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A new model for closed-loop control in type 1 diabetes

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Abstract: A new control model for type 1 diabetes mellitus (T1DM) is designed with the aim to represent accurately the plasma insulin-glucose dynamics. It is in the form of a nonlinear system of three time-continuous state equations. The model includes two successive remote compartments for plasma insulin, accounting for a slow and a fast dynamics. The modeling of the insulin action on the glucose disappearance is in an original nonlinear form. This new model is identified and validated using data from adult subjects of the UVa T1DM simulator training database. The parametric identification of the model provides in each case an accurate representation of the insulin-glucose dynamics of the subjects.

Keywords: Type 1 Diabetes, Control Model, Parametric identification, Closed Loop Control.

1. INTRODUCTION

The treatment of type 1 diabetes mellitus (T1DM) consists of an exogenous insulin injection to regulate the blood glucose level in a normal range value (70-110 mg/dl). Such a regulation is difficult to achieve because of the complexity of the insulin-glucose system (Tuch et al. [2004]) and its strong disturbances: meal, exercise or stress. The current therapy of this disease is a "human" closed-loop where the patient himself plays the role of the controller. However, in this type of control, mistakes are frequent. A better and safer control is thus expected from an automatic closed loop (Bruttomesso et al. [2009], Hovorka et al. [2010]). Artificial pancreas is the name of this kind of solution in T1DM. Many techniques are available to design automatic closed-loops. In the case of model based control (Model Predictive Control, H^∞ Control, Passivity Based Control, Sliding Mode Control, etc.), a control model of the system is necessary. This model should be sufficiently simple to allow the computation of the control law and sufficiently accurate to represent the actual insulin-glucose system. During the last decade, numerous models have been published with diverse mathematical forms: ordinary differential equations, delay differential equations, partial differential equations, stochastic differential equations, etc. as indicated in Makroglou et al. [2006]. Nevertheless, the continuous time state space representation seems to be a relevant mathematical form, in that parameters may have a physiological meaning. Indeed, physicians may be able to validate the obtained parameters values. For instance, the "minimal model" of Bergman (Bergman et al. [1979]) and its extension to type 1 diabetes (Pistikopoulos et al. [2007]) correspond to this frame. The latter has been used as control model in a lot of articles, as in Kaveh and Shtessel [2008] or Gillis et al. [2007]. However, Fernandez et al. [2007] used this model for parametric identification and highlighted some limitations. More particularly, they underlined that this model is not able to follow complex situations in T1DM treatment data (several bolus, inappropriate insulin dosage, etc.). In order to take into account the effect of insulin saturation and the time-varying utilization of insulin and glucose removal, Chase et al. [2005] and Hann et al. [2005] developed a modified version of the minimal model. In their model, five of the seven parameters are assumed to be fixed from average values stemming from literature. This *a priori* choice of constant values was questioned in their outcomes. Consequently, it seems relevant to develop new control models for T1DM with the purpose of representing more accurately the insulin-glucose dynamics.

In this article, we propose to build such a control model based on two features. Firstly, the dynamical action of the plasma insulin on the glucose in T1DM is defined by three ordinary differential equations. Secondly, the equilibrium points of our model have to be closed to observed equilibrium points either from real or virtual patients. Yet in the current paper, the study is restricted to virtual patients.

The paper proceeds as follows. In section 2, we present the *in silico* model used to generate the data for the identification and validation of our own model. Next, section 3 deals with the design and the presentation of our new control model. The outcomes of the parametric identification of our model and its validation are presented in section 4.

