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# A Long-term Model of the Glucose-Insulin Dynamics of type 1 Diabetes

Nicolas Magdelaine<sup>1</sup>, Lucy Chaillous<sup>2</sup>, Isabelle Guilhem<sup>3</sup>, Jean-Yves Poirier<sup>3</sup>, Michel Krempf<sup>2</sup>, Claude H. Moog<sup>1</sup>, *Fellow, IEEE* and Eric Le Carpentier<sup>1</sup>

**Abstract**—A new glucose-insulin model is introduced which fits with the clinical data from in- and outpatients for two days. Its stability property is consistent with the glycemia behavior for type 1 diabetes. This is in contrast to traditional glucose-insulin models. Prior models fit with clinical data for a few hours only or display some non-natural equilibria. The parameters of this new model are identifiable from standard clinical data as continuous glucose monitoring (CGM), insulin injection and carbohydrate estimate. Moreover, it is shown that the parameters from the model allow the computation of the standard tools used in *functional insulin therapy* as the basal rate of insulin and the insulin sensitivity factor. This is a major outcome as they are required in therapeutic education of type 1 diabetic patients.

**Index Terms**—clinical data, functional insulin therapy, glycemia, modeling, type 1 diabetes

## I. INTRODUCTION

**T**YPE 1 diabetes mellitus (T1DM) is an auto-immune disease leading to the destruction of the pancreatic  $\beta$ -cells. Thus, the endogenous insulin secretion disappears and the natural mechanisms of glycemic regulation is dysfunctional. type 1 diabetes was a rapidly fatal disease until the discovery of insulin in 1921 by Banting and Best [1]. Besides, uncontrolled blood glucose (BG) leads to severe burden as blindness or kidney failure. One of the best current treatment is functional insulin therapy (FIT). FIT consists of a number of daily insulin injections depending on measurements of glycemia and carbohydrate food intake (CHO), with the purpose of maintaining normoglycemia (range: 70 - 120 mg/dl). FIT provides four tools, *e.g.* basal rate, insulin sensitivity factor (ISF), to help patients compute insulin doses [2], [3].

Despite these tools, most of the patients have difficulties in computing the correct amount of insulin to be injected due to incorrect estimates of carbohydrate food intake. The

incidence of physical activity or stress is also known to lead to a variability of the patient's insulin needs. Therefore, patients with type 1 diabetes often face disorders such as hypo- (BG < 70 mg/dl) and hyperglycemia (BG > 180 mg/dl) due to too large or too small insulin dose.

The fully automated artificial pancreas could significantly reduce the hypoglycemia and hyperglycemia events, and thus the risk of complications for T1DM patients. A model of insulin and glucose dynamics is required to design a model-based controller. Many glucose-insulin models have been developed [4], [5], [6], [7], tracing back to [8], with various complexity [9]. Unfortunately, as is shown in this paper, these models feature apparent equilibria in fasting periods so that, for each blood glucose value, a different insulin infusion rate is needed to maintain constant blood glucose level. Real life displays exactly the opposite situation as there is one single insulin infusion rate, known as the basal rate, which does not depend on the value of the glycemia, and which ensures the equilibrium of any value of the glycemia in fasting periods.

The consequence is that :

- most of these models enable a short-term BG prediction from 30 minutes to 5 hours ([10], [11], [12], [7]) or can fit with clinical data for 20 hours at most [13].
- they are unable to describe the tools for the FIT.

The aim of this article is to introduce a new model which fits with clinical data for over two days, although it remains elementary. Its main features rely on realistic stability properties and a long-term fit. This model is supported by identification results from clinical data. In addition, the computation of such FIT tools as the insulin basal rate and the insulin sensitivity factor is a byproduct from this mathematical model.

The outline of the paper is as follows. In Section II, existing glucose-insulin models are recalled and the existence of a non desired equilibrium is argued. The latter may hinder a long term fit with clinical data. This section also explains how the previous models are unable to compute FIT tools. The new model and the identification technique are presented in Section III. Section IV is initially devoted to analysis of the new model's stability properties, after which the tools of FIT are computed based on its parameters. Finally the results of parameter identification are presented. The identification is performed for clinical data with observation duration of a few days. Perspectives and a scientific discussion are initiated in the concluding section V.

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## II. PRELIMINARIES

### A. The state of art of modeling

In 1961, Bolie introduced the first glucose-insulin model and computed the "coefficients of normal blood regulation" [14] *i.e.* for healthy subjects.

The *Minimal Model*, developed by Bergman in 1981, enabled the estimation of the insulin sensitivity index [8] for healthy subjects and type 2 diabetic patients. This nonlinear model became very popular [15] and some modified versions are still used in applications for the artificial pancreas [16].

To overcome some drawbacks of the *Minimal Model* [4] De Gaetano introduced the *Dynamical Model* which is a nonlinear differential delay model. This model was shown to fit with glucose tolerance test data from healthy individuals [4].

