2023 62nd IEEE Conference on Decision and Control (CDC)
December 13-15, 2023. Marina Bay Sands, Singapore

On the Digital Event-Based Implementation of a Glucose Regulator via Subcutaneous Insulin Infusion

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Abstract— **In this paper, an event-based quantized sampled-data control strategy is proposed for the plasma glucose regulation problem in Type 2 diabetic patients. In particular, the proposed event-triggered digital glucose regulator is designed by exploiting a nonlinear time-delay model of the glucose-insulin regulatory system which takes into account the subcutaneous infusion of insulin. It is proved that the provided quantized sampled-data glucose controller, updated via a proposed event-based mechanism, guarantees the semi-global practical stability property of the related closed–loop tracking error system, with arbitrarily small steady–state tracking error. The stabilization in the sample–and–hold sense theory is used as a tool to prove the results. An approximation scheme based on first–order splines is used in order to cope with the problem of the possible non–availability in the buffer of the value of the system variables at some past times which are needed for the implementation of the proposed digital controller. The possible non-uniform quantization of the input/output channels as well as the case of time–varying sampling periods are included in the theory here developed. The validation of the proposed glucose control strategy is carried out via simulations.**

I. Introduction

Diabetes Mellitus (DM) is a chronic disease caused by high levels of blood glucose concentrations which are generated from defects in insulin secretion, insulin action, or both. The most widespread type of diabetes is Type 2 DM (T2DM) which is mostly related to an inadequate production of insulin and/or to insulin resistance. T2DM involves about 415 million patients worldwide and its management has a heavy impact on national healthcare budgets ([33]) with a recent amplification due to pandemic COVID–19 and the related effects on diabetic patients (see, for instance, [20], [44]). Glucose control strategies are built-up in practice by combining a set of technologies, such as computing systems, actuators and sensors, to realize an Artificial Pancreas (AP). 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, [2], [3], [8], [18], [19], [22], [24], [25], [27], [31], [47] and the references therein). In the context of the AP, glucose control strategies for T2DM are commonly actuated by: the direct infusion of insulin in vein resulting in an invasive therapy for the patients (see, for instance, [4], [10], [13], [15], [16], [30], [39]); the subcutaneous infusion of insulin (see, for instance, [5], [9], [35], [36] and [37]). A crucial aspect to take into account in the design and practical implementation of glucose regulators is the unavoidable presence of sampling and quantization in the digital devices composing the AP. In [9], a quantized sampled-data glucose regulator using a subcutaneous insulin infusion strategy is proposed and theoretical results are provided concerning the semi-global practical stability property of the related tracking error system. A popular approach for the design of sampled–data stabilizers, not considered in [9], is the one based on the event–triggered control, which has been proved to be successful in properly managing shared computation and communication resources in the digital world [21], [46] as necessary, for instance, in the context of AP where glucose control algorithm are implemented on microcontrollers. The main idea behind such an approach is to control the system whenever it really needs attention, by avoiding continuous-time state/output monitoring and control updates unless they are necessary (see, for instance, [1], [4], [17], [23], [43], [45] and references therein). In this paper, for the first time in the literature concerning the AP, a quantized sampled–data glucose regulator for T2DM patients, updated via a proposed event-based mechanism and actuated by means of subcutaneous insulin infusion, is provided. Indeed, to our best knowledge, theoretical results concerning event-triggered quantized sampled-data glucose control strategies based on the subcutaneous infusion of insulin have never been provided in the literature of the AP for T2DM.

In this paper, we fill this gap. In particular, in the present contribution, an event-based mechanism is proposed for the update of the quantized sampled-data glucose control law provided in [9] and the recent results in [10] concerning the stabilization in the sample–and–hold sense theory (see, for instance, [6], [11], [12], [14], [43] and the references therein) are used in order to prove the semi-global practical stability property of the related closed–loop tracking error GI system, with arbitrarily small final target ball of the origin. We highlight here that: (i) differently from [9] here an event-based quantized sampled-data glucose controller is proposed; (ii) differently from [10], in which an an event-based quantized sampled-data glucose controller based on the intravenous insulin administration strategy is proposed, here the subcutaneous infusion of insulin is considered, leading to a complete reformulation of the controller in order to take into account the subcutaneous insulin absorption. In the theory here developed the non–uniform quantization of the input/output channel and aperiodic sampling are taken into

This work is supported in part by the Atheneum Project RIA 2023.

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account. The results are validated through simulations which pave the way for further investigations.

