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Time-Delay Model-Based Control of the Glucose–Insulin System, by Means of a State Observer

Pasquale Palumbo[1,*], Pierdomenico Pepe[2], Simona Panunzi[1], Andrea De Gaetano[1]

[1] Istituto di Analisi dei Sistemi ed Informatica "A. Ruberti", Consiglio Nazionale delle Ricerche (IASI-CNR), BioMatLab - UCSC - Largo A. Gemelli 8, 00168 Rome, Italy;
[2] Dipartimento di Ingegneria Elettrica e dell'Informazione, Università degli Studi dell'Aquila, 67040 Poggio di Roio, L'Aquila, Italy

The problem of tracking a desired plasma glucose evolution is considered, for cases of basal hyperglycemia. A time-delay model is used to describe the glucose–insulin regulatory system, aiming to detail the endogenous pancreatic insulin release, which is not negligible in Type 2 diabetic patients. Insulin is assumed to be administered by means of intra-venous infusions. Only measurements of glycemia are considered: to this aim a nonlinear observer for time-delay systems is used to estimate the plasma insulin concentration. In the spirit of the separation theorem, a nonlinear control law is proposed, based on the exact input/output feedback linearization, which makes use of the observer estimates instead of the full state measurements. The local convergence of the tracking error to zero is theoretically proved. Simulations are performed in a virtual environment, taking into account the standard technology concerning blood glucose sensors and insulin delivery devices. Numerical results show the robustness of the proposed approach with respect to the uncertainties of the model parameters, as well as to the glucose measurement errors and insulin pump malfunctioning.

Keywords: Time-delay systems, nonlinear systems, state observers, glucose–insulin system.

1. Introduction

Diabetes is a major chronic disease affecting around 5 to 6% of the world population, with a heavy impact on national public health budgets. The term "diabetes" comprises a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Several processes are in fact involved in the development of diabetes, ranging from autoimmune destruction of pancreatic beta-cells with attendant insulin deficiency, to metabolic abnormalities resulting in resistance to insulin action, with consequent hyperglycemia. The chronic hyperglycemia of diabetes is associated with several long-term damage, dysfunction, and failure of different organs, especially eyes, kidneys, nerves, heart, and blood vessels. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular disease. Hypertension, abnormalities of lipoprotein metabolism, and periodontal disease are often found in people with diabetes. 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

*Correspondence to: P. Palumbo, E-mail: pasquale.palumbo@iasi.cnr.it

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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 any 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). From a clinical point of view, different therapeutic schemes can be considered, depending on the accuracy of the *a priori* knowledge of the patient's own glucose–insulin homeostasis and on the technology available for actuating the designed control law. Glucose control strategies are mainly actuated by subcutaneous or intravenous injections or infusions. Other drug delivery methods are still under investigation, even though the *Food and Drug Administration (FDA)* has recently approved a device for delivery of a powder form of insulin by inhalation, as an alternative to subcutaneous injections, [31]. Control of glycemia by means of subcutaneous insulin injections, with the dose adjusted on the basis of capillary plasma glucose concentration measurements, is by far more widespread than control by means of intravenous insulin, since the dose is habitually administered by the patients themselves (see [2] 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 e.g., [28, 35, 44, 54] for a comprehensive review of subcutaneous absorption models and [11] 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., [7, 23, 32, 50]). 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. Model-based glucose control has been mainly developed for the Ackerman's linear model, [1] (e.g., adaptive control in [37], optimal control in [17, 51], H_∞ control in [27]); more recently, different approaches have been proposed, based on nonlinear models such as the Minimal Model, [3, 52], or more exhaustive compartmental models, [12, 26, 49], (e.g., Model Predictive Control in [25], Parametric Programming in [15], Neural Predictive Control in [53], H_∞ control in [43], non-standard H_∞ control in [8, 46]). 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). 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 [6] and references therein.

In the present work, a model-based closed-loop control scheme is proposed. Exogenous insulin is supposed to be administered intra-venously like many of the previously cited approaches ([8, 15, 17, 27, 43, 46]), and glucose measurements are also assumed to be acquired intra-venously, for instance by using implanted devices like the ones supplied by Medtronic MiniMed Inc. (www.minimed.com). Differently from previously mentioned model-based approaches, which use nonlinear Ordinary Differential Equation (ODE) models, the one presented here uses a nonlinear discrete-Delay Differential Equation (DDE) model of the glucose/insulin system, [38, 42]. Since the work of [13], several DDE models have been published, mainly aiming at a better representation of the pancreatic Insulin Delivery Rate (IDR) (e.g., [29, 30] and references therein). It has to be stressed that 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 the present work we do take into account spontaneous pancreatic IDR, thereby treating healthy, Type 2 diabetic and Type 1 diabetic patients in a unified fashion. The glucose/insulin model we use to represent the natural dynamics of the system has been shown to exhibit a number of desirable characteristics, such as to conform to established physiological concepts (e.g., pancreatic insulin secretion rate is limited), to exhibit satisfactory properties of the solutions (e.g., positivity and boundedness of solutions, local attractivity of a single positive equilibrium, [38]), and to be statistically

robust, in that its parameters are identifiable with very good precision by means of standard perturbation experiments, such as the Intra-Venous Glucose Tolerance Test (IVGTT), [42].

The proposed control law aims to track a desired glucose reference level by means of intravenous insulin infusion, according to a given smooth glucose trajectory. To this aim, in [39] the input–output feedback linearization with delay cancellation has been used (see [19, 21, 36]), with a state-feedback depending on both glucose and insulin measurements at the present and at a delayed time. Nevertheless, insulin measurements are slower and more cumbersome to obtain, more expensive, and also less accurate than glucose measurements: a need exists, therefore, to construct a control law avoiding the measurements of insulin in serum. The present paper makes use of a state observer for nonlinear time-delay systems in order to perform the glucose reference tracking by means of only glucose measurements. Most works concerning observers for time-delay systems consider the linear case (see, for instance, [48] and references therein). Among the most recent works on observers for nonlinear time-delay systems we may cite [16] and references therein. The observer, here adopted in order to compensate for the lack of insulin measures and to close the loop by using only glucose measurements, is the one developed in [20, 22] for nonlinear time-delay systems. The local convergence of the tracking error to zero is theoretically proved. Some preliminary results have been presented in [40].

In order to show the good performance provided by the proposed control law, a virtual environment has been implemented to test the insulin infusion programme according to a device implementable algorithm which takes into account the available technology concerning both glucose sensors and insulin delivery devices, as well as the unavoidable uncertainties regarding the model parameter estimates. In fact, before arranging an *in-vivo* clinical setting of experiments (which are usually costly, time-consuming and confounded by ethical issues) *in-silico* tests need to be thoroughly carried out on a virtual patient (or even on a population of virtual patients), making it possible to evaluate a possibly exhaustive set of different scenarios, including cases of measurement error and other failures, [5].

The paper is organized as follows: next section deals with some preliminaries, including a short description of the adopted DDE model of the glucose–insulin system and previous results on the input–output state-feedback linearization related to it; Section 3 is devoted to develop the main results, detailing on the theoretical properties concerning the proposed observer-based control algorithm. Simulations are reported in Section 4. Conclusions follow.

2. Preliminaries

Denote with $G(t)$, [mM], $I(t)$, [pM], plasma glycemia and insulinemia, respectively. The glucose–insulin model considered here belongs to the family of DDE models described in [38] and consists of a single discrete-delay differential equation system:

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

with

$$G(\tau) = G_0(\tau), \quad I(\tau) = I_0(\tau), \qquad \tau \in [-\tau_g, 0], \tag{2}$$

where K_{xgi}, [$\text{min}^{-1}\,\text{pM}^{-1}$], is the rate of glucose uptake by tissues (insulin-dependent) per pM of plasma insulin concentration; T_{gh}, [min^{-1}(mmol/kgBW)], is the net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake (mainly by the brain); V_G, [L/kgBW], is the apparent distribution volume for glucose; K_{xi}, [min^{-1}], is the apparent first-order disappearance rate constant for insulin; T_{iGmax}, [min^{-1}(pmol/kgBW)], is the maximal rate of second-phase insulin release; V_I, [L/kgBW], is the apparent distribution volume for insulin; τ_g, [min], is the apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations; $u(t)$, [pM/min], is the exogenous intra-venous insulin delivery rate, i.e., the control input.

$\big(G_0(\tau), I_0(\tau)\big)$ is the pair of initial conditions, corresponding to the plasma glucose/insulin concentrations before the control input $u(t)$ is applied. For instance, they can be assumed equal to the constant basal levels (G_b, I_b).