In 2008, the "Uva/Padova T1DM Metabolic Simulator" was accepted by the Food and Drug Administration for the preclinical testing of control strategies in artificial pancreas studies. This simulator is based on glucose tracer data of healthy and type 2 diabetes. The parameter distributions were altered to create profiles of 300 type 1 diabetes virtual patients [17]. The parameters of this model can not be estimated from standard clinical data (CGM, injection, amount of CHO) [17].

The Hovorka maximal model is based on an intravenous glucose tolerance test of 6 healthy lean male subjects [5]. Nevertheless, this model was shown to describe the 20 hours collected data in 12 young subjects with type 1 diabetes [13]. However, non-standard clinical measure of insulin concentration every 30 minutes and advanced analysis methods [13] are needed to fit the parameters of the model.

In 2011 a linear model, with digestion dynamics, 5 states and 4 parameters, was developed to describe the blood glucose post-prandial breakfast excursions of a group of 10 type 1 diabetes patients [7].

### B. Functional insulin therapy

Improvements in glycemic control have been realized using "basal-bolus" injection schemes. The basal and bolus amounts are adjusted for hospitalized patients with a standardized protocol [2]. For outpatients, FIT provides four tools in order to help the patient to estimate his insulin needs [3].

- *Basal rate* is the constant insulin infusion rate that maintains glycemia at a constant value during fasting.
- *ISF* is the glycemic drop per unit of extra insulin when the basal infusion rate is correctly set.
- *Raise* is the resulting increase in BG of digestion of 15 g CHO when the basal rate is correctly set.
- *U/P* is the ratio of  $U$  units of insulin and  $P$  portions of CHO.  $U$  denotes the required units to recover the BG value prior to the digestion of  $P$  portions of CHO when the basal rate is correctly set. In this study one portion contains 20 g of CHO.

### C. Some drawbacks from existing models

What follows may be stated for several models. To be more concise, we will focus on the *Dynamical Model* [4] which is

written as:

$$\dot{I}(t) = -b_2 \cdot I(t) + \frac{b_6}{\Delta t} \int_{t-\Delta t}^t G(\tau) d\tau + u(t)/V_i \quad (1)$$

$$\dot{G}(t) = -b_1 \cdot G(t) - b_4 \cdot I(t) \cdot G(t) + b_7 + J(t) \quad (2)$$

The glycemia is denoted  $G(t)$  and  $I(t)$  is the plasma insulin concentration (*insulinemia*).  $J(t)$  is an intravenous glucose perfusion rate and  $u(t)$  is an insulin infusion rate.  $V_i$  is the insulin distribution volume. The constant increase in plasma glucose concentration due to constant baseline liver glucose release is denoted  $b_7$  [4]. For most of the newer model, the endogenous glucose production (EGP) is dependent on glucose [18] and goes to zero when plasma glucose is high.

It has been proven in [4] that the *Dynamical Model* (1), (2) is stable and has an equilibrium point for type 2 diabetic patients as well as for healthy individuals.

For type 1 diabetics, the pancreas does not secrete any insulin which leads to  $b_6 = 0$ . Considering fasting periods ( $J(t) = 0$ ), and using  $b_7$  as a simple description of EGP, the equations (1), (2) reduce to:

$$\dot{I}(t) = -b_2 \cdot I(t) + u(t)/V_i \quad (3)$$

$$\dot{G}(t) = -b_1 \cdot G(t) - b_4 \cdot I(t) \cdot G(t) + b_7 \quad (4)$$

The equilibrium point of (3), (4) is computed in fasting period. Setting the right hand side of (3) to 0, it is found that the pair  $(U_{eq}, I_{eq})$  is an equilibrium of (3) for any constant insulin infusion rate  $U_{eq}$ .

$$\left( U_{eq} \ ; \ I_{eq} = \frac{U_{eq}}{b_2 V_i} \right) \quad (5)$$

Consequently, the stable equilibrium  $G_{eq}$  for  $G(t)$  is found as

$$G_{eq} = \frac{b_7}{b_1 + b_4 \cdot \frac{U_{eq}}{b_2 V_i}} \quad (6)$$

Any constant insulin infusion rate may yield an apparent equilibrium. This conclusion remains valid whether the EGP  $b_7$  is constant or dependent on insulinemia or glycemia. This result stands in contradiction with clinical practice.

From (3), (4) and (6) the FIT tools necessarily fulfill the following equations:

- 1) The basal rate  $U_b$  is computed by solving (6) in  $U_{eq}$

$$U_b = U_{eq} = \frac{b_2 V_i}{b_4} \cdot \left( \frac{b_7}{G_{eq}} - b_1 \right) \quad (7)$$

This value depends on the glycemia  $G_{eq}$ . It stands in contradiction with functional insulin therapy [2], [3]. In the clinical practice a single value of the constant insulin infusion rate, known as the *basal rate*, independent from glycemia, maintains glycemia at any constant value during fasting periods.