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 $x_t(\tau)=x(t+\tau)$, $\tau\in[-\Delta,0]$. $C^1(\mathbb{R}^+;\mathbb{R}^+)$ denotes the space of the continuous functions from $\mathbb{R}^+$ to $\mathbb{R}^+$, admitting continuous derivatives; $C_L^1(\mathbb{R}^+;\mathbb{R}^+)$ denotes the subset of the functions in $C^1(\mathbb{R}^+;\mathbb{R}^+)$ admitting locally Lipschitz 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 [42]) $D^+V:\mathcal{C}^n\times\mathbb{R}^m\to\mathbb{R}^\star$, of the functional V, is defined, for $\phi\in\mathcal{C}^n$, $u\in\mathbb{R}^m$, as:

$$D^+V(\phi,u)=\limsup_{h\to0^+}\frac{V(\phi_{h,u})-V(\phi)}{h},$$

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

II. The Glucose-Insulin model

The nonlinear DDE model exploited for the design of the proposed glucose regulator is composed by the coupling of the GI system [34], [41] with a two-compartmental model of the subcutaneous insulin absorption ([7], [28], [32], [48])

$$\begin{aligned}\dot G(t)&=-K_{xgi}G(t)I(t)+\tfrac{T_{gh}}{V_G},\\ \dot I(t)&=-K_{xi}I(t)+\tfrac{T_{iGmax}}{V_I}\varphi(G(t-\tau_g))+\tfrac{S_2(t)}{V_I t_{\max,I}},\\ \dot S_2(t)&=\tfrac{S_1(t)}{t_{\max,I}}-\tfrac{S_2(t)}{t_{\max,I}},\\ \dot S_1(t)&=-\tfrac{S_1(t)}{t_{\max,I}}+u(t),\end{aligned}\tag{1}$$

$G(\tau)=G_0(\tau)$, $I(\tau)=I_0(\tau)$, $S_2(\tau)=S_{2,0}(\tau)$, $S_1(\tau)=S_{1,0}(\tau)$, $\tau\in[-2\tau_g,0]$, where: $G(t)$, [mmol/L], and $I(t)$, [pmol/L] are the plasma glucose and insulin concentrations, respectively; $S_1(t)$ and $S_2(t)$ [pmol/L] are the insulin in the mass accessible and not–accessible subcutaneous depot, respectively. $\varphi(\cdot)$ models the endogenous pancreatic insulin delivery rate according to the following sigmoidal function:

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

In case of no exogenous insulin input, by neglecting the insulin dynamics in the subcutaneous depot, model (1) reduces to a basic GI regulatory system, and belongs to the family of DDE models described in [34] (see [34], [41] for more details on the qualitative behaviour and model parameters) which are clinical validated in [40], [41]. $(G_0(\tau),\, I_0(\tau),\, S_{2,0}(\tau),\, S_{1,0}(\tau))$ constitute the initial conditions of the model usually assessed equal to the constant basal levels $(G_b, I_b, 0, 0)$. $u(t)$, [pmol/min], is the subcutaneous insulin delivery rate, i.e., the control input. By the choice of a desired glucose concentration $G_{\rm ref}$, from the first equation in (1), the related insulin reference is obtained:

$$I_{\rm ref}=\frac{T_{gh}}{V_G G_{\rm ref}K_{xgi}}.$$

On the other hand, the references $S_{1,\rm ref}$ and $S_{2,\rm ref}$, related to the subcutaneous compartments (i.e. related to $S_1(t)$ and $S_2(t)$) will be treated as virtual inputs (see (5)).

III. Subcutaneous Digital Control for the Glucose-Insulin System

In the following, the subcutaneous glucose controller provided in [9] is recalled and an event-based digital implementation is proposed by making use of the results in [10]. In particular, we will theoretically show that the proposed event-based quantized sampled-data implementation of the considered continuous-time controller ensures the semi-global practical stability property of the related closed–loop tracking error system with arbitrarily small final tracking error. The continuous-time glucose regulator for the system (1) is here described by (see [9])

$$\begin{aligned}u(t)=k(\sigma(x_t))&=\dot S_{1,\rm ref}(t)+\tfrac{S_{1,\rm ref}(t)}{t_{\max,I}}-\tfrac{x_3(t)}{t_{\max,I}}-K_{S_1}x_4(t)\\ &=k_4(\sigma(x_t))+\tfrac{k_3(\sigma(x_t))}{t_{\max,I}}-\tfrac{x_3(t)}{t_{\max,I}}-K_{S_1}x_4(t),\end{aligned}\tag{2}$$

