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Tests on a virtual patient for an observer-based, closed-loop control of plasma glycemia

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Abstract— **Exogenous insulin administration is the basic way to face the widespread disease of Diabetes Mellitus. To this aim, closed-loop approaches, though theoretically realizable according to the control theory results and to the recent technology concerning continuous glucose measurements and affordable insulin infusion pumps, require a careful and thorough testing ground on a virtual environment before arranging an *in-vivo* clinical setting of experiments. In this work, a model-based control law for the plasma glycemia, recently published by the same authors, is evaluated by closing the loop on a virtual patient, whose model equations are different from the ones used to synthesize the control law. That means: a minimal model of the glucose-insulin system to design the insulin therapy, and a different, more detailed, comprehensive model to test *in silico* the control scheme. Uncertainties on the blood glucose measurements, as well as malfunctioning on the insulin delivery devices are considered, according to the standard technology, in order to obtain an effective benchmark for the closed-loop control and to show in fact the robustness of the proposed approach.**

I. Introduction

The term "diabetes" comprises a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In one category (Type 1 diabetes), there is an absolute deficiency of insulin secretion caused by an autoimmune pathologic process occurring in the pancreatic islets. Individuals with this extensive beta-cell destruction, and therefore no residual insulin secretion, require insulin for survival. In the other, much more prevalent category (Type 2 diabetes), the cause is 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, in the face of increased levels of circulating insulin.

Exogenous insulin administration is a basic procedure 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). Glucose control strategies are mainly actuated by subcutaneous or intravenous injections or infusions. Control of glycemia by means of subcutaneous insulin injections is by far more widespread than control by means of intravenous insulin, since the dose is habitually administered by the patients themselves (see [1] and references therein). However, only open loop or semiclosed loop control strategies can be used in this situation, mainly due to the problem of accurately modeling the absorption of the hormone from the subcutaneous depot into the plasma circulation (see [20] for a critical review of subcutaneous absorption models and [7] for a model of intra/inter subject variability of the absorption of subcutaneous insulin preparations). On the other hand, 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 and ensures a rapid delivery with negligible delays. As a matter of fact, control algorithms based on intravenous insulin administration 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.

A closed loop control strategy may be implemented according to a model-less or to a model-based approach. The first approach does not use a mathematical model of the glucose-insulin system, and provides an arbitrary (while possibly very effective) control rule for insulin infusion rate, based on experimental data: recent papers on this topic are mainly devoted to the application of PID controllers aiming to mimic the pancreatic glucose response (see e.g. [5], [32], [14], [19]). Clearly, before applying these empirical therapies in a clinical setting, they need to be tested on a virtual environment, usually provided by a total-body comprehensive model of the glucose-insulin system, which details about the many organs and tissues involved in the insulin dependent/independent glucose uptake as well as in the endogenous/exogenous insulin administration [8], [31], [9]. On the other hand a model-based approach presupposes sufficiently detailed knowledge of the physiology of the system under investigation. The advantages of a model-based approach are evident since, by using a glucose/insulin model, the control problem may be treated mathematically and optimal strategies may be determined. Clearly, the more accurate the model, the more effective is the control law. Recently, model-based glucose controls have been proposed, based on nonlinear models such as the Minimal Model, [2], [33], or more exhaustive compartmental models, [8], [31], [16], (e.g. Model Predictive Control in [15], Parametric Programming in [10], Neural Predictive Control in [34], H_∞ control in [28], non-standard H_∞ control in [6], [30]). It has to be stressed that most of these approaches are based on the approximation of the original nonlinear model, provided by linearization, discretization and model reduction (balanced truncation). In most of the above mentioned papers, insulin

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is assumed to be intra-venously administered. An excellent review of the available models presently adopted for blood glucose regulation as well as the closed loop control methodologies and technical devices (blood glucose sensors and insulin pumps) may be found in [4].

In this paper, the attention is focused on a model-based, closed-loop control scheme, recently published by the same authors in [24]. Differently from previously mentioned model-based approaches, which use nonlinear Ordinary Differential Equation (ODE) models, the one presented in [24] uses a nonlinear discrete-Delay Differential Equation (DDE) model of the glucose/insulin system, [22], [27]. Despite the great spread of DDE models in the last decade, which allow a better representation of pancreatic Insulin Delivery Rate (IDR) (see e.g. [18] and references therein), their use is still lacking in the field of glucose control, according to the authors' knowledge. Indeed, when attempting to design a closed-loop glucose control, the works published so far have concentrated on Type 1 diabetic patients (who have essentially no endogenous insulin production), avoiding in this way the need to take pancreatic IDR into account. In [24] we do take into account spontaneous pancreatic IDR, thereby treating healthy, Type 2 diabetic and Type 1 diabetic patients in a unified fashion.

