

Closed-loop control scheme for the Euglycemic Hyperinsulinemic Clamp: validation on virtual patients

P. Palumbo* G. Pizzichelli** P. Pepe*** S. Panunzi*
A. De Gaetano*

* *Istituto di Analisi dei Sistemi ed Informatica "A. Ruberti", Consiglio Nazionale delle Ricerche (IASI-CNR), BioMatLab - UCSC - Largo A. Gemelli 8, 00168 Roma, Italy. (e-mails: pasquale.palumbo@iasi.cnr.it, simona.panunzi@biomatematica.it, andrea.degaetano@biomatematica.it)*

** *Center for Micro-BioRobotics@SSSA, Istituto Italiano di Tecnologia & The BioRobotics Institute, Scuola Superiore Sant'Anna, V.le Rinaldo Piaggio, 34, 56025 Pontedera, Pisa, Italy (e-mail: giulia.pizzichelli@iit.it)*

*** *Department of Information Engineering, Computer Science, and Mathematics, University of L'Aquila, Via Gronchi 18, 67100 L'Aquila, Italy (e-mail: pierdomenico.pepe@univaq.it)*

Abstract: A closed-loop control scheme is here investigated, for the Euglycemic Hyperinsulinemic Clamp (EHC), the *gold standard* experiment to estimate the individual insulin sensitivity. During the EHC large amounts of insulin are administered intra-venously to the subject, and plasma glycemia is maintained at a normal, baseline level by means of an exogenous glucose infusion, according to established protocols. Based on a Delay Differential Equation (DDE) model of the glucose-insulin system, a closed-loop control has been recently proposed by the same authors showing that, in way of principle, it is possible to design an observer-based control law for the exogenous glucose profile, by solely exploiting real-time plasma glucose measurements. This note further investigates the closed-loop control scheme in order to validate it in spite of the many sources of uncertainties and malfunctioning that inevitably arise. The main feature is to close the feedback onto a different, large-scale multi-compartmental model (standing for a Virtual Patient, VP), instead of the small-scale, DDE model adopted to design the control law. The chosen large-scale model for the VP has been recently accepted by the Food and Drug Administration as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas. A benchmark based on a population of heterogeneous virtual patients has been implemented and the very good results show the robustness of the proposed methodology.

Keywords: Delay Differential Equations; Glucose-Insulin System; Nonlinear Observer; Glucose Control.

1. INTRODUCTION

The Euglycemic Hyperinsulinemic Clamp (EHC) consists of the rapid administration of decreasing boli of insulin, followed by a constant insulin administration, in order to maintain an elevated, constant insulinemia, supposed to stimulate peripheral tissues to clear glucose from plasma and produce hypoglycemia. At the same time, an intra-venous infusion of glucose is administered, at a variable rate, in order to maintain glycemia at a normal, baseline level, see DeFronzo et al., 1979. The EHC is widely considered in the diabetological community as the *gold standard* for the determination of insulin sensitivity, since its interpretation requires no modeling and no mathematics

* The first two authors equally contributed to the manuscript. The work is supported in part by the Italian MIUR Project PRIN 2009 and by the Center of Excellence for Research DEWS.

beyond the computation of the average glucose infusion rate.

According to the great availability of data coming from the EHC-based experiments, mathematical models of the EHC have been recently published (see e.g. Picchini et al., 2006 and references therein); nonetheless, the daily conduction of the experiment on patients makes use of the empirical algorithm, described in DeFronzo et al., 1979, whose aim is to attain steady glycemia levels by the end of two hours, the typical duration of the EHC. In Palumbo et al., 2013, a model-based control is proposed to automatically design the exogenous glucose profile to keep the actual plasma glucose concentration as close as possible to the normoglycemia level. To this aim a small-scale Delay Differential Equation (DDE) model has been adopted, and the control law suitably exploits a state

observer for nonlinear DDE systems to design the feedback by solely glucose measurements.