The nonlinear function $f(\cdot)$ models the pancreatic Insulin Delivery Rate as:

$$f(G) = \frac{\left(\dfrac{G}{G^*}\right)^{\gamma}}{1 + \left(\dfrac{G}{G^*}\right)^{\gamma}}, \tag{3}$$

where γ (dimensionless parameter) 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 maximal rate.

In [38] it has been proven that model (1) provides persistent positive bounded solutions for any positive, continuous initial condition, with no exogenous input

function, that means:

$$\begin{aligned} 0 < \liminf_{t\mapsto+\infty} G(t) \le \limsup_{t\mapsto+\infty} G(t) < +\infty, \\ 0 < \liminf_{t\mapsto+\infty} I(t) \le \limsup_{t\mapsto+\infty} I(t) < +\infty \end{aligned} \tag{4}$$

The extension of the above mentioned properties to the actual case with physically meaningful exogenous inputs (i.e., $u(\cdot)$ non-negative and bounded on $\mathbb{R}^+$) is straightforward. Moreover, model (1) with $u(t) \equiv 0$ admits a unique locally/globally asymptotically stable equilibrium point, according to necessary and sufficient conditions; the case of local stability is usually satisfied according to a very wide range of model parameters (in fact, the whole admissible parameter space).

It has to be stressed that the DDE model (1) represents equally well healthy subjects and insulin-resistant or severe diabetic patients, changing the parameter values as appropriate. 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 is identifiable from data with very good precision, according to standard perturbation experiments (e.g., the IVGTT) (see [42]).

A nice structural property of the chosen glucose–insulin model is that it allows local input–output feedback linearization with delay cancellation (see [19, 21, 36]) with respect to the output $y(t) = G(t)$ and the input $u(t)$. We stress that it is not always possible, for a nonlinear time-delay system, to cancel nonlinearities and delays by means of an inner feedback control law, in order to obtain a linear input–output map. Causality problems as well as internal instabilities can occur even in the case the system at hand admits full relative degree. In fact, dealing with time-delay systems, there can be found different definitions of relative degree, according to the different purposes they may be used for (see [21], [33], [36]). An analysis of such definitions is given in [21], where the relative degrees of Type I, Type II and Type III are reported. According to that notation, as far as the input–output linearization (and stabilization) is concerned, a sufficient condition which allows local input–output feedback linearization with delay cancelation, without any problem of causality or internal stability, is that the system at hand admits full relative degree of Type III [21, 36]. On the other hand, in case of full relative degree of Type I, causality problems can occur since the input–output linearization may require a delayed input to be a feedback of the system variables at the present time. Finally, in case of full relative degree of Type II, in general, the input-to-output stability of the closed-loop system does not guarantee the input-to-state stability of the closed-loop system. Indeed, the overall closed-loop system is in general described by coupled delay differential and difference equations, and it may well happen that the state variables diverge, though the output variable and its derivative up to a suitable order converge to zero or are taken bounded by the control law. Also, the controller may exhibit a dynamics described by a continuous time difference equation which has to be taken into account (see [21] for the relationship between internal dynamics and controller dynamics).

According to the above mentioned notation, the DDE model (1) admits full (equal to 2) relative degree of Type III. Therefore, input–output linearization with delay cancelation, and tracking of a suitable output reference signal can be achieved, by means of suitable inner and outer feedback control laws, with guaranteed internal stability (see [18], [36]). In particular, a reliable, causal state feedback which allows to reduce a high basal plasma glucose concentration to a lower level, according to a smooth reference glucose trajectory $G_{\text{ref}}(t)$, can be designed. Related results are shown in [39], where the following feedback control law is found, in the case the full state is accessible to measures:

$$u(t) = \frac{S\big(G(t), I(t), G(t-\tau_g)\big) - v(t)}{K_{xgi} G(t)}, \qquad t \ge 0, \tag{5}$$

where

$$\begin{aligned} &S\big(G(t), I(t), G(t-\tau_g)\big) \\ &\quad = -K_{xgi} I(t) \left(-K_{xgi} I(t) G(t) + \frac{T_{gh}}{V_G}\right) \\ &\qquad - K_{xgi} G(t) \left(-K_{xi} I(t) + \frac{T_{iGmax}}{V_I} f\big(G(t-\tau_g)\big)\right) \end{aligned} \tag{6}$$

and

$$v(t) = \ddot{G}_{\text{ref}}(t) + Re(t); \tag{7}$$

$R \in \mathbb{R}^{1\times 2}$ is a matrix such that:

$$H = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} R \tag{8}$$

has prescribed eigenvalues in the left half complex plane and

$$e(t) = \begin{bmatrix} e_1(t) \\ e_2(t) \end{bmatrix} = Z(t) - Z_{\text{ref}}(t), \tag{9}$$

with

$$\begin{aligned} Z(t) &= \begin{bmatrix} z_1(t) \\ z_2(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ -K_{xgi} G(t) I(t) + \dfrac{T_{gh}}{V_G} \end{bmatrix}, \\ Z_{\text{ref}}(t) &= \begin{bmatrix} G_{\text{ref}}(t) \\ \dot{G}_{\text{ref}}(t) \end{bmatrix}. \end{aligned} \tag{10}$$

$G_{\text{ref}}(t)$ is the glucose reference signal to be tracked: it is supposed to be bounded (with lower bound strictly positive), twice continuously differentiable, with bounded first and second derivatives. Since $G_{\text{ref}}(t)$ provides the desired plasma glucose concentration, it clearly comes that all the previously mentioned constraints readily match with a physiologically meaningful choice.

It is shown in [39] that, by applying (5)–(10) the tracking error variable $e(t)$ asymptotically converges to zero, since:

$$\dot{e}(t) = He(t), \quad H \text{ Hurwitz, according to (8).} \tag{11}$$

Before stating the main results in the next section, it will be useful to define the following signals related to the reference glucose trajectory:

$$\begin{aligned} I_{\text{ref}}(t) &= \frac{\dfrac{T_{gh}}{V_G} - \dot{G}_{\text{ref}}(t)}{K_{xgi} G_{\text{ref}}(t)}, \qquad t \geq 0, \\ u_{\text{ref}}(t) &= \dot{I}_{\text{ref}}(t) + K_{xi} I_{\text{ref}}(t) \\ &\quad - \frac{T_{iGmax}}{V_I} f(G_{\text{ref}}(t - \tau_g)), \quad t \geq \tau_g \end{aligned} \tag{12}$$

If, given a time instant $\bar{t} \geq \tau_g$, it is:

$$G(\tau) = G_{\text{ref}}(\tau), \quad I(\tau) = I_{\text{ref}}(\tau), \quad \tau \in [\bar{t} - \tau_g, \bar{t}], \tag{13}$$

and the control law $u(t)$ designed as in (5)–(10) is applied, then the solution of (1) is

$$G(t) = G_{\text{ref}}(t), \quad I(t) = I_{\text{ref}}(t), \quad t \geq \bar{t}, \tag{14}$$

and the control law becomes $u(t) = u_{\text{ref}}(t)$, $t \geq \bar{t}$. In other words, once G_{ref} has been chosen, we may compute I_{ref} and u_{ref} (as in (12)) as the insulinemia and the input references which asymptotically correspond to a perfect tracking of G_{ref}. In order to extend the input reference signal u_{ref} also in $[0, \tau_g]$, we will formally consider G_{ref} also in $[-\tau_g, 0]$ and, consequently, also I_{ref} by (12). For instance we can choose in $[-\tau_g, 0]$ any bounded (with lower bound strictly positive), continuously differentiable function, such that $G_{\text{ref}}(0^-) = G_{\text{ref}}(0^+)$. Note that by defining G_{ref} also in $[-\tau_g, 0]$, the perfect tracking in (14) holds for any $\bar{t} \geq 0$, under conditions (13). In the following, whenever used, the derivatives of $G_{\text{ref}}(t)$ in $t = 0$ are right-hand ones.

