Low-Complexity MISO Models of T1DM Glucose Metabolism

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Abstract— **One of the main limiting factor in developing a control algorithm for glycemia regulation is the lack of a control-oriented, parsimonious yet physiologically sound and individualized model able to reflect the basic dynamical features of the glucose-insulin metabolic system required for the control design. In this paper we focus on estimating low-complexity MISO models of the glucose metabolism in T1DM developed specifically for a controller implementing a basal-bolus therapy. The models are continuous-time second-order transfer functions relating the amount of carbohydrate of a meal and the insulin dose administered accordingly (inputs) to plasma glucose evolution (output) and consist of 4 parameters clinically relevant to be identified.**

I. Introduction

Diabetes Mellitus is a chronic disease of disordered glucose metabolism due to defects in either insulin secretion by the pancreatic β-cells or insulin action [1]. In particular, Type 1 Diabetes Mellitus (T1DM), being caused by no production of insulin whatsoever, is characterized by abnormally high blood glucose levels (hyperglycemia, blood glucose > 180 [mg/dL]) leading to serious health damages. In order to prevent the long term complications associated to the sustained hyperglycemia it becomes critical, then, for diabetic patients to regulate their blood glucose tightly, maintaining its level within the near-normal range ($70-180$ [mg/dL]) [2]. Because insulin lack defines the disease, exogenous insulin replacement administered with either multiple daily injections (MDI) or with an external insulin infusion pump (CSII) is the hallmark of the treatments. The idea behind conventional therapy insulin regimens is to mimic the physiological insulin secretion pattern of the non-diabetic subjects using delayed-acting (basal) doses to provide a background insulin concentration throughout the day and short-acting (bolus) doses to simulate the normal prandial insulin levels, this strategy being called basal-bolus regimen. 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 [3] and is progressing towards a fully automated closed-loop control artificial pancreas [4], [5]. 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 [3]. 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 an advice is suggested by the algorithm, the patient can accept or reject it, remaining firmly in the loop. As a matter of fact, this was the focus of the major European project DIAdvisor ^{TM} [6]. The development of such a controller requires mathematical models able to quantify the effect on plasma glucose of insulin injections and meal intakes, represented as impulses applied at irregularly sampled discrete time instants. To date several types of glucose metabolism models have been proposed (see e.g. [3] for a comprehensive review), most of these efforts being first-principles based descriptions of diabetes physiology [7], [8], [9] and only to a lesser extent mathematical modeling by means of system identification [10], [11], [12]. Neverthless, despite significant attention to the problem, the idea of building models specifically for control purposes has not emerged in the field until very recently [13], [14] [15]. That said, keeping in mind that modeling is efficient when it is tailored to the control design applications it was formulated for [16], [17], our purpose is to estimate approximate, low-order, physiologically sound models from real T1DM patients data for future use in a model-based control framework targeting a basal-bolus treated population. In the application considered the two control inputs are simultaneous, since according to clinical practice, the subject boluses at the same time of the meal intake, making it difficult to distinguish each input's contribution to blood glucose fluctuations. In addition, the possibilities for experiment design are limited due to strict safety requirements and patient risk. In the light of the above considerations and bearing in mind that ideally the collected data should be maximally informative with respect to the intended use of the model [18] revealing exactly the information required for the control design [16], a novel and unique clinical database was created and exploited to our objectives. The remainder of the paper is organized as follows. Section II deals with data collection and the explanation of the modeling work. Section III presents identification and validation results for the estimated models over the considered population, while the discussion on the achievements is left to Sec. IV. Finally, Sec. V concludes the paper with final remarks and considerations for future work.