The control law aims to track a desired glucose reference trajectory by means of intravenous insulin infusions (like many of the previously cited approaches [10], [28], [6], [30]). To this aim, the input-output feedback linearization with delay cancelation has been used (see [12], [21]), with a feedback depending on glucose measurements acquired intra-venously, for instance by using implanted devices like the ones supplied by Medtronic MiniMed Inc. (www.minimed.com). Insulinemia levels are assumed to be estimated by means of a state observer for nonlinear time-delay systems [11], [13].

The contribute of the present paper is devoted to build a virtual environment in order to effectively test the methodology developed in [24]. Being synthesized by suitably exploiting a minimal DDE model, the control law requires to be tested in closed-loop onto a different, more detailed, comprehensive model of the glucose-insulin system. *In silico* tests are usually needed to be thoroughly carried out on a virtual patient (VP, shortly) (or better on a population of VPs), making it possible to evaluate a possibly exhaustive set of different scenarios, including cases of measurement error and other failures, [3], before to arrange a set of reliable clinical experiments (which are usually costly, time-consuming and confounded by ethical issues). The multi-compartmental model chosen for the VP is [9], which relates in as much details as possible the glucose-insulin evolution with respect to possible exogenous perturbations such as meals or insulin infusions. Based on these model equations, a computer simulator of diabetic patients has been recently accepted by the *Food and Drug Administration (FDA)* as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas [17]. The crucial point to ensure attainable experiments is to make the two models consistent each other. Such a task is performed by considering a virtual Intra-Venous Glucose Tolerance Test (IVGTT) on the VP in order to identify the DDE model parameters which best fit the glucose-insulin evolutions. Then, the model-based control law is synthesized, and the control parameters are tuned by simulations on the DDE, just as it should be done before to apply the control law to a real patient. Finally, the control law is applied to the VP.

Uncertainties on the blood glucose measurements, as well as malfunctioning on the insulin delivery devices are considered, according to the standard technology, in order to obtain an effective benchmark for the closed-loop control and to show in fact the robustness of the proposed approach. Criteria of safety and efficacy will be adopted in order to stress the robustness of the control methodology with respect to a population of VPs.

II. Preliminiaries on the model-based control scheme

Denote $G(t)$, [mM], $I(t)$, [pM], plasma glycemia and insulinemia, respectively. The model considered to synthesize the closed-loop glucose control consists of a single discrete-delay differential equation system [27], [22]:

$$\begin{aligned} &\frac{dG(t)}{dt} = -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G}, \\ &\frac{dI(t)}{dt} = -K_{xi}I(t) + \frac{T_{iGmax}}{V_I} f\big(G(t-\tau_g)\big) + u(t), \\ &G(\tau) = G_0(\tau), \quad I(\tau) = I_0(\tau), \qquad \tau \in [-\tau_g, 0], \end{aligned} \tag{1}$$

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

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

and $u(t)$, [pM/min], is the the control input, i.e. the exogenous intra-venous insulin delivery rate. Refer to [27], [22] for a detailed description of the model parameters and their physiological meaning. $\big(G_0(\tau), I_0(\tau)\big)$ is the pair of initial conditions, equal to the constant basal levels (G_b, I_b).

It has to be stressed that model (1) represents equally well healthy subjects and insulin-resistant or severe diabetic patients, changing the parameter values as appropriate.

The aim of the considered control law is to reduce a high basal plasma glucose concentration G_b to a lower level, according to a smooth reference glucose trajectory $G_{\mathrm{ref}}(t)$, by means of intra-venous insulin administration. No exogenous glucose intake is considered, thus the patient is assumed to be controlled out of meals.