where: $x_t \in \mathcal{C}^4$ is the extended state variable defined as

$$x_t(\tau) = \begin{bmatrix} x_{1,t}(\tau) \\ x_{2,t}(\tau) \\ x_{3,t}(\tau) \\ x_{4,t}(\tau) \end{bmatrix} = \begin{bmatrix} G_t(\tau) - G_{\rm ref} \\ I_t(\tau) - I_{\rm ref} \\ S_{2,t}(\tau) - S_{2,{\rm ref},t}(\tau) \\ S_{1,t}(\tau) - S_{1,{\rm ref},t}(\tau) \end{bmatrix}, \ \tau \in [-2\tau_g, 0]\,; \tag{3}$$

the map $\sigma : \mathcal{C}^4 \to \mathbb{R}^{12}$ is defined as

$$\sigma(\phi) = \begin{bmatrix} \phi(0)^T & \phi(-\tau_g)^T & \phi(-2\tau_g)^T \end{bmatrix}^T, \quad \phi \in \mathcal{C}^4; \tag{4}$$

the functions $k_i : \mathbb{R}^{12} \to \mathbb{R}$, $i = 1, \cdots, 4$, are defined as

$$\begin{aligned} k_1(\sigma(x_t)) &= S_{2,{\rm ref}}(t) = V_I t_{{\max},I}\big(K_{xi}(x_2(t) + I_{\rm ref}) \\ &\quad - K_I x_2(t) - \tfrac{T_{iG_{max}}}{V_I}\varphi(x_1(t-\tau_g) + G_{\rm ref}) \\ &\quad + \tfrac{K_{xgi}}{\rho}x_1^2(t) + \tfrac{K_{xgi}G_{\rm ref}}{\rho}x_1(t)\big), \\ k_2(\sigma(x_t)) &= \dot{S}_{2,{\rm ref}}(t), \\ k_3(\sigma(x_t)) &= S_{1,{\rm ref}}(t) = t_{{\max},I}\big(\tfrac{x_3(t)+k_1(\sigma(x_t))}{t_{{\max},I}} + k_2(\sigma(x_t)) \\ &\quad - K_{S_2}x_3(t) - \tfrac{\rho}{V_I t_{{\max},I}}x_2(t)\big), \\ k_4(\sigma(x_t)) &= \dot{S}_{1,{\rm ref}}(t), \end{aligned} \tag{5}$$

with $\dot{S}_{2,{\rm ref}}(t)$ and $\dot{S}_{1,{\rm ref}}(t)$ denoting the first-order time derivatives of the virtual control inputs $S_{2,{\rm ref}}(t)$ and $S_{1,{\rm ref}}(t)$, respectively; ρ, K_I, K_{S_1} and K_{S_2} are scalar positive control tuning parameters; the function $k : \mathbb{R}^{12} \to \mathbb{R}$ is readily defined by (2). In the following, the proposed quantized sampled-data event-based implementation of the continuous–time controller is presented. It is highlighted here that the first–order splines approximation method will be used in order to obtain an approximation of the required delayed measurements $x(t-\tau_g)$ and $x(t-2\tau_g)$ (see (2)-(5)) which, in real practice, are often not available in the buffer due to technological constraints mainly related to the involved sensors. Firstly, in order to present the proposed event-based quantized sampled-data implementation of the controller (2), the notions of quantizer ([29]), of partition with a dwell time ([6], [43]) and of spline approximation (see [10], [43]) are recalled.

For a given positive real n and $x \in \mathbb{R}^n$, a *quantizer* is a piecewise constant function $q_x : \mathbb{R}^n \to \mathcal{Q}_x^n$, $\mathcal{Q}_x^n \subset \mathbb{R}^n$, characterized, for some given positive reals E (range of the quantizer) and μ_x (error bound of the quantizer), by the following implication ([29])

$$|x| \le E \quad \Rightarrow \quad |q_x(x) - x| \le \mu_x, \tag{6}$$

Definition 1: For a positive integer l, a partition $\pi = \{t_i,\ i = -l, -l+1, \cdots\}$ of $[-2l\tau_g, +\infty)$ is a countable, strictly increasing sequence $t_i \in [-2l\tau_g, +\infty)$, with $t_0 = 0$, such that $t_i \to +\infty$ as $i \to +\infty$. The diameter of π, denoted $\mathrm{diam}(\pi)$, is defined as $\sup_{i \ge -l} t_{i+1} - t_i$. The dwell time of π, denoted $\mathrm{dwell}(\pi)$, is defined as $\inf_{i \ge -l} t_{i+1} - t_i$. For any positive real $a \in (0, 1]$, $\delta > 0$, $\pi_{a,\delta}$ is any partition π with $a\delta \le \mathrm{dwell}(\pi) \le \mathrm{diam}(\pi) \le \delta$.

