Mathematical Biosciences 257 (2014) 2–10

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

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# Model-based control of plasma glycemia: Tests on populations of virtual patients

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ARTICLE INFO

*Article history:*
Available online 16 September 2014

*Keywords:*
Artificial pancreas
Feedback control law
Time-delay systems

ABSTRACT

Closed-loop devices delivering medical treatments in an automatic fashion clearly require a thorough preliminary phase according to which the proposed control law is tested and validated as realistically as possible, before arranging *in vivo* experiments in a clinical setting. The present note develops a virtual environment aiming to validate a recently proposed model-based glucose control law on a solid simulation framework. From a theoretical viewpoint, the artificial pancreas has been designed by suitably exploiting a minimal set of delay differential equations modeling the glucose–insulin regulatory system; on the other hand, the validation platform makes use of a different, multi-compartmental model to build up a population of virtual patients. Simulations are carried out by properly addressing the available technological limits and the unavoidable uncertainties in real-time continuous glucose sensors as well as possible malfunctioning on the insulin delivery devices. The results show the robustness of the proposed control law that turns out to be efficient and extremely safe on a heterogenous population of virtual patients.



## 1. Introduction

Diabetes Mellitus is a major chronic disease that comprises a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Being definitely deficient of the endogenous pancreatic insulin release, Type 1 diabetic patients require exogenous insulin administration to survive. Another, much more prevalent form of the disease (Type 2 diabetes) is caused by a combination of resistance to insulin action and inadequate compensatory insulin secretory response. These individuals have therefore insulin resistance and usually have relative (rather than absolute) insulin deficiency.

The *Artificial Pancreas* refers to the set of glucose control strategies aiming to cope with most malfunctioning of the endogenous insulin feedback action (in Type 1 diabetes only exogenous insulin is available, while in Type 2 exogenous insulin complements pancreatic production) by means of exogenous insulin administration, usually delivered with subcutaneous or intravenous infusions. The use of intravenous insulin administration, delivered by automatic, variable speed pumps under the direct supervision of a physician, provides a wider range of possible strategies with respect to the subcutaneous route, and ensures a rapid delivery with negligible delays. As a matter of fact, control algorithms based on intravenous infusions (we can cite, among the others, [29,31,4,6,15,14,25]) are directly applicable so far only to problems of glycemia stabilization in critically ill subjects, such as in surgical Intensive Care Units after major procedures, [33].

In the present paper a virtual environment is developed, aiming to test and validate a recently proposed model-based glucose control law. Closed-loop algorithms for the artificial pancreas can be designed according to a "model-based" or to a "model-less" approach, see e.g. [3]. The former approach properly exploits the chosen mathematical structure of the glucose–insulin system, thus allowing to face the control problem from a mathematical viewpoint. To this aim, small-scale "minimal models", according to which closed-loop control strategies can be found in the literature, are usually preferred (see, e.g. [6,13,25]). Unfortunately, a model-based approach cannot exploit the mathematical structure of a, presumably more realistic, multi-compartmental "maximal model" because of its complexity, unless deciding to make linearization, discretization or model reduction. On the other hand model-less approaches allow to consider "maximal models" straightforwardly

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http://dx.doi.org/10.1016/j.mbs.2014.09.003
0025-5564/

as virtual patients themselves: the control law is designed by means of optimization algorithms implemented accounting for the input–output time-courses provided by the model, but we give up the opportunity to make proofs of the closed-loop theoretical validity of the chosen insulin infusion therapy. In this framework there can be cited, among the others, [29,11,31,4,20,18,15,14,17]. The present paper aims to bridge the two approaches providing a virtual environment (built up according to a population of virtual patients generated by a "maximal model") to a model-based control strategy synthesized according to a "minimal model". To this end, we make a specific choice (from the recent literature) for both the model-based control law and the "maximal model" of the virtual patients. However, in principle, the philosophy of the paper can be applied to any model-based control law, according to virtual patients generated by any "maximal model".

The model-based control law to be validated in the proposed virtual algorithm has been presented by the authors in the recent literature by suitably exploiting a Delay Differential Equation (DDE) model of the glucose–insulin system [25]. In [25] it has been mathematically proven that the system described by such a DDE model can be controlled to track a desired glucose profile in order to reduce a hyperglycemic basal state down to a safe euglycemic level by means of glucose measurements only, and that such a safe basal level for the closed loop system is asymptotically stable. Differently from other closed-loop approaches, which make use of Ordinary Differential Equation (ODE) models of the glucose–insulin system to design the feedback control law according to many different control strategies (see, e.g. Model Predictive Control in [11,18], Parametric Programming in [6], $H_\infty$ control in [29,15,14], non-standard $H_\infty$ control in [4,31]), a DDE model-based control law is able to take into account irregularly varying pancreatic Insulin Delivery Rate (IDR) (see e.g. [19] and references therein), thus allowing the construction of a control scheme also applicable to Type 2 diabetic patients. Despite the great spread of DDE models of the glucose–insulin system in the last decade, their use in the field of the artificial pancreas has only recently sparked interest, mainly limited to open-loop approaches (see [12] and references therein). Indeed, attempts to design closed-loop ODE model-based glucose controls have been limited so far to Type 1 diabetic patients (who have essentially no endogenous insulin production), circumventing in this way the need to model pancreatic IDR. The DDE model here considered can realistically account for endogenous IDR, thereby modeling in a unified fashion healthy subjects, insulin resistant and insulin-deficient diabetic patients.

The large-scale mathematical model of the virtual patient used in the present work [5] has been chosen because of its widespread use in this field: indeed, a computer simulator of diabetic patients based on this extended model has been the first of its kind to be accepted by the *Food and Drug Administration (FDA)* as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas [16].

The novel contribution of the present work is the construction of the virtual environment making it possible to evaluate whether a model-based theoretical control law, designed according to a parsimonious or compact model of the glucose insulin system, is robust enough to ensure high levels of safety and efficacy also when closed onto a different, multi-compartmental (presumably more realistic) model, in spite of the many unavoidable sources of uncertainties pertaining to a real-time closed-loop setting. A pivotal role in building up the *in silico* environment is played by the identification procedure, necessary to make the two models consistent with each other. This task is accomplished by considering a virtual Intra-Venous Glucose Tolerance Test (IVGTT) generated by the *Average Virtual Patient (AVP)* representative of a population of virtual patients, and by fitting the compact model parameters on the glucose–insulin evolutions given by the AVP. The model-based control law [25] is synthesized by suitably exploiting the identified compact model parameters: to this end the control parameters are tuned by simulations of the compact model, in the same way as it should be done for individualized insulin therapy before applying the control law to a real patient. In this way a fixed, unique insulin infusion therapy scheme is designed, to be administered to a population of virtual patients generated by properly varying the AVP parameters. Uncertainties in blood glucose measurements, as well as malfunctioning of the insulin delivery devices are considered, consistently with current technology, in order to obtain an effective benchmark for the closed-loop control and to show in fact the robustness of the proposed approach. Safety and efficacy criteria will be adopted in order to stress the robustness of the control methodology with respect to a rather heterogeneous population of virtual patients, according to recent literature [2]. A preliminary version of the paper has been presented in [26].

