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Regulation of the Human Plasma Glycemia by Means of Glucose Measurements and Subcutaneous Insulin Administration

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Abstract: A glucose control problem is considered, with the aim to regulate a basal hyperglycemic state down to a safe euglycemic level. A discrete Delay Differential Equation (DDE) model of the glucose-insulin system is considered, that properly takes into account also the pancreatic insulin release, not negligible in Type 2 diabetic patients. Insulin is supposed to be administered subcutaneously. A geometric approach is considered, according to which the feedback linearization with delay cancelation theory is applied. In order to use only glucose measurements to synthesize the control law an observer for nonlinear delay systems is exploited, and the local convergence of the tracking error to zero is theoretically proven. Simulations are performed in a virtual environment, that properly takes into account input saturation: numerical results show the effectiveness of the proposed approach as well as that of the observer.

Keywords: Delay Differential Equations; Nonlinear Observer; Glucose Control.

1. INTRODUCTION

Diabetes Mellitus is a major chronic disease that comprises a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Another, much more prevalent appearance of the disease (Type 2 diabetes) is caused by a combination of resistance to insulin action and inadequate compensatory insulin secretory response. These individuals have therefore insulin resistance and usually have relative (rather than absolute) insulin deficiency.

Exogenous insulin administration is the basic procedure for chronic diabetic patients (in Type 1 diabetes only exogenous insulin is available, while in Type 2, exogenous insulin complements pancreatic production). Glucose control strategies are mainly actuated by subcutaneous administration of the hormone (see Belazzi, Nucci & Cobelli, 2001, and references therein). However, in order to design closed-loop control strategies, the insulin absorption from the subcutaneous depot needs also to be considered.

In this note a model-based control law is designed by means of subcutaneous insulin infusion. The advantages are evident since, by using a mathematical model of glucose-insulin homeostastis, the control problem may be treated mathematically and optimal strategies may then be determined. Different solutions have been recently proposed, based on nonlinear models such as the Minimal Model (Bergman et al., 1979), or more exhaustive compartmental models, e.g. (Sorensen et al., 1982), (Hovorka et al., 2007), (Dalla Man, Rizza & Cobelli, 2007): see, among the others, papers on Model Predictive Control (Hovorka et al., 2004), (Magni et al., 2009), on Parametric Programming (Dua, Doyle & Pistikopoulos, 2006), on H_∞ control (Ruiz-Velzquez, Fermat & CamposDelgado, 2004), (Chee et al., 2005), (Kovacs et al., 2011). 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 (Chee & Fernando, 2007) and references therein.

Differently from previously mentioned model-based approaches, that use nonlinear Ordinary Differential Equation (ODE) models, the one presented here exploits a nonlinear discrete Delay Differential Equation (DDE) model

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of the glucose-insulin system, (Palumbo, Panunzi & De Gaetano, 2007, Panunzi, Palumbo & De Gaetano, 2007). Despite the great diffusion of DDE models in the last decade, due to the fact that they allow a better representation of pancreatic Insulin Delivery Rate (IDR) (see e.g. Li & Johnson, 2009, and references therein), they have as yet not found widespread application in the field of glucose control, according to the authors' knowledge. Notice that when attempting to design a model-based glucose control, the works published so far have concentrated on Type 1 diabetic patients (who have essentially no endogenous insulin production and are very well represented by ODE models), avoiding in this way the need to take the pancreatic insulin delivery rate into account. On the other hand, the closed-loop control here considered can take into account also spontaneous pancreatic insulin release, thereby treating Type 1 and Type 2 diabetic patients in a unified fashion. The above mentioned DDE model of the glucose-insulin system has been coupled to a linear model of subcutaneous insulin absorption, analyzed in (Wilinska et al., 2005), (Clausen, De Gaetano & Volund, 2006) and already exploited with the aim of glucose control in (Hovorka et al., 2004).

The control law proposed in this note is based on recent results on differential geometry for time-delay systems (see Germani, Manes & Pepe, 2000, Germani, Manes & Pepe, 2003, Oguchi, Watanabe & Nakamizo, 2002, Marquez-Martinez & Moog, 2004). Based on a DDE model of the glucose-insulin system and subcutaneous absorption, in (Palumbo et al., 2011) the input/output feedback linearization with delay cancellation has been applied with the aim of tracking a desired glucose profile. That was a purely theoretical work, since the control law required a complete knowledge of the state of the system, including intra-venous and subcutaneous insulin measurements. However, insulin measurements are slower, more expensive and less accurate and, in case of subcutaneous insulin measurements, they are not accessible at all. To overcome such a drawback, the present paper proposes the use of a state observer to estimate in real-time both plasma insulinemia and the subcutaneous insulin depot. The observer, here adopted to close the loop by using only glucose measurements, is the one developed in (Germani, Manes & Pepe, 2001) for nonlinear time-delay systems. The local convergence of the tracking error to zero is theoretically proven, and it constitutes the novel and main contribution of the paper. Preliminary results have been presented in (Palumbo et al. 2012) by using a different observer, (Germani & Pepe, 2005), with no proof of convergence.