2. *IN SILICO* MODEL OR VIRTUAL PATIENTS

Simulation models of T1DM have been developed these last few years to accelerate the development of the artificial pancreas. A review of available different models can be found in Wilinska and Hovorka [2008]. We are interested in a specific simulation model based on the work of Dalla Man et al. [2007]. It is a detailed model of the insulin-glucose system composed of 13 differential equations. It considers the main aspects of the glucose metabolism, through two submodels and unitary processes. The submodels are the

glucose and insulin systems which are both described by a two-compartment model. The unitary processes are the liver (hepatic production), the kidneys (kidney excretion), the gut (meal absorption) and the subcutaneous insulin infusion. This model has been implemented as a simulation toolbox developed by Kovatchev et al. [2009] in the framework of Matlab-Simulink. Furthermore, this simulation model is approved by the FDA (Food and Drug Administration) as an *in silico* model of diabetes for closed-loop algorithms pre-clinical tests. Hence it was the simulation model selected to generate our experimental data.

Ten adult subjects are included in a so-called "training database" associated with this software. They are assumed to be representative of both intrasubject and intersubject variations found among people with T1DM. In our approach, we shall use them as virtual patients in order to generate pseudo-clinical data to identify and validate our control model.

3. DESIGN OF A NEW CONTROL MODEL

Currently, the insulin is injected subcutaneously (s.c.) via an insulin pump and the blood glucose level is measured in the interstitial fluid with continuous glucose monitoring sensor (CGMS). Figure 1 represents a decomposition, to simplify the modeling process, of the actual system of s.c insulin and interstitial glucose in three blocks. The first one represents a model of the diffusion of the injected insulin to the plasma, the second one represents a model of the plasma insulin-glucose system and the last one a model of a CGMS.

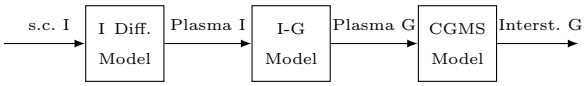

Fig. 1. Block diagram of the decomposition of the s.c. insulin-glucose system in three parts

This decomposition is quite common in existing insulin-glucose models (Cobelli et al. [2009]) and all the inputs-outputs of the blocks of Fig. 1 are accessible to measurement in a clinical protocol: the s.c insulin and interstitial glucose values are obtained through data from the insulin pump and the CGMS, the plasma and insulin glucose concentrations are obtained from blood samples analysis. Then, the three different models are identifiable separately.

In this paper, we focus on a model of the plasma insulin-glucose system (block 2) because studied models of this system (Bergman et al. [1979], Chase et al. [2005], Li et al. [2001], etc.) present the same characteristic that we question, namely they are of variation around a basal value of plasma glucose and plasma insulin. The issue raised by this is detailed in section (3.1).

Before introducing the design of our new control model, we first present the minimal model of Bergman as it is at the root of most of insulin-glucose system models and of our new control model.

3.1 The minimal model of Bergman and its limitations

The minimal model of Bergman was developed in 1979 for intravenous glucose tolerance test (IVGTT) for non-diabetic and type II diabetic patients. It was modified for T1DM by adding a compartment for external insulin injection.

This model is based on three assumptions. The first assumption is that the glucose acts to inhibit its own production and to increase its utilization. The second one is that the insulin acts to synergize these glucose effects. The last one is that the insulin effect is delayed and presumably depends on its concentration in a compartment remote from plasma. The model assumes single-compartment glucose distribution kinetics with constant volume and its mathematical description is given by eq. 1:

$$\begin{aligned} \dot{G}(t) &= -P_1 (G(t) - G_b) - X(t) G(t) \\ \dot{X}(t) &= -P_2 X(t) + P_3 (I(t) - I_b) \end{aligned} \tag{1}$$

where G (mg/dl) is the plasma glucose concentration, I $(pmol/l)$ is the plasma insulin concentration, X (min^{-1}) is the plasma insulin concentration in the remote compartment, G_b (mg/dl) is the basal value of glucose concentration, I_b $(pmol/l)$ is the basal value of insulin concentration. The rate coefficient P_1 (min^{-1}) governs the ability of glucose to increase its own disappearance. P_2 (min^{-1}) and P_3 $(l/pmol.min^{-2})$ are the rate coefficients of the insulin into and out of the remote compartment.