The novel contribution of the present paper is the construction of a virtual environment in order to effectively test the feedback control law proposed in Palumbo et al., 2013. Since it is synthesized by suitably exploiting a small-scale DDE model, the control law requires to be tested in closed-loop onto a different, large-scale, multi-compartmental 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 yet, 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, see Chassin et al., 2004, before arranging a set of reliable clinical experiments (which are usually costly, time-consuming and confounded by ethical issues). The large-scale model chosen for the VP is Dalla Man et al., 2007, which describes in great details the glucose-insulin evolution with respect to possible exogenous perturbations. Based on these model equations, a computer simulator of the 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 (Kovatchev et al., 2008). The crucial point to ensure attainable experiments is to make the two models consistent with 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 small-scale 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 small-scale DDE model, just as it should be done on an individualized insulin therapy before to apply the control law to a real patient. Finally, the control law is applied in closed loop to the VP.

Uncertainties on blood glucose measurements, as well as malfunctioning on glucose delivery devices are considered, according to the standard technology, in order to obtain an effective benchmark for the closed-loop control and to show the robustness of the proposed approach. Criteria of safety and efficacy inspired to Chassin et al., 2004, will be adopted in order to stress the robustness of the control methodology with respect to a population of VPs.

The idea to validate a glucose control algorithm on a virtual patient modeled by a different, large-scale system has been presented in Palumbo et al., 2011, in the different framework provided by Type 2 diabetic patients.

2. PRELIMINARIES

In this section we report for the reader's convenience the main results presented in Palumbo et al, 2013, which will be used in the next sections.

2.1 A mathematical model for the Clamp

Denote $G(t)$, [mM], $I(t)$, [pM], plasma glycemia and insulinemia, respectively. The glucose-insulin model considered for the EHC is a slight modification of the DDE one in Panunzi et al., 2007, Palumbo et al., 2007, already exploited with the purpose of glucose control in Type 2

diabetic patients (see Palumbo et al., 2009, Palumbo et al., 2011, Palumbo et al., 2012 for the details on the model parameters):

$$\begin{aligned} \frac{dG(t)}{dt} &= -T_{xg} \frac{G(t)}{G(t) + \bar{G}} - K_{xgi} G(t) I(t) \\ &\quad + \frac{T_{ghmax}}{V_G} e^{-\lambda G(t) I(t)} + \frac{u(t)}{V_G}, \\ \frac{dI(t)}{dt} &= -K_{xi} I(t) + \frac{T_i Gmax}{V_I} f(G(t - \tau_g)) + \frac{d(t)}{V_I}, \end{aligned} \quad (1)$$

where the nonlinear function $f(\cdot)$ models the pancreas insulin delivery rate as:

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

The present model differs from the DDE model of Panunzi et al., 2007, Palumbo et al., 2007 in two terms of the first equation of (1) related to the insulin-independent glucose elimination and to the liver glucose production. The elimination term properly accounts for the brain and the nerve tissues uptake, and it may well be approximated by a constant term except for very low values of plasma glycemia. On the other hand the production term describes the Hepatic Glucose Output (HGO) as dependent on circulating plasma glucose and insulin: liver glucose production is suppressed and glycogen-synthesis is enhanced in the presence of high plasma glucose and insulin concentrations. Motivations for the exponential fashion of the HGO term can be found also in OGTT models (see the recent De Gaetano et al., 2013). Both the terms have already been considered in a previous model of the EHC, Picchini et al., 2006, with a different mathematical framework (stochastic instead of deterministic).

The signal $d(t)$, [(pmol/kgBW)/min], is the piecewise-constant insulin infusion rate, the known disturbance perturbing the system. The signal $u(t)$, [(mmol/kgBW)/min], is glucose infusion rate, the control input to be designed in order to control the level of plasma glycemia in spite of the exogenous insulin perturbation.

Initial conditions are:

$$G(\tau) = G_0(\tau), \quad I(\tau) = I_0(\tau), \quad \tau \in [-\tau_g, 0], \quad (3)$$

corresponding to the plasma glucose/insulin concentrations before the exogenous inputs $u(t)$ and $d(t)$ are applied. According to the EHC experimental framework, they can be assumed equal to the constant basal levels (G_b, I_b).

