Sampled-Data Static Output Feedback Control of the Glucose-Insulin System ⋆

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Abstract: In this paper, the plasma glucose regulation problem for Type 2 diabetic patients is studied. A nonlinear time-delay model of the glucose-insulin regulatory system is exploited in order to design a sampled-data static output feedback control, which makes use of only sampled glucose measurements. It is shown that the proposed control law is a stabilizer in the sampled-and-hold sense. The presence of a state-delay in the model prevents the availability in the buffer of suitable needed past values of the glucose. Such a drawback is overcome by means of spline interpolation. A pre-clinical validation, concerning the performances of the proposed glucose control law, is carried-out by means of a well known simulator of diabetic patients broadly accepted for testing insulin infusion therapies. Simulations results are encouraging for further evaluation.

Keywords: Sampled-Data Static Output Feedback Controllers, Nonlinear Time-Delay Systems, Stabilization in the Sample-and-Hold sense, Glucose-Insulin model, *In silico* validation.

1. INTRODUCTION

Diabetes Mellitus (DM) is a chronic condition arising due to high levels of blood glucose concentrations occurring because of a disruption of the physiological glucose control exerted by the hormone insulin. Type 2 DM (T2DM) is the most common type of diabetes, related to an inadequate production of insulin and to insulin resistance, i.e. the inability of the body to fully respond to insulin. T2DM accounts for about 415 million patients worldwide of all cases of diabetes, with a non-trivial draining of the national healthcare budgets (Ogurtsova et al. (2017)).

The Artificial Pancreas (AP) is a set of technologies combining computing systems, actuators and sensors which are used in order to carry out a proposed plasma glucose control therapy. In the literature concerning AP, many results are given for Type 1 DM (T1DM), i.e. for diabetic patients that totally lack of a pancreatic endogenous insulin release (see among the others, Cobelli et al. (2011); Doyle et al. (2014); Kovatchev et al. (2016); Turksoy et al. (2014); Zavitsanou et al. (2015); Gondhalekar et al. (2018); Messori et al. (2018) and references therein).

In this paper, a closed-loop sampled-data glucose control law for T2DM patients, by means of a model-based approach, is provided. The proposed control law is designed by means of a nonlinear Delay Differential Equation (DDE) model (see Palumbo et al. (2007); Panunzi et al. (2007)), modeling the endogenous Insulin Delivery Rate (IDR), which cannot be neglected in T2DM patients (see Makroglou and J. Li (2006); Palumbo et al. (2013)). Such model is fitted and clinically validated by means of Intra-Venous Glucose Tolerance Test (IVGTT) data coming from a wide range of rather heterogeneous individuals enrolled in different clinical studies (see Panunzi et al. (2007, 2010)). Similarly to Dua et al. (2006); Kovàcs et al. (2013)), the intra-venous route is here considered, providing insulin appearance in circulating blood without delays. Although of limited application, the intra-venous route is straightforwardly applicable to problems of glycemia stabilization in critically ill subjects, such as in surgical Intensive Care Units after major procedures (see den Berghe (2003)).

The adopted DDE model has been recently exploited in many different AP architectures (see Palumbo et al. (2014); Di Ferdinando et al. (2017, 2020)). Within the sampled-and-hold framework, in Di Ferdinando et al. (2017), a sampled-data static state feedback controller for T2DM patients, using both measurements of glucose and insulin concentrations, is provided. The use of the insulin

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measurements in the control law makes these therapies just a proof-of-concept, since insulin measurements are time-consuming, cumbersome to achieve and, in no way, exploitable for real-time applications. In Di Ferdinando et al. (2020), a sampled-data dynamic output feedback controller for T2DM patients is provided. The sampled-data control law, proposed in Di Ferdinando et al. (2020) overcomes the aforementioned drawback, since it exploits only glucose measurements. At each sampling instant, it makes contemporary use of both the actual glucose measurement and a suitable past value of the glucose concentration. Problems related to the non-availability in the buffer of the delayed values of the glucose are not taken into account in Di Ferdinando et al. (2020) and theoretical results are given assuming the availability in the buffer of such measurements. Moreover, the implementation of the controller, proposed in Di Ferdinando et al. (2020), is restricted by assumptions involving the control parameters. These drawbacks are overcome in the present contribution. In particular, in this paper, a sampled-data static output feedback control is provided for the plasma glucose regulation problem in T2DM patients. Theoretical results are provided taking into account the problems related to the non-availability in the buffer of the past values of the glucose required by the proposed controller and no assumption are introduced on the control parameters. Spline approximation methodologies will be used in order to provide an approximation of the suitable needed past values of the glucose (see Pepe (2016)).