Now, two remarks on the minimal model are introduced in order to highlight the design of our control model.

The first one is about the parameters G_b and I_b, which are specific equilibrium values of the state variables (G and I). In case of a non diabetic subject, I_b corresponds to the value of insulin produced by the pancreas in fasting resting states and G_b is the glucose value associated. In case of T1DM, I_b and G_b are unknown. Indeed, a large number of values of the couple (G_b , I_b) correspond to a value of glucose in the normal metabolic range in fasting resting states; I_b is the result of a human choice. But if I_b or G_b are not fixed, the model is structurally non identifiable. To overcome this point, our method is to design a model not of variation around basal values of the plasma insulin and glucose concentrations, and to set a generic condition about equilibrium points.

Static equilibrium condition: the mathematical relation on the equilibrium points of the control model has to be consistent with the observation of the simulation model equilibrium points. This condition, which implies a coherence in statics between the control model and the simulation model, simplifies the parametric identification process, the time constants are then uniquely adjusted to follow the dynamics of the system.

The second remark is on the single compartment hypothesis of the minimal model (Caumo et al. [1996]) leading to coarse estimations. Cobelli et al. [1998] addressed this problem and proposed a two compartment model for the glucose kinetics. Our choice here is to address this problem by making more complex the model of the insulin kinetics.

3.2 Static equilibrium condition: equilibrium equations

The new model should follow *static equilibrium condition*, thus for each adult, its equilibrium curve was determined. Twenty different basal values of insulin were injected, the

length of the simulation was of 6000 minutes so that the blood glucose level reached a quasi-constant level.

The simplest mathematical equation found from trials on the obtained data is given by (2):

$$G_{eq} = \frac{1}{aI_{eq}^{\alpha} + b} \tag{2}$$

To estimate the best α value for each virtual adult subject, the Matlab Curve Fitting Toolbox was used to determine the best parameters a and b of (2) to fit the twenty equilibrium points values. Three different values of α ($\alpha = 1, \frac{3}{2}, 2$) were considered, as higher or lower values led to no interesting results.

The *adjusted* R^2 statistic is the indicator chosen to represent our results, as it is an indicator of the quality of the fit, a good fit being indicated by a value of the R^2 close to 1:

$$adjusted\ R^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2 (n-1)}{\sum_{i=1}^{n} (y_i - \overline{y})^2 (n-m)}$$

where n is the number of observed values, m is the number of fitted coefficients, the y_i are the observed values, the $\hat{y}_i$ are the modeled values and $\overline{y}$ is the mean value of observed values.

Table 1 presents the value of the *adjusted* R^2 for the ten adults.

Table 1. values of the *adjusted* R^2 for all adults

Subjects	$\alpha = 1$	$\alpha = 3/2$	$\alpha = 2$
Adult 1	0.97	0.99	1
Adult 2	0.98	1	1
Adult 3	0.98	1	1
Adult 4	0.78	0.96	1
Adult 5	0.99	1	0.99
Adult 6	0.89	0.98	0.98
Adult 7	0.62	0.84	0.96
Adult 8	0.95	0.98	1
Adult 9	0.97	0.99	1
Adult 10	0.99	1	0.99
mean (R^2)	0.91	0.97	0.99
σ (R^2)	0.12	0.05	0.01

A threshold on the value of the *adjusted* R^2 was fixed at 0.9, as only a very good fit implies the verification of our *static equilibrium condition*. The R^2 values for $\alpha = 1$ and adults (4-6-7) are under 0.9. The R^2 value of adult 7 for $\alpha = \frac{3}{2}$ is under 0.9. For $\alpha = 2$, the threshold is respected for all adults and the obtained R^2 are homogeneous, standard deviation is 0.01. Thus, the equilibrium equation (2) with $\alpha = 2$ is consistent for all adults and so it was the value chosen for the equilibrium equation.