For given $\delta \in (0, 2\tau_g)$ and $a \in (0, 1]$, let l be the smallest positive integer such that $la\delta \ge 2\tau_g$. Let $\mathcal{T}_{l,a,\delta} \subset \mathbb{R}^{l+1}$ be the set defined as follows ([43])

$$\begin{aligned} \mathcal{T}_{l,a,\delta} = \big\{ & w = \begin{bmatrix} w_0 & w_1 & \cdots & w_l \end{bmatrix}^T \in \mathbb{R}^{l+1}, \\ & w_i \in [-l\delta, 0],\ i = 0, 1, \cdots, l, w_0 = 0,\ w_0 - w_l \ge 2\tau_g, \\ & \delta \ge w_i - w_{i+1} \ge a\delta,\ i = 0, 1, \cdots, l-1 \big\}. \end{aligned} \tag{7}$$

Let $P_{l,a,\delta} : \mathbb{R}^{4(l+1)} \times \mathcal{T}_{l,a,\delta} \to \mathcal{C}^4$ be the map defined [43], for $z = \begin{bmatrix} z_0 & z_1 & \cdots & z_l \end{bmatrix}^T \in \mathbb{R}^{4(l+1)}$, $z_i \in \mathbb{R}^4$, $i = 0, 1, \cdots, l$, $w = \begin{bmatrix} w_0 & w_1 & \cdots & w_l \end{bmatrix}^T \in \mathcal{T}_{l,a,\delta}$, $\tau \in [-2\tau_g, 0]$, as follows

$$(P_{l,a,\delta}(z,w))(\tau) = z_{i+1} + \tfrac{\tau - w_{i+1}}{w_i - w_{i+1}}(z_i - z_{i+1}), \tag{8}$$

where i is the smallest integer in $\{0, 1, \cdots, l-1\}$ such that $w_i \ge \tau \ge w_{i+1}$. In order to introduce the event-based mechanism which will be used for the update of the quantized sampled-data controller, let:

(a) $P = 0.5 \begin{bmatrix} h & 0 & 0 & 0 \\ 0 & \rho h & 0 & 0 \\ 0 & 0 & h & 0 \\ 0 & 0 & 0 & h \end{bmatrix},\ h > 0;$

(b) $V_3 : \mathcal{C}^4 \to \mathbb{R}^+$ be the functional defined, for $\phi \in \mathcal{C}^4$, as $V_3(\phi) = \sup_{\theta \in [-\Delta, 0]} e^{\mu\theta}\phi^T(\theta)P\phi(\theta)$;

(c) $V_\infty : \mathcal{C}^4 \to \mathbb{R}^+$ be the functional defined, for $\phi \in \mathcal{C}^4$, as $V_\infty(\phi) = \phi^T(0)P\phi(0) + \eta V_3(\phi)$;

(d) $\mathcal{D}_\infty : \mathcal{C}^4 \times \mathbb{R} \to \mathbb{R}$ be the functional defined, for $\phi \in \mathcal{C}^4$, $u \in \mathbb{R}$, as

$$\begin{aligned} \mathcal{D}_\infty(\phi, u) &= D^+V(\phi, u) - \eta\mu V_3(\phi) \\ &\quad + \eta \max\left\{0, D^+V_1(\phi, u) + \mu V_1(\phi\,(0))\right\}, \end{aligned} \tag{9}$$

with $\mu \le \min\{K_{xgi}I_{\rm ref},\ K_I,\ K_{S_2},\ K_{S_1}\}$ and $\eta > 0$.

For a given partition $\pi_{a,\delta}$, for given quantizers $q_x : \mathbb{R}^4 \to \mathcal{Q}_x^4$, $q_u : \mathbb{R} \to \mathcal{Q}_u$ and $q_\sigma : \mathbb{R}^{12} \to \mathcal{Q}_\sigma^{12}$, the proposed event-based quantized sampled-data glucose regulator is described by

$$\begin{aligned} & u(t) = q_u(k\,(q_\sigma(\sigma(P_{l,a,\delta}(B_S^{q_x}(i_j), B_{\mathcal{T}}(i_j)))))), \\ & t \in [t_j, t_{j+1})\,, \quad j = 0, 1, ..., \quad t_j, t_{j+1} \in \pi_{a,\delta} \end{aligned} \tag{10}$$