2.2 Observer-based glucose control

The goal of the closed-loop regulator proposed in Palumbo et al., 2013 is to keep plasma glucose concentration fixed at its basal level G_b , despite the exogenous insulin perturbation. To this aim, the following control law has been proposed:

$$\begin{aligned} u(t) &= V_G \left(T_{xg} \frac{\hat{G}(t)}{\hat{G}(t) + \bar{G}} + K_{xgi} \hat{G}(t) \hat{I}(t) \right. \\ &\quad \left. - \frac{T_{ghmax}}{V_G} e^{-\lambda \hat{G}(t) \hat{I}(t)} - r(\hat{G}(t) - G_b) \right), \end{aligned} \quad (4)$$

with r a tunable control positive parameter and $\hat{G}(t), \hat{I}(t)$ the glucose and insulin estimates provided by the following state-observer for nonlinear DDE systems:

$$\begin{aligned} & \begin{bmatrix} \dot{\hat{G}}(t) \\ \dot{\hat{I}}(t) \end{bmatrix} \\ &= \begin{bmatrix} -T_{xg} \frac{\hat{G}(t)}{\hat{G}(t) + \tilde{G}} - K_{xgi} \hat{G}(t) \hat{I}(t) + \frac{T_{ghmax}}{V_G} e^{-\lambda \hat{G}(t) \hat{I}(t)} \\ -K_{xi} \hat{I}(t) + \frac{T_i Gmax}{V_I} f(\hat{G}(t - \tau_g)) \end{bmatrix} \\ &+ \begin{bmatrix} u(t)/V_G \\ d(t)/V_I \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ p_1(\hat{G}(t), \hat{I}(t)) & p_2(\hat{G}(t), \hat{I}(t)) \end{bmatrix}^{-1} \\ & \quad \cdot \Gamma(G(t) - \hat{G}(t)), \end{aligned} \quad (5)$$

with $p_1, p_2 : \mathbb{R}^2 \mapsto \mathbb{R}$ given, for $(x, y) \in \mathbb{R}^2$, by

$$\begin{aligned} p_1(x, y) &= -T_{xg} \frac{\tilde{G}}{(x + \tilde{G})^2} - K_{xgi} y - \lambda y \frac{T_{ghmax}}{V_G} e^{-\lambda xy}, \\ p_2(x, y) &= -K_{xgi} x - \lambda x \frac{T_{ghmax}}{V_G} e^{-\lambda xy}, \end{aligned} \quad (6)$$

and the observer gain $\Gamma \in \mathbb{R}^{2 \times 1}$ suitably chosen such that the following matrix H is Hurwitz (see Ciccarella et al., 1993)

$$H = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} - \Gamma [1 \ 0] \quad (7)$$

The observer allows to synthesize the glucose control without real-time insulin measurements, that are expensive and less accurate than glucose measurements.

Convergence results for the observer are resumed by the following theorem, that holds true under the assumption, satisfied in the EHC experiment, that signals $d(t)$ and $u(t)$ are non-negative, bounded and piece-wise constant. For further details the reader may refer to Palumbo et al., 2013, and references therein.

Theorem 1. (Palumbo et al., 2013). Let α be any positive real. Then, there exist positive reals δ, M and a suitable choice for the observer gain $\Gamma \in \mathbb{R}^{2 \times 1}$ such that if the observer initial states \hat{G}_0, \hat{I}_0 satisfy the inequalities

$$\left\| \begin{bmatrix} G_0(\tau) - \hat{G}_0(\tau) \\ I_0(\tau) - \hat{I}_0(\tau) \end{bmatrix} \right\| \leq \delta, \quad \tau \in [-\tau_g, 0], \quad (8)$$

then, it is:

$$\left\| \begin{bmatrix} G(t) - \hat{G}(t) \\ I(t) - \hat{I}(t) \end{bmatrix} \right\| \leq M e^{-\alpha t} \cdot \sup_{\tau \in [-\tau_g, 0]} \left\| \begin{bmatrix} G_0(\tau) - \hat{G}_0(\tau) \\ I_0(\tau) - \hat{I}_0(\tau) \end{bmatrix} \right\|, \quad (9)$$

for $t \geq 0$.