Figure 2 lays out the equilibrium curves for two subjects (adult 1 and 4) having different insulin-glucose dynamics to illustrate our results on virtual patients.

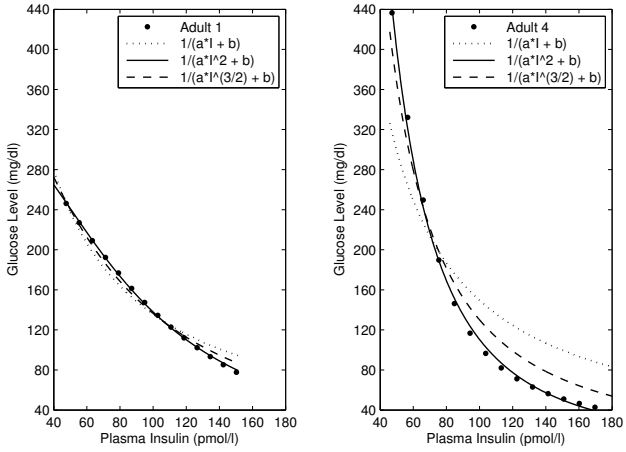

Fig. 2. Steady states point of plasma insulin and glucose for adult 1 and adult 4 and the equilibrium curves determined by (2) for $\alpha = 1, 2, \frac{3}{2}$

3.3 The insulin kinetics

A first form of the equation of the model issued from (2) with $\alpha = 2$ and by setting ${}^{S_I}/_{k_{g0}} = a$ and ${}^{P_1}/_{k_{g0}} = b$ is presented in (3):

$$\begin{aligned} \dot{G}(t) &= -P_1 G(t) - S_I G(t) X^2(t) + k_{g0} \\ \dot{X}(t) &= -k\,(X(t) - I(t)) \end{aligned} \tag{3}$$

where G (mg/dl), I $(pmol/l)$ and X $(pmol/l)$ are the same than above. The parameter P_1 (min^{-1}) describes a glucose action, S_I $((pmol/l)^{-2}.min^{-1})$ describes an insulin action, k_{g0} $(mg.(dl.min)^{-1})$ represents some endogenous glucose production, and the parameter k (min^{-1}) is an insulin time constant.

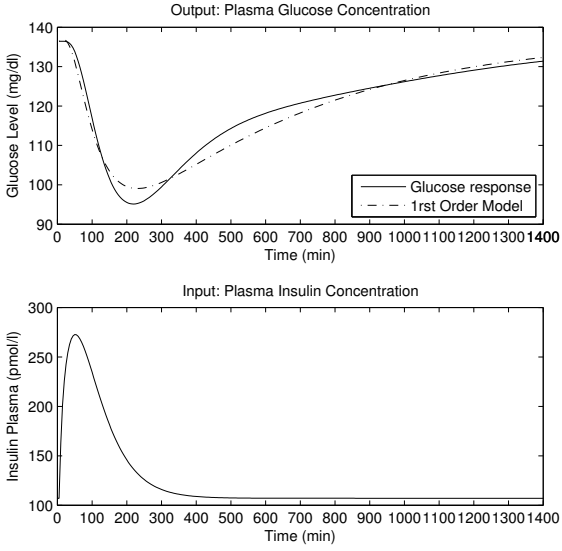

Fig. 3. Glucose evolution after an insulin bolus given by the simulation model and model (3) for adult 2

Let us assume that a one time-constant is sufficient to represent the dynamics, as it is the case in (3). Figure 3

represents the actual glucose evolution after a bolus against the one issued from the model for adult 2. There is a gap between the two trajectories of glucose, and this is the case for all the adults of the simulator. Then, a one time-constant is not sufficient.

The insulin compartment was therefore modified by considering a higher order model. Linear first order models in series were considered and the simplest model found to represent the simulation model data is a model with two poles and one zero. It is presented in the block diagram (Fig. 4) where p is the differentiation operator and T_1, T_2, T_3 (min) are time constants.