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TABLE I

SELECTED POPULATION: PATIENTS CHARACTERISTICS

Name	*Gender*	*BMI* [kg/m^2]	Age	Therapy
P4	M	25.39	41	MDI
P5	M	31.07	61	CSII
P8	F	31.51	56	CSII
P10	F	25.50	27	CSII
P12	M	23.38	36	CSII

II. MATERIAL AND METHODS

A. Experimental conditions

The clinical protocol for data acquisition was designed under the aegis of DIAdvisor ™ [6], a large scale FP7-IST European project, reviewed and approved by the ethical committee of the Clinical Investigation Center (CIC) in Montpellier, France. A population of T1DM subjects using basal-bolus insulin regimen participated in the study signing an informed and witnessed consent form. Patients characteristics are reported in Table I. The trial comprised a series of experiment sessions for a duration of up to 9 weeks per patient. In particular, a novel meal test was carried out as follows. Patients were admitted at the clinic for a 6 hours observation period, from 7:00 am to 1:00 pm, fasting from the midnight. A standardized breakfast, the amount of carbohydrate being 40 [g], was served at 8:00 am. The patients calculated and noted on their personal logbook the amount of insulin needed to cover this meal, based on the outcome of their personal glucose meter. However, contrary to standard practice, the insulin bolus was administered 2 hours later. No other meals nor snacks were consumed up 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. A second meal test was performed 14±3 days apart, on day 3 of a 72-hours long in-hospital visit. Blood samples were drawn every 15 minutes for the 4 hours following carbohydrate ingestion to assess glucose concentration with the YSI. Prior to the above mentioned 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. Figures 1-4 show such experiments for two representative subjects.

B. Modeling strategy

Second order linear transfer function models were proposed to approximate the behaviour of glucose in response to 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, at 8.00 am an input was applied, namely 40 [g] of carbohydrate intake, which caused the controlled variable to rise (figs. 1-4).

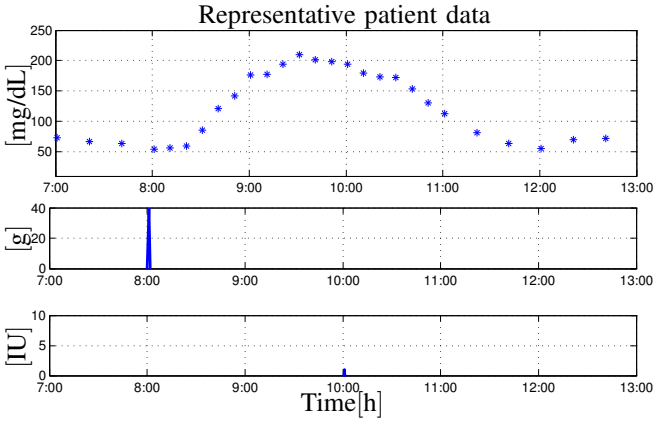

Fig. 1. Patient 4. Meal test data, first admission. *Top* Blood glucose measured by the YSI [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. Time of the day [h]

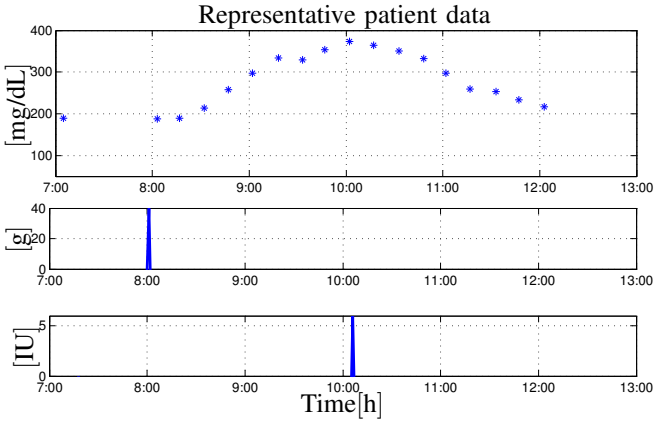

Fig. 2. Patient 8. Meal test data, second admission. *Top* Blood glucose measured by the YSI [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin dose [IU]. All the measurements vs. Time of the day [h]

