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Robust Closed-Loop Control of Plasma Glycemia: a Discrete-Delay Model Approach

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Abstract— **The paper investigates the problem of tracking a desired plasma glucose evolution by means of intra-venous insulin administration. A model-based approach is followed, according to a recent model of the glucose/insulin regulatory system which consists of a discrete-delay nonlinear differential equation model. A disturbance is added to the insulin kinetics in order to model uncertainties concerning both the insulin delivery rate and the mechanism actuating the insulin pump. A feedback control law which yields input-to-state stability of the closed loop error system with respect to such a disturbance is provided, which depends on the glucose and insulin measurements at the present and at a delayed time. In silico simulations validate the theoretical results.**

Index Terms—**Glucose-Insulin System, Glucose Control, Delay Differential Equations, Input-to-State Stability, Feedback Linearization.**

I. INTRODUCTION

The design of insulin infusion devices able to control plasma glucose concentration is of great importance when attempting to gain control of decompensated hyperglycemia in selected clinical situations (e.g. perioperative control of glycemia in a decompensated, acutely ill diabetic patient undergoing emergency surgery). From an applicative point of view, different therapeutic schemes can be considered, according to the accuracy of the glucose-insulin model adopted and to the technology available in 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 if recently the *Food and Drug Administration* (*FDA*) has approved a device for the delivery of a powder form of insulin by inhalation, as an alternative to subcutaneous injections, [17]. 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 administered by the patients themselves (see [2] and references therein). However, only open loop or semiclosed loop control strategies can be used, mainly due to the problem of modeling accurately the absorption from the subcutaneous depot in the plasma circulation (see [18] for a critical review of subcutaneous absorption models and [6] 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 (see [26] and references therein for a survey of the intravenous route to plasma glucose control).

In this paper, a model-based closed loop control scheme is proposed. The advantages of a model-based approach (with respect to an empirical 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 appropriate and effective will the control law be. Model-based glucose control literature has been mainly developed for the Ackerman's linear model [1] (e.g. optimal control [32, 10], adaptive control [20], H_∞ control [14]); more recently, different approaches have been proposed, based on nonlinear models (on linearization of nonlinear models, actually), such as the Minimal Model [3, 33] or more complex [7, 31] (e.g. Model Predictive Control [27], Neural Predictive Control [34], non-standard H_∞ control [4, 28], feedback linearization [22, 21]). 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 [5] and references therein.

Compared with existing model-based approaches, the one presented here relies directly on a nonlinear discrete delay differential equation (DDE) model of the glucose/insulin system [23, 25]. Since [8], where qualitative properties of the solutions of the Minimal Model were shown to be incompatible with accepted physiology, several DDE models have been published, mainly

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devoted to better represent pancreatic Insulin Delivery Rate (IDR) [15, 16]. 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 IDR into account. In the present work we may take into account spontaneous pancreatic IDR, thereby treating healthy, Type 2 diabetic and Type 1 diabetic patients, because the glucose/insulin model we use to represent the natural dynamics of the system [25] has been shown to exhibit a number of desirable characteristics, which previous models were lacking. This model conforms to established physiological concepts (e.g. pancreatic insulin secretion rate is limited), exhibits satisfactory properties of the solutions [23] (e.g. positivity and boundedness of solutions, local attractivity of a single positive equilibrium), is statistically robust, in that its parameters are statistically identifiable with very good precision by means of standard perturbation experiments, such as the Intra-Venous Glucose Tolerance Test (IVGTT) [25].

The proposed control aims to track a lower desired glucose reference level by means of intravenous insulin infusion, according to a given smooth glucose trajectory. A disturbance affecting the insulin kinetics is also assumed. The followed approach is based on the theory of the input-output feedback linearization with delay cancellation [11, 19], and on the theory of the input-to-state stabilization with respect to disturbances adding to the control law [29]. The proposed feedback control law depends on glucose and insulin measurements at the present and at a delayed time, and yields input-to-state stability of the closed loop error system with respect to the disturbance.

The paper is organized as follows. Immediately below a brief notation Section is reported to clarify the mathematical tools required by the proposed control law. Section II deals with the proposed discrete-delay differential equations model, detailing its properties. The control law is designed in Section III. Simulations are finally reported in Section IV, employing sets of parameters derived from real data. Conclusions follow.

