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MPC based Artificial Pancreas: Strategies for individualization and meal compensation

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ABSTRACT

This paper addresses the design of glucose regulators based on Model Predictive Control (MPC) to be used as part of Artificial Pancreas devices for type 1 diabetic patients. Two key issues are deeply investigated: individualization, needed to cope with intersubject variability, and meal compensation, interpreted as a disturbance rejection problem. The individualization is achieved either by tuning the cost function, based on few well known clinical parameters (MPC1) or through the use of an individual model obtained via system identification techniques and an optimal tuning of the cost function based on real-life experiments (MPC2). The *in silico* tests, performed on 4 different scenarios using a simulator equipped with 100 patients, show that the performances of MPC1 are very promising, supporting its current use in an in vivo multicenter trial on 47 patients that is being carried out within the European Research Project AP@home. At the same time, further improvements are achieved by MPC2, showing that there is scope for in vivo experimentation of control strategies employing individually estimated patient models.

1. Introduction

Diabetes is a pathology that involves glucose regulation and can be divided in two main types: type 1, or insulin dependent, and type 2 or insulin resistant. The first one is characterized by the destruction of the beta cells in the pancreas, responsible for the insulin production, and, as a consequence, by the complete dependency of the patient on external insulin administration. In type 2 diabetic patients, there are an alteration of insulin secretion and a reduction of sensitivity to this hormone. A good glucose regulation, with glucose levels in the range 70–140 mg/dl, is mandatory for both types of diabetes because low blood glucose levels, *hypo-glycemia*, can lead to coma and, if not treated, to death. Conversely, high blood glucose levels, *hyper-glycemia*, maintained for too long can lead to the onset of long term problems such as cardiovascular diseases, chronic renal failures and retinal damages.

Scientific research devoted to diabetes is motivated by its prevalence, the estimated increase of new cases in the future and also because, with its complications, it imposes heavy charges on individuals, families, health systems, and countries. The World Health Organization (WHO), estimates that more than 346 million people worldwide have diabetes, a number destined to more than double by 2030. Diabetes is a major cause of death and in 2004 an estimated 3.4 million people died from consequences of high blood sugar (World Health Organization).

Research addresses several issues (Cobelli et al., 2009; Cobelli, Renard, & Kovatchev, 2011) and has different objectives: prevent the diffusion of the pathology, optimize therapy and develop automatic devices for regulating glucose in diabetic patients. The first example of device, developed in 1970s, for glucose regulation is the Biostator® that used glucose measurements, obtained with an intravenous sensor, to suggest insulin values, injected with an intravenous pump (Albisser et al., 1974; Clemens, Chang, & Myers, 1977; Marliss et al., 1977). This method is too invasive and not suitable for outpatient use. For this reason, of great interest are devices employing a subcutaneous glucose sensor and a subcutaneous insulin pump. The integration of these two components with a control algorithm is called *Artificial Pancreas* (AP). A new era for the AP started in 1999 when the MiniMed introduced a commercial continuous glucose monitoring (CGM) system. Since then, several research project studied and experimented AP systems, starting from the MiniMed AP project (Steil, Rebrin, Darwin, Hariri, & Saad, 2006), with an acceleration caused by the launch of research projects funded by the JDRF, the European Commission and the NIH (El-Khatib, Russell, Nathan, Sutherlin, & Damiano, 2010; Hovorka et al., 2004, 2010; Kovatchev et al., 2010; Weinzimer et al., 2008). Among the most notable results is the approval by the Food and Drugs Administration (FDA) of a large scale

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in silico simulator developed by the University of Padova and the University of Virginia (Kovatchev, Breton, Dalla Man, & Cobelli, 2008) as a substitute to animal trials in the preclinical testing of AP control strategies.

Designing a control algorithm for the sc to sc glucose–insulin system is challenging because the system is characterized by significant interindividual variability, time varying dynamics, nonlinear phenomena and time delays due to the absorption of insulin from the subcutaneous level to the blood and, on reverse, of glucose from the blood to the subcutaneous level. Moreover the glucose profile depends on the insulin delivered, bounded from zero to a maximal value given by the pump, but also on very important disturbances such as meals and physical exercises that could be predicted to some extent.

The objective of the control algorithm is to keep the glucose levels within an optimal range (70–140 mg/dl). In the literature, several algorithms have been presented starting from PID schemes such as the work of Marchetti, Barolo, Jovanovicy, Zisser, and Seborg (2006) and Steil et al. (2006).

One of the most promising approaches to glucose regulation is Model Predictive Control. Three examples of MPC glucose regulation are the study of Parker, Doyle, and Peppas (1999), that considers a linear model identified with step responses and the work of Hovorka et al. (2004) that relies on a nonlinear time varying model whose parameters are adapted via Bayesian estimation and Magni et al. (2007) that is based on a mean linear model with an individualized cost function. Other interesting approaches are presented in Bequette (2005), Dua, Doyle, and Pistikopoulos (2006), Grosman, Dassau, Zisser, Jovanovic, and Doyle (2010), Hovorka (2005a, 2005b), Magni, Raimondo, et al. (2009), Magni, Forgione, et al. (2009), Patek et al. (in press). So far, encouraging pilot results have been reported using Proportional-Integral-Derivative (PID) control (Steil et al., 2006; Weinzimer et al., 2008) and MPC strategies (Dassau et al., 2010; Hovorka et al., 2010; Kovatchev et al., 2010). In the technological implementation of the Artificial Pancreas, the control algorithm can be embedded in a modular architecture, (Patek et al., in press), including a safety module that checks the insulin suggested by the algorithm and approves or reduces this value.

The results illustrated in this article have been obtained *in silico*, using a simulator equipped with a cohort of virtual subjects that span sufficiently well the interindividual variability of key metabolic parameters in the general population of diabetic patients. In particular, the *in silico* experiments were performed using the glucose–insulin simulator developed by the University of Padova and University of Virginia (see Dalla Man, Rizza, & Cobelli, 2007). Underlying this simulator there is a high-order nonlinear model, characterized by several physiological parameters and incorporating all available knowledge about system functionality so as to be able to provide realistic glucose–insulin simulations in diabetes.

The paper is organized as follows. Section 2 is devoted to discussing the structure of the control system. The main contribution is the analysis of alternative feedback–feedforward schemes that exploit conventional therapy in order to improve the effectiveness of meal compensation. The novel scheme proposed in this paper combines a feedforward action derived from conventional therapy with feedforward action optimized by the MPC based on a meal absorption model. In Section 3, a general framework for controller individualization is described that hinges on two models, one for control design purposes and the other for tuning the cost function. Three possible implementations of this framework are discussed in Section 4. The first control strategy is an ideal one as it assumes availability of an accurate model of the true patient. The second one pursues individualization without assuming knowledge of individual patient dynamics, but exploiting only the knowledge of standard clinical parameters obtainable from screening questionnaires. The third control strategy individualizes the regulator on the basis of an individual linear model identified from real life experiments. The comparison of the three control strategies is carried out *in silico* in Section 5 considering four different scenarios: nominal, randomly perturbed meals, randomly perturbed insulin sensitivity and perturbation of basal insulin delivery. Some conclusions end the paper.