3. Main Results

The control law provided by (5)–(10) 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. A need exists, therefore, to construct a control law avoiding the measurements of insulin serum. To this aim a state observer for system (1) is considered in order to estimate the plasma insulin concentration and to design a feedback control law based on only glucose measurements $y(t) = G(t)$. By suitably exploiting the state observer theory for nonlinear time-delay systems developed in [22] (indeed, model (1) belongs to the class of DDE systems considered in [22]), the observer equations for the glucose/insulin estimates $\widehat{G}(t)$ and $\widehat{I}(t)$ are given by

$$\begin{aligned} \begin{bmatrix} \dfrac{d\widehat{G}(t)}{dt} \\ \dfrac{d\widehat{I}(t)}{dt} \end{bmatrix} &= \begin{bmatrix} -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \dfrac{T_{gh}}{V_G} \\ -K_{xi}\hat{I}(t) + \dfrac{T_{iGmax}}{V_I} f\big(\widehat{G}(t - \tau_g)\big) + u(t) \end{bmatrix} \\ &\quad + Q^{-1}\big(\widehat{G}(t), \widehat{I}(t)\big) W \big(G(t) - \widehat{G}(t)\big), \end{aligned} \tag{15}$$

for $t \geq 0$, with

$$\widehat{G}(\tau) = \widehat{G}_0(\tau), \quad \widehat{I}(\tau) = \widehat{I}_0(\tau), \quad \tau \in [-\tau_g, 0], \tag{16}$$

where:

- $Q^{-1} \in \mathbb{R}^{2\times 2}$ is the inverse matrix (not the inverse function, see [9, 14]) of the Jacobian of the observability map (see [20]), here given, for $\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \in \mathbb{R}^2$, by $\begin{bmatrix} x_1 \\ -K_{xgi}x_1x_2 + \frac{T_{gh}}{V_G} \end{bmatrix}$; therefore, $Q(x_1, x_2)$ is given by

$$Q(x_1, x_2) = \begin{bmatrix} 1 & 0 \\ -K_{xgi}x_2 & -K_{xgi}x_1 \end{bmatrix}; \tag{17}$$

- the gain matrix $W \in \mathbb{R}^{2\times 1}$ is chosen in order to assign suitable eigenvalues to matrix $\widehat{H}$, defined by means of the Brunowski pair (A_b, C_b) as

$$\begin{aligned} &\widehat{H} = A_b - WC_b, \\ &\text{where} \quad A_b = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}, \quad C_b = \begin{bmatrix} 1 & 0 \end{bmatrix}. \end{aligned} \tag{18}$$

Notice that the observer algorithm (15)–(18) is described by a delay differential equation, as for the class of systems studied in [22], and not by a neutral delay differential equation as in general it may happen for the class of systems studied in [20]. A nice property concerning the observer (15)–(18) is that, by assuming physically meaningful input signals, a matrix W can be designed such that, if the estimation error at zero is sufficiently small, the estimation error converges exponentially to zero (see [22]). Moreover, the decay rate can be arbitrarily fixed by the choice of W. We do not go into the details, here, on how to design W for the observer. It will be the matter of the main

theorem below. We stress here that our objective is the convergence to zero of the tracking error, when the control law (5)–(10) recalled in the previous section makes use of the estimated variables provided by the observer (15)–(18), instead of the state variables.

Indeed, in order to close the loop from the observed state, we consider the feedback control law:

$$u(t) = \frac{S\big(\widehat{G}(t), \widehat{I}(t), \widehat{G}(t-\tau_g)\big) - v(t)}{K_{xgi}\widehat{G}(t)}, \qquad t \geq 0 \tag{19}$$

with

$$v(t) = \ddot{G}_{\text{ref}}(t) + R\hat{e}(t), \tag{20}$$

where

$$\hat{e}(t) = \begin{bmatrix} \hat{e}_1(t) \\ \hat{e}_2(t) \end{bmatrix} = \widehat{Z}(t) - Z_{\text{ref}}(t), \tag{21}$$

and

$$\widehat{Z}(t) = \begin{bmatrix} \hat{z}_1(t) \\ \hat{z}_2(t) \end{bmatrix} = \begin{bmatrix} \widehat{G}(t) \\ -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \dfrac{T_{gh}}{V_G} \end{bmatrix}. \tag{22}$$

Such control law does not make use of insulin measurements, differently from the control law (5)–(10). Actually, it makes use of the glucose and insulin estimations provided by the observer, on the basis of only glucose measurements.

Note that if $G_0(\tau) = \widehat{G}_0(\tau) = G_{\text{ref}}(\tau)$ and $I_0(\tau) = \widehat{I}_0(\tau) = I_{\text{ref}}(\tau)$, for $\tau \in [-\tau_g, 0]$, i.e., the initial tracking error and the initial estimation error are zero, then the solution of the closed-loop system (1), (15)–(22) is given by:

$$\begin{bmatrix} G(t) \\ I(t) \\ \widehat{G}(t) \\ \widehat{I}(t) \end{bmatrix} = \begin{bmatrix} G_{\text{ref}}(t) \\ I_{\text{ref}}(t) \\ G_{\text{ref}}(t) \\ I_{\text{ref}}(t) \end{bmatrix}, \qquad t \geq 0, \tag{23}$$

with the input reference signal u_{ref} as in (12). We will refer to the solution (23) as the *state reference trajectory*.

Before to state the main Theorem, it is useful to recall the following Lemma, already used in [20], which will be suitably exploited. It concerns a particular case covered by the Bellman-Gronwall Lemma (see Proposition 3.21 at p. 86, in [47]).

Lemma 1: *Let $m : \mathbb{R}^+ \mapsto \mathbb{R}^+$ and $v : \mathbb{R}^+ \mapsto \mathbb{R}^+$ be continuous functions, α, β be positive constants, such that the following inequality holds, $\forall\, t \geq 0$:*

$$m(t) \leq \alpha + \int_0^t v(\tau)d\tau + \beta \int_0^t m(\tau)d\tau. \tag{24}$$

Then, the following inequality holds, $\forall\, t \geq 0$:

$$m(t) \leq \alpha e^{\beta t} + \int_0^t e^{\beta(t-\tau)} v(\tau)d\tau. \tag{25}$$

Also, in the proof of the forthcoming Theorem, the following time functions $r_0(t) = \begin{bmatrix} r_{0,a}(t) & r_{0,b}(t) \end{bmatrix} : \mathbb{R}^+ \mapsto \mathbb{R}^{1\times 2}$ and $r_1(t) : \mathbb{R}^+ \mapsto \mathbb{R}$ will be used, well defined once the reference signals have been chosen:

$$\begin{aligned} r_{0,a}(t) = &-K_{xgi}^2 I_{\text{ref}}^2(t) + K_{xgi}\frac{T_{gh}}{V_G}\frac{I_{\text{ref}}(t)}{G_{\text{ref}}(t)} \\ &- K_{xgi}\frac{T_{iGmax}}{V_I} f\big(G_{\text{ref}}(t-\tau_g)\big) \\ &+ \frac{\ddot{G}_{\text{ref}}(t) - S\big(G_{\text{ref}}(t), I_{\text{ref}}(t), G_{\text{ref}}(t-\tau_g)\big)}{G_{\text{ref}}(t)}, \end{aligned} \tag{26}$$

$$r_{0,b}(t) = -2K_{xgi}I_{\text{ref}}(t) + \frac{T_{gh}}{V_G G_{\text{ref}}(t)} - K_{xi}, \tag{27}$$

$$r_1(t) = -K_{xgi}G_{\text{ref}}(t)\frac{T_{iGmax}}{V_I}\left.\frac{df(y)}{dy}\right|_{y=G_{\text{ref}}(t-\tau_g)}. \tag{28}$$

Note that, since G_{ref} (and consequently I_{ref}) is chosen by the designer as a physiologically meaningful signal, r_0 and r_1 are bounded in $\mathbb{R}^+$. Thus, the following bounds are well defined for the chosen reference signal:

$$\begin{aligned} &r = \sup_{t\geq 0} \max\{\|r_0(t)\|, |r_1(t)|\}, \qquad \underline{r_{0,a}} = \inf_{t\geq 0} r_{0,a}(t), \\ &\overline{r_{0,a}} = \sup_{t\geq 0} r_{0,a}(t), \qquad \underline{r_{0,b}} = \inf_{t\geq 0} r_{0,b}(t), \\ &\overline{r_{0,b}} = \sup_{t\geq 0} r_{0,b}(t), \qquad \underline{r_1} = \inf_{t\geq 0} r_1(t), \qquad \overline{r_1} = \sup_{t\geq 0} r_1(t), \\ &r_{0,m} = \left[\frac{1}{2}\left(\overline{r_{0,a}} + \underline{r_{0,a}}\right) \quad \frac{1}{2}\left(\overline{r_{0,b}} + \underline{r_{0,b}}\right)\right], \\ &r_{1,m} = \frac{1}{2}\left(\overline{r_1} + \underline{r_1}\right). \end{aligned} \tag{29}$$