- 2)  $U/P$  : the basal rate is assumed to be set to  $U_b$ . After a meal containing CHO without extra insulin injection, glycemia  $G(t)$  would first rise during digestion and then decrease towards its equilibrium  $G_{eq}$  which depends on  $U_b$  (6). Consequently, an extra insulin injection seems not be required for a meal containing CHO and  $U/P$  fulfills:

$$U/P = 0 \quad (8)$$

This stands again in contradiction with FIT : an extra insulin injection (*bolus*) is required [2], [3] for every meal containing carbohydrates. The apparent equilibrium ( $U_{eq}$ ;  $I_{eq}$ ;  $G_{eq}$ ) is asymptotically stable whereas it should be critically stable for T1DM patients.

Thus (3), (4) can not be used to compute the insulin basal rate nor  $U/P$ .

The model (3), (4) has shown to be efficient to represent the short term behavior of the glycemia dynamics but its long term validity is affected by its asymptotic properties described above.

### III. METHODS

To enable long-term validity and fit with clinical data, a new model with realistic equilibrium points is introduced in this section . It is an elementary type 1 glucose-insulin and digestion model with 5 states and 6 independent parameters.

#### A. Glucose dynamics

The glucose dynamics consists in a single equation, where  $\dot{G}(t)$  equals to the production of glucose minus the consumption of glucose.

The increase of glucose includes the liver endogenous glucose production  $k_1$  and the digestion of CHO  $D(t)$ . The endogenous glucose production  $k_1$  is assumed to be constant for simplicity, but a more accurate model may be derived.

The glucose absorption rate includes the consumption by the brain  $k_b$  without need of insulin, the storage by the liver and the consumption by the muscles under the action of insulin.

The insulin-dependent term of glucose consumption is not dependent of plasma glucose concentration. A study including 18 T1DM patients [19] shows that insulin action is proportional to the injection when it is between 0.075 U/kg and 0.3 U/kg. This assumption in type 1 diabetes is also supported by hyperglycemic clamp studies: hyperinsulinic clamp was performed on 16 T1DM patients in isoglycemic (6.5 mmol/L i.e. 120 mg/dl) and hyperglycemic (12 mmol/L i.e. 220 mg/dl) conditions in [20]. Glucose disposal rate and metabolic clearance of glucose were similar and not statistically different between the two blood glucose levels. These data support the assumption that the insulin-dependent term of glucose consumption does not depend on the plasma glucose concentration. Thus, the insulin dependent glucose decrease rate is written as  $-k_{si} \cdot I(t)$ . Other glucose elimination phenomena, dependent of glucose concentration, are neglected.

At this stage, the glycemia dynamics is written as:

$$\dot{G}(t) = -k_{si} \cdot I(t) + k_1 - k_b + D(t) \quad (9)$$

#### B. Insulin dynamics

The relationship between the insulin infusion rate  $u(t)$  and the insulinemia  $I(t)$  is derived from the pharmacokinetic characteristics of insulin [19]. As in [7], the insulin dynamics is given by a second order model with a single time constant  $T_u$ . Using  $U(s)$  and  $I(s)$ , the Laplace transforms of  $u(t)$  and  $I(t)$ , the transfert function is written as:

$$I(s) = \frac{k_u/V_i}{(1 + T_u \cdot s)^2} U(s) \quad (10)$$

$T_u$  is the time constant and  $k_u/V_i$  the static gain where  $V_i$  denotes the insulin distribution volume.

#### C. Digestion dynamics

A similar second order system is used to model the relationship between CHO in meal  $r(t)$  and  $D(t)$ . Its time constant is  $T_r$  and it uses the blood volume  $V_B$ . A state space representation of the digestion dynamics is:

$$\begin{bmatrix} \dot{D}(t) \\ \dot{D}(t) \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{1}{T_r^2} & -\frac{2}{T_r} \end{bmatrix} \cdot \begin{bmatrix} D(t) \\ \dot{D}(t) \end{bmatrix} + \begin{bmatrix} 0 \\ \frac{k_r}{V_B \cdot T_r^2} \end{bmatrix} r(t) \quad (11)$$

$T_r$  and the static gain  $k_r/V_B$  are tuned to reflect the glycemic index depending on the meal composition [21].

