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Sampled-data Observer-based Glucose Control for the Artificial Pancreas

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Abstract: Artificial Pancreas (AP) is an expression referred to a set of techniques for the closed-loop control of the plasma glucose concentration by means of exogenous insulin administration in diabetic individuals. Diabetes comprises a group of metabolic disorders characterized by high blood sugar levels over a prolonged period, due to pancreas failure to produce enough insulin and/or insulin resistance, so that higher amounts of insulin are usually required in order to keep glycemia in a safe range. In this work, we face the problem of glucose control for a class of Type-2 diabetic patients, in the presence of sampled glucose measurements and without any information about the time course of insulinemia. A compact physiological model of the glucose-insulin system is reviewed, then an observer (based on this model) is designed to estimate the insulin trajectory from the glucose samples. Finally, a feedback control law (based on the reconstructed state) is designed to deliver exogenous intra-venous insulin to each individual. Simulations have been performed in-silico on models of virtual patients, whose parameters are tuned according to real data, and aim at validating the method in the presence of parameter variations and quantization errors.

Keywords: Diabetes, Artificial Pancreas, Glucose Control, Observers, Feedback Systems

1 Introduction

Diabetes Mellitus (DM) is a widespread disease (affecting millions of people worldwide) characterized by the lack of insulin production (Type-1 Diabetes Mellitus, T1DM) or resistance to insulin action (Type-2 Diabetes Mellitus, T2DM). In insulin-sensitive (non-diabetic) individuals, the insulin hormone, released when blood glucose levels increase, normally promotes glucose utilization by enhancing glucose uptake by peripheral tissues and by suppressing endogenous production. This mechanism progressively deteriorates in insulin-resistant people, so that, especially at

early stages of the diabetic conditions, life-style modifications, dietary instructions and metformin therapy try to offer a non-invasive solution to reduce the worsening of the disease.

On top of that, especially when the conditions of diabetic people become critical, it becomes more important to properly determine an additional quantity of exogenous insulin to be supplied to maintain blood glucose levels within a normal range, while avoiding dangerous hypoglycemic episodes. In this context, Artificial Pancreas (AP) is a general expression to describe a set of techniques for the closed-loop control of the glucose behaviour by means of exogenous insulin administration in diabetic people (see e.g. [1, 2]), usually via intravenous or subcutaneous infusions. Several techniques have become available in the last few years for the automatic control of glucose levels, which need to manage the several non-idealities of the underlying dynamics, among which we recall the delayed nonlinear insulin response [3, 4] and the difficulty in obtaining precise and frequent measurements of the current levels of insulinemia [5].

The approach followed in this work belongs to the field of model-based techniques, according to which the controller is synthesized by explicitly exploiting the model equations. In particular, we consider the DDE (Delay Differential Equation) compact model introduced in [6, 7] and exploited e.g. in [8–11] in different clinical settings. This model well represents the glucose and insulin concentrations observed during an Intra-Venous Glucose Tolerance Test (IVGTT) [6, 12], it allows to estimate the insulin sensitivity of a patient by fitting the patient's glucose-insulin dynamics, and it has been shown to admit mathematically consistent solutions with physiologically feasible parameter values [7]. More generally, small-scale *minimal models* are usually preferred since they allow to provide an analytical solution to the control problem under investigation [13]. In this particular application, the use of DDE models when seeking model-based glucose control laws applicable not only to T1DM but also to T2DM patients is motivated by the need for modeling the pancreatic Insulin Delivery Rate (IDR), which is known to show irregular variations [4]. In this context, the results in [8] allowed to track plasma glycemia down to a safe euglycemic level for a T2DM patient, while [9] performed a validation of the DDE model closing the observer-based control loop on a population of virtual patients modeled by a different maximal model [14], accepted by the Food and Drug Administration (FDA) as an alternative to animal trials for the pre-clinical testing of control strategies in AP.

In this paper, we investigate the design of model-based controllers that explicitly account for the discrete nature of the available glucose sampled measurements, usually provided by Continuous Glucose Monitoring (CGM) devices [15]. Insulin measurements are also unavailable. This setting is more realistic with respect to most of the approaches available in the literature. Then, we consider the sampled-data observer developed in [16, 17], and apply it to the problem of model-based reconstruction of glucose and insulin trajectories from the glucose samples [18]. Again, a difference with respect to the approach followed in [8] consists in not assuming the availability of glycemia at all times. On the other hand, the construction in [16, 17] cannot be applied to DDE models, so we restrict our attention to the cases in which

the apparent delay in the insulin response is negligible (less than 1 minute). As a consequence, we consider a particular case of the glucose-insulin model developed in [6, 7]. On top of that, a feedback algorithm (based on the reconstructed state) is designed to continuously deliver exogenous intra-venous insulin to the patient. The control law is a piecewise-constant function of time, where the insulin delivery rate is also assumed to be changed at the sampling times.

