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# 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 population of* 4 *virtual, i.e., in-silico, T1DM patients. Low-order physiologically sound transfer function models were estimated for each of the in-silico subjects from simulated data and exploited in an optimization-based control algorithm, the objective being sustainment of glycemia in the near-normal range (*$70-180$ *[mg/dL]).*

## 1 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 strategies 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 $H_\infty$ 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 for aiding patients. 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].

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Table 1. IN-SILICO PATIENTS CHARACTERISTICS

| Patient ID | $G_b$ [mg/dL] | $I_b$ [IU] |
|---|---|---|
| 1 | 138.0469 | 113.8919 |
| 2 | 138.6503 | 132.0216 |
| 3 | 129.1278 | 90.0357 |
| 4 | 180 | 40.95 |

Table 2. 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 |

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 blood glucose concentration. 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 low-order, physiologically sound, individualized models were estimated for each of the subjects from *in-silico* patients data obtained with a state-of-the-art simulation model [19].

The remainder of the paper is organized as follows. Section 2 deals with the simulation set-up, the explanation of the modeling work and the presentation of the control algorithm. Section 3 shows modeling results as well as the control performances in closed-loop achieved exploiting the in-silico patients. The discussion on the achievements is left to Sec. 4. Finally, Sec. 5 concludes the paper with final remarks and considerations for future work.

## 2 MATERIAL AND METHODS

### 2.1 Experimental Conditions

This *in-silico* study considers the 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 the glucose metabolism of 4 virtual T1DM patients. The virtual subjects underwent a 3-days *in-silico* visit, starting from steady-state fasting conditions corresponding to a basal plasma glucose concentration $G_b$ and a basal plasma insulin concentration $I_b$ reported in Table 1 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 2. In particular, a big lunch on day 2, the amount of carbohydrate served being 100 [g], and a time-split between 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. Last, plasma glucose concentration was assumed to be readily available. We mention in passing that the same experiments were carried out on real diabetic patients within the project DIAdvisor $^{TM}$ [16], highlighting the clinical feasibility of the proposed virtual trial. Figure 1 shows the simulated data.

### 2.2 Control-relevant Modeling

The first step in our methodology consisted in analyzing the simulated data for breakfast in day 3. 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 causes the controlled variable to rise with a 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 supposed to be available to measurement without delay, we can formulate the glucose balance equation (1), where $t$ is the time index, $t_g$ is the time of carbohydrate ingestion, $t_i$ is the time when insulin is injected, $y_{BG}(t) \in \mathbb{R}_+$ is the output blood 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, $\delta_t$ 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 $y_{BG}(t)$ related to glucose and insulin intakes, respectively.

$$\begin{aligned} 0 = &-T_g T_i \ddot{y}_{BG} - (T_g + T_i)\dot{y}_{BG} - y(t) + K_g u_g \mathbb{1}(\mathrm{t} - \mathrm{t_g}) \\ &+ K_g u_g T_i \delta(t - t_g) + K_i u_i \mathbb{1}(\mathrm{t} - \mathrm{t_i}) + \mathrm{K_i u_i T_g} \delta(\mathrm{t} - \mathrm{t_i}) \end{aligned} \quad (1)$$

In the Laplace domain, the impact of carbohydrate and insulin, respectively, on blood glucose, is given by the following transfer