## 2. Material and methods

The basic idea of the paper is to use a simplified (though accurate) model of the glucose–insulin system to synthesize a model-based glucose control law, and to use a different, more exhaustive, comprehensive model to test the control law on a rather heterogenous population of virtual patients. This idea is developed in this section in two steps: the former is devoted to briefly recap the feedback control scheme adopted for the exogenous insulin administration; the latter deals with the development of the virtual environment in details.

### 2.1. The model-based control law

The insulin infusion therapy under investigation is the one recently published in [25], whose design principles make use of the following DDE mathematical model of the glucose–insulin system, [22,28]. The equations are written with respect to plasma glycemia, $G(t)$, [mM], and insulinemia, $I(t)$, [pM]:

$$\begin{aligned}\frac{dG(t)}{dt} &= -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G},\\ \frac{dI(t)}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g)) + \frac{u(t)}{V_I},\end{aligned} \tag{1}$$

with $K_{xgi}$, [$\mathrm{min}^{-1}\,\mathrm{pM}^{-1}$], the rate of (insulin-dependent) glucose uptake by tissues per pM of plasma insulin concentration; $T_{gh}$, [(mmol/kg BW)/min], the net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake; $V_G$, $V_I$, [L/kg BW], the apparent distribution volumes for glucose and insulin, respectively; $K_{xi}$, [$\mathrm{min}^{-1}$], the apparent first-order disappearance rate constant for insulin; $T_{iGmax}$, [(pmol/kg BW)/min], the maximum rate of second-phase insulin release; $\tau_g$, [min], the apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations.

The nonlinear map $f(\cdot)$ models the endogenous pancreatic insulin delivery rate as:

$$f(G) = \frac{(G/G^*)^\gamma}{1+(G/G^*)^\gamma}, \tag{2}$$

where $\gamma$ is the progressivity with which the pancreas reacts to circulating glucose concentrations and $G^*$, [mM], is the glycemia at which the insulin release is half of its maximum rate.

The signal $u(t)$, [(pmol/kg BW)/min], is the control input, i.e. the exogenous insulin delivery rate.

The subject is supposed to be at rest before the insulin therapy starts, so that the initial conditions are equal to the constant, hyperglycemics basal levels $(G_b, I_b)$:

$$G(\tau) = G_b, \quad I(\tau) = I_b, \quad \tau \in [-\tau_g, 0]. \tag{3}$$

It has to be stressed that model (1) may represent equally well healthy subjects and insulin-resistant or severely insulin-deficient diabetic patients, by appropriately changing the parameter values. Moreover, it does belong to the class of "minimal models", in the sense that according to a "minimal" set of independent parameters, it allows to very well resemble the physiology of the glucose/insulin kinetics, and it is identifiable from data with very good precision, according to IVGTT standard perturbation experiments (see [28,27]).

The adopted control strategy is to reduce the high basal plasma glucose concentration $G_b$ down to a lower level, according to a smooth reference glucose trajectory $G_{\mathrm{ref}}(t)$, by means of intravenous insulin administration. To this aim, the input–output feedback linearization with delay cancelation has been applied in [25], with respect to the output $y(t) = G(t)$ and the input $u(t)$ (see also [9,21,24]). The real-time control law makes use of only glucose measurements, according to a state observer for time-delay systems (see [8,10]) that allows to estimate the plasma insulin concentration, whose measurements are known to be slower and more cumbersome to obtain, more expensive and also less accurate than glucose measurements. In summary, denoting with $\widehat{G}(t)$, $\widehat{I}(t)$ the glucose and insulin estimates, the regulator is given by:

$$\frac{u(t)}{V_I} = \frac{S(\widehat{G}(t), \widehat{I}(t), \widehat{G}(t-\tau_g)) - v(t)}{K_{xgi}\widehat{G}(t)}, \quad t \geqslant 0, \tag{4}$$

where

$$S(\widehat{G}(t), \widehat{I}(t), \widehat{G}(t-\tau_g)) = -K_{xgi}\widehat{I}(t)\left(-K_{xgi}\widehat{I}(t)\widehat{G}(t) + \frac{T_{gh}}{V_G}\right) - K_{xgi}\widehat{G}(t)\left(-K_{xi}\widehat{I}(t) + \frac{T_{iGmax}}{V_I} f\left(\widehat{G}(t-\tau_g)\right)\right) \tag{5}$$

and $v(t) = \ddot{G}_{\mathrm{ref}}(t) + R\hat{e}(t)$ with matrix $R \in \mathbb{R}^{1\times 2}$ designed to ensure that

$$H = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} R \tag{6}$$

is Hurwitz with prescribed eigenvalues in the left half complex plane. The target error $\hat{e}(t)$ is defined by $\hat{e}(t) = \widehat{Z}(t) - Z_{\mathrm{ref}}(t)$, with:

$$\widehat{Z}(t) = \begin{bmatrix} \hat{z}_1(t) \\ \hat{z}_2(t) \end{bmatrix} = \begin{bmatrix} \widehat{G}(t) \\ -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \frac{T_{gh}}{V_G} \end{bmatrix}, \tag{7}$$

and

$$Z_{\mathrm{ref}}(t) = \begin{bmatrix} G_{\mathrm{ref}}(t) \\ \dot{G}_{\mathrm{ref}}(t) \end{bmatrix}. \tag{8}$$

Finally, the state estimates for $\widehat{G}(t)$ and $\widehat{I}(t)$ obey the following equations for $t \geqslant 0$:

$$\begin{bmatrix} d\widehat{G}/dt \\ d\widehat{I}/dt \end{bmatrix} = \begin{bmatrix} -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \frac{T_{gh}}{V_G} \\ -K_{xi}\widehat{I}(t) + \frac{T_{iGmax}}{V_I} f\left(\widehat{G}(t-\tau_g)\right) + \frac{u(t)}{V_I} \end{bmatrix} + Q^{-1}(\widehat{G}(t), \widehat{I}(t))W(G(t) - \widehat{G}(t)), \tag{9}$$

where $Q^{-1}$ is the inverse matrix of the matrix function $Q(x_1, x_2) \in \mathbb{R}^{2\times 2}$ defined as:

$$Q(x_1, x_2) = \begin{bmatrix} 1 & 0 \\ -K_{xgi}x_2 & -K_{xgi}x_1 \end{bmatrix}, \tag{10}$$

and the observer gain matrix $W \in \mathbb{R}^{2\times 1}$ is designed to ensure that

$$\widehat{H} = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} - W[1 \quad 0] \tag{11}$$

is Hurwitz with prescribed eigenvalues in the left half complex plane. The initial conditions for (9) are formally given by:

$$\widehat{G}(\tau) = \widehat{G}_0(\tau), \quad \widehat{I}(\tau) = \widehat{I}_0(\tau), \quad \tau \in [-\tau_g, 0], \tag{12}$$

According to [25] and references therein, it comes that the observer can be designed such that, if the estimation error at zero is sufficiently small, the estimation error converges exponentially to zero, with arbitrary decay rate fixed by means of a suitable choice of $W$. Moreover, in [25] it has been proven that there exist gains $R$ and $W$ such that, for the closed-loop system (1), (9), (4), the plasma glycemia is controlled to track the reference trajectory, with the error tracking asymptotically converging to zero, provided that the initial tracking and observer errors are suitably small.

