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RESEARCH ARTICLE

Identification of individualized empirical models of carbohydrate and insulin effects on T1DM blood glucose dynamics

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(*version 0*)

One of the main limiting factors in improving glucose control for T1DM subjects is the lack of a precise description of meal and insulin intake effects on blood glucose. Knowing magnitude and duration of such effects would be useful not only for patients and physicians but also for the development of a controller targeting glycemia regulation. Therefore, in this paper we focus on estimating low-complexity yet physiologically sound and individualized MISO models of the glucose metabolism in T1DM able to reflect the basic dynamical features of the glucose-insulin metabolic system in response to a meal intake or an insulin injection. The models are continuous-time second-order transfer functions relating the amount of carbohydrate of a meal and the insulin units of the accordingly administered dose (inputs) to plasma glucose evolution (output) and consist of few parameters clinically relevant to be estimated. The estimation strategy is continuous-time data-driven system identification and exploits a database in which meals and insulin boluses are separated in time, allowing the unique identification of the model parameters.

Keywords: continuous-time identification, metabolic systems, linear systems, diabetic blood glucose dynamics

1 Introduction

1.1 *Diabetes Mellitus*

Diabetes Mellitus is a chronic disease characterized by the inability of the organism to autonomously regulate the blood glucose levels. It is due to defects in either insulin secretion by the pancreatic β-cells or insulin action (Williams and Pickup 1999). The basic effect of insulin lack or insulin resistance to glucose metabolism is the prevention of efficient uptake and utilization of glucose by most cells of the body. As a result, blood glucose concentration increases (hyperglycemia, blood glucose > 180 [mg/dL]), cell utilization of glucose falls and consequently utilization of fat and proteins for energy increases. Free fatty acids, cholesterol and phospholipids produced during fat and protein metabolism are, then, released in the plasma causing multiple effects throughout the body. The main long-term complications are associated with damage, dysfunction and failure of various organs (Nathan 1993), (Klein et al. 1988). In order to prevent the complications associated to the sustained hyperglycemia, tight regulation of patients blood glucose levels within the near-normal range ($70 - 180$ [mg/dL]) (The American Diabetes Association 2010) has been strongly promoted during the last decade, following the results of the major Diabetes Control and Complications Trial (DCCT) (The Diabetes Control and Complications

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Trial Research Group 1993) and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group 2005) studies.

1.2 *Diabetes care*

Because insulin deficiency defines T1DM, insulin replacement is the hallmark of the therapy. Focusing on tight blood glucose targets, i.e., $70-140$ [mg/dL] (The American Diabetes Association 2010), the philosophy of insulin replacement is to mimic the physiological insulin secretion pattern of the non-diabetic person. In the non-diabetic subjects, insulin is secreted into the portal circulation at two rates: a slow basal secretion throughout the 24 hours and an augmented rate at meal times. Hence, the most common therapy for T1DM patients is the so-called basal-bolus regime: a basal dose of long-acting insulin is sufficient to keep a constant glucose concentration during fasting conditions and a prandial, i.e., at meal times, bolus of rapid-acting insulin enhances an increased glucose uptake during and after meals. Insulin is administered either with multiple daily injections (MDI) using a pen or as continuous subcutaneous insulin infusion (CSII) from a pump.

Standard practice insulin therapy therefore comprises the assessment of current blood glucose levels by means of self-monitored glucose measurements and consequent therapy adjustments several times a day towards maintainance of normoglycemia. The most widespread approach to self glucose monitoring is based on finger sticks $4-8$ times a day, typically, and to a lesser extent to subcutaneous interstitial fluid samples, the sampling period being $5-10$ minutes. Daily glucose goals are $70-120$ [mg/dL] before meal and peak levels of less than 180 [mg/dL] after meal, as well as maintainance of glycosylated hemoglobin ($HbA1_c$) less than 6.05% (The American Diabetes Association 2010). In current medical practice, the rough calculation of insulin doses and eventually extra carbohydrate intakes is based on empirical rules-of-thumbs taking into account patients personal knowledge of his/her own metabolism, expected future glycemia evolution and approximation of the estimated meal carbohydrate content effects as well as insulin impact on the subject own blood glucose. In practice, most patients are rather conservative in order to prevent insulin-induced hypoglycemia, remaining far from the optimal treatment. The task is non trivial and demanding, therefore the development of control tools aiming at assisting the patients in the management of their disease has been the focus of extensive research for almost 40 years (Cobelli et al. 2009) and is progressing towards a fully automated closed-loop control artificial pancreas (The Artificial Pancreas Project 2011, Cobelli et al. 2011, De Nicolao et al. 2011). However, while such a system is expected to improve the quality of life reducing the time plasma glucose is outside the target range, it will be suitable and affordable only for a minority. In addition, closed-loop control introduces certain risks, the most dangerous being potentially severe and unavoidable hypoglycemia induced by overdelivery of insulin compensating for hyperglycemia following a meal (Cobelli et al. 2009). Against this background, the availability of an "advisory system" recommending the user to take appropriate insulin injections and eventually recovery carbohydrates, would be desirable. Within this scenario the controller is expected to determine impulse-like control inputs, namely insulin shots and amount of carbohydrate of a meal, which are not automatically applied but rather suggested to the patient, thereby assuring safety. When a therapeutic action is suggested by the algorithm, the patient can accept or reject it, remaining firmly in the loop. The development of such decision support system was the focus of the major European project DIAdvisor ^{TM} (Diadvisor 2008, Poulsen et al. 2010, The DIAdvisor Consortium 2012).

1.3 *Motivation*

Both in the semi-closed and in the fully closed-loop scenario, there is the need of a mathematical model able to describe blood glucose evolution in response to the main driving sources, i.e., a meal

intake and an insulin dose. In the application at hand the two control inputs are impulse-formed and taken at discrete instants in time albeit simultaneously, since according to clinical practice, the subject boluses at the same time of the meal intake. In addition, carbohydrate and insulin have opposite influence on the glucose level, making it non-trivial to distinguish each input's contribution to blood glucose fluctuations. To date several types of glucose metabolism models have been proposed to the purpose of simulation and *in-silico* trial, glucose changes prediction and hypo-, hyperglycemia early detection (see e.g. (Cobelli et al. 2009) for a comprehensive review). Most of these efforts were first-principles based descriptions of diabetes physiology (Bergman et al. 1981, Dalla Man et al. 2007, Wilinska et al. 2005) and only to a lesser extent mathematical modeling by means of system identification (Ståhl and Johansson 2009, Cescon et al. 2009, Finan et al. 2010, Kirchsteiger et al. 2011a,b, van Heudsen et al. 2012, Cescon et al. 2012). However, while many of these models exhibit good predictive performances, less attention has been dedicated to the fundamental aspects of estimating correct signs and time constants of the identified models impulse responses as pointed out in (Ståhl 2012). Moreover, desirable features of a glucose metabolism model would include a clinician-friendly structure and few tunable parameters with physiological meaning. The objective of this work was, therefore, to estimate low-complexity yet physiologically sound and individualized transfer function models of glucose metabolism in response to meal and insulin inputs, addressing the problem in T1DM therapy related to the quantification of magnitude and duration effects of carbohydrate and insulin on blood glucose. These information can be used by physicians as support in treatment analysis and planning, and by practitioners in model-based controller development.
In the light of the above discussion a continuous time-domain identification approach, namely the predictor based identification ($\text{PBSID}_{\text{cont}}$) method (Chiuso 2007, Bergamasco and Lovera 2010), was taken. Advantages of such an approach are listed below:

(1) Physical insight into the glucose metabolism system
   - a continuous-time (CT) model is preferred to its discrete-time (DT) counterpart when parameters with physiologic meaning are desired, e.g., static gain and time constants for glucose and insulin. While these parameters are directly linked to the CT model, the parameters of DT models are a function of the sampling interval and do not normally have any physical interpretation (Aström et al. 1984);

(2) Non-uniformly sampled data
   - meal and insulin intakes appears at sparse discrete time instants, non equidistantly spaced and not synchronized with blood glucose self-monitoring. In addition, in the situation of a subcutaneous glucose sensor often samples are missed every now and then, due to loss of connection between transmitter and receiver and sensor misplacement. Hence, the standard DT LTI model will not be applicable because the assumption of a uniformly sampled environment no longer holds. The coefficients of CT models, instead, are assumed to be independent of the sampling period, the measurements are considered as points on a continuous line which do not need to be equidistantly spaced (Aström et al. 1984);

(3) Transformation between CT and DT models
   - Inter-sample behaviour assumption (e.g., ZOH)

(4) Use of linear algebra tools in the algorithms (Golub and Van Loan 1996)
   - robust implementation and overcome being trapped into local minima

The aim of this paper is to promote the use of the continuous-time PBSID approach to the problem of obtaining personalized models of T1DM patients glucose dynamics from actual patients sampled input-output data.

The article is organized as follows. Section 2 deals with the experimental conditions while Sec. 3 presents the explanation of the modeling work. Section 4 shows identification and validation results for the estimated models over the considered population, whereas the discussion on the achievements is left to Sec. 5. Last, Sec. 6 concludes the paper with final remarks and

considerations for future work.