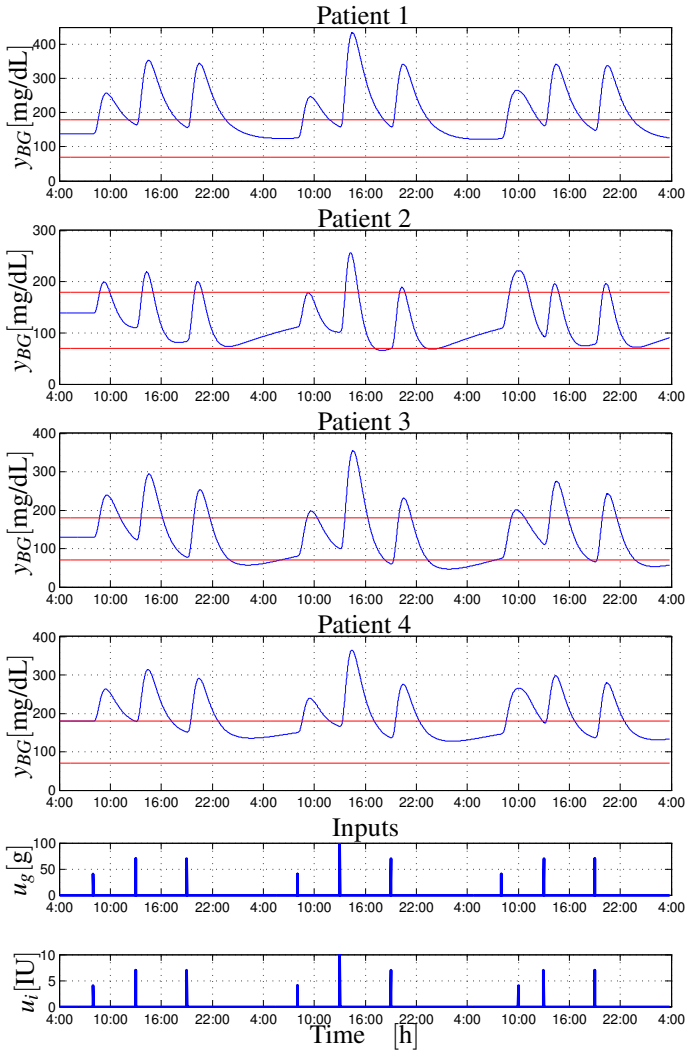


Figure 1. Simulated patient data using the physiological model in [19]. *Top panels* Blood glucose concentration [mg/dL]; *Bottom panels* Inputs: *Top* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. time [h]

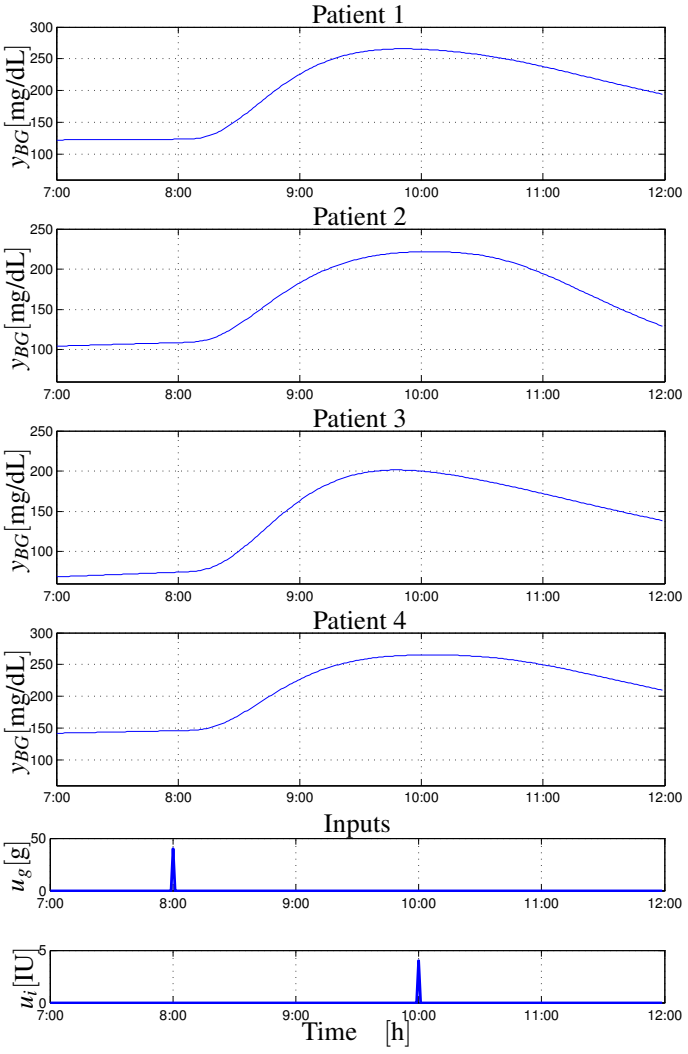


Figure 2. Simulated patient data using the physiological model in [19]. Meal test on breakfast in day 3. *Top panels* Blood glucose concentration [mg/dL]; *Bottom panels* Inputs: *Top* Carbohydrate intake [g]; *Bottom* Insulin bolus [IU]. All the measurements vs. time [h]