In absence of any action taken, plasma glucose concentration didn't fall (time interval 8.00 am to 10.00 am). Then, the insulin shot which was previously calculated by the patient was administered, making glucose concentration to fall. 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, rather we modeled the inputs as impulses applied at time instants $t_{carb} = 8.00$ am and $t_{ins} = 10.00$ am, respectively. We assumed noise-free conditions, as plasma glucose is directly available thanks to the YSI. All these facts, led us to the formulation of the following OE-model structure [19]:

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

where $Y_{BG}(s)$ is the Laplace transform of the output blood glucose concentration; the transfer functions from carbohydrate to blood glucose and from insulin to blood glucose are given in Eq. 2 and 3, respectively.

$$G_{carb}(s) = \frac{K_{carb}}{s(1+sT_{carb})} \qquad (2)$$

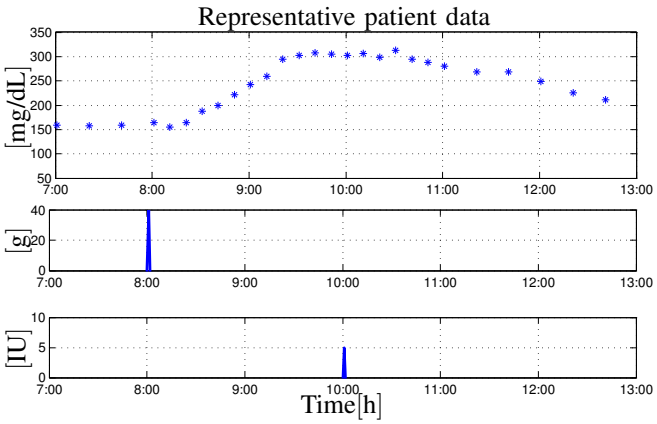

Fig. 3. Patient 12. Meal test data, first admission. *Top* Blood glucose measured by the YSI [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. Time of the day [h]

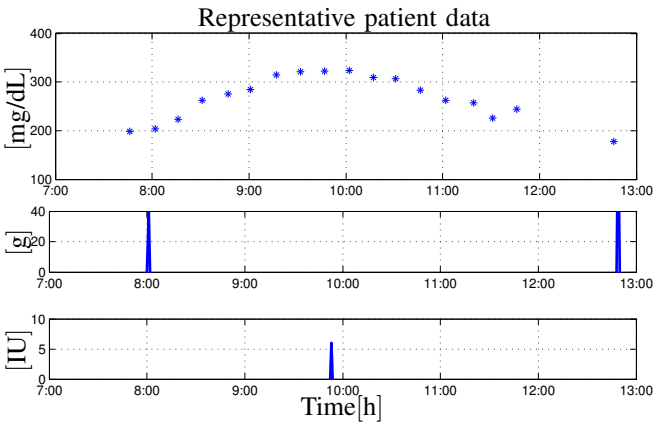

Fig. 4. Patient 12. Meal test data, second admission. *Top* Blood glucose measured by the YSI [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin dose [IU]. All the measurements vs. Time of the day [h]

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

Further, $u_{carb}, u_{ins} \in \mathbb{Z}_+$ are the inputs carbohydrate amount and insulin doses, respectively, $K_{carb}, K_{ins} \in \mathbb{R}$ are the gains and $T_{carb}, T_{ins} \in \mathbb{R}$ time constants governing rise and fall, respectively, of plasma glucose. Our objective was to estimate the unknown parameter vector $\hat{\theta} = [\hat{K}_{carb} \quad \hat{K}_{ins} \quad \hat{T}_{carb} \quad \hat{T}_{ins}]$ so that the estimation error between the actual blood glucose data $y_{BG}(t)$ and the simulated model data $\hat{y}_{BG}(t)$ is minimized in a least-squares sense:

$$\hat{\theta} = \arg\min_{\theta} \int_0^T (y_{BG}(t) - \hat{y}_{BG}(t))^2 dt \tag{4}$$

where t is the continuous-time index and $T = 5$ [h], 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 $\hat{T}_{carb}, \hat{T}_{ins} > 0$ to guarantee stability. Now, the search for the solution of the non-convex problem in Eq. 4 may lead to local minima and possibly ill-conditioned calculations, so to limit these problems we first tuned the parameter values empirically by trial and error using intuition