### 2.2. The virtual environment

The virtual environment is built up according to the following steps:

(a) define an Average Virtual Patient (AVP), according to a large scale multi-compartmental model;
(b) identify the best-fitting small-scale or compact model for the AVP in order to make the two models consistent one each other;
(c) synthesize the glucose control law for the chosen compact model;
(d) generate a population of Virtual Patients (VPs) by randomly drawing the large-scale model parameters;
(e) define a set of quantitative criteria according to which evaluate the performances of the chosen control law when applied to the population of VPs.

#### 2.2.1. The Average Virtual Patient (AVP)

The AVP aims to model in detail the glucose/insulin dynamics of an average subject, representative of the population under investigation. The chosen model for the AVP consists of a 12th order ODE system with about 30 parameters [5], accounting for insulin-dependent and insulin-independent glucose uptake in the tissues as well as for renal extraction and endogenous glucose production; it incorporates a two-compartment subsystem for insulin kinetics (detailing the pancreatic insulin production and the degradation in the liver and the peripheral tissues), and a three-compartment subsystem for the gastro-intestinal tract. For the purposes of the present paper, the AVP is representative for a Type 2 diabetic patient, identified by the parameters taken from Table I of [5], whose corresponding basal glycemia and insulinemia are $G_b = 8.85$ mM and $I_b = 59.85$ pM. Refer to [5] and references therein for details of the construction of the model. In principle, any comprehensive model can be chosen to validate the proposed control law (e.g. [32]). The motivations of the present choice of large-scale model, as stated before, is that it has been recently accepted by the *Food and Drug Administration (FDA)* as an alternative to animal trials for preclinical testing of control strategies in artificial pancreas [16].

#### 2.2.2. Small-scale model identification

The model-based control law is designed to regulate the hyperglycemic state of the AVP: as a matter of fact, the compact DDE model is required to *match* the large-scale ODE model of the AVP. This means that we need to identify the DDE model parameters that best fit the AVP. It is a preliminary step similar to what can be imagined (in the future) for a personalized insulin therapy: the model exploited to synthesize the control law needs to be tailored to the patient (real or virtual). To this end, a virtual IVGTT experiment is simulated on the AVP: the experiment consists in administering intra-venously a glucose bolus $D_g$ after an overnight

fast and then sampling plasma glucose and serum insulin concentration during the following 3 h. The bolus administration at time $t = 0$ produces an instantaneous increase of both plasma glucose and insulin concentration (first phase of insulin release, see e.g. [1]), so that:

$$G(0) = G_b + \frac{D_g}{V_G}, \quad I(0) = I_b + I_\Delta \frac{D_g}{V_G}, \tag{13}$$

with $I_\Delta$ a further parameter to be estimated. The bolus $D_g$ is fixed to 265 mg/kg BW, and blood samples are acquired every 2 min for the first 10-min interval, every 5 min for the next 30-min interval, every 10 min for the next 20-min interval and finally every 20 min for the last 120-min interval (an overall sampling period of 3 h). Glycemia and insulinemia measurements are supposed to be affected by a Gaussian random noise with Coefficients of Variation (CVs) fixed at 1.5% for glycemia and 7% for insulinemia, to reflect unmodeled measurement errors [1].

The identification task is performed by Generalized Least Square method [28]. The basal values of glycemia and insulinemia, $G_b$ and $I_b$, enter the identification scheme as covariates, and are supposed to be measured before the experiments. We introduce a measurement noise for $G_b$ and $I_b$ as well. Indeed, for the simulations reported here we adopted the values $G_b = 8.45$ mM and $I_b = 47.85$ pM (a displacement from the true values of about 4.5% and 20%, respectively). It has to be stressed that this source of uncertainty directly affects the design of the control law, for instance in terms of the reference signal $G_{\text{ref}}$, which is built by means of the measured basal glycemia, as it will be clearer in the following subsection.

As far as the other model parameters, $V_I = 0.25$ L/kg BW and $G^\star = 9$ mM are fixed by the investigator and kept constant, $V_G$, $\tau_g$, $K_{xgi}$, $K_{xi}$, $\gamma$, $I_\Delta$ are free model parameters to be estimated and $T_{iGmax}$, $T_{gh}$ are determined from the other parameters according to the algebraic steady-state conditions.

Fig. 1 shows the DDE model fitting (continuous red line) for a set of noisy data (blue dots) coming from the AVP, with the estimated DDE model parameters reported in Table 1. In order to assess the impact of the noisy measurements on the identification procedure we repeated many times the virtual IVGTT to the same AVP according to different time-courses of the noisy glucose–insulin measurements. The results showed a very low variability of the estimated DDE-model parameters (with CVs smaller than 2.5% on a set of 100 runs), thus supporting the robustness of the AVP fitting.

These values are characteristic of the frank clinical picture of Type 2 Diabetes Mellitus. This subject presents with a decreased insulin sensitivity, which however would not be incompatible with maintained glycemic levels, were pancreatic insulin secretion able to compensate by increasing sufficiently. Conversely, basal insulin levels are relatively normal, which, in the face of markedly increased fasting glycemia, denotes a secretory insufficiency. In this context, low insulin sensitivity ($K_{xgi}$) is an indicator of the likely previous history of the subject, being a prime determinant of the development of glucose toxicity and eventual derangement of glucose homeostatic control. It is to be expected that the further evolution of this subject would be marked by progressively accelerating decrease of fasting insulinemia and increase of fasting glycemia, unless adequate pharmacological therapy is administered.