functions:

$$\begin{aligned} Y_g(s) &= \frac{K_g}{s(1+sT_g)}U_g(s) \\ Y_i(s) &= \frac{K_i}{s(1+sT_i)}U_i(s) \end{aligned} \tag{2}$$

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

$$Y_{BG}(s) = Y_g(s) + Y_i(s) \tag{3}$$

Our objective is to estimate the unknown parameter vector

$$\theta = \begin{bmatrix} K_g & K_i & T_g & T_i \end{bmatrix} \tag{4}$$

so that the estimation error between the given virtual patient blood glucose data $y_{BG}(t)$ and the estimated data $\hat{y}_\theta(t)$ is minimized in a least-squares sense:

$$\hat{\theta} = \arg\min_{\theta} \int_0^T (y_{BG}(t) - \hat{y}_\theta(t))^2 dt \tag{5}$$

where $T = 5$ [h], subject to some constraints on $\theta$, 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 injection) and $T_g, T_i > 0$ to guarantee stability. [19]. 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.

### 2.3 The Control Algorithm

As mentioned in Sec. 1, the control algorithm determines the doses of insulin and glucose to be administered to the subject by solving an optimization problem, the time of the intakes being known in advance. 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].

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

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

where $y_{BG}(t) = \bar{y}(t,u_g,u_i) + y_P(t)$, $y_P(t)$ being the predicted blood glucose assuming no insulin or glucose intakes in the future horizon and $\bar{y}(t,u_g,u_i)$ the deviation of the blood glucose concentration after an intake of insulin or glucose, using the patient model estimated in Sec. 2.2. 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 asymmetric cost function shown in fig. 3 was used to correct hypoglycemia more immediately compared to hyperglycemia, based on the more serious short-term consequences of the former. The minimization in the optimization problem (6) is done using the Matlab® Optimization Toolbox [20].

This optimization is included in an algorithm, which solves problem (6) when the blood glucose concentration leaves a certain range, see Fig. 4. When the blood glucose concentration falls under 90 [mg/dL] and at least 120 [min] have passed since the last intake, or it falls under 80 [mg/dL] and at least 15 [min] have past since the last intake, the optimization problem is solved to determine time and dose for an insulin or glucose intake. Similarly, when the blood glucose concentration rises over 130 [mg/dL] and at least 120 [min] have passed since the last intake, the optimization problem is solved to determine the needed insulin doses.

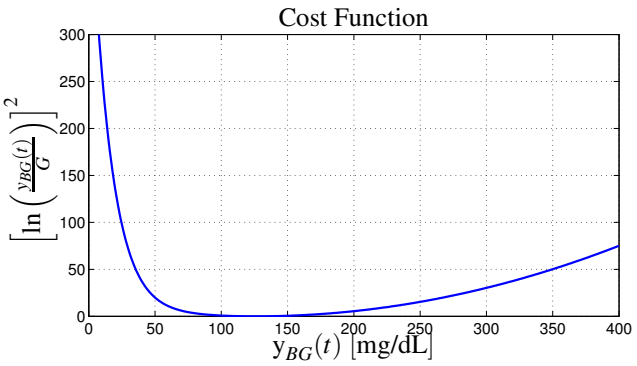


Figure 3. The risk-related cost function in Eq. (6) used in the optimization problem.