Basic Definitions and Notations

Given a function $v : \mathbb{R}^+ \to \mathbb{R}^m$, the *essential supremum norm* is defined as $\|v\|_\infty = ess\sup_{t\geq 0}\|v(t)\|$; if it is finite, function v is said to be *essentially bounded*. For given times $0 \leq T_1 < T_2$, we indicate with $v_{[T_1,T_2)} : \mathbb{R}^+ \to \mathbb{R}^m$ the function given by $v_{[T_1,T_2)}(t) = v(t)$ for all $t \in [T_1, T_2)$ and $= 0$ elsewhere. An input v is said to be *locally essentially bounded* if, for any $T > 0$, $v_{[0,T)}$ is essentially bounded. A function $\delta : \mathbb{R}^+ \to \mathbb{R}^+$ is *positive definite* if it is continuous, zero at zero and $\delta(s) > 0$ for all $s > 0$; it is *of class* $\mathcal{G}$ if it is continuous, zero at zero, and nondecreasing; it is *of class* $\mathcal{K}$ if it is of class $\mathcal{G}$ and strictly increasing; it is *of class* $\mathcal{K}_\infty$ if it is of class $\mathcal{K}$ and it is unbounded; it is *of class* $\mathcal{L}$ if it monotonically decreases to zero as its argument tends to $+\infty$. A function $\beta : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ is *of class* $\mathcal{KL}$ if $\beta(\cdot, t)$ is of class $\mathcal{K}$ for each $t \geq 0$ and $\beta(s, \cdot)$ is of class $\mathcal{L}$ for each $s \geq 0$.

II. THE DDE GLUCOSE-INSULIN MODEL

The glucose-insulin model considered here belongs to the family of DDE models described in [23], which has been proven to provide persistent positive bounded solutions for any admissible initial condition and 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).

Denote $G(t)$, [mM], $I(t)$, [pM], plasma glycemia and insulinemia, respectively. The model considered consists of a single discrete-delay differential equation system:

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

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

$$f\big(G(t-\tau_g)\big) = \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}. \tag{2}$$

A detailed description of all the physical parameters may be found in [25].

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 perfectly identifiable from data according to standard perturbation experiments (IVGTT), [25].

III. THE CONTROL LAW

The aim of control is to reduce a high basal plasma glucose concentration to a lower level, according to a reference glucose trajectory, by means of intra-venous insulin administration. Basal glycemia/insulinemia will be referred in the following as G_b and I_b, respectively.

To do so, a control input $u(t)$ is added as well as a disturbance $d(t)$ (due to often unavoidable actuator errors) to the insulin kinetics, so that the insulin kinetics in (1) may be rewritten as:

$$\frac{dI(t)}{dt} = -K_{xi}I(t) + \frac{T_{iGmax}}{V_I} f\big(G(t-\tau_g)\big) + u(t) + d(t). \tag{3}$$

The disturbance $d(t)$ is assumed measurable and locally essentially bounded.

Note that by applying the theory of input-output feedback linearization with delay cancellation, with respect to the output $y(t) = G(t)$ and the input $u(t)$, the system (1-3) has full (equal to 2) relative degree of type III (see e.g. [11, Def.2.4] and [19]). Indeed, by ready computation, it is:

$$\begin{aligned}\dot{y}(t) &= \dot{G}(t) = -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G},\\ \ddot{y}(t) &= \ddot{G}(t)\\ &= S\big(G(t), I(t), G(t-\tau_g)\big) - K_{xgi}G(t)\big(u(t)+d(t)\big),\end{aligned} \tag{4}$$

with:

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

Let us consider

$$Z(t) = \begin{bmatrix} z_1(t) \\ z_2(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G} \end{bmatrix}. \tag{6}$$

The aim is that the output $y(t) = z_1(t)$ tracks a desired smooth reference glycemia, named $G_{\rm ref}(t)$. By setting the error

$$e(t) = \begin{bmatrix} e_1(t) \\ e_2(t) \end{bmatrix} = Z(t) - Z_{\rm ref}(t), \tag{7}$$

with $Z_{\rm ref}(t) = [G_{\rm ref}(t) \;\; \dot{G}_{\rm ref}(t)]^T$, the following equation holds for the error dynamics:

$$\begin{aligned}\dot{e}(t) = &\begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} e(t) + \begin{bmatrix} 0 \\ 1 \end{bmatrix} \Big(S\big(G(t), I(t), G(t-\tau_g)\big)\\ &- K_{xgi}G(t)\big(u(t)+d(t)\big) - \ddot{G}_{\rm ref}(t)\Big).\end{aligned} \tag{8}$$