#### D. A state space representation of the complete model

With the state  $X(t) = [G(t) \ I(t) \ \dot{I}(t) \ D(t) \ \dot{D}(t)]^T$ , the inputs  $u(t)$  and  $r(t)$ , and the output  $y = G(t)$ , a state representation of the model (9), (10) and (11) reads as:

$$\begin{aligned} \dot{X}(t) &= A \cdot X(t) + [B_u \ B_r] \cdot \begin{bmatrix} u(t) \\ r(t) \end{bmatrix} + E \\ \dot{X}(t) &= \begin{bmatrix} 0 & -k_{si} & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & -\frac{1}{T_u^2} & -\frac{2}{T_u} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & -\frac{1}{T_r^2} & -\frac{2}{T_r} \end{bmatrix} \cdot X(t) \\ &+ \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & \frac{k_r}{V_B \cdot T_r^2} \end{bmatrix} \begin{bmatrix} u(t) \\ r(t) \end{bmatrix} + \begin{bmatrix} k_1 - k_b \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \\ y &= C \cdot X(t) = [1 \ 0 \ 0 \ 0 \ 0] \cdot X(t) \end{aligned} \quad (12)$$

To end this section we will discuss the parameters which have to be identified. If the body weight  $M$  [kg] is known, three parameters ( $V_B$ ,  $V_i$  and  $k_b$ ) can be computed using the following assumptions from [22], [23] and [6]:

- the insulin distribution volume is  $V_i$  [dl] =  $2.5M$
- the blood volume is  $V_B$  [dl] =  $0.65M$ .
- the brain consumes 5 g/h for adults independently of the body weight even after 12 hours fasting :

$$k_b [\text{mg/dl/min}] = 5000/60/V_B = 128/M \quad (13)$$

The model has six parameters ( $k_{si}$  [mg/U/min],  $T_u$  [min],  $k_u$  [min],  $T_r$  [min],  $k_r$  [min] and  $k_1$  [mg/dl/min]) to be identified. The insulin sensitivity  $k_{si}$  is one major parameter which has to be identified for each patient as it reflects the well-known variability of the metabolic effect of insulin. The insulin sensitivity  $k_{si}$  is assumed to be a constant parameter. Thus the intra-patient variability effect of insulin is not taken into account in this new elementary model.

### E. Clinical data and Estimation of parameters

Standard clinical data (CGM, injection, CHO) from Nantes University Hospital and Rennes University Hospital have been used to support these modeling results. Data from five type 1 diabetic patients using insulin pumps and CGM (5 minutes sampling rate) were analyzed.

Four patients were hospitalized : the amount of CHO was measured by dietitians. They have no physical activity. The records start with a fasting period.

One patient was an outpatient : the amount of CHO was *estimated* by the patient himself and there might have been some physical activity as walking.

The parameters  $V_i$ ,  $V_B$  and  $k_b$  were derived from the body weight  $M$ . We run off-line the least square method on the  $n$  samples of the output error. The optimal value  $\theta^* = [k_{si} \ T_u \ k_u \ T_r \ k_r \ k_l]$  is the vector of parameters that minimizes the criterion  $J_n$ :

$$J_n(\theta) = \frac{1}{n} \sum_{k=1}^n (G_{CGM}[k] - \hat{y}(\theta)[k])^2 = \frac{1}{n} \sum_{k=1}^n \epsilon^2(\theta)[k]$$

$$\theta^* = \underset{\theta}{\text{Arg min}} (J_n)$$

The recursive optimization method of Quasi-Newton is initialized with a rough estimate of vector  $\theta_0$  found using standard values of the FIT (Basal = 0.35 U/h/kg ; ISF = 50 mg/dl/U ; Raise = 50 mg/dl/15g<sub>CHO</sub>) and average values taken from [19].

We made the assumption that insulinemia is at equilibrium and that stomach is empty at the beginning of identification ( $I(0) = I_{eq} = \frac{k_u}{V_i} U_{eq}$ ,  $D(0) = 0$ ).

## IV. RESULTS

In this section, it is proven that the new model (12) features realistic asymptotic properties. It is also shown that the tools of functional insulin therapy can be derived from the parameters of the model (12). This is a major outcome as these tools are required in therapeutic education of type 1 diabetic patients and because alternative models do not provide them. Finally the identification results are presented for five patients.

### A. Equilibrium

The equilibrium point on a fasting period ( $D(t) = 0$ ) with a constant insulin infusion rate  $u(t) = U_{eq}$  is computed solving  $\dot{G}(t) = 0$  in (9):

$$\left( G = G_{eq} \ ; \ I_{eq} = \frac{k_l - k_b}{k_{si}} \right) \quad (14)$$

Consequently, with (10) the only value of  $u(t)$  that provides an equilibrium is:

$$U_{eq} = \frac{k_l - k_b}{k_{si}} \cdot \frac{V_i}{k_u} \quad (15)$$

This result is consistent with FIT, validating the *basal rate* on fasting period [2], [3].

**Property 1** : the equilibrium (14), (15) is unstable. ■

*Proof*: See Appendix A

This result is consistent with the observed glycemic deviation when basal rate is not set correctly [2], [3].