### 2.2.3. Synthesis of the glucose control law

A preliminary step to the design of the control law is the choice of the reference glucose trajectory to be tracked. This step involves the knowledge of the basal glycemia, since we design the reference glycemia as a (possibly) smooth signal, decreasing from the actual hyperglycemic state down to a desired healthy value $G_d$:

$$G_{\text{ref}}(t) = G_d + (G_b - G_d) \cdot e^{-t/T} \tag{14}$$

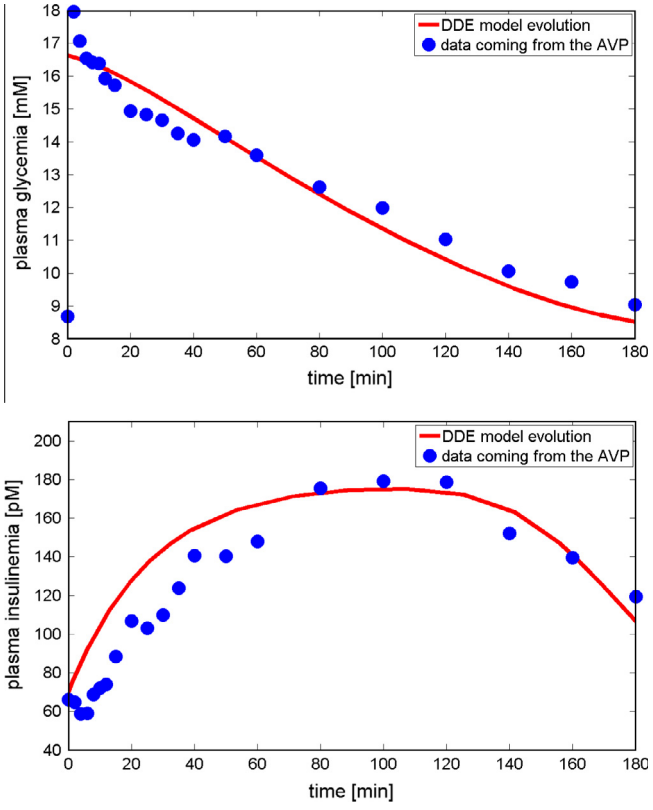


**Fig. 1.** Plasma glucose (upper panel) and insulin (lower panel) concentration best fitting for the DDE model applied to the AVP.

**Table 1**
DDE model parameters fitting the AVP.

| | | |
|---|---|---|
| $V_G$ | 0.18 | L/kg BW |
| $\tau_g$ | 6.5 | min |
| $K_{xgi}$ | $3.15 \times 10^{-5}$ | $\text{min}^{-1}\ \text{pM}^{-1}$ |
| $K_{xi}$ | 0.038 | $\text{min}^{-1}$ |
| $\gamma$ | 15.92 | – |
| $T_{iGmax}$ | 1.695 | $\text{min}^{-1}$(pmol/kg BW) |
| $T_{gh}$ | 0.0023 | $\text{min}^{-1}$(mmol/kg BW) |

Here $G_d$ has been fixed at 5 mM, while $G_b = 8.45$ mM is the noisy glycemia, also used in the virtual IVGTT. The positive real $T$ is the exponential time-constant, set equal to 30 min.

The control parameters are given by the eigenvalues of matrices $H$ and $\widehat{H}$ in (6)–(11), according to which the control gains $R$ and $W$ are readily designed by methods of basic control theory. The choice of the eigenvalues is guided by both theoretical results and numerical simulations. The theory hinges on the observer-based feedback linearization with delay cancelation (see [25] and references therein), which ensures the local convergence of the tracking error to zero. However, the theory does not take into account further requirements of paramount importance in the medical framework. One such requirement is the avoidance of negative insulin release (the theory is developed without sign constraints on the control input): in this case the regulator would temporarily switch off, leaving the patient without control for an unpredictable period. This is clearly an undesirable situation, to be avoided. Another important requirement is to prevent glucose oscillations, possibly determining dangerous hypoglycemia. Both these issues need to be addressed in the setting of the control parameters, as well as

in the setting of the reference glucose trajectory, realizing a trade-off between closed-loop fast asymptotic stability (suitably negative real part eigenvalues) and transient behavior (possibly smooth trajectories without oscillations). This goal is achieved by running simulations closing the loop on the DDE model itself (not on the AVP), since the regulator needs to be tuned and checked *in silico* before being applied on a real/virtual patient. In fact simulations closing the loop on the compact model itself are exploited in the design of the control law, instead of in its test and validation.

Below, the chosen control parameters (eigenvalues $\lambda$ of matrices $H$ and $\widehat{H}$) are reported:

$$\lambda(H) = \{-0.15, -0.06\}, \quad \lambda(\widehat{H}) = \{-0.1, -0.4\}. \tag{15}$$

As a further remark, we need also to properly address limitations for the control input to avoid it becomes unfeasible large. In our simulations the control input never exceeds 40 pmol/kg BW/min, which corresponds, for an average person of 70 kg BW, to 2800 pmol/min. On the other hand, the standard literature on artificial pancreas reports a limit of 4U/h for the insulin infusion rate (see e.g. [2]), corresponding to about 466 pmol/min. As a matter of fact, this bound may well be overcome in our simulations. However, though approximately six times larger than the ones usually employed in anti-diabetic therapy, the rates of insulin infusion coming from the proposed simulations are not unheard of: different high-dose insulin protocols have been employed in the treatment of severe beta-blocker and calcium channel-blocker poisoning with insulin infusion ranges up to 22U/kg BW/h (about 180,000 pmol/min), [7], a much larger upper bound than the one suggested by simulations.

#### 2.2.4. Population of VPs

Each individual of the population of VPs is obtained by randomly sampling the large-scale model parameters, according to a log-normal distribution with average values given by the AVP parameters. Different setting of the CVs will provide different types of populations. For the simulations here proposed we have set all the CVs at 5%, thus obtaining a rather heterogeneous population of Type 2 diabetic patients. Basal glycemia and insulinemia are computed by means of the steady-state constraints. As a matter of fact, the patient characteristic can change so much that the resulting subject may not be a diabetic patient any more. Since the working hypothesis is to build up a population of Type 2 diabetic patients, only virtual patients with a resulting basal glycemia of at least 6.5 mM have been considered.

### 2.3. The feedback control scheme

The feedback control scheme further accounts for a couple of important features that emerge when dealing with real-time devices involving continuous glucose sensors and insulin pumps. Indeed, the former provide quite reliable measurements of plasma glycemia at given sample times, whose frequency is limited by the time needed to analyze plasma glucose on a bed-side analyzer, [2]; the latter are used to administer insulin by means of piecewise-constant infusions. Therefore, in order to make the simulations performed on the population of VPs more realistic, both of these technical assumptions will be addressed. To this end, let $\Delta$ be the sampling period, according to which the glucose measurements are acquired at times $t = k\Delta$, and constant insulin infusion rates are administered, during intervals $[k\Delta, (k+1)\Delta), k = 0, 1, \ldots$. The numerical algorithm is then as follows.