By designing the control law $u(t)$ as:

$$u(t) = \frac{S\big(G(t), I(t), G(t-\tau_g)\big) - v(t)}{K_{xgi}G(t)}, \tag{9}$$

where $v(t)$ is a new input which will be chosen in the following, the error dynamics becomes:

$$\begin{aligned}\dot{e}(t) = &\begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} e(t) + \begin{bmatrix} 0 \\ 1 \end{bmatrix} v(t)\\ &- \begin{bmatrix} 0 \\ 1 \end{bmatrix} \ddot{G}_{\rm ref}(t) - \begin{bmatrix} 0 \\ 1 \end{bmatrix} K_{xgi}G(t)d(t).\end{aligned} \tag{10}$$

Remark 1: From a theoretical point of view, the control law (9) may always be computed because, following the same reasoning of [23, Th.1] the glucose evolution is strictly positive for any admissible initial condition. •

Then, set:

$$v(t) = \ddot{G}_{\rm ref}(t) + Ke(t), \tag{11}$$

with the gain $K \in I\!R^{1\times 2}$ such that the matrix:

$$H = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} K \quad \text{is} \quad \text{Hurwitz.}$$

With the choice of the input $u(t)$ given by (9),(11), the error dynamics becomes:

$$\dot{e}(t) = He(t) - \begin{bmatrix} 0 \\ 1 \end{bmatrix} K_{xgi}(e_1(t) + G_{\rm ref}(t))d(t) \tag{12}$$

According to the case of a continuous and bounded reference $G_{\rm ref}(t)$, as it is reasonable and desirable, a new disturbance $w(t)$ is defined, with the same characteristics of $d(t)$ (measurable and locally essentially bounded), as follows:

$$w(t) = \begin{bmatrix} w_1(t) \\ w_2(t) \end{bmatrix} = \begin{bmatrix} d(t) \\ G_{\rm ref}(t)d(t) \end{bmatrix}. \tag{13}$$

Then, the error dynamics is described by the following equation:

$$\dot{e}(t) = He(t) + \begin{bmatrix} 0 \\ -K_{xgi} \end{bmatrix} e_1(t)w_1(t) + \begin{bmatrix} 0 \\ -K_{xgi} \end{bmatrix} w_2(t). \tag{14}$$

If the disturbance is zero, then the error decays exponentially to zero. If the disturbance is not zero, system (14) is a bilinear system and, by a well known result in [30], it is integral input-to-state stable with respect to the disturbance $w(t)$, that is, there exist a $\mathcal{K}_\infty$ function χ, a $\mathcal{KL}$ function α and a $\mathcal{K}$ function δ such that the following inequality holds for all $t \geq 0$:

$$\chi(\|e(t)\|) \leq \alpha(\|e(0)\|, t) + \int_0^t \delta(w(\tau))d\tau. \tag{15}$$

A further significant improvement can be achieved by the result in [29] on the input-to-state stabilization of nonlinear systems. According to the main theorem in [29], consider for system (1-3) the following feedback control law:

$$u(t) = u_1(t) + u_2(t), \qquad \text{where} \tag{16}$$

$$u_1(t) = \frac{S\big(G(t), I(t), G(t-\tau_g)\big) - \ddot{G}_{\rm ref}(t) - Ke(t)}{K_{xgi}G(t)}, \tag{17}$$

is the previous designed control law (9),(11), and $u_2(t)$ is given by:

$$u_2(t) = -e^T(t)Pe(t)e^T(t)Q \begin{bmatrix} 0 \\ -K_{xgi} \end{bmatrix} G(t), \tag{18}$$

P is any symmetric positive-definite matrix, and Q is the symmetric positive-definite matrix solution of the Liapunov equation: $H^TQ + QH = -P$. When the feedback control law (16) is chosen, the closed loop error dynamics is described by the equations

$$\begin{aligned} \dot{e}(t) =& He(t) - \begin{bmatrix} 0 \\ 1 \end{bmatrix} K_{xgi}(e_1(t) + G_{\rm ref}(t))\cdot \\ & e^T(t)Pe(t)e^T(t)Q \begin{bmatrix} 0 \\ 1 \end{bmatrix} K_{xgi}\big(e_1(t) + G_{\rm ref}(t)\big) \\ & - \begin{bmatrix} 0 \\ 1 \end{bmatrix} K_{xgi}\big(e_1(t) + G_{\rm ref}(t)\big)d(t) \end{aligned} \tag{19}$$