2 Methods and materials

2.1 *Glucose sensors*

Dexcom Seven®Plus (Dexcom 2011) continuous glucose monitoring sensor (CGMS) was used for interstitial glucose samples. The system consists of three components: a disposable sensor unit including a subcutaneous probe, a radio transmitter connected to the external part of the sensor and a hand-held receiver device that displays the sensor-measured glucose information sent wirelessly from the transmitter. The sensor provides an automatic glucose reading every 5 minutes, lasting for up to 7 days of uninterrupted wear-time. Besides the start-up calibration performed at sensor insertion, a calibration update to fingertip blood glucose was required every 12 hours to make sure the sensor readings remain accurate. To this purpose, the HemoCue Glucose 201+ Analyzer (Hemocue 2011) was adopted for capillary blood glucose measurements. A small drop of blood was taken from the fingertip and analyzed in a test strip by the meter. The results of the test were then entered in the receiver by the subject to update calibration of the CGM device.

2.2 *Experimental conditions*

The clinical protocol for data acquisition was designed under the aegis of DIAdvisor ^{TM} (Diadvisor 2008), a large scale FP7-IST European project, reviewed and approved by the ethical committees of the Clinical Investigation Centers participating in the trials, namely, Montpellier University Hospital (CHU) in Montpellier, France, Padova University Clinics (UNIPD) in Padova, Italy and the Clinical Institute of Experimental Medicine (IKEM) in Prague, Czech Republic. A population of T1DM subjects using basal-bolus insulin regimen participated in the study signing an informed and witnessed consent form. The trial comprised a series of experiment sessions for a duration of up to 9 weeks per patient. In particular, to the purpose of separately estimating meal and insulin impact on blood glucose dynamics, overcoming therefore the lack of input excitation observed in almost all the data-sets treated in the literature (Finan et al. 2009) a novel meal test was carried out as follows. Patients were admitted to the clinic for a 6.5 hours observation period, from 6:30 am to 1:00 pm, fasting from the midnight, equipped with a Dexcom Seven®Plus (Dexcom 2011) continuous glucose monitoring sensor for interstitial glucose samples and a HemoCue Glucose 201+ Analyzer (Hemocue 2011) for capillary blood glucose measurements. After arrival, a recalibration of the CGM system was performed by the subjects using the HemoCue meter, in order to be able to start data collection at 7:00 am with a well calibrated glucose monitoring device. A standardized breakfast, the amount of carbohydrate being 40 [g], was served at 8:00 am and fully ingested within 20 minutes. The patients calculated and noted on their personal logbook the amount of insulin needed to cover this meal, based on the outcome of the HemoCue glucose meter at the start of the meal. However, contrary to standard practice, the insulin bolus was administered 2 hours later. No other meals nor snacks were consumed until 1:00 pm. Blood samples were drawn every 10 minutes for the 3 hours following the meal intake and every 20 minutes otherwise to assess glucose concentration by means of a Yellow Spring Instrument (YSI) 2300 STAT Plus blood glucose analyzer (Yellow Spring Instruments 2013). The medical information of patients is reported in Table 1. Representative patients data are shown in Figs. 2, 4, the remaining patients in the population behaving similarly. A second meal test was performed 14±3 days apart, on day 3 of a 72-hours long in-hospital visit. Prior to this test, the subjects performed an exercise test on an ergo-cyclometer on day 1, whereas they were served a big meal containing 100 [g] carbohydrate on day 2, in order to excite the system making hospital conditions closer to outpatient conditions. For the whole duration of the second admission test, the same protocol for data collection used in the first admission was followed,

Table 1. Patients informations

Name	*Gender*	*Age* [yr]	*Dd** [yr]	*BMI* [kg/m^2]	HbA1$_c$	*Therapy*	*TDI*** [IU]
CHU101	M	25	15	23.7	9	MDI	50
CHU107	M	62	19	24.3	8.9	CSII	30.7
CHU117	M	61	42	31.1	8	CSII	53
CHU118	M	35	10	24.6	7.2	MDI	46
CHU125	F	69	25	28.7	7.6	MDI	25
CHU136	M	40	9	26.8	9.6	MDI	29
CHU138	M	46	33	22	7.5	CSII	28
CHU143	M	36	26	23.4	7.5	CSII	36.4
CHU144	F	38	31	22.6	7.2	CSII	30
CHU145	M	34	9	23	7.1	CSII	37
UNIPD201	M	28	7	21.7	7.1	MDI	55
UNIPD217	M	46	14	28.4	9.3	MDI	60
UNIPD219	M	48	36	21.1	7.6	MDI	40
UNIPD233	M	36	33	26.5	7.3	MDI	57
UNIPD234	M	24	11	21.7	7.1	MDI	55
IKEM302	M	29	10	23.5	5.7	CSII	60
IKEM306	M	35	7	21.8	5.9	CSII	31
IKEM309	F	51	11	23.5	7.4	MDI	31
IKEM311	M	44	38	24.5	6.8	MDI	48
IKEM324	F	28	16	21.5	6.4	CSII	36
IKEM326	F	50	12	23.9	8.2	CSII	29
IKEM330	M	64	18	25	5.4	MDI	48
MEAN		42	19.5	24.5	7		42.1

* *Disease duration*

** *Total Daily Insulin*

except for the blood samples to assess glucose concentration with the YSI, this time drawn every 15 minutes for the 4 hours following carbohydrate ingestion.

3 Modeling the impact of meal and insulin intakes on blood glucose

3.1 *Model structure*

Second order linear transfer function models with time delays were proposed to approximate the behaviour of glucose in response to inputs, namely meal and insulin intakes. The choice was based on the analysis of the collected data and confirmed by physiology as follows. From steady-state conditions during the sleep and almost constant blood glucose levels corresponding to the overnight fast as seen in the time interval before 8:00 am (Figs. 2, 4), at 8:00 am an input was applied, namely 40 [g] of carbohydrate intake, which caused the controlled variable to rise (Figs. 2, 4). In absence of any action taken, for some patients plasma glucose concentration began to fall after about 90 minutes from carbohydrate ingestion (Fig. 2) suggesting the presence of 2 poles in the transfer function from carbohydrate to blood glucose, one faster than the other. For other patients, plasma glucose didn't fall during the time interval 8:00 am to 10:00 am (Fig. 4) leading to the assumption of an integrator term in the transfer function as glucose storage term. At 10:00 am, the insulin shot which was previously calculated by the patient was administered, making glucose concentration to clearly fall for both the previously described type of subjects with an integrator-like behaviour. Further, time delays associated with both inputs were observed in each of the data series and have been easily incorporated in the model structure. It is well known from physiology, indeed, that there are time delays accounting for glucose intestinal absorption dynamics and insulin pharmacokinetics/pharmacodynamics. In contrast to most of the existing models in the literature, we did not use any compartment model for the description of the rate of appearance in plasma following a food intake, nor for the subcutaneous depots-to-plasma insulin dynamics, overcoming the limitations introduced by the nonlinear nature of such models (Dalla Man et al. 2007) and most importantly the lack of appropriate tracer data required to fit the unknown parameters of those models to the individuals. Rather, the meal input was represented by a pulse of the duration of 15 minutes (since the food was completely ingested by the patients

within 20 minutes at maximum to comply with the clinical protocol) applied at the time instant t_{carb} = 8:00 am, while the insulin dose was considered an impulse-formed input applied at time instant t_{ins} = 10:00 am.

Realization theory was used as support for model order. Indeed, looking at the singular values of the Hankel matrix constructed from the output blood glucose a model order $n = 2$ could be confirmed for both the meal impact and the insulin impact transfer function models (see Fig. 1). All these facts, led us to the formulation of the following model structure:

$$Y_{BG}(s) = G_{carb}(s)u_{carb}(s) + G_{ins}(s)u_{ins}(s) \tag{1}$$

where $Y_{BG}(s)$ is the Laplace transform of the output blood glucose concentration, $u_{carb}, u_{ins} \in \mathbb{Z}_+$ are the inputs carbohydrate amount and insulin doses, respectively, while the transfer functions from carbohydrate to blood glucose $G_{carb}(s)$ and from insulin to blood glucose $G_{ins}(s)$ are given in Eq. 2 and 3, respectively:

$$G_{carb}(s) = e^{-s\tau_{carb}} \frac{K_{carb}}{(1 + sT_{carb,1})(1 + sT_{carb,2})} \tag{2}$$

$$G_{ins}(s) = e^{-s\tau_{ins}} \frac{K_{ins}}{s(1 + sT_{ins})} \tag{3}$$

Further, $K_{carb}, K_{ins} \in \mathbb{R}$ are the gains and $T_{carb,1}, T_{carb,2}, T_{ins} \in \mathbb{R}$ are the time constants governing rise and fall, respectively, of plasma glucose, $\tau_{carb}, \tau_{ins} \in \mathbb{R}_+$ are the time delays associated with carbohydrate and insulin appearance in plasma, respectively. Actually, for the type of patients behaving like the one depicted in Fig. 4, $T_{carb,2} = \infty$ and the transfer function becomes:

$$G_{carb}(s) = e^{-s\tau_{carb}} \frac{K_{carb}}{s(1 + sT_{carb,1})} \tag{4}$$

The proposed model structure has some interesting properties. First of all it is simple, containing only a few parameters to be identified from data. $K_{carb}, T_{carb,1}, T_{carb,2}$ can be related to glucose tolerance, i.e., how the body metabolizes glucose, while K_{ins}, T_{ins} can be related to insulin sensitivity or resistance, i.e., how effective is insulin in lowering blood sugar levels. Moreover, τ_{carb}, τ_{ins} account for food transportation and absorption along the gastro-intestinal tract and insulin transit from the subcutaneous tissues to plasma, respectively. All these factors are of uttermost importance in diabetes treatment and failure to estimate them correctly leads not only to unsuccessful glucose control but also to serious health damages. We believe this type of model easy to understand by practitioners, since all the parameters can be given a clinical interpretation. In particular, it would be straightforward for a physician to assess whether a model is physiologically plausible or not.