**Algorithm**

1. at time $k\Delta$ the measurement of $G(k\Delta)$ is delivered by the sensor;
2. at time $k\Delta$ the control input is computed by means of the available state estimates $\widehat{G}(k\Delta)$, $\widehat{G}(k\Delta - \tau_g)$, $\widehat{I}(k\Delta)$, see (4):
$$\frac{u(k\Delta)}{V_I} = \frac{S(\widehat{G}(k\Delta), \widehat{I}(k\Delta), \widehat{G}(k\Delta - \tau_g)) - v(k\Delta)}{K_{xgi}\widehat{G}(k\Delta)}; \tag{16}$$
if $u(k\Delta) < 0$, then $u(k\Delta)$ is forced to 0;
3. the constant infusion $u(k\Delta)$ is administered to the patient in the time interval $[k\Delta, (k+1)\Delta)$;
4. simultaneously with item [3], the controller device integrates numerically the following equation, see (9), in the time interval $[k\Delta, (k+1)\Delta]$, using the available measurement $G(k\Delta)$:
$$\begin{bmatrix} \frac{d\widehat{G}}{dt} \\ \frac{d\widehat{I}}{dt} \end{bmatrix} = \begin{bmatrix} -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \frac{T_{gh}}{V_G} \\ -K_{xi}\widehat{I}(t) + \frac{T_{iGmax}}{V_I} f(\widehat{G}(t - \tau_g)) + \frac{u(k\Delta)}{V_I} \end{bmatrix} + Q^{-1}(\widehat{G}(t), \widehat{I}(t)) W (G(k\Delta) - \widehat{G}(k\Delta)); \tag{17}$$
5. the value of $k$ is incremented by 1.

Simulations have been carried out according to a couple of sampling period choices: one finer, $\Delta = 5$ min, the other courser, $\Delta = 15$ min. To build up a virtual environment, the sampling period is fundamental, since it provides the available time to compute the measurements from real-time sensors adopted for Continuous Glucose Monitoring. Both the adopted sampling periods have been exploited in previous literature (e.g. $\Delta = 5$ min in [30,6,20], and $\Delta = 15$ min in [11,18]).

Glucose measurement errors and insulin pump malfunctioning have also been considered. More in details, if $G(k\Delta)$ is the real plasma glycemia at sampling time $k\Delta$, the controller actually exploits the noisy measurement $G_m(k\Delta)$ with

$$G_m(k\Delta) = G(k\Delta) + C_g G(k\Delta) N_k, \tag{18}$$

where $N_k$ is a sequence of independent, zero-mean Gaussian random variables with unitary variance, and $C_g$ is the coefficient of variation, assumed equal to 5%. Analogously, if $u(k\Delta)$ is the real control input synthesized by the regulator at sampling time $k\Delta$, the controller actually delivers the noisy value $u_m(k\Delta)$ with

$$u_m(k\Delta) = u(k\Delta) + C_u u(k\Delta) M_k, \tag{19}$$

where $M_k$ is a sequence of independent, zero-mean Gaussian random variables with unitary variance, and $C_u$ is the coefficient of variation, assumed equal to 15%. The above mentioned values for CVs have been taken after reference [2].

## 3. Results and discussion

Simulations performed by closing the loop on the AVP are reported in Fig. 2 for $\Delta = 5$ min, on a time horizon of 6 h. Despite the many errors affecting the basal values, the measured glycemias, the input actuator and the discretization of the regulator, a reasonable (<6 mM) normo-glycemia is definitely reached within 120 min, with no episodes of hypoglycemia. Notice that, due to a non-trivial discretization time, there is a non-negligible portion (about 35%) of the simulation period during which the control law is switched off. The apparently very good performances are partially related to the fact that the control law has been somehow tailored for the AVP. The next question is: what happens if the

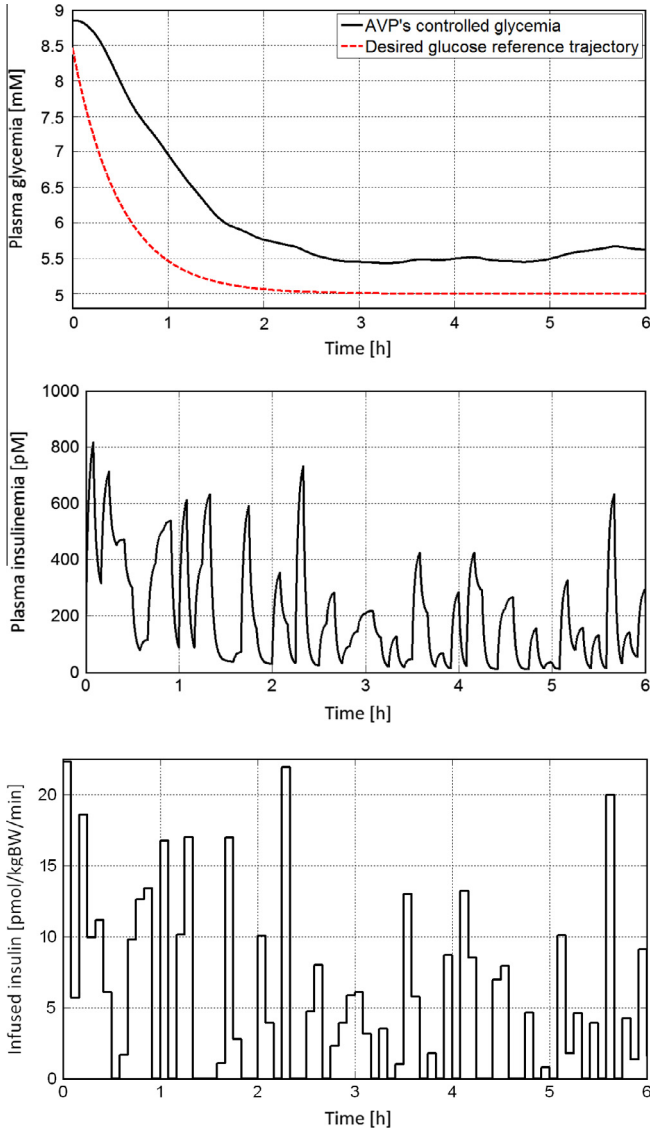


**Fig. 2.** Upper panel: AVP's controlled glycemia; middle panel: AVP's plasma insulinemia; bottom panel: AVP's applied control input. $\Delta = 5$ min.

same insulin infusion therapy is administered to a different individual?

To answer this question the control law will be closed on each individual of the generated population of VPs, and evaluated according to preliminarily established criteria. Two set-ups have been considered. The first consists of a patient at rest, to whom the proposed insulin therapy is provided without any disturbance such as meal or other oral glucose ingestion. The second consists of a patient under examination within a 24 h scenario, during which three meals are delivered (breakfast at 8 a.m. with 45 g of glucose, lunch at 12 a.m. and dinner at 8 p.m. both with 70 g of glucose). Within this second set-up, the control law is applied at time $t = 0$ h so that when the first meal is administered (at time $t = 8$ h) the patient is expected to be at the steady-state of the closed-loop control.

