# Local Sampled-Data Control of the Glucose-Insulin System

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*Abstract*— **In this work we consider the local sampled-data stabilization of human plasma glycemia. It is proved theoretically that the implementation by sampling and holding, for suitable small sampling period, of a state feedback which is shown in the literature to yield local stabilization when applied in a continuous time basis, yields local practical stabilization, with arbitrarily small final target ball. The model of the system is given by a nonlinear retarded functional differential equation and the above state feedback is provided by standard tools of differential geometry for time-delay systems. The proposed theoretical result proves an important property for the digital implementation of the controller, which has been shown in past literature to perform very well when checked in closed-loop with well known computer simulators of diabetic patients approved by the Food and Drug Administration as a substitute of animal trials.**

## I. Introduction

The problem of stabilization of systems described by ordinary differential equations by means of sampled-data control laws has been studied in many papers and many approaches are available in the literature in both the linear case (see, for instance, [5], [6], [7], [19], [37], [38]) and the nonlinear case (see, for instance, [10], [18], [22], [23], [25], [33], [35], [36], [39]). The sampled-data stabilization of nonlinear systems with delays in the input/output channels has been investigated in [13]. As far as systems described by retarded functional differential equations, an approach based on the notion of stabilization in the sample-and-hold sense, introduced in [3] (see also [2]), is proposed in [32], [34].

In this work we deal with an application of the methodology of the sample-and-hold stabilization. The problem at hand is the regulation of plasma glycemia at a desired level. We prove that it is possible to locally stabilize, in the sample-and-hold sense, the glucose-insulin system as described in the literature by retarded functional differential equations (see [26], [31] and references therein). Many results are nowadays available in the literature, mainly addressing glucose control problems on Type 1 diabetic patients, (see, for instance, [1], [4], [12], [16], [20], [30]). However, most of the proposed closed-loop control laws are designed in the continuous-time basis or, even when the discrete-time framework is preferred to cope with technological devices providing glucose measurements at sampling instants, very few theoretical results are available for their sampled-data implementation onto the physical continuous-time model. In [27], a sampled-data control law is proposed and stabilization is proved for just a suitable, discrete time approximation of the original continuous time model. No theoretical results are there given for the glucose-insulin system described by retarded functional differential equations. Here, instead, we provide local stabilization results for the closed-loop system, without any approximation, and in continuous time. Stabilization in the sample-and-hold sense is a practical stabilization with arbitrary small final target (i.e. arbitrary small neighborhood of the origin). A state feedback (continuous or not) is said to be a local stabilizer in the sample-and-hold sense if, for a suitable initial ball and an arbitrary small ball of the origin, there exists a suitable small sampling period such that the feedback control law obtained by sampling and holding the above state feedback, with the given sampling period, keeps uniformly bounded all the trajectories starting in any point of the initial ball and, moreover, drives all such trajectories into the small ball, uniformly in a maximum finite time, keeping them in, thereafter. Here, it is proved theoretically that the implementation by sampling and holding, for suitable small sampling period, of a given state feedback designed in the continuous time basis, which is shown in the literature to yield local stabilization (see [28]), provides local stabilization in the sample-and-hold sense. This result is expected, nevertheless its non trivial theoretical proof allows us to add a further important property to this controller proposed in the literature by the authors, which has been shown to perform very well when checked in closed-loop on a population of virtual patients modeled by means of the computer simulator in [17], accepted by the Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas (see [30]). The proof is obtained with the assumption of availability of the full state, that is, of insulin and glucose measurements, at sampling times. We believe that this theoretical proof provides a nice further property of the controller proposed in the literature, in the line of a safe use in practice. Indeed, in practice, measurements are available only at sampling times, as well as the control law is applied by means of digital devices.

The results provided here rely upon the paper [32], on the stabilization in the sample-and-hold sense of nonlinear retarded systems.