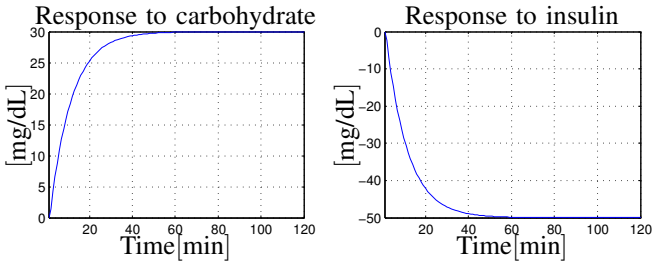

Fig. 5. Patient 4. Impulse responses of the proposed model structure. *Left* Response to carbohydrate; *Right* Response to insulin

until we obtained a reasonable fit with the data. Next, we refined the choice by means of the Matlab® [20] function *pem.m* initialized with the hand-tuned parameters. Last, the output plasma glucose was interpolated and uniformly resampled, the sampling period being 1 [min].

III. Results

The identified models were the following:

$$y(t) = \frac{3}{s(s+0.1)}u_1\delta(t) + \frac{-5}{s(s+0.1)}u_2\delta(t)$$

$$y(t) = \frac{5}{s(s+0.3)}u_1\delta(t) + \frac{-20}{s(s+0.3)}u_2\delta(t)$$

$$y(t) = \frac{30}{s(s+0.1)}u_1\delta(t) + \frac{-41}{s(s+5)}u_2\delta(t)$$

$$y(t) = \frac{20}{s(s+0.1)}u_1\delta(t) + \frac{-20}{s(s+18)}u_2\delta(t)$$

$$y(t) = \frac{45}{s(s+0.1)}u_1\delta(t) + \frac{-20}{s(s+25)}u_2\delta(t)$$

for patient 4, 5, 8, 10 and 12, respectively.

Table II summarizes the model parameters across the population. Figure 5 gives an example of impulse responses to carbohydrate and insulin, respectively, obtained with a model of structure (1) for a representative patient. Figures 6-10 left panels show the simulated models output using calibration data.

As for the assessment of model performances, the following metrics were considered:

- Percentage FIT:

$$\text{FIT} = \left(1 - \frac{\|y(t) - \hat{y}(t)\|}{\|y(t) - \bar{y}(t)\|}\right) \times 100\%$$

  where $y(t)$ are the actual measurements, $\hat{y}(t)$ are the model predictions, $\bar{y}$ is the mean value of $y(t)$ and $\|\cdot\|$ is the Euclidean norm. This metric measures how much variability in the data is explained by the model prediction.
- Percentage Variance Accounted For (VAF) calculated as:

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

TABLE II

ESTIMATED MODELS: IDENTIFIED PARAMETERS

Name	$\hat{K}_{carb}$	$\hat{K}_{ins}$	$\hat{T}_{carb}$	$\hat{T}_{ins}$
P4	3	-5	10	10
P5	5	-20	3.3	3.3
P8	30	-41	10	0.2
P10	20	-20	10	0.05
P12	45	-20	10	0.04

TABLE III

ESTIMATED MODELS: PERFORMANCE METRICS ON CALIBRATION DATA

Name	FIT [%]	VAF [%]	RMSE [mg/dL^2]
P4	95.9674	79.9187	10.9273
P5	94.2674	80.0200	12.39
P8	96.8484	82.2500	10.3631
P10	98.4969	87.7398	7.0873
P12	96.9014	82.3971	7.9706

TABLE IV

ESTIMATED MODELS: PERFORMANCE METRICS ON VALIDATION DATA

Name	FIT [%]	VAF [%]	RMSE [mg/dL^2]
P4	98.3433	87.1287	10.5380
P5	96.4356	81.1203	15.4572
P8	86.0122	62.5997	25.3631
P10	98.4299	87.4697	9.9095
P12	93.7859	75.0718	11.0476

where $\mathbb{E}[\cdot]$ 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.

