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Practical identification of a glucose-insulin dynamics model

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Abstract: Glycemia regulation algorithms which are designed to be implemented in several artificial pancreas projects are often model based control algorithms. However, actual diabetes monitoring is based throughout the world on the so-called Flexible Insulin Therapy (FIT) which does not always cope with current mathematical models. In this paper, we initiate an identification methodology of those FIT parameters from some standard ambulatory clinical data. This issue has an interest *per se*, or for a further use in any closed-loop regulation system.

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Keywords: Type 1 diabetes, Flexible insulin therapy, Glycemia regulation, Positive systems, Identification.

1. INTRODUCTION

Type 1 diabetes is considered in this paper. It is an auto-immune disease in which the pancreas does not produce any endogenous insulin. It is thus mandatory for patients with diabetes to inject a suitable amount of exogenous insulin to regulate their blood plasma glycemic level. This is done either manually, based on the so-called Flexible Insulin Therapy (FIT), or thanks to an automated insulin pump. The FIT includes the basal insulin rate which enables to stabilize the glycemia level during fasting; it also includes for instance the Carbohydrates-to-Insulin Ratio (CIR) which assumes that the necessary amount of additional insulin is proportional to the amount of ingested carbohydrates.

The idea of closing the loop between a continuous glycemia measurement and an insulin pump traces back to the 1960's. The hardware exists since at least two decades, but a fully automated system is not yet available. Some of the most advanced hybrid solutions, i.e. with announcement of meals, are either based on some advanced PID control (US FDA, (2018)) or on MPC (Hoskins, (2018)).

Several models for the glycemia-insulinemia dynamics do exist and the identification of their parameters remains an open problem. Here we stick to the model in Magdelaine et al., (2015), Magdelaine et al., (2020) as it is derived from the FIT fundamentals.

Ambulatory clinical data (which are made away from medical supervision) are subject to severe uncertainties affecting specially the declarations about the meals. Both the amount of carbohydrates and the schedule of their ingestion are stated by the patient. These declarations may appear to be inconsistent with the glycemia measurements. Thus, identification remains a major challenge and an open problem to get a reliable estimation of the model parameters.

In this paper, we change the paradigm of identification as our goal will not be to fit to rough clinical data, but rather to identify the FIT parameters.

The outline of the paper is as follows. In Section 2 we review the classes of inputs which may occur and which are classified into four types of events, including fasting for instance. Section 3 is devoted to the most elementary discrete-time model and to fundamental recalls on positivity of systems dynamics. At this stage, the model ignores the dynamics of the digestion and of the insulin diffusion. It only involves patient dependent parameters including the sensitivity to carbohydrates. A special focus is made on the identification of this parameter and worked out on clinical data. A simple first-order dynamics is added in Section 4 for the digestion. A main achievement is that it is shown that the time constant of this first-order dynamics no more depends on the patient, but it is related to the glycemic index of the food which is also intuitively realistic. A global identification is made in Section 5 on a larger time window of 24 hours, combining all types of input events.

2. THE CLASSES OF INPUTS

The considered system is subject to a control input, that is the injected insulin rate, and to several disturbance inputs including meals. Inputs are not random, but rather the sequence of four types of events, including a meal or not, and including an insulin bolus or not. It is shown that (locally) the system is never fully identifiable due to these classes of inputs. One has to have information over a period of time large enough to include different types of events. Nevertheless, even with a single event or a limited number of events, the system is partially identifiable. This partial identification is investigated in Sections 3 and 4 with a focus on the digestion subsystem. The full set of input classes is considered in Section 5 for some general identification methodology.

2.1 Event 1 : Constant insulin basal rate without insulin bolus or meal

In this case, the insulin I_k injected at time k remains equal to some constant value I_b during fasting.

This event is identified in practice on clinical data windows which correspond to a constant insulin injection, do not include any meal, and are such that the glucose concentration is monotonic with respect to time.

2.2 Event 2 : Insulin bolus without meal

Assume now that a single insulin bolus occurs at some time k ; for the rest of the time, the glycemia dynamics is just fed by the basal rate I_b , and there is no meal.

In practice, one has to search for clinical data windows which correspond to a constant basal rate, with one or more insulin boluses, which do not include any meal, and consequently are such that the glucose concentration is decreasing with respect to time.

2.3 Event 3 : Meal without insulin bolus

As in the case of Event 1, the insulin injection remains constant to the level of the basal rate I_b , but there is a nonzero amount R_k of carbohydrates which is ingested.