2. PRELIMINARIES

The model-based control law is achieved by exploiting a DDE system that couples the glucose-insulin dynamics (Panunzi, Palumbo & De Gaetano, 2007) to the subcutaneous insulin absorption (Puckett & Lightfoot, 1995):

$$\begin{aligned}
&\dot{G}(t) = -K_{xgi}G(t)I(t) + T_{gh}/V_G,\\
&\dot{I}(t) = -K_{xi}I(t) + T_{iGmax}f\big(G(t-\tau_g)\big)/V_I\\
&\qquad\qquad + S_2(t)/\big(V_I t_{max,I}\big),\\
&\dot{S}_2(t) = S_1(t)/t_{max,I} - S_2(t)/t_{max,I},\\
&\dot{S}_1(t) = -S_1(t)/t_{max,I} + u(t),
\end{aligned} \tag{1}$$

with $G(t)$, [mM], $I(t)$, [pM], plasma glycemia and insulinemia, and S_1, S_2 [pmol] the insulin mass in the accessible and not-accessible subcutaneous depot, respectively. $u(t)$, [pmol/min], is the exogenous insulin infusion rate, delivered subcutaneously, i.e. the control input. The nonlinear function $f(\cdot)$ models the pancreatic Insulin Delivery Rate. As far as the model parameters and the shape of $f(\cdot)$, refer to (Panunzi, Palumbo & De Gaetano, 2007).

Initial conditions are $G(\tau) = G_0(\tau)$, $I(\tau) = I_0(\tau)$, $S_2(\tau) = S_{2,0}(\tau)$, $S_1(\tau) = S_{1,0}(\tau)$, $\tau \in [-\tau_g, 0]$. We assume, without loss of generality, that the control input acts from $t \geq 0$ on, and that the patient's glucose-insulin system, for at least $t \in [-2\tau_g, 0]$, is at the equilibrium point with zero input. That is, we assume that the patient is at rest (steady state solution for plasma glycemia) before the controller is applied.

The aim of the proposed control law is to design a model-based subcutaneous insulin infusion in order to reduce a hyperglycemic state down to a desired, euglycemic one, G_d. Only glucose measurements are allowed.

According to (Palumbo et al., 2011), by applying the theory of exact input-output feedback linearization with delay cancellation (see Germani, Manes & Pepe, 2000,Germani, Manes & Pepe, 2003, Oguchi, Watanabe & Nakamizo, 2002, Marquez-Martinez & Moog, 2004), with respect to the input $u(t)$ and the output $G(t) - G_d$, the following control law is found:

$$u(t) = V_I t_{max,I}^2 \frac{\alpha(\cdot) - v(t)}{K_{xgi}G(t)}, \tag{2}$$

where $\alpha(\cdot)$ is a function of the system variables at the present time $G(t)$, $I(t)$, $S_1(t)$, $S_2(t)$, and of some of them at delayed times (i.e. of $G(t-\tau_g)$, $I(t-\tau_g)$, $S_2(t-\tau_g)$ and $G(t-2\tau_g)$). By applying (2) to (1), it comes that the closed-loop system may be written by using the new variables $z(t) = [G(t)\ \ G^{(1)}(t)\ \ G^{(2)}(t)\ \ G^{(3)}(t)]^T$ as:

$$\dot{z}(t) = A_b z(t) + B_b v(t), \qquad t \geq 0, \tag{3}$$

with A_b, B_b the fourth-order Brunowski pair. Notice that the equation (3) holds for all $t \geq 0$ and not only after some delay intervals (see Germani, Manes & Pepe, 2000, Germani, Manes & Pepe, 2003). This is obtained in (Palumbo et al., 2011) by making use of the initial conditions derivatives for $t \in [0, \tau_g]$. Here, since the patient is at rest for $t \in [-2\tau_g, 0]$, the delay differential equations in the model (1) are satisfied also for $t \in [-\tau_g, 0]$, with $u(t) = 0$. In this way, when delayed derivates of the glucose variable are required in the expression of $\alpha(\cdot)$, we can use the first two equations in the model (1), at delayed time $t - \tau_g$, also when $t \in [0, \tau_g]$. By setting the outer input $v(t) = \Gamma e(t)$, with $e(t) = z(t) - z_d$, $z_d = [G_d\ \ 0\ \ 0\ \ 0]^T$, we may choose the gain matrix $\Gamma \in \mathbb{R}^{1\times 4}$ to make Hurwitz the matrix $H = A_b + B_b\Gamma$, since the Brunowski pair is controllable. Therefore, the tracking error between plasma glycemia and its reference signal converges exponentially to zero.