The notion of stabilization in the sample-and-hold sense (see Clarke et al. (1997), Di Ferdinando and Pepe (2019), Pepe (2016)) is used in order to prove the results. In particular, the results, provided in Pepe (2016), which address the problems related to the non-availability in the buffer of the value of the system variables at some past times, are used in order to prove that the proposed sampled-data glucose control law ensures the semi-global practical stability of the closed-loop glucose-insulin system, with arbitrary small steady-state tracking error. The improvements of the proposed controller with respect to the one in Di Ferdinando et al. (2020) are mainly two: from one hand, new theoretical results are provided taking into account the problems related to the necessity for the controller of the knowledge of the past glucose values (see Remark 1 in Di Ferdinando et al. (2020)); from the other hand, the proposed controller is simpler to implement since no assumption is introduced on the control parameters involved in the controller (see Assumption 2 in Di Ferdinando et al. (2020)). A pre-clinical validation of the proposed glucose control law is performed by the use of the comprehensive mathematical model provided by Dalla Man et al. (2007), which allows dealing with T2DM patients and provides the bases for the UVA/Padua Type 1 Diabetes Simulator (see Kovatchev et al. (2008)), accepted by the Food and Drug Administration (FDA) for testing insulin infusion therapies for diabetic patients. The simulations show good performances of the proposed controller.

Notation. $\mathbb{N}$ denotes the set of integer numbers in $[0, +\infty)$, $\mathbb{R}$ denotes the set of real numbers, $\mathbb{R}^\star$ denotes the extended real line $[-\infty, +\infty]$, $\mathbb{R}^+$ denotes the set of nonnegative reals $[0, +\infty)$. The symbol $|\cdot|$ stands for the Euclidean norm of a real vector, or the induced Euclidean norm of a matrix. For a positive integer n, for a positive scalar Δ, a Lebesgue measurable function $f : [-\Delta, 0] \to \mathbb{R}^n$ is said to be essentially bounded if $\operatorname{ess\,sup}_{t\in[-\Delta,0]} |f(t)| < +\infty$, where $\operatorname{ess\,sup}_{t\in[-\Delta,0]} |f(t)| = \inf\{a \in \mathbb{R}^\star : \lambda(\{t \in [-\Delta, 0] : |f(t)| > a\}) = 0\}$, λ denoting the Lebesgue measure. 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 Δ (maximum involved time-delay): $\mathcal{C}^n$ and $W_n^{1,\infty}$ denote the space of the continuous functions mapping $[-\Delta, 0]$ into $\mathbb{R}^n$ and the space of the absolutely continuous functions, with essentially bounded derivative, mapping $[-\Delta, 0]$ into $\mathbb{R}^n$, respectively. For a positive scalar p, for $\phi \in \mathcal{C}^n$, $\mathcal{C}_p^n(\phi) = \{\psi \in \mathcal{C}^n : \|\psi - \phi\|_\infty \le p\}$. The symbol $\mathcal{C}_p^n$ denotes $\mathcal{C}_p^n(0)$. For a continuous function $x : [-\Delta, c) \to \mathbb{R}^n$, with $0 < c \le +\infty$, for any real $t \in [0, c)$, x_t is the function in $\mathcal{C}^n$ defined as $x_t(\tau) = x(t + \tau)$, $\tau \in [-\Delta, 0]$. For a positive integer n, for $\mathbb{S} = \mathbb{R}^n$ (or $\mathbb{R}^+$): $C^1(\mathbb{S}; \mathbb{R}^+)$ denotes the space of the continuous functions from $\mathbb{S}$ to $\mathbb{R}^+$, admitting continuous (partial) derivatives; $C_L^1(\mathbb{S}; \mathbb{R}^+)$ denotes the subset of the functions in $C^1(\mathbb{S}; \mathbb{R}^+)$ admitting locally Lipschitz (partial) derivatives. Let us here recall that a continuous function $\gamma : \mathbb{R}^+ \to \mathbb{R}^+$ is: of class $\mathcal{P}_0$ if $\gamma(0) = 0$; of class $\mathcal{P}$ if it is of class $\mathcal{P}_0$ and $\gamma(s) > 0$, $s > 0$; of class $\mathcal{K}$ if it is of class $\mathcal{P}$ and strictly increasing; of class $\mathcal{K}_\infty$ if it is of class $\mathcal{K}$ and unbounded. The symbol I_d denotes the identity function in $\mathbb{R}^+$. For a given positive integer n, for a symmetric, positive definite matrix $P \in \mathbb{R}^{n\times n}$, $\lambda_{max}(P)$ and $\lambda_{min}(P)$ denote the maximum and the minimum eigenvalue of P, respectively. The symbol $\circ$ denotes composition (of functions). For positive integers n, m, for a map $f : \mathcal{C}^n \times \mathbb{R}^m \to \mathbb{R}^n$, and for a locally Lipschitz functional $V : \mathcal{C}^n \to \mathbb{R}^+$, the derivative in Driver's form (see Pepe (2007) and the references therein) $D^+V : \mathcal{C}^n \times \mathbb{R}^m \to \mathbb{R}^\star$, of the functional V, is defined, for $\phi \in \mathcal{C}^n$, $u \in \mathbb{R}^m$, as:

$$D^+V(\phi, u) = \limsup_{h\to 0^+} \frac{V(\phi_{h,u}) - V(\phi)}{h},$$

where, for $0 \le h < \Delta$, $\phi_{h,u} \in \mathcal{C}^n$ is defined, for $s \in [-\Delta, 0]$, as $\phi_{h,u}(s) = \begin{cases} \phi(s + h), & s \in [-\Delta, -h), \\ \phi(0) + (s + h) f(\phi, u), & s \in [-h, 0]. \end{cases}$

2. THE GLUCOSE-INSULIN MODEL

The AP control law is designed by properly exploiting the following nonlinear DDE model, Palumbo et al. (2007); Panunzi et al. (2007)

$$\begin{aligned} \dot{G}(t) &= -K_{xgi} G(t) I(t) + \frac{T_{gh}}{V_G}, \\ \dot{I}(t) &= -K_{xi} I(t) + \frac{T_{iGmax}}{V_I} \varphi(G(t - \tau_g)) + \frac{v(t)}{V_I}, \\ y(t) &= G(t),\ G(\tau) = G_0(\tau),\ I(\tau) = I_0(\tau),\ \tau \in [-\tau_g, 0], \end{aligned} \tag{1}$$

where: $G(t)$, [mmol/L], and $I(t)$, [pmol/L] are the plasma glucose and insulin concentrations, respectively; $\varphi(\cdot)$ models the endogenous pancreatic insulin delivery rate according to the following sigmoidal function:

$$\varphi(G(t - \tau_g)) = \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}{1 + \left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma};$$

see Palumbo et al. (2007); Panunzi et al. (2007) for the details concerning the model parameters.

The pair $(G_0(\tau), I_0(\tau))$ constitutes the initial condition of the model, corresponding to the plasma glucose/insulin concentrations before the control input is applied, and they are usually assessed equal to the constant basal levels (G_b, I_b). $v(t)$, [(pmol/kgBW)/min], is the exogenous intravenous insulin delivery rate, i.e., the control input. $y(t)$ [mmol/L], is the continuous-time glucose measurement i.e., the output signal. Set G_{ref} be the desired glucose reference, supposed to be tracked by the control law. The choice of G_{ref} as a reference for the desired glycemia leads to the definition of the insulin and input references, I_{ref} and v_{ref}, respectively

$$I_{ref} = \frac{T_{gh}}{V_G G_{ref} K_{xgi}},\ v_{ref} = V_I I_{ref} K_{xi} - T_{iGmax}\varphi(G_{ref}). \tag{2}$$

The pair (G_{ref}, I_{ref}) is associated to the trivial solution obtained by fixing: $v(t) \equiv v_{ref}$, $t \geq 0$, $G_0(\tau) \equiv G_{ref}$, $I_0(\tau) \equiv I_{ref}$, $\tau \in [-\tau_g, 0]$.

Remark 1. Notice that, since it is usually assumed that the plasma glycemia and insulinemia are fixed at their constant basal values before the insulin administration therapy starts, then we can assume that the initial condition in (1) is such that $\begin{bmatrix} G_0(\tau) - G_{ref} \\ I_0(\tau) - I_{ref} \end{bmatrix} \in W_2^{1,\infty}$, $\tau \in [-\tau_g, 0]$ and, moreover, that there exists a positive real q such that

$$\operatorname*{ess\,sup}_{\theta \in [-\tau_g, 0]} \left| \frac{d}{d\theta} \begin{bmatrix} G_0(\theta) - G_{ref} \\ I_0(\theta) - I_{ref} \end{bmatrix} \right| \leq q. \tag{3}$$

3. SAMPLED-DATA CONTROL FOR THE GLUCOSE-INSULIN SYSTEM

In Di Ferdinando et al. (2020), results concerning a semi-global nonlinear sampled-data dynamic output regulator for the glucose-insulin system (1) are provided: at each sampling time t_k, $k = 0, 1, 2, ...$, the control law makes use of the sampled glucose measurement $G(t_k)$ as well as of the delayed value of the glucose concentration $G(t_k - \tau_g)$ (see (6) in Di Ferdinando et al. (2020)). Theoretical results, concerning such control law, are provided by assuming the availability in the buffer of the past value $G(t_k - \tau_g)$ for any $k = 0, 1, ...$ (see Remark 1 in Di Ferdinando et al. (2020)). Such hypothesis is often prevented by technological constraints mainly related to the glucose sensors. Moreover, in Di Ferdinando et al. (2020), assumptions involving the control parameters are introduced (see Assumption 2 in Di Ferdinando et al. (2020)), leading to a harder implementation of the proposed controller. In the following, a sampled-data static output feedback controller for the glucose-insulin system is provided, and theoretical results are given without assuming the availability in the buffer of the past values $G(t_k - \tau_g)$, $k = 0, 1, ...$, and without introducing any assumption on the control parameters involved in the glucose control strategy. Indeed, these problems are here overcome by the use of spline approximation methods. In particular, the proposed sampled-data static output feedback controller for the system (1) is designed by properly exploiting the results, in Pepe (2016), concerning the theory on the stabilization in the sample-and-hold sense and the use of an approximated feedback based on first order splines. Firstly, in the spirit of the emulation approach as generally shared by the sample-and-hold sense methodology, we design a continuous-time controller for the system (1):