Theorem 2: *Consider the closed-loop system (1), (15)–(22), with the state reference trajectory given by* (23). *Choose matrix R in order to assign (arbitrary) negative real eigenvalues to matrix H. Then, there exist a matrix W such that:*

i) for any $\epsilon > 0$ there exist $\delta > 0$ such that, if the initial conditions (2) *and* (16) *satisfy*

$$\begin{aligned} &\sup_{\tau\in[-\tau_g,0]} |G_0(\tau) - G_{\text{ref}}(\tau)| < \delta, \\ &\sup_{\tau\in[-\tau_g,0]} |G_0(\tau) - \widehat{G}_0(\tau)| < \delta, \end{aligned} \tag{30}$$

and

$$|I_0(0) - I_{\text{ref}}(0)| < \delta, \qquad |I_0(0) - \widehat{I}_0(0)| < \delta, \quad (31)$$

then the corresponding solution and control law satisfy

$$\left\| \begin{bmatrix} G(t) \\ I(t) \\ \widehat{G}(t) \\ \widehat{I}(t) \end{bmatrix} - \begin{bmatrix} G_{\text{ref}}(t) \\ I_{\text{ref}}(t) \\ G_{\text{ref}}(t) \\ I_{\text{ref}}(t) \end{bmatrix} \right\| < \epsilon,$$
$$|u(t) - u_{\text{ref}}(t)| < \epsilon, \qquad t \geq 0; \quad (32)$$

ii) there exists $\eta > 0$ *such that, if the initial conditions* (2) *and* (16) *satisfy*

$$\begin{aligned} &\sup_{\tau \in [-\tau_g, 0]} |G_0(\tau) - G_{\text{ref}}(\tau)| < \eta, \\ &\sup_{\tau \in [-\tau_g, 0]} |G_0(\tau) - \widehat{G}_0(\tau)| < \eta, \end{aligned} \quad (33)$$

and

$$|I_0(0) - I_{\text{ref}}(0)| < \eta, \qquad |I_0(0) - \widehat{I}_0(0)| < \eta, \quad (34)$$

then the corresponding solution and control law satisfy

$$\lim_{t \to +\infty} \begin{bmatrix} G(t) - G_{\text{ref}}(t) \\ I(t) - I_{\text{ref}}(t) \end{bmatrix} = \lim_{t \to +\infty} \begin{bmatrix} \widehat{G}(t) - G_{\text{ref}}(t) \\ \widehat{I}(t) - I_{\text{ref}}(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \quad (35)$$

$$\lim_{t \to +\infty} \left| u(t) - u_{\text{ref}}(t) \right| = 0. \quad (36)$$

Proof: As in [10], concerning nonlinear delay-free systems, the closed-loop system (1), (15)–(22), can be rewritten, by introducing the new variables $\hat{e}(t)$ (defined in (21)) and

$$\xi(t) = \begin{bmatrix} \xi_1(t) \\ \xi_2(t) \end{bmatrix} = e(t) - \hat{e}(t), \quad (37)$$

in the following form, for $t \geq 0$,

$$\begin{aligned} \dot{\hat{e}}(t) &= H\hat{e}(t) + WC\xi(t) \\ \dot{\xi}(t) &= \widehat{H}\xi(t) + BL\big(t, \xi(t), \xi(t-\tau_g), \hat{e}(t), \hat{e}(t-\tau_g)\big), \end{aligned} \quad (38)$$

where: $B = \begin{bmatrix} 0 & 1 \end{bmatrix}^T$, $C = \begin{bmatrix} 1 & 0 \end{bmatrix}$, and L is the nonlinear function defined as

$$\begin{aligned} &L\big(t, \xi(t), \xi(t-\tau_g), \hat{e}(t), \hat{e}(t-\tau_g)\big) \\ &\quad = -\ddot{G}_{\text{ref}}(t) - R\hat{e}(t) + S\Bigg(\xi_1(t) + \hat{e}_1(t) + G_{\text{ref}}(t), \\ &\qquad \frac{\frac{T_{gh}}{V_G} - \xi_2(t) - \hat{e}_2(t) - \dot{G}_{\text{ref}}(t)}{K_{xgi}(\xi_1(t) + \hat{e}_1(t) + G_{\text{ref}}(t))}, \\ &\qquad \xi_1(t-\tau_g) + \hat{e}_1(t-\tau_g) + G_{\text{ref}}(t-\tau_g)\Bigg) \\ &\qquad - \frac{\xi_1(t) + \hat{e}_1(t) + G_{\text{ref}}(t)}{\hat{e}_1(t) + G_{\text{ref}}(t)} \\ &\qquad \cdot \Bigg(S\Bigg(\hat{e}_1(t) + G_{\text{ref}}(t), \frac{\frac{T_{gh}}{V_G} - \hat{e}_2(t) - \dot{G}_{\text{ref}}(t)}{K_{xgi}(\hat{e}_1(t) + G_{\text{ref}}(t))}, \\ &\qquad \hat{e}_1(t-\tau_g) + G_{\text{ref}}(t-\tau_g)\Bigg) \\ &\qquad - \ddot{G}_{\text{ref}}(t) - R\hat{e}(t)\Bigg) \end{aligned} \quad (39)$$

As far as the solutions of the closed-loop system (1), (15)–(22) are concerned, the hypotheses i), ii) of the theorem are equivalent to the asymptotic stability of the origin of system (38). Such a task will be achieved by suitably exploiting the linear approximation of the closed loop system (38) around zero. To this aim, note that the nonlinear function L is such that, $L(t, 0, 0, 0, 0) = 0$, $\forall t \geq 0$ and, moreover, by denoting with $\nabla_{\alpha_i} L(t, \alpha_1, \alpha_2, \alpha_3, \alpha_4)$ the gradient vector of L with respect to $\alpha_i \in \mathbb{R}^2$, $i = 1, 2, 3, 4$, it is:

$$\begin{aligned} &\nabla_{\alpha_3} L(t, \alpha_1, \alpha_2, \alpha_3, \alpha_4)\big|_{\alpha_1=\alpha_2=\alpha_3=\alpha_4=0} = 0, \\ &\nabla_{\alpha_4} L(t, \alpha_1, \alpha_2, \alpha_3, \alpha_4)\big|_{\alpha_1=\alpha_2=\alpha_3=\alpha_4=0} = 0. \end{aligned} \quad (40)$$

Thus, the linearization around zero of the closed loop system (38) returns the following time-delay system:

$$\begin{aligned} \dot{\hat{e}}(t) &= H\hat{e}(t) + WC\xi(t) \\ \dot{\xi}(t) &= \widehat{H}\xi(t) + Br_0(t)\xi(t) + r_1(t)BC\xi(t-\tau_g), \end{aligned} \quad (41)$$

with $r_0(t) = \begin{bmatrix} r_{0,a}(t) & r_{0,b}(t) \end{bmatrix}$ and $r_1(t)$ given in (26)–(28). Therefore, by stability in the first approximation method, the asymptotic stability of the origin (the uniformity here is not necessary) of the closed loop, nonlinear, time-varying, time-delay system (38) is guaranteed by the asymptotic stability of the linear, time-varying, time-delay system (41). In the following it will be proven that, once matrix R has been chosen in order to assign (arbitrarily) negative real eigenvalues to matrix H, there exist a matrix W such

that the linear time-delay system (41) is asymptotically stable, for every bounded functions $r_0(t)$, $r_1(t)$.