where: k is the controller in (2); $P_{l,a,\delta}$ is the map defined in (8); $B_S^{q_x} : \mathbb{N} \to \mathbb{R}^{4(l+1)}$, $B_{\mathcal{T}} : \mathbb{N} \to \mathbb{R}^{l+1}$ are defined (recursively) as

$$\begin{aligned} & B_S^{q_x}(0) = \begin{bmatrix} q_x(\bar{x}_0(0))^T & q_x(\bar{x}_0(t_{-1}))^T & ... & q_x(\bar{x}_0(t_{-l}))^T \end{bmatrix}^T, \\ & q_x(\bar{x}_0(\tau)) = q_x(x_0(\tau)),\ \tau \in [-\Delta, 0]\,, \\ & q_x(\bar{x}_0(\tau)) = q_x(x_0(-\Delta)),\ \tau \in [t_{-l}, -\Delta]\,, \\ & B_S^{q_x}(j) = \begin{bmatrix} q_x(x(t_j)) \\ 0_{4l\times 1} \end{bmatrix} + \begin{bmatrix} 0_{4\times 4l} & 0_4 \\ I_{4l} & 0_{4l\times 4} \end{bmatrix} B_S^{q_x}(j-1), \\ & B_{\mathcal{T}}(0) = \begin{bmatrix} 0 & t_{-1} & ... & t_{-l} \end{bmatrix}^T, \\ & B_{\mathcal{T}}(j) = \begin{bmatrix} 0_{1\times l} & 0 \\ I_l & 0 \end{bmatrix} \left(B_{\mathcal{T}}(j-1) - (t_j - t_{j-1}) \begin{bmatrix} 1 \\ \vdots \\ 1 \end{bmatrix} \right), \end{aligned} \tag{11}$$

$j = 1, 2, ...$; the sequence i_j, $j = 0, 1, \ldots$, is defined as $i_0 = 0$ and, for $j \ge 1$, $i_j = j$ in the event that (see [43] for the case without quantization)

$$\begin{aligned} & -\mathcal{D}_\infty(P_{l,a,\delta}(B_S^{q_x}(j), B_{\mathcal{T}}(j)), u^*(i_{j-1})) \\ & \qquad + \lambda\mathcal{D}_\infty(P_{l,a,\delta}(B_S^{q_x}(j), B_{\mathcal{T}}(j)), u^*(j)) \le 0 \end{aligned} \tag{12}$$

and $i_j = i_{j-1}$ otherwise.

In the following, the main theoretical results of the paper are provided. In the forthcoming Theorem 1, it is shown that there exist a suitably fast sampling δ and an accurate quantization of the input/output channels (i.e., ranges and error bounds for the quantizers q_x, q_σ and q_u in (10)) such that the semi-global practical stability, with arbitrarily small steady–state tracking error, is guaranteed for the related quantized sampled–data closed–loop tracking error system (see (1), (3), (5), (14) and the corresponding closed–loop system (15)–(10)).

Theorem 1: 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, H, U, μ_x, μ_σ and μ_u, such that: for any state quantizer $q_x : \mathbb{R}^4 \to \mathcal{Q}_x^4$ with error bound μ_x and range E, for any σ-quantizer $q_\sigma : \mathbb{R}^{12} \to \mathcal{Q}_\sigma^{12}$ with error bound μ_σ and range H, for any input quantizer $q_u : \mathbb{R} \to \mathcal{Q}_u$ with error bound μ_u and range U, for any initial condition such that

$$\left\| \begin{bmatrix} G_0(\tau) - G_{\rm ref} \\ I_0(\tau) - I_{\rm ref} \\ S_{2,0}(\tau) - S_{2,{\rm ref},0}(\tau) \\ S_{1,0}(\tau) - S_{1,{\rm ref},0}(\tau) \end{bmatrix} \right\| \leq R,\ \tau \in [-2\tau_g, 0],$$

for any partition $\pi_{a,\delta} = \{t_i,\ i = -l, -l+1, ...\}$, where l is the smallest (nonnegative) integer such that $la\delta \geq 2\tau_g$ and $\{t_{-l}, t_{-l+1}, ..., 0\} \in \mathcal{T}_{l,a,\delta}$, the corresponding unique locally absolutely continuous solution of the quantized sampled–data closed–loop system (1)-(10) exists $\forall\, t \geq 0$ and, furthermore, satisfies

