Observer-based closed-loop control of plasma glycemia

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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. Only measurements of glycemia are considered. A nonlinear observer for delay differential systems is used for the estimation of insulinemia. In the spirit of the separation theorem, a nonlinear control law is proposed, based on the feedback linearization, which makes use of the observer estimations instead of the full state measurements. The local convergence of the tracking error to zero is theoretically proved. In silico simulations, which also take into account input saturation, show the very good performance of the proposed control technique.

I. INTRODUCTION

The design of insulin infusion devices able to control plasma glucose concentration is of great importance when attempting to gain control of decompenated hyperglycemia in selected clinical situations (e.g. perioperative control of glyceremia in a compensated, 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, [25]. 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 [4] 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 [27] for a critical 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 (see [34] and references therein for a survey of intravenous administration for plasma glucose control).

A closed loop control strategy may be implemented according to a model-less or to 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. Earlier empirical algorithms are due to Albisser et al. [2], [3]: recent papers on this topic are mainly devoted to the application of PID controllers aiming to mimic the pancreatic glucose response (see e.g. [6], [39], [19], [26]). On the other hand a model-based approach presupposes sufficiently detailed knowledge of the physics 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 is, the more effective will the control law be. Model-based glucose control has been mainly developed for the Ackerman’s linear model [1] (e.g. adaptive control [29], optimal control [40], [14], $H_\infty$ control [22]); more recently, different approaches have been proposed, based on nonlinear models such as the Minimal Model [5], [41], or more exhaustive compartmental models [12], [38], [21] (e.g. Model Predictive Control [35], nonlinear Model Predictive Control [20], Neural Predictive Control [42], $H_\infty$ control [36], non-standard $H_\infty$ control [7], [37]). 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 [8] and references therein.

In the present work, a model-based closed-loop control scheme is proposed, with glucose feedback only. 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 [31], [33]. Since [13], several DDE models have been published, mainly devoted to better represent pancreatic Insulin Delivery Rate (IDR) (e.g. [23], [24] 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 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 [33] 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 [31] (e.g. positivity and boundedness of solutions, local attractivity of a single positive equilibrium), and is 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) [33].

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 [30] the input-output feedback linearization with delay cancellation has been used, [15], [17], [28], 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: an incentive exists, therefore, to construct a control law avoiding the need for insulin measures. In the present work, feedback linearization is provided by using only glucose measurements, using a nonlinear observer ([16], [18]) for time-delay systems to compensate for the lack of insulin measures. The local convergence of the tracking error to zero is theoretically proved.

II. PRELIMINARIES

The glucose-insulin model considered here belongs to the family of DDE models described in [31], 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:

$$\frac{dG}{dt} = -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G},$$

$$\frac{dI}{dt} = -K_{xi}I(t) + \frac{T_{Gi\max}}{V_I}f(G(t - \tau_g)) + u(t),$$

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

where $K_{xgi}$, [min$^{-1}$ 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; $T_{Gi\max}$, [min$^{-1}$ (pmol/kgBW)], is the maximal rate of second-phase insulin release; $V_I$, [L/kgBW], is the apparent distribution volume for insulin; $\tau_g$, [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 intra-venous insulin delivery rate, i.e. the control input.

$$(G_0(\tau), I_0(\tau))$$ is the pair of initial conditions, equal to the constant basal levels ($G_b$, $I_b$).

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

$$f(G) = \frac{(\frac{G}{G_\ast})^\gamma}{1 + (\frac{G}{G_\ast})^\gamma},$$

where $\gamma$ is the progressivity with which the pancreas reacts to circulating glucose concentrations and $G_\ast$ [mM] is the glycemia at which the insulin release is half of its maximal rate.

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) (see [31]).

The aim of the proposed control law is to reduce a high basal plasma glucose concentration to a lower level, according to a smooth reference glucose trajectory, by means of intra-venous insulin administration.