### Notations

$R$ denotes the set of real numbers, $R^+$ denotes the set of non negative reals $[0, +\infty)$, $R^\star$ denotes the extended positive

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real line $[0,+\infty]$. The symbol $|\cdot|$ stands for the Euclidean norm of a real vector, or the induced Euclidean norm of a matrix. The essential supremum norm of an essentially bounded function is indicated with the symbol $\|\cdot\|_\infty$. For a positive integer $n$, for a positive real $\Delta$ (maximum involved time-delay), $\mathcal{C}$ and $W^{1,\infty}$ denote the space of the continuous functions mapping $[-\Delta,0]$ into $R^n$ and the space of the absolutely continuous functions, with essentially bounded derivative, mapping $[-\Delta,0]$ into $R^n$, respectively. A Lebesgue measurable function $w:[-\Delta,0]\to R^n$ is said to be essentially bounded if $ess\sup_{t\in[-\Delta,0]}|w(t)|<\infty$, where $ess\sup_{t\in[-\Delta,0]}|w(t)| = \inf\{a\in R^\star : \lambda(\{t\in[-\Delta,0] : |w(t)|>a\})=0\}$, $\lambda$ denoting the Lebesgue measure. For a positive real $p$, for $\phi\in\mathcal{C}$, $\mathcal{C}_p(\phi)=\{\psi\in\mathcal{C} : \|\psi-\phi\|_\infty\le p\}$. The symbol $\mathcal{C}_p$ denotes $\mathcal{C}_p(0)$. For a continuous function $x:[-\Delta,c)\to R^n$, with $0<c\le+\infty$, for any real $t\in[0,c)$, $x_t$ is the function in $\mathcal{C}$ defined as $x_t(\tau)=x(t+\tau)$, $\tau\in[-\Delta,0]$. For a positive integer $n$, a positive real $q$, $B_q$ denotes the set of vectors $z\in R^n$, satisfying $|z|\le q$. For given positive integers $n,m$, a map $f:\mathcal{C}\times R^m\to R^n$ is said to be Lipschitz on bounded sets if, for any positive real $q$, there exists a positive real $L_q$ such that, for any $\phi_i\in\mathcal{C}_q$, $u_i\in B_q$, $i=1,2$, the inequality holds $|f(\phi_1,u_1)-f(\phi_2,u_2)|\le L_q(\|\phi_1-\phi_2\|_\infty+|u_1-u_2|)$. Let us here recall that a continuous function $\gamma_R^+\to R^+$ is said to be of class $\mathcal{K}_\infty$ if it is zero at zero, strictly increasing, and unbounded. Throughout the paper, RFDE stands for Retarded Functional Differential Equation.

## II. Preliminary Results on Nonlinear Retarded Systems

We report here for the reader's convenience some notions and results in [32], which will be used in next section devoted to the glucose-insulin system. Let us consider the system described by the following RFDE (see [11], [15])

$$\begin{aligned}&\dot x(t)=f(x_t,u(t)), \qquad t\ge0,\ a.e.,\\ &x(\tau)=x_0(\tau), \qquad \tau\in[-\Delta,0], \qquad x_0\in\mathcal{C},\end{aligned}\quad(1)$$

where: $x(t)\in R^n$, $n$ is a positive integer; $\Delta$ is a non-negative integer, the maximum involved time-delay; $x_t\in\mathcal{C}$; $f$ is a map from $\mathcal{C}\times R^m$ to $R^n$, Lipschitz on bounded sets; $m$ is a positive integer; $u(t)\in U$ is a measurable signal, $U\subset R^m$ is a compact set containing the origin in the interior. We assume that $f(0,0)=0$. The equation (1) admits a locally absolutely continuous solution in a maximal time interval $[0,b)$, with $0<b\le+\infty$ (see [11]). We introduce here the following assumption.

*Assumption 1:* (see [32]) The initial state belongs to $W^{1,\infty}$ and there exists a positive real $q$ such that $ess\sup_{\tau\in[-\Delta,0]}\left|\frac{dx_0}{d\tau}\right|\le q$.

We recall here the notion of partition of $[0,+\infty)$ (see [3], [2]).

*Definition 1:* ([3], [2], [32]) A partition

$$\pi=\{t_i,\ i=0,1,\dots\}$$

of $[0,+\infty)$ is a countable, strictly increasing sequence $t_i$, with $t_0=0$, such that $t_i\to+\infty$ as $i\to+\infty$. The diameter of $\pi$, denoted $diam(\pi)$, is defined as $\sup_{i\ge0}t_{i+1}-t_i$. The dwell-time of $\pi$, denoted $dwell(\pi)$, is defined as $\inf_{i\ge0}t_{i+1}-t_i$. For any positive reals $a\in(0,1]$, $b>0$, $\pi_{a,b}$ is any partition $\pi$ with $ab\le dwell(\pi)\le diam(\pi)\le b$.