### B. The tools for functional insulin therapy

1) *Basal rate*: It is the constant insulin infusion rate  $U_b$  that maintains glycemia at a constant value during fasting period.

$$\text{Property 2 : } U_b \text{ [U/min]} = \frac{k_l - k_b}{k_{si}} \cdot \frac{V_i}{k_u}$$

*Proof*: Follows from equation (15) ■

2) *ISF*: Assume that the *basal rate*  $U_b$  is injected. The *ISF* is the glycemic drop per unit of extra insulin, injected at  $t = t_1^+$ , on an empty stomach ( $D(t) = 0$ ).

$$\text{Property 3 : } \text{ISF [mg/dl/U]} = k_{si} \cdot \frac{k_u}{V_i}$$

*Proof*: See Appendix A ■

3) *Raise*: Assume that the *basal rate*  $U_b$  is injected, the *raise* is the resulting increase in BG of digestion of 15 g of CHO, ingested at  $t = t_1^+$ .

$$\text{Property 4 : } \text{Raise [mg/dl/15g}_{\text{CHO}}] = 15 \cdot 10^3 \frac{k_r}{V_B}$$

*Proof*: See Appendix A ■

4) *U/P*: Assume that the *basal rate*  $U_b$  is injected, *U/P* is the ratio of  $U$  units of insulin and  $P$  portions of CHO.  $U$  denotes the units, injected at  $t = t_1^+$ , required to recover the BG value prior to the digestion of  $P$  portions of CHO, ingested at  $t = t_1^+$ . In this study one portion contains 20 g of CHO.

$$\text{Property 5 : } U/P \text{ [U/20g}_{\text{CHO}}] = 20 \cdot 10^3 \frac{V_i}{k_{si} \cdot k_u} \frac{k_r}{V_B}$$

*Proof*: See Appendix A ■

The parameters from the model (12) allow the computation of the tools of functional insulin therapy. Using clinical data, the value of these tools will be computed for each patient after the identification process.

### C. Identifiability

Straightforward but lengthy computations prove that (12) is identifiable from the standard clinical data (CGM, insulin injection, amount of CHO) for any  $u(t)$  and  $r(t)$  such that  $\dot{u}$ ,  $\ddot{u}$ ,  $u^{(3)}$ ,  $\dot{r}$ ,  $\ddot{r}$  and  $r^{(3)}$  are non zero. However, for standard patterns of insulin infusion rate ( $u(t) = U_b$ ) these singularities do exist.

### D. Identification results

Identification results using clinical data are presented in Table I, including parameters and FIT tools, and through Figures 1 to 5. Although the optimization algorithm remains very simple, it provides a long-term fit with clinical data. The standard deviation is about 20 mg/dl for each patient. The worst value of standard deviation is for the outpatient LR and might be due to some incorrect CHO estimation or exercise. Table I shows the inter-patient variability effect of insulin:

the parameter  $k_{si}$  and the ISF are highly variable from one patient to another. The dispersion in the insulin dynamics parameters  $T_u$  and  $k_u/V_1$ , reflects the inter-variability of the pharmacokinetic profile of insulin.

Although the identification algorithm is unconstrained:

- the range of values of  $T_u$  ( $59 < T_u < 122$  min) is consistent with the range of the time overshoot ( $34 < T_u < 112$  min) given in [19].
- the range of values of  $k_1$  ( $1.72 < k_1 < 3.33$  mg/dl /min i.e. from 1.1 to 2.2 mg/kg/min) is consistent with the range of the hepatic glucose production in fasting periods given in [22] (i.e. from 1.5 to 2.5 mg/kg/min).
- The dispersion (from 10 to 83 mg/dl/U) of the value of ISF is consistent with classical values given in [24] (from 15 to 90 mg/dl/U).

For patient IF3 the fasting period (23 first hours) is interrupted by many CHO intakes due to recurrent hypoglycemia. These are due to too high basal rate as confirmed by the progressive decrease according to the clinical protocol (from 2.0 U/h to 1.0 U/h). This result is consistent with the basal rate value computed from IF3's parameters (1.3 U/h - see table I).

The computed *basal rate* can not reflect the basal rate pattern as for patient LR, IF9 and BE.

The computed values of the tools for functional insulin therapy are all consistent with the real insulin needs determined by the clinical protocol. It is worth noting that those values are also consistent when they are computed from the identification results on a 20 hours record.

## V. CONCLUSION

It was shown, in this paper, how historical models of dynamic BG display apparent equilibria which are not desired. The implication of these equilibria is a basal insulin depending on BG level. Such equilibria do not exist for real life T1DM patients. It is foreseen that using such models will impact the long-term efficiency of prediction and control of the disease.

To have realistic equilibrium properties, a new model of glucose-insulin dynamics has been introduced which is linear and consists of 5 states and 6 independent parameters. In this model, any value of BG is critically stable and there exists one single basal insulin rate independent on BG.

Its parameters, identified from standard clinical data, provide the computation of the tools of the FIT. The latter are all consistent with the real insulin needs determined by the clinical protocol.

Despite simple linear differential equations and a simple identification algorithm, the type 1 diabetes model of glucose-insulin dynamics was shown to describe clinical data for two days.