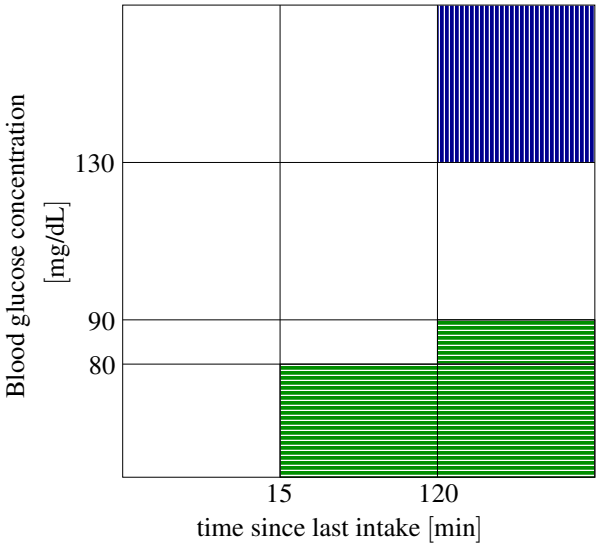


Figure 4. Optimization-Based Control Algorithm: The filled areas represent the condition under which the optimization problem is solved in the space of time since last intake vs. BG concentration. The blue, vertically striped area for hyperglycemia and the green, horizontally striped area for hypoglycemia.

## 3 RESULTS

### 3.1 Modeling

The estimated transfer function models are the following:

$$\begin{aligned} Y_{BG_{\text{pat1}}}(s) &= \frac{0.1}{s(s+0.0099)}U_g(s) \quad -\frac{0.1}{s(s+0.2)}U_i(s) \\ Y_{BG_{\text{pat2}}}(s) &= \frac{0.5}{s(s+0.00009)}U_g(s) \quad -\frac{0.1}{s(s+0.5)}U_i(s) \\ Y_{BG_{\text{pat3}}}(s) &= \frac{0.1}{s(s+0.00009)}U_g(s) \quad -\frac{1}{s(s+0.5)}U_i(s) \\ Y_{BG_{\text{pat4}}}(s) &= \frac{0.5}{s(s+0.0099)}U_g(s) \quad -\frac{0.1}{s(s+4)}U_i(s) \end{aligned} \tag{7}$$

Table 3. Performance metrics on identification data

| patient | VAF [%] | FIT [%] | RMSE [(mg/dL)$^2$] |
|---|---|---|---|
| 1 | 95.4547 | 78.6802 | 9.1050 |
| 2 | 90.8866 | 69.8116 | 13.2923 |
| 3 | 93.7460 | 74.9919 | 9.3152 |
| 4 | 97.2989 | 83.5650 | 6.0322 |

where the subscript indices denote the patient number. Figure 5 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):

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

Percentage FIT:

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

Root Mean Square Error (RMSE) [(mg/dL)$^2$]:

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

where $\mathbb{E}[\cdot]$ denotes mathematical expectation, $\|\cdot\|$ is the Euclidean norm, $n$ denotes the number of samples, $y(t)$ are the given measurements, $\hat{y}(t)$ are the model estimations, $\bar{y}$ is the mean value of $y(t)$.

Table 3 presents the results obtained.

### 3.2 Controller

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

The simulation setup is shown in Fig. 6. Inputs to the virtual patient were glucose and insulin, whereas the output $y_{BG}(t)$ was blood glucose concentration. A parallel prediction algorithm based on a linear model of the virtual patient and a Kalman filter, was used to calculate the future plasma gluocose concentration values $y_P(t)$. Estimated and measured blood glucose from the simulator were used by the controller to determine the doses of insulin and glucose to be given to the virtual patient.

Figures 7, **??**, 8 and **??** presents the simulation results for the four virtual patients. We assume the simulation starting at