To this aim, consider the second equation in (41). Without loss of generality, assume that matrix $\widehat{H}$ has distinct negative real eigenvalues $\lambda = (\lambda_1, \lambda_2)$, with $\lambda_1 > \lambda_2$. Let $V(\lambda)$ be the Vandermonde matrix associated to λ (see [9, 14]):

$$V(\lambda) = \begin{bmatrix} \lambda_1 & 1 \\ \lambda_2 & 1 \end{bmatrix}. \tag{42}$$

By setting $\psi(t) = V(\lambda)\xi(t)$ and $\chi(t) = e^{-\lambda_1 t}\|\psi(t)\|$, the following inequality holds:

$$\begin{aligned}\chi(t) \leq \chi(0) &+ \int_0^t \sqrt{2}r\|V^{-1}(\lambda)\|\chi(\tau)d\tau \\ &+ \int_0^t \sqrt{2}r\|V^{-1}(\lambda)\|e^{-\lambda_1\tau}\|\psi(\tau-\tau_g)\|d\tau,\end{aligned} \tag{43}$$

with r defined in (29). Then, by applying (25) in Lemma 1, it is:

$$\begin{aligned}\|\psi(t)\| &\leq e^{(\sqrt{2}r\|V^{-1}(\lambda)\|+\lambda_1)t}\|\psi(0)\| \\ &+\int_0^t \sqrt{2}r\|V^{-1}(\lambda)\|e^{(\sqrt{2}r\|V^{-1}(\lambda)\|+\lambda_1)(t-\tau)}\|\psi(\tau-\tau_g)\|d\tau.\end{aligned} \tag{44}$$

The next step of the proof is to show that there exists a function $s : [-\tau_g, +\infty) \mapsto \mathbb{R}^+$ defined by:

$$s(t) = e^{\varrho t}\|V(\lambda)\| \sup_{\tau\in[-\tau_g,0]} \|\xi(\tau)\|, \qquad t \geq -\tau_g, \tag{45}$$

for some negative real ϱ, which satisfies the equation

$$\begin{aligned}s(t) &= e^{(\sqrt{2}r\|V^{-1}(\lambda)\|+\lambda_1)t}s(0) \\ &+ \int_0^t \sqrt{2}r\|V^{-1}(\lambda)\|e^{(\sqrt{2}r\|V^{-1}(\lambda)\|+\lambda_1)(t-\tau)}s(\tau-\tau_g)d\tau.\end{aligned} \tag{46}$$

To this aim, if we substitute $s(t) = \beta e^{\varrho t}$ in (46), with $\beta = \|V(\lambda)\| \sup_{\tau\in[-\tau_g,0]} \|\xi(\tau)\|$, it is:

$$\begin{aligned}\beta e^{\varrho t} &= e^{(\sqrt{2}r\|V^{-1}(\lambda)\|+\lambda_1)t}\beta \\ &+ \int_0^t \sqrt{2}r\|V^{-1}(\lambda)\|e^{(\sqrt{2}r\|V^{-1}(\lambda)\|+\lambda_1)(t-\tau)+\varrho(\tau-\tau_g)}\beta d\tau,\end{aligned} \tag{47}$$

and, if we explicitly compute the integral in (47), we obtain the following condition to be fulfilled for ϱ:

$$\sqrt{2}r\|V^{-1}(\lambda)\|e^{-\varrho\tau_g} = \varrho - \sqrt{2}r\|V^{-1}(\lambda)\| - \lambda_1, \tag{48}$$

which admits a unique negative solution for ϱ, provided that the eigenvalues λ are chosen such that

$$2\sqrt{2}r\|V^{-1}(\lambda)\| + \lambda_1 < 0. \tag{49}$$

In [9] it has been shown that a set of eigenvalues λ can always be chosen in order to satisfy condition (49). Therefore, by setting the eigenvalues in order to obtain (49), it is true that by choosing $s(t)$ as in (45), there exists some negative ρ such that equality (46) holds.

Now, for $\tau \in [-\tau_g, 0]$, it is $s(\tau) \geq \|\psi(\tau)\|$, in that:

$$s(\tau) \geq e^{\varrho\tau}\|V(\lambda)\| \cdot \|\xi(\tau)\| \geq \|V(\lambda)\xi(\tau)\| = \|\psi(\tau)\|. \tag{50}$$

Therefore, by standard step procedure with step-size equal to τ_g, it follows that $s(t) \geq \|\psi(t)\|$, $t \geq -\tau_g$, from which it is:

$$\|\xi(t)\| \leq e^{\varrho t}\|V(\lambda)\|\cdot\|V^{-1}(\lambda)\| \sup_{\tau\in[-\tau_g,0]} \|\xi(\tau)\|, \tag{51}$$

for $\varrho < 0$. This proves the exponential convergence to zero of $\xi(t)$. Then, since the matrix R is such that the eigenvalues of the matrix H are negative reals, taking into account the first equation in (41) and the result concerning the variables $\xi(t)$, we can conclude about the asymptotic stability of the system described by (41). As far as the results concerning the control input, we obtain, by using (19)–(22), (12):

$$\begin{aligned}u(t) = K_{xi}\widehat{I}(t) &- \frac{T_{iGmax}}{V_I} f(\widehat{G}(t-\tau_g)) \\ &- \frac{\ddot{G}_{\text{ref}}(t) + K_{xgi}\widehat{I}(t)\left(-K_{xgi}\widehat{I}(t)\widehat{G}(t) + \dfrac{T_{gh}}{V_G}\right)}{K_{xgi}\widehat{G}(t)} \\ &- \frac{1}{K_{xgi}\widehat{G}(t)} R \begin{bmatrix} \widehat{G}(t) - G_{\text{ref}}(t) \\ -K_{xgi}\widehat{G}(t)\widehat{I}(t) + K_{xgi}G_{\text{ref}}(t)I_{\text{ref}}(t) \end{bmatrix},\end{aligned} \tag{52}$$

$$\begin{aligned}u_{\text{ref}}(t) = K_{xi}I_{\text{ref}}(t) &- \frac{T_{iGmax}}{V_I} f(G_{\text{ref}}(t-\tau_g)) \\ &- \frac{\ddot{G}_{\text{ref}}(t) + K_{xgi}I_{\text{ref}}(t)\left(-K_{xgi}I_{\text{ref}}(t)G_{\text{ref}}(t) + \dfrac{T_{gh}}{V_G}\right)}{K_{xgi}G_{\text{ref}}(t)}.\end{aligned} \tag{53}$$

From the asymptotic stability of the state reference trajectory, taking into account the boundedness of $\ddot{G}_{\text{ref}}(t)$, it follows that, by exploiting the locally Lipschitz property, if the initial conditions and estimations are suitably near the reference signals, there exist a positive real l

such that:

$$|u(t) - u_{\text{ref}}(t)| \le l\big(|\widehat{G}(t) - G_{\text{ref}}(t)| + |\widehat{G}(t-\tau_g) - G_{\text{ref}}(t-\tau_g)| + |\widehat{I}(t) - I_{\text{ref}}(t)|\big), \quad (54)$$

for $t \ge 0$. Therefore, again from the asymptotic stability of the state reference trajectory, the results concerning the control input follow. □

Remark 3: *Notice that, in* (31) *and* (34)*, the initial values concerning the insulin are considered in* 0 *and not in the interval* $[-\tau_g, 0]$*. This is due to the fact that in the equation* (38) *the initial values of the variables* $\hat{e}_2(t)$ *and* $\xi_2(t)$*, in the interval* $[-\tau_g, 0)$*, are not involved.*

The results stated in Theorem 2 hold for any chosen physically meaningful glucose reference signal, namely for any bounded $r_0(t)$, $r_1(t)$ defined in (26)–(28). Once the reference signal is chosen, and thus the bounds of r_0, r_1, defined in (29), are known, then one can use many procedures in order to design the gain matrices R and W. As far as the matrix R is concerned, the Ackermann's formula can be used, once (arbitrary) negative real eigenvalues have been chosen for the matrix H. As far as the matrix W is concerned, the following procedures can be used, one based on the proof of Theorem 2, and the other ones based on some of the many LMIs available in the literature (see [4], [24], [34]) for the asymptotic stability of linear time delay systems, applied to the second equation in (41), i.e., the equation involving only the state variable $\xi(t)$.