In practice, the interest is for clinical data windows which correspond to a constant insulin injection, do not include any insulin bolus, but include one or more meals, and are consequently such that the glucose concentration is increasing with respect to time.

From the given data, since the meals are declared data, they may be rescheduled to fit to some glycemia increase. Since the beginning of the meal only is stated, the amount of ingested carbohydrates may also be expanded over some short or longer time duration, especially when the model does not include any digestion dynamics.

2.4 Event 4 : Meal with an insulin bolus

In this case we consider a single instant k for which $R_k \neq 0$ associated with an insulin bolus $I_k - I_b$.

2.5 Clinical data: a case study

Consider three days of clinical data (borrowed from Rennes' hospital, France) as in Figure 1. The top figure displays a (slightly varying) basal insulin infusion, together with boluses. The middle figure instead gives the data about carbohydrates intakes (full meals and re-intakes). Finally the bottom figure shows the glucose concentration measurements. For a better readability, we focus on 24 hours whose data are displayed separately below.

The time response of the digestion and insulin subsystems have been definitely neglected in our elementary first-order model. Obviously the clinical data are not characteristic of a sequence of impulsive responses of a first-order system as considered in (1) below. One way to circumvent the lack of modelling of the digestion and insulin subsystems will consist in stretching the impulsive inputs over a finite range of time.

2.6 Processing of the impulsive inputs

The impulse input of carbohydrates is applied at the declared starting time of a meal. This input is thus stretched out over a range of time corresponding to an increase of glycemia in Event 3, preserving the total amount of carbohydrates which are digested.

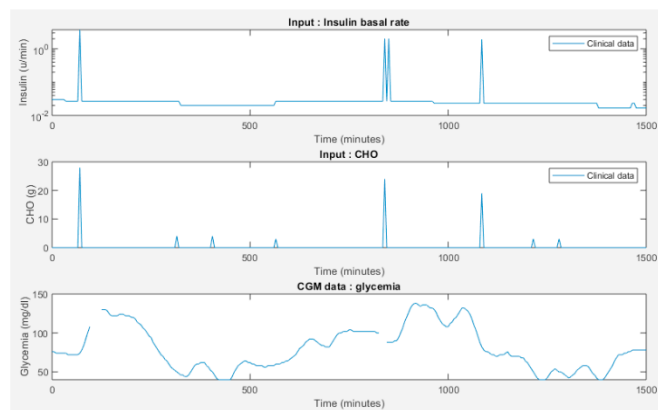


Fig. 1. Clinical data over 24 hours

In a similar vein, in Event 2, the impulse insulin bolus is stretched out over a range of time corresponding to a decrease of glycemia, respecting the total amount of insulin which is injected.

In the rest of this paper, the focus will be mainly on Event 3, i.e. a meal or glucose re-intake without any insulin bolus.

3. MODELLING THE DYNAMICS OF GLYCEMIA

In this Section, we don't consider the dynamics of digestion or of the assimilation of the injected insulin.

As the assimilation of carbohydrates is not instantaneous, all meals and carbohydrates intakes are expanded over an arbitrary duration of the meal estimated of 20 minutes.

Although this is a rather rough model, the main achievement is that it enables to estimate parameters such as the sensitivity to insulin and the sensitivity to carbohydrates.

At this stage, the glycemia dynamics reads in continuous-time

$$\dot{G} = \theta_1 - \theta_2 I + \theta_3 R, \quad (1)$$

where I denotes the injected insulin rate and R is the rate of ingested carbohydrates during some meal. The underlying assumption is that the blood plasma insulin rate is supposed to be equal to I and the blood plasma carbohydrates rate is supposed to be equal to R as well.

The discrete time equivalent of (1) is then

$$G_{k+1} = G_k + \theta_1 - \theta_2 I_k + \theta_3 R_k. \quad (2)$$

Let T_s denote the sampling time, so that the amount of insulin I_k injected at time kT_s is computed as $I_k = T_s \cdot I$ and the amount of carbohydrates R_k is instead $R_k = T_s \cdot R$.

It may be argued that (1) and (2) are not positive models. In particular, a large injected insulin rate I will drive a low valued glucose concentration onto a negative value. This is avoided by replacing θ_2 by a nonlinear function $\theta_2(G)$, or $\theta_2(G_k)$, which vanishes when G goes to zero (Califano et al., (2019)). At this stage, it is worth to recast the properties of (1) and (2) in the perspective of the positivity of general linear and nonlinear systems, in continuous time as well as in discrete-time.