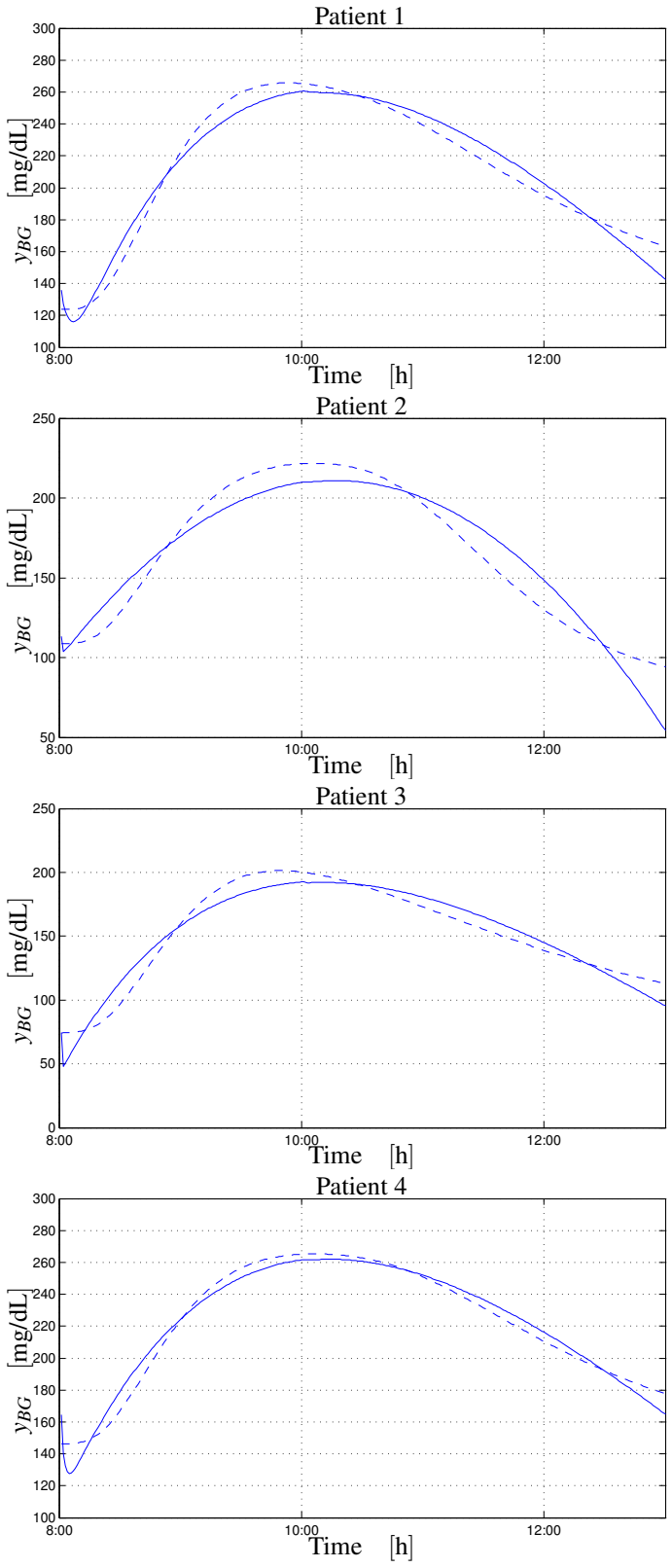


Figure 5. Identification results. Blood glucose concentration obtained with the estimated models (solid); in-silico patient blood glucose concentration (dashed) [mg/dL] vs. time [h]

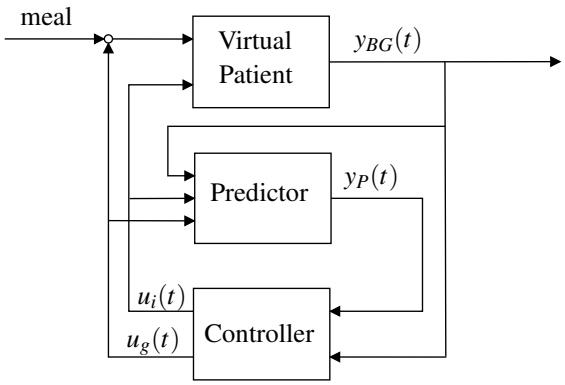


Figure 6. The simulation set-up.

midnight, with the virtual patients 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 for all patients.

