Impulsive Predictive Control of T1DM Glycemia: an In-Silico Study

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***Abstract*— The most widespread approach for glycemic control in diabetic patients is the so-called basal-bolus insulin regimen, comprising insulin injections at meal times, correction doses in hyperglycemia and compensatory carbohydrate in case of insulin-induced hypoglycemia. The present contribution represents an attempt at implementing such a strategy on a virtual, i.e., *in-silico*, T1DM patient. A low order physiologically sound transfer function model was estimated from simulated data and exploited using an optimization-based control algorithm, the objective being sustainment of glycemia in the near-normal range (**$70-180$ **[mg/dL]).**

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 deficiency 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. Until today sustained improvement of diabetes control by using insulin has in many cases been associated with a reduced safety, i.e., increase in hypoglycemic events and reduced quality of life [3], [4]. Despite advances in diabetes care over the past decades, insulin therapy still remains one of the most difficult to manage, as it depends on patient's daily decisions about insulin delivery adaptations in relation to various factors, the most important being food intake, physical exercise and stress. As a matter of fact, the problem of maintaining glucose levels within a predefined range is a control problem which has been and still is focus of extensive studies, the control schemes proposed reaching from classical control strategy such as PID control [5] [6] [7] and cascade control [8], to adaptive [9], run-to-run [10] [11] model predictive control (MPC) [12] [13] and H_∞ control [14]. Most of this research targets continuous insulin administration via a subcutaneous pump, resulting in suitable therapy only for a minority and without taking into account the risks connected with insulin-induced hypoglycemia [15]. Against this background, the availability of an 'advisory system' recommending the user to take appropriate insulin injections and eventually compensatory snacks, to maintain glucose levels within the predefined target range, would be desirable. Within this scenario the controller is expected to determine impulse-like control inputs, namely insulin injections and amount of additional carbohydrates, 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. This is the focus of the major European project DIAdvisor ^{TM} [16].

The present contribution aims at proposing one such a scheme. The controller is optimization-based, similar to MPC-type controllers [17] [18] and the control variables are doses of insulin to be injected and number of grams of carbohydrate to be administered, while the measured output is the subcutaneous glucose concentration measured by a subcutaneous continuous glucose monitoring sensor (CGMS). The algorithm solves an optimization problem either when a meal is taken, to determine the insulin dose needed to cover the meal, or when the blood glucose concentration leaves the euglycemic range, to bring it back to near-normal by taking recovery carbohydrates in case of hypoglycemia, or an extra insulin dose in case of hyperglycemia. To fit the controller a low-order, physiologically sound, individualized model was estimated from in-silico patient data obtained with a state-of-the-art simulation model [19].

The remainder of the paper is organized as follows. Section II deals with the simulation set-up, the explanation of the modeling work and the presentation of the control algorithm. Section III shows modeling results as well as the control performances in closed-loop achieved exploiting the in-silico patient. The discussion on the achievements is left to Sec. IV. Finally, Sec. V concludes the paper with final remarks and considerations for future work.

II. Material and Methods

A. Experimental conditions

This *in-silico* study considers a fine-grain nonlinear meal simulation model first proposed in [19]. Model parameters were obtained from the authors in order to reproduce as faithfully as possible a virtual T1DM patient glucose metabolism. The virtual patient underwent a 3-days *in-silico* visit, starting

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$$T_g T_i \ddot{y} + (T_g + T_i)\dot{y} + y(t) = K_g u_g \mathbb{1}(t - t_g) + K_g u_g T_i \delta(t - t_g) + K_i u_i \mathbb{1}(t - t_i) + K_i u_i T_g \delta(t - t_i) \quad (1)$$

TABLE I

IN-SILICO PROTOCOL

Day	Meal time	CHO [g]	Injection time	Insulin [IU]
1	8:00	40	8:00	4
	13:00	70	13:00	7
	19:00	70	19:00	7
2	8:00	40	8:00	4
	13:00	100	13:00	10
	19:00	70	19:00	7
3	8:00	40	8:00	4
	13:00	70	13:00	7
	19:00	70	19:00	7