In [30], by applying the theory of input-output feedback linearization with delay cancellation (see [15],[17], [28]), with respect to $y(t) = G(t)$ and the input $u(t)$, the following feedback control law is found:

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

where:

$$S(G(t), I(t), G(t - \tau_g))$$

$$= -K_{xgi}I(t) - K_{xgi}I(t)G(t) + \frac{T_{gh}}{V_G}$$

$$-K_{xgi}G(t)\left(-K_{xi}I(t) + \frac{T_{Gi\max}}{V_I}f(G(t - \tau_g))\right);$$

and

$$v(t) = \dot{G}_{ref}(t) + Re(t);$$

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

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

has prescribed eigenvalues in the left half complex plane and

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

with

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

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for $t \geq -\tau_g$, and $Z_{\text{ref}}(t) = [G_{\text{ref}}(t) \ G_{\text{ref}}(t)^T]$, $t \geq -\tau_g$. $G_{\text{ref}}(t)$ is the glucose reference signal to be tracked: it is supposed to be at least twice continuously differentiable except, possibly, in $0$ where the right-hand first and second derivatives can be considered.

It is shown in [30] that, by applying (3-5) the tracking error variable $e(t)$ asymptotically converges to zero, since:

$$
\dot{e}(t) = H e(t), \quad H \text{ Hurwitz, according to (6).} \tag{9}
$$

Such a control law (3-5) 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: an incentive exists, therefore, to construct a control law avoiding the need for insulin measures.

In order to avoid the former problem, concerning the measurement of the insulin, we shall consider in next section an observer for the system (1), with the aim of estimating the insulin on the basis of continuous time glucose measures.

III. MAIN RESULTS

On the basis of the theoretical results in [16], [18], concerning the construction of observers for time-delay systems, the following observer is proposed:

$$
\begin{bmatrix}
\frac{d\hat{G}(t)}{dt} \\
\frac{d\hat{I}(t)}{dt}
\end{bmatrix} = -K_{xgi} \hat{G}(t) \hat{I}(t) + \frac{T_{gh}}{V_G} + u(t)
\begin{bmatrix}
1 \\
0
\end{bmatrix}
+ Q^{-1}(\hat{G}(t), \hat{I}(t)) W (G(t) - \hat{G}(t)),
$$

$$
\hat{G}(t) = \hat{G}_0(t), \quad \hat{I}(t) = \hat{I}_0(t), \quad \tau \in [-\tau_g, 0], \tag{10}
$$

where $Q^{-1}$ is the inverse matrix (not the inverse function, see [9]) of the matrix function $Q(x_1, x_2) \in \mathbb{R}^{2 \times 2}$ defined as:

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

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

$$
\hat{H} = \begin{bmatrix}
0 & 1 \\
0 & 0
\end{bmatrix} - W \begin{bmatrix}
1 & 0
\end{bmatrix} \tag{12}
$$

has prescribed eigenvalues in the left half complex plane.

According to results in [16], [18], the observer (10) guarantees local exponential convergence of the estimation error $[G(t) - \hat{G}(t) \ I(t) - \hat{I}(t)]^T$ to zero. More specifically, if the estimation error at zero is sufficiently small, then the estimation error converges exponentially to zero, with arbitrary decay rate fixed by means of the choice of $W$.

In order to close the loop from the observed state, let us consider the feedback control law:

$$
u(t) = S(\hat{G}(t), \hat{I}(t), \hat{G}_0(t) - \hat{G}(t)) - v(t), \tag{13}
$$

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

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

Such control law does not make use of insulin measurements, differently from the control law (3-5). Actually, it makes use of the glucose and insulin estimations provided by the observer, on the basis of the only glucose measurements.

In the following it will be referred to:

$$
I_{\text{ref}}(t) = \frac{\dot{G}_{\text{ref}}(t) - \frac{T_{gh}}{V_G} + K_{xgi} \dot{G}_{\text{ref}}(t)}{\hat{G}_{\text{ref}}(t)}, \tag{15}
$$

and

$$
u_{\text{ref}}(t) = \dot{I}_{\text{ref}}(t) + K_{xi} \dot{I}_{\text{ref}}(t) - \frac{T_{Igmax}}{V_I} f(G_{\text{ref}}(t) - \tau_g) \tag{16}
$$

for $t \geq 0$ to denote the insulin and control signals in the case of tracking error equal to zero (i.e. $G(t) = \hat{G}_{\text{ref}}(t), \quad t \geq -\tau_g, \quad G(t) = G_{\text{ref}}(t), \quad t \geq 0$), respectively.