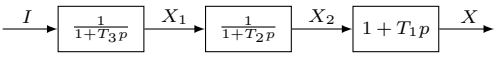

Fig. 4. Block diagram of the insulin kinetics

Then the states equations of the model presented in figure 4 are:

$$\begin{aligned} X(t) =& X_2(t)\frac{k_1-k_2}{k_1} + X_1(t)\frac{k_2}{k_1} \\ \dot{X}_2(t) =& -k_2\left(X_2(t) - X_1(t)\right) \\ \dot{X}_1(t) =& -k_3\left(X_1(t) - I(t)\right) \end{aligned} \tag{4}$$

by setting $k_1 = \frac{1}{T_1}$, $k_2 = \frac{1}{T_2}$ and $k_3 = \frac{1}{T_3}$.

The coefficients k_2 and k_3 allow the description of a slow and a fast dynamics of the glucose and the coefficient k_1 allows an adjustment of the dynamics.

3.4 The new control model

The combination of (4) and (3) leads to our new control model, it is described by system (5):

$$\begin{aligned} \dot{G}(t) =& -P_1 G(t) + k_{g0} - \\ & S_I G(t)\left(X_2(t)\frac{k_1-k_2}{k_1} + X_1(t)\frac{k_2}{k_1}\right)^2 \\ \dot{X}_2(t) =& -k_2\left(X_2(t) - X_1(t)\right) \\ \dot{X}_1(t) =& -k_3\left(X_1(t) - I(t)\right) \end{aligned} \tag{5}$$

where G (mg/dl) is the plasma glucose concentration, I $(pmol/l)$ is the plasma insulin concentration, X_1 $(pmol/l)$ is the first remote compartment, X_2 $(pmol/l)$ is the second remote compartment. The parameter P_1 (min^{-1}) describes a glucose action, S_I $((pmol/l)^{-2}.min^{-1})$ describes an action of the insulin on glucose, k_{g0} $(mg.(dl.min)^{-1})$ represents some endogenous glucose production. k_3 & k_2 (min^{-1}) are the insulin time constant in respective compartments X_1 & X_2. k_1 (min^{-1}) is the reverse time constant adjusting the action of X_1 and X_2 on the glucose.

The model includes six parameters, which have to be identified, as well as the three initial conditions. However, if the experiment starts at some steady-state, the initial conditions are fixed: $I(0)$ and $G(0)$ are known and an unitary gain on the last two equations of (5) ensures that $X_2(0) = X_1(0) = I(0)$. Besides, as we have constrained equation (2) to verify *static equilibrium condition*, the terms S_I/k_{g0} and P_1/k_{g0} are computable with the data of two equilibrium points. Therefore only four parameters remain to be identified: k_{g0}, k_1, k_2, k_3.

4. IDENTIFICATION RESULTS

4.1 Data

For each adult subject, three experiments are done to obtain our data. The length of the simulation is of 1440 min, the sampling is 5 min and the number of points considered is 288. In each case the blood glucose and the plasma insulin are initially at equilibrium. The data are noise free. The insulin is injected subcutaneously.

- Experiment 1:
  Initial points: $I(0) = I_b$ and $G(0) = G_b$
  T=5 min: bolus of 5 units
- Experiment 2:
  Initial points: $I(0) < I_b$ and $G(0) > G_b$
  T=5 min: bolus of 5 units
- Experiment 3:
  Initial points: $I(0) = I_b$ and $G(0) = G_b$
  T=5 min: basal=$0.7 * I_b$
  T=200 min: bolus of 5 units
  T=720 min: basal=I_b

where G_b and I_b are the basal values of the simulation model.

These experiments are done to challenge our new control model as the simulation model is non linear. Two different initial points (experiment 1 & experiment 2) and two different input signals (experiment 1 & experiment 3) are used.