Table III presents results obtained on the estimation data.

Last, we compare the statistics across the population on identification data in figs. 11, where the central mark in each box is the median of the empirical variance over the population, the edges are the 25th and 75th percentiles.

A. Model Validation

Validation was perfomed on a completely new set of data collected 14 ± 3 days apart, in different conditions with respect to those of the first admission: in the first visit, indeed, the patients were admitted to the hospital the exact day of the meal test, in the second visit the patients spent already 2 days in hospital in a controlled environment, being served standardized meals, conditions that certainly affects glucose metabolism. However, the experimental data exibited a feature of reproducibility in response to the inputs. This characteristic was verified by cross validation (Figs. 6-10 and 11 right panels, Table IV).

IV. DISCUSSION

We have proposed continuous-time transfer function models of second order to be used in a model-based controller

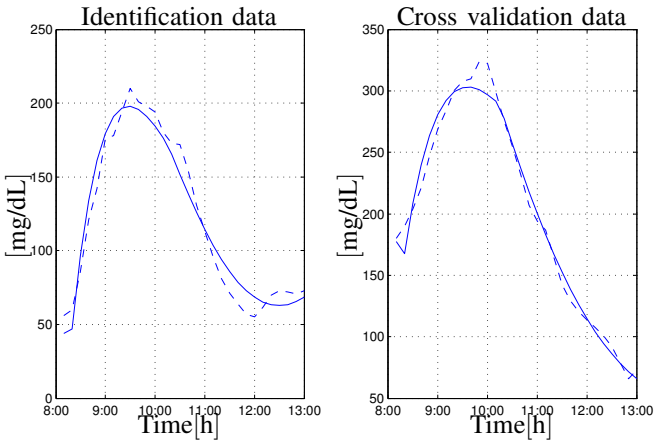

Fig. 6. Patient 4. Validation results. *Left* Simulation using identification data; *Right* Simulation using validation data. Actual interpolated blood glucose (dotted) and estimated blood glucose from the model (solid) vs. Time [h].

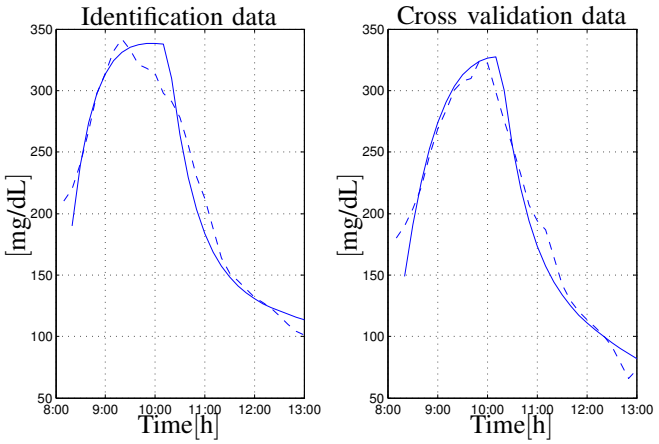

Fig. 7. Patient 5. Validation results. *Left* Simulation using identification data; *Right* Simulation using validation data. Actual interpolated blood glucose (dotted) and estimated blood glucose from the model (solid) vs. Time [h].

for glycemia regulation. The set-up is that of a basal-bolus therapy, involving impulsive control variables, namely insulin shots and meal carbohydrates, administered several times over the course of the day at irregularly spaced time instants. We remind the reader in passing that this framework differs from most of the proposed strategies to manage diabetes in an automated fashion [4], [5], [21], [22], [23], [24] nevertheless, it is the most widespread approach among the diabetics to cure their disease and in the authors' opinion it represents a viable path worth pursuing and investigating. 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. Actually, 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