Note that, by suitably exploiting the desired glucose level G_d, the following levels for the state variables are defined:

$$\begin{aligned}
&I_d = T_{gh}/\big(V_G K_{xgi} G_d\big),\\
&S_{2,d} = \big(K_{xi}I_d - T_{iGmax}f(G_d)/V_I\big)V_I t_{max,I},\\
&S_{1,d} = S_{2,d}, \qquad u_d = S_{1,d}/t_{max,I},
\end{aligned} \tag{4}$$

which have the following meaning. If, given a time instant $\bar{t} \geq 0$, it is $G(\tau) = G_d$, $I(\tau) = I_d$, $S_2(\tau) = S_{2,d}$, $S_1(\tau) = S_{1,d}$, for $\tau \in [\bar{t} - \tau_g, \bar{t}]$, and the control law $u(t)$ designed as in (2) is applied, then the solution of (1) is $G(t) = G_d$, $I(t) = I_d$, $S_2(t) = S_{2,d}$, $S_1(t) = S_{1,d}$, for $t \geq \bar{t}$, and the control law becomes $u(t) = u_d$, $t \geq \bar{t}$. In other words, once G_d has been chosen, we may compute I_d, $S_{2,d}$, $S_{1,d}$ and u_d (as in (4)) as the reference levels of the system variables and of the control input that asymptotically correspond to a perfect tracking of G_d. As a matter of fact, the state $X_E = [G_d \;\; I_d \;\; S_{2,d} \;\; S_{1,d}]^T \in \mathbb{R}^4$ is the equilibrium point of the closed loop system (1)-(2).

The main drawback of such a control law is that it requires both glucose and insulin measurements: on the other hand, plasma insulin measurements are slower and more cumbersome to obtain, more expensive, and also less accurate than glucose measurements. Moreover, subcutaneous insulin measurements are quite impossible to obtain, especially in a real-time closed-loop framework. An incentive exists, therefore, to construct a control law avoiding the need for insulin measures. In order to overcome such a problem, we consider a state observer for system (1), with the aim of estimating the insulin on the basis of continuous time glucose measurements.

3. OBSERVER-BASED CONTROL LAW

Define the vector of variables

$$X(t) = [G(t) \;\; I(t) \;\; S_2(t) \;\; S_1(t)]^T \in \mathbb{R}^4 \tag{5}$$

such that the DDE system (1) can be written as:

$$\dot{X}(t) = \mathcal{F}\big(X(t), X(t-\tau_g)\big) + B_b u(t), \tag{6}$$

with $\mathcal{F} : \mathbb{R}^4 \times \mathbb{R}^4 \mapsto \mathbb{R}^4$ coming straightforwardly. The measured output is, then, given by $y(t) = G(t) = C_b X(t)$, where $C_b = [1 \;\; 0 \;\; 0 \;\; 0]$.

The observer for system (6) here adopted is the one developed in (Germani, Manes & Pepe, 2001), given by the following neutral system, with $\widehat{X}(t), w(t) \in \mathbb{R}^4$:

$$\dot{\widehat{X}}(t) = \mathcal{F}\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big) + B_b u(t) + w(t), \qquad t \geq 0, \tag{7}$$

$$w(t) = Q^{-1}\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big)\Big(W\big(y(t) - C_b\widehat{X}(t)\big) - Q_1\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big)w(t-\tau_g)\Big). \tag{8}$$

Matrices

$$Q\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big) = \frac{\partial \Theta\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big)}{\partial \widehat{X}(t)}$$

$$Q_1\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big) = \frac{\partial \Theta\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big)}{\partial \widehat{X}(t-\tau_g)} \tag{9}$$

are obtained from the partial derivatives of the function $\Theta(\cdot,\cdot)$ (see Germani, Manes & Pepe, 2001), formally defined as the aggregate of the output $G(t)$ and its first 3 time derivatives, obtained according to (1). It comes out that $\Theta(\cdot,\cdot)$ is a function of the system variables at the present time (i.e. $G(t)$, $I(t)$, $S_1(t)$, $S_2(t)$) and of some of them at the delayed time (i.e. $G(t-\tau_g)$ and $I(t-\tau_g)$). When the function Θ is used for computations in (9), $\widehat{X}(t)$ takes the place of $[G(t) \;\; I(t) \;\; S_2(t) \;\; S_1(t)]^T$, for any required time t. The gain matrix $W \in \mathbb{R}^{4\times 1}$ is chosen such that the matrix $\widehat{H} = A_b - WC_b$ is Hurwitz.