Notice, in Definition 1, that $\pi_{1,\delta}$ is the partition with dwell-time equal to the diameter $\delta$ (i.e., the partition related to uniform sampling).

*Definition 2:* ([2], [3], [32]) Let $Q$ be a positive real. We say that a feedback $F:\mathcal{C}_Q\to U$ (continuous or not) stabilizes the system described by (1) in the sample-and-hold sense, in $\mathcal{C}_Q$, if, for every positive reals $r$, $R$, $0<r<R\le Q$, $a\in(0,1]$, there exist a positive real $\delta$ depending upon $r$, $R$, $q$ and $\Delta$, a positive real $T$, depending upon $r$, $R$, $q$, $\Delta$ and $a$, and a positive real $E$, depending upon $R$ and $\Delta$, such that, for any partition $\pi_{a,\delta}=\{t_i,\ i=0,1,\dots\}$, for any initial state $x_0\in\mathcal{C}_R$, the solution corresponding to $x_0$ and to the sampled-data feedback control law

$$u(t)=F(x_{t_k}),\quad t_k\le t<t_{k+1},\quad k=0,1,\dots,\qquad(2)$$

exists $\forall t\ge0$ and, furthermore, satisfies:

$$x_t\in\mathcal{C}_E,\ \forall t\ge0;\qquad x_t\in\mathcal{C}_r,\ \forall t\ge T.\qquad(3)$$

*Theorem 1:* (see [32]) Let there exist a diffeomorphism $\Psi:\Omega_x\to\Omega_z$, with $\Omega_x,\Omega_z\subset R^n$ open, bounded neighborhoods of the origin, functions $\underline{\gamma}_\psi$, $\overline{\gamma}_\psi$, of class $\mathcal{K}_\infty$, a Hurwitz matrix $F\in R^{n\times n}$, a positive real $S$, a Lipschitz feedback $k:\mathcal{C}_S\to U$, zero at zero, such that: $\Omega_x\cap B_S=B_S$ (i.e., $\Omega_x$ contains the ball of the origin with radius $S$);

$$\underline{\gamma}_\psi(|x|)\le|\Psi(x)|\le\overline{\gamma}_\psi(|x|),\qquad\forall x\in\Omega_x;\qquad(4)$$

$$\left.\frac{\partial\Psi(x)}{\partial x}\right|_{x=\phi(0)}f(\phi,k(\phi))=F\Psi(\phi(0)),\qquad\forall\phi\in\mathcal{C}_S.\quad(5)$$

Then, there exists a positive real $Q<S$ such that the feedback $k:\mathcal{C}_S\to U$ stabilizes in the sample-and-hold sense, in $\mathcal{C}_Q$, the system described by (1).

## III. Stabilization by sampling and holding of the glucose-insulin system

We show here that Theorem 1 can be successfully applied to the glucose-insulin system. Let us consider the following RFDE, mathematical model of the glucose-insulin system (see [26], [31])

$$\begin{aligned}&\frac{dG(t)}{dt}=-K_{xgi}G(t)I(t)+\frac{T_{gh}}{V_G},\\ &\frac{dI(t)}{dt}=-K_{xi}I(t)+\frac{T_{iGmax}}{V_I}h\big(G(t-\tau_g)\big)+v(t),\\ &G(\tau)=G_0,\qquad I(\tau)=I_0,\qquad\tau\in[-\tau_g,0],\end{aligned}\quad(6)$$

where $G(t)$ (measurement unit [mM]) is the plasma glycemia, $I(t)$ (measurement unit [pM]) is the insulinemia, $t\ge0$, and $G_0$, $I_0$ are related initial values. As far as the model parameters are concerned:

- $K_{xgi}$, [$\text{min}^{-1}$ $\text{pM}^{-1}$], is the rate of glucose uptake by tissues (insulin-dependent) per pM of plasma insulin concentration;
- $T_{gh}$, [$\text{min}^{-1}$(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;
- $K_{xi}$, [$\text{min}^{-1}$], is the apparent first-order disappearance rate constant for insulin;
- $T_{iGmax}$, [$\text{min}^{-1}$(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.