$$\begin{aligned} &\left\| \begin{bmatrix} G_t(\tau) - G_{\rm ref} \\ I_t(\tau) - I_{\rm ref} \\ S_{2,t}(\tau) - S_{2,{\rm ref},t}(\tau) \\ S_{1,t}(\tau) - S_{1,{\rm ref},t}(\tau) \end{bmatrix} \right\| \leq E,\ \tau \in [-2\tau_g, 0],\ \forall\, t \in \mathbb{R}^+, \\ &\left\| \begin{bmatrix} G_t(\tau) - G_{\rm ref} \\ I_t(\tau) - I_{\rm ref} \\ S_{2,t}(\tau) - S_{2,{\rm ref},t}(\tau) \\ S_{1,t}(\tau) - S_{1,{\rm ref},t}(\tau) \end{bmatrix} \right\| \leq r,\ \tau \in [-2\tau_g, 0],\ \forall\, t \geq T. \end{aligned} \tag{13}$$

A. Proof of Theorem 1

In order to prove Theorem 1, we will make use of the results concerning the stabilization in the sample-and-hold sense theory in [10] applied to the glucose-insulin system here considered. Firstly, taking into account (3), from (1), we obtain the corresponding system rewritten with respect to the displacement:

$$\begin{aligned} \dot{x}_1(t) &= -K_{xgi}\left(x_1(t) + G_{\rm ref}\right)\left(x_2(t) + I_{\rm ref}\right) + \tfrac{T_{gh}}{V_G}, \\ \dot{x}_2(t) &= -K_{xi}\left(x_2(t) + I_{\rm ref}\right) \\ &\quad + \tfrac{T_{iGmax}}{V_I}\varphi(x_1(t-\tau_g) + G_{\rm ref}) + \tfrac{x_3(t)+S_{2,{\rm ref}}(t)}{V_I t_{{\rm max},I}}, \\ \dot{x}_3(t) &= \tfrac{x_4(t)+S_{1,{\rm ref}}(t)}{t_{{\rm max},I}} - \tfrac{x_3(t)+S_{2,{\rm ref}}(t)}{t_{{\rm max},I}} - \dot{S}_{2,{\rm ref}}(t), \\ \dot{x}_4(t) &= -\tfrac{x_4(t)+S_{1,{\rm ref}}(t)}{t_{{\rm max},I}} + u(t) - \dot{S}_{1,{\rm ref}}(t), \end{aligned} \tag{14}$$

$x(\tau) = x_0,\ \tau \in [-2\tau_g, 0]$, where $x_t,\ x_0 \in \mathcal{C}^4$. By substituting the proposed virtual control inputs $S_{2,{\rm ref}}(t)$ and $S_{1,{\rm ref}}(t)$ (5) in the second and third equation of (14), we have

$$\begin{aligned} \dot{x}_1(t) &= -K_{xgi}\left(x_1(t) + G_{\rm ref}\right)\left(x_2(t) + I_{\rm ref}\right) + \tfrac{T_{gh}}{V_G}, \\ \dot{x}_2(t) &= \tfrac{x_3(t)}{V_I t_{{\rm max},I}} + \tfrac{K_{xgi}}{\rho}x_1^2(t) - K_I x_2(t) + \tfrac{K_{xgi}G_{\rm ref}}{\rho}x_1(t), \\ \dot{x}_3(t) &= \tfrac{x_4(t)}{t_{{\rm max},I}} - K_{S_2}x_3(t) - \tfrac{\rho}{V_I t_{{\rm max},I}}x_2(t), \\ \dot{x}_4(t) &= -\tfrac{x_4(t)+k_3(\sigma(x_t))}{t_{{\rm max},I}} + u(t) - k_4(\sigma(x_t)). \end{aligned} \tag{15}$$