## 4 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 injections 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 control 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. A simple, low-order, physiologically sound model tailored to the intended controller was estimated from simulated breakfast data for each of the *in-silico* subjects. 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 is personalized, like standard clinical practice, and particularly appealing as it amounts to estimating only 4 parameters in the plausible range. A nominal model instead of an individualized one, could have been used in this study, as the simulated data don't reproduce the high inter-subject variability experienced in

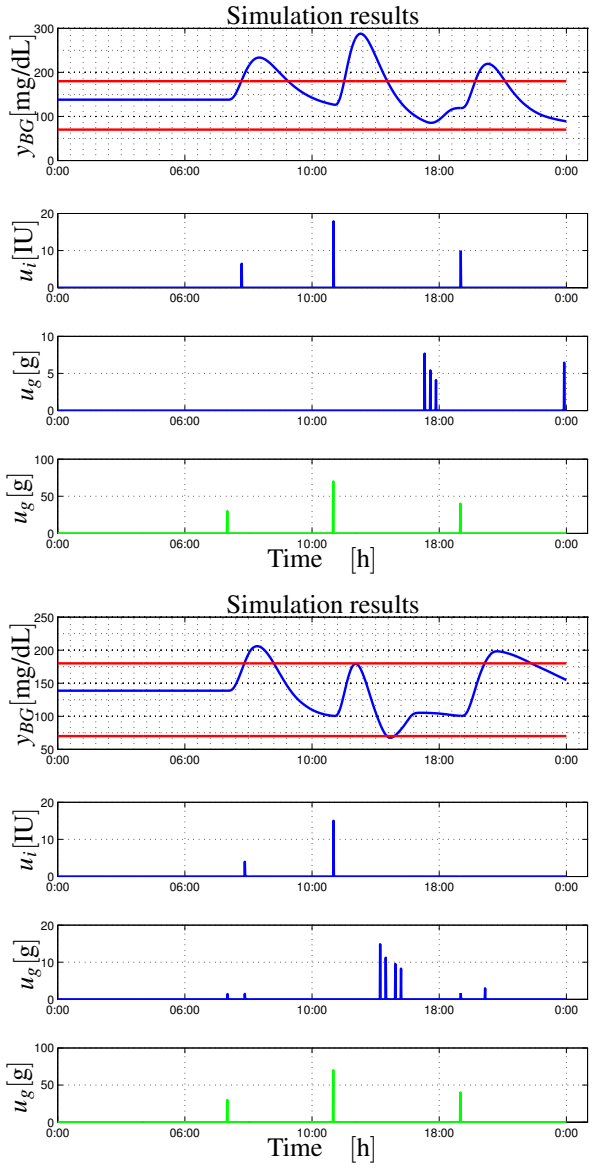


Figure 7. Simulation results of the closed-loop controller evaluation for Patient 1 (*Top Panels*) and Patient 2 (*Bottom Panels*). *Top* Virtual patient blood glucose (blue) and near-normal glycemia range (red) [mg/dL]; *Top Center* Insulin advices by the controller [IU]; *Bottom Center* Glucose advices by the controller [g]; *Bottom* Meal intakes [g] vs. Time [h]

real life. Neverthless, keeping in mind that glucose metabolism is affected by individual factors such as insulin sensitivity, glucose tolerance, body-mass index, age and disease duration just to mention a few, that cannot be capture by a nominal model we opted for a personalized approach. 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 struc-