Theorem 1: There exist gains $R$ and $W$ such that, for the closed-loop system (1), (10), (13), it is:

$$
\lim_{t \to +\infty} \begin{bmatrix}
\hat{G}(t) \\
\hat{I}(t)
\end{bmatrix} = \lim_{t \to +\infty} \begin{bmatrix}
\hat{G}(t) \\
\hat{I}(t)
\end{bmatrix} = \begin{bmatrix}
G_{\text{ref}}(t) \\
I_{\text{ref}}(t)
\end{bmatrix}, \tag{17}
$$

$$
\lim_{t \to +\infty} u(t) = u_{\text{ref}}(t), \tag{18}
$$

provided that the initial tracking and observer errors

$$
\sup_{\tau \in [-\tau_g, 0]} |G_0(\tau) - \hat{G}_0(\tau)|, \quad \sup_{\tau \in [-\tau_g, 0]} |I_0(\tau) - \hat{I}_0(\tau)| \tag{19}
$$

are suitably small.

Proof: The closed-loop system (1), (10), (13), can be rewritten, by introducing the new variables $\hat{e}(t)$ and

$$
\xi(t) = \begin{bmatrix}
\xi_1(t) \\
\xi_2(t)
\end{bmatrix} = e(t) - \hat{e}(t), \tag{20}
$$

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

$$
\dot{\hat{e}}(t) = H \hat{e}(t) + WC \xi(t)
\xi(t) = \hat{H} \xi(t) + BL(t, \xi(t), \xi(t - \tau_g), \hat{e}(t), \hat{e}(t - \tau_g)), \tag{21}
$$

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

$$
L(t, \xi(t), \xi(t - \tau_g), \hat{e}(t), \hat{e}(t - \tau_g))
= -\dot{G}_{\text{ref}}(t) - R \hat{e}(t) + S(\xi_1(t) + \xi_1(t) + \hat{G}_{\text{ref}}(t),
\dot{\xi}_2(t) + \hat{e}_2(t) + \hat{G}_{\text{ref}}(t) - \frac{T_{gh}}{V_G}
- K_{xgi} (\hat{e}_1(t) + \hat{e}_1(t) + \hat{G}_{\text{ref}}(t)),
\xi_1(t - \tau_g) + \hat{e}_1(t - \tau_g) + \hat{G}_{\text{ref}}(t - \tau_g)
- \xi_1(t) + \hat{e}_1(t) + \hat{G}_{\text{ref}}(t)
- \hat{e}_1(t) + \hat{G}_{\text{ref}}(t) \left[ S(\hat{e}_1(t) + \hat{G}_{\text{ref}}(t),
- \hat{G}_{\text{ref}}(t) - \hat{R}(t) \right]. \tag{22}
$$

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The function \( L \) is such that, \( \forall t \geq 0 \) (involved \( \alpha_i \in \mathbb{R}^2, \ i = 1, 2, 3, 4 \)),
\[
L(t, 0, 0, 0, 0) = 0,
\]

\[
\frac{\partial L}{\partial \alpha_3} \bigg|_{\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = 0} = 0,
\]
\[
\frac{\partial L}{\partial \alpha_4} \bigg|_{\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = 0} = 0 \quad (23)
\]
The linearization around zero of the closed loop system (21) returns the following time-delay system

\[
\dot{\hat{\xi}}(t) = H\hat{\xi}(t) + W\hat{C}\xi(t),
\]
\[
\dot{\hat{\xi}}(t) = \hat{H}\xi(t) + B\hat{r}_0(t)\xi(t) + r_1(t)BC\xi(t - \tau_g), \quad (24)
\]
where \( r_0(t) = [r_{0,a}(t), r_{0,b}(t)] \in \mathbb{R}^{1 \times 2} \), \( r_1(t) \in \mathbb{R} \) are given by:

\[
\begin{align*}
\dot{r}_{0,a}(t) &= -K_{xg_{1}}r_{ref}(t) + K_{xg_{1}}K_{x1}r_{ref}(t), \\
\dot{r}_{0,b}(t) &= -K_{xg_{1}}r_{ref}(t) + \frac{T_{gh}}{V_{G}G_{ref}(t)} - K_{x1}, \\
\dot{r}_{1}(t) &= -K_{xg_{1}}G_{ref}(t)\frac{T_{G_{max}}}{V_{T}} \left. \frac{df(y)}{dy} \right|_{y = G_{ref}(t)} - K_{x1}.
\end{align*}
\]  

(25)  (26)  (27)