3.2 *Identification method*

Let $u(t) \in \mathbb{R}^2$ and $y(t) \in \mathbb{R}$ be breakfast carbohydrate, insulin injection and blood glucose, respectively, which are input and output, respectively, of the linear, continuous-time time-invariant system $\Sigma_n(A, B, C)$ described by the differential equations:

$$\begin{cases} dx(t) = Ax(t)dt + Bu(t)dt + dw(t) \\ dz(t) = Cx(t)dt + dv(t) \\ y(t)dt = dz \end{cases} \tag{5}$$

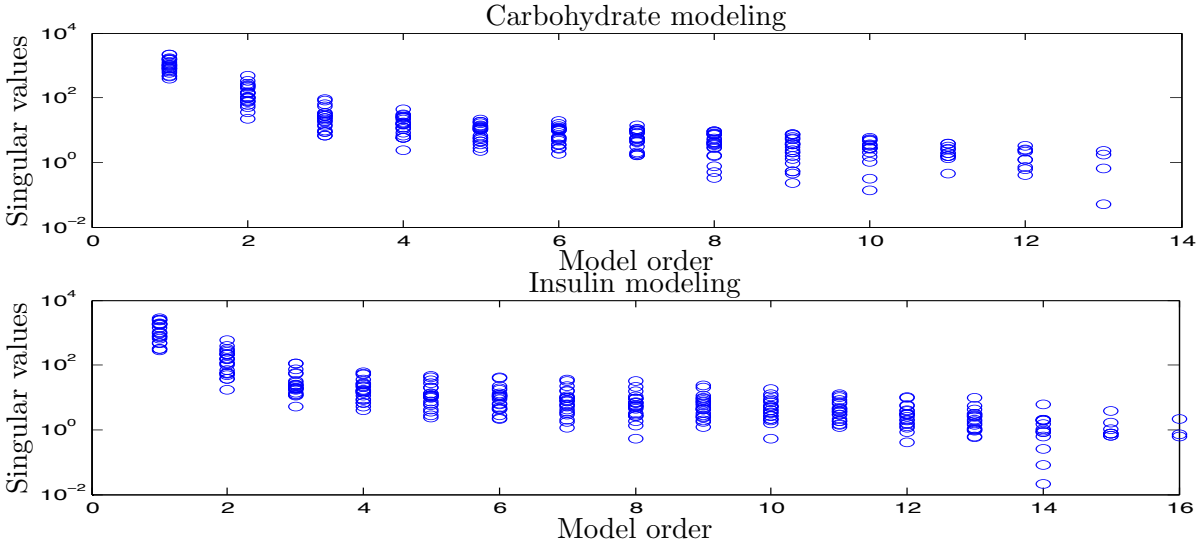

Figure 1. Model-order selection for all the patients. *Top* Carbohydrate modeling, *Bottom* Insulin modeling

Without loss of generality it is assumed that the dimension $n = 2$. The noise $w(t) \in \mathbb{R}^n$ and $v(t) \in \mathbb{R}^l$ are Wiener processes with incremental covariance given by:

$$\mathcal{E}\{\begin{bmatrix} w(t)dt \\ v(t)dt \end{bmatrix} \begin{bmatrix} w(t)dt \\ v(t)dt \end{bmatrix}^\intercal\} = \begin{bmatrix} Q & S \\ S^\intercal & R \end{bmatrix} dt \tag{6}$$

The initial state, $w(t)$, $v(t)$ and $u(t)$ are assumed to be mutually independent. The system matrices $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{p\times n}$ are such that (A, C) is observable, $(A, [B, Q^{\frac{1}{2}}])$ is controllable and the system is stable. The input-output data sequences of system (5) are observed at the sample times not necessarily equidistantly spaced $\{t_k\}_0^N$, $t_{k+1} \geq t_k$ for all k and are denoted as $\{u(t_k)\}_0^N$, $\{y(t_k)\}_0^N$. The continuous-time model identification problem, thus, consists in identifying the system parameters A, B, C up to a similarity transformation or equivalently the (system invariant) transfer function $F(s) = C(sI - A)^{-1}B$ starting from $\{u(t_k)\}_0^N$, $\{y(t_k)\}_0^N$.

From the set of first-order differential equations, we have in the Laplace domain notation:

$$\begin{aligned} sX(s) &= AX(s) + BU(s) + W(s) + sx_0, \qquad x_0 = x(t_0) \\ Y(s) &= CX(s) + V(s) \end{aligned} \tag{7}$$

Introduction of the causal, stable, realizable linear operator proposed in (Johansson 1994)

$$\lambda(s) = \frac{1}{1 + s\tau} \tag{8}$$

in order to replace the Laplace domain differentiation as represented by s, mapping the left-half plane into the disc Ω centered in 0.5, permits an algebraic reformulation of the model:

$$\begin{aligned} X &= (I + \tau A)[\lambda X] + \tau B[\lambda U] + \tau[\lambda W] + (1 - \lambda)x_0 \\ Y &= CX + V \end{aligned} \tag{9}$$

Reformulation to linear system equations while disregarding the initial conditions gives:

$$\begin{aligned}\begin{bmatrix}\xi\\ y\end{bmatrix} &= \begin{bmatrix}(I+\tau A)\ \tau B\\ C\quad 0\end{bmatrix}\begin{bmatrix}x\\ u\end{bmatrix} + \begin{bmatrix}\tau v\\ e\end{bmatrix}, \quad x(t) = [\lambda\xi](t)\\ &= \begin{bmatrix}A_\lambda\ B_\lambda\\ C\quad 0\end{bmatrix}\begin{bmatrix}x\\ u\end{bmatrix} + \begin{bmatrix}\tau v\\ e\end{bmatrix}, \qquad \begin{cases}A_\lambda &= I+\tau A\\ B_\lambda &= \tau B\end{cases}\end{aligned} \tag{10}$$

the mapping between (A, B) and (A_λ, B_λ) being bijective. Provided that a standard positive semi-definiteness condition of Q is fulfilled so that the Riccati equation has a solution

$$\begin{aligned}P_\lambda &= A_\lambda P_\lambda A_\lambda^\intercal + Q_\lambda - (A_\lambda P_\lambda C_\lambda^\intercal + S_\lambda^\intercal)(C_\lambda P_\lambda C_\lambda^\intercal + R_\lambda)^{-1}(C_\lambda P_\lambda A_\lambda^\intercal + S_\lambda)\\ K_\lambda &= (A_\lambda P_\lambda C_\lambda^\intercal + S_\lambda^\intercal)(C_\lambda P_\lambda C_\lambda^\intercal + R_\lambda)^{-1}\end{aligned} \tag{11}$$

with noise covariance

$$\mathcal{E}\{\begin{bmatrix}\tau v(t)dt\\ e(t)dt\end{bmatrix}\begin{bmatrix}\tau v(t)dt\\ e(t)dt\end{bmatrix}^\intercal\} = \begin{bmatrix}Q_\lambda\ S_\lambda\\ S_\lambda^\intercal\ R_\lambda\end{bmatrix}dt \tag{12}$$

it is possible to replace the linear model of Eq. (10) by the innovations model

$$\begin{bmatrix}\xi\\ y\end{bmatrix} = \begin{bmatrix}A_\lambda\ B_\lambda\\ C\quad 0\end{bmatrix}\begin{bmatrix}x\\ u\end{bmatrix} + \begin{bmatrix}K_\lambda\\ I\end{bmatrix}w, \qquad K_\lambda = \tau K \tag{13}$$

Taking the innovations model inverse (predictor form) we have

$$\begin{aligned}\begin{bmatrix}\xi\\ w\end{bmatrix} &= \begin{bmatrix}A_\lambda - K_\lambda C & B_\lambda\\ -C & 0\end{bmatrix}\begin{bmatrix}x\\ u\end{bmatrix} + \begin{bmatrix}K_\lambda\\ I\end{bmatrix}y\\ &= \begin{bmatrix}\bar{A}_\lambda\ B_\lambda\\ -C\quad 0\end{bmatrix}\begin{bmatrix}x\\ u\end{bmatrix} + \begin{bmatrix}K_\lambda\\ I\end{bmatrix}y, \quad \bar{A}_\lambda = A_\lambda - K_\lambda C\\ y &= Cx + w\end{aligned} \tag{14}$$

Further, all the eigenvalues of $\bar{A}_\lambda$ are assumed to be inside the disc Ω. Now, in this framework, the PBSID algorithm which was originally developed in discrete-time (Chiuso 2007) can be reformulated for the continuous-time case (Bergamasco and Lovera 2010). By recursion it is found that

$$\begin{aligned}[\lambda^p y](t) &= C\bar{A}_\lambda^p\xi(t) + \sum_{h=1}^{p} C\bar{A}_\lambda^{h-1}(B_\lambda[\lambda^{p-h}u](t) + K_\lambda[\lambda^{p-h}y](t)) + [\lambda^p w](t)\\ [\lambda^{p+1} y](t) &= C\bar{A}_\lambda^{p+1}\xi(t) + \sum_{h=1}^{p+1} C\bar{A}_\lambda^{h-1}(B_\lambda[\lambda^{p+1-h}u](t) + K_\lambda[\lambda^{p+1-h}y](t)) + [\lambda^{p+1} w](t)\\ &\vdots\\ [\lambda^{p+f} y](t) &= C\bar{A}_\lambda^{p+f}\xi(t) + \sum_{h=1}^{p+f} C\bar{A}_\lambda^{h-1}(B_\lambda[\lambda^{p+f-h}u](t) + K_\lambda[\lambda^{p+f-h}y](t)) + [\lambda^{p+f} w](t)\end{aligned} \tag{15}$$