Motivated by the convergence results provided by Theorem 1 and by the necessity to cope with sampled glucose measurements, a digital control scheme will be adopted and accurately validated in the next section.

3. VALIDATION OF THE CONTROL ALGORITHM

The basic idea of the paper is to use a small-scale (though accurate) model of the glucose-insulin system to synthesize a model-based glucose control for the EHC experiment, and to use a different, large-scale, multi-compartmental model to test the control law on a realistic virtual environment, built according to the following rules:

- i) define an Average Virtual Patient (AVP), identified by choosing a set of parameters for the large-scale model;
- ii) identify the best-fitting small-scale model for the AVP in order to make the two models consistent with each other;
- iii) synthesize the glucose control law for the small-scale chosen model;
- iv) generate a population of heterogenous VPs with average model parameters given by the ones of the AVP;
- v) test the same, fixed control law versus the population of VPs.

3.1 The Average Virtual Patient (AVP)

As far as the first item is concerned, the chosen glucose-insulin model is the one developed in Dalla Man et al., 2007, described by means of a two-compartmental subsystem for the glucose kinetics (plasma and tissues glucose masses), a two-compartmental subsystem for the insulin kinetics (insulin masses in plasma and in the liver) and a two-compartmental subsystem for the insulin production (including the flow through the portal vein into the liver). The model includes also a two-compartmental subsystem for the endogenous glucose production and a further compartment for the insulin in the interstitial fluid, assumed to be responsible for the insulin-dependent glucose uptake. The overall system consists of a 9th order ODE model with about 30 parameters. The AVP is a healthy subject, identified by the parameters taken from Table I of Dalla Man et al., 2007, whose corresponding basal glycemia and insulinemia are $G_b = 5.1\text{mM}$ and $I_b = 25.59\text{pM}$. Refer to Dalla Man et al., 2007 and references therein for the many contributions which allowed to build up the model.

3.2 Small-scale model identification

Once the AVP is chosen, the DDE model parameters are estimated in order to approximate the AVP by means of eq.s(1). To this aim, a virtual IVGTT experiment is simulated on the AVP, which consists in administering intravenously 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. According to the usual IVGTT models, the bolus D_g , administered at time $t = 0$, produces an instantaneous increase in both glycemia and insulinemia, so that:

$$G(0) = G_b + \frac{D_g}{V_G} \quad I(0) = I_b + I_\Delta \frac{D_g}{V_G} \quad (10)$$

with I_Δ , a further parameter to be estimated. By following standard IVGTT clinical criteria, D_g is set at 300mg/kgBW and blood samples are acquired 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).

Like in Panunzi et al., 2007, the Generalized Least Square method has been applied, with:

- parameters G_b and I_b measured before the experiment (they enter the model as covariates);

Table 1. DDE model parameters of the AVP

T_{xg}	0.02	mM/min
\tilde{G}	$5.38 \cdot 10^{-4}$	mM
K_{xgi}	$6.55 \cdot 10^{-5}$	$\text{min}^{-1} \text{pM}^{-1}$
T_{ghmax}	0.0081	(mmol/kgBW)/min
V_G	0.24	L/kgBW
λ	$1.3 \cdot 10^{-3}$	$\text{mM}^{-1} \text{pM}^{-1}$
K_{xi}	0.0567	min^{-1}
T_{iGmax}	4.606	(pmol/kgBW)/min
τ_g	36.5	min
γ	4.33	-

- $V_I = 0.25 \text{L/kgBW}$ and $G^* = 9 \text{mM}$ fixed by the investigator and kept constant;
- $V_G, T_{xg}, \tilde{G}, K_{xgi}, K_{xi}, \gamma, \tau_g, \lambda$ free model parameters to be estimated;
- T_{iGmax}, T_{ghmax} determined from the other parameters according to the algebraic steady-state conditions.

Estimated small-scale DDE model parameters are reported in Table 1 for the AVP.