$$v(t) = V_I \Bigg(K_{xi} I_{ref} - \frac{T_{iGmax}}{V_I} \varphi(y(t - \tau_g)) + \frac{K_{xgi}}{\rho}(y(t) - G_{ref})^2 + \frac{K_{xgi} G_{ref}}{\rho}(y(t) - G_{ref}) \Bigg), \tag{4}$$

where $\rho > 0$ is a scalar control tuning parameter. Differently from Di Ferdinando et al. (2020), here only one tuning parameter is involved and, furthermore, the theoretical results here provided are valid for any positive value of this parameter. Instead, in Di Ferdinando et al. (2020), four control parameters have to be tuned, and they must satisfy suitable inequalities involving also the model parameters as well as parameters related to a Lyapunov-Krasovskii functional (see Assumption 2 in Di Ferdinando et al. (2020)). So, a preliminary check is necessary which is here avoided. This simplification is mainly due to the fact that the continuous-time controller in (4) is a static output feedback and no dynamic equation is involved, making its implementation much easier with respect to the dynamic output feedback controller proposed in Di Ferdinando et al. (2020) (see (5) in Di Ferdinando et al. (2020)).

Before stating the main theoretical results, the notion of partition with a dwell time is recalled (see Clarke et al. (1997), Pepe (2016)).

Definition 2. For a positive integer l and for a positive real $\bar{\Delta}$, a partition $\pi = \{t_i,\ i = -l, -l+1, ...\}$ of $\left[-\bar{\Delta}, +\infty\right)$ is a countable, strictly increasing sequence $t_i \in \left[-\bar{\Delta}, +\infty\right)$, with $t_0 = 0$, such that $t_i \to +\infty$ as $i \to +\infty$. The diameter of π, denoted $\operatorname{diam}(\pi)$, is defined as $\sup_{i \geq -l} t_{i+1} - t_i$. The dwell time of π, denoted $\operatorname{dwell}(\pi)$, is defined as $\inf_{i \geq -l} t_{i+1} - t_i$. For any positive real $a \in (0, 1]$, for any $\delta > 0$, $\pi_{a,\delta}$ is any partition π such that $a\delta \leq \operatorname{dwell}(\pi) \leq \operatorname{diam}(\pi) \leq \delta$.

Remark 3. Given a partition $\pi_{a,\delta}$, the discrete-time controller obtained by (4) is described, for $t_k \in \pi_{a,\delta}$, $k = 0, 1, ...$, by the following equation:

$$v(t_k) = V_I \Bigg(K_{xi} I_{ref} - \frac{T_{iGmax}}{V_I} \varphi(y(t_k - \tau_g)) + \frac{K_{xgi}}{\rho}(y(t_k) - G_{ref})^2 + \frac{K_{xgi} G_{ref}}{\rho}(y(t_k) - G_{ref}) \Bigg). \tag{5}$$

As in Di Ferdinando et al. (2020), the controller (5) makes use, at sampling instant t_k, $k = 0, 1, ...$, of the output delayed measurement $y(t_k - \tau_g)$.

In the following, the notion of spline approximation is introduced (see Pepe (2016)). The spline approximation method will be used in order to obtain the approximated value of $y(t_k - \tau_g)$, so allowing us to remove, in the theoretical results, the assumption concerning the availability in the buffer of the glucose measurement at the exact time $t_k - \tau_g$ (see Remark 1 in Di Ferdinando et al. (2020) and forthcoming Theorem 4).