A control system is said to be positive if the positivity of all inputs and of all components of the initial condition yields that any component of the state remains positive at any time $k > 0$. Equivalently, the first orthant is said to be positively invariant under any positive input. Its characterization is as follows.

Theorem 1. (Farina et al., (2000)). The linear continuous-time system

$$\dot{x}(t) = Ax(t) + Bu(t)$$

is positive if and only if each entry of matrix B is non negative and matrix A is Metzler, i.e. each off-diagonal entry a_{ij} , for $i \neq j$, is non negative.

Obviously, those conditions are not fulfilled by (1) in case θ_2 is constant. When θ_2 is a function of the glycemia instead, then the dynamics becomes nonlinear and the following characterizations apply.

Theorem 2. The nonlinear continuous-time system

$$\dot{x}(t) = f(x(t), u(t))$$

is positive if and only if

- (i) $f_i(0, \dots, 0, u)$ is non negative for any i and any non negative u , and
- (ii) $f_i(0, \dots, 0, x_j, 0, \dots, 0)$ is non negative for any $i \neq j$ and any non negative x_j .

The latter conditions are fulfilled by (1) for any $\theta_2(G)$ such that $\theta_2(0) = 0$.

3.1 Identifiability in case of Event 3.

During Event 3, the injected insulin I_k is equal to some constant basal quantity I_b . A single moment k is also considered at which $R_k \neq 0$, so that over the interval $[k, k + j]$ $j \geq 2$:

$$\begin{aligned} G_k &= G_{k-1} - \theta_2 I_b + \theta_1 + 0 \\ G_{k+1} &= G_k - \theta_2 I_b + \theta_1 + \theta_3 R_k \\ G_{k+2} &= G_{k+1} - \theta_2 I_b + \theta_1 + 0 \\ &\vdots \end{aligned} \quad (3)$$

then we obtain the Jacobian matrix :

$$\frac{\partial G_*}{\partial (\theta_1, \theta_2, \theta_3)} = \begin{pmatrix} 1 & -I_b & 0 \\ 1 & -I_b & R_k \\ 1 & -I_b & 0 \\ \vdots & \vdots & \vdots \end{pmatrix}.$$

The rank of this Jacobian matrix is equal to 2. It's noted that the third column is now "essential". We thus have that with a meal at time k , the parameter θ_3 and the combination $\theta_1 - \theta_2 I_b$ which represents the basal indicator θ_0 , become identifiable. In fact one gets that

$$\begin{aligned} \theta_3 &= \frac{G_{k+1} - 2G_k + G_{k-1}}{R_k} \\ \theta_1 - \theta_2 I_b &= G_k - G_{k-1}. \end{aligned}$$

These computations can be performed in practice on clinical data windows $[k, k + j]$, $j \geq 2$ which correspond to a constant insulin injection, do not include any insulin bolus, but include one or more meals, and such that the glucose concentration is increasing with respect to time.

Declared data, as the starting time of a meal, are subject to major inaccuracies. So the starting time of a meal has eventually to be rescheduled to fit to the corresponding increase of glycemia to avoid the identification of some negative parameter. After such a treatment, the corresponding set of clinical data will be suitable for identification.

3.2 Identification of the sensitivity to carbohydrates θ_3 , in the case of glucose re-intakes (Event 3)

Let us now focus on glucose re-intakes, without insulin bolus, as described is Section 2.3 and named "Event 3". A "local"

identification of parameter θ_3 can be processed on some of those glucose re-intakes. As the glucose intake has no instantaneous effect but spreads out over about 20 minutes, all carbohydrates (CHO) impulsive inputs are replaced by an equivalent step input corresponding to the same amount of ingested glucose. One of those identification results is displayed in Figure 2.

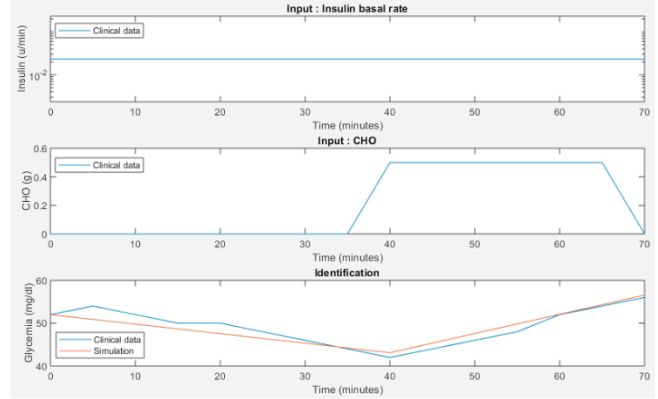


Fig. 2. Local identification of parameter θ_3 from one single glucose re-intake (Event 3).