Introducing the matrix notation (Bergamasco and Lovera 2010)

$$\begin{aligned}
\mathcal{Y}_{[p,p+f]}(t) &= \left[[\lambda^p y](t)\ [\lambda^{p+1} y](t) \cdots\ [\lambda^{p+f} y](t)\right] \\
\mathcal{U}_{[p,p+f]}(t) &= \left[[\lambda^p u](t)\ [\lambda^{p+1} u](t) \cdots\ [\lambda^{p+f} u](t)\right] \\
\mathcal{W}_{[p,p+f]}(t) &= \left[[\lambda^p w](t)\ [\lambda^{p+1} w](t) \cdots\ [\lambda^{p+f} w](t)\right] \\
\mathcal{Z}_{[p-1,p+f-1]}(t) &= \begin{bmatrix} [\lambda^{p-1} z](t) & [\lambda^p z](t) & \cdots & [\lambda^{p+f-1} z](t) \\ \vdots & \vdots & \cdots & \vdots \\ [\lambda^0 z](t) & [\lambda z](t) & \cdots & [\lambda^{f-1} z](t) \end{bmatrix}, \quad z(t) = \begin{bmatrix} u(t) \\ y(t) \end{bmatrix}
\end{aligned} \tag{16}$$

we have

$$\mathcal{Y}_{[p,p+f]}(t) = \bar{\mathcal{O}}_{[p,p+f]}\xi(t) + \Xi_0 \mathcal{Z}_{[p-1,p+f-1]}(t) + \mathcal{W}_{[p,p+f]}(t) \tag{17}$$

where

$$\begin{aligned}
\Xi_0 &= \left[C\bar{A}_\lambda^{p-1}[B_\lambda \quad K_\lambda]\ C\bar{A}_\lambda^{p-2}[B_\lambda \quad K_\lambda] \cdots \cdots\ C[\bar{B}_\lambda \quad K_\lambda]\right] \\
\bar{\mathcal{O}}_{[p,p+f]} &= \left[C\bar{A}_\lambda^{p}\ C\bar{A}_\lambda^{p+1} \cdots\ C\bar{A}_\lambda^{p+f}\right]^\intercal
\end{aligned} \tag{18}$$

Let us consider, now, the finite sequences of (possibly non-uniformly) sampled input-output data $\{u(t_k)\}_0^N, \{y(t_k)\}_0^N$ at sample times $\{t_k\}_0^N$, $t_{k+1} \geq t_k$, $\forall k$. As the regression model of Eq. (17) is valid for all times, it is also a valid regression model at sample times $\{t_k\}_0^N$

$$\mathcal{Y}_{[p,p+f]}(t_k) = \bar{\mathcal{O}}_{[p,p+f]}\xi(t_k) + \Xi_0 \mathcal{Z}_{[p-1,p+f-1]}(t_k) + \mathcal{W}_{[p,p+f]}(t_k) \tag{19}$$

Let p be sufficiently large as compared to the eigenvalues of $\bar{A}_\lambda$. Then, $\bar{\mathcal{O}}_{[p,p+f]}$ can be neglected, i.e., $\bar{A}_\lambda^j \in o(1/\sqrt{N})$, $\forall j \geq p$, N number of available samples (Chiuso 2007), so that finally we obtain

$$\mathcal{Y}^N_{[p,p+f]} = \Xi_0 \mathcal{Z}^N_{[p-1,p+f-1]} + \mathcal{W}^N_{[p,p+f]} + o(1/\sqrt{N}) \tag{20}$$

where

$$\mathcal{Y}^N_{[p,p+f]} = \left[[\lambda^p y](t_0) \cdots\ [\lambda^p y](t_N) \cdots\ [\lambda^{p+f} y](t_0) \cdots\ [\lambda^{p+f} y](t_N)\right] \tag{21}$$

and similarly for $\mathcal{U}^N_{[p,p+f]}, \mathcal{Z}^N_{[p-1,p+f-1]}, \mathcal{W}^N_{[p,p+f]}$. Matrix Ξ_0 is estimated solving the least-squares problem

$$\hat{\Xi}_0 = \underset{\Xi_0, D}{\operatorname{argmin}}\ ||\ \mathcal{Y}^N_{[p,p+f]} - \Xi_0 \mathcal{Z}^N_{[p-1,p+f-1]}\ ||_F^2 \tag{22}$$

where $||\cdot||_F$ stands for the Frobenius norm of a matrix (Golub and Van Loan 1996). For finite p the solution of this linear problem will be biased due the approximation made disregarding the initial states. In the LTI literature a number of contributions studied the effect of the window size and although they proved the asymptotic properties of the algorithms (if $p \to \infty$ the bias disappears) it is hard to quantify the effect for finite p (Knudsen 2001, Chiuso and Picci 2005, Chiuso 2007). Once the Markov parameters of the system are found in Ξ_0 estimated solving Eq. (22), the next step consists in estimating the state sequence. To this end, consider the following

matrices

$$\Xi = \begin{bmatrix} \Xi_0 \\ \Xi_1 \\ \vdots \\ \Xi_{f-1} \end{bmatrix} = \begin{bmatrix} C\bar{A}_\lambda^{p-1}[B_\lambda & K_\lambda] & C\bar{A}_\lambda^{p-2}[B_\lambda & K_\lambda] & \cdots & \cdots & \cdots & C[B_\lambda & K_\lambda] \\ 0 & & C\bar{A}_\lambda^{p-1}[B_\lambda & K_\lambda] & \cdots & \cdots & \cdots & C\bar{A}_\lambda[B_\lambda & K_\lambda] \\ \vdots & & & \ddots & \ddots & \ddots & \ddots & \vdots & \\ 0 & & & \cdots & 0 & C\bar{A}_\lambda^{p-1}[B_\lambda & K_\lambda] \cdots & C\bar{A}_\lambda^{f-1}[B_\lambda & K_\lambda] \end{bmatrix} \tag{23}$$

$$\bar{\mathcal{O}}_{[0,p-1]} = \begin{bmatrix} C \\ C\bar{A}_\lambda \\ C\bar{A}_\lambda^2 \\ \vdots \\ C\bar{A}_\lambda^{p-1} \end{bmatrix} \tag{24}$$

It holds

$$\bar{\mathcal{O}}_{[0,p-1]}\mathcal{X}^N_{[p,p]} = \Xi\mathcal{Z}^N_{[p-1,p-1]} \tag{25}$$

By singular value decomposition

$$\Xi\mathcal{Z}^N_{[p-1,p-1]} = \begin{bmatrix} U & U_\perp \end{bmatrix} \begin{bmatrix} \Sigma_n & 0 \\ 0 & \Sigma \end{bmatrix} \begin{bmatrix} V \\ V_\perp \end{bmatrix} \tag{26}$$

the state can be estimated:

$$\hat{\mathcal{X}^N_{[p,p]}} = \Sigma_n V \tag{27}$$

From the output equation in Eq.(14) an estimate of C can be obtained by means of least-squares estimation, i.e.,

$$\hat{C} = \underset{C}{\operatorname{argmin}} \; || \; \mathcal{Y}^N_{[p,p]} - C\mathcal{X}^N_{[p,p]} \; ||^2_F \tag{28}$$

as well as the innovation sequence

$$\mathcal{W}^N_{[p,p]} = \mathcal{Y}^N_{[p,p]} - \hat{C}\hat{\mathcal{X}}^N_{[p,p]} \tag{29}$$

Finally, the matrices $A_\lambda, B_\lambda, K_\lambda$ are found solving the least-squares problem

$$\hat{A}_\lambda, \hat{B}_\lambda, \hat{K}_\lambda = \underset{A_\lambda, B_\lambda, K_\lambda}{\operatorname{argmin}} \; || \; \hat{\mathcal{X}}^N_{p+1,p} - A_\lambda\hat{\mathcal{X}}^N_{p,p-1} - B_\lambda\mathcal{U}^N_{p,p-1} - K_\lambda\mathcal{W}^N_{p,p-1} \; ||^2_F \tag{30}$$

A summary of the steps carried out in the identification procedure is reported in Algorithm **1**.

Algorithm 1:

(1) Construct the matrices $\mathcal{U}^N_{[p,p+f]}$, $\mathcal{Y}^N_{[p,p+f]}$, $\mathcal{Z}^N_{[p-1,p+f-1]}$ according to Eq. (21)
(2) Solve Eq.(22) for $\hat{\Xi}_0$
(3) Compute the SVD in Eq.(26)
(4) Choose the model order by inspecting the singular values from step (3)
(5) Get the estimated state-sequence $\hat{\mathcal{X}}^N_{[p,p]}$ using Eq.(27)
(6) With $\hat{\mathcal{X}}^N_{[p,p]}$ solve Eq.(28)

(7) Compute the innovation sequence from Eq.(29)
(8) Obtain $A_\lambda, B_\lambda, K_\lambda$ solving the least-squares in Eq.(30)
(9) Calculate the state-space matrices A, B, K by means of the relations: $A = \frac{1}{\tau}(A_\lambda - I)$, $B = \frac{1}{\tau}B_\lambda$, $K = \frac{1}{\tau}K_\lambda$.