We can notice that the form of the input signal chosen, bolus and or basal variation, are feasible in an identification process on real patients. Yet, the experiment length would be shorter (5-6h) for safety reasons.

4.2 Parametric identification

The parametric identification is done using the Matlab System Identification Toolbox with the *Non Linear Least Square* method. An initial value of the parameters is needed by the algorithm. This initial value is determined, for each adult, with the Genetic Algorithm Toolbox of Matlab. However, for a specific adult, the same initial value of parameters is used on the three data sets.

The quality of the estimated model is assessed with these indicators: the *fit function* and the *Loss Function* (Matlab [2009]).

The *fit function* is:

$$fit = 100 * \left(1 - \frac{\|\hat{y} - y\|}{\|y - \overline{y}\|}\right)$$

where $\hat{y}$ is the estimated output, y the measured output and $\overline{y}$ is the mean value of the output. A good estimated model is when the fit tends to 100%.

The *Loss Function* is defined by:

$$Loss\ Function = \frac{1}{N}\sum_{t=1}^{N} \epsilon^2(t, \theta_N)$$

where N is the number of values of the data set, θ_N represents the estimated parameters and $\epsilon(t, \theta_N)$ is the residual error. This indicator provides a quantitative description of the model quality. Lower is this value, better is the estimated model.

4.3 Identification of the new control model

The two initial points of experiment 1 and 2 are used to compute the terms S_I/k_{g0} and P_1/k_{g0}, so the parameters S_I and P_1 are not identified (cf. section 3.3).

The four parameters of our new control model (5) are identified on the three data sets (identification). So, for each adult, three estimated models are obtained. Then, each estimated model is simulated on the other two data sets in a cross-validation purpose (validation).

Table 2. Mean and standard deviation of the fits for each adult

	IDENTIFICATION		VALIDATION	
Subjects	*mean*	σ	*mean*	σ
Adult 1	97%	1%	82%	8%
Adult 2	97%	1%	80%	7%
Adult 3	97%	1%	88%	3%
Adult 4	96%	4%	86%	8%
Adult 5	96%	1%	85%	6%
Adult 6	97%	3%	65%	11%
Adult 7	96%	4%	85%	7%
Adult 8	94%	3%	78%	8%
Adult 9	93%	1%	90%	2%
Adult 10	97%	4%	86%	3%
Global (all adults)	96%	3%	81%	9%

As the number of experiments for each adult is not significant, the conclusions are drawn on the global mean and standard deviation of the fits (identification: 30 values & validation: 60 values). The mean fit obtained for the identification is 96% with a standard deviation of 3% and for the validation the mean is 81% with a standard deviation of 9%. The dispersion of the results is low in both cases with a high mean, then the proposed model seems accurate. Although, for one subject (adult 6), the mean fit obtained for validation is only 65%. Since the data considered in these experiments are noise free, this value is not satisfactory. The proposed model seems not to be correct for this adult, so this point is under investigation.

Table 3. Parameters of adult 2 for the three experiments

States	Exp. 1	Exp. 2	Exp. 3
$X_1(0)$	108	55	108
$X_2(0)$	108	55	108
$G(0)$	137	226	137

	Exp. 1		Exp. 2		Exp. 3	
Param.	values	σ	values	σ	values	σ
k_1	4.6e-3	1.5e-4	4.1e-3	1.6e-4	2.7e-3	1.9e-4
k_2	1.6e-2	2.29e-3	1.5e-2	2.69e-4	1.1e-2	3.3e-4
k_3	1.5e-3	2.3e-3	1.7e-3	2e-5	1.2e-3	1.3e-5
S_I/k_{g0}	3.4e-7	Fixed	3.4e-7	Fixed	3.4e-7	Fixed
P_1/k_{g0}	3.4e-3	Fixed	3.4e-3	Fixed	3.4e-3	Fixed
k_{g0}	1.5	2.4e-1	1.6	5.2e-2	1.6	5.7e-2

Estimator	Exp. 1	Exp. 2	Exp. 3
Loss Fct	0.19	0.15	0.11
Fit	96%	98%	98%

Table 3 presents the values of the parameters obtained for adult 2 as an illustration. The estimated models have a good fit for each experiment. The values of the Loss Function are low and are equivalent in all the three cases. Then the behavior of the proposed model compared with the simulation model is similar. Besides, the mean values of the fit for the cross-validation is 80% with a worst value of 71%. Then each estimated model is valid on the other data sets. The input/output behavior between experiments is consistent, even if we note some discrepancy between the parameters values.