System (19) is not time-invariant because of the presence of the time function $G_{\rm ref}(t)$. Nevertheless, here the results in [29], which concern with time-invariant systems, can be applied as well, since it can be easily proven by using Theorem 4.19, p.176 in [13], dealing with time-varying systems, that the control law (16-18) yields input-to-state stability of system (19). The time-invariant function $V(e) = e^TQe$ can be used as an ISS-Liapunov function for system (19). In this case, the functions α_1, α_2, ρ in the above mentioned Theorem 4.19 are given by:

$$\begin{aligned} &\alpha_1(s) = \lambda_{min}(Q)s^2, \qquad \alpha_2(s) = \lambda_{max}(Q)s^2, \\ &\rho(s) = \sqrt{\frac{1}{\lambda_{max}(P)}}\sqrt{s} \end{aligned} \tag{20}$$

with $\lambda_{min}(\cdot)$ and $\lambda_{max}(\cdot)$ the minimum and maximum eigenvalues of a symmetric, positive-definite matrix. Then, according to the given feedback control law (16-18), it results that the following ISS inequality holds for the error $e(t)$:

$$\|e(t)\| \le \alpha(\|e(0)\|, t) + \delta(\|d_{[0,t)}\|_\infty), \qquad t \ge 0 \tag{21}$$

where α is a $\mathcal{KL}$ function and δ is a $\mathcal{K}$ function. The function δ is very important since it describes some attenuation or amplification of the disturbance effect. In this case, by the above Theorem 4.19:

$$\delta(s) = \alpha_1^{-1} \circ \alpha_2 \circ \rho(s) = \sqrt{\frac{\lambda_{max}(Q)}{\lambda_{min}(Q)\lambda_{max}(P)}}\sqrt{s} \tag{22}$$

Note that P and H depend on the choice of the control designer. With the choice of H as in the following section, we have seen that, if $P = pI$ is chosen, with p positive real, I the indentity matrix, then the larger p is, the more little the term $\sqrt{\frac{\lambda_{max}(Q)}{\lambda_{min}(Q)\lambda_{max}(P)}}$ is.

Remark 2: In this paper we have not considered, from a theoretical point of view, saturation problems for the control law. Actually, the control input cannot be negative. We have taken into account this fact in simulations, where, whenever the projected control law is negative, a zero control input is given to the system. Saturation problems will be studied also from a theoretical point of view in forthcoming work. •

V. SIMULATION RESULTS

Simulations have been performed in order to test *in silico* the proposed methodology. Parameter values are those of an obese, insulin-resistant subject, identified by means of Generalized Linear Square fitting of an IVGTT perturbation experiment [24]. For system (1), some parameters are directly measured, such as G_b and I_b; others are known and kept constant, such as V_I and $G^\star$; others are estimated, such as K_{xgi}, τ_g, K_{xi}, V_G, γ; others are computed according to the algebraic steady-state conditions, such as T_{iGmax} and T_{gh}.

Case 1. The following parameters have been used (refer to [25] for the unit measurements): $G_b = 5.611$, $\gamma = 3.205$, $V_G = 0.187$, $V_I = 0.25$, $I_b = 93.669$, $G^\star = 9$, $K_{xi} = 1.211 \cdot 10^{-2}$, $K_{xgi} = 3.11 \cdot 10^{-5}$, $T_{iGmax} = 1.573$, $\tau_g = 24$, $T_{gh} = 0.003$. In the present simulation case, all parameters used were those actually estimated from the IVGTT test conducted on an obese patient (Body Mass Index $\simeq 50$) [24]: they show high-normal glycemia ($G_b = 5.61$) a substantial degree of insulin resistance ($K_{xgi} \ll 10^{-4}$) and a sub-normal Insulin Delivery Rate. This picture (moderate hyperglycemia, obesity, insulin resistance, low IDR) 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 not vigorously employed.

As far as the control law, we choose K such that the matrix H has eigenvalues -0.1, -0.2, $P = 10^3 \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$, $G_{\rm ref}(t) = 4.7 + (5.61 - 4.7) \cdot exp(-0.01t)$. The reference signal is chosen such to obtain the plasma glycemia decreasing exponentially from the value of 5.61 to the new value 4.7. We choose the disturbance as $d(t) = 0.1sin(0.05t)$. Fig. 1 is obtained when the control law is designed as in (16-18). With this choice of H and P, the function δ in (21) is given by $\delta(s) = 0.2335\sqrt{s}$, thus ensuring a good attenuation of the disturbances effects.