3.2.1 Comments

Four parameters have to be chosen : (i) the low-pass filter pole location $1/\tau$, (ii) the system order n, (iii) the length of the past horizon p and (iv) the length of the future horizon f. The parameter τ is related to the expected bandwidth of the system to identify, and is chosen such that $1/\tau \geq \omega_b$. As the model order n is concerned in this paper we shall consider it as given. The length of the past horizon has to be estimated from data, e.g., using standard criterions for VARX model order estimation (Peternell 1995, Chiuso 2007). A suitable future horizon can be taken $f \leq p$, as suggested in (Chiuso 2010).

3.3 *Identification strategy*

Our objective was to estimate the unknown parameter vector

$$\hat{\theta} = \left[\hat{K}_{carb}\ \hat{K}_{ins}\ \hat{T}_{carb,1}\ \hat{T}_{carb,2}\ \hat{T}_{ins}\ \hat{\tau}_{carb}\ \hat{\tau}_{ins}\right]^{\mathsf{T}} \tag{31}$$

so that the estimation error between the actual blood glucose data $y_{BG}(t)$ and the simulated model data $\hat{y}_{BG}(t)$ was minimized in a least-squares sense:

$$\hat{\theta} = \arg\min_{\theta} \int_0^T (y_{BG}(t) - \hat{y}_{BG}(t,\theta))^2 dt \tag{32}$$

where t is the continuous-time index and $T = 4$ [h], i.e., time interval 8:00-10:00 am, subject to some constraints on θ, namely $\hat{K}_{carb} > 0$, $\hat{K}_{ins} < 0$ to guarantee qualitatively correct responses to inputs (blood glucose increases after a meal intake and decreases after an insulin shot) and $\hat{T}_{carb,1}, \hat{T}_{carb,2}, \hat{T}_{ins} > 0$ to guarantee stability. To this end, data collected during the first admission visit were exploited, in particular, the CGMS data were used as measurements of glycemia, being easily available in standard clinical practice and in the specific case of the trial resulting in accordance with the YSI measurements. The equilibrium glycemia level, i.e., the value of blood glucose just before breakfast was administered, was taken away from the data series. Subsequently, the meal test data sequences were splitted into 2 parts: the interval [8:00+τ_{carb}, 10:00+τ_{ins}) for the quantification of the breakfast impact and the interval [10:00+τ_{ins}, 1:00] for that of the insulin bolus impact, the time delays being determined empirically. The continuous-time predictor-based identification (PBSID$_{cont}$) algorithm shown in Sec. 3.2 was applied to the first portion of the data and the parameters K_{carb}, $T_{carb,1}, T_{carb,2}$ were estimated. Next, the effect of such carbohydrate intake predicted by the identified model if no insulin would have been taken at 10:00 am was removed (black dotted curve in Fig. 2, 4) and the PBSID$_{cont}$ algorithm applied to the resulting data in order to get an estimate of K_{ins}, T_{ins}.

Up to 6% missing CGMS data points for one single subject was reported; however, this didn't play a major role as the continuous-time set-up for the identification can handle non-uniformly sampled records.

The user parameters were chosen as follows:

- $\tau = 10$ was selected at first, then refined by trial and error
- $n = 2$ according to the Hankel singular values (see fig. 1)
- $p = f = 3$ based on standard criteria for model order estimation Ljung (1999)

Table 2. Estimated model parameters

Name	τ_{carb} [min]	K_{carb}	$T_{carb,1}$	$T_{carb,2}$	τ_{ins} [min]	K_{ins}	T_{ins}
CHU101	6	42.7822	11.7786	37.1747	2	-16.3552	14.48
CHU107	4	6.2703	6.8259	∞	6	-85.4642	76.10
CHU117	3	29.2354	11.0011	12.5000	4	-90.0913	9.1324
CHU118	3	25.8144	7.5019	12.6263	6	-17.5864	17.19
CHU125	4	3.9614	10.8530	∞	4	-55.2759	44.15
CHU136	5	40.9486	6.6269	19.8807	3	-21.8811	17.7462
CHU138	5	2.5881	18.5529	∞	10	-4.5	100
CHU143	4	4.0786	4.5725	∞	2	-70.5128	94.9668
CHU144	4	8.2976	22.3414	∞	3	-85.4118	58.8235
CHU145	5	2.2107	10.6746	∞	8	-4.4030	21.4362
UNIPD201	3	75.9147	12.0192	26.4550	8	-33.5649	41.8410
UNIPD217	3	3.7976	3.2020	∞	3	-254.3849	588.5815
UNIPD219	6	55.2045	2.7420	27.6243	3	-18.4587	15.5376
UNIPD233	5	97.8365	2.3827	71.4286	3	-146.3858	443.4590
UNIPD234	2	4.0998	5.2826	∞	6	-19.0558	10.6815
IKEM302	7	3.4471	7.7220	∞	3	-16.7655	11.8652
IKEM306	4	6.7401	8.9928	∞	3	-39.6333	55.55
IKEM309	5	6.4525	6.8871	∞	12	-51.9976	59.6303
IKEM311	3	5.5341	8.4104	∞	5	-31.4745	39.2157
IKEM324	4	3.2397	9.1827	∞	8	-32.4379	36.5497
IKEM326	4	4.6976	11.1185	∞	9	-16.0565	20.0280
IKEM330	9	1.5772	4.0420	∞	5	-13.9050	32.2997

4 Results

Table 2 collects the estimated parameters for all the patients. The top plots in Figs. 2 and 4 presents simulation results on identification data for some representative patients. In particular, the actual CGMS data used for model parameters identification is compared with the glycemia level predicted by the meal model when no insulin is taken and the estimated glycemia level resulting from the application of both meal and insulin model. Figures 3 and 5 show the response to 10 [g] of carbohydrate and to 1 [IU] predicted by the models for the representative patients. Notice that without loss of generality the equilibrium level at the start of the simulation was chosen as the actual CGMS value at the beginning of the breakfast as far as the carbohydrate response is concerned, and as the highest glucose peak for insulin response. Validation was performed on the second admission set of data. The YSI measurements were taken as glycemia assessment, due to poor CGM data. We recall in passing that the second admission took place 14 ± 3 days after the first admission and that in the days prior to the test the subjects glucoregulatory system was challenged by an exercise test and a big lunch containing 100 [g] carbohydrate. Results of such validation are shown in the bottom plots of Figs. 2 and 4 for some representative patients. As for performance assessment, the following metrics were considered:

- Percentage Variance Accounted For (VAF):

$$\text{VAF} = \left(1 - \frac{\mathcal{E}[(y(t) - \hat{y}(t))(y(t) - \hat{y}(t))^\intercal]}{\mathcal{E}[y(t)y^\intercal(t)]}\right) \times 100\%$$

  where $\mathcal{E}[\cdot]$ denotes mathematical expectation. The VAF of two signals that are the same is 100%. If they differ, the VAF will be lower.
- Root Mean Square Error (RMSE) [mg/dL^2]:

$$\text{RMSE} = \sqrt{\frac{(y(t) - \hat{y}(t))(y(t) - \hat{y}(t))^\intercal}{N}}$$

  where N denotes the number of samples.

Results of performance statistics compared across the population are presented in tables 3 and 4 and in Figs. 6 and 7.