2. Control structure

The Artificial Pancreas has to do with closed-loop control of blood glucose profile. In such a context the blood glucose profile plays the role of controlled variable. The noisy measurements however, are provided by CGM readings that refer to subcutaneous glucose concentration, which is known to be a unit-gain lowpass filtered version of the controlled variable (the time constant being of the order of 5 min). The control variable is the injected insulin which is used to keep the blood glucose close to the euglycemic zone ranging from 70 to 140 mg/dl. The system is subject to substantial disturbances, the most important being meals. The amplitude of the meal disturbance is measured in terms of ingested carbohydrates that in the subsequent hours are converted into glucose. The conventional therapy addresses glucose regulation by a mix of piecewise constant insulin infusion, also called *basal insulin*, and impulse-like injections that are made just before meals to prevent excessive rises of blood glucose also called *insulin bolus*. In absence of meals, the basal insulin, which varies from patient to patient, would eventually bring blood glucose to a steady-state value, called *basal glucose*. Pre-meal boluses are self administered assuming that occurrence and size of the upcoming meal are known in advance (meal announcement). The amount of the insulin bolus is scaled to the meal size through a constant, specific to each individual, called carbo-ratio.

An essential feature of glucose control in diabetic patients is the need of compensating large external disturbances given by the meals. On one side, nocturnal glucose control is a rather standard regulation problem where a constant or slowly varying set-point is to be tracked. On the other hand, meals produce substantial excursions of glycemic values that can be handled only by injecting sufficient insulin in a relatively short time window.

The basic control architecture of the Artificial Pancreas is displayed in Fig. 1, where an MPC module uses real time *CGM* readings and future predicted meals to decide the control action, combining in an automatic way the feedback and feedforward actions. Note that m is the real meal affecting patient's glycemic profile, while $\hat{m}$ is a presumed meal signal, known in advance by the patient, whose knowledge is forwarded to the controller as an announced disturbance d. The inherent delays of the physiological system, the saturation constraints on the insulin pump and the lack of a reliable individual patient model impose intrinsic limitations to the achievable time constant of the closed-loop, so that prompt controller responses may be not compatible with closed-loop stability and avoidance of hypoglycemic events. As a consequence, for the controller it may be impossible to generate the large insulin boluses needed for an effective meal compensation.

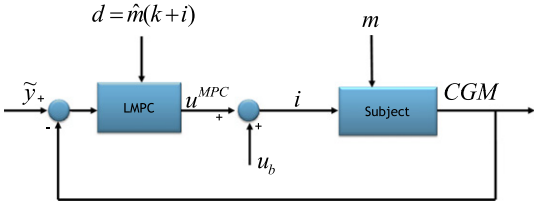


Fig. 1. Basic closed-loop scheme.

In order to circumvent this problem, the feedback and feedforward actions can be split (Patek et al., in press), letting the latter be handled by an open-loop scheme inspired by conventional insulin therapy followed by the patient, see Fig. 2. In this scheme, the meals are compensated by the signal u_c generated by the therapeutic rules represented by means of the block R yielding the usual pre-meal boluses. An explicit or implicit patient model is used to compute the expected effect of meal and pre-meal boluses on the glucose profile. The MPC is in charge of feedback compensation so as to track the basal glucose profile, far from meals, and the expected glucose profile $y_r + \hat{y}$, immediately after meals. The feedback action is essential in order to handle exogenous disturbances as well as model and meal uncertainties. This scheme has the merit of incorporating valuable individual knowledge embedded in the consolidated therapeutic practice but suffers from several drawbacks. In fact, the pre-meal boluses are essentially decided according to empirical and static rules and delivered irrespective of real time and historical information coming from *CGM* measures and past delivered insulin. Another drawback has to do with the need of providing an approximation of the response $\hat{y}$ to the pre-meal bolus u_c. This is usually accomplished by some empirical and rough patient model that might give barely acceptable predictions.

If a reliable model of the meal effect on glucose response were available, an optimized computation of pre-meal boluses would become possible, as illustrated in Fig. 3. The main difference of this last scheme with respect to the one of Fig. 1, is that the conventional pre-meal bolus u_0 acts as a reference for the administration of insulin profile. The other two inputs of the LMPC are the error e between the prescribed set point $\tilde{y}$ and the measured output CGM and the signal d representing a prediction of the next meal. Due to inter- and intra-patient variability, it can happen that scheme Fig. 2 (MPC with open-loop meal compensation) may preform better than scheme Fig. 3 (MPC with open-loop insulin reference) or vice-versa. Therefore, there is scope for a further hybrid scheme Fig. 4, where meal compensation combines the two previous schemes, using the scalar weight α to control the balance between open-loop compensation and MPC compensation informed by the open-loop reference. In particular, scheme Fig. 2 is a particular case of scheme Fig. 4 for $\alpha = 1$ whereas scheme Fig. 3 is obtained for $\alpha = 0$.

2.1. Linear Model Predictive Control

The control algorithm described in this article is a Linear Model Predictive Controller (LMPC) law that uses a linear discrete time model to predict future outputs (subcutaneous glucose) as a function of an input (subcutaneously injected insulin) and a disturbance (meal consumption). This model can be written in the following form:

$$\begin{cases} x(k+1) = Ax(k) + Bu(k) + Md(k) \\ y(k) = Cx(k) \end{cases} \quad (1)$$

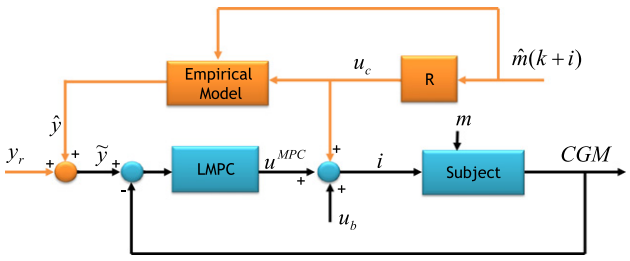


Fig. 2. Closed-loop scheme: MPC with open-loop meal compensation.

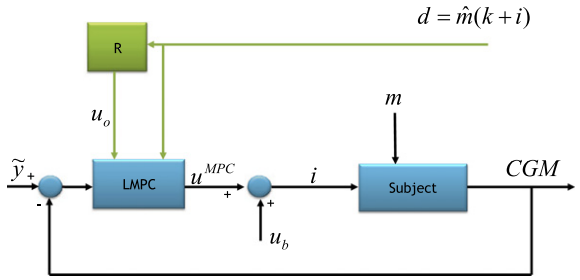


Fig. 3. Closed-loop scheme: MPC with open-loop insulin reference.