Repeating this process on several glucose re-intake episodes yields the following values for parameter θ_3 and shows a good stability of the identification at least for these glucose re-intakes (corresponding for instance to a sweet drink). These values are also meaningful as they are positive, as expected.

Table 1. Identification of θ_3 for the Event 3

Event 3	θ_3
n_1	1.34
n_2	1.77
n_3	1.64
n_4	1.14

One can expect that the time to assimilate a full meal is rather longer than the time to assimilate a drink which is designed to correct a previously overestimated insulin bolus. This requires a specific dynamic for digestion including a time constant θ_5 and this is done next.

4. A FIRST-ORDER MODEL FOR THE DIGESTION

The previous elementary and rough model is now completed by considering a first-order dynamics for the digestion with its own time constant. The identification of the latter time constant will replace the above arbitrary duration of the meal of 20 minutes.

The main outcome is the dependence of this time constant of the food glycemic index. This makes sense and improves dramatically the fit of the model. Standard models consider constant parameters, rather than depending on the glycemic index of the specific food.

The glycemic index (GI) is an empirical index used to describe the rise in the blood glucose level two hours after consuming food (Monro et al., (2008)). The GI tells how fast and high the blood glucose level will rise after eating carbohydrates contained in a meal, in comparison with the ingestion of pure glucose. The rise depends on the type of carbohydrates, for example food with a high GI (simple carbohydrates) are easily digested and cause a quick rise in blood glucose level whereas

food with a lower GI (complex carbohydrates) get digested more slowly and cause a slower rise in blood glucose level. The GI ranks food in a scale from 0 to 100. A high GI corresponds to a score over 70.

The first-order model (2) is thus replaced by the second order one

$$\begin{cases} G_{k+1} = G_k + \theta_1 - \theta_2 I_k + \theta_3 X_k \\ X_{k+1} = (1 - \theta_4)X_k + \theta_4 R_k. \end{cases} \quad (4)$$

The parameters θ_1 , θ_2 and θ_3 involved on the glycemia dynamics are basically unchanged.

4.1 Identifiability of parameters θ_3, θ_4 in case of the Event 3.

With computations similar to the ones done in Section 3.1, it is easily proven that the parameters θ_3 and θ_4 can be identified from the data involving Event 3. Assume that we are away from any meal so that the initial condition of the carbohydrates on board X is zero.

Consider a single instant k for which $R_k \neq 0$, so that over the interval $[k, k + j]$ $j \geq 2$:

$$\begin{aligned} G_{k+1} &= G_k - \theta_2 I_b + \theta_1 + 0 \\ X_{k+1} &= 0 + \theta_4 R_k \\ G_{k+2} &= G_{k+1} - \theta_2 I_b + \theta_1 + \theta_3 \theta_4 R_k \\ X_{k+2} &= (1 - \theta_4)X_{k+1} + 0, \\ G_{k+3} &= G_{k+2} - \theta_2 I_b + \theta_1 + \theta_3 \theta_4 (1 - \theta_4) R_k \\ X_{k+3} &= (1 - \theta_4)X_{k+2} + 0 \\ &\vdots \end{aligned} \quad (5)$$

then we obtain the Jacobian matrix :

$$\frac{\partial G_*}{\partial(\theta_1, \theta_2, \theta_3, \theta_4)} = \begin{pmatrix} 1 - I_b & 0 & 0 & 0 \\ 1 - I_b & \theta_4 R_k & \theta_3 R_k & 0 \\ 1 - I_b & \theta_4 (1 - \theta_4) R_k & \theta_3 (1 - 2\theta_4) R_k & 0 \\ \vdots & \vdots & \vdots & \vdots \end{pmatrix}.$$

The rank of this Jacobian matrix is equal to 3. The two last columns are "essential", which means that θ_3 and θ_4 are identifiable. In fact θ_3 and θ_4 can be computed from (5).

4.2 Identification of parameter θ_4

The identification process performed on the same samples as in Section 3.2 yields the results displayed in Figure 3 and Table 2.