Taking into account that it is usually assumed that the glucose and the insulin concentrations in the blood as well as the insulin concentrations in the subcutaneous depots are equal to their constant basal values before the beginning of the insulin administration therapy, the initial state $x_0 \in W_4^{1,\infty}$ and, there exist a positive real q such that $\operatorname{ess\,sup}_{\theta\in[-2\tau_g,0]}\left|\frac{dx_0(\theta)}{d\theta}\right| \leq q$ (see Remark 1 in [9]). In order to prove Theorem 1, thanks to the results in [10], we have to check that Assumption 2 in [10] (see also Assumption 1 in [11]) holds for the GI system (15) and the static state feedback controller (2). Indeed, if Assumption 2 in [10] holds for the GI system (15), from Theorem 4 in [10], there exist a suitably fast sampling and an accurate quantization of the input/output channels such that the quantized sampled–data implementation of the continuous-time static state feedback controller k in (2), updated via the proposed event-based mechanism (see (10)-(12)), ensures the semi–global practical stability property of the related closed–loop system by (first–order) spline approximation and thus the results in Theorem 1 follow. According to Assumption 2 in [10], we have to prove that there exist a smoothly separable functional $V = V_1 + V_2$ (see Definition 1 in [10]), positive reals η, μ, a function p in $C_L^1(\mathbb{R}^+;\mathbb{R}^+)$ of class $\mathcal{K}_\infty$, functions γ_i of class $\mathcal{K}_\infty$, $i = 1, 2, 3$, such that: (1) the map $(\phi, u) \to D^+V_2(\phi, u)$ is Lipschitz on bounded subsets of $\mathcal{C}^4 \times \mathbb{R}$; (2) for any $\phi \in \mathcal{C}^4$, the following inequalities hold (with respect to the system described by (15))

$$\begin{aligned} &\gamma_1(|\phi(0)|) \leq V(\phi) \leq \gamma_2(\|\phi\|_\infty), \\ &D^+V(\phi, k(\sigma(\phi))) \leq -\gamma_3(|\phi(0)|), \end{aligned} \tag{16}$$

$$\begin{aligned} D^+V(\phi, k(\sigma(\phi))) + \eta D^+p \circ V_1(\phi, k(\sigma(\phi))) \\ +\eta\mu p \circ V_1(\phi(0)) \leq 0. \end{aligned} \tag{17}$$

The above conditions (i.e. Assumption 2 in [10]) are here satisfied by choosing:
(i) the function $V_1 : \mathbb{R}^4 \to \mathbb{R}^+$ as $V_1(\tilde{x}) = \tilde{x}^T P \tilde{x}$, $\tilde{x} \in \mathbb{R}^4$, with P the matrix in point **(a)**;
(ii) the functional $V_2 : \mathcal{C}^4 \to \mathbb{R}^+$ as $V_2(\phi) = 0$;
(iii) the functional $V : \mathcal{C}^4 \to \mathbb{R}^+$ as $V(\phi) = V_1(\phi(0)) + V_2(\phi)$, $\phi \in \mathcal{C}^4$;
(iv) 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 1 in [10]);
(v) functions γ_i of class $\mathcal{K}_\infty$, $i = 1, 2, 3$ defined, for $s \in \mathbb{R}^+$, as $\gamma_1(s) = \lambda_{\min}(P)s^2$, $\gamma_2(s) = \lambda_{\max}(P)s^2$, and $\gamma_3(s) = \min\{hK_{xgi}I_{\rm ref},\, h\rho K_I,\, hK_{S_2},\, hK_{S_1}\}s^2$;
(vi) $p = I_d$ and the positive real μ, η as in point **(d)**.
The proof of Theorem 1 is complete.

IV. Application to a T2DM Patient

In the following, the proposed event-based quantized sampled-data controller is validated through an application on a T2DM virtual patient and the related performances are compared with the ones of the time-triggered counterpart (see [9]). In particular, simulations have been carried out on a T2DM virtual patient on the basis of parameter estimates obtained from experimental data related to an IVGTT experiment conducted on a real patient (see [38], [40]). In the following, the estimated values are reported (see [22], [38], [40]): $G_b = 10.66$[mmol/L], $I_b = 49.29$[pmol/L], $T_{iGmax} = 0.236$[min^{-1}(pmol/kgBW)], $t_{\max,I} = 55$[min], $V_G = 0.187$[L/kgBW], $K_{xi} = 1.211 \cdot 10^{-2}$[min^{-1}], $T_{gh} = 0.003$[min^{-1}(mmol/kgBW)], $\tau_g = 24$[min], $V_I = 0.25$[L/kgBW], $K_{xgi} = 3.11 \cdot 10^{-5}$[min^{-1}(pmol/L)$^{-1}$], $\gamma = 3.205$, $G^* = 9$[mmol/L]. In the performed simulations, it has been chosen: $G_{\text{ref}} = 4.5$ [mmol/L]; $K_I = 0.01$, $K_{S_1} = 0.05$, $K_{S_2} = 0.02$ and $\rho = 10^{-3}$; an uniform sampling (i.e. $a = 1$) with $\delta = 10$[min]; logarithmic quantizers characterized by $\mathcal{Q}_x^4 = \{x \in \mathbb{R}^4 | \, x_i = \pm 0.01j, \, i = 1, \cdots, 4, \, j = 0, 1, \cdots, 10^4\}$, $\mathcal{Q}_\sigma^{12} = \{\sigma(\phi) \in \mathbb{R}^{12}, \phi \in \mathcal{C}^4 | \, \sigma(\phi)_i = \pm 0.01j, \, i = 1, \cdots, 12, \, j = 0, 1, \cdots, 10^4\}$ and $\mathcal{Q}_u = \{u \in \mathbb{R} | \, u = \pm 0.01j, \, j = 0, 1, \cdots, 200\}$. In Fig. 1, the evolution of the state variables $G(t)$, $I(t)$, $S_2(t)$, $S_1(t)$ and of the control input $u(t)$ are reported in the case of time-triggered controller (red line) and in the case of event-based controller (black line) with $\lambda = 0.3$. Fig. 1 clearly shows that the event-triggered solution achieves very good performances, similar to the ones of the time–triggered solution, in spite of the much lower average frequency of control updates with respect to the quantized sampled-data time-triggered controller with the same sampling interval (around 8% of the sampling intervals).