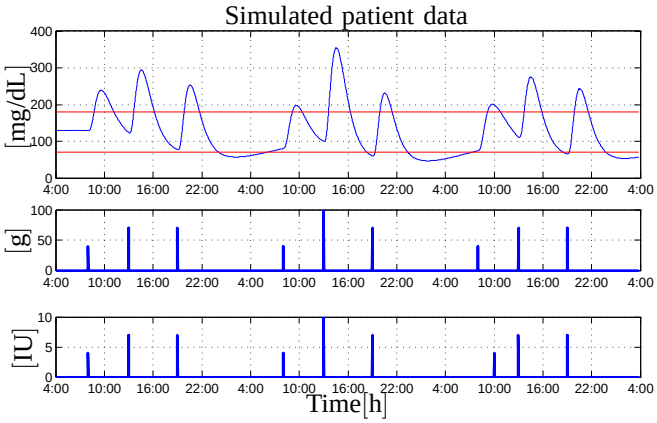

Fig. 1. Simulated patient data. *Top* Blood glucose concentration [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. Time [h]

from steady-state fasting conditions corresponding to a basal plasma glucose concentration $G_b = 129.1278$ [mg/dL] and a basal plasma insulin concentration $I_b = 90.0357$ [pmol/L] at 4:00 of day 1. Meals and corresponding insulin doses calculated according to an insulin-to-carbohydrate ratio (ICR) 1 : 10 were administered complying with the scheme in Table I. In particular, a big lunch on day 2, the amount of carbohydrate served being 100 [g], and a time-split bewteen carbohydrate ingestion and insulin intake at breakfast on day 3, the time interval between the two being 2 [h], were realized to excite the system properly. We mention in passing that the same experiments were carried out on real diabetic patients within the project DIAdvisor ™ [16], highlighting the clinical feasibility of the proposed trial. Figure 1 shows the simulated data.

B. Control-relevant modeling

The first step in our methodology consisted in analyzing the simulated data for breakfast on day 3. From steady-state conditions and almost constant blood glucose levels, at 8.00 am an input is applied, namely 40 [g] of carbohydrate intake, which causes the controlled variable to rise with a

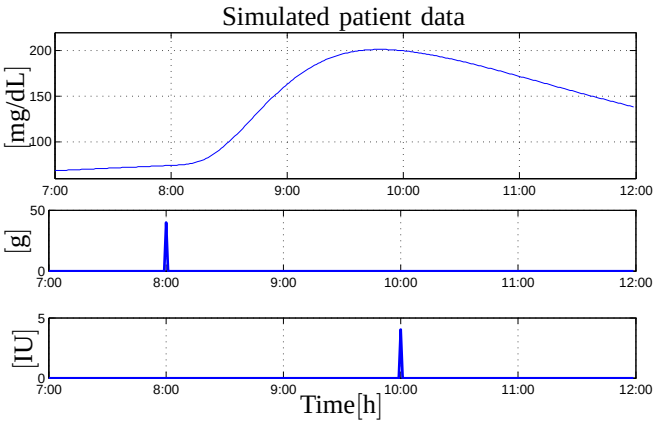

Fig. 2. Simulated patient data. Meal test on breakfast in day 3. *Top* Blood glucose concentration [mg/dL]; *Center* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. Time [h]

double integrator like behavior (Fig. 2). In absence of any action taken, plasma glucose concentration doesn't fall (time interval 8.00 am to 10.00 am). Then, an insulin dose of 4 [IU] was administered, making glucose concentration to fall piece-wise linearly. Assuming noise-free conditions, as plasma glucose is directly available, we can formulate the model structure in Eq. (1), where t is the time index, t_g is the time of carbohydrate ingestion, t_i is the time when insulin is injected, $y(t) \in \mathbb{R}_+$ is the output plasma glucose , $u_g, u_i \in \mathbb{Z}_+$ are the inputs carbohydrate amount and insulin doses, respectively, $\mathbb{1}_t$ is the Heaviside step function centered in the origin, δ_t is the Dirac function centered in the origin, $K_g, K_i \in \mathbb{R}$ are static gains while $T_g, T_i \in \mathbb{R}$ time constants governing rise and fall of $y(t)$ related to glucose and insulin intakes, respectively. In the Laplace domain, the impact of carbohydrate and insulin, respectively, on blood glucose, is given by the following transfer functions:

$$Y_g(s) = \frac{K_g}{s(1 + sT_g)} U_g(s) \quad (2)$$

$$Y_i(s) = \frac{K_i}{s(1 + sT_i)} U_i(s) \quad (3)$$

so that the total effect on blood glucose is expressed by the following:

$$Y_{BG}(s) = Y_g(s) + Y_i(s) \quad (4)$$

Our objective is to estimate the unknown parameter vector $\theta = [K_g \quad K_i \quad T_g \quad T_i]$ so that the estimation error between the actual blood glucose data $y(t)$ and the simulated data $\hat{y}_\theta(t)$ is minimized in a least-squares sense:

$$\underset{\theta}{\operatorname{argmin}} \int_0^T (y(t) - \hat{y}_\theta(t))^2 dt \quad (5)$$

where $T = 5$ [h], subject to some constraints on θ, namely $K_g > 0$, $K_i < 0$ to guarantee qualitatively correct responses

to inputs (blood glucose increases after a meal intake and decreases after an insulin shot) and $T_g, T_i > 0$ to guarantee stability. The problem is difficult, as it is non-convex. We therefore start off by empirically fitting the data to the model with initial guesses for the parameters dictated by intuition.

C. The control algorithm

As mentioned in Sec. I, the control algorithm determines the doses of insulin and glucose to be administered to the subject by solving an optimization problem when a meal occurs or the BG concentration leaves the near-normal range. Hence, the time of the intakes is supposed to be known. The assumption is realistic, since according to standard clinical practice the patients bolus at meal time and take correction insulin injections when the blood glucose rises above $y_U = 180$ [mg/dL]; conversely, compensatory carbohydrate are administered when the blood glucose concentration falls below $y_L = 70$ [mg/dL].

Hence, the optimization problem that needs to be solved is the following:

$$\begin{aligned} \underset{u_g,u_i}{\text{minimize}} \quad & \sum_{t=1}^{H_p} \left[\ln\left(\frac{y(t)}{G}\right) \right]^2 \\ \text{subject to} \quad & u_g < 80 \\ & u_i < 20 \\ & y_L \le y(t) \le y_U \end{aligned} \tag{6}$$

where $y(t) = \bar{y}(t, u_g, u_i) + y_P(t)$, $y_P(t)$ is the predicted blood glucose assuming no insulin or glucose intakes in the future horizon and $\bar{y}(t, u_g, u_i)$ is the deviation of the blood glucose concentration after an intake of insulin or glucose, using the patient model estimated in section II-B. Furthermore, y_L and y_U are the lower and upper bounds, respectively, for the target range, u_g and u_i are the amount of glucose and insulin, respectively, to be given to the patient and H_p stands for the prediction horizon. The cost function used in the minimization is shown in Fig. 3. The idea is to minimize the risk connected to a certain amount of blood glucose concentration $y(t)$ over the doses of glucose and insulin intakes. The cost function has an asymmetric shape, emphasizing the higher risk of hypoglycemia compared to hyperglycemia. The minimization in the optimization problem (6) is done using the Matlab® Optimization Toolbox [20].

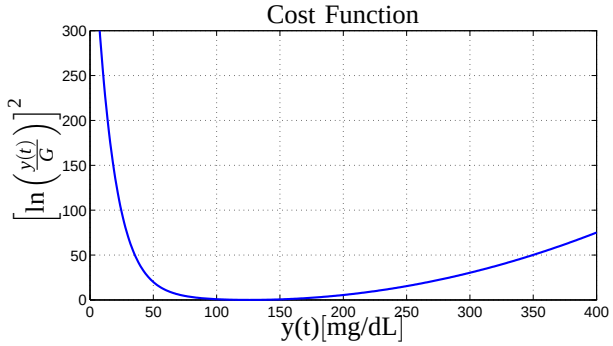

Fig. 3. The Cost function used in the optimization problem.