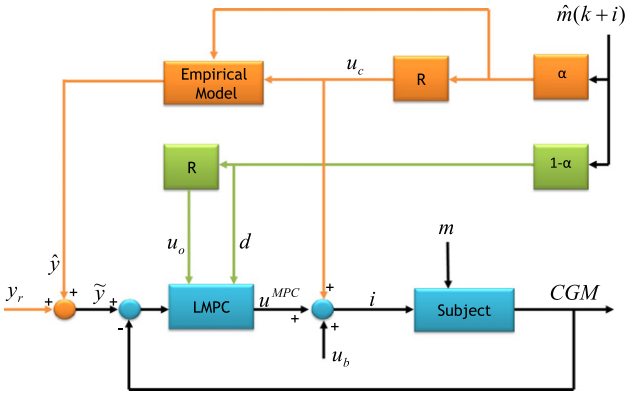


Fig. 4. Closed-loop scheme: mixed open-loop and closed-loop meal compensation.

where

- $x(k) \in R^n$, is the state;
- $y(k) = CGM(k) - G_b$ (mg/dl), is the difference between the subcutaneous glucose and the basal value (G_b);
- $u(k) = i(k) - u_b(k)$ (pmol/kg), is the difference between the injected insulin and its basal value, that could be time varying. The insulin is normalized by the patient weight;
- $d(k)$ (mg), represents the meal.

Thereafter, it is assumed that the triplet (A, B, C) is both stabilizable and detectable.

The LMPC algorithm uses this model to predict the future glucose profile given the carbohydrates and insulin taken in by the patient. Based on this prediction it is possible to find the optimal profile of the future insulin administration, according to the following cost function:

$$J(x(k), u(\cdot), k) = \sum_{i=0}^{N-1} (q(y(k+i) - y_o(k+i))^2 + (u(k+i) - u_o(k+i))^2) + \|x(k+N)\|_P^2 \quad (2)$$

where q is a positive scalar weight to be tuned by the user, N is the prediction horizon. Moreover, $\|x(k+N)\|_P = x(k+N)'Px(k+N)$, where P is a nonnegative definite matrix, e.g the unique nonnegative solution of the discrete time Riccati equation

$$P = A'PA + qC'C - A'PB(1 + B'PB)B'PA$$

and

- $y_o(k) = \tilde{y}(k) - G_b$ (mg/dl), is the difference between the reference value ($\tilde{y}$) of the subcutaneous glucose and the glucose and the basal value (G_b);
- $u_o(t) = \tilde{u}(k) - u_b(k)$ (pmol/kg), is the difference between the reference value ($\tilde{u}$) of the insulin profile and the insulin basal value (u_b).

In order to avoid on-line optimization or the computational and memory burden of an explicit MPC for constraints systems, the proposed algorithm does not include constraints. Hence, it is possible to calculate the closed form solution exploiting the Lagrange formula. In particular, the predicted vector

$$Y(k) = [\, y(k+1) \quad \dots \quad y(k+N-1) \quad x(k+N) \,]'$$

can be written as a function of the initial state $x(k)$, the vector of future insulin administrations

$$U(k) = [\, u(k) \quad \dots \quad u(k+N-2) \quad u(k+N-1) \,]'$$

and the vector of future meals

$$D(k) = [\, d(k) \quad \dots \quad d(k+N-2) \quad d(k+N-1) \,]'$$

in the following way

$$Y(k) = \mathcal{A}_c x(k) + \mathcal{B}_c U(k) + \mathcal{M}_c D(k) \tag{3}$$

$$\mathcal{A}_c = \begin{bmatrix} CA & \dots & CA^{N-1} & A^N \end{bmatrix}'$$

$$\mathcal{B}_c = \begin{bmatrix} CB & 0 & \cdots & 0 \\ CAB & CB & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ CA^{N-2}B & CA^{N-3}B & \cdots & 0 \\ A^{N-1}B & A^{N-2}B & \cdots & B \end{bmatrix}$$

$$\mathcal{M}_c = \begin{bmatrix} CM & 0 & \cdots & 0 \\ CAM & CM & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ CA^{N-2}M & CA^{N-3}M & \cdots & 0 \\ A^{N-1}M & A^{N-2}M & \cdots & M \end{bmatrix} \tag{4}$$

Defining the matrix:

$$\mathcal{Q} = \begin{bmatrix} q & 0 & \cdots & 0 & 0 \\ 0 & q & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & q & 0 \\ 0 & 0 & \cdots & 0 & P \end{bmatrix} \tag{5}$$

and the reference vectors

$$Y_o(k) = [\, y_o(k+1) \quad \dots \quad y_o(k+N-1) \quad 0 \,]' \in R^{1\times(N-1+n)}$$

$$U_o(k) = [\, u_o(k) \quad \dots \quad u_o(k+N-2) \quad u_o(k+N-1) \,]' \tag{6}$$

the cost in (2) can be replaced by

$$\begin{aligned} J(x(k), u(\cdot), k) = {} & (\mathcal{A}_c x(k) + \mathcal{B}_c U(k) + \mathcal{M}_c D(k) \\ & - Y_o(k))' \mathcal{Q} (\mathcal{A}_c x(k) + \mathcal{B}_c U(k) + \mathcal{M}_c D(k) \\ & - Y_o(k)) + (U(k) - U_o(k))' (U(k) - U_o(k)) \end{aligned} \tag{7}$$

Note that the term $qy^2(k)$ has been dropped: in fact, it does not affect the solution of the optimization problem because it does not depend on $u(k+j), j \geqslant 0$. Zeroing the gradient, the vector of future optimal inputs is found to be

$$\begin{aligned} U^o(k) = {} & \left(\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + \mathcal{R}\right)^{-1} \left(-\mathcal{B}_c' \mathcal{Q} \mathcal{A}_c x(k) - \mathcal{B}_c' \mathcal{Q} \mathcal{M}_c D(k) \right. \\ & \left. + \mathcal{B}_c' \mathcal{Q} Y_o(k) + \mathcal{R} U_o(k)\right) \end{aligned} \tag{8}$$

which depends on the state at sample time k, the output and control variable future references and the future vector $D(k)$.

According to the Receding Horizon principle the time-invariant LMPC control law is then given by:

$$u^{MPC}(k) = [\, 1 \quad 0 \quad \cdots \quad 0 \,](-K_x x(k) - K_d D(k) + K_{Y_o} Y_o(k) + K_{U_o} U_o(k)) \tag{9}$$

where the gains are:

$$K_x = \left(\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + I\right)^{-1} \mathcal{B}_c' \mathcal{Q} \mathcal{A}_c$$

$$K_d = \left(\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + I\right)^{-1} \mathcal{B}_c' \mathcal{Q} \mathcal{M}_c$$

$$K_{Y_o} = \left(\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + I\right)^{-1} \mathcal{B}_c' \mathcal{Q}$$

$$K_{U_o} = \left(\mathcal{B}_c' \mathcal{Q} \mathcal{B}_c + I\right)^{-1}$$

The state $x(k)$ of the model in general is not measurable. To circumvent this problem, in Magni et al. (2007) the use of a nonminimal state-space realization of the input–output model was proposed, whose state is made by past input and output values. However, also in this case, just noisy measures of the output (the subcutaneous glucose concentration) would be available with the consequent impact of sensor noise on the closed-loop performance. In this paper, the use of a Kalman Filter, exploiting the knowledge included in the model and the past injected insulin, is added in order to improve the quality of the information provided to the LMPC algorithm.