Therefore, by stability in the first approximation method, the asymptotic stability (the uniformity here is not necessary) of the closed loop, nonlinear, time-varying, time-delay system (21) is guaranteed by the asymptotic stability of the linear, time-varying, time-delay system (24). In the following we shall show that, for every bounded (this happens in practice) functions \( r_0(t), r_1(t) \), there exist gains \( R \) and \( W \) such that the linear time-delay system (24) is asymptotically stable. Let \( r = \sup_{t \geq 0} \max\{\|r_0(t)\|, \|r_1(t)\|\} \). Consider the second equation in (24). Without loss of generality, assume that matrix \( \hat{H} \) have distinct negative real eigenvalues \( \lambda = (\lambda_1, \lambda_2) \), with \( \lambda_1 > \lambda_2 \). Let \( V(\lambda) \) be the Vandermonde matrix associated to \( \lambda \) (see [9]):

\[
V(\lambda) = \begin{bmatrix}
\lambda_1 & 1 \\
\lambda_2 & 1
\end{bmatrix}
\]  

(28)

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

\[
\chi(t) \leq \chi(0) + \int_0^t \sqrt{2r}\|V^{-1}(\lambda)\|\chi(\tau)\,d\tau + \int_0^t \sqrt{2r}\|V^{-1}(\lambda)\|e^{-\lambda_1 \tau}\|\psi(\tau - \tau_g)\|\,d\tau. \quad (29)
\]

By applying the Bellman-Gronwall Lemma (for the ease of the reader reported in Appendix) as in [16] (proof of Theorem 3.4), the following inequality holds:

\[
\|\psi(t)\| \leq e^{c(\sqrt{2r}\|V^{-1}(\lambda)\|\|\psi(0)\|} + \int_0^t \sqrt{2r}\|V^{-1}(\lambda)\|e^{c(\sqrt{2r}\|V^{-1}(\lambda)\|\|\psi(\tau - \tau_g)\|}\,d\tau. \quad (30)
\]

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

\[
s(t) = e^{e^t}\|V(\lambda)\| \sup_{\tau \in [-\tau_g, 0]} \|\xi(\tau)\|, \quad t \geq -\tau_g, \quad (31)
\]

for some negative real \( \rho \), which satisfies the equation:

\[
s(t) = e^{c(\sqrt{2r}\|V^{-1}(\lambda)\|\|\psi(\tau - \tau_g)\|)}s(0) + \int_0^t \sqrt{2r}\|V^{-1}(\lambda)\|e^{c(\sqrt{2r}\|V^{-1}(\lambda)\|\|\psi(\tau - \tau_g)\|)}s(\tau - \tau_g)\,d\tau. \quad (32)
\]

To this aim, if we substitute \( s(t) = \beta e^t \) in (32), with \( \beta = \|V(\lambda)\| \sup_{\tau \in [-\tau_g, 0]} \|\xi(\tau)\| \), it is:

\[
\beta e^{e^t} = e^{c(\sqrt{2r}\|V^{-1}(\lambda)\|\|\psi(\tau - \tau_g)\|)} + \int_0^t \sqrt{2r}\|V^{-1}(\lambda)\|e^{c(\sqrt{2r}\|V^{-1}(\lambda)\|\|\psi(\tau - \tau_g)\|)}e^{e^{\tau - \tau_g}}\,d\tau, \quad (33)
\]

and, if we explicitly compute the integral in (33), we obtain the following condition to be fulfilled for \( \rho \):

\[
\sqrt{2r}\|V^{-1}(\lambda)\|e^{-\tau_g} = \rho - \sqrt{2r}\|V^{-1}(\lambda)\| - 1, \quad (34)
\]

which admits a unique negative solution for \( \rho \), provided that the eigenvalues \( \lambda \) are chosen such that:

\[
2\sqrt{2r}\|V^{-1}(\lambda)\| + 1 < 0. \quad (35)
\]

In [9] it has been shown that a set of eigenvalues \( \lambda \) can always be chosen in order to satisfy condition (35). Therefore, it is true that by choosing \( s(t) \) as in (31), equality (32) holds.

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

\[
s(\tau) \geq e^{e^\tau}\|V(\lambda)\|\|\xi(\tau)\| \geq \|V(\lambda)\|\|\xi(\tau)\| = \|\psi(\tau)\|. \quad (36)
\]

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

\[
\|\xi(t)\| \leq e^{e^t}\|V(\lambda)\|\|V^{-1}(\lambda)\| \sup_{\tau \in [-\tau_g, 0]} \|\xi(\tau)\|, \quad \rho < 0. \quad (37)
\]

This proves the exponential convergence to zero of \( \xi(t) \).