3.3 Glucose control synthesis

Once the DDE model parameters are identified for the AVP, the control scheme may be designed. According to the clamp experimental framework (DeFronzo et al., 1979), numerical simulations are carried out by assuming a staircase insulin input as described in Fig.1, with the insulin boli delivered each minute for 10 minutes, before administering a constant insulin infusion. By exploiting the theory developed in Palumbo et al. 2013 (and briefly reported in SubSection 2.2), the control law is designed by suitably choosing the control parameter r in (4) and the eigenvalues of matrix H in (7). Such a task is performed by means of simulations run by closing the loop on the DDE model itself (not on the AVP), since the regulator needs to be tuned and checked in silico before to be applied on a real/virtual patient. Below are reported the chosen parameters that will be adopted to design the controller when applied to the VPs:

$$r = 0.5 \quad \text{eig}(H) = \{-0.5, -0.6\} \quad (11)$$

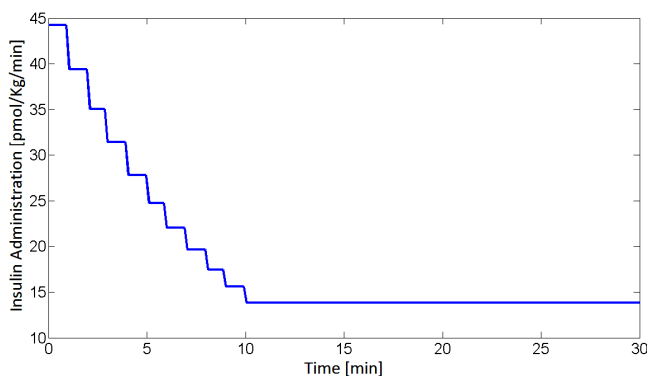


Fig. 1. Exogenous insulin administration for the EHC experiment.

Fig.2 shows the very good results when the closed-loop control law is applied to the DDE model, and the regulator works in a continuous-time fashion. The observer

initial estimates have been given with an error of 5% and 15% with respect to the real basal glycemia and insulinemia, respectively. Indeed, there are no significant glucose oscillations (with corresponding dangerous cases of hypoglycemia), as well as no periods of theoretical negative glucose 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 glucose). Notice that the exogenous insulin administration holds for the first 120min; nevertheless, the rest of the simulation is still under the control law.