2.2. Kalman Filter

In order to design the Kalman Filter, noises are introduced in the linear system (1):

$$\begin{cases} x(k+1) = Ax(k) + Bu(k) + Md(k) + v_x(k) \\ y(k) = Cx(k) + v_y(k) \end{cases} \tag{10}$$

where $v = [\, v_x \quad v_y \,]$ is a multivariate zero-mean white Gaussian noise with covariance matrix:

$$V = \begin{bmatrix} Q_{KF} & 0 \\ 0 & R_{KF} \end{bmatrix}, \; Q_{KF} > 0 \; R_{KF} > 0 \tag{11}$$

Moreover, the initial state $x_0 = x(0)$ is assumed to be a zero mean Gaussian random variable independent of v.

Under these assumption, the steady-state Kalman filter has the following equations:

$$\begin{aligned} \hat{x}(k+1|k) &= A\hat{x}(k|k) + Bu(k) + Md(k) \\ \hat{x}(k|k) &= \hat{x}(k|k-1) + L(y(k) - C\hat{x}(k|k-1)) \end{aligned} \tag{12}$$

where

$$L = PC'[CPC' + R_{KF}]^{-1} \tag{13}$$

and P is the unique positive define solution of the algebraic Riccati equation

$$P = APA' + Q_{KF} - APC'[CPC' + R]^{-1} CPA'$$

The Kalman filter is used to update the estimated glucose-insulin state using past information about glucose, insulin and carbohydrates.

According to the separation principle, the estimated state is plugged into the control law (9)

$$u^o(k) = [\, 1 \quad 0 \quad \cdots \quad 0 \,](-K_x \hat{x}(k|k) - K_d D(k) + K_{Y_o} Y_o(k) + K_{U_o} U_o(k)) \tag{14}$$

The main advantage of using the Kalman filter is that, by properly tuning Q_{KF} and R_{KF}, the controller can be made less sensitive to sensor noise.

3. MPC individualization

When controlling physiological systems, two major issues are the inherent inter-individual variability and the limited amount

of information that can be gathered on the single subject under control. Hence, the importance but also the difficulty of controller individualization, that should ensure the needed flexibility without compromising simplicity and robustness. For this reasons, attention is focused on few but essential design choices, keeping fixed the less critical ones. In the algorithm proposed in this paper the control horizon N is kept equal to 10 h, a value compatible with the time constants of the insulin-glucose system. Also the Kalman Filter weights Q_{KF} and R_{KF} are fixed at values obtained from the analysis of simulated and clinical insulin-meal glucose profiles. These weights are mainly related to the quality of the sensor and the model included in the filter and less to the single patient, meaning that they should be retuned if the quality of the model or the sensor change significantly. Controller individualization is obtained by tailoring the model and/or the cost function to the patient. As a matter of fact there are three main elements that can be individualized. First of all, there is the linear model used for synthesizing the MPC regulator. Ideally, such model should reflect the individual patient dynamics although sufficient information to derive an accurate individual model may be difficult to obtain. The second element is given by the reference signals u_o and y_o appearing in the cost function. With reference to scheme Fig. 4, a suitable choice, adopted herein, is to select profiles associated with the nominal/desired courses obtained under conventional pre-meal boluses. In order to prevent excessive insulin administration, $\hat{d}$ is conservatively assessed as 90% of expected meals. A third element that can be individualized is given by the weights of the cost function. For the sake of simplicity, only the scalar q is hereafter considered since it directly affects the aggressiveness of the controller and, hence, the trade-off between sluggish control and the risk of hypoglycemic episodes induced by insulin spikes delivered by an exceedingly sensitive regulator.

3.1. Calibration procedure

The tuning of q is done through the iterative procedure described by the flow chart in Fig. 5. The main ingredients are: a performance index, a model for the control synthesis and a model for performance testing.

Concerning the performance index, the goal is to keep the glucose profile close to the reference 110 mg/dl. The testing is performed on an *in silico* experiment following a protocol that specifies meal times and amounts. Larger values of q yields aggressive control that, in view of uncertainty and disturbances, may trigger hypoglycemic episodes. Conversely, small values of q may be insufficient to counter glycemic rises subsequent to meals so that

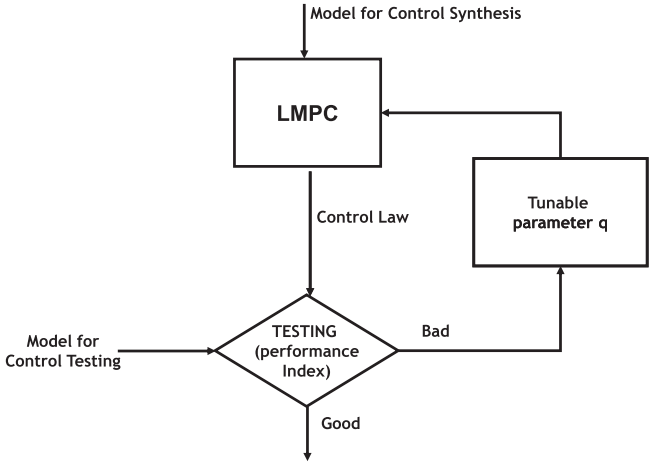


Fig. 5. Control design procedure.

hyperglycemic episodes are more likely. When assessing performance, attention is focused on the worst hypoglycemic episode and the worst hyperglycemic one (without considering the first 2 h after a meal). The error associated with the minimum glucose value is defined as $\epsilon_{MIN} = 110 - G_{MIN}$ while the one associated with the maximal glucose value is $\epsilon_{MAX} = G_{MAX} - 110$. Only these two errors are considered and combined to obtain a single index characterizing the whole glucose profile.

The weight given to ϵ_{MIN} is higher with respect to the one given to ϵ_{MAX} because it is more important to avoid hypo than hyperglycemia (Kovatchev, Clarke, Breton, Brayman, & McCall, 2005). A good metrics can be derived from the Control Variability Grid Analysis (CVGA) (Magni et al., 2008) where each profile collapses to a point whose x coordinate is a function of the minimal glucose value and whose y coordinate is a function of the maximal one. It is important to acknowledge that the risk associated with different hypoglycemic states is a linear function of blood glucose whereas the risk associated to hyperglycemic states is a nonlinear function of blood glucose. Several studies have investigated this point and, following (Kovatchev et al., 2005), we assume that an increase from 110 to 180 mg/dl is as risky as a −20 decrease from 110 to 90 mg/dl; an increase from 110 to 300 mg/dl is as risky as a −40 decrease from 110 to 70 mg/dl. Finally, an increase from 110 to 400 mg/dl is as risky as a −60 decrease from 110 to 50 mg/dl. In particular, the coordinates X_{CVGA} and Y_{CVGA} are defined as:

$$\begin{aligned} X_{CVGA} &= \max(\min(110 - G_{MIN}, 60), 0) \\ Y_{CVGA} &= \max(\min(p(G_{MAX}), 60), 0) \end{aligned} \tag{15}$$

where

$$p(x) = 2.683\dot{1}0^{-6}x^3 - 2.210\dot{1}0^{-3}x^2 + 0.754x - 59.77 \tag{16}$$

is the polynomial that interpolates the points (110,0), (180,20), (300,40) and (400,60). Note that the ideal reference point is placed in the lower left corner.