For given $\delta > 0$, $a \in (0, 1]$, let l be the smallest positive integer such that $la\delta \geq \tau_g$. Let $\mathcal{T}_{l,a,\delta} \subset \mathbb{R}^{l+1}$ be the set defined as follows (see Pepe (2016)) $\mathcal{T}_{l,a,\delta} = \{w = [w_0\ w_1\ ...\ w_l]^T \in \mathbb{R}^{l+1},\ w_i \in [-l\delta, 0], i = 0, 1, ..., l,\ w_0 =$

$0,\ w_0 - w_l \geq \tau_g,\ \delta \geq w_i - w_{i+1} \geq a\delta, i = 0, 1, ..., l-1\}$. Let $P_{l,a,\delta} : \mathbb{R}^{l+1} \times \mathcal{T}_{l,a,\delta} \to \mathcal{C}$ be the map defined (see Pepe (2016)), for $z = [z_0\ z_1\ ...\ z_l]^T \in \mathbb{R}^{l+1}$, $z_i \in \mathbb{R}$, $i = 0, 1, ..., l$, $w = [w_0\ w_1\ ...\ w_l]^T \in \mathcal{T}_{l,a,\delta}$, $\tau \in [-\tau_g, 0]$, as follows

$$(P_{l,a,\delta}(z,w))(\tau) = z_{i+1} + \frac{\tau - w_{i+1}}{w_i - w_{i+1}}(z_i - z_{i+1}), \qquad (6)$$

where i is the smallest integer in $\{0, 1, ..., l-1\}$ such that $w_i \geq \tau \geq w_{i+1}$.

Theorem 4. Let a be an arbitrary real in $(0, 1]$. Then, for any positive reals r, R with $0 < r < R$, there exist positive reals δ, T, E, such that: for any partition $\pi_{a,\delta} = \{t_k,\ k = -l, -l+1, ...\}$ where l is the smallest (nonnegative) integer such that $la\delta \geq \tau_g$, $\{t_{-l}, t_{-l+1}, ..., 0\} \in \mathcal{T}_{l,a,\delta}$ and $\bar{\Delta} = \max\{l\delta, l\tau_g\}$, for any initial condition such that $\left|\begin{matrix} G_0(\tau) - G_{ref} \\ I_0(\tau) - I_{ref} \end{matrix}\right| \leq R$, $\tau \in [-\tau_g, 0]$, the corresponding unique locally absolutely continuous solution of the sampled-data closed-loop system, described by (1) with

$$\begin{aligned} v(t) = V_I \Bigg(& K_{xi} I_{ref} + \frac{K_{xgi}}{\rho}(G(t_k) - G_{ref})^2 \\ & - \frac{T_{iGmax}}{V_I} \varphi\left((P_{l,a,\delta}(B_S(k), B_{\mathcal{T}}(k)))(-\tau_g)\right) \\ & + \frac{K_{xgi} G_{ref}}{\rho}(G(t_k) - G_{ref}) \Bigg), \quad t_k \leq t < t_{k+1}, \end{aligned} \qquad (7)$$

where $P_{l,a,\delta}$ is the map defined in (6), $B_S : \mathbb{N} \to \mathbb{R}^{l+1}$, $B_{\mathcal{T}} : \mathbb{N} \to \mathbb{R}^{l+1}$ are defined (recursively) as

$$B_S(0) = \begin{bmatrix} \bar{G}_0(0) \\ \bar{G}_0(t_{-1}) \\ \vdots \\ \bar{G}_0(t_{-l}) \end{bmatrix}, \ \bar{G}_0(\tau) = \begin{cases} G_0(\tau),\ \tau \in [-\tau_g, 0], \\ G_0(-\tau_g),\ \tau \in [t_{-l}, -\tau_g], \end{cases}$$

$$B_S(k) = \begin{bmatrix} G(t_k) \\ 0_{l\times 1} \end{bmatrix} + \begin{bmatrix} 0_{1\times l} & 0 \\ I_l & 0_{l\times 1} \end{bmatrix} B_S(k-1), \quad k = 1, 2, ...,$$

$$B_{\mathcal{T}}(0) = [0\ t_{-1}\ \cdots\ t_{-l}]^T,$$

$$B_{\mathcal{T}}(k) = \begin{bmatrix} 0_{1\times l} & 0 \\ I_l & 0 \end{bmatrix} (B_{\mathcal{T}}(k-1) - (t_k - t_{k-1})[1\ 1\ \cdots\ 1]^T),$$

$k = 1, 2, ...$, exists $\forall t \geq 0$ and, furthermore, satisfies:

$$\left|\begin{matrix} G(t) - G_{ref} \\ I(t) - I_{ref} \end{matrix}\right| \leq E,\ \forall t \in \mathbb{R}^+, \quad \left|\begin{matrix} G(t) - G_{ref} \\ I(t) - I_{ref} \end{matrix}\right| \leq r,\ \forall t \geq T. \qquad (8)$$