In (Germani, Manes & Pepe, 2001) conditions are given such that, properly assigning the gain matrix W, the asymptotic convergence to zero of the observation error is guaranteed. Such conditions are not completely satisfied by the system at hand (for instance, the functions involved in (1) are not globally Lipschitz). Here, however, we are not interested in the convergence of the observation error to zero for any bounded input signal, as in (Germani, Manes & Pepe, 2001), but in the convergence of the state variables to the desired equilibrium. At that aim, we exploit the observer equations to close the loop from the observed state $\widehat{X}(t)$, so that the state variables in (2) are replaced by their estimates. Then, the control law becomes:

$$u(t) = V_I t_{max,I}^2 \frac{\alpha(\hat{\cdot}) - v(t)}{K_{xgi} C_b \widehat{X}(t)}, \qquad v(t) = \Gamma\big(\hat{z}(t) - z_d\big), \tag{10}$$

with $\hat{z}(t) = \Theta(\widehat{X}(t), \widehat{X}(t-\tau_g)$ and $\alpha(\hat{\cdot})$ denotes function $\alpha(\cdot)$ computed in the observed state variables $\widehat{X}(t)$, $\widehat{X}(t-\tau_g)$, $\widehat{X}(t-2\tau_g)$, instead of the real ones.

Remark. Since $\alpha(\hat{\cdot})$ is a function of the state variable at present and past time, with maximum involved time-delay equal to $2\tau_g$, the closed-loop system (6)-(10) is a retarded system with delay $2\tau_g$ as well. Therefore, the initial conditions for the observer are set as follows (see Germani, Manes & Pepe, 2001):

$$\widehat{X}(\tau) = \zeta(\tau), \qquad \zeta \in C^1([-2\tau_g, 0]; \mathbb{R}^4) \tag{11}$$

$$w(\tau) = \dot{\zeta}(\tau) - \mathcal{F}\big(\zeta(\tau), \zeta(\tau-\tau_g)\big), \quad \tau \in [-\tau_g, 0] \tag{12}$$

The function $\tilde{u}(\tau)$, $\tau \in [-\tau_g, 0]$, involved in (Germani, Manes & Pepe, 2001), is here useless since $Q_1(\cdot,\cdot)B_b = 0$. Indeed, function Θ does not depend of $S_1(t-\tau_g)$. •

Notice that $\mathcal{X}_E = [X_E^T \;\; X_E^T]^T \in \mathbb{R}^8$ is the equilibrium point of the observer-based closed-loop system (6)-(10).

Theorem 1. There exist matrices W and Γ such that the equilibrium point $\mathcal{X}_E$ of the closed-loop system (6)-(10) is asymptotically stable.

Proof: The proof is developed by taking into account the closed-loop system (6)-(10), in terms of new variables (see z, $\hat{z}$ below). The path indicated in (Ciccarella, Dalla Mora & Germani, 1995) for finite dimensional systems will be followed here. Consider the variables transformation:

$$z(t) = \Theta\big(X(t), X(t-\tau_g)\big), \quad t \geq -\tau_g, \tag{13}$$

$$\hat{z}(t) = \Theta\big(\widehat{X}(t), \widehat{X}(t-\tau_g)\big), \quad t \geq -\tau_g \tag{14}$$

According to its structure, Θ can be inverted in order to write, for $t \geq 0$, $X(t)$ (and $\widehat{X}(t)$) as a function of the only variable $z(\cdot)$ (and $\hat{z}(\cdot)$), namely: $X(t) = \widetilde{\Theta}\big(z(t), z(t-\tau_g)\big)$ (and $\widehat{X}(t) = \widetilde{\Theta}\big(\hat{z}(t), \hat{z}(t-\tau_g)\big)$). Taking into account of the hypothesis of patient at rest, for $t \in [-2\tau_g, 0]$, the system dynamics can be written in the z variables, with suitable functions m_1, m_2, as (see Palumbo et al., 2011):

$$\begin{aligned}
&\dot{z}(t) = A_b z(t) + B_b\big(m_1(z_t) + m_2\big(z(t)\big)u(t)\big), \;\; t \geq 0,\\
&z(\tau) = \Theta(X(\tau), X(\tau-\tau_g)), \;\; \tau \in [-\tau_g, 0],\\
&z(\tau) = [X_1(\tau) \;\; 0 \;\; 0 \;\; 0]^T, \tau \in [-2\tau_g, -\tau_g),
\end{aligned} \tag{15}$$

where X_1 is the first component of X and, with a little abuse of notation:

$$m_1(z_t) = m_1\big(z(t), z(t-\tau_g), z(t-2\tau_g)\big),$$
$$m_2\big(z(t)\big) = -K_{xgi}C_b z(t)/\big(V_I t^2_{max,I}\big) \quad (16)$$