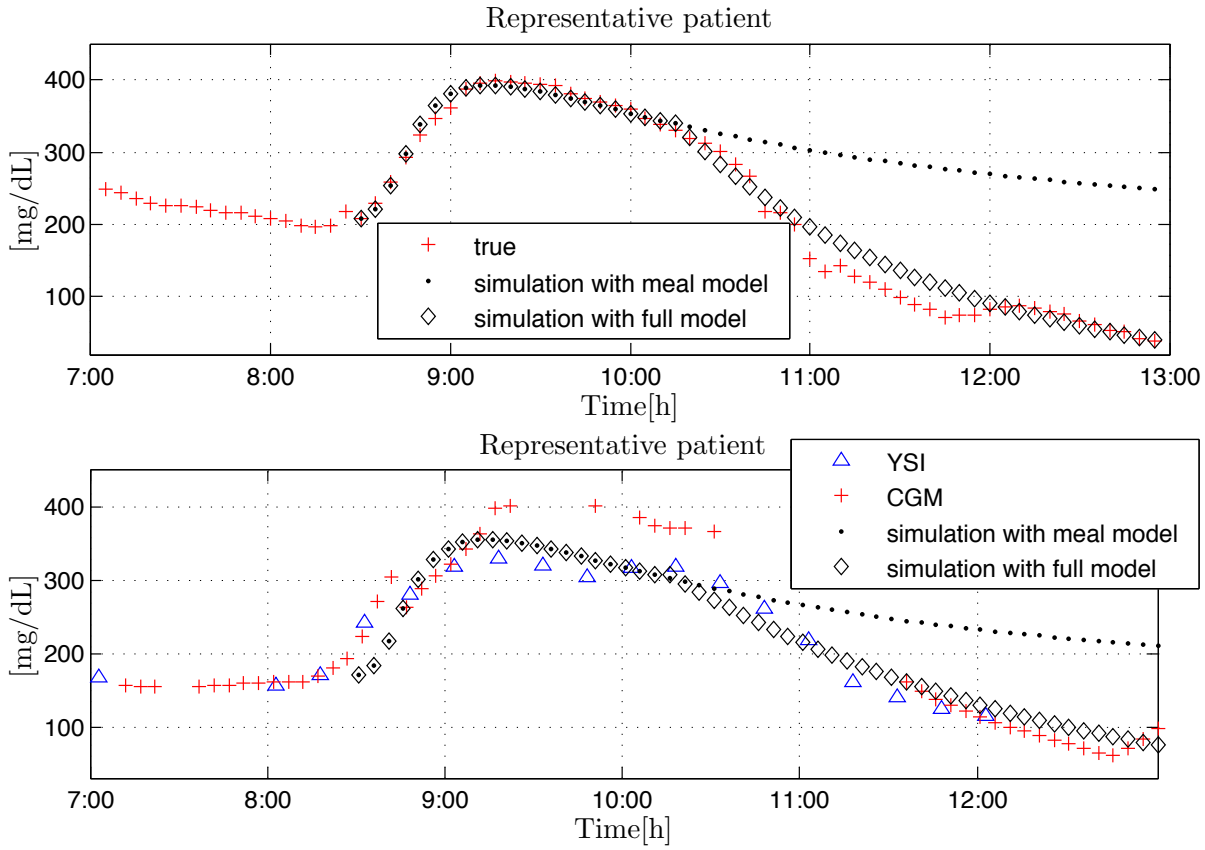

Figure 2. Patient UNIPD219. DIAdvisor II trial. *Top Visit 2*, identification data; *Bottom Visit 3* cross-validation data. Actual CGMS (star) vs. simulated breakfast impact (dot) and simulated joint meal and insulin intakes (diamond) [mg/dL]. All the measurements vs. time of the day [h]

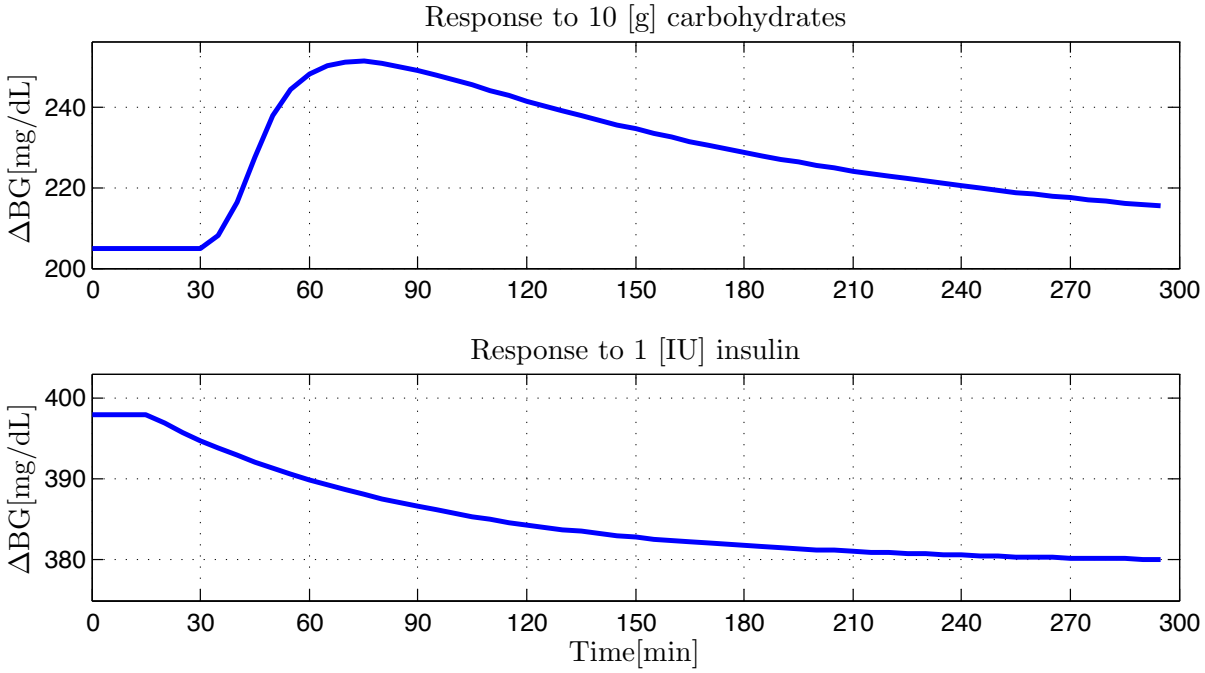

Figure 3. Patient UNIPD219. Response to *Top* 10 [g] of carbohydrate *Bottom* 1 [IU] of insulin. Blood glucose excursion [mg/dL] vs. time [min]

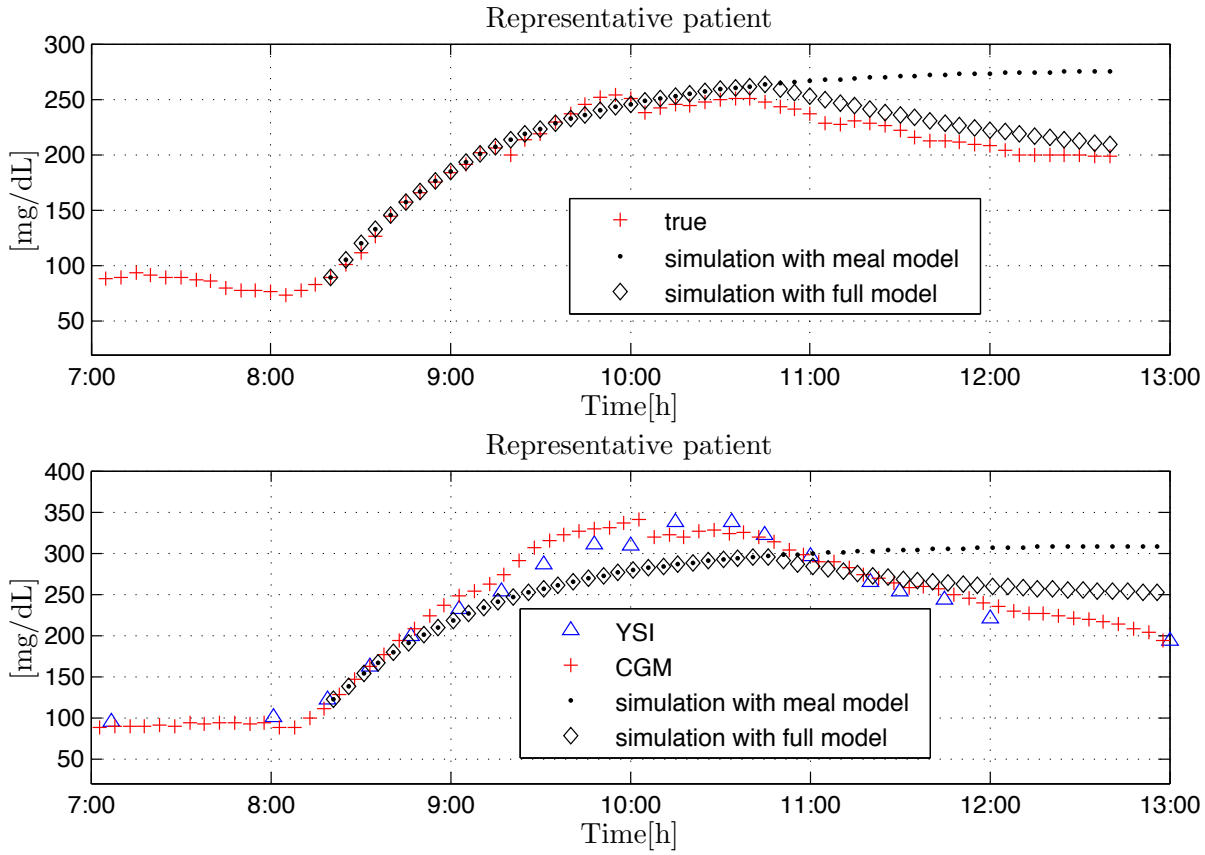

Figure 4. Patient IKEM326. DIAdvisor II trial. *Top Visit 2*, identification data; *Bottom Visit 3* cross-validation data. Actual CGMS (star) vs. simulated breakfast impact (dot) and simulated joint meal and insulin intakes (diamond) [mg/dL]. All the measurements vs. time of the day [h]

