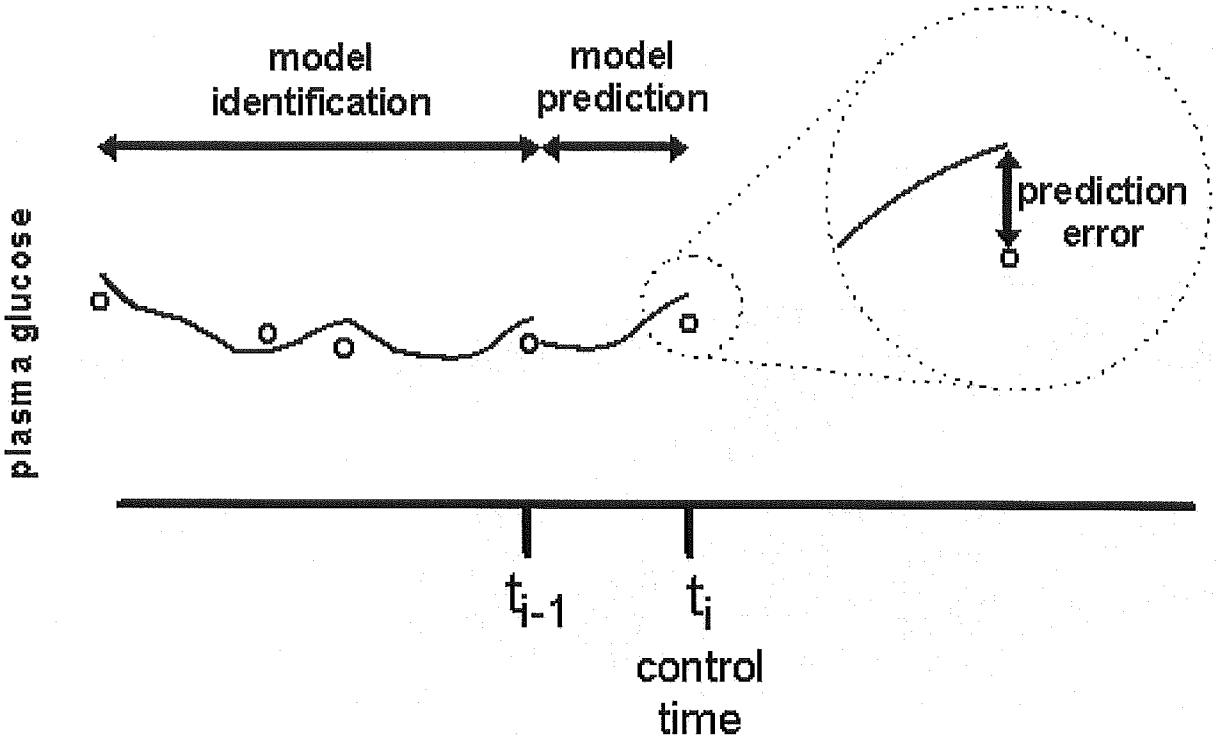

Figure 5

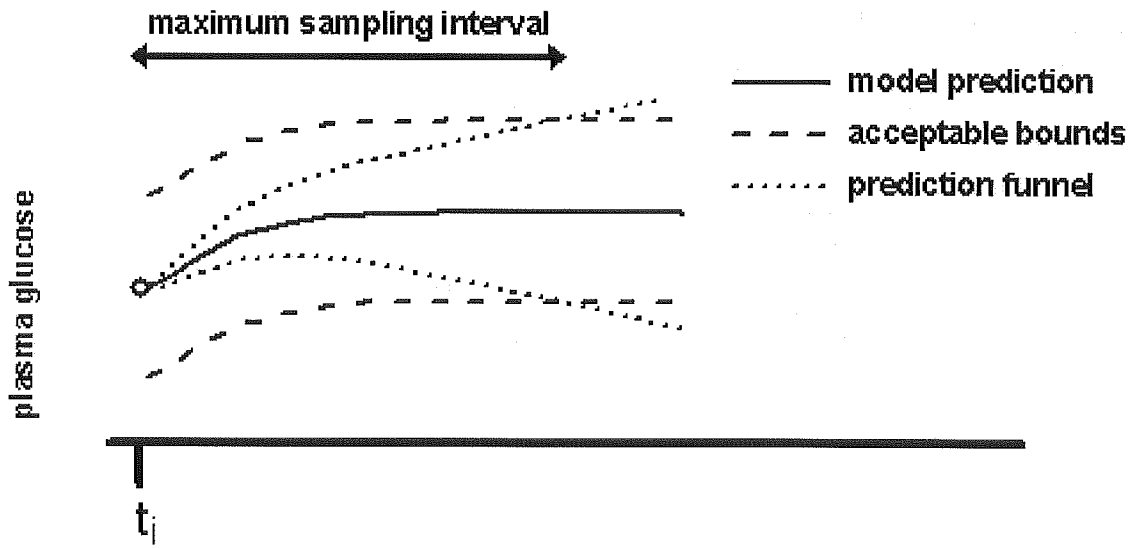

Figure 6

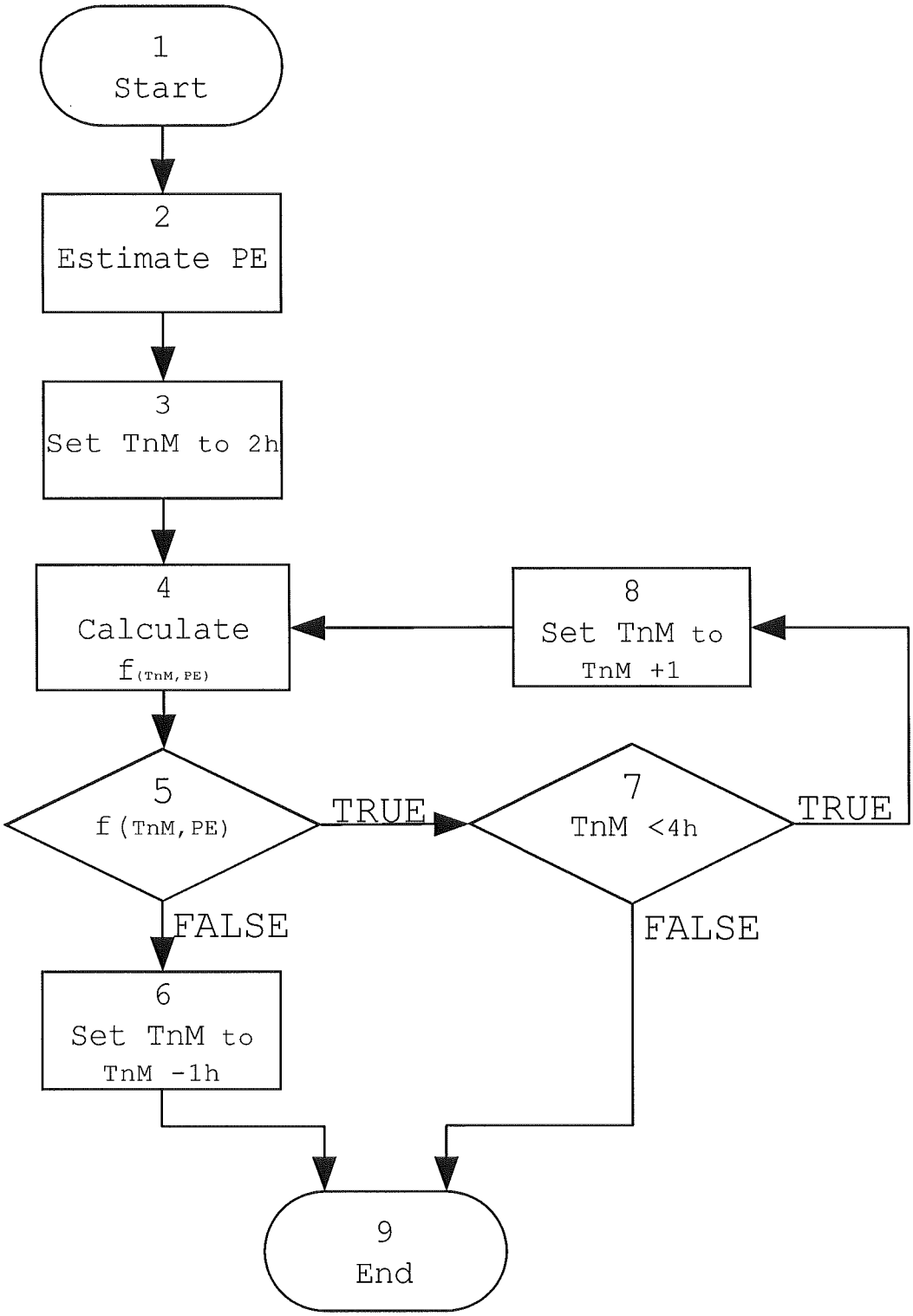
1
Start
2
Estimate PE
3
Set TnM to 2h
4
Calculate
f(TnM, PE)
8
Set TnM to
TnM +1
5
f(TnM, PE)
TRUE
7
TnM <4h
TRUE
FALSE
FALSE
6
Set TnM to
TnM -1h
9
End

Figure 7