As standard, z_t denotes the function in $C([-2\tau_g, 0]; \mathbb{R}^4)$ given, for $\tau \in [-2\tau_g, 0]$, by $z_t(\tau) = z(t+\tau)$ (the same notation will be used in the following for $\hat{z}$, ξ, e, $\hat{e}$). The values of the second, the third and the fourth components of the vector $z(t)$, $t \in [-2\tau_g, -\tau_g)$ are not needed. For simplicity they are here set equal to zero, in order to provide the initial conditions for z in the same interval as for the variables X, and also in order to avoid non uniformity of time domain definitions for next introduced variables (e, $\hat{e}$, ξ). The observed variables $\hat{z}(t)$ obey to delay differential equations (instead of neutral differential equations), as follows (see Germani, Manes & Pepe, 2001):

$$\begin{aligned}\dot{\hat{z}}(t) &= A_b\hat{z}(t) + B_b\left(m_1(\hat{z}_t) + m_2\big(\hat{z}(t)\big)u(t)\right)\\ &\quad + W(C_b z(t) - C_b\hat{z}(t)), \qquad t \geq 0,\\ \hat{z}(\tau) &= \Theta(\zeta(\tau), \zeta(\tau-\tau_g)), \quad \tau \in [-\tau_g, 0],\\ \hat{z}(\tau) &= [\zeta_1(\tau)\ 0\ 0\ 0]^T, \quad \tau \in [-2\tau_g, 0], \end{aligned} \quad (17)$$

with ζ_1 the first component of ζ. The values of the second, the third and the fourth components of the vector $\hat{z}(t)$, $t \in [-2\tau_g, -\tau_g)$ are not needed. For simplicity they are here set equal to zero, in order to provide the initial conditions for $\hat{z}$ in the same interval as for the variables $\widehat{X}$, and, as stated for the initial condition of the system equations in z variables, also in order to avoid non uniformity of time domain definitions for next introduced variables. The control input (10) becomes, with the introduced notations, $u(t) = p_1(\hat{z}_t)$, with:

$$\begin{aligned}p_1(\hat{z}_t) &= p_1\big(\hat{z}(t), \hat{z}(t-\tau_g), \hat{z}(t-2\tau_g)\big)\\ &= -\big(m_1(\hat{z}_t) - \Gamma\big(\hat{z}(t) - z_d\big)\big)/m_2\big(\hat{z}(t)\big),\end{aligned} \quad (18)$$

so that system (15) becomes:

$$\dot{z}(t) = A_b z(t) + B_b\Big(m_1(z_t) + m_2\big(z(t)\big)p_1(\hat{z}_t)\Big) \quad (19)$$

By the theory developed in (Germani, Manes & Pepe, 2001, Germani, Manes & Pepe, 2003, Palumbo et al., 2011), the following result holds:

$$m_1(\hat{z}_t) + m_2\big(\hat{z}(t)\big)p_1(\hat{z}_t) = \Gamma\big(\hat{z}(t) - z_d\big), \qquad t \geq 0. \quad (20)$$

Taking into account of (20) and (17), we obtain

$$\dot{\hat{z}}(t) = H\hat{z}(t) - B_b\Gamma z_d + WC_b(z(t) - \hat{z}(t)), \quad t \geq 0, \quad (21)$$

with $H = A_b + B_b\Gamma$. Define the errors $e(t) = z(t) - z_d$ and $\hat{e}(t) = \hat{z}(t) - z_d$, $t \geq -2\tau_g$. Then, since $A_b z_d = 0$, it is:

$$\begin{aligned}\dot{e}(t) &= A_b e(t) + B_b\left(q_1(e_t) + q_2\big(e(t)\big)p_2(\hat{e}_t)\right)\\ \dot{\hat{e}}(t) &= H\hat{e}(t) + WC_b\xi(t)\end{aligned} \quad (22)$$

with $\xi(t) = e(t) - \hat{e}(t) = z(t) - \hat{z}(t)$, $q_1(e_t) = m_1(e_t + z_d)$, $q_2\big(\hat{e}(t)\big) = m_2\big(\hat{e}(t) + z_d\big)$, $p_2(\hat{e}_t) = p_1(\hat{e}_t + z_d)$ where, for $e_t + z_d$ (and for $\hat{e}_t + z_d$) is meant the function in $C([-2\tau_g, 0]; \mathbb{R}^4)$ given, for $\tau \in [-2\tau_g, 0]$, as $(e_t + z_d)(\tau) = e_t(\tau) + z_d$ (and $(\hat{e}_t + z_d)(\tau) = \hat{e}_t(\tau) + z_d$). Therefore, the closed loop system in the variables $(\hat{e}, \xi)$ becomes:

$$\begin{aligned}\dot{\hat{e}}(t) &= H\hat{e}(t) + WC_b\xi(t)\\ \dot{\xi}(t) &= \widehat{H}\xi(t) + B_b L(\xi_t, \hat{e}_t)\end{aligned} \quad (23)$$

$$\begin{aligned}L(\xi_t, \hat{e}_t) &= q_1(\xi_t + \hat{e}_t) + q_2\big(\xi(t) + \hat{e}(t)\big)p_2(\hat{e}_t)\\ &\quad - q_1(\hat{e}_t) - q_2\big(\hat{e}(t)\big)p_2(\hat{e}_t)\end{aligned} \quad (24)$$

According to its definition the nonlinear function L in (24) has 6 entries, namely: $l_1 = \xi(t)$, $l_2 = \xi(t-\tau_g)$, $l_3 = \xi(t-2\tau_g)$, $l_4 = \hat{e}(t)$, $l_5 = \hat{e}(t-\tau_g)$, $l_6 = \hat{e}(t-2\tau_g)$. By linearizing the closed loop system (24) around the steady state $[0,0,0,0,0,0]^T$, it is:

$$\begin{aligned}\dot{\hat{e}}(t) &= H\hat{e}(t) + WC_b\xi(t)\\ \dot{\xi}(t) &= \widehat{H}\xi(t) + B_b\big(r_0\xi(t) + r_1\xi(t-\tau_g) + r_2\xi(t-2\tau_g)\\ &\quad + r_3\hat{e}(t) + r_4\hat{e}(t-\tau_g) + r_5\hat{e}(t-2\tau_g)\big)\end{aligned} \quad (25)$$

$$\begin{aligned}r_0 &= \left.\frac{\partial L}{\partial l_1}\right|_{l_i=0}, \quad r_1 = \left.\frac{\partial L}{\partial l_2}\right|_{l_i=0}, \quad r_2 = \left.\frac{\partial L}{\partial l_3}\right|_{l_i=0},\\ r_3 &= \left.\frac{\partial L}{\partial l_4}\right|_{l_i=0}, \quad r_4 = \left.\frac{\partial L}{\partial l_5}\right|_{l_i=0}, \quad r_4 = \left.\frac{\partial L}{\partial l_6}\right|_{l_i=0}\end{aligned} \quad (26)$$

with $r_i \in \mathbb{R}^{1\times 4}$. Since $r_3 = r_4 = r_5 = 0$ (it readily comes from (24)), the linearized time-delay system (25) becomes:

$$\begin{aligned}\dot{\hat{e}}(t) &= H\hat{e}(t) + WC_b\xi(t)\\ \dot{\xi}(t) &= \widehat{H}\xi(t) + B_b\left(r_0\xi(t) + r_1\xi(t-\tau_g) + r_2\xi(t-2\tau_g)\right)\end{aligned} \quad (27)$$

In the following it will be shown that there exist matrices W, Γ such that the linearized system (27) is asymptotically stable. To this aim, denote $\lambda = \{\lambda_1, \lambda_2, \lambda_3, \lambda_4\}$, with $-\infty < \lambda_4 < \lambda_3 < \lambda_2 < \lambda_1 < 0$ the eigenvalues of $\widehat{H}$, chosen by means of matrix W, and let $V(\lambda)$ be the Vandermonde matrix associated to λ (see Ciccarella, Dalla Mora & Germani, 1993). From the second equation of (27), the evolution of $\xi(t)$ is given by:

$$\begin{aligned}\xi(t) = e^{\widehat{H}t}\xi(0) + \int_0^t e^{\widehat{H}(t-\tau)}B_b\big(r_0\xi(\tau) + r_1\xi(\tau-\tau_g)\\ + r_2\xi(\tau-2\tau_g)\big)d\tau.\end{aligned} \quad (28)$$