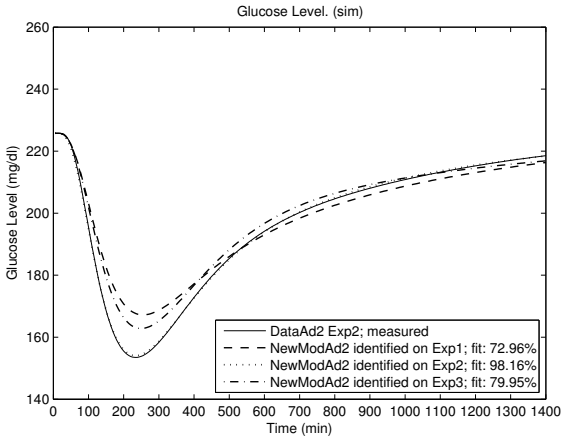

Fig. 5. New control model: each estimated model for adult 2 is simulated on the data of experiment 2

Figure 5 illustrates the results of our new control model for adult 2 simulated on data of experiment 2. Figure 6 illustrates the results of the minimal model of Bergman in the same case for comparison. We observe that the simulation of the model of Bergman estimated on experiment 1 shows a gap in statics between the model and the data. This lays out the role of the *static equilibrium condition* as it prevents this kind of behavior.

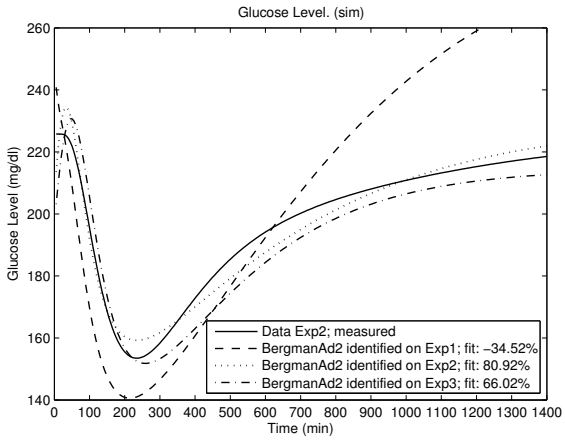

Fig. 6. Bergman model: each estimated model for adult 2 is simulated on the data of experiment 2

5. CONCLUSION

The interest of this novel T1DM control model is in its accurate representation of the virtual patients plasma

insulin-glucose dynamics. The proposed model is simple, it is described by only three differential equations and it is not a model of variation around basal values of the glucose and insulin concentration. Then its design is defined by two features. The first one concerns the introduction of two successive remote compartments for the insulin. Indeed, it allows accounting for slow and fast glucose dynamics. The second one concerns the modeling of the insulin action in glucose disappearance, which is done through an original nonlinear form. This nonlinear form is chosen so that the mathematical equilibrium relation of the control model is consistent with observed equilibrium points. Thus, the proposed model is able to follow accurately the insulin-glucose system from a static and dynamic point of view.

Further work are needed to correct the observed discrepancy between identified parameters from different data sets of the same subject. The similarity between the behavior of the proposed model and the virtual patients simulation model allows us to expect consistent results on real patient data. This assessment will be performed in a future work. To conclude, this T1DM control model is expected to be a basis for closed-loop control algorithms of type 1 diabetes in order to provide an artificial pancreas.

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