In the in-silico evaluation of the described techniques, we take account of further non-idealities, by introducing quantization both in the measurement and in the control phases (modeling the possible lack of accuracy of the instrument as well as the analog-to-digital and digital-to-analog conversion processes), and we consider parameter variations for the sake of a preliminary robustness test of the control law. The parameters of the virtual patients are identified from real data of non-diabetic/pre-diabetic individuals, later modified to simulate a natural progression towards diabetes. The chosen sampling rate mimics the utilization of a real CGM device, with a sampling time of 5 minutes. The prescribed goal is to track some desired good trajectories of glucose and insulin, reaching a prescribed "healthy" set point of glycemia within a time horizon of a few hours.

The paper is structured as follows: in Section 2, we review some theoretical results about observer-based closed-loop control methods; in Section 3 we describe the ODE model of the glucose-insulin system; in Section 4, we apply the methods described in Section 2 to the glucose-insulin model to find a control law (in terms of exogenous insulin rate) aiming at tracking desired glucose trajectories; Section 5 shows some simulations, based on data taken from real patients, in an experimental setting; Section 6 offers concluding remarks.

2 Review of observer-based closed-loop control design

Consider a system in compact form

$$\begin{cases} \dot{x}(t) &= f(x(t)) + g(x(t))u(t), \qquad t \geq 0 \\ y(t) &= c(x(t-\delta(t))), \qquad t \geq \Delta \end{cases} \tag{1}$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $\dot{x}(t) := \frac{dx(t)}{dt}$ denotes its time derivative, $u(t) \in \mathbb{R}$ is the input function, $y(t) \in \mathbb{R}$ is the measured output, $\delta(t) \in [0, \Delta]$ is the known time-varying measurement delay of the output, $x_0 \in \mathbb{R}^n$ is the initial state, $g(x)$ and $f(x)$ are C^∞ vector fields and $c(x)$ is a C^∞ function.

Generally speaking, the problem of asymptotic state observation consists in finding a causal system (asymptotic observer), driven by the pair $(u(t), y(t))$, that produces a vector variable $\hat{x}(t)$ (observed state) asymptotically converging to the state $x(t)$ (i.e., $\|x(t) - \hat{x}(t)\| \to 0$). Furthermore, an observer is said to be an *exponential observer* if there exist $\mu > 0$ and $\alpha > 0$ such that

$$\|x(t) - \hat{x}(t)\| \leq \mu\, e^{-\alpha t} \|x(0) - \hat{x}(0)\|, \tag{2}$$

for any $x(0)$ and $\hat{x}(0)$ in $\mathbb{R}^n$.

In order to design such an observer, we preliminarily define the drift-observability map $z = \phi(x)$, stacking the first n Lie derivatives (from 0 to $n-1$) of the output function $c(x)$ along the drift vector field $f(x)$, and its Jacobian $Q(x)$, as

$$z = \begin{bmatrix} z_1 \\ z_2 \\ \vdots \\ z_n \end{bmatrix} = \phi(x) := \begin{bmatrix} h(x) \\ L_f c(x) \\ \vdots \\ L_f^{n-1} c(x) \end{bmatrix}, \qquad Q(x) := \frac{\partial \phi(x)}{\partial x}. \tag{3}$$

The observer in [16, 17], also reviewed in [18], takes the following form:

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + g(\hat{x}(t))u(t) + e^{-\eta\delta(t)} Q^{-1}(\hat{x}(t)) K \big\{ y(t) - c(\hat{x}(t - \delta(t))) \big\}, \tag{4}$$

where K assigns the n eigenvalues of $(A - KC)$ to obtain convergence to zero of the estimation error $x(t) - \hat{x}(t)$, with

$$A := \begin{bmatrix} 0_{(n-1)\times 1} & I_{(n-1)\times(n-1)} \\ 0 & 0_{1\times(n-1)} \end{bmatrix}, \quad C := \begin{bmatrix} 1 & 0_{1\times(n-1)} \end{bmatrix}, \tag{5}$$

and $\eta > 0$ being a design parameter, giving more weight to recent measurements with respect to the older ones.

Under some technical hypotheses (including, in particular, uniform Lipschitz drift-observability and uniform input boundedness), it is possible to prove the following result, establishing the exponential convergence to zero of the observation error.