The nonlinear map $h(\cdot)$ models the endogenous pancreatic insulin delivery rate as $h(G) = \frac{\left(\frac{G}{G^*}\right)^\gamma}{1+\left(\frac{G}{G^*}\right)^\gamma}$, where $\gamma$ is the progressivity with which the pancreas reacts to circulating glucose concentrations and $G^*$ is the glycemia at which the insulin release is half of its maximal rate. The control input, $v(t)$ (measurement unit $[pM/min]$), is the exogenous intra-venous insulin delivery rate. Let $G_{ref}$ be a positive constant, chosen as a reference level of glycemia instead of a hyperglycemic basal level $G_b > G_{ref}$ ($G_b$ is the steady state value of glycemia when no input is applied, see Section IV). Let $I_{ref}$ and $v_{ref}$ be the positive reals such that $(G_{ref}, I_{ref})$ is an equilibrium point for the system described by (6), forced by the constant input $v(t) = v_{ref}$ (see [29]). The positive reals $I_{ref}$ and $v_{ref}$ are obtained as solutions of the following algebraic equations

$$\begin{aligned} &-K_{xgi}G_{ref}I_{ref} + \frac{T_{gh}}{V_G} = 0, \\ &-K_{xi}I_{ref} + \frac{T_{iGmax}}{V_I}h\big(G_{ref}\big) + v_{ref} = 0 \end{aligned} \tag{7}$$

The RFDE (6) can be rewritten with the new variables $x(t) = \begin{bmatrix} G(t) - G_{ref} \\ I(t) - I_{ref} \end{bmatrix}$ and with the new input $u(t) = v(t) - v_{ref}$, as follows

$$\begin{aligned} &\frac{dx_1(t)}{dt} = -K_{xgi}(x_1(t) + G_{ref})(x_2(t) + I_{ref}) + \frac{T_{gh}}{V_G}, \\ &\frac{dx_2(t)}{dt} = -K_{xi}(x_2(t) + I_{ref}) \\ &+\frac{T_{iGmax}}{V_I}h\big(x_1(t-\tau_g) + G_{ref}\big) + v_{ref} + u(t), \\ &x_1(\tau) = G_0 - G_{ref},\ x_2(\tau) = I_0 - I_{ref},\ \tau \in [-\tau_g, 0], \end{aligned} \tag{8}$$

Since the exogenous intra-venous insulin delivery rate cannot be negative, we have that the input $v(t)$ in (6) belongs to the following compact set $\overline{V} = [0, v_{max}]$, where $v_{max} > v_{ref}$ is a suitable positive bound due to technological as well as to physiological constraints (see [30]). It follows that $u(t)$ in (8) belongs to the set $U = [-v_{ref}, v_{max} - v_{ref}]$. The system described by (8) can be rewritten in the form of (1). Indeed, in this case, define $f : \mathcal{C} \times R \to U$, for $\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \end{bmatrix} \in \mathcal{C}$, $\phi_i(\tau) \in R$, $\tau \in [-\tau_g, 0]$, $u \in U$, as

$$f(\phi, u) = \begin{bmatrix} -K_{xgi}(\phi_1(0) + G_{ref})(\phi_2(0) + I_{ref}) + \frac{T_{gh}}{V_G} \\ -K_{xi}(\phi_2(0) + I_{ref}) \\ +\frac{T_{iGmax}}{V_I}h\big(\phi_1(-\tau_g) + G_{ref}\big) + v_{ref} + u \end{bmatrix} \tag{9}$$

If $\phi \in \mathcal{C}$, $u \in U$, in (9), are replaced with $x_t \in \mathcal{C}$, $u(t) \in U$, where (see notations) $x_t(\tau) = x(t+\tau) = \begin{bmatrix} x_1(t+\tau) \\ x_2(t+\tau) \end{bmatrix}$, $\tau \in [-\tau_g, 0]$, then system (8) is equivalent to system (1), with $f$ as in (9). The initial condition $x_0 \in \mathcal{C}$, for the glucose-insulin system written in the form of (1), is given by $x_0(\tau) = \begin{bmatrix} G_0 - G_{ref} \\ I_0 - I_{ref} \end{bmatrix}$, $\tau \in [-\tau_g, 0]$.

Let $\Psi : R^2 \to R^2$ be defined, for $x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \in R^2$, as

$$\Psi(x) = \begin{bmatrix} x_1 \\ -K_{xgi}(x_1 + G_{ref})(x_2 + I_{ref}) + \frac{T_{gh}}{V_G} \end{bmatrix}. \tag{10}$$

The state feedback $\overline{k}$ in forthcoming Theorem 2 has been designed in a continuous time basis in [28], by means of the change of variables in (10).