TABLE II
PERFORMANCE METRICS ON IDENTIFICATION DATA

VAF [%]	FIT [%]	RMSE [(mg/dL)^2]
93.7502	75.0004	9.3121

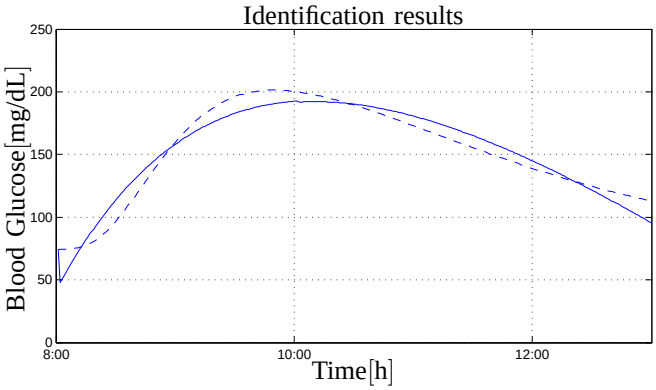

Fig. 4. Identification results. Simulated blood glucose concentration (solid); actual blood glucose concentration (dashed) [mg/dL] vs. time [h]

III. RESULTS

A. Modeling

The estimated transfer function model is the following:

$$Y(s) = \frac{0.1}{s(s+0.0099)} U_g(s) - \frac{1}{s(s+4)} U_i(s) \tag{7}$$

Figure 4 presents validation results showing the performances achieved in simulation using identification data. As for model evaluation, the metrics considered were the following:

- Percentage Variance Accounted For (VAF) calculated as:

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

  where $\mathbb{E}[\cdot]$ denotes mathematical expectation.
- 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.
- 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 the results obtained.

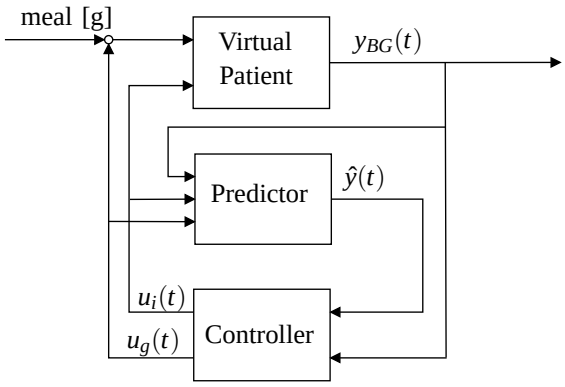

Fig. 5. The simulation set-up.

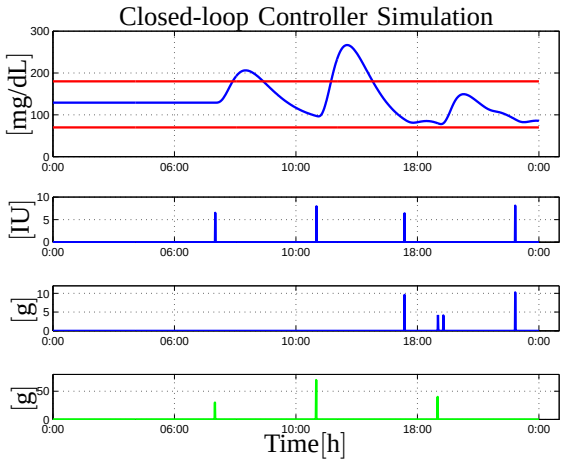

Fig. 6. Simulation results of the closed-loop controller evaluation. *Top* CGMS at the virtual patient output (blue) and borders of the near-normal range (red) [mg/dL]*Top Center* Insulin Advices by the controller [IU]; *Bottom Center* Glucose Advices by the controller [g]; *Bottom* Meal intakes [g]. All the signals vs. time [h]

B. Controller

In order to simulate the controller in a closed-loop for testing and evaluation, the same virtual patient considered in the modeling phase was used.