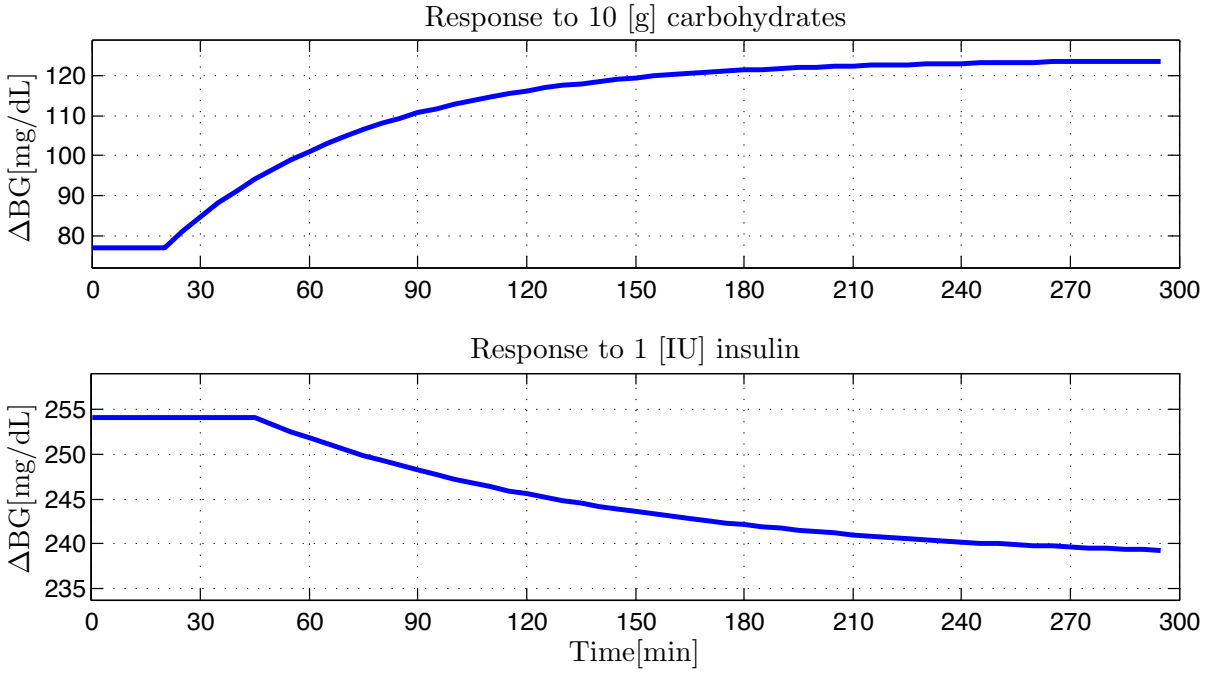

Figure 5. Patient IKEM326. Response to *Top* 10 [g] of carbohydrate *Bottom* 1 [IU] of insulin. Blood glucose excursion [mg/dL] vs. time [min]

Table 3. Carbohydrate effect modeling: performance evaluation

	On estimation data		On validation data	
Name	VAF [%]	RMSE [mg/dL^2]	VAF [%]	RMSE [mg/dL^2]
CHU101	96.05	4.99	data not available	data not available
CHU107	96.30	22.81	data not available	data not available
CHU117	91.35	10.81	81.84	35.90
CHU118	91.71	13.42	39.37	42.56
CHU125	97.08	11.38	data not available	data not available
CHU136	92.90	16.03	data not available	data not available
CHU138	96.59	6.19	79.58	24.30
CHU143	92.27	21.75	78.09	51.57
CHU144	99.81	6.60	data not available	data not available
CHU145	97.83	5.62	data not available	data not available
UNIPD201	98.97	6.40	94.81	16.63
UNIPD217	92.21	14.67	86.84	25.99
UNIPD219	97.62	8.61	69.11	151.33
UNIPD233	95.92	9.94	69.46	42.74
UNIPD234	93.19	22.18	73.96	36.94
IKEM302	95.48	12.64	71.39	53.50
IKEM306	99.17	11.25	67.74	21.20
IKEM309	92.38	19.98	82	79.49
IKEM311	93.98	28.16	data not available	data not available
IKEM324	98.09	6.79	70.37	52.35
IKEM326	98	7.98	77.97	127.82
IKEM330	94.49	5.64	data not available	data not available
MEAN	95.51	12.44	74.46	54.45

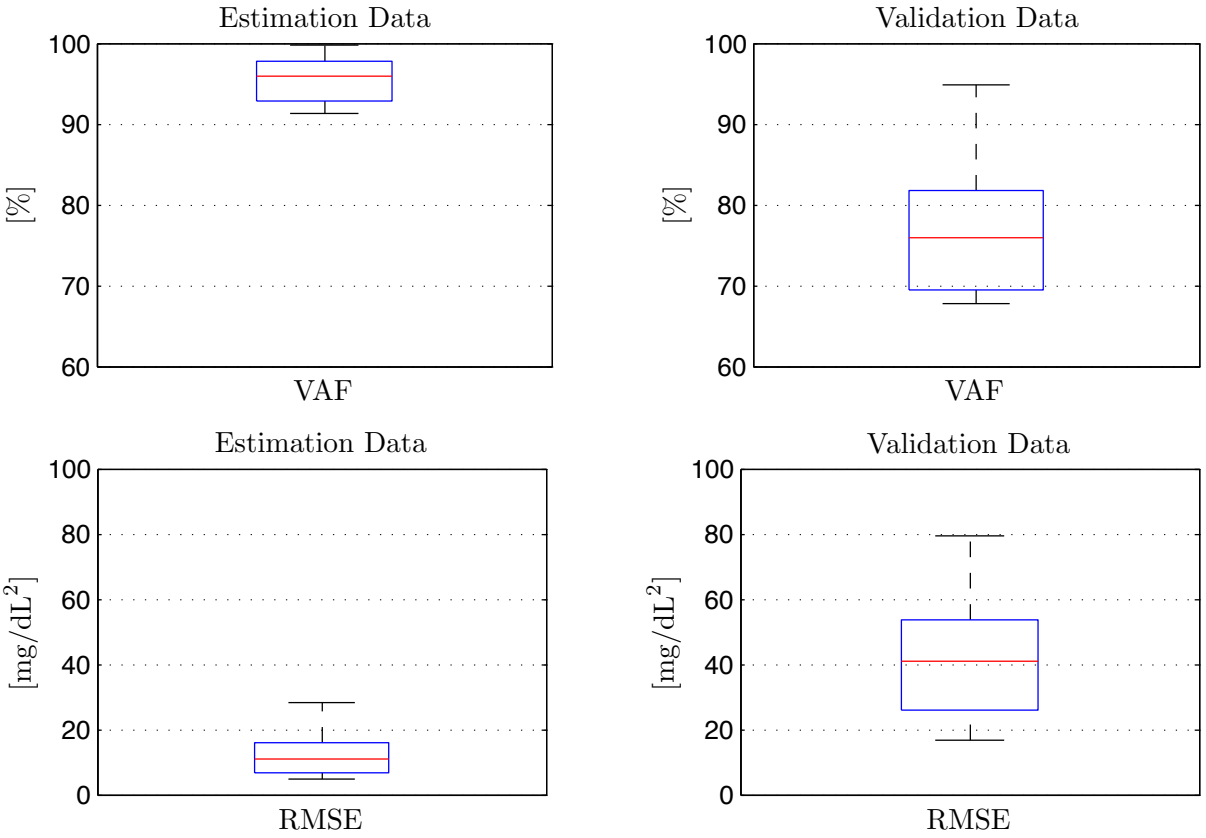

Figure 6. Population study. Breakfast impact modeling. *Top Panels* Percentage VAF; *Bottom Panels* RMSE [mg/dL^2]. *Left* Performances evaluated on the first admission (estimation) data; *Right* Performances evaluated on the second admission (validation) data. Each box presents the results achieved over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles.

Table 4. Insulin effect modeling: performance evaluation

	On estimation data		On validation data	
Name	VAF [%]	RMSE [mg/dL^2]	VAF [%]	RMSE [mg/dL^2]
CHU101	95.63	18.08	data not available	data not available
CHU107	99.75	1.65	data not available	data not available
CHU117	98.52	6.58	73.09	168.34
CHU118	98.96	3.90	53.89	176.58
CHU125	99.35	2.64	data not available	data not available
CHU136	97.27	6.69	data not available	data not available
CHU138	98.71	3.01	42.19	48.45
CHU143	98.88	4.36	71.87	91.22
CHU144	98.98	12.48	data not available	data not available
CHU145	97.17	2.88	data not available	data not available
UNIPD201	99.49	5.88	22.88	141.93
UNIPD217	99.30	7.38	64.71	116.17
UNIPD219	89.79	20.90	62.75	99.71
UNIPD233	97.70	10.47	57.61	202.78
UNIPD234	96.17	14.16	11.57	98.11
IKEM302	97.39	15.35	86.93	182.47
IKEM306	99.81	2.58	63.67	57.71
IKEM309	94.40	8.63	71.34	56.68
IKEM311	97.89	10.47	data not available	data not available
IKEM324	98.16	4.44	20.58	134.16
IKEM326	98.47	2.71	74.45	46.67
IKEM330	98.44	2.96	data not available	data not available
MEAN	94.79	9.88	62.67	115.78