*Theorem 2:* Let $\overline{k} : \mathcal{C} \to R$ be defined, for $\phi \in \mathcal{C}$, as

$$\begin{aligned} \overline{k}(\phi) = &-v_{ref} + \frac{1}{K_{xgi}(\phi_1(0) + G_{ref})} \cdot \\ &\big(\mathcal{P}\big(\phi_1(0) + G_{ref}, \phi_2(0) + I_{ref}, \phi_1(-\tau_g) + G_{ref}\big) \\ &-\Gamma\Psi(\phi(0))\big), \qquad \phi_1(0) \neq -G_{ref}, \\ \overline{k}(\phi) = &-v_{ref}, \qquad \phi_1(0) = -G_{ref}, \end{aligned} \tag{11}$$

where $\mathcal{P} : R^3 \to R$ is defined, for $y = \begin{bmatrix} y_1 & y_2 & y_3 \end{bmatrix}^T \in R^3$ as

$$\begin{aligned} \mathcal{P}\big(y_1, y_2, y_3\big) = &-K_{xgi}y_2\left(-K_{xgi}y_1y_2 + \frac{T_{gh}}{V_G}\right) \\ &-K_{xgi}y_1\left(-K_{xi}y_2 + \frac{T_{iGmax}}{V_I}h\big(y_3\big)\right) \end{aligned} \tag{12}$$

and the matrix

$$\Gamma = \begin{bmatrix} \Gamma_1 & \Gamma_2 \end{bmatrix} \in R^{1\times 2}, \tag{13}$$

$\Gamma_i \in R$, $i = 1, 2$, is designed to ensure that the matrix

$$H = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix}\Gamma \tag{14}$$

is Hurwitz with (any) prescribed eigenvalues in the left half complex plane. Let $k : \mathcal{C} \to U$ be defined, for $\phi \in \mathcal{C}$, as

$$k(\phi) = \begin{cases} \overline{k}(\phi), & \overline{k}(\phi) \in U, \\ v_{max} - v_{ref}, & \overline{k}(\phi) > v_{max} - v_{ref}, \\ -v_{ref}, & \overline{k}(\phi) < -v_{ref} \end{cases} \tag{15}$$

Then, there exists a positive real $Q$ such that the feedback $k$ stabilizes, in the sample-and-hold sense, in $\mathcal{C}_Q$ (i.e., locally), the system described by (8) (see Definition 2).

*Proof:* Let $\Omega_x = \{x \in R^2 : |x| < \frac{1}{2}\min\{G_{ref}, I_{ref}\}\}$. Let $\Omega_z$ be an open neighborhood of the origin such that the map $\overline{\Psi} : \Omega_x \to \Omega_z$ defined, for $x \in \Omega_x$, as

$$\overline{\Psi}(x) = \Psi(x), \tag{16}$$

is a diffeomorphism. The feedback $\overline{k}$ is zero at zero. Indeed, from (7), the following equalities hold

$$\begin{aligned}
&\frac{\mathcal{P}(G_{ref}, I_{ref}, G_{ref})}{K_{xgi}G_{ref}} = \frac{1}{K_{xgi}G_{ref}} \cdot \\
&\left(-K_{xgi}I_{ref}\left(-K_{xgi}G_{ref}I_{ref} + \frac{T_{gh}}{V_G}\right)\right. \\
&\left.-K_{xgi}G_{ref}\left(-K_{xi}I_{ref} + \frac{T_{iGmax}}{V_I}h\big(G_{ref}\big)\right)\right) = \\
&\frac{1}{K_{xgi}G_{ref}}\left(K_{xgi}G_{ref}v_{ref}\right) = v_{ref}
\end{aligned} \tag{17}$$