Table 2. Identification of θ_3 and θ_4 for the Event 3

Event 3	θ_3	θ_4
n_1	1.31	0.06
n_2	1.52	0.12
n_3	1.72	0.09
n_4	1.87	0.07

As expected, in Table 2 the sensitivity to carbohydrates θ_3 remains essentially unchanged whereas θ_4 represents a time constant which is rather small. This is due to the fact that these events are some carbohydrates re-intakes with a large glycemic index, as it is for an orange juice for instance.

4.3 Glycemic index

The type of CHO influences directly the parameter θ_4 . So, the same amount of CHO can give different dynamics depending

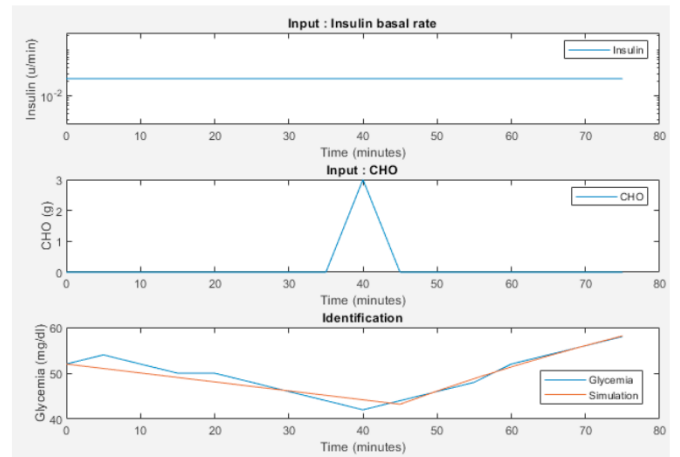


Fig. 3. Local identification of parameter θ_3 and θ_4 from one single glucose re-intake (Event 3).

on the GI (Bellmann et al., (2018)). The practical identification results of the parameter θ_4 prove its correlation with the GI: a low value is found for θ_4 when the GI is low while a larger value is identified for θ_4 for higher GIs. Finally, parameter θ_4 depends much more on the food which is ingested rather than on the patient. On the clinical data window in Figure 4, θ_4 was

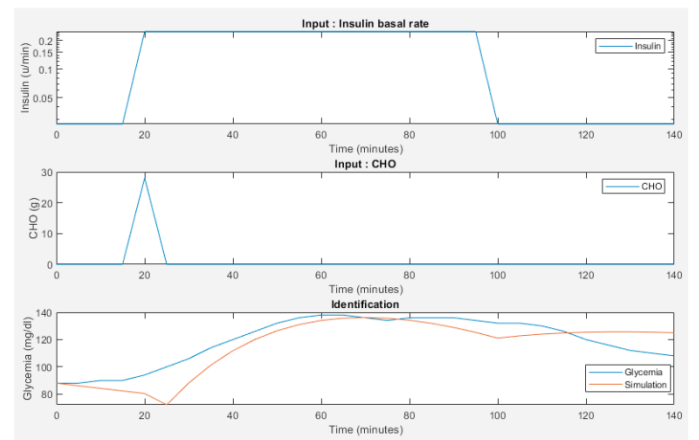


Fig. 4. Local identification of parameter θ_3 and θ_4 from one meal with an insulin bolus (Event 4).

found to be equal to 0.014. Three others meals were tested for which θ_4 ranges from 0.006 to 0.024. This corresponds to a time constant $1/\theta_4$ that ranges from 42 minutes to 167 minutes in the case of a full meal. The same time constant $1/\theta_4$ ranges from 8 to 16 minutes in the case of a re-intake. These results are actually consistent with the physiology.

The previous modelling procedure can be performed on the insulin subsystem to model the insulin diffusion. In this case, we end up with the following third order model in discrete time:

$$\begin{cases} G_{k+1} = G_k + \theta_1 - \theta_2 Y_k + \theta_3 X_k \\ X_{k+1} = (1 - \theta_4)X_k + \theta_4 R_k \\ Y_{k+1} = (1 - \theta_5)Y_k + \theta_5 I_k \end{cases} \quad (6)$$

where Y_k represents the insulin on board at time k .

In the next Section, we come back to the elementary model (2) and to the identification of the three parameters, considering a larger window of 24 hours of clinical data.