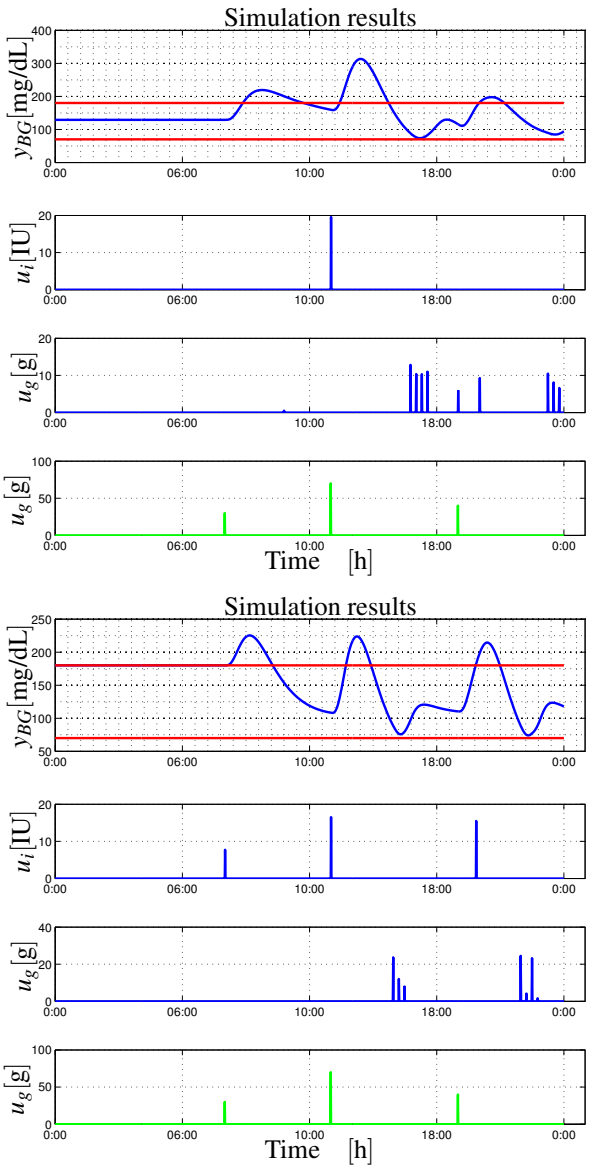


Figure 8. Simulation results of the closed-loop controller evaluation for Patient 3 (*Top Panels*) and Patient 4 (*Bottom Panels*). *Top* Virtual patient blood glucose (blue) and near-normal glycemia range (red) [mg/dL]; *Top Center* Insulin advices by the controller [IU]; *Bottom Center* Glucose advices by the controller [g]; *Bottom* Meal intakes [g] vs. Time [h]

ture.

The control 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.

The control system's performances are illustrated using four separate virtual patients. No hypoglycemic events occured during the 24-hours long *in-silico* test (top panels in Figs. 7, **??**, 8 and **??**). The suggested snacks to avoid too low glycemia were feasible both in the number of episodes and in the quantity of carbohydrate suggested (bottom center panels in Figs. 7, **??**, 8 and **??**). However, little improvement was registered in the hyperglycemia range compared to standard basal-bolus therapy. This may be attributed to unaccounted for subcutaneous insulin absorption dynamics which introduces delays in insulin action that the controller is not able to cope with. Moreover, the cost function used in the optimization may not be appropriate in penalizing enough hyperglycemic excursions. Physical activity or other circumstances influencing blood glucose concentration like stress and illness were not included in the virtual patient model. Hence, the reaction of the control algorithm to such factors 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.

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 to our assumption of noise-free set-up and would require additional components to the control system, i.e., a sensor model.

## 5 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.

An optimization-based controller using the estimated models 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 penalizing the risk connected to hypoglycemia more than that connected to hyperglycemia, the control algorithm manage to maintain blood glucose concentration always above 70 [mg/dL].

Future work will be devoted to estimating control-oriented models for meals or snacks other than breakfast and subsequently apply them in the controller design step. Further, the case in which the patient does not readily obey the advice of the control system and how the algorithm would eventually handle such irregular behaviour will be considered in future work.

## ACKNOWLEDGMENT

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## REFERENCES

[1] Williams, G., and Pickup, J. C., 1999. *Handbook of Diabetes*. MSD, Oxford.

[2] The American Diabetes Association, 2010. "Standards of medical care in diabetes 2010". *Diabetes Care,* **33, Supplement 1**, pp. S11–S61.

[3] The Diabetes Control and Complications Trial Research Group, 1993. "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". *N Eng J Med,* **329**(14), September, pp. 977–986.

[4] The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, 2005. "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes". *N Eng J Med,* **353**(25), December, pp. 2643–2653.

[5] Chee, F., Fernando, T., Savkin, A., and van Heeden, V., 2003. "Expert PID control system for blood glucose control in critically ill patients". *IEEE Transactions on Information Technology in Biomedicine,* **7**(4), December, pp. 419–425.