From (11), (17), taking into account that $\Psi(0) = 0$, it follows that $\overline{k}(0) = 0$. The feedback $\overline{k}$ is continuous in an open neighborhood of the origin. It follows from (11) that there exists a positive real $\overline{S}$ such that, for all $\phi \in \mathcal{C}_{\overline{S}}$, $\overline{k}(\phi) \in U$. Thus, in $\mathcal{C}_{\overline{S}}$, $k(\phi) = \overline{k}(\phi)$ (i.e., input saturation constraints are avoided). Let $S = \min\{\overline{S}, \frac{1}{3}\min\{G_{ref}, I_{ref}\}\}$. We have to show that the change of coordinates $\overline{\Psi}$ and the feedback $k$ satisfy the hypotheses of Theorem 1 in $\mathcal{C}_S$, for this chosen positive real $S$. The relation $B_S \cap \Omega_x = B_S$ holds. As far as inequalities (4) are concerned, we have that the function $x \to |\psi(x)|$, $x \in R^2$ (see (10)), is positive definite and radially unbounded. Therefore, from Lemma 4.3, p. 145, in [14], it follows that there exist two functions $\underline{\gamma}_\Psi$ and $\overline{\gamma}_\Psi$, of class $\mathcal{K}_\infty$, such that the inequalities (4) hold satisfied. As far as the equality (5) is concerned, it is sufficient to consider (see [8], [9], [21], [24], [29]) that, in the new variables $z = \psi(x)$, $x \in \Omega_x$, the chosen feedback, if applied in continuous time, linearizes and stabilizes the system at hand. In details, for any $\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \end{bmatrix} \in \mathcal{C}_S$, $\phi_i(\tau) \in R$, $\tau \in [-\tau_g, 0]$, from (9), (10), (11), (13), (14), (16), we have

$$\begin{aligned}
&\left.\frac{\partial\overline{\Psi}(x)}{\partial x}\right|_{x=\phi(0)} f(\phi, k(\phi)) = \\
&\begin{bmatrix} 1 & 0 \\ -K_{xgi}(\phi_2(0) + I_{ref}) & -K_{xgi}(\phi_1(0) + G_{ref}) \end{bmatrix}. \\
&f(\phi, k(\phi)) =
\end{aligned}$$

$$\begin{bmatrix}
-K_{xgi}(\phi_1(0) + G_{ref})(\phi_2(0) + I_{ref}) + \frac{T_{gh}}{V_G} \\
\\
-K_{xgi}(\phi_2(0) + I_{ref})\cdot \\
(-K_{xgi}(\phi_1(0) + G_{ref})(\phi_2(0) + I_{ref}) + \frac{T_{gh}}{V_G}) \\
-K_{xgi}(\phi_1(0) + G_{ref})\cdot \\
(-K_{xi}(\phi_2(0) + I_{ref}) \\
+\frac{T_{iGmax}}{V_I}h\big(\phi_1(-\tau_g) + G_{ref}\big) + v_{ref}) \\
-K_{xgi}(\phi_1(0) + G_{ref})\cdot \\
(-v_{ref} \\
+\frac{\mathcal{P}\left(\phi_1(0)+G_{ref}, \phi_2(0)+I_{ref}, \phi_1(-\tau_g)+G_{ref}\right) - \Gamma\Psi(\phi(0))}{K_{xgi}(\phi_1(0)+G_{ref})})
\end{bmatrix} =$$

$$\begin{bmatrix}
\begin{bmatrix} 1 & 0 \end{bmatrix}\overline{\psi}(\phi(0)) \\
\\
-K_{xgi}(\phi_2(0) + I_{ref})\cdot \\
(-K_{xgi}(\phi_1(0) + G_{ref})(\phi_2(0) + I_{ref}) + \frac{T_{gh}}{V_G}) \\
-K_{xgi}(\phi_1(0) + G_{ref})\cdot \\
(-K_{xi}(\phi_2(0) + I_{ref}) \\
+\frac{T_{iGmax}}{V_I}h\big(\phi_1(-\tau_g) + G_{ref}\big) + v_{ref}) \\
+K_{xgi}(\phi_1(0) + G_{ref})v_{ref} \\
-\mathcal{P}\big(\phi_1(0) + G_{ref}, \phi_2(0) + I_{ref}, \phi_1(-\tau_g) + G_{ref}\big) \\
-\Gamma\overline{\Psi}(\phi(0))
\end{bmatrix} =$$

$$\begin{bmatrix} 0 & 1 \\ \Gamma_1 & \Gamma_2 \end{bmatrix}\overline{\Psi}(\phi(0)) = H\overline{\Psi}(\phi(0)) \tag{18}$$

