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

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Abstract— **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 identified. The estimation strategy is data-driven and exploits a database in which meals and insulin boluses are separated in time, allowing the unique identification of the model parameters.**

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. Actually, this was the focus of the major European project DIAdvisor ^{TM} [6].

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, our purpose is to estimate approximate, low-order, physiologically sound models from actual T1DM patients data for future use in a model-based control framework. In the application at hand 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 a novel and unique clinical database was created and exploited to our objectives, building on what was presented in [16].

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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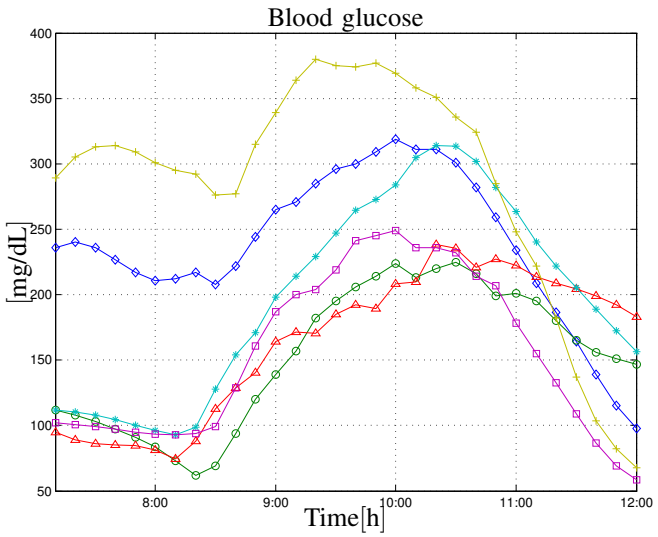

Fig. 1. Interpolated blood glucose for the selected population [mg/dL] vs. time of the day [h]

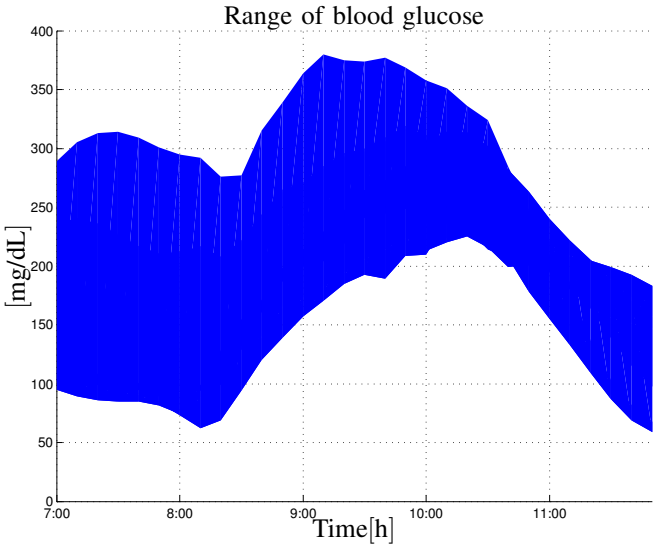

Fig. 2. The coloured area represents the range of the interpolated blood glucose for the selected population [mg/dL] vs. time of the day [h].

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. 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. Figure 3 shows such experiments for one representative subject. Figure 1 depicts the interpolated blood glucose for all of the subjects in the population. Figure 2 displays the range of the interpolated blood glucose for the selected population.

B. Modeling strategy

The first step in our methodology consisted in analyzing the collected data. From steady-state conditions and almost constant blood glucose levels, at 8.00 am an input was applied, namely 40 [g] of carbohydrate intake, which caused the controlled variable to rise (fig. 3). 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 piece-wise linearly. 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 [17]:

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

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

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

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

The choice of the integrators was motivated by looking at the data series for the available 5 hours test. 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, $\tau_{carb}, \tau_{ins} \in \mathbb{R}_+$ are the time delays associated with carbohydrate and insulin appearance in plasma, respectively. Our objective was to estimate the unknown parameter vector $\hat{\theta} = [\hat{K}_{carb} \quad \hat{K}_{ins} \quad \hat{T}_{carb} \quad \hat{T}_{ins} \quad \hat{\tau}_{carb} \quad \hat{\tau}_{ins}]$ 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:

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

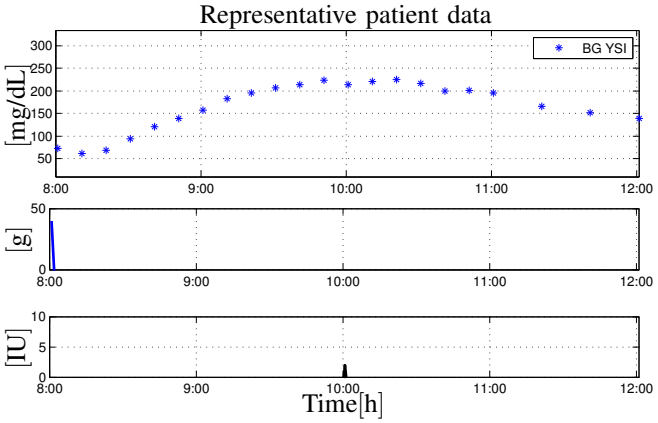

Fig. 3. Patient 2. Meal test data, first admission. *Top* Blood glucose measured by the YSI [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. Time of the day [h]

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, we determined the time delays empirically, while the estimation of the remaining parameters was performed applying a continuous-time subspace based identification methods as outlined as follows. First of all, the steady state glycemia level, i.e., the value of blood glucose before breakfast is administered, was taken away from the data series. Subsequently, the records were splitted in 2 parts: the first corresponding to the time interval 8:00-10:00, while the second corresponding to the time interval 10:00-12:00, the first being used for quantifying the impact of carbohydrate whereas the second for the impact of insulin. The continuous-time predictor-based identification (PBSID$_{cont}$) algorithm proposed in [18] was applied to the first portion of the data and the parameters K_{carb}, T_{carb} were estimated. Next, the effect of such carbohydrate predicted by the identified model if no insulin would have been taken after 10:00 was removed (Fig. 4) and the PBSID$_{cont}$ algorithm applied to the resulting data in order to get an estimate of K_{ins}, T_{ins}. Last, the output plasma glucose was interpolated and uniformly resampled, the sampling period being 1 [min].

III. Results

A. Models

Table I summarizes the model parameters for the population. The steady-state level of blood glucose, i.e., the value of glycemia just before 08:00, was removed so that the model outputs in Fig. 4 represent the deviation in blood glucose due to the inputs. The top panel in Fig. 6 shows the impulse responses to 10 [g] of carbohydrate while the bottom panel shows the responses to 1 [IU] of insulin obtained with the identified models for all the patients in the population. 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.

TABLE I

ESTIMATED MODELS: IDENTIFIED PARAMETERS

Name	$\hat{\tau}_{carb}$ [min]	$\hat{K}_{carb}$	$\hat{T}_{carb}$	$\hat{\tau}_{ins}$ [min]	$\hat{K}_{ins}$	$\hat{T}_{ins}$
P1	20	0.53	7.69	10	-4.79	55.86
P2	20	0.79	6.78	20	-7.30	22.64
P3	10	0.61	5.84	20	-8.36	34.48
P4	10	0.70	11.21	20	-7.07	22.07
P5	20	0.97	4.52	10	-6.86	33.89
P6	30	1.23	2.14	10	-3.87	17.12

B. Model performances

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):

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

  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 II presents performance results for the carbohydrate effect modeling obtained on the estimation data, whereas Table III presents performance results for the insulin effect modeling obtained on the estimation data. Last, we compare the statistics across the population in Fig. 7, 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.

C. Model Validation

A second meal test was performed 14$\pm$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 ergocyclometer 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, except for the blood samples to assess glucose concentration with the YSI, this time drawn every 15 minutes for the 4 hours following carbohydrate

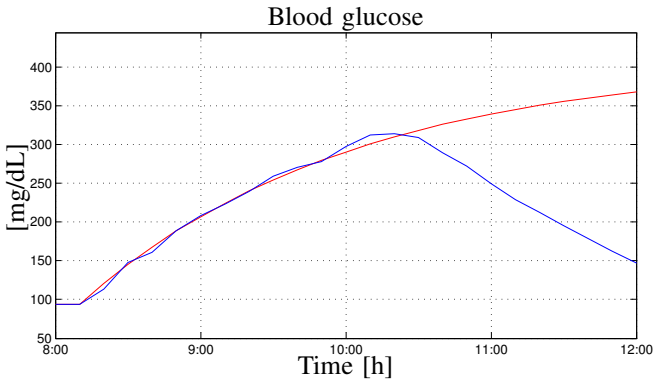

Fig. 4. Patient 4. Actual interpolated blood glucose data (blue), simulated blood glucose response to actual carbohydrate intake using the identified model (red) [mg/dL] vs. Time [h]