Case 2. In this case we are considering the same patient as in case 1, but with an acute increase in insulin

resistance, such as may be due to infection or surgery: in this case the infectious process and the accompanying hormonal changes (such as increased plasma concentrations of cortisol and catecholamines) contrast the action of insulin at the periphery and the K_{xgi} falls. This produces a consequent hyperglycemia, to which the pancreas responds by increasing (to the extent possible) insulin secretion and insulinemia. Therefore, the following parameters are changed, keeping unchanged the others of case 1: $K_{xgi} = 10^{-5}$, $G_b = 7.856$, $I_b = 204.11$.

We choose K such that the matrix H has eigenvalues -0.2, -0.3, $P = 10^4 \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$, $G_{\text{ref}}(t) = 4.7 + (7.344 - 4.7) \cdot exp(-0.005t)$. The reference signal is chosen such to obtain the plasma glycemia decreasing exponentially from the value of 7.344. to the new value 4.7. We choose the disturbance as $d(t) = 0.1sin(0.05t)$. The plot 2 is obtained when the control law is designed as in (16-18). With this choice of H and P, the function δ in (21) is given by $\delta(s) = 0.0457\sqrt{s}$, thus ensuring a good attenuation of the disturbances effects.

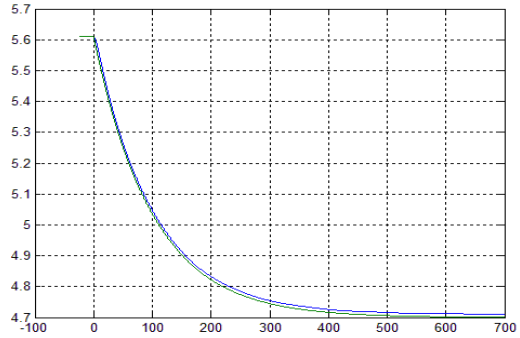

Fig.1: Plasma glycemia (true and reference ones)

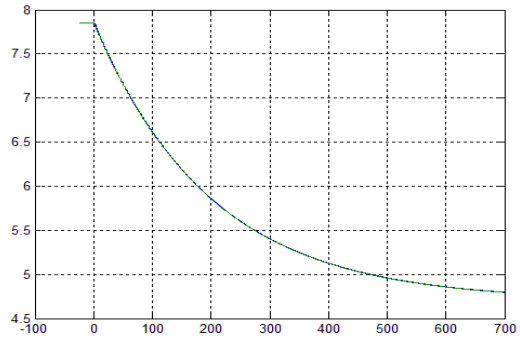

Fig.2: Plasma glycemia (true and reference ones)

Case 3. In this case we again consider the same patient as in Case 1, but allow for a certain length of time (one or two years, say) to have passed without any effective therapy having been followed. 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 following parameters are changed, keeping unchanged the others of case 1: $T_{iGmax} = 0.242$, $G_b = 10.37$, $I_b = 48.95$.

We choose K such that the matrix H has eigenvalues -0.1, -0.2, $P = 10^3 \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$, $G_{\text{ref}}(t) = 4.7 + (10.37 - 4.7) \cdot exp(-0.005t)$. The reference signal is chosen such to obtain the plasma glycemia decreasing exponentially from the value of 10.37. to the new value 4.7. We choose the disturbance as $d(t) = 0.1sin(0.05t)$. The plot 3 is obtained when the control law is designed as in (16). With this choice of H and P, the function δ in (21) is given by $\delta(s) = 0.2335\sqrt{s}$, thus ensuring a good attenuation of the disturbances effects.

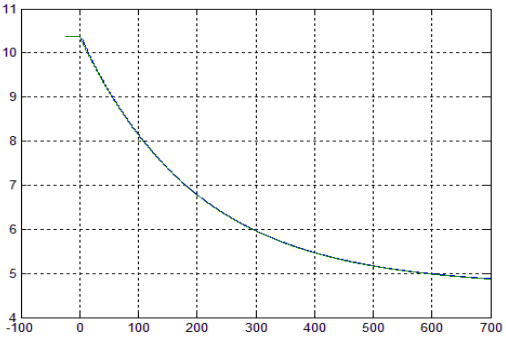

Fig.3: Plasma glycemia (true and reference ones)

VI. CONCLUSIONS

The control problem of tracking a desired plasma glucose evolution by means of insulin administration has been investigated. A feedback control law which yields input-to-state stability of the closed loop error system with respect to a disturbance adding to the control law is provided. The feedback control law depends on the glucose and insulin measurements at the present and at a delayed time. Performed simulations validate the theoretical results. Future developments will concern the construction of a feedback control law by means of the measurement of plasma glucose only, which is the more common situation. To this end, a nonlinear observer will have to be built for the system (1-3): some important results have already been achieved in [9, 12].

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