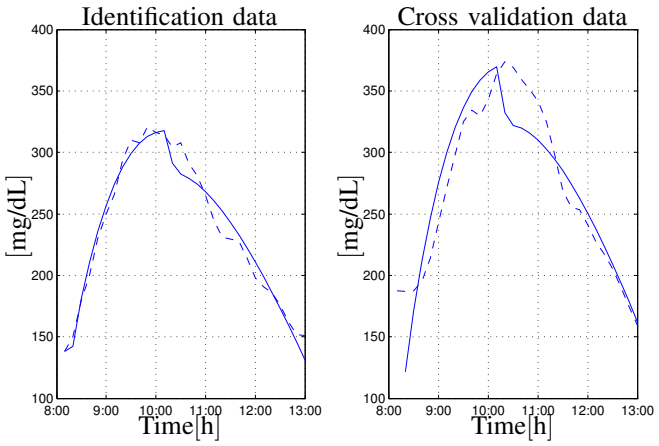

Fig. 8. Patient 8. Validation results. *Left* Simulation using identification data; *Right* Simulation using validation data. Actual interpolated blood glucose (dotted) and estimated blood glucose from the model (solid) vs. Time [h].

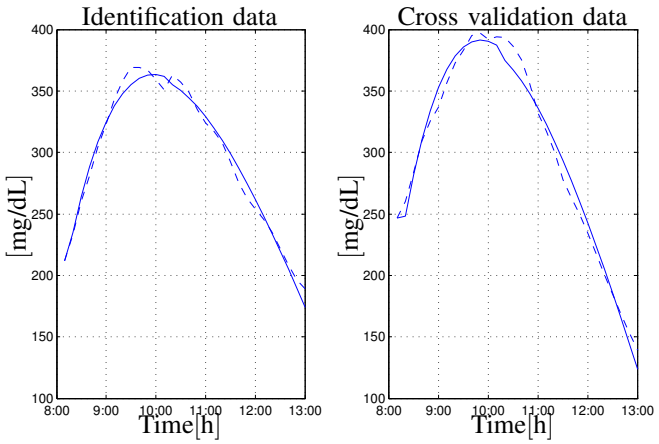

Fig. 9. Patient 10. Validation results. *Left* Simulation using identification data; *Right* Simulation using validation data. Actual interpolated blood glucose (dotted) and estimated blood glucose from the model (solid) vs. Time [h].

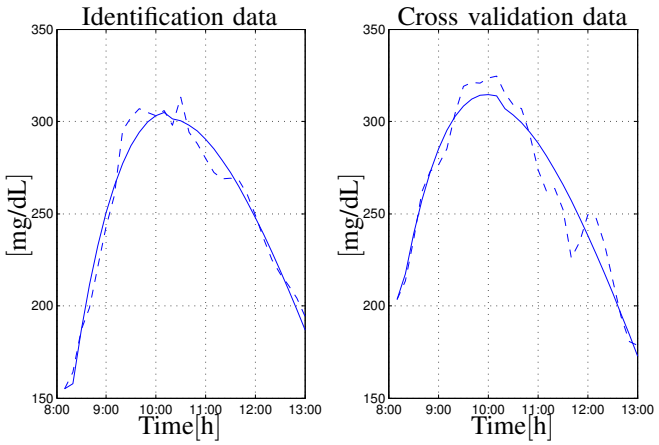

Fig. 10. Patient 12. Validation results. *Left* Simulation using identification data; *Right* Simulation using validation data. Actual interpolated blood glucose (dotted) and estimated blood glucose from the model (solid) vs. Time [h].