Remark 5. Notice that, in Theorem 4, spline approximation method has been used in order to obtain the approximated values of $G(t_k - \tau_g)$ (see (7)). Then, differently from Di Ferdinando et al. (2020), theoretical results have been provided overcoming the problems related to the non-availability in the buffer of the glucose measurements at the exact time $t_k - \tau_g$ (see Remark 1 in Di Ferdinando et al. (2020)). Indeed, in Di Ferdinando et al. (2020), the theoretical results are provided assuming the availability in the buffer of such measurements (see Remark 1 and Theorem 1 in Di Ferdinando et al. (2020)). Moreover, differently from Di Ferdinando et al. (2020) (see Assumption 2 and Theorem 1 in Di Ferdinando et al. (2020)), the theoretical results are here provided without introducing any constraint concerning the control parameters (see ρ in (4) and Assumption 2 in Di Ferdinando et al. (2020)), making easier the implementation of the proposed controller with respect to the one in Di Ferdinando et al. (2020). The simplification of the sampled-data implementation is mainly due to the use of a continuous-time static output feedback, instead of a dynamic one (see (5) in Di Ferdinando et al. (2020) and (4), as well as (6) in Di Ferdinando et al. (2020) and (5), which is the controller in the case past measurements were available in the buffer). The use of the splines, for the case past measurements may be not available in the buffer, does not introduce any new difficulty in the implementation process of the provided controller (see (7)). Indeed, the practical implementation of the splines approximation method consists in the linear interpolation of the available measurements $G(t_k)$ which is used to obtain the approximated values of $G(t_k - \tau_g)$ required by the controller (see (5), (6), (7)).

Proof. In order to prove Theorem 4, we will make use of the results concerning the stabilization in sampled-and-hold sense theory in Pepe (2016). The first step is to rewrite system (1) with respect to the displacement $x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} = \begin{bmatrix} G(t) - G_{ref} \\ I(t) - I_{ref} \end{bmatrix}$, with the new control input $u(t) = v(t) - v_{ref}$ and the new output signal $\bar{y}(t) = y(t) - G_{ref}$ (see Di Ferdinando et al. (2020)). By letting $x_t(\tau) = \begin{bmatrix} x_{1,t}(\tau) \\ x_{2,t}(\tau) \end{bmatrix} = \begin{bmatrix} G(t+\tau) - G_{ref} \\ I(t+\tau) - I_{ref} \end{bmatrix}$, $\tau \in [-\tau_g, 0]$, we have:

$$\begin{aligned} \dot{x}_1(t) &= -K_{xgi}(x_1(t) + G_{ref})(x_2(t) + I_{ref}) + \frac{T_{gh}}{V_G}, \\ \dot{x}_2(t) &= -K_{xi}(x_2(t) + I_{ref}) \\ &\quad + \frac{T_{iGmax}}{V_I}\varphi(x_1(t - \tau_g) + G_{ref}) + \frac{v_{ref} + u(t)}{V_I}, \\ \bar{y}(t) &= x_1(t), \quad x(\tau) = x_0(\tau) = \begin{bmatrix} G_0(\tau) - G_{ref} \\ I_0(\tau) - I_{ref} \end{bmatrix}. \end{aligned} \qquad (9)$$

Moreover, taking into account $\bar{y}(t)$ in (9), the static output feedback controller (4), rewritten with respect to the displacement, is described by:

$$\begin{aligned} u(t) = V_I \Bigg(& K_{xi} I_{ref} - \frac{T_{iGmax}}{V_I}\varphi(\bar{y}(t - \tau_g) + G_{ref}) \\ & + \frac{K_{xgi}}{\rho}\bar{y}^2(t) + \frac{K_{xgi} G_{ref}}{\rho}\bar{y}(t) \Bigg) - v_{ref} = \\ V_I \Bigg(& K_{xi} I_{ref} - \frac{T_{iGmax}}{V_I}\varphi(x_1(t - \tau_g) + G_{ref}) \\ & + \frac{K_{xgi}}{\rho}x_1^2(t) + \frac{K_{xgi} G_{ref}}{\rho}x_1(t) \Bigg) - v_{ref} = k(x_t), \end{aligned} \qquad (10)$$

where $x_t \in \mathcal{C}^2$ and the map $k : \mathcal{C}^2 \to \mathbb{R}$ is readily defined by (10). Notice that, the initial state $x_0 \in W_2^{1,\infty}$ and $\operatorname{ess\,sup}_{\theta\in[-\tau_g,0]} \left|\frac{dx_0(\theta)}{d\theta}\right| \leq q$ (see Remark 1). In order to prove Theorem 4, thanks to the results in Pepe (2016), we have to check that Assumption 1 in Pepe (2016) holds for the glucose-insulin system (9), and the static output feedback controller k defined in (10). Indeed, if Assumption 1 in Pepe (2016) holds, then from Theorem 4.1 in Pepe (2016), the static output feedback controller k, provided in (10), is a stabilizer in the sample-and-hold sense, for the system (9), by (first order) spline approximation (see Definition 3.2 in Pepe (2016)) and thus the results in Theorem 4 follows. According to Assumption 1 in Pepe (2016), we have to prove that there exist a smoothly separable functional $V = V_1 + V_2$ (see Definition