### 3.1. Safety/efficiency criteria for a patient at rest

The utility criteria chosen in order to check whether the proposed control law is sufficiently safe and provides efficient results with respect to the population of VPs are inspired by [2] and are the following. As far as *safety criteria*, the control law applied to a single VP could cause:

- *severe hypoglycemia*, when plasma glycemia falls to 2 mM or lower, within the simulation period;
- *hypoglycemia*, when plasma glycemia falls to 3.3 mM or lower, but always remains above 2 mM, within the simulation period.

A set of simulations is then said to provide *excellent safety* if neither hypoglycemia nor severe hypoglycemia occur; it provides *good safety* if less than 5% of simulations show hypoglycemia, with no cases of severe hypoglycemia; it provides *satisfactory safety* if less than 20% of simulations show hypoglycemia, with no cases of severe hypoglycemia. In any other case the simulation is *unsafe*.

As far as *efficacy*, the control law applied to a single fasting state virtual patient may provide:

- *excellent efficacy*, when plasma glycemia is constrained below 6 mM within the first 3 h of treatment;
- *good efficacy*, when plasma glycemia is constrained below 7 mM (but not below 6 mM) within the first 3 h of treatment;
- *satisfactory efficacy*, when plasma glycemia is constrained below 8 mM (but not below 7 mM) within the first 3 h of treatment;
- *unsatisfactory efficacy*, when plasma glycemia is not constrained below 8 mM within the first 3 h of treatment.

This efficacy criterion is equivalent to assign a label (excellent/good/satisfactory/unsatisfactory) to a VP of the population. Another possibility is to assign a fraction of each label to the VP, given by the percentage of VP's glycemia samples that comply with the excellent/good/satisfactory/unsatisfactory efficacy. For instance, a VP simulation could provide 0.85 of excellent efficacy if 85% of the glucose samples after the first 3 h is constrained below 6 mM, and 0.15 of good efficacy if 15% of the glucose samples after the first 3 h is constrained within 6 mM and 7 mM. Of course, the fractions sum up to 1 for each VP. In the following, the former efficacy criterion will be referred to as the *label efficacy criterion*, whilst the latter efficacy criterion will be referred to as the *fractional efficacy criterion*.

### 3.2. Safety/efficiency criteria for a 24 h simulation, including meals

The safety criteria are the same adopted for the patient at rest. Efficacy is evaluated taking into account what happens after the first 2 h of glucose administration (post-prandial glycemia) [2]. To this aim, for each VP we can obtain:

- *excellent efficacy* when, for each meal, within 2 h from the meal administration and during the period before the successive meal, glycemia is constrained below 8 mM;
- *satisfactory efficacy* when excellent efficacy fails but, for each meal, within the 2 h from the meal administration and during the period before the successive meal, glycemia is constrained below 11 mM;
- *unsatisfactory efficacy* when, at least for one meal, after the 2 h from the meal administration, glycemia is not constrained below 11 mM.

Both label/fractional efficacy criteria are considered.

### 3.3. Data analysis and discussion

According to the safety/efficiency criteria adopted to validate the feedback control law on the population of VPs, each individual

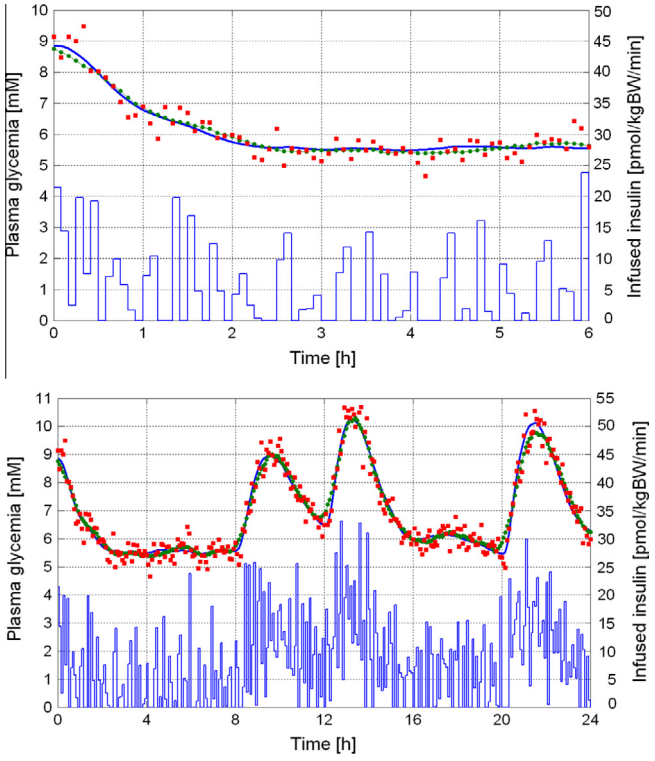


**Fig. 3.** Plasma glycemia (*Y*-axis on the left) and insulin infusion rate (*Y*-axis on the right) for a VP during the first 6 h (no meals, upper panel) of closed-loop control, and during the whole 24 h (lower panel) of the virtual experiment. Red squares are the noisy glucose samples, green circles are the 13-points moving average glucose samples, blue continuous line is the VP controlled glycemia, and the piecewise-constant line is the control input. Sampling period $\Delta = 5$ min. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

simulation is required to provide plasma glucose measurements. It is assumed to have sampled noisy measurements in the same way as the control law uses real-time discrete glucose samples to determine the insulin infusion therapy. A useful way to filter out this kind of noise is to consider a finite length moving average so that criteria established in Sections 3.1 and 3.2 are applied to an *M*-points moving average of the noisy sampled glucose measurements. Fig. 3 shows the quality of the moving average estimate of the original plasma glycemia on a VP, compared with the original plasma glycemia produced by the simulations.

Results related to the control law applied on a population of 10,000 VPs in fasting state (no meals) showed excellent safety (no cases of hypoglycemia) and overall good efficacy results for both $\Delta = 5$ min and $\Delta = 15$ min, Table 2. Indeed, by applying the label efficacy criterion, more than 99% of patients were regulated below 7 mM, a threshold proposed by the World Health Organization for the diagnosis of impaired glucose tolerance, and more than 64% of patients (*excellent efficacy*) resulted to be controlled in a fashion comparable to that of healthy subjects (see [2] and references therein). The efficacy results clearly improve when the fractional efficacy criterion is adopted, with the percentages obtained as the average values of the fractional efficacies showed by each VP. It worths notice that these results are very robust in spite of the different sampling times.