The identification algorithm gives a vector of constant parameters and provides constant values of the FIT tools. Thus,  $T_r$  and  $k_r$  as well as  $k_1$  are constant parameters and do not reflect variability anticipated in the glycemic index of various meals and the hepatic glucose production respectively. Thus, the computed *basal rate* (depending on  $k_1$ ) will not display a basal rate pattern as used by some patients. Insulin inpatient variability (e.g. in case of physical activity or stress)

is also not reflected using the constant parameter  $k_{si}$ . Thus, an on-line identification for these parameters could display a basal rate pattern and a better fit. These issues remain open for further research.

An effective assessment on how the model impacts the performance of glycemia regulation using model based algorithms is subject to further investigation as well.

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TABLE I  
RESULTS OF IDENTIFICATION

Patient	Glucose dynamics		Parameters		Digestion dynamics	FIT Tools	length [hours]	Error mean [%] SD [mg/dl]
	$k_{si}$ [mg/U/min]	$k_l$ [mg/dl/min]	Insulin dynamics $T_u ; k_u/V_i$ [min] ; [min/dl]	Digestion dynamics $T_r ; k_r/V_B$ [min] ; [min/dl]				
IF2 hospitalized	197	1.94	122 min ; 55 10 <sup>-3</sup>	183 min ; 2.4 10 <sup>-3</sup>	Basal 0.8 U/h ; U/P = 4 ISF = 11 ; Raise +34	50	1.0 % 18 mg/dl	
IF3 hospitalized	274	1.72	88 min ; 64 10 <sup>-3</sup>	49 min ; 2.0 10 <sup>-3</sup>	Basal 1.3 U/h ; U/P = 2.4 ISF = 17 ; Raise +31	48	5.0 % 20 mg/dl	
LR outpatient	460	3.33	70 min ; 177 10 <sup>-3</sup>	34 min ; 4.9 10 <sup>-3</sup>	Basal 0.7 U/h ; U/P = 1.2 ISF = 83 ; Raise +73	45	11.6 % 39 mg/dl	
IF9 hospitalized	380	2.32	74 min ; 118 10 <sup>-3</sup>	73 min ; 7.0 10 <sup>-3</sup>	Basal 0.6 U/h ; U/P = 3.1 ISF = 45 ; Raise +100	38	2.5 % 24 mg/dl	
BE hospitalized	186	1.91	59 min ; 54 10 <sup>-3</sup>	38 min ; 2.7 10 <sup>-3</sup>	Basal 1.0 U/h ; U/P = 5.6 ISF = 10 ; Raise +42	30	3.7 % 22 mg/dl	