Once the outcome of the experiment is summarized by a point on the CVGA, the definition of the performance index becomes equivalent to selecting a particular norm in the CVGA plane. In our previous works, the infinity norm was employed mainly because it eased the iterative tuning of the aggressiveness parameter q. Accordingly, the performance index coincided with the larger CVGA coordinate. The main drawback is that such an index can be improved by a slight reduction of the larger coordinate even if at the cost of a substantial increase of the smaller one. To make an example, in order to slightly reduce the amplitude of the maximum glucose peak, it may be accepted a substantial decrease of the minimal glucose value. In order to avoid this problem, herein we propose to define the performance index as the 2-norm in the CVGA plane.

Once the performance index has been defined, it is possible to implement the iterative calibration procedure shown in the flow chart of Fig. 5 to obtain the optimal weight

$$q_o = \arg\min_q \| [X_{CVGA} \quad Y_{CVGA}] \|_2 \tag{17}$$

At each iteration the weight q is increased or decreased depending on previous results. As a consequence, at each iteration it is necessary to recalculate the MPC gains and assess the corresponding performance using the model for control testing.

4. From *in silico* to real patients

Mathematical models of glucose metabolism enter the flow chart of Fig. 5 in two distinct steps: control synthesis and control testing. The control design strategies discussed in the present section will differ in the choice of the models used for control

synthesis and testing. For ease of future reference, the models to be used are listed and named below:

IDM: nonlinear and time varying model associated with one particular *in silico* patient, drawn from the 100 patients provided by the Padova–Virginia simulator (Kovatchev et al., 2008). Used for control testing
ADM: nonlinear and time varying model (Kovatchev et al., 2008) associated with the average patient, i.e. the patient whose physiological parameters coincide with the average values in the population of patients.
L-IDM: linear individual model obtained by linearizing IDM around the basal. Used for control synthesis;
L-ADM: linear model obtained linearizing ADM around the basal. Used for control synthesis;
E-IP: linear model for an individual patient identified from either *in silico* of clinical experimental data. Used for control synthesis and testing.

4.1. Controlling in silico patients (I-MPC)

The first control strategy, called Ideal MPC (I-MPC), assumes that the nonlinear model of the patient is known. This is possible only *in silico* where a cohort of 100 adults with known parameters is available. In this context, L-IDM is used as model for control testing.

In a real case, it is not possible to implement this strategy because the *in silico* maximal model is neither known nor identifiable for each patient without expensive experiments.

As a consequence, it is necessary to work out alternative strategies that can do without individual models. Herein, two main approaches are considered: MPC1 that uses L-ADM and L-IDM and MPC2 that relies on a linear model E-IP identified from easily available information.

4.2. Controlling real patients: average model design (MPC1)

In the control synthesis step, the L-ADM model is used for all patients. In view of the remarkable patient inter variability, individual tuning, carried out through the individualization of the cost function, is particularly important.

Unfortunately, the calibration procedure described in the previous section cannot be applied to real patients neither via clinical experiments nor via *in silico* tests. In fact, the former solution would require lengthy and expensive experiments on the patients, while the latter would rely on an individual model of the patient which, as just said, is hardly available. A feasible individualization method, introduced in Patek et al. (in press), is to find a function $f(\vartheta_1, \cdots, \vartheta_2)$ that, given a set of parameters $\{\vartheta_1, \cdots, \vartheta_2\}$ derived from the patient screening questionnaire, returns a scalar value q that approximates the weight q_o, according to some suitable metric.

In order to derive a linear tuning rule for the weight q, the considered model is

$$q_o(i) = \phi(i)'\theta + \epsilon(i), \quad i = 1, \ldots, 100 \tag{18}$$

where q_o is the optimal weight for the ith virtual patient, $\phi(i)$ is the vector of clinical parameters for the ith patient, θ is the parameter vector to be estimated and $\epsilon(i)$ is an error term. In the proposed implementation, the clinical parameters are the so-called Carb Ratio (CR) and the daily average basal insulin $\bar{u}_b$, so that

$$\phi(i) = [\,1 \quad CR \quad \bar{u}_b\,] \tag{19}$$

where the first element introduces a constant term in the regression. In order to "learn" the function $f(CR, \bar{u}_b)$, the tuning procedure of Section 3 is applied to a cohort of *in silico* patients (i.e. all the 100 patients of the Padova-Virginia simulator) to obtain the optimal weights $q_o(i)$ for each of them. Note that for these virtual patients the clinical parameters CR and $\bar{u}_b$ are made available by the simulator. Using this information, the Least Square (LS) estimate is given by

$$\theta^{LS} = \left(\sum_{i=1}^{100}\phi(i)\phi(i)'\right)^{-1}\sum_{i=1}^{100}\phi(i)q_o(i) \tag{20}$$

Then, the weight q^* of a (possibly real) patient whose clinical parameter are $\phi^* = [\,1 \quad CR^* \quad \bar{u}_b^*\,]$ is estimated as

$$\hat{q}_o^* = \phi^{*\prime}\theta^{LS} = f(CR, \bar{u}_b) \tag{21}$$

In order to reduce the probability of hypoglycemic events, a reduction factor is applied to the parameter q^*.

4.3. Controlling real patients: individualized model design (MPC2)

For individualized model design, we mean a control design procedure based on a linear model identified from individual experiments. For the approach to be widely usable, it is essential that such experiments are as close as possible to real life conditions, involving just CGM collection and insulin and meal recordings. It has been observed (Finan et al., 2009) that the identification from real life data of black-box input–output models, e.g. ARX, ARMAX and Box & Jenkins, can suffer from poor input excitation, because meals and pre-meal insulin boluses tend to be synchronized and proportional. To overcome this issue, the use of ad-hoc experiment designs, i.e. perturbating pre-meal boluses and giving additional correction boluses, has been suggested and tested *in silico* as a way to improve input excitation and hence the predictive performances of identified models. The cost and safety issues associated with ad-hoc experiment designs are apparent. Conversely, in this paper, the possibility of identifying an individual model from everyday's real life data is investigated.

The two subsystems, from insulin to glucose and from meal carbohydrates to glucose, can be described by two continuous-time transfer functions $G_1(s)$ and $G_2(s)$. First of all, the structure and complexity of the transfer functions were determined by impulse response experiments on the 100 *in silico* subjects of the simulator starting from basal conditions. The use of the simulator for this preliminary analyses is motivated by the impossibility of performing extensive and possibly unsafe experiments on real subjects. A main finding was that the impulse responses are characterized by a slow onset, suggestive of a high relative degree. More specifically, it was found that fourth-order all-pole transfer functions gave a flexible, yet parsimonious, description of the observed impulse responses. Then, the actual system identification phase was performed by estimating individual parameter values (the two gains and the eight poles) using standard real life data collected either in open- or closed-loop under a known regulator, e.g. that developed in the previous section using the average patient model. Note that closed-loop data are expected to have better excitation properties, leading therefore to more accurate estimates, compared to open-loop data where the insulin signal is just the superposition of a basal profile and few pre-meal boluses synchronized, and hence correlated, with meals. On the contrary, the closed-loop insulin signal depends on the CGM readings, whose time variations provide the needed excitation.