The simulation setup is shown in Fig. 5. The virtual patient takes glucose and insulin as an input and gives out the measured CGMS signal $y_{BG}(t)$. All these signals are used by a prediction algorithm to predict the CGMS over a future horizon. The predictor uses a linear model of the patient, here a virtual patient, and a Kalman filter to calculate the predictions. The CGMS predictions and the measured CGMS are used by the controller to determine the doses of insulin and glucose to be given to the virtual patient.

Figure 6 presents the simulation results. We assume the simulation starting at midnight, with the virtual patient in steady-state condition and meals of carbohydrate content 30 [g], 70 [g] and 40 [g], respectively, administered at 8 : 00, 13 : 00 and 19 : 00.

IV. Discussion

We have proposed a model-based controller for glycemia regulation that uses continuous-time transfer function models of second order identified from *in-silico* simulated T1DM patient data. 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 [9], [12], [13], [21], [22], [23] in which glycemia is regulated only with a continuous insulin infusion pump, neverthless, it is the most widespread approach among the diabetics to cure their disease. Previous attempts at producing impulsive control signals include approximation of the continuous insulin signal from a model predictive controller ([24], [25]). Opposed to this, the controller we are concerned with explicitly considers the amounts for insulin and glucose administration as optimization variables, rather than a discrete approximation of their continuous signal counterparts. The algorithm determines the advices of insulin and glucose only from predictions and measurements of the blood glucose concentrations, giving freedom to the diabetic patient in the management of the disease. An asymmetric cost function, which penalizes blood glucose concentrations falling under 70 [mg/dL] more than blood glucose concentration rising over 180 [mg/dL], is used by the control algorithm. In this way, the higher risk connected to hypoglycemia compared to hyperglycemia is accounted for. A simple, low-order, physiologically sound model tailored to the intended controller was estimated from simulated breakfast data. The parameters in the models are linked to clinical variables. In particular, K_1, T_1 can be related to glucose tolerance, i.e., how the body metabolizes glucose, whereas K_2, T_2 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. 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. Time delays accounting for food transportation along the gastro-intestinal tract and insulin kinetics from the subcutaneous tissues to plasma has not been considered but could be easily incorporated in the model structure. 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.

For the virtual patient used as an example here, the control algorithm can bring the blood glucose concentration back

into the normal range between 70 [mg/dL] and 180 [mg/dL] after meals by suggesting additional insulin bolus intakes. After the first and second meal intake, the BG concentration leaves the near-normal range before brought back into it. However, after the third meal the controller gives insulin and glucose advices that keep the patient inside the near-normal range. The virtual patient used for the simulations does not include the effect of, for example, exercise on the blood glucose concentration or other factors like stress that also influence the blood glucose concentration. Hence, the reaction of the control algorithm to lowering blood glucose could not be tested here. To determine the doses of insulin and glucose advices, the controller uses blood glucose predictions calculated by a predictor that is not part of the control algorithm. If this predictor delivers unreliable BG predictions to the controller, for example, due to bad quality of measured data, the controller will not be able to produce a reliable advice.

V. Conclusions and Future work

Low order continuous-time transfer function models have been identified from simulated T1DM patient data, exploiting the meal simulation model in [19]. The estimated model parameters have intuitive meaning that can be linked to clinical practice. Moreover, the structure appears to be suitable for controller design mimicking a basal-bolus type of therapy for insulin treated subjects.

A optimization-based controller using the estimated model was implemented, where the control variables are insulin doses and amount of carbohydrate to be suggested to the subject. By using an asymmetric cost function, the optimization minimizes the risk connected to a certain blood glucose concentration. After a meal and for increased BG concentration, the controller suggests insulin doses that bring the patient's blood glucose back into the near-normal range.

As for the control-oriented models, *in-silico* breakfast data only were considered. Thus, future work will be devoted to performing the same type of modeling for other meals or snacks and subsequently apply them in the controller design step. Further, future work will be carried out to extend the study on a larger population.

VI. Acknowledgments

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