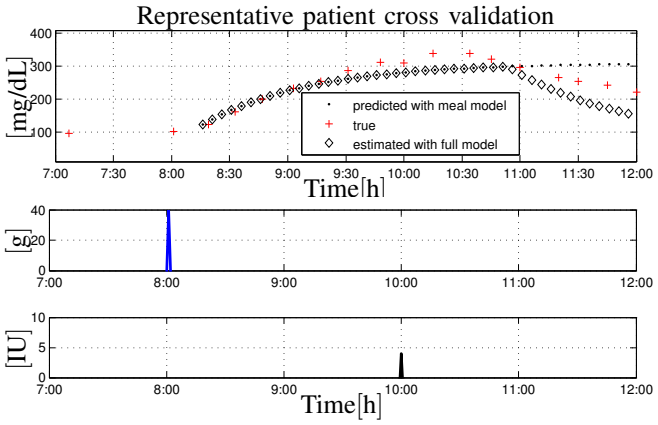

Fig. 5. Representative Patient. Meal test data, second admission. Cross validation. *Top* Breakfast impact modelling on fasting blood glucose: actual YSI data (red star) vs estimated response from the identified model (black dot) [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. Time of the day [h]

TABLE II

CARBOHYDRATE EFFECT MODELING:PERFORMANCE EVALUATION

Name	VAF [%]	FIT [%]	RMSE [mg/dL^2]
P1	99.39	90.96	3.2
P2	99.70	91.48	4.30
P3	98.80	88.97	4.26
P4	99.63	93.87	3.68
P5	98.96	88.25	5.63
P6	96.16	80.04	6.66

TABLE III

INSULIN EFFECT MODELING:PERFORMANCE EVALUATION

Name	VAF [%]	FIT [%]	RMSE [mg/dL^2]
P1	98.87	89.30	8.74
P2	97.95	80.69	6.71
P3	95.74	79.16	4.34
P4	99.65	85.04	10.85
P5	97.23	82.30	12.01
P6	97.68	74.90	26.35

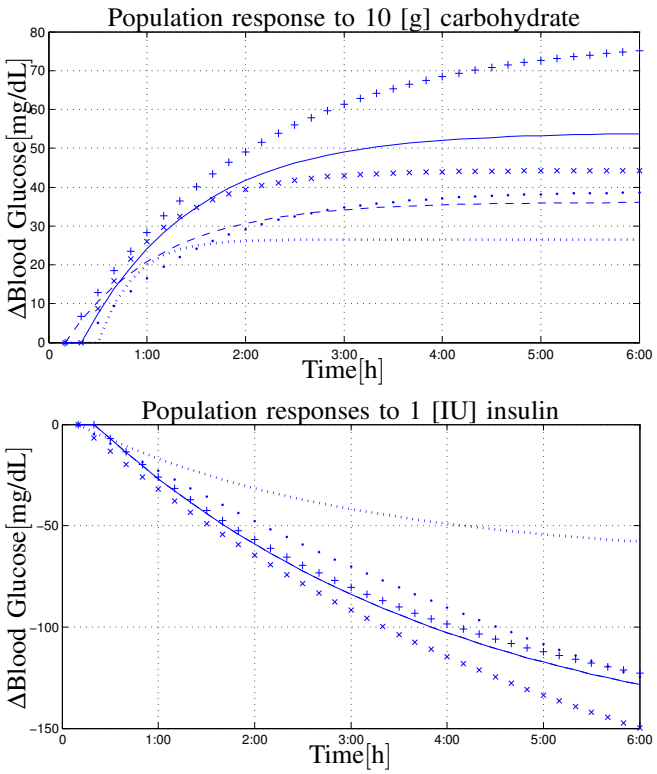

Fig. 6. Responses of the identified models for the selected population to: *Top* carbohydrate 10 [g]; *Bottom* insulin 1 [IU]. Each plot represents the variation of blood glucose [mg/dL] vs. time [h]

ingestion. Validation was perfomed on this set of data for those patients partecipating in the trial. The experimental data exibited a feature of reproducibility in response to the inputs. This characteristic was verified by cross validation (Fig. 5, Tables IV, V).

IV. DISCUSSION

We have proposed continuous-time transfer function models of second order with time delays quantifying the impact of a meal intake and an insulin injection on blood glucose dynamics. The selection of integrating models seemed suitable for the description of the 5-hours test data. To make it more physiologically plausible we may have replaced the integrators with another pole with a very slow time constant, that eventually brings blood glucose back to steady state due to clearance of glucose and insulin, respectively, in the kidneys. However, the correct estimation of such time constants would have required data sets with a larger time splits between inputs. Time delays accounting for food transportation along the gastro-intestinal tract and insulin kinetics from the subcutaneous tissues to plasma have been easily incorporated in the model structure as in [16]. The remaining 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,

TABLE IV

CARBOHYDRATE EFFECT MODELING:CROSS VALIDATION. PERFORMANCE EVALUATION

Name	VAF [%]	RMSE [mg/dL^2]
P1	not participating	not participating
P2	not participating	not participating
P3	39.37	42.56
P4	not participating	not participating
P5	94.81	16.63
P6	86.84	25.99