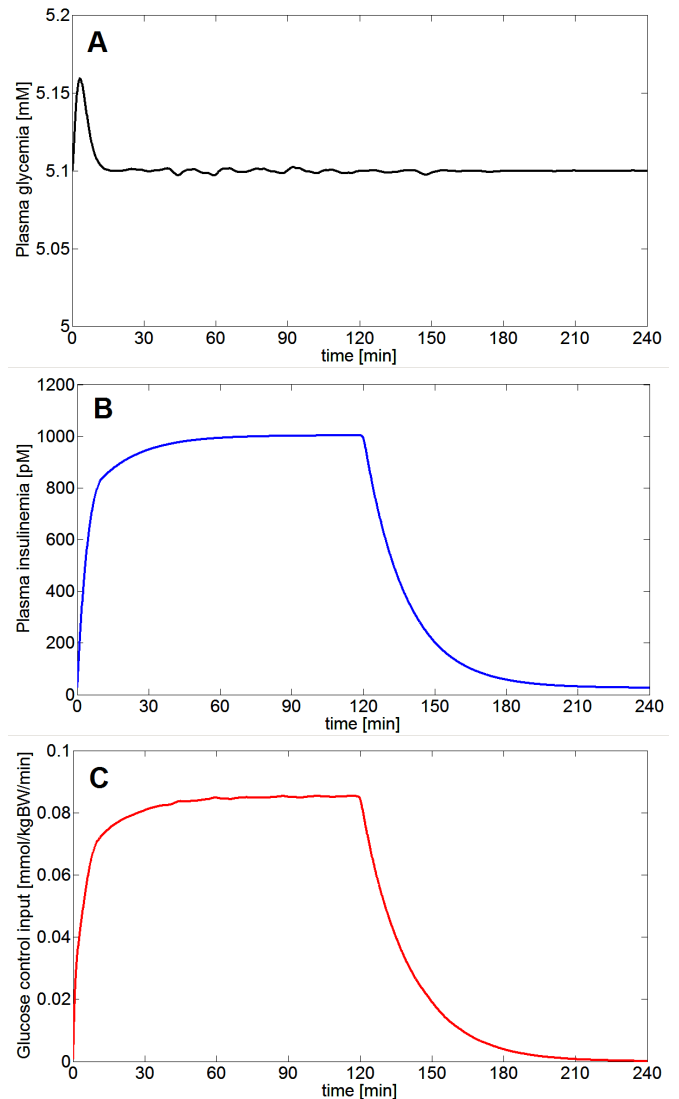


Fig. 2. Glucose (panel A) and insulin (panel B) profiles when closing the loop on the DDE model. Panel C reports the exogenous glucose administration.

3.4 Population of VPs

Once the control law parameters have been fixed, such a unique control law is applied to a population of 1,000 heterogeneous VPs, whose model parameters are distributed according to a log-normal distribution with population means given by the values taken from the AVP, and Coefficients of Variation (CV) set at 5%. It has to be stressed

that, by doing so, the patient characteristics may change so far that the resulting subject may not be any more a healthy subject. For this reason each virtual patient of the population has been chosen with a resulting basal glycemia between 4.5mM and 5.5mM.

3.5 The virtual environment

In real cases glucose measurements are not available in continuous time, but only at given sample times (whose frequency is limited by the time needed to analyze plasma glucose on a bed-side analyzer, see Chassin et al., 2004), nor the controller may work in continuous time, instead glucose is administered by means of piecewise-constant infusions.

Both these technical limitations will be taken into account to build the virtual environment. Indeed, let T be the sampling time according to which glucose measurements are acquired at times $t = kT$, and constant glucose and insulin infusion rates are administered, during intervals $[kT, (k + 1)T)$, $k = 0, 1, \dots$. Then, the regulator (4) is modified as follows, with the sampling time for simulations chosen equal to the sampling time adopted in the EHC experiment for the exogenous insulin administration: $T = 1\text{min}$.

$$\begin{aligned}
 u(t) &= u_k, \quad kT \leq t < (k + 1)T, \quad k = 0, 1, 2, \dots, \\
 u_k &= V_G \left(T_{xg} \frac{\hat{G}(kT)}{\hat{G}(kT) + \tilde{G}} + K_{xgi} \hat{G}(kT) \hat{I}(kT) \right. \\
 &\quad \left. - \frac{T_{ghmax}}{V_G} e^{-\lambda \hat{G}(kT) \hat{I}(kT)} - r(\hat{G}(kT) - G_b) \right),
 \end{aligned} \tag{12}$$

where $\hat{G}(t)$, $\hat{I}(t)$ are the estimates provided by the observer (5) with sampled-data measurements, i.e.

$$\begin{aligned}
 &\begin{bmatrix} \dot{\hat{G}}(t) \\ \dot{\hat{I}}(t) \end{bmatrix} \\
 &= \begin{bmatrix} -T_{xg} \frac{\hat{G}(t)}{\hat{G}(t) + \tilde{G}} - K_{xgi} \hat{G}(t) \hat{I}(t) + \frac{T_{ghmax}}{V_G} e^{-\lambda \hat{G}(t) \hat{I}(t)} \\ -K_{xi} \hat{I}(t) + \frac{T_{iGmax}}{V_I} f(\hat{G}(t - \tau_g)) \end{bmatrix} \\
 &+ \begin{bmatrix} u(t)/V_G \\ d(t)/V_I \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ p_1(\hat{G}(t), \hat{I}(t)) & p_2(\hat{G}(t), \hat{I}(t)) \end{bmatrix}^{-1} \\
 &\quad \cdot \Gamma(G(kT) - \hat{G}(kT)),
 \end{aligned} \tag{13}$$

with functions p_1, p_2 defined in (6) and the observer gain $\Gamma \in \mathbb{R}^2$ suitably chosen such that matrix H in (7) is Hurwitz.