Since the matrix $H$ in (14) is Hurwitz, the hypotheses of Theorem 1 are satisfied. It follows that there exists a positive real $Q$ such that the (bounded) state feedback $k$ stabilizes in the sample-and-hold sense, in $\mathcal{C}_Q$, the glucose-insulin system described by (8), which describes the deviation from the reference value of glucose and insulin. We conclude that, if the initial value of the glucose and the insulin are sufficiently near $(G_{ref}, I_{ref})$, then the feedback $k$ yields stabilization in the sample-and-hold sense of the system described by (6), in a neighborhood of $(G_{ref}, I_{ref})$. ■

According to (11), (15), recalling the relation $u(t) = v(t) - v_{ref}$, the piece-wise constant control law $v(t)$ in (6) is defined as follows, for $t \geq 0$,

$$v(t) = \begin{cases}
\frac{1}{K_{xgi}G(t_k)}\left(\mathcal{P}\big(G(t_k), I(t_k), G(t_k - \tau_g)\big)\right. \\
\left.-\Gamma\begin{bmatrix} G(t_k) - G_{ref} \\ -K_{xgi}G(t_k)I(t_k) + \frac{Tgh}{V_G} \end{bmatrix}\right), \\
G(t_k) \neq 0, \\
\\
0, \qquad G(t_k) = 0, \\
t_k \leq t \leq t_{(k+1)},\ k = 0, 1, \ldots,\ t_0 = 0,
\end{cases} \tag{19}$$

with $\mathcal{P}$ defined in (12). If the right-hand side of (19) exceeds $v_{max}$ or is negative, then it is set $v(t) = v_{max}$ or $v(t) = 0$, respectively. At this stage, such cases cannot be *a-priori* excluded, though Theorem 1 ensures that, if the sampling period is chosen suitably small and the initial values of glucose and insulin are sufficiently near the desired values $G_{ref}$, $I_{ref}$, the saturation constraints are avoided. Indeed, here just the existence of a suitable region of attraction $\mathcal{C}_Q$ and of a suitable small sampling period is proved, for

TABLE I

GLUCOSE-INSULIN SYSTEM PARAMETERS

| | |
|---|---|
| $G_b$ | $10.37\ mM$ |
| $\gamma$ | 3.205 |
| $V_G$ | $0.187\ \ L/kgBW$ |
| $V_I$ | $0.25\ \ L/kgBW$ |
| $I_b$ | $48.95\ pM$ |
| $G^\star$ | $9\ mM$ |
| $K_{xi}$ | $1.211e{-}2\ min^{-1}$ |
| $K_{xgi}$ | $3.11e{-}5\ min^{-1}pM^{-1}$ |
| $T_{iGmax}$ | $0.242\ min^{-1}pmol/kgBW$ |
| $\tau_g$ | $24\ min$ |
| $T_{gh}$ | $0.003\ min^{-1}mmol/kgBW$ |

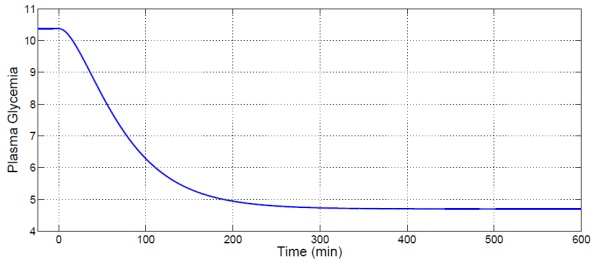


Fig. 1. Evolution of the plasma glycemia $G(t)$, [mM], with sampling period $\delta = 10\ min$

the stabilization in the sample-and-hold sense. An analysis of the region of attraction $Q$, as well as of the required suitably small sampling period, are not studied here and are left for future work. Theorem 5.3, 5.5, and their proofs, in [32], provide some insights for this further theoretical investigation.

## IV. SIMULATIONS

We considered, for simulation, the case 3 (severe hyperglycemia, establishment of a state of frank Type 2 Diabetes Mellitus) reported in [28] (see Table I, where $G_b$ and $I_b$ denote steady state values of glycemia and insulinemia when no control action is taken, i.e., when $v(t) \equiv 0, t \in R^+$). As far as the eigenvalues for the matrix $H$ in (14) are concerned, they are chosen equal to $-0.02$, $-0.03$. The desired level of glycemia is set at $G_{ref} = 4.7\ mM$. The initial value of glycemia $G_0$ and initial value of insulinemia $I_0$ are set equal to the (input-free) steady state values $G_b$ and $I_b$, respectively. Simulation results are reported for the sampling period $\delta$ set