By suitably exploiting the Vandermonde matrix construction, it is $V(\lambda)B_b = \mathbb{1}$, and

$$V(\lambda)e^{\widehat{H}t}V^{-1}(\lambda) = e^{\Lambda t}, \qquad \Lambda = \mathrm{diag}\{\lambda_1, \ldots, \lambda_4\} \quad (29)$$

with $\mathbb{1}$ a column vector of 1's in $\mathbb{R}^4$. Thus, by setting $\psi(t) = V(\lambda)\xi(t)$, and by applying the Bellman-Gronwall lemma (see, e.g., Sastry, 1999), it is:

$$\begin{aligned}\|\psi(t)\| &\leq e^{\left(\lambda_1 + 2\|r_0\|\|V^{-1}(\lambda)\|\right)t}\|\psi(0)\|\\ &\quad + \int_0^t e^{\left(\lambda_1 + 2\|r_0\|\|V^{-1}(\lambda)\|\right)(t-\tau)}2\|V^{-1}(\lambda)\|\\ &\quad \cdot\left[\|r_1\|\cdot\|\psi(\tau-\tau_g)\| + \|r_2\|\cdot\|\psi(\tau-2\tau_g)\|\right]d\tau\end{aligned} \quad (30)$$

To complete the proof, it will be shown that $\|\psi(t)\|$ is bounded by a positive function $s : [-2\tau_g, +\infty) \to \mathbb{R}^+$ asymptotically converging to zero. To this aim, define

$$s(t) = Me^{\rho t}, \qquad M = \sup_{\tau\in[-2\tau_g, 0]}\|V(\lambda)\|\cdot\|\xi(\tau)\| \quad (31)$$

for some negative real value $\rho < 0$. Then, it is $\|\psi(t)\| \leq s(t)$ for $t \in [-2\tau_g, 0]$, since:

$$\begin{aligned}\|\psi(t)\| \leq \|V(\lambda)\|\cdot\|\xi(t)\| &\leq \sup_{\tau\in[-2\tau_g, 0]}\|V(\lambda)\|\cdot\|\xi(\tau)\|\\ &= M \leq Me^{\rho t} = s(t)\end{aligned} \quad (32)$$

Moreover, there exists a negative value for ρ such that $s(t)$ defined in (31) obeys to the following equality for $t \geq 0$:

$$\begin{aligned}s(t) &= e^{\left(\lambda_1 + 2\|r_0\|\|V^{-1}(\lambda)\|\right)t}s(0)\\ &\quad + \int_0^t e^{\left(\lambda_1 + 2\|r_0\|\|V^{-1}(\lambda)\|\right)(t-\tau)}\\ &\quad \cdot 2\|V^{-1}(\lambda)\|\left[\|r_1\|\cdot\|s(\tau-\tau_g)\| + \|r_2\|\cdot\|s(\tau-2\tau_g)\|\right]d\tau\end{aligned} \quad (33)$$

Indeed, by substituting $s(t)$ in (33) to find the required ρ, it comes that a negative real solution with respect to the unknown ρ exists, if the following equation admits negative real solutions for the unknown ρ:

$$\rho = b_1 + b_2 e^{-\rho\tau_g} + b_3 e^{-2\rho\tau_g}, \tag{34}$$

with

$$b_1 = \lambda_1 + 2\|r_0\|\cdot\|V^{-1}(\lambda)\|,$$
$$b_2 = 2\|r_1\|\cdot\|V^{-1}(\lambda)\|, \qquad b_3 = 2\|r_2\|\cdot\|V^{-1}(\lambda)\| \tag{35}$$

that is: if, and only if, the right-hand-side computed for $\rho = 0$ is negative, that is, if, and only if:

$$b_1+b_2+b_3 = \lambda_1 + 2\|V^{-1}(\lambda)\|\big(\|r_0\|+\|r_1\|+\|r_2\|\big) < 0 \tag{36}$$

Such a condition can always be satisfied by suitably choosing the eigenvalues λ, by means of matrix W (Ciccarella, Dalla Mora & Germani, 1993). Therefore, by standard step procedure with step-size equal to τ_g, it follows that $\|\psi(t)\| \mapsto 0$, since:

$$0 \le \|\psi(t)\| \le s(t) \mapsto 0 \tag{37}$$

Finally, since matrix Γ is such that the eigenvalues of H are negative real, taking into account the first equation in (25) we can conclude about the asymptotic stability. □

4. NUMERICAL SIMULATIONS

Proposed simulations have been carried out on virtual patients on the basis of model parameter estimates obtained from data related to an IVGTT experiment conducted on obese patients (Body Mass Index $\simeq$ 50), studied at Catholic University of Rome, Department of Metabolic Diseases (see Panunzi, De Gaetano & Mingrone, 2010). These data have been further manually modified in order to simulate the development of Type 2 diabetes as below reported (refer to Section 2 for the measurement units):

$$\begin{aligned} &G_b = 10.66, \quad I_b = 49.29, && T_{iGmax} = 0.236 \\ &V_G = 0.187, \quad K_{xi} = 1.211\times10^{-2}, && \tau_g = 24 \\ &V_I = 0.25, \quad K_{xgi} = 3.11\times10^{-5}, && T_{gh} = 0.003 \\ &\gamma = 3.205, \quad G^* = 9 \end{aligned} \tag{38}$$

The subcutaneous absorption parameter, i.e. $t_{max,I}$, has been taken from (Hovorka et al., 2004). The same set of parameters has been previously exploited in (Palumbo et al., 2011), without the use of an observer, and in (Palumbo et al. 2012), according to a different choice of observer.