Remark 2. It has to be stressed that the $\hat{G}(kT)$ in (12) can be replaced by $G(kT)$. Indeed, when using two distinct models (one for synthesizing the control law, the other for the VP onto the control loop is closed), as a matter of fact, the use of available (though noisy) glucose measurements instead of the ones estimated by means of an unmatched model, could be a successful heuristic. Of course, as far as the insulin is concerned, only the estimated one can be used.

Finally, glucose measurement errors and glucose pump malfunctioning have also been considered. The CVs used

Table 2. Safety and efficacy results on 1,000 VPs

Severe hypoglycemia (0%)
Hypoglycemia (0%)
Excellent efficacy (93.01%)
Good efficacy (6.88%)
Satisfactory efficacy (0.1%)
Unsatisfactory efficacy (0.01%)

for real-time glucose measurements and the glucose delivery rate have been assumed equal to 5% and 7%, respectively.

4. TESTS ON THE VIRTUAL ENVIRONMENT

Once the virtual environment has been designed, criteria for the evaluation of the proposed methodology need to be given, in order to properly test the effectiveness of the control scheme. The utility criteria chosen in order to state whether the proposed control reveals to be sufficiently safe and provides efficient results with respect to the population of VPs are inspired by Chassin et al., 2004, 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 fasting state virtual patient may provide

- *excellent efficacy*: plasma glycemia is constrained below 6.0mM within the simulation period;
- *good efficacy*: plasma glycemia is constrained below 7.0mM within the simulation period, and it exceeds 6.0mM in some points;
- *satisfactory efficacy*: plasma glycemia is constrained below 8.0mM within the simulation period, and it exceeds 7.0mM in some points;
- *unsatisfactory efficacy*: plasma glycemia exceeds the value of 8.0mM in some points.

Fig.3 reports plasma glycemia/insulinemia and the exogenous glucose infusion rate for one representative of the population of heterogenous virtual patients. The simulation period lasts for 240min: 120min during the EHC and the following 120min. Notice that despite the many errors affecting the measured glycemias, the input actuator and the discretization of the regulator, there are no episodes of hypoglycemia and excellent efficacy results.

Such a trend is obtained on a wide range of virtual patients, as it comes out from Table 2

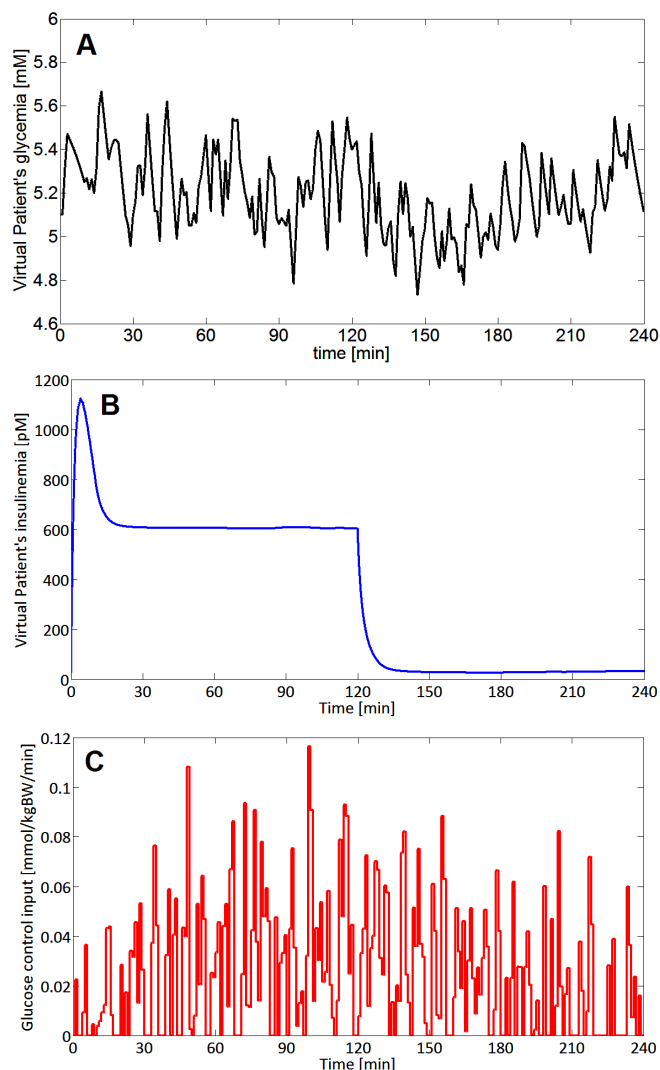


Fig. 3. Glucose (panel A) and insulin (panel B) profiles when closing the loop on a virtual patient. Panel C reports the exogenous glucose administration.