- *Procedure # 1.* This procedure is based on the proof of Theorem 2. One has to choose a set of eigenvalues such that the inequality (49) is satisfied. Then matrix W is found consequently by the Ackermann's formula. We recall that a set of eigenvalues satisfying (49) always exists: one way to find them is to set $\lambda_1 = -\rho$, $\lambda_2 = -\rho^2$, with ρ positive real and to increase ρ up to when condition (49) is satisfied (see [9]).
- *Procedure # 2.* This procedure is based on Theorem 4.2, p. 72, in [4], concerning robust stability of linear time-delay systems. As a preliminary step, one has to rewrite the dynamics of $\xi(t)$ in equation (41) according to the form of reference [4] (see system (4.1), with constraints (4.2), p. 70, in [4]), making use of the bounds $r_{0,m}$, $r_{1,m}$, $\underline{r_{0,a}}$, $\overline{r_{0,a}}$, $\underline{r_{0,b}}$, $\overline{r_{0,b}}$, $\underline{r_1}$ $\overline{r_1}$ defined in (29). Then, choose a set of candidate eigenvalues with negative real part for matrix $\widehat{H}$, according to which matrix W is consequently computed, by the Ackermann's formula. Finally, check the asymptotic stability of the second equation in (41) by suitably exploiting the LMI (4.5) in Theorem 4.2 of reference [4]. If the LMI is not satisfied, then choose a different set of eigenvalues (with lower real part) and repeat the LMI procedure.
- *Procedure # 3.* This procedure is still based on Theorem 4.2, p. 72, in [4]. As a preliminary step, one has to rewrite the dynamics of $\xi(t)$ in equation (41) according to the form of reference [4] (see system (4.1), with constraints (4.2), p. 70, [4]), making use of the bounds $r_{0,m}$, $r_{1,m}$, $\underline{r_{0,a}}$, $\overline{r_{0,a}}$, $\underline{r_{0,b}}$, $\overline{r_{0,b}}$, $\underline{r_1}$ $\overline{r_1}$ defined in (29). Set $W = P^{-1}X$, where P is the symmetric, positive definite matrix decision variable in the LMI (4.5) in [4], and X is a new vector decision variable in $\mathbb{R}^2$, with no constraints. Then, after standard computation, the LMI (4.5) in [4] may be written as a new LMI with the added decision variable X. If the newly obtained LMI is satisfied, the solution provides the decision variables P and X, according to which matrix W is readily computed.
- *Procedure # 4.* This procedure is based on the application of Proposition 6.10, p. 214, in [24], concerning the robust stability of linear time-delay systems with polytopic uncertainty. One has to apply Proposition 6.10 to the second equation in (41), by considering $\underline{r_{0,a}}$, $\overline{r_{0,a}}$, $\underline{r_{0,b}}$, $\overline{r_{0,b}}$, $\underline{r_1}$, $\overline{r_1}$ in (29). Then, choose a set of candidate eigenvalues with negative real part for matrix $\widehat{H}$, according to which matrix W is consequently computed, by the Ackermann's formula. Finally, check the asymptotic stability of the second equation in (41) by suitably exploiting the LMIs involved in Proposition 6.10 of [24]. If the LMIs are not satisfied, then choose a different set of eigenvalues (with lower real part) and repeat the procedure.
- *Procedure # 5.* This procedure is still based on Proposition 6.10, p. 214, in [24], by considering $\underline{r_{0,a}}$, $\overline{r_{0,a}}$, $\underline{r_{0,b}}$, $\overline{r_{0,b}}$, $\underline{r_1}$, $\overline{r_1}$ in (29). Set $W = P^{-1}X$, where P is the symmetric, positive definite matrix decision variable in the LMIs (6.70), in [24], and X is a new vector decision variable in $\mathbb{R}^2$, with no constraints. Then, after standard computation, the LMIs in (6.70) in [24] may be written as new LMIs with the added decision variable X. If the newly obtained LMIs are satisfied, the solution provides the decision variables P and X, according to which matrix W is readily computed.

Remark 4: *We stress that the Procedure # 1 always admits a solution. As already pointed out, by setting* $\lambda_1 = -\rho$, $\lambda_2 = -\rho^2$*, with* ρ *a positive real, there exists a positive real* $\overline{\rho}$ *such that* (49) *is satisfied for any* $\rho > \overline{\rho}$*. On the other hand, it is not proved here that the other procedures, based on LMIs obtained by Lyapunov-Krasovskii stability criteria with quadratic functionals, provide a solution. It should also be noticed that the method given by LMIs, besides being simple to use, given the large availability of related software, may provide less conservative solutions (i.e., eigenvalues closer to the imaginary axis). Many other LMIs in the literature could be used to check the asymptotic stability of the second equation in* (41).

Notice that the LMIs involved in the above procedures concern the delay-independent stability case. Indeed, the results stated in Theorem 2 hold for any given value of the delay τ_g. All the above procedures have been used with the upper and lower bounds given in (29) for the chosen glucose reference signal, and they all provide a solution for the matrix W which guarantees the results stated in Theorem 2. Numerical results will be shown and discussed in the next section.

4. Simulations with a Device Implementable Algorithm

4.1. Experiments on a Virtual Patient

Simulations have been carried out on a virtual patient on the basis of parameter estimates obtained from data related to an IVGTT experiment conducted on an obese patient (Body Mass Index $\simeq$ 50), studied at the Catholic University of Rome, Department of Metabolic Diseases, [41]. According to model (1) parameters G_b and I_b are measured before the beginning of the experiment so that they enter the model as covariates. V_I and G^* are considered known and kept constant; V_G, τ_g, K_{xgi}, K_{xi} and γ are the free model parameters to be estimated whereas T_{iGmax} and T_{gh} are determined according to the algebraic steady-state conditions. To avoid nonnegative values, the estimation process has been conducted on the logarithms of the above free parameters by means of a General Least Square approach. Below the estimated values are reported in terms of their original scale:

$$\begin{array}{llll} G_b = 5.611 & I_b = 93.669 & T_{iGmax} = 1.573 & \\ V_G = 0.187 & K_{xi} = 1.211 \cdot 10^{-2} & \tau_g = 24 & \gamma = 3.205 \\ V_I = 0.25 & K_{xgi} = 3.11 \cdot 10^{-5} & T_{gh} = 0.003 & G^* = 9 \end{array} \tag{55}$$

They show high-normal glycemia ($G_b = 5.611$) and a substantial degree of insulin resistance ($K_{xgi} \ll 10^{-4}$). This picture (moderate hyperglycemia, obesity, insulin resistance) is consistent with the picture of a pre-diabetic patient, whose long-standing obesity has induced such a state of insulin resistance for such a long time that pancreatic glucose toxicity is apparent and insulin delivery (which should be above normal to compensate for increased insulin resistance) is progressively failing. This subject would be expected to develop frank Type 2 Diabetes Mellitus within a relatively short time, unless therapeutic maneuvers (first of all weight loss) are vigorously employed. We allow for a certain length of time (one or two years, say) to have gone by without any effective therapy. In this case, the natural progression of disease has determined the failure of pancreatic insulin secretion and, in the face of unchanged insulin resistance, a dropping insulin concentration. This in turn determines the emergence of severe hyperglycemia and the establishment of a state of frank Type 2 Diabetes Mellitus. Therefore, the pancreatic glucose sensitivity T_{iGmax} is reduced to 15% of its "normal" value, consequently determining new values of the G_b and I_b parameters:

$$T_{iGmax} = 0.236, \qquad G_b = 10.66, \qquad I_b = 49.29. \tag{56}$$

Parameters (55), with the substitution of the first line with (56), identify our virtual diabetic patient.

The reference signal is chosen to allow a decreasing plasma glycemia from the value of 10.66 to the new value 5.0 in an exponential fashion:

$$G_{\text{ref}}(t) = 5.0 + (10.66 - 5.0) \cdot \exp(-0.01t). \tag{57}$$

According to the chosen reference signal $G_{\text{ref}}(t)$, the following bounds are found (see (29)):

$$\begin{array}{ll} \underline{r_{0,a}} = -1.0243 \cdot 10^{-4}, & \overline{r_{0,a}} = -3.9578 \cdot 10^{-5}, \\ \underline{r_{0,b}} = -0.0243, & \overline{r_{0,b}} = -0.0154, \\ \underline{r_1} = -2.3520 \cdot 10^{-5}, & \overline{r_1} = -1.0776 \cdot 10^{-5} \end{array} \tag{58}$$

In order to regulate the resulting hyperglycemia down to a safe level, we choose R, by the Ackermann's formula, such that the matrix H has eigenvalues -0.15, -0.06. As far as the gain matrix W is concerned, Procedure #1 ends successfully if the eigenvalues $\lambda_1 = -1.2$, $\lambda_2 = -1.44$ are chosen for the matrix $\widehat{H}$ (corresponding to the choice $\rho = 1.2$). Procedure #2 ends successfully if the eigenvalues -0.25, -0.26 are chosen for the matrix $\widehat{H}$. Procedure #3 ends successfully and provides $W = [\,0.5226 \quad 1.4604\,]^T$, to which the eigenvalues $-0.2613 + 1.1799i$, $-0.2613 - 1.1799i$ correspond for the matrix $\widehat{H}$. Procedure #4 ends successfully if the eigenvalues -0.001, -0.002 are chosen for the matrix $\widehat{H}$. Finally, Procedure #5 ends successfully and provides $W = [\,0.1603 \quad 1.0095\,]^T$, to which the eigenvalues $-0.0801 + 1.0016i$, $-0.0801 - 1.0016i$ correspond for the matrix $\widehat{H}$. We choose the results given by Procedure #4, which are the least conservative as far as the proximity of the eigenvalues to the imaginary axis is concerned. Moreover, such procedure avoids complex eigenvalues which may be cause of undesired oscillations.