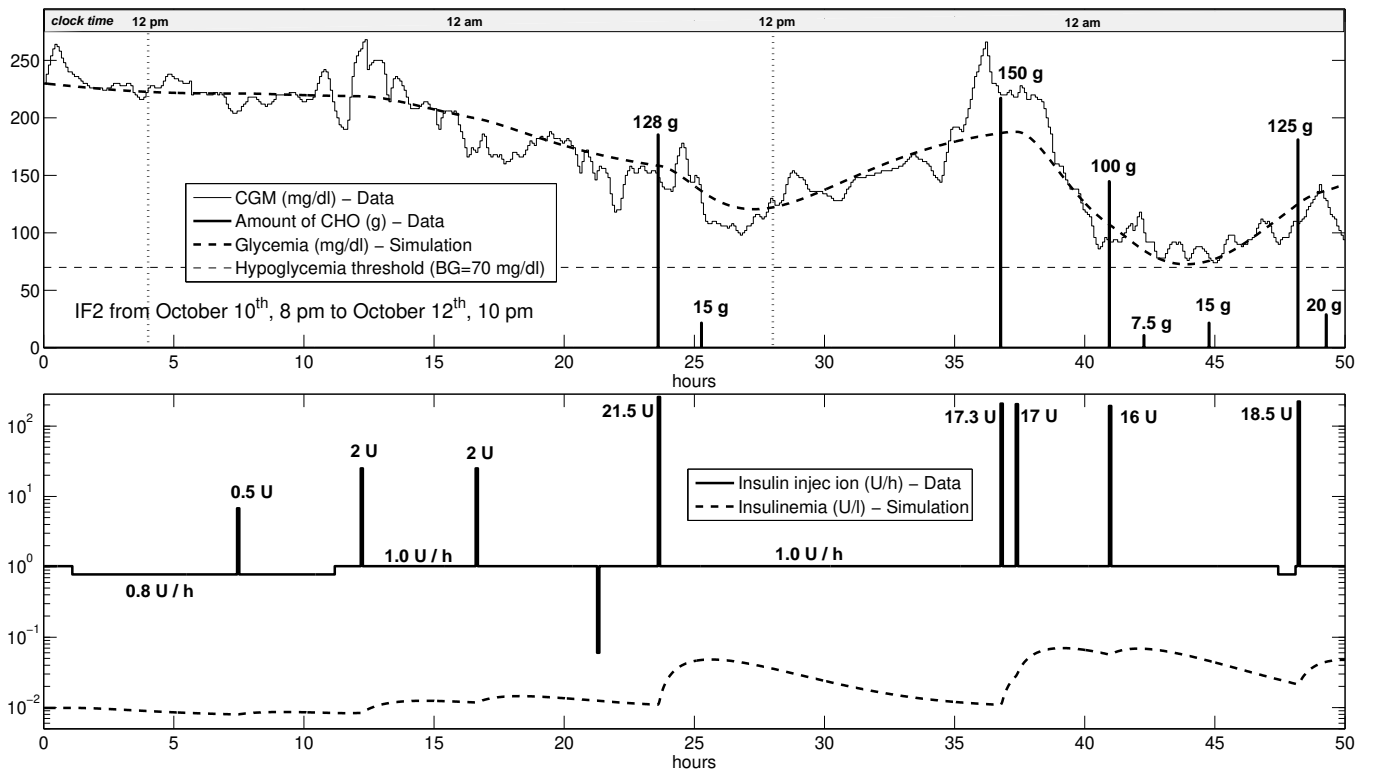


Fig. 1. Patient IF2: M = 72 kg

APPENDIX A  
PROOF OF THE MODEL PROPERTIES

**Property 1 :** the equilibrium (14), (15) is unstable.

*Proof:* The range of the hepatic glucose production in fasting periods, from 1.5 to 2.5 mg/kg/min, is given in [22] and [23]. With the average value 2 mg/kg/min

$$k_l = 2 \cdot M / V_B = 3 \text{ mg/dl/min} \quad (16)$$

For  $M > 40$  kg and with (13) and (16) we have  $k_l - k_b > 0$ .

Assume that  $u(t)$  equals a constant  $U_{\text{high}}$  larger than  $U_{\text{eq}}$  in (15). Then from (10) the corresponding insulinemia  $I_{\text{high}}$  is such that  $I_{\text{high}} > \frac{k_l - k_b}{k_{si}}$  which yields from (9) :  $\dot{G}(t) < 0$ .

Assume that  $u(t)$  equals a constant  $U_{\text{low}}$  smaller than  $U_{\text{eq}}$  in (15). Then from (10) the corresponding insulinemia  $I_{\text{low}}$  is such that  $I_{\text{low}} < \frac{k_l - k_b}{k_{si}}$  which yields from (9) :  $\dot{G}(t) > 0$ . ■