2.2 in Pepe (2016)), positive reals η, μ, a function p in $C_L^1(\mathbb{R}^+;\mathbb{R}^+)$ of class $\mathcal{K}_\infty$, $m \in \{0,1\}$, functions γ_i of class $\mathcal{K}_\infty$, $i=1,2$, and a function $\bar{\alpha}$ of class $\mathcal{P}_0$ such that $I_d - \bar{\alpha}$ is of class $\mathcal{K}_\infty$, such that: (1) the map $(\phi,u) \to D^+V_2(\phi,u)$ is Lipschitz on bounded subsets of $\mathcal{C}^2 \times \mathbb{R}$; (2) for any $\phi \in \mathcal{C}^2$, the following inequalities hold:

$$\begin{aligned} &\gamma_1(|\phi(0)|) \le V(\phi) \le \gamma_2(\|\phi\|_\infty), \\ &mD^+V(\phi,k(\phi)) + \eta \max\{D^+p \circ V_1(\phi,k(\phi)) \\ &\quad +\mu p \circ V_1(\phi(0))\} \le \bar{\alpha}(\eta\mu e^{-\mu\tau_g} p \circ \beta_1(\|\phi\|_\infty)), \end{aligned} \tag{11}$$

where β_1 is the function of class $\mathcal{K}_\infty$ related to the smoothly separability property of the functional V (see Definition 2.2 in Pepe (2016)). To this aim, let $P, Q \in \mathbb{R}^{2\times 2}$ be two symmetric positive definite matrices, defined as follows $P = \begin{bmatrix} p_1 & 0 \\ 0 & \rho p_1 \end{bmatrix}$, $Q = \begin{bmatrix} q_1 & 0 \\ 0 & q_2 \end{bmatrix}$, where p_1, q_1, q_2, are positive reals such that

$$q_1 < 2p_1 K_{xgi} I_{ref} \quad q_2 < 2\rho p_1 K_{xi}. \tag{12}$$

Define the function $V_1 : \mathbb{R}^2 \to \mathbb{R}^+$ as $V_1(\tilde{x}) = \tilde{x}^T P \tilde{x}$, $\tilde{x} \in \mathbb{R}^2$, the functional $V_2 : \mathcal{C}^2 \to \mathbb{R}^+$ as $V_2(\phi) = \int_{-\tau_g}^0 \phi(\tau)^T Q \phi(\tau)\, d\tau$, $\phi \in \mathcal{C}^2$, and the functional $V : \mathcal{C}^2 \to \mathbb{R}^+$ as

$$V(\phi) = V_1(\phi(0)) + V_2(\phi), \qquad \phi \in \mathcal{C}^2. \tag{13}$$

The functional V is smoothly separable with the functions $\beta_i \in \mathcal{K}_\infty$, $i=1,2$, defined, for $s \in \mathbb{R}^+$, as $\beta_1(s) = \lambda_{min}(P)s^2$ and $\beta_2(s) = \lambda_{max}(P)s^2$, respectively (see Definition 2.2 in Pepe (2016)). The point (1) is clearly satisfied. It remains to prove point (2). The functional V satisfies the first two inequalities in (11) with the functions $\gamma_i \in \mathcal{K}_\infty$, $i=1,2$ defined, for $s \in \mathbb{R}^+$, as $\gamma_1(s) = \lambda_{min}(P)s^2$ and $\gamma_2(s) = (\lambda_{max}(P) + \tau_g \lambda_{max}(Q))\, s^2$, respectively. Taking into account (9), (10), (12), (13) and according with (2), for any $\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \end{bmatrix} \in \mathcal{C}^2$ (ϕ_1, $\phi_2 \in \mathcal{C}$), the following equality/inequality hold

$$\begin{aligned} &D^+V(\phi,k(\phi)) = -(2p_1 K_{xgi} I_{ref} - q_1)\phi_1^2(0) \\ &\quad -(2p_1\rho K_{xi} - q_2)\phi_2^2(0) - q_1\phi_1^2(-\tau_g) - q_2\phi_2^2(-\tau_g) \le 0. \end{aligned} \tag{14}$$

Moreover, taking into account (9), (10), (12), (13), (14) and according with (2), for any $\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \end{bmatrix} \in \mathcal{C}^2$ (ϕ_1, $\phi_2 \in \mathcal{C}$), the following equality holds

$$\begin{aligned} &D^+V(\phi,k(\phi)) + \eta D^+V_1(\phi,k(\phi)) + \eta\mu V_1(\phi(0)) = \\ &-(2p_1 K_{xgi} I_{ref} - q_1)\phi_1^2(0) - (2p_1\rho K_{xi} - q_2)\phi_2^2(0) \\ &-q_1\phi_1^2(-\tau_g) - q_2\phi_2^2(-\tau_g) - 2\eta p_1 K_{xgi} I_{ref}\phi_1^2(0) \\ &-2\eta p_1 \rho K_{xi}\phi_2^2(0) + \eta\mu p_1\phi_1^2(0) + \eta\mu p_1\rho\phi_2^2(0). \end{aligned} \tag{15}$$