In [23], by applying the theory of input-output feedback linearization with delay cancellation (see [12], [21]), with respect to the output $y(t) = G(t)$ and the input $u(t)$, the following feedback control law is found:

$$u(t) = \frac{S\big(G(t), I(t), G(t-\tau_g)\big) - v(t)}{K_{xgi}G(t)}, \qquad t \geq 0, \tag{3}$$

where

$$S\big(G(t),I(t),G(t-\tau_g)\big) = -K_{xgi}I(t)\left(-K_{xgi}I(t)G(t)+\tfrac{T_{gh}}{V_G}\right) -K_{xgi}G(t)\left(-K_{xi}I(t)+\tfrac{T_{iGmax}}{V_I}f\big(G(t-\tau_g)\big)\right) \quad (4)$$

and $v(t)=\ddot{G}_{\rm ref}(t)+Re(t)$; matrix $R\in\mathbb{R}^{1\times 2}$ is such that:

$$H=\begin{bmatrix}0&1\\0&0\end{bmatrix}+\begin{bmatrix}0\\1\end{bmatrix}R \quad (5)$$

has prescribed eigenvalues in the left half complex plane and

$$e(t)=\begin{bmatrix}e_1(t)\\e_2(t)\end{bmatrix}=Z(t)-Z_{\rm ref}(t) \quad (6)$$

with:

$$Z(t)=\begin{bmatrix}z_1(t)\\z_2(t)\end{bmatrix}=\begin{bmatrix}G(t)\\-K_{xgi}G(t)I(t)+\frac{T_{gh}}{V_G}\end{bmatrix}, \quad (7)$$

and

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

It is shown in [23] that, by applying (3-8) the tracking error variable $e(t)$ asymptotically converges to zero, since:

$$\dot{e}(t)=He(t), \quad H \text{ Hurwitz, according to (5).} \quad (9)$$

Such a control law (3-8) requires both glucose and insulin measurements: on the other hand, insulin measurements are slower and more cumbersome to obtain, more expensive, and also less accurate than glucose measurements: therefore, a state observer for system (1) has been considered, in order to estimate the plasma insulin concentration and design a feedback control law based on only glucose measurements [24]:

$$\begin{bmatrix}\frac{d\widehat{G}}{dt}\\\frac{d\widehat{I}}{dt}\end{bmatrix}=\begin{bmatrix}-K_{xgi}\widehat{G}(t)\widehat{I}(t)+\frac{T_{gh}}{V_G}\\-K_{xi}\widehat{I}(t)+\frac{T_{iGmax}}{V_I}f\big(\widehat{G}(t-\tau_g)\big)+u(t)\end{bmatrix} +Q^{-1}\big(\widehat{G}(t),\widehat{I}(t)\big)W(G(t)-\widehat{G}(t)), \qquad t\geq 0,$$
$$\widehat{G}(\tau)=\widehat{G}_0(\tau),\ \widehat{I}(\tau)=\widehat{I}_0(\tau), \qquad \tau\in[-\tau_g,0], \quad (10)$$

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

$$Q(x_1,x_2)=\begin{bmatrix}1&0\\-K_{xgi}x_2&-K_{xgi}x_1\end{bmatrix}, \quad (11)$$

and $W\in\mathbb{R}^{2\times 1}$ is such that the matrix

$$\widehat{H}=\begin{bmatrix}0&1\\0&0\end{bmatrix}-W\begin{bmatrix}1&0\end{bmatrix} \quad (12)$$

has prescribed eigenvalues in the left half complex plane.

According to results in [11], [13], the observer (10) guarantees local exponential convergence of the estimation error to zero. More specifically, if the estimation error at zero is sufficiently small, then the estimation error converges exponentially to zero, with arbitrary decay rate fixed by means of a suitable choice of W.

In order to close the loop from the observed state, the following feedback control law has been considered:

$$u(t)=\frac{S\big(\widehat{G}(t),\widehat{I}(t),\widehat{G}(t-\tau_g)\big)-v(t)}{K_{xgi}\widehat{G}(t)}, \quad (13)$$

with $v(t)=\ddot{G}_{\rm ref}(t)+R\hat{e}(t)$, where $\hat{e}(t)=\widehat{Z}(t)-Z_{\rm ref}(t)$, $t\geq-\tau_g$, and

$$\widehat{Z}(t)=\begin{bmatrix}\hat{z}_1(t)\\\hat{z}_2(t)\end{bmatrix}=\begin{bmatrix}\widehat{G}(t)\\-K_{xgi}\widehat{G}(t)\widehat{I}(t)+\frac{T_{gh}}{V_G}\end{bmatrix}. \quad (14)$$

Such control law (13-14) does not make use of insulin measurements, differently from the control law (3-8). Actually, it makes use of the glucose and insulin estimations provided by the observer, on the basis of the only glucose measurements.

In [24] it has been proven that there exist gains R and W such that, for the closed-loop system (1), (10), (13-14), 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.