$$\text{Property 3 : ISF [mg/dl/U]} = k_{si} \cdot \frac{k_u}{V_i}$$

**Definition :** With  $D(t) = 0$  and  $u(t) = U_b + 1 \cdot \delta(t_1^+)$

$$\text{ISF} = - \int_{t_1}^{t_2} \dot{G}(t) dt \text{ for } t_2 - t_1 \gg T_u$$

*Proof:*

Assuming  $u(t) = U_b + 1 \cdot \delta(t_1^+) = U_b + \tilde{u}(t)$  and

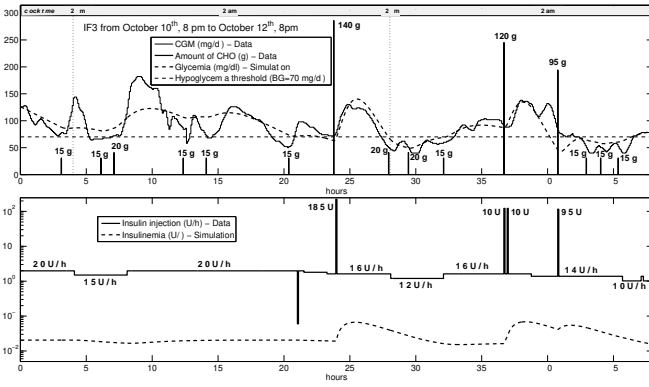


Fig. 2. Patient IF3: M = 94 kg

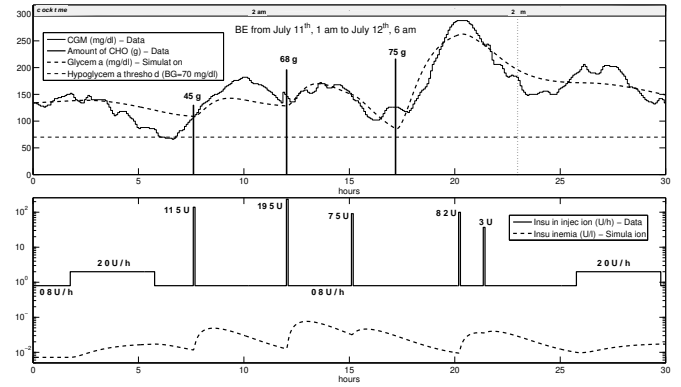


Fig. 5. Patient BE: M = 73.5 kg

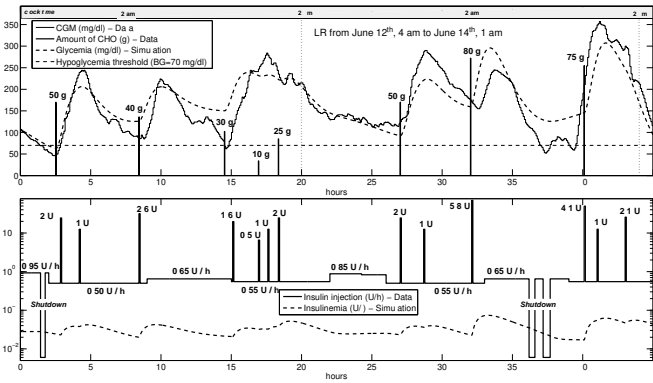


Fig. 3. Patient LR: M = 54 kg

with (14) one gets  $I(t) = I_{eq} + \tilde{I}(t) = \frac{(k_1 - k_b)}{k_{si}} + \tilde{I}(t)$

The latter is substituted in (9) so that

$$\dot{G}(t) = -k_{si} \cdot (I_{eq} + \tilde{I}(t)) + k_1 - k_b = -k_{si} \cdot \tilde{I}(t)$$

$$\text{consequently } \text{ISF} = - \int_{t_1}^{t_2} \dot{G}(t) dt$$

$$\text{ISF} = k_{si} \cdot \int_{t_1}^{t_2} \tilde{I}(t) dt = k_{si} \cdot \frac{k_u}{V_i}$$

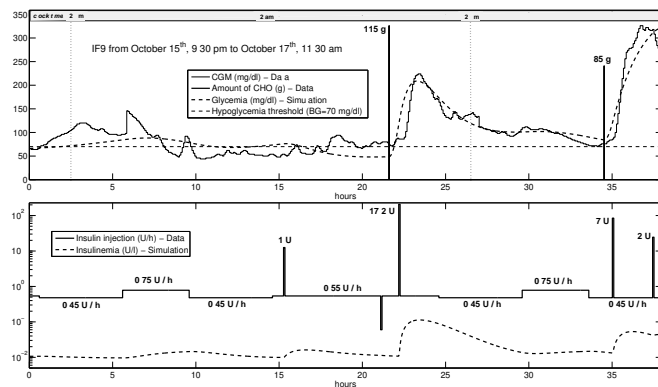


Fig. 4. Patient IF9: M = 68 kg

$$\text{Property 4 : Raise [mg/dl/15g}_{\text{CHO}}] = 15 \cdot 10^3 \frac{k_r}{V_B}$$

**Definition :** With  $r(t) = 15 \cdot 10^3 \delta(t_1^+)$  and  $u(t) = U_b$

$$\text{Raise} = \int_{t_1}^{t_2} \dot{G}(t) dt \text{ for } t_2 - t_1 \gg T_r$$

*Proof:* Assuming  $u(t) = U_b$  and using (14)

$$\text{one gets } I(t) = I_{eq} = \frac{(k_1 - k_b)}{k_{si}} \text{ which is substituted}$$

in (9) so that  $\dot{G}(t) = -k_{si} \cdot I_{eq} + k_1 - k_b + D(t) = D(t)$

$$\text{consequently } \text{Raise} = \int_{t_1}^{t_2} D(t) dt = 15 \cdot 10^3 \frac{k_r}{V_B}$$

$$\text{Property 5 : U/P [U/20g}_{\text{CHO}}] = 20 \cdot 10^3 \frac{V_i}{k_{si} \cdot k_u} \frac{k_r}{V_B}$$

**Definition :** Assume  $t_2 - t_1 \gg T_r$ ,  $t_2 - t_1 \gg T_u$ . P defines the meal  $r(t) = 20 \cdot 10^3 \cdot P \cdot \delta(t_1^+)$  and U/P is the ratio where U defines the insulin injection  $u(t) = U_b + U \cdot \delta(t_1^+)$  such that  $\int_{t_1}^{t_2} \dot{G}(t) dt = 0$

*Proof:* With (12) and (14) we can write :

$$I(t) = I_{eq} + \tilde{I}(t) = \frac{(k_1 - k_b)}{k_{si}} + \tilde{I}(t)$$

$$\dot{G} = -k_{si} \cdot I + k_1 - k_b + D = -k_{si} \cdot \tilde{I}(t) + D$$

$$\Delta G = \int_{t_1}^{t_2} \dot{G} dt = -k_{si} \cdot \int_{t_1}^{t_2} \tilde{I}(t) dt + \int_{t_1}^{t_2} D dt = 0$$

$$\Delta G = -k_{si} \cdot \frac{k_u}{V_i} \cdot U + 20 \cdot 10^3 \cdot \frac{k_r}{V_B} \cdot P = 0$$

$$U/P = \frac{U}{P} = 20 \cdot 10^3 \frac{V_i}{k_{si} \cdot k_u} \frac{k_r}{V_B}$$