Taking into account (15) and choosing $\eta = 1$ and $\mu < \min\left\{\frac{4p_1 K_{xgi} I_{ref} - q_1}{p_1}, \frac{4p_1\rho K_{xi} - q_2}{p_1\rho}\right\}$, for any $\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \end{bmatrix} \in \mathcal{C}^2$ (ϕ_1, $\phi_2 \in \mathcal{C}$), the following inequality holds

$$D^+V(\phi,k(\phi)) + \eta D^+V_1(\phi,k(\phi)) + \eta\mu V_1(\phi(0)) \le 0. \tag{16}$$

Then, taking into account (16), the third inequality in (11) holds by choosing $m=1$, $p = I_d$ and $\bar{\alpha} = 0$. The proof of Theorem 4 is complete.

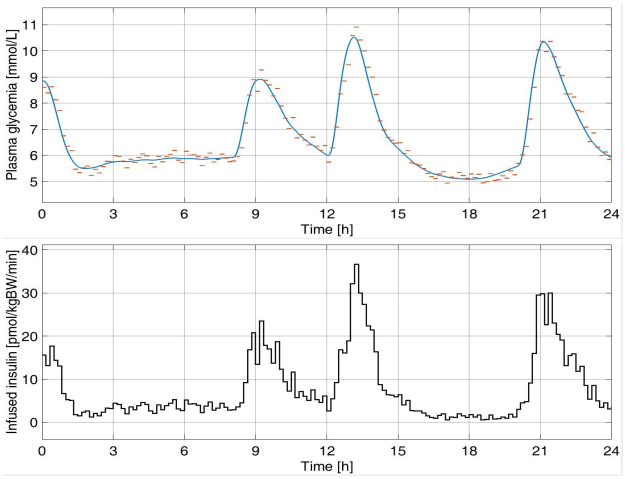

Fig. 1. Three meal administration of 45[g], 70[g] and 70[g] of CHO in 24[h]: plasma glycemia (first panel), insulin infusion rate (second panel).

4. SIMULATIONS ON AN AVERAGE VIRTUAL PATIENT

In the following, a preliminary validation is carried out by closing the loop on to a different, comprehensive mathematical model of the glucose-insulin system. More in detailed, the proposed sampled-data glucose control law (7) is applied to the model developed in Dalla Man et al. (2007), extensively used in the AP literature for the preclinical validation of glucose control laws (see, for instance, Magni et al. (2009); Turksoy et al. (2014); Zavitsanou et al. (2015); Gondhalekar et al. (2018); Lunze et al. (2013); Messori et al. (2018); Di Ferdinando et al. (2020); Palumbo et al. (2014)). In Dalla Man et al. (2007), a set of parameters are provided, allowing to build a T2DM average Virtual Patient (AVP) with $G_b = 8.85$[mmol/L] and $I_b = 59.85$[pmol/L] (see Table I in Dalla Man et al. (2007)). In Palumbo et al. (2014), the DDE model parameters in (1) are estimated by means of a virtual IVGTT, in order to best fit the compact model onto the comprehensive one. For the details concerning the model parameters as well as the initial conditions of the T2DM patient in exam the reader can refer to Palumbo et al. (2014). In the performed simulations with the comprehensive mathematical model in Dalla Man et al. (2007), in order to comply with safety clinical requirements, errors in blood glucose measurements, malfunctioning of the insulin delivery pumps and a Health Monitoring System (HMS) have been also considered (see (18), (19) in Palumbo et al. (2014) and Harvey et al. (2012)). The simulations have been performed by choosing a sampling period $\delta = 10$[min] and the control parameter $\rho = 2 \times 10^{-5}$. Fig. 1 shows the good performances of the proposed sampled-data control law in the case of three meals administration during a day: plasma glycemia is always driven into health safety range according to a smooth trajectory that avoids dangerous oscillations.

5. CONCLUSIONS

In this paper, a sampled-data static output feedback regulator for the glucose-insulin system has been provided. Only glucose measurements are used by the proposed

glucose control law. The stabilization in the sampled-and-hold sense theory has been exploited in order to prove the theoretical results. Spline approximation has been used in order to cope with the problem of non-availability in the buffer of suitable needed past values of glucose concentration. Moreover, no assumption has been introduced concerning the control parameters involved in the controller. A pre-clinical test on an average virtual patient has been performed within the framework of a virtual environment accepted by the Food and Drug Administration (FDA) for testing insulin infusion therapies, Kovatchev et al. (2008). Further investigations concerning the proposed glucose controller are encouraged by the simulation results.

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