**Table 2**
Label and fractional efficacy results on a population of fasting 10,000 VPs.

| Efficacy | Δ (min) | Label (%) | Fractional (%) |
|---|---|---|---|
| Excellent | 5 | 69.37 | 93.16 |
| Good | 5 | 30.47 | 6.83 |
| Satisfactory | 5 | 0.16 | 0.01 |
| Unsatisfactory | 5 | 0.00 | 0.00 |
| Excellent | 15 | 65.69 | 94.37 |
| Good | 15 | 34.29 | 5.63 |
| Satisfactory | 15 | 0.02 | 0.00 |
| Unsatisfactory | 15 | 0.00 | 0.00 |

**Table 3**
Label and fractional efficacy results on population of 10,000 VPs, during meals administration.

| Efficacy | Δ (min) | Label (%) | Fractional (%) |
|---|---|---|---|
| Excellent | 5 | 5.07 | 83.72 |
| Satisfactory | 5 | 92.47 | 16.22 |
| Unsatisfactory | 5 | 2.46 | 0.06 |
| Excellent | 15 | 2.85 | 82.82 |
| Satisfactory | 15 | 92.63 | 17.03 |
| Unsatisfactory | 15 | 4.52 | 0.15 |

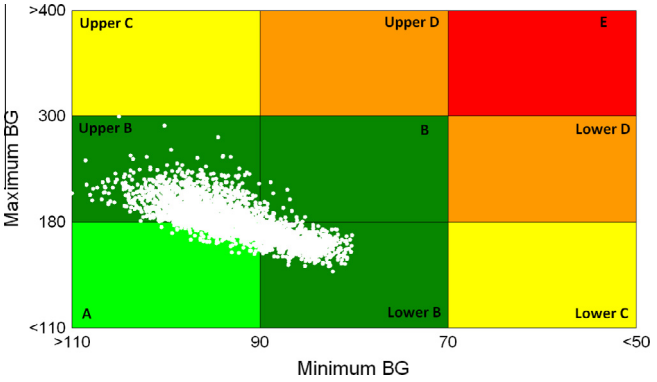


**Fig. 4.** Control-variability grid of the control law action on a population of 3000 feeded VPs. $\Delta = 5$ min.

Results related to the control law applied on a population of 10,000 VPs on a 24-h period, during meals, showed as well excellent safety (no hypoglycemia cases) but only overall label satisfactory efficacy, with a small percentage of excellent results (about 5% for $\Delta = 5$ min and less than 3% for $\Delta = 15$ min), as shown in Table 3. However, efficacy results dramatically improve when the fractional efficacy criterion is considered because, apparently, only few glucose samples exceed the threshold of 8 mM two hours after

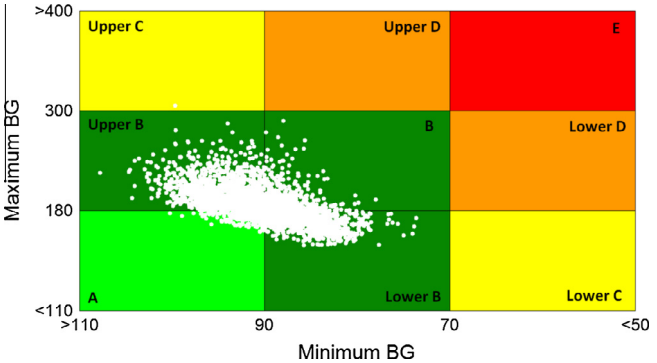


**Fig. 5.** Control-variability grid of the control law action on a population of 3000 feeded VPs. $\Delta = 15$ min.

**Table 4**
Control-variability grid results on a population of 3000 VPs

| Grid zone | $\Delta = 5$ min (%) | $\Delta = 15$ min (%) |
|---|---|---|
| A | 20.97 | 8.33 |
| B | 1.47 | 15.80 |
| Upper B | 49.13 | 46.17 |
| Lower B | 28.40 | 29.67 |
| Upper C | 0.00 | 0.03 |
| Lower C | 0.00 | 0.00 |
| Upper D | 0.00 | 0.00 |
| Lower D | 0.00 | 0.00 |
| E | 0.00 | 0.00 |

the meal administration. Also in this case, results are fairly robust with respect to the choice of the sampling time.

A further evaluation of the efficacy of closed-loop glucose regulation on feeding patients was conducted using the control-variability grid analysis [18]. The grid allows us to visualize the largest glucose excursions produced by a control algorithm in a group of subjects, each subject being represented by one data point for any observation period. The data point is obtained by plotting the minimum (reversed $X$-axis) and maximum ($Y$-axis) blood glucose values within the considered time period. The grid is divided in nine square zones in order to classify the controller's performances as follow:

–*A*: accurate control;
–*Lower B*: benign deviations into hypoglycemia;
–*B*: benign control deviations;
–*Upper B*: benign deviations into hyperglycemia;
–*Lower C*: over-correction of hyperglycemia;
–*Upper C*: over-correction of hypoglycemia;
–*Lower D*: failure to deal with hypoglycemia;
–*Upper D*: failure to deal with hyperglycemia;
–*E*: erroneous control.

Here we present a couple of grids, both made on 3000 VPs, one associated to the sampling time $\Delta = 5$ min, the other to the sampling time $\Delta = 15$ min, Figs. 4 and 5 respectively. The good performance of the proposed control law can be clearly appreciated, since almost all points belong to the safe green zone in both cases. More details are summarized in Table 4.

## 4. Conclusion

In the present work a virtual environment is set up in order to test a DDE-model-based glucose control law at a very realistic level of detail, consistent with the available technology of glucose sensors and insulin pump actuators. The control law is evaluated by closing the loop on a population of virtual patients, generated by a model recently accepted by the *Food and Drug Administration (FDA)* as an alternative to animal trials for the preclinical testing of control strategies in artificial pancreas.

Because of the intra-venous administration of the insulin therapy, the clinical application of the control algorithm presented in this work relates to the somewhat niche problem of glycemia stabilization in critically ill subjects, such as can be found in surgical Intensive Care Units after major procedures. However, because of the robustness of the method as demonstrated by the simulations reported here, extensions of the basic DDE-model could directly lead to the application in wider contexts, such as insulin administration by means of subcutaneous infusions. Preliminary results in this direction are extremely promising, and have recently been presented in [23].