5. TOWARDS A METHODOLOGY FOR PARAMETER IDENTIFICATION

5.1 Global identification

The following figure displays the rough clinical data over 24 hours, including the insulin rate and boluses, the declared starting times of meals and the glycemia measurement from the continuous glucose monitoring (CGM), and the response of the model after the identification of the three parameters (using a standard least squares method).

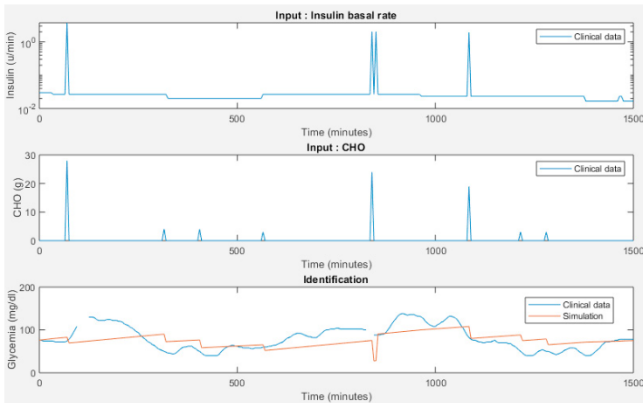


Fig. 5. Global identification of a 24h period from patient data

Table 3. Global parameters identification

Parameters	Parameters values
θ_1	-0.08
θ_2	-6.19
θ_3	-0.91

Obviously, the model captures the most essential features but it is not able to track the details of the real dynamics. In addition, the identified parameters have an unexpected negative value. This is due to the following reasons.

- (i) the model neglects the digestion dynamics and the time constant of the insulin subsystem which allows the subcutaneous insulin to spread out into the blood plasma;
- (ii) the carbohydrates data are not measured but only declared by the patient. Furthermore they display the starting time of a meal rather than the rate of the carbohydrates absorption;
- (iii) some episodes in the clinical data appear to be erroneous since in some cases the ingestion of carbohydrates is synchronous with a decrease of the measured glycemia, or some increase of the infused insulin is synchronous with an increase of the measured glycemia. Those episodes will lead to identify some negative parameters.

To circumvent these issues and obtain a better fit and more reliable values for the model parameters, one has to define an *ad hoc* methodology that is able to cope with the real life clinical data. This is done next through a sequential identification of the three parameters and using only so-called ‘local’ data.

5.2 Identification of θ_3 , in the case of glucose re-intakes (Event 3)

Let us now focus again on glucose re-intakes, without insulin bolus, as described in Section 2.3 and named “Event 3”. A

“local” identification of parameter θ_3 can be processed on some of those glucose re-intakes. As the glucose intake has no instantaneous effect but spreads out over about 20 minutes, all CHO impulsive inputs are replaced by an equivalent step input corresponding to the same amount of ingested glucose. One of those identification results is displayed in Figure 6.

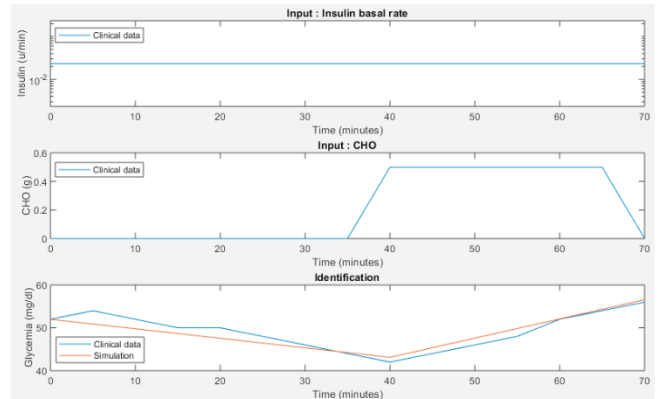


Fig. 6. Local identification of parameter θ_3 from one single glucose re-intake (Event 3).

Repeating this process on several glucose re-intake episodes yields the following values for parameter θ_3 and shows a good stability of the identification at least for these glucose re-intakes (corresponding for instance to a sweet drink). These values are also meaningful as they are positive, as expected.

Table 4. Identification of θ_3 for the Event 3

Event 3	θ_3
n_1	1.34
n_2	1.77
n_3	1.64
n_4	1.14

One can expect that the time to assimilate a full meal is rather longer than the time to assimilate a drink which is designed to correct a previously overestimated insulin bolus. Thus, the estimation of parameter θ_3 deserves a specific treatment in the case of a full meal. This is done next.