The cost function of the system identification algorithm is the sum of squares of differences between observed CGM data and CGM obtained by running a simulation using the model. Since the residuals are a nonlinear function of the model parameters, an iterative nonlinear least squares algorithm is needed. Therefore, the final result may be sensitive to the adopted initialization. This

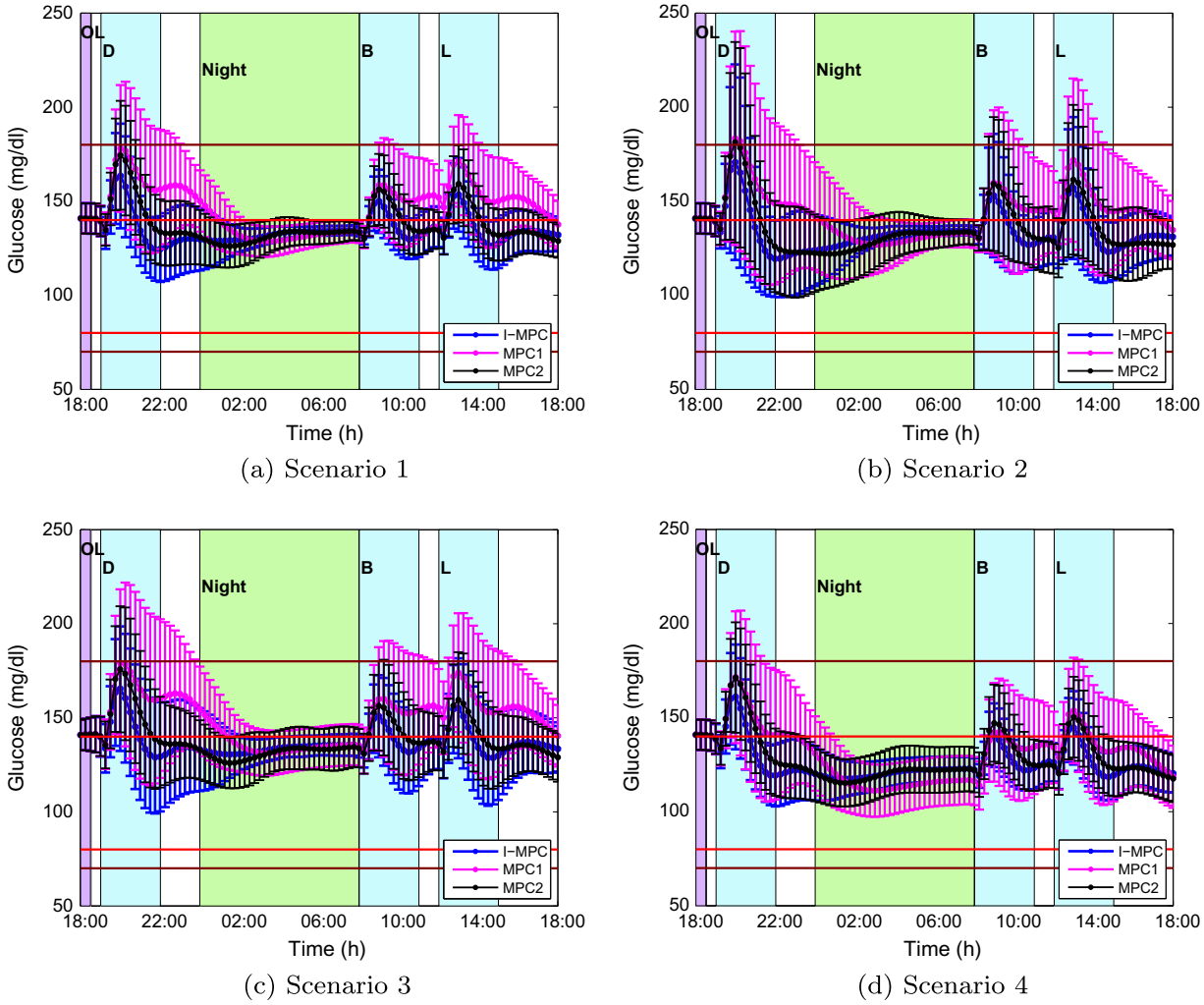


Fig. 6. Each figure shows for I-MPC (blue), MPC1 (magenta) and MPC2 (black) the mean (dots) and the variability (±SD) of the glucose profiles obtained in 100 virtual patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

issue can be addressed by initializing the algorithm with the parameters of the average subject, identified from impulse response experiments run using ADM.

After the identification procedure, the model is discretized and converted to the general form (1). Also the weight q in Eq. (2) can be tailored to each patient according to the procedure described Section 3.1 with E-IP used as model for both control synthesis and control testing. This procedure may yield an excessively aggressively regulator, because the same model is used in both the control synthesis and testing phase. Moreover, using the linear E-IP model for testing neglects the nonlinear nature of glucose dynamics. A possible way to address for this mismatch is to augment the system dynamics by introducing a stochastic term accounting for unmodeled dynamics. Also in the context of mixed-sensitivity design for H_2 or H_∞ control, the introduction of a low-pass stochastic disturbance on the output is a well-known expedient to introduce frequency weighting on the sensitivity function, see pag. 369 of Skogestad & Postlethwaite (1996). More precisely, the following first order low-pass stochastic process $x_w(k)$ is defined:

$$\begin{aligned} x_w(k+1) &= a x_w(k) + b v_w(k) \\ v_w(k) &\sim WN(\sigma_w^2) \end{aligned} \tag{22}$$

where $0 < a < 1$. For control design, the dynamics of the augmented system becomes

$$\begin{cases} \bar{x}(k+1) = \bar{A}\bar{x}(k) + \bar{B}\bar{u}(k) \\ y(k) = \bar{C}\bar{x}(k) \end{cases} \tag{23}$$

where $\bar{x}(k) = [\,x(k)' \quad x_w(k)\,]'$, $\bar{u}(k) = [\,u(k) \quad d(k)\,]'$

$$\bar{A} = \begin{bmatrix} A & 0 \\ 0 & a \end{bmatrix}, \quad \bar{B} = \begin{bmatrix} B & M \\ 0 & 0 \end{bmatrix}, \quad \bar{C} = [\,C \quad 1\,] \tag{24}$$

The augmented model used for the Kalman Filter design includes also the stochastic noises:

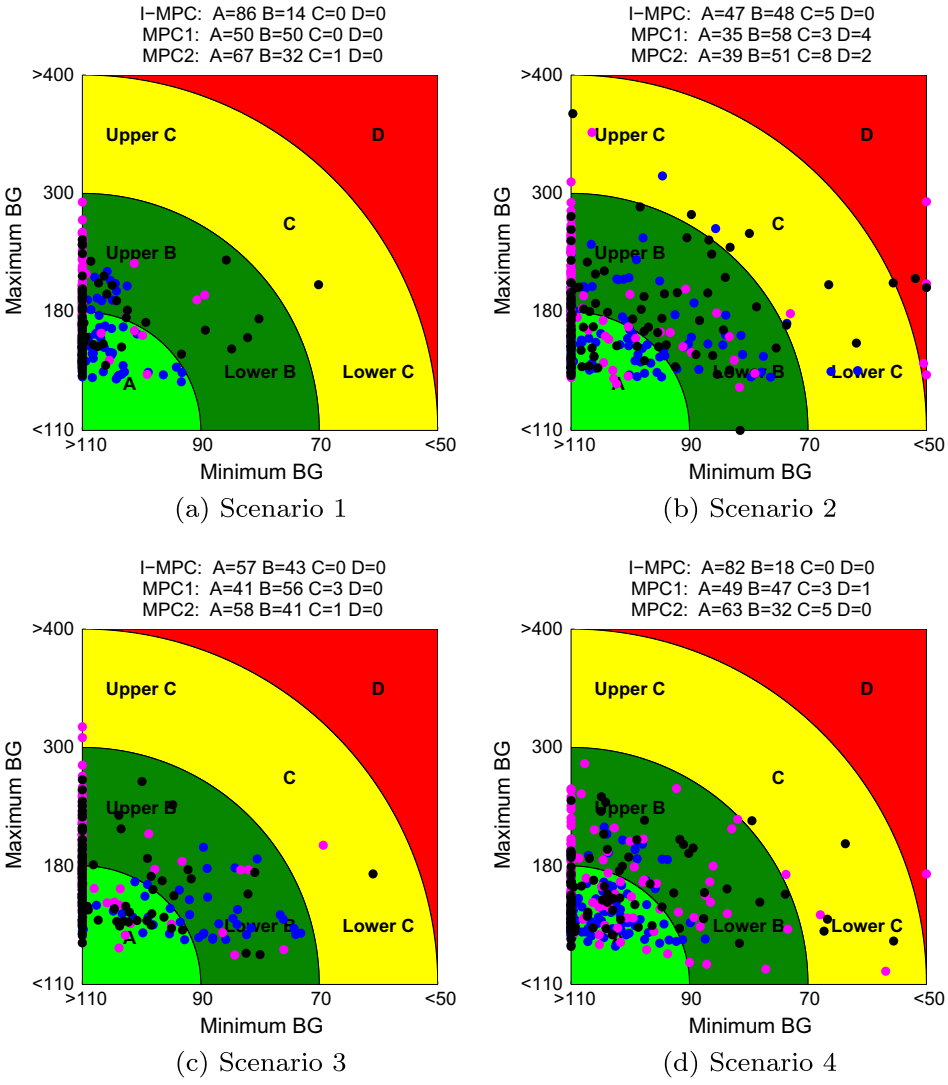
$$\begin{cases} \bar{x}(k+1) = \bar{A}\bar{x}(k) + \bar{B}\bar{u}(k) + \bar{v}_{\bar{x}}(k) \\ y(k) = \bar{C}\bar{x}(k) + v_y(k) \end{cases} \tag{25}$$

where $\bar{v}_{\bar{x}}(k) = [\,v_x(k) \quad b v_w(k)\,]'$ with the white noises v_x and v_w independent of each other and of $v_y(k)$ and the initial state.

5. Results

The strategies described in this article have been evaluated *in silico* (Patek et al., 2009), running simulations for 100 virtual patients on a set of four scenarios obtained from a *nominal protocol*[1] that starts at 6:00 pm and lasts 24 h. The state of each patient is ini-

[1] This protocol is similar to the one used for the in vivo multicenter trial of the AP@home project.



(a) Scenario 1 (b) Scenario 2

(c) Scenario 3 (d) Scenario 4

Fig. 7. CVGA representing the results obtained on different scenarios with the three strategies I-MPC (blue), MPC1 (magenta) and MPC2 (black). Each point represents the coordinates (x is a function of the minimal glucose value and y a function of the maximal value) associated with a single patient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tialized at the steady-state associated with the basal insulin. The first half an hour is managed with an open-loop therapy while at 6:30 pm the selected closed loop therapy is started. The meals during this protocol are: 80 g dinner at 7:00 pm, 50 g breakfast at 8:00 am and 60 g lunch at 12:00 am. The individualized models considered in MPC2 are identified on closed-loop data generated by the simulator using MPC1 and the same protocol.

The four scenarios are:

Scenario 1: nominal protocol
Scenario 2: the ingested amount of carbohydrates is the nominal one multiplied by a random factor uniformly distributed in $[0.5 \quad 1.5]$. This scenario is meant to reproduce a possible error in meal amount calculation
Scenario 3: a ±25% variation is randomly applied to the insulin sensitivity of each *in silico* patient. This scenario represents possible uncertainty on individual insulin sensitivity
Scenario 4: a 25% increase of the nominal basal insulin rate is introduced to simulate a suboptimal open-loop therapy.

The results are reported in Figs. 6 and 7. Fig. 6 compares I-MPC with MPC1 and MPC2 reporting the mean and the variability of the glucose profiles obtained simulating 100 virtual patients on each specific scenario. Fig. 7 shows four CVGA plots, one for each of the four scenarios.

Note that the CVGA plot used herein is a modification of the original CVGA plot. In fact, in Magni et al. (2008), the grid is divided into nine square zones associate with different degrees of risk ranging from A (Accurate Control) to E (Erroneous Control). The choice of square regions is consistent with the use of the infinity norm in order to measure performance of glucose control. Herein, since a 2-norm is adopted, see Eq. (17), the consistent way to define an outcome measure (i.e. number of subjects in the different safety zones) is to refer to concentric rings, see Fig. 7, ranging from A to D. An advantage of this modified CVGA is that all patients suffering from sever hypo- or hyper-glycemic episodes will fall in region D.

Furthermore, Table 1 summarizes all the outcomes: means and standard deviations of glucose values, the percentage of time spent in euglycemic target range $[70 \quad 180]$, in tight target range $[80 \quad 140]$), above 300 mg/dl and below 70 mg/dl. These outcomes are reported for the four scenarios and the three control schemes.

The glucose profiles are at first studied considering the whole period (first column of Table 1), then they are divided into different time ranges (remaining columns of Table 1), as illustrated also in Fig. 6:

Table 1
Results obtained simulating the strategies I-MPC, MPC1, and MPC2 on the scenarios Scenario 1, Scenario 2, Scenario 3, and Scenario 4, where O is overall, N is night, D is is dinner, B is breakfast, L is lunch, *M* is the mean of the blood glucose (mg/dl), SD is the standard deviation of the blood glucose (mg/dl), Tt is the percentage of time spent in euglycemic target [70–180] (mg/dl), Ttt is the percentage of time spent in tight target [80–140] (mg/dl), Ta is the percentage of time spent above 300 (mg/dl), Tb is the percentage of time spent below 70 (mg/dl).