## References


[1] R.N. Bergman, Y.Z. Ider, C.R. Bowden, C. Cobelli, Quantitative estimation of insulin sensitivity, Am. J. Physiol. 236 (1979) 667–677.
[2] L.J. Chassin, M.E. Wilinska, R. Hovorka, Evaluation of glucose controllers in virtual environment: methodology and sample application, Artif. Intell. Med. 32 (2004) 171–181.
[3] F. Chee, T. Fernando, Closed Loop Control of Blood Glucose, Heidelberg, Springer-Verlag, Berlin, 2007.
[4] F. Chee, A.V. Savkin, T.L. Fernando, S. Nahavandi, Optimal $H_\infty$ insulin injection control for blood glucose regulation in diabetic patients, IEEE Trans. Biomed. Eng. 52 (2005) 1625–1631.
[5] C. Dalla Man, R.A. Rizza, C. Cobelli, Meal simulation model of the glucose–insulin system, IEEE Trans. Biomed. Eng. 54 (2007) 1740–1749.
[6] P. Dua, F.J. Doyle, E.N. Pistikopoulos, Model-based blood glucose control for Type 1 diabetes via parametric programming, IEEE Trans. Biomed. Eng. 53 (2006) 1478–1491.
[7] K.M. Engebretsen, K.M. Kaczmarek, J. Morgan, J.S. Holger, High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning, Clin. Toxicol. 49 (4) (2011) 277–283.
[8] A. Germani, C. Manes, P. Pepe, An asymptotic state observer for a class of nonlinear delay systems, Kybernetika 37 (4) (2001) 459–478.
[9] A. Germani, C. Manes, P. Pepe, Input–output linearization with delay cancellation for nonlinear delay systems: the problem of the internal stability, Int. J. Robust Nonlinear Control 13 (9) (2003) 909–937.
[10] A. Germani, P. Pepe, A state observer for a class of nonlinear systems with multiple discrete and distributed time delays, Eur. J. Control 11 (3) (2005) 196–205.
[11] R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M.O. Federici, T.R. Pieber, H.C. Schaller, L. Schaupp, T. Vering, M.E. Wilinska, Nonlinear model predictive control of glucose concentration in subjects with type I diabetes, Physiol. Measure. 25 (2004) 905–920.
[12] M. Huang, J. Li, X. Song, H. Guo, Modeling impulsive injections of insulin: towards artificial pancreas, SIAM J. Appl. Math. 72 (5) (2012) 1524–1548.
[13] P. Kaveh, Y.B. Shtessel, Blood glucose regulation using higher-order sliding mode control, Int. J. Robust Nonlinear Control 18 (2008) 557–569.
[14] L. Kovàcs, B. Benyò, J. Bokor, Z. Benyó, Induced L2-norm minimization of glucose–insulin system for type I diabetic patients, Comput. Methods Programs Biomed. 102 (2011) 105–118.
[15] L. Kovàcs, B. Kulcsàr, A. Gyŏrgy, Z. Benyó, Robust servo control of a novel Type 1 diabetic model, Opt. Control Appl. Methods 32 (2011) 215–238.
[16] B.P. Kovatchev, M.D. Breton, C. Dalla Man, C. Cobelli, In Silico Model and Computer Simulation Environment Approximating the Human Glucose/Insulin Utilization. Food and Drug Administration Master File MAF 1521, 2008.
[17] S. Laxminarayan, J. Reifman, G.M. Steil, Use of a food and drug administration-approved Type 1 Diabetes Mellitus simulator to evaluate and optimize a proportional–integral–derivative controller, J. Diabetes Sci. Technol. 6 (6) (2012) 1401–1412.
[18] L. Magni, D.M. Raimondo, C. Dalla Man, G. De Nicolao, B. Kovatchev, C. Cobelli, Model predictive control of glucose concentration in type I diabetic patients: an in silico trial, Biomed. Signal Process. Control 4 (2009) 338–346.
[19] A. Makroglou, J. Li, Y. Kuang, Mathematical models and software tools for the glucose–insulin regulatory system and diabetes: an overview, Appl. Numer. Math. 56 (2006) 559–573.
[20] G. Marchetti, M. Barolo, L. Jovanovic, H. Zisser, D.E. Seborg, An improved PID switching control strategy for Type 1 diabetes, IEEE Trans. Biomed. Eng. 55 (3) (2008) 857–865.
[21] T. Oguchi, A. Watanabe, T. Nakamizo, Input–output linearization of retarded non-linear systems by using an extension of lie derivative, Int. J. Control 75 (8) (2002) 582–590.
[22] P. Palumbo, S. Panunzi, A. De Gaetano, Qualitative behavior of a family of delay differential models of the glucose insulin system, Discrete Continuous Dyn. Syst. – B 7 (2007) 399–424.
[23] P. Palumbo, P. Pepe, J.D. Kong, S.S. Kumar, S. Panunzi, A. De Gaetano, Regulation of the human plasma glycemia by means of glucose measurements and subcutaneous insulin administration, in: Proc. 3rd IFAC International Conference on Intelligent Control and Automation Science (ICONS13), Chengdu, China, 2013, pp. 96–101.
[24] P. Palumbo, P. Pepe, S. Panunzi, A. De Gaetano, Robust closed-loop control of plasma glycemia: a discrete-delay model approach, Discrete Continuous Dyn. Syst. – B 12 (2) (2009) 455–468.
[25] P. Palumbo, P. Pepe, S. Panunzi, A. De Gaetano, Time-delay model-based control of the glucose–insulin system, by means of a state observer, Eur. J. Control 6 (2012) 591–606.
[26] P. Palumbo, G. Pizzichelli, P. Pepe, S. Panunzi, A. De Gaetano, Tests on a virtual patient for an observer-based, closed-loop control of plasma glycemia, in: Proc. 50th IEEE Conf. on Decis. and Control, Orlando, USA, 2011, pp. 6936–6941.
[27] S. Panunzi, A. De Gaetano, G. Mingrone, Advantages of the single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test, Theoret. Biol. Med. Modell. 7 (9) (2010).
[28] S. Panunzi, P. Palumbo, A. De Gaetano, A discrete single delay model for the intra-venous glucose tolerance test, Theoret. Biol. Med. Modell. 4 (35) (2007).

[29] R.S. Parker, F.J. Doyle III, J.H. Ward, N.A. Peppas, Robust $H_\infty$ glucose control in diabetes using a physiological model, AIChE J. 46 (2000) 2537–2549.
[30] G. Reach, G.S. Wilson, Can continuous glucose monitoring be used for the treatment of diabetes, Anal. Chem. 64 (1992) A381–A386.
[31] E. Ruiz-Velázquez, R. Femat, D.U. Campos-Delgado, Blood glucose control for type I diabetes mellitus: a robust $H^\infty$ tracking problem, Control Eng. Practice 12 (2004) 1179–1195.
[32] J.T. Sorensen, C.K. Colton, R.S. Hillman, J.S. Soeldner, Use of a physiologic pharmacokinetic model of glucose homeostasis for assessment of performance requirements for improved insulin therapies, Diabet. Care 5 (1982) 148–157.
[33] G. Van den Berghe, Insulin therapy for the critically ill patient, Clinical Cornerstone 5 (2) (2003) 56–63.