The desired reference level of glycemia is set at 5mM.

The gain matrices Γ, W are chosen to assign eigenvalues $-[0.055 \quad 0.019 \quad 0.029 \quad 0.030]^T$ and $-5{\cdot}10^{-10}[4 \quad 3 \quad 2 \quad 1]^T$ to matrices H and $\widehat{H}$, respectively. Initial values for state variables are $G_0(\tau) = G_b$, $I_0(\tau) = I_b$, $S_{2,0}(\tau) = 0$, $S_{1,0}(\tau) = 0$ for $\tau \in [-2\tau_g, 0]$, while the observer initial conditions have been set as $\widehat{G}_0(\tau) = 15$, $\widehat{I}_0(\tau) = 100$, $\widehat{S}_{2,0}(\tau) = 5$, $\widehat{S}_{1,0}(\tau) = 5$ for $\tau \in [-2\tau_g, 0]$. $w(\tau)$ has been initialized according to (12).

Notice that the control parameters have been chosen in order not to have a theoretical negative control input (i.e. negative insulin administration), as it appears from Fig.2. Fig.1 shows the glucose and insulin concentrations, compared to their estimated profiles. Notice that the initial basal hyperglycemia is reduced to a safe level (below 6.5mM) after about 3 hours of closed loop therapy, with no dangerous oscillations, nor hypoglycemic episodes.

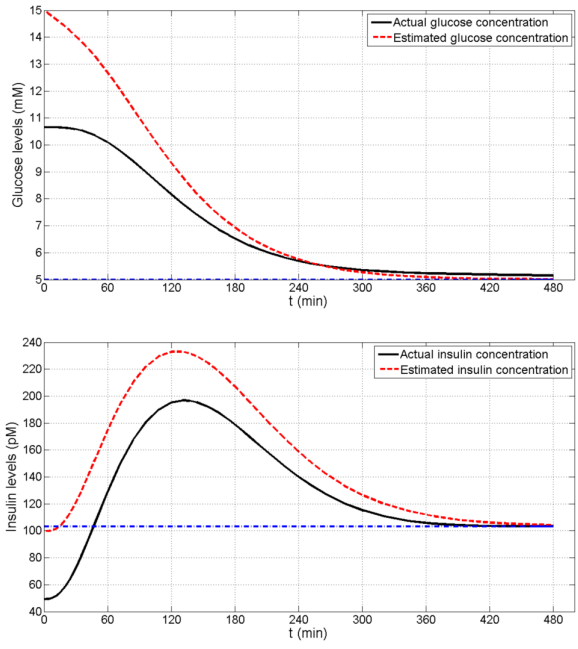

Fig. 1. Plasma glycemia/insulinemia: the actual concentration compared to the estimated one. Blue dotted lines are desired values for subcutaneous depot.

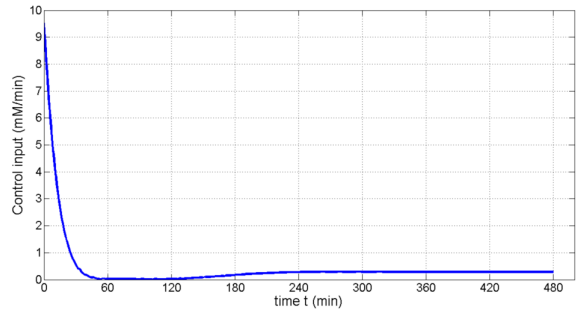

Fig. 2. Exogenous insulin infusion rate

5. CONCLUSIONS

In this note, a time-delay model-based control law is proposed to track a desired level of plasma glycemia from a diabetic hyperglycemic state. The DDE model here adopted is a minimal model of the glucose insulin system, that allows a good representation of both Type I and Type II diabetic patients in a unified fashion. First attempts to exploit such a model by the authors have been reported in (Palumbo et al., 2009, Palumbo et al., 2012, A), where intravenous insulin administration was considered, and in (Palumbo et al., 2011) where subcutaneous insulin administration has been considered. The novelty of the present paper relies in the use of a proper observer to estimate those state variables which cannot be directly measured (i.e. insulin in plasma and in the subcutaneous depot). The main result reported here is the proof of convergence to zero of the tracking error.

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