		Scenario 1					Scenario 2					Scenario 3					Scenario 4				
		O	N	D	B	L	O	N	D	B	L	O	N	D	B	L	O	N	D	B	L
M (mg/dl)	I-MPC	135	132	142	138	138	134	131	144	138	138	137	133	145	139	140	126	120	138	129	129
	MPC1	147	133	161	150	158	144	131	161	148	155	150	136	163	152	161	131	116	152	133	140
	MPC2	138	131	152	143	144	135	129	153	144	142	139	131	154	144	145	128	120	148	134	135
SD (mg/dl)	I-MPC	13	5	16	9	13	19	6	22	13	17	15	6	17	10	13	13	5	17	9	12
	MPC1	19	7	18	12	13	24	8	23	15	17	20	8	19	13	13	20	7	19	12	13
	MPC2	15	7	17	11	13	21	8	23	14	18	16	7	17	11	13	16	7	18	11	13
Tt (%)	I-MPC	99	100	93	98	97	96	100	85	92	91	97	100	87	96	93	99	100	94	99	99
	MPC1	91	100	75	89	85	88	98	71	83	78	86	98	68	85	72	94	99	80	94	92
	MPC2	97	100	87	96	95	94	99	81	88	88	95	100	81	93	91	98	99	89	98	98
Ttt (%)	I-MPC	76	97	54	67	61	79	98	55	67	63	64	86	45	55	49	86	99	62	82	78
	MPC1	49	83	29	40	23	56	83	37	50	37	45	71	30	37	27	68	94	39	61	50
	MPC2	69	92	37	51	50	72	91	47	59	57	61	84	34	44	43	80	97	45	66	65
Ta (%)	I-MPC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	MPC1	0	0	0	0	0	0	0	2	0	0	0	0	1	0	0	0	0	0	0	0
	MPC2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Tb (%)	I-MPC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	MPC1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0
	MPC2	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0

Night: from 24:00 to 08:00;
Post Prandial: 3 h after each meal, namely *Dinner* (D), *Breakfast* (B) or *Lunch* (L).

5.1. Effect of different strategies on mean glucose

As seen in Fig. 6, the mean glucose profile obtained with I-MPC is always, but the post prandial periods, characterized by values below the upper limit (140 mg/dl) of the tight target range. In fact, after each meal the mean glucose returns below 140 mg/dl before the end of the post prandial period. A similar behavior is observed with MPC2. On the contrary, with MPC1 the mean glucose profile is generally higher after meals and exceeds the upper limit of the tight target range even after the end of the postprandial period.

5.2. Glucose variability

In Fig. 6 it is seen that all strategies maintain all 100 virtual patients near the mean profile during all night, although responses are more heterogeneous after meals, where larger error bars are observed, see also the SD values corresponding to columns D, B, L in Table 1. Among the three strategies, the largest variability is observed with MPC1.

Comparing the different scenarios, it is possible to see that in Scenario 2, in which the nominal meal amount is randomly perturbed, the variability is obviously higher after the meals. Instead, in Scenario 3, in which random perturbations affect insulin sensitivity, a higher variability with respect to the nominal scenario is observed throughout the whole trial.

5.3. Time in euglycemic target range [70–180] (mg/dl)

MPC1, that does not rely on an individualized model, but only on standard clinical parameters, achieves a percentage of overall time in target ranging from 86% (Scenario 3) to 94% (Scenario 4) across the four scenarios. The most critical time window is the post-dinner one (D) especially in Scenario 3 (randomly perturbed insulin sensitivity) where percent time in target is 68%. Although these performances are to be regarded as fully satisfactory, the performance of I-MPC shows that a substantial improvement would be made possible if the correct patient model were available. Indeed, for I-MPC the overall time in target ranges from 96% (Scenario 2) to 99% (Scenario 1 and 4). The worst result is obtained in the post-dinner time window for Scenario 2, where percent time in target is 85%. Remarkably, if the correct model, which cannot be known for real patients, is surrogated by an identified individual model (strategy MPC2), a performance very close to that of I-MPC can be recovered. Indeed, for MPC2, the overall time in target ranges from 94% to 98%, the most critical time window being the post-dinner one in Scenarios 2 and 3 (time in target: 81%).

If we focus the attention on the night time-window, it is seen that all the three strategies achieve nearly optimal performances, as the percent time in target ranges from 98% to 100% across the different scenarios. On the other hand, a more demanding score of nocturnal regulation is the percent time in tight target, see below.

5.4. Time in tight target range [80–140] (mg/dl)

Without an explicit individual model, the achievement of a large percent time in the tight target range is not straightforward. In fact, for MPC1, the percent time in tight target ranges from 71% (Scenario 3) to 94% (Scenario 4). Conversely, the ideal (but not implementable) strategy I-MPC performs much better yielding a percent time ranging from 86% (Scenario 3) to 99% (Scenario 4). It is very remarkable that the practically implementable strategy MPC2 achieves excellent percent times ranging from 84% (Scenario 3) to 99% (Scenario 4).

5.5. Hyper- and hypo-glycemia

In Table 1 it is seen that all the three control strategies succeed in avoiding hyper- and hypo-glycemic episodes, above 300 and below 70 mg/dl, respectively. Indeed the percent times spent in hyper- or hypo-glycemic conditions are equal to zero in most scenarios and never greater than 2%.

The ability of the control strategies to prevent hyper- and hypoglycemic can also be assessed by examining the locations of the single patients onto the CVGA plots. In particular, patients falling in the red D region are to be regarded as critical in terms of either

hyper- or hypo-glycemic or even a mix of the two. If individual information is limited to clinical parameters (strategy MPC1), the number of critical patients ranges from 0 (Scenarios 1 and 3) to 4 (Scenario 2). Under the ideal strategy I-MPC, no critical patient is found. Finally, under the practically implementable strategy MPC2 just 2 critical patients are found in Scenario 2.

6. Conclusions

The paper has addressed two major issues. The first one is the development of feedback–feedforward MPC structure that incorporates the knowledge embedded in the conventional insulin therapy consisting of basal administration and pre-meal boluses. The second issue has to do with the individualization of the MPC regulator in order to cope with the substantial inter-individual variability observed in diabetic patients. Two implementable strategies are proposed and compared to an ideal strategy (I-MPC) that assumes perfect knowledge of individual dynamics. The simpler strategy (MPC1) does not employ any individualized model but rather achieves individualization by tuning the MPC cost function based on patient's clinical parameters. The other strategy (MPC2) relies on a low-order linear model identified from easy-to-collect individual data. The comparison is performed on four realistic scenarios representing different uncertainties and perturbations. The results show that MPC1 performs more that satisfactorily but that MPC2 may offer further improvement approaching the ideal performances achieved by I-MPC.

It is worth noting that the results of a multicenter study funded by the EC Project AP@home are expected to become available in the next months. This study uses MPC1 as control algorithm complemented with the safety supervision module described in Patek et al. (in press) that interacts with the real-time controller according to the modular architecture already recalled in the introduction. The presence of a safety module, algorithmically independent of the controller, is important for study approval and also prospectively for possible widespread adoption as clinical device.

Finally, the excellent results obtained with MPC2 suggest that in the future there might be scope for move sophisticated individualization based on system identification performed on individual data.

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