III. The virtual environment

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, and to use a different, more exhaustive, comprehensive model to test the control law on a realistic virtual patient. To this aim, it has been chosen the model dealt with in [9], where the glucose-insulin system is described by means of a two-compartmental subsystem for the glucose kinetics (detailing insulin dependent/independent glucose uptake in the tissues as well as the renal extraction and the endogenous glucose production) and a two-compartmental subsystem for the insulin kinetics (detailing the pancreatic insulin production and the degradation in the liver and the peripheral tissues), for an overall 9th order ODE model with about 30 parameters. Since no exogenous glucose intake is considered in this paper, the gastro-intestinal tract equations, though thoroughly treated in [9], are not considered in this framework, and their contributes are, therefore, cleared from the model. Refer to [9] and reference therein for the many contributes which allowed to build up the model.

The chosen VP is a Type II diabetic patient, body weight of 90kg, identified by the parameters taken from Table I of [9], whose corresponding basal glycemia and insulinemia are $G_b=8.85$mM and $I_b=59.85$pM. Once the VP is chosen, the DDE model parameters need to be estimated in order to approximate the VP by means of eq.s(1-2). To this aim, a virtual IVGTT experiment is simulated on the VP, which consists in administering intra-venously a glucose bolus D_g after an overnight fast and, then, sampling blood glucose and insulin concentration at fixed instants during the following 3 hours. From a modeling point of view, the bolus D_g, administered at time $t=0$, produces an instantaneous increase in both glycemia and insulinemia, so that:

$$G(0)=G_b+\frac{D_g}{V_G}, \qquad I(0)=I_b+I_\Delta\frac{D_g}{V_G}, \quad (15)$$

TABLE I

DDE MODEL PARAMETERS OF THE VP

V_G	0.18	L/kgBW
τ_g	6.5	min
K_{xgi}	$3.15 \cdot 10^{-5}$	$\text{min}^{-1}\text{pM}^{-1}$
K_{xi}	0.038	min^{-1}
γ	15.92	-
T_{iGmax}	1.67	min^{-1}(pmol/kgBW)
T_{gh}	0.0023	min^{-1}(mmol/kgBW)

with I_Δ a further parameter to be estimated. According to standard IVGTT clinical criteria:

- the bolus D_g is fixed equal to 300mg/kg Body Weight;
- blood samples are obtained every 2 minutes for the first 10-minute interval, every 5 minutes for the next 30-minute interval, every 10 minutes for the next 20-minute interval and finally every 20 minutes for the last 120-minute interval (an overall sampling period of 3 hours);

Glycemia and insulinemia measurements are provided by the VP according to the previous item: coefficients of variation (CVs) have been considered of 1.5% for glycemia and 7% for insulinemia, to reflect unmodeled measurement errors [2].

The Generalized Least Square method has been applied [27], with:

- parameters G_b and I_b measured before the experiment (they enter the model as covariates); to stress the robustness of the algorithm, these basal values are assumed to be measured with greater CVs than the ones stated before: $G_b = 8.46$mM ($\simeq 4.5\%$ error) and $I_b = 47.85$pM ($\simeq 17\%$ error). Note that these noisy values will be used also to design the control law.
- $V_I = 0.25$L/kgBW and $G^\star = 9$mM fixed by the investigator and kept constant;
- V_G, τ_g, K_{xgi}, K_{xi}, γ, I_Δ free model parameters to be estimated;
- T_{iGmax}, T_{gh} determined from the other parameters according to the algebraic steady-state conditions.

Estimated DDE model parameters are reported in Table I. 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. Viceversa, 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.

Once the DDE model parameters are identified for the VP, the control scheme may be designed. At first, the reference glucose trajectory is chosen as follows:

$$G_{\text{ref}}(t) = G_d + (G_b - G_d) \cdot e^{-t/T} \tag{16}$$

where $G_d = 5$mM is the desired plasma glycemia to track, $G_b = 8.46$mM is the noisy glycemia, also used in the virtual IVGTT and $T = 30$min is set in order to have a reference signal which smoothly reduces the hyperglycemic level G_b down to a healthy level within about $3T = 90$ minutes.