TABLE V

INSULIN EFFECT MODELING:CROSS VALIDATION. PERFORMANCE EVALUATION

Name	VAF [%]	RMSE [mg/dL^2]
P1	not participating	not participating
P2	not participating	not participating
P3	81.84	35.90
P4	not participating	not participating
P5	36.22	151.33
P6	42.80	127.82

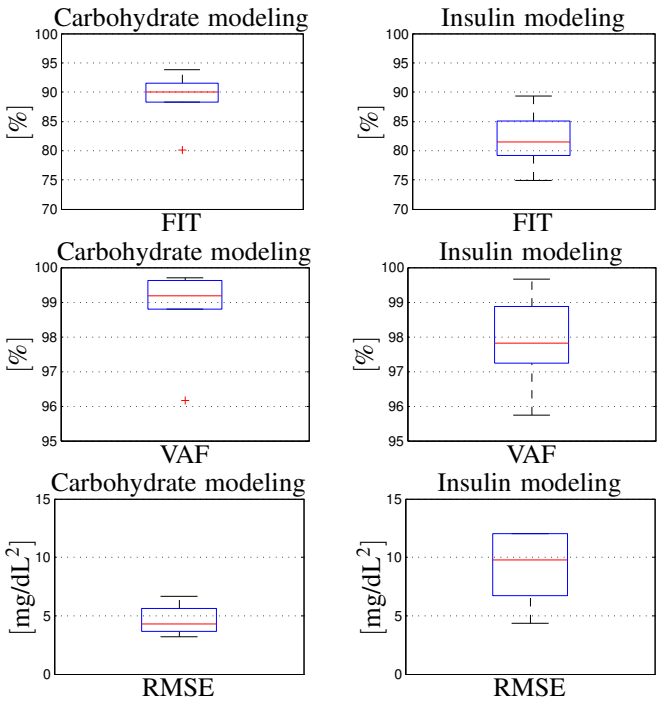

Fig. 7. Population study. *Top Panels* Percentage FIT; *Center Panels* Percentage VAF; *Bottom Panels* RMSE [mg/dL^2]. Each box presents the results achieved over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles. *Left* Carbohydrate effect modeling *Right* Insulin effect modeling.

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. The approach resembles standard clinical practice being personalized due to the high inter-subject variability and particularly appealing as it amounts to estimating only 6 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], [19], 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 models 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. A representative scenario would be that of basal-bolus therapy, involving impulsive control variables, namely insulin injections and meal carbohydrates, administered several times over the course of the day at irregularly spaced time instants. A possible controller, then, would consider in the control algorithm the effects of a meal or an insulin intake on blood glucose concentration predicted by the proposed models, in order to determine the appropriate control moves, the objective being the maintainance of blood glucose in the normoglycemic range. As a matter of fact, such strategy was proposed in [20], [21]. Cross-validation was performed on a completely new set of data collected 14 ± 3 days apart, in different conditions, for that subset of subjects participating in both of the visits. Intra-patient variability was observed for some of the subjects, as highligthed by the poor VAF values for P3 in Table IV, and P5-P6 in Table V. This fact may suggest the need of a model parameters updating scheme. 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, 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. This could be realized admitting the patients at the clinical investigation center for a 8-hours fasting period prior to the meal test. In the actual setting the YSI measurements will not be available as it is standard clinical practice assessing glycemia levels by a subcutaneous continuous glucose monitoring sensor (CGMS) or a self-monitoring finger-stick glucose meter (SMBG), introducing issues such as sensor noise, device recalibration, time delays just to mention a few. This contrasts to our assumption of noise-free set-up and would require additional components to the control system, i.e., a sensor model [22], [23]. Further investigation is required also to understand whether or not it is more appropriate and physiologically plausible to replace the integrator with a very slow pole,

accounting for clearance of blood glucose from the kidneys. Correlation between the identified model parameters and patients characteristics, namely, BMI, HbA1c and total daily insulin intake, was investigated. However, probably due to the small size of the population taken into consideration no clear correlation was detected.

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 6 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. However, in order to assess whether or not modeling was successful, the model needs to be implemented in the controller and then the performances of the closed-loop evaluated. Indeed, whether or not a model is appropriate it depends as much on the controller that will be implemented as it depends on the model-physiology mismatch. Hence, future work will be devoted to this analysis. The paper considered breakfast data only. Thus, it would be interesting to perform the same type of modeling for other meals or snacks. No clear correlation between model parameters and patient characteristics such as BMI, HbA1c and total daily insulin was noticed. 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 reasonable nominal models for each of the category.

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