5.3 Identification of θ_3 , in the case of a full meal intake (Event 4)

A similar procedure of ‘local’ identification is now performed on events of the type Event 4 to estimate parameter θ_3 when a full meal is digested. Once again, the impulsive input of carbohydrates is expanded over a range of 30 minutes and the insulin bolus is expanded as a step input over about 120 minutes to reflect the duration of the insulin action (DIA).

Repeating such an identification on three different events including a meal and an insulin bolus allows to estimate a (positive) value for parameter θ_3 which is significantly smaller than in the case of a glucose re-intake, see Section 2.3.

Table 5. Identification of θ_3 from Event 4

Event 4	θ_3
n_1	0.46
n_2	0.73
n_3	0.44

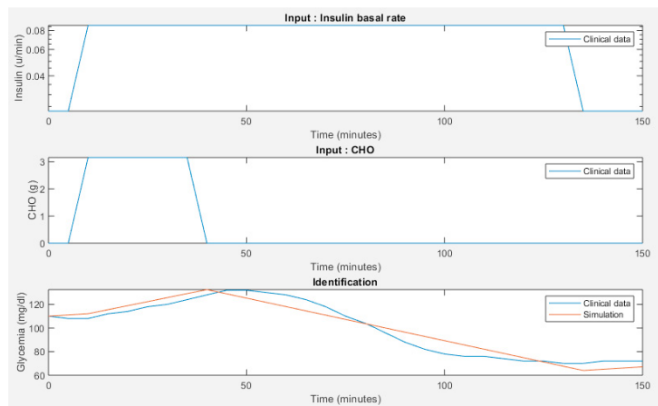


Fig. 7. Local identification of parameter θ_3 from one single meal, synchronous with an insulin bolus (Event 4).

These local identifications show the variability of the parameter θ_3 as the time constant involved in the digestion of a real meal is about (three times) longer than the time constant involved in the assimilation of a glucose re-intake (such as a sweet drink).

The next step consists in considering that θ_3 is no more a parameter to be identified, but is the constant identified as above.

Global identification of θ_1 and θ_2 (θ_3 being constant) Further steps of identification will now be processed considering only the two parameters θ_1 and θ_2 . The parameter θ_3 is definitely a known constant.

These values of the parameters which have been obtained from local identifications, event by event, are now plugged in the model whose response is as displayed in Fig. 8.

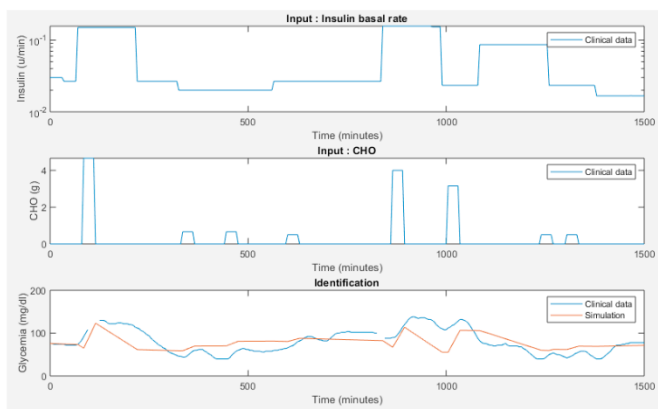


Fig. 8. Model response, with the locally identified parameters.

In this hybrid case, by mixing a local and a global identification, the fit is improved when considering the simulation over the full range of time.

5.4 An ad hoc methodology for identification

Based on the discussion carried out in the previous Sections, some specific steps must be taken to identify the parameters. These steps can be summarized as follows.

- Select elementary events which are suitable for identification.
- Identify the rises of blood glucose concentration due to the ingestion of carbohydrates.

- Relocate the beginning of the meal input and extend the ingestion of carbohydrates over a period of 20 minutes.

6. CONCLUSION AND PERSPECTIVES

A special attention was paid to the model parameters identification because they are meaningful by their own since they determine the basal insulin infusion rate and other Flexible Insulin Therapy parameters. They also determine the future performance of any model based glycemia regulation in closed-loop.

It was shown that some parameters do not depend on the patient but rather on the glycemic index of the ingested carbohydrates. The identification of the model will thus provide an indirect estimation of this glycemic index.

To display tractable computations, an elementary model was used for the glycemia dynamics. The basic methodological principles remain valid when considering more realistic mathematical models and introduce a methodology for the clinical data processing preliminary to parameter identification.

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