The control law is designed by suitably choosing the eigenvalues of matrices H and $\widehat{H}$ in (5-12). Such a task needs to be performed taking into account both theory and numerical simulations. The theory is the one concerning the convergence of the observer [11], [13], according to which the following choices are taken:

$$\lambda(H) = \{-0.15, -0.06\}, \qquad \lambda(\widehat{H}) = \{-0.1, -0.4\}. \tag{17}$$

Simulations are required to check that no glucose oscillations occur (with corresponding dangerous cases of hypoglycemia), as well as to avoid periods of theoretical negative insulin administration, which would be treated as a temporary switch off of the control law (undesired as well, since the patient glucose-insulin system would be left in free evolution, while it would require negative insulin). Such a task is performed by closing the loop on the DDE model itself (not on the VP), since the regulator needs to be tuned and checked *in silico* before to be applied on a real/virtual patient. Indeed, simulations reported in Fig.1 show excellent results on a 3-hour horizon, and the control input $u(t)$ is never switched off, being always positive throughout the simulation.

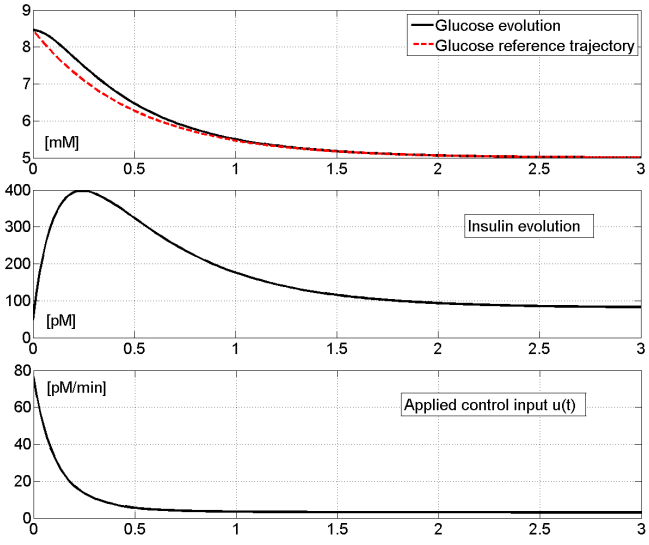

Fig. 1. Glucose control closed on the DDE model. x-axis is time in hours.

The designed control law is then applied to the VP. In order to make more effective these simulations, it has to be taken into account the fact that in the real case glucose measurements are not available in continuous time, nor the controller may work in continuous time. Indeed, in practice, standard devices:

– provide glucose measurements only at given sample times, whose frequency is limited by the time needed to analyze plasma glucose on a bed-side analyzer, [3];
– administer insulin by means of piecewise-constant infusions.

Both technical assumptions will be taken into account in the simulations concerning the VP. Indeed, let ΔT be the sampling time according to which glucose measurements are acquired at times $t = k\Delta T$, and constant insulin infusion rates are administered, during intervals $[k\Delta T, (k+1)\Delta T)$, $k = 0, 1, \ldots$ Then the numerical algorithm is as follows, and the chosen sampling time for simulations is $\Delta T = 5$min, which is reasonable according to current technology [29].

ALGORITHM

1. at time $k\Delta T$ the measurement of $G(k\Delta T)$ is delivered by the sensor;
2. from the available state estimates $\widehat{G}(k\Delta T)$, $\widehat{G}(k\Delta T - \tau_g)$, $\widehat{I}(k\Delta T)$, the control input is computed by (13):
$$u(k\Delta T) = \frac{S\big(\widehat{G}(k\Delta T), \widehat{I}(k\Delta T), \widehat{G}(k\Delta T - \tau_g)\big) - v(k\Delta T)}{K_{xgi}\widehat{G}(k\Delta T)}; \tag{18}$$
3. the constant infusion $u(k\Delta T)$ is administered to the patient in the time interval $[k\Delta T, (k+1)\Delta T)$;
4. contemporary to item [3.], the controller device runs in the time-interval $[k\Delta T, (k+1)\Delta T]$, by way of (10), using the measurement $G(k\Delta T)$:
$$\begin{bmatrix} \frac{d\widehat{G}}{dt} \\ \frac{d\widehat{I}}{dt} \end{bmatrix} = \begin{bmatrix} -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \frac{T_{gh}}{V_G} \\ -K_{xi}\widehat{I}(t) + \frac{T_{iGmax}}{V_I} f\big(\widehat{G}(t-\tau_g)\big) + u(k\Delta T) \end{bmatrix}$$
$$+ Q^{-1}\big(\widehat{G}(t), \widehat{I}(t)\big) W\big(G(k\Delta T) - \widehat{G}(k\Delta T)\big); \tag{19}$$
5. the value of k is incremented by 1.