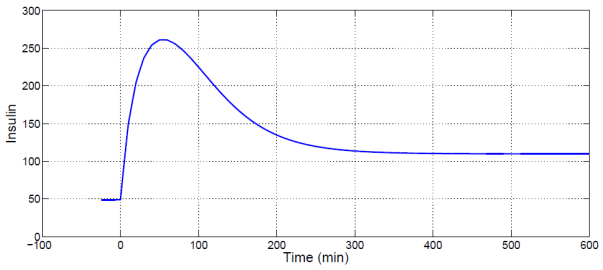


Fig. 2. Evolution of the insulin $I(t)$, [pM], with sampling period $\delta = 10\ min$

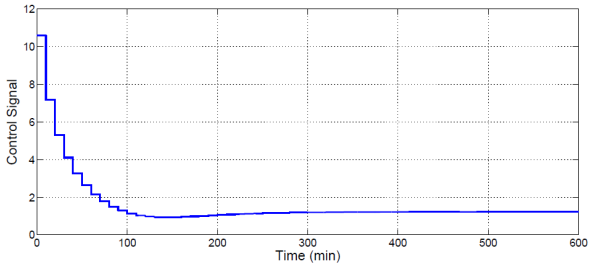


Fig. 3. Control Signal $v(t)$, [pM/min], with sampling period $\delta = 10\ min$

equal to $10\ min$. With sampling period equal to $120\ min$, saturation constraints and dangerous oscillations appear, and the controller does not provide acceptable performances. In the case of $\delta = 60\ min$, saturations constraints appear too. Indeed the controller (19) provides infeasible negative values for the control signal. By imposing in the simulations that the control law is equal to 0 whenever the controller provides a negative control law, the plasma glycemia is driven to a sufficiently small neighborhood of the desired value. If the sampling period is chosen equal to $30\ min$, saturations problem do not appear any more and the plasma glycemia is driven to the desired value in a good fashion, without dangerous oscillations. By choosing the sampling period equal to $10\ min$, the behavior of the plasma glycemia and of the insulin are reported in Figs. 1 and in Fig. 2, respectively. The input signal is reported in Fig. 3. The plasma glycemia is driven to the desired level, in an excellent fashion without oscillations. The piece-wise constant control law never becomes negative. Practically the same results are obtained with sampling period equal to $5\ min$.

*Remark 1:* The simulation results here shown for the case of $\delta = 10\ min$, for the glucose-insulin system (6), are well known in the literature (see [29], where an observer to avoid insulin measures is even exploited), and are reported here only for reader's convenience, in order to validate the theoretical results here provided. A theoretical proof of the (local) convergence of the glucose variable to (an arbitrarily small neighborhood of) the reference value, by means of the sampled-data controller (19), though well known in the literature from the many performed simulations, was missing so far. The algorithm here provided has been validated by simulations in closed loop with standard computer simulators for the artifical pancreas (see [17], [30]). The theoretical proof here provided adds a further property to the controller proposed first in [28] and improved by the use of observers in [29].

## V. CONCLUSIONS

A stabilizing continuous-time controller proposed in the literature for the regulation of plasma-glycemia has been here proved to be a local stabilizer in the sample-and-hold sense. This theoretical proof adds an important property to a controller which has been shown in the literature to perform very well in closed loop with standard computers simulators of human glucose-insulin system. An interesting topic to

be investigated concerns the stabilization in the sample-and-hold sense of the glucose-insulin system, by means of the sampled-data implementation of the observer-based (continuous time) controller proposed in [29], which allows to avoid insulin measures. A theoretical proof of the stabilization in the sample-and-hold sense when the above controller is implemented by digital devices, as standard in practice, is not yet available in the literature. The many simulations performed in [29], with a sampled-data implementation of the observer-based state feedback, encourage to look for this (expected, not yet proved) theoretical result.

A further theoretical investigation will concern the possibility of achieving stabilization in the sample-and-hold sense, by means of a sampled-data state feedback which makes use of measurements not at the current sampling time, but (at least) at the previous one. This theoretical result would allow to use more trustworthy glucose measurements for actual glucose control therapies, and would lay the foundations, in the future, for an artificial pancreas exploiting insulin measurements as well, known to be much more cumbersome to obtain in real-time.

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