5. CONCLUDING REMARKS

In this work a virtual environment is set in order to test a DDE-model-based glucose control law in the experimental framework of the Euglycemic Hyperinsulinemic Clamp. The simulations are run in as much realistic details as possible, compatible with the available technology of glucose sensors and pump actuators. The control law is evaluated by closing the loop on a virtual patient, whose model equations have 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.

Despite the many sources of uncertainties, simulations on a rather heterogenous population of virtual patients revealed to be very encouraging, since no cases of hypoglycemias occurred, with the plasma glucose concentration quite never exceeding a too high level of hyperglycemia (only 1 case of unsatisfactory efficacy over a set of 1,000).

REFERENCES

- L.J. Chassin, M.E. Wilinska and R. Hovorka (2004), "Evaluation of glucose controllers in virtual environment: methodology and sample application," *Artificial Intelligence in Medicine*, 32, 171-181
- G. Ciccarella, M. Dalla Mora, A. Germani (1993), "A Luenberger-Like Observer for Nonlinear Systems," *International Journal of Control*, 57, 537-556.
- C. Dalla Man, R.A. Rizza and C. Cobelli (2007), "Meal simulation model of the glucose-insulin system," *IEEE Trans. Biomedic. Eng.*, 54, 1740-1749
- R.A. DeFronzo, J.D. Tobin, R. Andres, "Glucose clamp technique: a method for quantifying insulin secretion and resistance", *Am J Physiol.*, 237(3), E214-23, 1979.
- A. De Gaetano, S. Panunzi, A. Matone, A. Samson, J. Vrbikova, et al. "Routine OGTT: A Robust Model Including Incretin Effect for Precise Identification of Insulin Sensitivity and Secretion in a Single Individual," *PLoS ONE*, 8(8), 2013.
- B.P. Kovatchev, M.D. Breton, C. Dalla Man and C. Cobelli (2008), "In silico model and computer simulation environment approximating the human glucose/insulin utilization", Food and Drug Administration Master File MAF 1521
- P. Palumbo, S. Panunzi, A. De Gaetano, "Qualitative behavior of a family of delay differential models of the glucose insulin system," *Discrete and Continuous Dynamical Systems - Series B*, 7, 399-424, 2007.
- P. Palumbo, P. Pepe, S. Panunzi, A. De Gaetano, "Robust closed-loop control of plasma glycemia: a discrete-delay model approach", *Discrete and Continuous Dynamical Systems - Series B, Special Issue on Mathematical Biology and Medicine*, Vol.12, No.2, 455-468, 2009.
- 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*, 18(6), 2012.
- P. Palumbo, P. Pepe, S. Panunzi, A. De Gaetano, "Closed-loop glucose Control: Application to the Euglycemic Hyperinsulinemic Clamp", *52nd IEEE Conference on Decision and Control (CDC13)*, Florence, Italy, 2013
- P. Palumbo, G. Pizzichelli, S. Panunzi, P. Pepe, A. De Gaetano, "Tests on a virtual patient for an observer-based, closed-loop control of plasma glycemia", *50th IEEE Conference on Decision and Control and European Control Conference (CDC11)*, Orlando, Florida, 2011
- S. Panunzi, P. Palumbo, A. De Gaetano, "A discrete single delay model for the Intra-Venous Glucose Tolerance Test," *Theoretical Biology and Medical Modelling*, 4(35), 1-16, 2007.
- U. Picchini, S. Ditlevsen, A. De Gaetano, "Modeling the euglycemic hyperinsulinemic clamp by stochastic differential equations", *J. Mathematical Biology*, 53, 771-796, 2006.