Moreover, glucose measurement errors and insulin pump malfunctioning have also been considered. The CVs used for real-time glucose measurements and the insulin delivery rate have been assumed equal to 5% and 15%, respectively, [3].

Simulations on the VP are reported in Fig.2, on the same 3-hours time horizon. Note that, despite the many errors affecting the basal values, the measured glycemias, the input actuator and the discretization of the regulator, there are only few cases of switching off the controller, with no episodes of hypoglycemia. Moreover, from an efficacy point of view, a reasonable (< 6mM) normo-glycemia is definitely reached within 90 minutes.

Finally, we considered the case of a population of 1,000 VPs, whose model parameters are distributed according to a log-normal distribution with population means given by the values taken from [9], and CVs set at 5%. It has to be stressed that, by doing so, the patient characteristic may change so far that the resulting subject may not be any more a diabetic patient. For this reason each of the 1,000 VPs has been chosen with a resulting basal glycemia of at least 6.5mM. The control law applied to the population of VPs is always the same, set for the VP with the mean value parameters. The utility criterion chosen in order to state whether a simulation associated to a stochastic realization of the virtual patient is

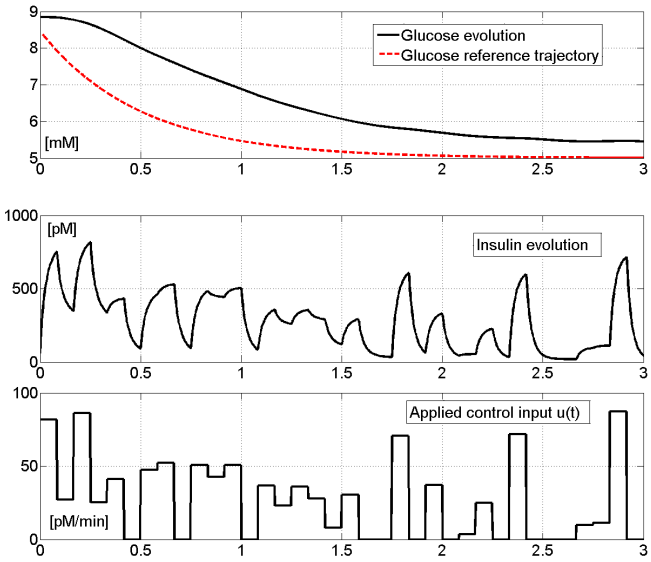

Fig. 2. Glucose control closed on the VP. x-axis is time in hours.

acceptable or not, needs to take into account both *safety* and *efficacy* criteria. These criteria have been inspired by [3] and are the following. As far as *safety*, the control law applied to a VP could cause:

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

Then, a set of simulations provides *excellent safety* if neither hypoglycemia nor severe hypoglycemia cases 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 virtual patient may provide

- *excellent efficacy*: plasma glycemia is constrained below 6mM after the first 3 hours of treatment;
- *good efficacy*: plasma glycemia is constrained below 7mM after the first 3 hours of treatment;
- *satisfactory efficacy*: plasma glycemia is constrained below 8mM after the first 3 hours of treatment;
- *unsatisfactory efficacy*: plasma glycemia is not constrained below 8mM after the first 3 hours of treatment;

Results showed excellent safety and overall excellent efficacy results ($\simeq 80\%$), as underlined by Table II

IV. Conclusions

In this work a virtual environment is set in order to test a DDE-model-based glucose control law in as much realistic details as possible, compatible with the available technology of glucose sensors and insulin pump actuators. The control law is evaluated by closing the loop on a virtual patient, whose model equations have been recently accepted by the

TABLE II

SAFETY AND EFFICACY RESULTS ON 1,000 VPS

Severe hypoglycemia	0 cases (0%)
Hypoglycemia	0 cases (0%)
Excellent efficacy	782 cases (78.2%)
Good efficacy	213 cases (21.3%)
Satisfactory efficacy	5 cases (0.5%)
Unsatisfactory efficacy	0 cases (0.0%)

Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas.

The clinical application of the control algorithms presented in this work relate 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 highlighted by the proposed simulations, extensions of the basic DDE-model could directly lead to the application in wider contexts, such as insulin administration by means of typical subcutaneous infusions, as well as glucose control in presence of incoming disturbances such as meals or other modes of oral glucose ingestion. A preliminary result upon the former case has been recently accepted for presentation at the 18th IFAC World Congress in Milan 2011 [25].

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