The subject is supposed to be at rest before the experiment begins, which means that the initial state is given by $G_0(\tau) = G_b$, $I_0(\tau) = I_b$ for $\tau \in [-\tau_g, 0]$; regarding the observer, we assume $\widehat{G}_0(\tau) = \widetilde{G}_b$, $\widehat{I}_0(\tau) = \widetilde{I}_b$ for $\tau \in [-\tau_g, 0]$), with $\widetilde{G}_b = 11.15$ mM and $\widetilde{I}_b = 59.65$ pM, that means and initial error for the observer of about 4.5% and 21% for glycemia and insulinemia, respectively.

As it clearly appears from the upper picture of Fig. 1, a reasonably low plasma glycemia (i.e., <6.5 mM) is

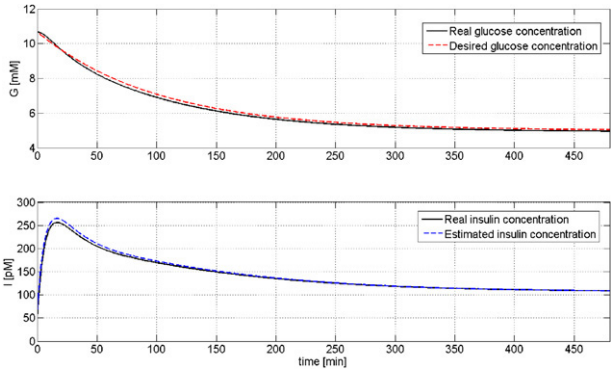

Fig. 1. Plasma glycemia/insulinemia: the former compared with the desired glucose reference, the latter compared with the observed insulinemia.

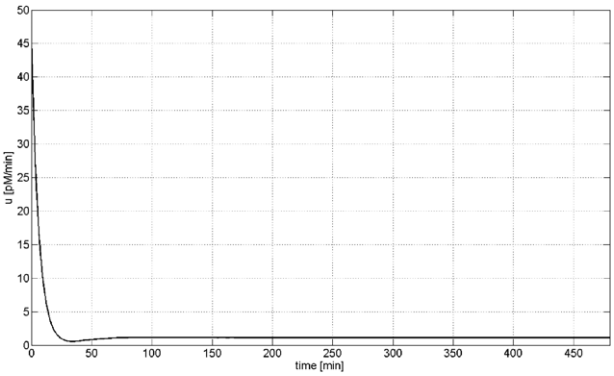

Fig. 2. Exogenous insulin infusion rate.

reached within the first two hours of simulation. The applied insulin infusion programme is pictured in Fig. 2. According to not reported simulations, we stress that the observer would have worked as well also with the unrealistic initial conditionof $\widetilde{I}_b = 0$.

Remark 5: *While the control input cannot be negative, this paper does not consider, from a theoretical point of view, saturation problems for the control law. We have taken into account this fact in the simulations: whenever the designed control law becomes negative, a zero control input is given to the system. Note that we have chosen the control parameters in order not to allow such a drawback, as it appears from Fig. 2.*

In the above simulations it is assumed that the controller works in continuous time and that the output measurement is also available in continuous time. On the other hand, in practice, standard devices:

– provide glucose measurements only at given sample times, whose frequency is limited by the time (about 3 min) needed to analyze plasma glucose on a bed-side analyzer, [5];

– administer insulin by means of piecewise-constant infusions.

Both technical assumptions will be taken into account in the following simulations. Let us consider a device-implementable algorithm, where ΔT is 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 $[k\Delta T, (k+1)\Delta T)$, $k = 0, 1, \ldots$.

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 (19):

$$u(k\Delta T) = \frac{S\big(\widehat{G}(k\Delta T), \widehat{I}(k\Delta T), \widehat{G}(k\Delta T - \tau_g)\big) - v(k\Delta T)}{K_{xgi}\widehat{G}(k\Delta T)}; \tag{59}$$

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 (15), using the measurement $G(k\Delta T)$:

$$\begin{bmatrix} \dfrac{d\widehat{G}(t)}{dt} \\ \dfrac{d\widehat{I}(t)}{dt} \end{bmatrix} = \begin{bmatrix} -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \dfrac{T_{gh}}{V_G} \\ -K_{xi}\widehat{I}(t) + \dfrac{T_{iGmax}}{V_I} f\big(\widehat{G}(t-\tau_g)\big) + u(k\Delta T) \end{bmatrix} + Q^{-1}\big(\widehat{G}(t), \widehat{I}(t)\big) W\big(G(k\Delta T) - \widehat{G}(k\Delta T)\big); \tag{60}$$

5. the value of k is incremented by 1.

In Figs. 3 and 4, the glucose and insulin behavior, when ΔT is chosen equal to 5 min and 10 min, respectively, is reported. The initial conditions and the observer gain matrices R, W are kept equal to the previous simulations. As can be seen, in both the cases the proposed implementable algorithm allows the subject to reach the desired

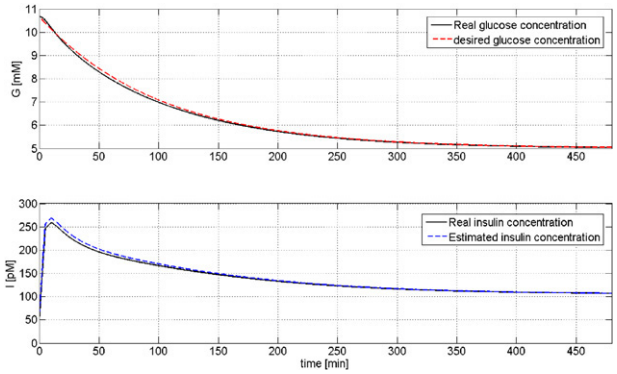

Fig. 3. Plasma glycemia/insulinemia with $\Delta T = 5$ min.

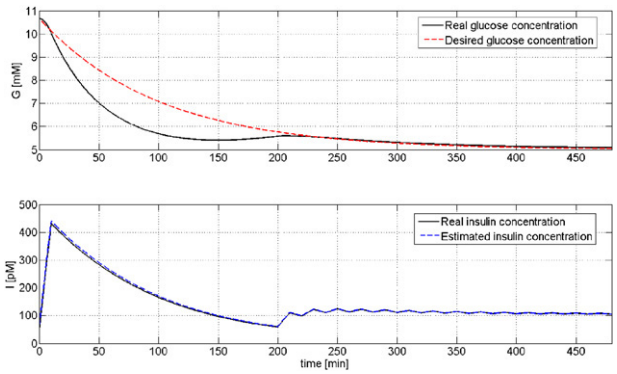

Fig. 4. Plasma glycemia/insulinemia with $\Delta T = 10$ min.

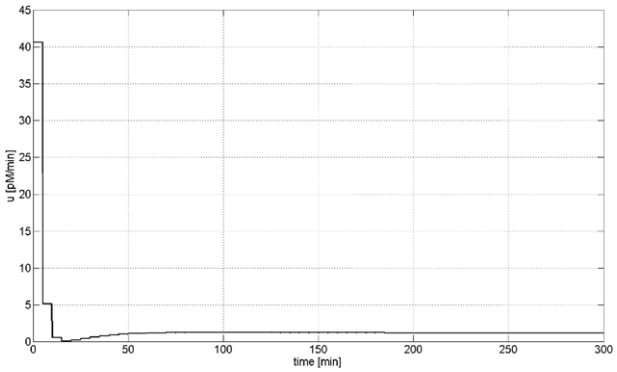

Fig. 5. Exogenous insulin infusion rate with $\Delta T = 5$ min.

plasma glycemia concentration, with a practically acceptable decay rate. In Figs. 5 and 6, the related piece-wise constant control signals are reported.

Note that, in the case of $\Delta T = 5$ min, the input saturation effect does not arise and indeed, the pictures in Fig. 3 are very close to the ones in Fig. 1. In the case of $\Delta T = 10$ min, the saturation effect is evident. This is due to the fact that the high insulin delivery rate computed at $t = 0$ is applied over a relatively long sampling period, equal to 10 min. However, also in this case, the behavior

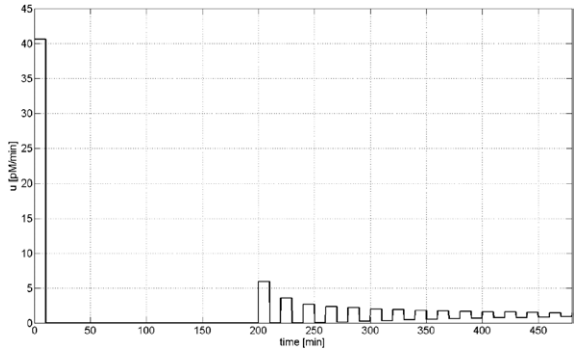

Fig. 6. Exogenous insulin infusion rate with $\Delta T = 10$ min.

of the closed loop glucose–insulin system is acceptable both from a safety point of view (there are no cases of hypoglycemia, since the plasma glucose concentration is always greater than 4 mM), and from an efficacy point of view (the desired normo-glycemia is definitely reached in a reasonable time). In this case, a useful improvement could be using a high sampling rate early on (e.g., the first 30 min), while using a longer sampling period for the rest of the simulation. In any case, a sampling time of 5 min is reasonable for the current glucose sensor technology, [45].