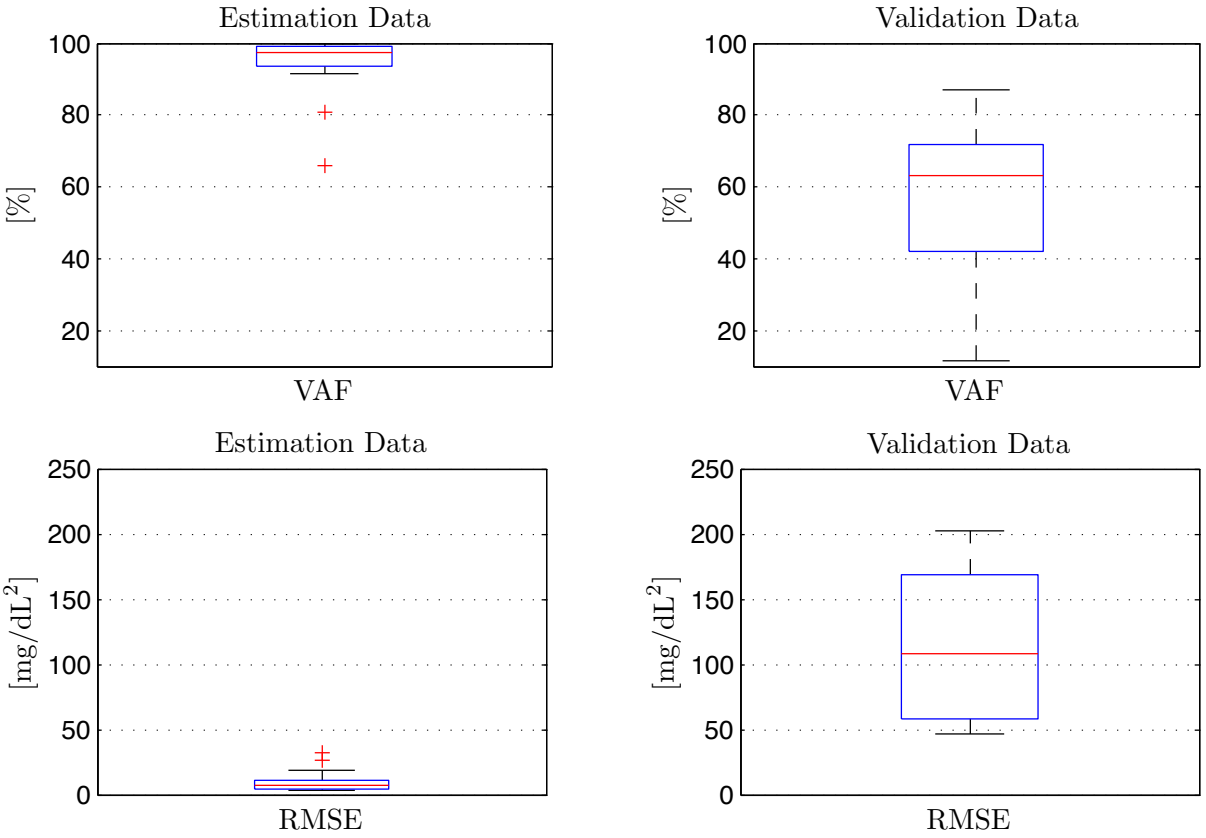

Figure 7. Population study. Insulin impact modeling. *Top Panels* Percentage VAF; *Bottom Panels* RMSE [mg/dL^2]. *Left* Performances evaluated on the first admission (estimation) data; *Right* Performances evaluated on the second admission (validation) data. Each box presents the results achieved over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles.

5 Discussions

Continuous-time transfer function models of second order with time delays were proposed to quantify the impact of a carbohydrate intake and an insulin injection on blood glucose dynamics. The choice of the model structure was motivated by inspection of the data series for the available 6 hours test with a physiologically sound interpretation. The glucoregulatory system was considered at steady-state during the overnight fast up until breakfast. Actually, small fluctuations around the blood glucose equilibrium level were noticed but were not considered significant nor affecting the estimation procedure. The parameters in the models are linked to clinical variables. In particular, K_{carb}, T_{carb} can be related to glucose tolerance, i.e., how the body metabolizes glucose, whereas K_{ins}, T_{ins} are connected to insulin sensitivity or resistance, i.e., how effective is insulin in lowering blood glucose. Time delays accounting for food transportation along the gastro-intestinal tract as well as insulin kinetics from the subcutaneous tissues to plasma have been incorporated in the models as in (Percival et al. 2010). Further, the long delays between subcutaneous insulin administration and insulin action in the identified transfer functions reflected what already known from clinical practice. Model responses to 10 [g] of carbohydrate and 1 [IU] of insulin were considered physiologically plausible, resulting in model behavior compatible with experimental evidence. Indeed, the empirical observations recently published by Elleri and co-workers (Elleri et al. 2013) and by Schmidt and co-workers (Schmidt et al. 2012) strengthened the achieved results. Specifically, Elleri and co-workers studied the effects of a low-glycemic-load (LG) meal and a high-glycemic-load (HG) meal matched for carbohydrates (121 [g]) on T1DM children (Brouns et al. 2005). The outcome was a sustained, slowly declining plasma glucose profile which continued beyond the 8 hours of observations with an unpronounced peak of 210.6±36 [mg/dL] within 153±104 [min] after the intake of the LG meal, and a distinct earlier peak of 248.4±63 [mg/dL] at 98±29 [min]. The first resembling the absorption profiles in Fig. 5, while the second that in Fig. 3. Similar experimental evidence was presented in (Schmidt et al. 2012), where solid meals and a liquid snack were compared, the first behaving like a LG meal, while the second like a HG meal. As for insulin response, the experiments in (Schmidt et al. 2012) showed a larger decrease in glycemia per insulin unit than that predicted by the proposed models, the reason being attributable to the different initial conditions of the subjects metabolism. Another critical issue concerns the pharmacokinetics of the rapid-acting insulin analogues used by the subjects at this stage. Unfortunately, we did not have any data collected after 1:00 pm, preventing us from the possibility of verifying the duration of insulin action predicted by the identified models.

Prior information could be incorporated in the tuning procedure, taking into account the patient personal history of the disease and the experience gained in its regulation. It is a well known fact, indeed, that the subjects learn by trial-and-error how their glycemia reacts to different sources of carbohydrate and different insulin analogues. However, as yet, it is not clear how this can be realized.

The inputs were considered impulse-formed, the only information required by the identification method being the size of the meal and of the insulin intake, retrieved from the patient's logbook. The approach resembles standard clinical practice, it's personalized and it takes into account the high inter-subject variability. The strategy is particularly appealing as it amounts to estimating only 7 parameters. We mention here that the most recent physiological model (Dalla Man et al. 2007) has 25 unknown patient-specific parameters. Contrary to previous contributions dealing with simulated data obtained with in-silico ad-hoc experiments, e.g. (van Heudsen et al. 2012), (Boiroux et al. 2012), we have employed actual T1DM patient data collected within DIAdvisor ™ (Diadvisor 2008). Moreover, estimation and validation were performed on separate sets of data, collected at least two weeks apart. To the best of the author's knowledge this is the first time that such a validation methodology is followed in diabetic blood glucose dynamics modeling. Intra-patient variability was observed by cross-validation, as highlighted by the poor performances reported in Tables 3 and 4 (right columns) and may suggest the need of a model

parameters updating scheme. The critical issue here is to capture qualitatively the dynamic behaviour of blood glucose levels in diabetes with a tolerance of $\pm$ 35 [mg/dL]. Experiment design turned out to be of crucial importance, not only being tightly connected to the intended use of the model but also being constrained due to safety issues when dealing with patients harm. Despite the simple structure the models are able to sufficiently describe the main dynamics of the gluco-regulatory system.The proposed models were obtained from breakfast data only and may, hence, turn out not to be accurate in modeling lunch and dinner. In order to assess whether or not this is the case, a clinical meal test similar to that used in this contribution should be carried out, provided a 4-hours at least period of steady state prior to the test so to be able to apply the same method to the new set of data. In addition to this, it would be appropriate to administer a high-glycemic-load and a low-glycemic-load (Brouns et al. 2005) meals containing the same type of food to different groups of subjects, in order to verify whether the dynamic behaviour of blood glucose in response to a meal intake is due to patients or food characteristics. Post-prandial glucose fluctuations, indeed, are likely to be critically dependent on a number of factors, including meal composition, small intestinal delivery and absorption of nutrients, rate of gastric emptying and hepatic and renal glucose metabolism, the relative contribution of these factors remaining unclear (Horowitz et al. 2002). In an ideal protocol, insulin administration should be postponed by at least 3 hours and patient monitoring should continue for at least 6-8 hours after insulin intake, in order to model the effects of the inputs accurately. In the actual setting glycemia levels were assessed by a subcutaneous continuous glucose monitoring sensor calibrated against a self-monitoring finger-stick glucose meter. This introduces issues such as sensor noise, device recalibration, sensor time delays just to mention a few, requiring additional components to the control system, i.e., a sensor model (Breton and Kovatchev 2008), which was disregarded.

In order to identify the unknown parameters in the transfer functions, a continuous time-domain identification approach was taken, specifically, the predictor based subspace identification (PBSID) method using low-pass filters. The algorithm requires a few user's parameters to be tuned. The pole of the low-pass filter was chosen larger than the expected bandwidth of the system and refined by trial and error; the length of the past and the future window size p and f, respectively, was chosen to be 3 according to standard criterions for model order estimations.

6 Conclusions and future work

The contribution presented a successful application of continuous-time identification methods to T1DM blood glucose dynamics modeling. Low-order continuous-time transfer function models were identified from actual T1DM patients data collected adhering to a unique protocol for a meal test and validated on a separate set of data collected 14 ± 3 days apart. The strategy is appealing as it amounts to estimating only 7 parameters. The model structure is simple and the parameters have intuitive meaning that can be linked to clinical practice. The estimated models are straigntforward and can be easily interpreted by health-care professionals and may guide development of clinical decision support systems or automated closed-loop insulin delivery. The work considered breakfast data only. Thus, it would be interesting to perform the same type of modeling for other meals or snacks, possibly administering both a high-glycaemic-load and a low-glycaemic-load meal to the same subject. Further, future work will be carried out to extend the study on a larger population. By doing so, it will become apparent whether or not it is possible to classify subjects based on their clinical characteristics so to build appropriate nominal models, suitable as instruments for therapy, for each of the category.

Acknowledgements

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