[6] Marchetti, G., Barolo, M., Jovanovic, L., Zisser, H., and Seborg, D., 2008. "A feedforward-feedback glucose control strategy for type 1 diabetes mellitus". *Journal of Process Control,* **18**, pp. 149–162.

[7] Marchetti, G., Barolo, M., Jovanovic, L., Zisser, H., and Seborg, D., 2008. "An improved PID switching control strategy for type 1 diabetes". *IEEE Transactions on Biomedical Engineering,* **55**(3), March, pp. 857–865.

[8] Ortiz-Vargas, M., and Puebla, H., 2006. "A cascade control approach for a class of biomedical systems". In Proc. of the 28th IEEE-EMBS Ann. Int. Conference, pp. 4420–4423.

[9] Hovorka, R., 2005. "Management of diabetes using adaptive control". *Int. J. Adapt. Control Signal Process,* **19**, pp. 309–325.

[10] Palerm, C., Zisser, H., Jovanovic, L., and Doyle, F., 2007. "A run-to-run framework for prandial insulin doses: handling real-life uncertainty". *Int. J. Robust Nonlinear Control,* **17**, pp. 1194–1213.

[11] Palerm, C., Zisser, H., Jovanovic, L., and Doyle, F., 2008. "A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes". *Journal of Process Control,* **18**, pp. 258–265.

[12] Magni, L., Raimondo, D., Bossi, L., Dalla Man, C., De Nicolao, G., Kovatchev, B., and Cobelli, C., 2007. "Model predictive control of type 1 diabetes: An in silico trial". *Journal of Diabetes Science and Technology,* **1**(6), pp. 804–812.

[13] Youqing, W., Zisser, H., Dassau, E., Jovanovic, L., and Doyle J. III, F., 2010. "Model predictive control with learning-type set-point: Application to artificial pancreatic beta-cell". *AIChE Journal,* **56**(6), pp. 1510–1518.

[14] Ruiz-Velazquez, E., Femat, R., and Campos-Delgado, D., 2004. "Blood glucose control for type 1 diabetes mellitus: A robust tracking $H_\infty$ problem". *Control Engineering Practice,* **12**, pp. 1179–1195.

[15] Cobelli, C., Dalla Man, C., Sparacino, G., Magni, L., De Nicolao, G., and Kovatchev, B., 2009. "Diabetes: Models, signals and control". *IEEE Reviews in Biomedical Engineering,* **2**, pp. 54–96.

[16] DIAdvisor www.diadvisor.eu.

[17] Maciejowski, J., 2002. *Predictive Control with Constraints*. Pearson Education Limited.

[18] James B., R., and Mayne, D., 2009. *Model Predictive Control:Theory and Design*. Nob Hill Publishing.

[19] Dalla Man, C., Rizza, R. R., and Cobelli, C., 2007. "Meal simulation model of the glucose-insulin system". *IEEE Transactions on Biomedical Engineering,* **54**(10), October, pp. 1740–1749.

[20] MATLAB, 2010. *version 7.10.0 (R2010a)*. The MathWorks Inc.

[21] Cobelli, C., Renard, E., and Kovatchev, B., 2011. "Artificial pancreas: Past, present, future". *Diabetes,* **60**, pp. 2672–2682.

[22] De Nicolao, G., Magni, L., Dalla Man, C., and Cobelli, C., 2011. "Modeling and control of diabetes: Towards the artificial pancreas". In Proc. of the 18th IFAC World Congress (IFAC2011), pp. 7092–7101.

[23] van Heudsen, K., Dassau, E., Zisser, H., Seborg, D., and Doyle J. III, F., 2011. Control-relevant models for glucose control using a priori patient characteristics.

[24] Kirchsteiger, H., and del Re, L., 2009. "Reduced hypoglycemia risk in insulin bolus therapy using asymmetric cost functions". In 7th Asian Control Conference (ASCC 2009), pp. 751 –756.

[25] Kirchsteiger, H., del Re, L., Renard, E., and Mayrhofer, M., 2009. "Robustness properties of optimal insulin bolus administrations for type 1 diabetes". In American Control Conference (ACC 2009), Vol. 47, pp. 2284 –2289.