4.2. Robustness Analysis

In the first half of the Section simulations have been carried out by assuming to have noise-free measurements and no malfunctioning of the insulin infusion devices, as well as to have a perfect knowledge of the virtual patient. On the other hand, this second half is devoted to check the effectiveness and robustness of the glucose control algorithm in presence of the above mentioned unavoidable uncertainties.

To this aim, criteria are required to define a measure of *safety* and *efficacy* for a given *in-silico* experiment, consisting in applying the proposed control law to a given virtual patient, according to a specific set of environmental conditions, including the above mentioned uncertainties. The question is to state whether the control law is able to provide satisfactory results in spite of the many inaccuracies and mistakes it may face. These criteria have been inspired by [5] and are the following.

- *Safety*. The control law applied to a virtual patient could cause:
  - *severe hypoglycemia*: plasma glycemia falls to 2 mM or lower, within the simulation period;
  - *hypoglycemia*: plasma glycemia falls to 3.3 mM or lower, but always remains above 2 mM, within the simulation period.

A set of simulations provides *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.

- *Efficacy*. The control law applied to a virtual patient may provide:
  - *excellent efficacy*: plasma glycemia is constrained below 6 mM after the first 3 hours of treatment;
  - *good efficacy*: plasma glycemia is constrained below 7 mM after the first 3 hours of treatment;
  - *satisfactory efficacy*: plasma glycemia is constrained below 8 mM after the first 3 hours of treatment;
  - *unsatisfactory efficacy*: plasma glycemia is not constrained below 8 mM after the first 3 hours of treatment.

As far as the measurement errors, they involve both basal and real-time plasma glucose/insulin concentrations. Basal levels G_b and I_b are required when computing parameters T_{gh} and T_{iGmax}, when determining the desired glycemia to be tracked, e.g., in (57), and when setting the initial conditions for the observer. Thus, in the following simulations, the basal values of plasma glycemia and insulinemia used to set the controller will be different from the virtual patient nominal ones, affected by Coefficients of Variation (CVs) equal to 1.5% and 7% respectively, according to standard results [3].

On the other hand, the observer-based algorithm requires real-time glucose measurements, usually affected by greater uncertainties than the case of basal measurements: the following simulations will assume real-time glucose measurements affected by a CV equal to 5%, [5]. Finally, in order to take into account the malfunctioning of the insulin devices, it will be assumed the insulin delivery rate affected by a CV equal to 15%, [5].

Besides copying with the above mentioned measurement errors and insulin device malfunctioning, a crucial source of uncertainties relies in the estimates of the virtual patient parameters, since they are achieved according to clinical trials, for instance the aforementioned IVGTT experiment and, therefore, the estimated values may well differ from the nominal ones.

All the above mentioned sources of uncertainties are properly taken into account in the following set of 1,000 virtual experiments, each consisting in the closed loop application of the proposed control law such that:

i) the virtual patient to whom the glucose control is applied is identified in all the 1,000 virtual experiments by the same set of nominal parameters (i.e., (55) with the substitution of the first line with (56));
ii) the control law is designed by using for each experiment a set of model parameters derived from a random realization drawn from a log-normal distribution, with mean values given by the virtual patient nominal values, and CVs as coming from the IVGTT estimation procedure, below reported for the ease of the Reader: $CV(V_g) = 7.84\%$, $CV(\tau_g) = 0.89\%$, $CV(K_{xgi}) = 9.99\%$, $CV(K_{xi}) = 14.46\%$, $CV(\gamma) = 74.02\%$;
iii) for each experiment, the observer initialization is set by suitably exploiting the noisy basal measurements of glycemia and insulinemia: $\widehat{G}_0(\tau) = G_{b,\text{measured}}$, $\widehat{I}_0(\tau) = I_{b,\text{measured}}$ for $\tau \in [-\tau_g, 0]$;
iv) for each experiment, the control law gain matrices R, W are set by suitably exploiting the estimates of the model parameters (i.e., V_g, τ_g, K_{xgi} K_{xi}, γ, achieved according to item ii)), by means of Procedure # 4 (see the following Remark 6 for more details).

Remark 6: *Recall that, according to Theorem 2, the gain matrix R needs to be chosen such that the matrix H admits real negative eigenvalues, regardless of the model parameters: thus we have chosen the gain matrix R as in Subsection 4.1, once and for all the 1,000 experiments. As far as the gain matrix W is concerned, we have found out that, due to the limited CVs of the model parameter values, if the matrix W is chosen by using the pair of eigenvalues* -0.001, -0.002 *previously set for matrix* $\widehat{H}$*, then the LMIs of Procedure # 4 are always satisfied for each of the 1,000 experiments. More in details, even if the amplitudes of the three intervals to which* $r_{0,a}(t)$, $r_{0,b}(t)$, $r_1(t)$, *defined in (26)–(28), belong, are increased of 200%, it happens that Procedure # 4 ends successfully with the above chosen W.*

Table 1. Safety and efficacy results on 1,000 simulations on the same virtual patient.

Severe hypoglycemia	0 cases (0%)
Hypoglycemia	13 cases (1.3%)
Excellent efficacy	865 cases (86.5%)
Good efficacy	134 cases (13.4%)
Satisfactory efficacy	1 cases (0.1%)
Unsatisfactory efficacy	0 cases (0.0%)

Results are shown in Table 1. Over a set of 1,000 simulations, only 13 cases of hypoglycemia occurred (1.3%) with no cases of severe hypoglycemia: *good* level of safety. Concerning efficacy, we have 99.9% of at least *good* results (only 1 satisfactory case and no unsatisfactory cases), with a high percentage of *excellent* results (86.5%).

A different class of 1,000 *in-silico* experiments has been finally proposed, aiming to test the same control algorithm to a set of heterogenous virtual patients (instead of a set of controllers applied to the same virtual patient): this would be the case, for instance, of a diabetologist trying to

Table 2. Safety and efficacy results on a set of 1,000 heterogeneous virtual patients.

Severe hypoglycemia	0 cases (0%)
Hypoglycemia	35 cases (3.5%)
Excellent efficacy	611 cases (61.1%)
Good efficacy	277 cases (27.7%)
Satisfactory efficacy	94 cases (9.4%)
Unsatisfactory efficacy	18 cases (1.8%)

control a previously unknown subject using an "average" control law. To this aim, besides assuming the same measurement errors and insulin device malfunctioning of the previous class of experiments, the following assumptions are taken:

i) the virtual patient population is assigned by assuming the model parameters distributed according to a log-normal distribution, with population means given by the nominal values (i.e., (55) with the substitution of the first line with (56)), and the CVs arbitrarily set at 30%: from a practical point of view the adopted CVs are compatible with a population of rather heterogeneous subjects;
ii) the control law is designed once and for all by using for all the experiments the nominal values used to assign the population means in item i); also, the controller parameters (i.e., gain matrices R and W) are set, once and for all the 1,000 experiments, by suitably exploiting the nominal model parameters and the noisy basal measurements. These values are the same adopted in Subsection 4.1.

By taking into account the same criteria defined for safety and efficacy, results detailed in Table 2 still ensure no dangerous cases of severe hypoglycemia (*good* level of safety), providing at least *satisfactory* results for the *efficacy*, with the very large percentage of 98.2%.

5. Conclusions and Future Works

The control problem of tracking a desired plasma glucose evolution by means of insulin administration has been investigated. A time-delay, model-based feedback control law has been formulated, which provides local asymptotic convergence of the tracking error, according to the theory of feedback linearization with delay cancelation. A partial knowledge of the state of the system is assumed, consisting of only glycemia measurements: the feedback control law is based on the use of a nonlinear observer for discrete-delay systems, in order to avoid the need for insulinemia measurements. No simplifying approximations have been adopted in order to design the model-based control law. Simulations have been performed in a virtual environment, which validate the theoretical results. These results have been shown to be robust with respect to a wide range of parameter uncertainties or device malfunctioning.

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 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.

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