Let \( \eta = (\eta_1, \eta_2) \) be the chosen eigenvalues of the Hurwitz matrix \( H \) (the matrix \( R \) is chosen consequently). Without loss of generality, let \( \eta_i \in \mathbb{R}^+, \ i = 1, 2 \), and let \( \eta_1 > \eta_2 \). From (37) and from the first equation in (24), by choosing \( \eta_1 \) such that \( \eta_1 > \rho \), the inequality follows:

\[
\|\dot{r}(t)\| \leq \eta_1 \|U\| \cdot \|U^{-1}\| \|\dot{r}(0)\| + M \quad (38)
\]

where \( U \) is a diagonalizing matrix for \( H \) and

\[
M = \frac{\|WC\|\|V(\lambda)\|\|V^{-1}(\lambda)\| \sup_{\tau \in [-\tau_g, 0]} \|\xi(\tau)\|}{\eta_1 - \rho} \quad (39)
\]
This proves the exponential convergence to zero of $\hat{e}(t)$, which completes the proof of the Theorem.

**Remark 2:** Notice that, in (19), 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 (21) the initial values of the variables $\hat{e}_2(t)$ and $\xi_2(t)$, in the interval $[-\tau_g, 0]$, are not involved.

**IV. Simulation results**

Simulations reported refer to a virtual patient, whose parameters have been estimated from the IVGTT test conducted on an obese patient (Body Mass Index $\approx 50$) [32].

$$
G_b = 5.611 \quad I_b = 93.669 \quad T_{iGmax} = 1.573
$$

$$
\gamma = 3.205 \quad G^* = 9 \quad \tau_g = 24
$$

$$
V_G = 0.187 \quad K_{xI} = 1.211 \cdot 10^{-2} \quad T_gh = 0.003
$$

$$
V_I = 0.25 \quad K_{xgi} = 3.11 \cdot 10^{-5}
$$

They show high-normal glycemia ($G_b = 5.61$) 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 not vigorously employed. We 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:

$$
T_{iGmax} = 0.242, \quad G_b = 10.37, \quad I_b = 48.95.
$$

We choose $R$ such that the matrix $H$ has eigenvalues $-0.15, -0.06$, and $W$ such that the matrix $H$ has eigenvalues $-1 \cdot 10^{-4}, -2 \cdot 10^{-4}$. The reference signal is chosen such to obtain the plasma glycemia decreasing exponentially from the value of 10.37 to the new value 5.0:

$$
G_{ref}(t) = 5.0 + (10.37 - 5.0) \cdot \exp(-0.01t).
$$

The subject is supposed to be at rest before the experiment begins, that means the initial state is given by $G_0(\tau) = G_b$, $I_0(\tau) = I_b$ for $\tau \in [-\tau_g, 0]$; as far as the observer, we assume to know the basal glycemia (i.e. $\hat{G}_0(\tau) = G_0(\tau) = G_b$ for $\tau \in [-\tau_g, 0]$) and to start with no a priori informations on the basal insulinemia (i.e. $\hat{I}_0(\tau) = 0$ for $\tau \in [-\tau_g, 0]$).

As it clearly appears from the pictures (Fig.1), the desired lower plasma glycemia is reached within the first three hours of simulation.

**Remark 3:** This paper does not consider, 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 designed control law is negative, a zero control input is given to the system. Note that in the simulation here reported (in Fig.2), such a drawback does not occur.

**V. Conclusions**

The control problem of tracking a desired plasma glucose evolution by means of insulin administration has been investigated. A 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 cancellation. Only 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 approximations have been adopted to simplify or reduce the original nonlinear model in order to design the model-based control law. Simulations have been performed, which validate the theoretical results.

**Appendix**

The Bellman-Gronwall inequality used in Theorem 1 to prove inequality (30) is the following.

Let $m : \mathbb{R}^+ \to \mathbb{R}^+$ and $v : \mathbb{R}^+ \to \mathbb{R}^+$ be continuous functions satisfying:

$$
m(t) \leq \alpha + \beta \int_0^t m(\tau)d\tau + \int_0^t v(\tau)d\tau
$$
for some positive constants $\alpha, \beta$. Then:

$$m(t) \leq \alpha e^{\beta t} + \int_0^t e^{\beta(t-\tau)} v(\tau) d\tau. \quad (43)$$

**REFERENCES**