V. Conclusions

In this paper, an event-based quantized sampled–data static state feedback glucose regulator for T2DM patients by means of subcutaneous insulin infusion has been provided. In particular, an event-triggered digital glucose regulator has been designed by exploiting a nonlinear time-delay model of the glucose-insulin regulatory system which takes into account the subcutaneous infusion of insulin. Quantization (also non–uniform) in both input/output channels and time–varying sampling periods have been taken into account. A spline approximation methodology has been exploited in order to cope with the problem of non-availability in the buffer of suitably needed past values of the system state. It has been proved that the digital event-based implementation of the proposed glucose control strategy guarantees the semi–global practical stability property of the related closed–loop tracking error system, with arbitrarily small final tracking error. The stabilization in the sample–and–hold sense theory has been used as a tool to prove the results. The proposed theoretical results have been validated through simulations. Further investigations will concern the design of an event-based quantized sampled–data glucose controller making use of the only glucose measurements as well as an intensive pre–clinical validation of the proposed glucose control strategy on a population of virtual patients: (1) by exploiting the framework of a virtual environment accepted by the Food and Drug Administration (FDA) for testing insulin infusion therapies (see [26]); (2) concerning the analysis of the efficacy and robustness properties with respect, for instance, to the influence of meals, physical exercises and the inter-individual variability.

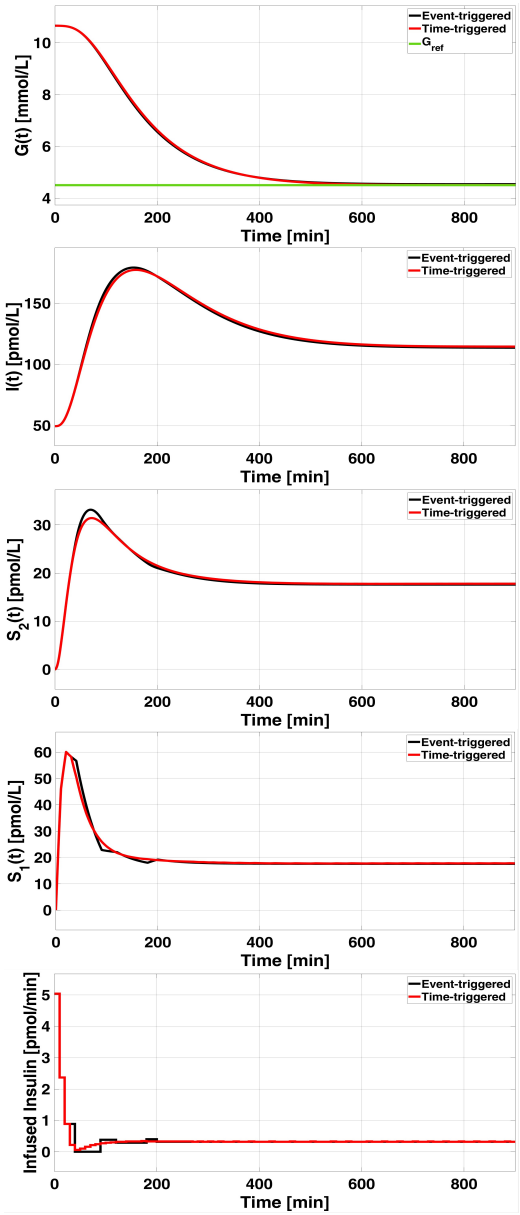

Fig. 1. Evolution of the state variables and of the control input.

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