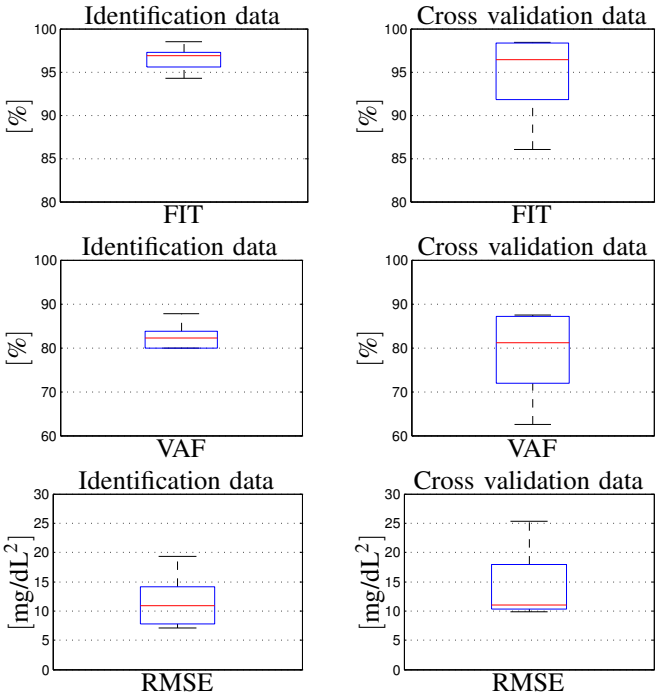

Fig. 11. Population study. *Top Panels* Percentage FIT; *Center Panels* Percentage VAF; *Bottom Panels* RMSE [mg/dL^2]. Each box presents the results achieved over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles. *Left* Using calibration data. *Right* Using validation data.

the subjects learn by trial-and-error how their glycemia reacts to different sources of carbohydrate and different insulin analogues. The approach resembles standard clinical practice being personalized due to the high inter-subject variability and particularly appealing as it amounts to estimating only 4 parameters in the plausible range, provided that the data for identification are informative enough with respect to the model application. Contrary to previous contributions dealing with simulated data obtained with in-silico ad-hoc experiments, e.g. [15], [24], we have employed actual T1DM patient data collected within a major European study, DIAdvisor ^{TM} [6]. 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 and in our opinion are suitable for controller design. The resulting blood glucose profile seems to reflect what observed by the clinicians in the care units, i.e., a plausible increase of glycemia in response to carbohydrate, and a decrease of glycemia in response to insulin. In addition, the time constants estimated seems to be appropriate, being in the range $40-60$ [min]. Time delays accounting for food transportation along the gastro-intestinal tract and insulin kinetics from the subcutaneous tissues to plasma has not been considered at this point but could be easily incorporated in the model structure as in [25]. The main reason for not including such delays

is that we are focusing on obtaining models useful for control applications, able to provide an approximation of the real system, that are as simple as possible, yet able to describe glucose evolution. The proposed models have been 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 and the same method applied to the new set of data. In the actual setting the controller performances will be assessed by subcutaneous continuous glucose monitoring sensor (CGMS) or self-monitoring finger-stick glucose meter (SMBG) measurements, introducing issues such as sensor noise, device recalibration, time delays just to mention a few. This contrasts our assumption of noise-free set-up and would require additional components to the control system, i.e., a sensor model [26], [27].

V. Conclusions and future work

Low order continuous-time transfer function models have been identified from actual T1DM patients data collected adhering to a unique protocol for a meal test. The strategy is appealing as it amounts to estimating only 4 parameters. The parameters have intuitive meaning that can be linked to clinical practice. The structure seems to be suitable for controller design mimicking a basal-bolus type of therapy for insulin treated subjects. The paper considered breakfast data only due to lack of data for lunch and dinner. Thus, it would be interesting to perform the same type of meal test experiments, upon protocol approval by the ethical committees and consequent modeling for other meals or snacks. Future work will be carried out to extend the study on a larger population.

VI. Acknowledgments

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