Theorem 1. [17] Consider the system (1), with $\delta(t) \in [0, \Delta]$. Then, for any assigned $\eta > 0$, there exists K and a positive $\bar{\Delta}$ such that, if $\Delta < \bar{\Delta}$, then the system in (4) is a global exponential observer for the system in (1) such that η is the decay rate of the estimation error (i.e., eq. (2) is verified for some $\mu > 0$ and $\alpha = \eta$).

Note that the previous result enables the use of the observer (4), provided that the sampling interval is upper-bounded by Δ. Otherwise, a chain of sampled observer is required (full details are given in [17]).

In order to close the control loop, we follow an input-output linearization approach, assuming that the relative degree of the system is n (see, e.g., [20]). The dynamics of the observability map in (3) is the following:

$$\dot{z} = \frac{\partial \phi(x)}{\partial x} \dot{x} = Q(x)(f(x) + g(x)u). \tag{6}$$

By imposing the virtual input $v := \dot{z}_n = L_f^n c(x) + L_g L_f^{n-1} c(x) u$, we get the linearizing feedback law:

$$u = \frac{v - L_f^n c(x)}{L_g L_f^{n-1} c(x)}. \tag{7}$$

We now need to choose v in order to achieve a desirable behavior. Consider a smooth reference output signal $y_{ref}(t)$. By defining the vector of its first n time derivatives

$$z_{ref}(t) = \begin{bmatrix} z_{1,ref}(t) \\ z_{2,ref}(t) \\ \vdots \\ z_{n,ref}(t) \end{bmatrix} = \begin{bmatrix} y_{ref}(t) \\ \dot{y}_{ref}(t) \\ \vdots \\ y_{ref}^{(n-1)}(t) \end{bmatrix},$$

and defining $e := z - z_{ref}$, the error dynamics is

$$\dot{e} = Ae + B(v - \dot{z}_{n,ref}), \qquad \text{with} \quad B := \begin{bmatrix} 0_{(n-1)\times 1} \\ 1 \end{bmatrix}.$$

Since the pair (A,B) is reachable, it suffices to impose

$$v = He + \dot{z}_{n,ref} \tag{8}$$

to obtain the convergence to zero of the linearized error dynamics, where H assigns the n eigenvalues of matrix $(A+BH)$.

Note that the control law given in Eq. (7)–(8) is a continuous state-feedback control law, depending on the continuous state $x(t)$, which is usually not available, since we only know its estimate $\hat{x}(t)$ from (4). In the linear case, the separation principle would guarantee the asymptotic convergence of the output $y(t)$ to its reference value $y_{ref}(t)$. This is not guaranteed in the non-linear case, in general (although local convergence results exist), but it is still possible to restate the control law in (7)–(8) in terms of a feedback from the reconstructed state. An example is given later in Section 4.

3 A continuous-discrete model of the glucose-insulin system

Continuous-discrete models refer to physical continuous-time systems with measurements acquired at discrete sampling times. These models often appear in clinical/medical applications like those related to the Artificial Pancreas, with control design problems related to the lack of a continuous stream of output data. According to [17], discrete measurements can still be formalized by means of a continuous-time output function. To this end, given the sampling sequence $\{t_i\}$ and assuming to measure plasma glucose concentration $G(t_i)$, we define the piecewise-constant output function $y(t)$ as

$$y(t) = G(t_i) \qquad t \in [t_i, t_{i+1}), \quad i = 0, 1, ...$$

which can be equivalently restated as a *delayed* output

$$y(t) = G(t - \delta(t)) \qquad t \geq 0 \tag{9}$$

with the time varying delay $\delta(t)$ defined within any two consecutive sampling instants as

$$\delta(t) = t - t_i, \qquad t \in [t_i, t_{i+1}), \quad i = 0, 1, \ldots \tag{10}$$

where we take $t_0 = 0$. The upper bound on the sampling interval is given by $\Delta := \max_i (t_{i+1} - t_i)$.

As shown in the previous section, this formal setting of the model output function allows to design exponential observers and observer-based control laws, which have been recently exploited also in the context of the artificial pancreas [8, 9, 19]. To this end, we consider a modified version of the DDE model presented in [6, 7] and exploited in [8, 9], which contains an explicit delay characterizing the secondary insulin release in response to varying plasma glucose concentration. Since we need to restate into the form of Eq. (1), the delay of the glucose-stimulated insulin production rate is neglected. This fact clearly limits the proposed feedback control law applicability and refers to further developments of the mathematical theory possibly including time-delay systems. Nonetheless, this works aims at showing the proof of concept of an observer-based control law in such continuous-discrete systems.

In absence of delay, the equations of model [6, 7] are particularized as follows:

$$\begin{cases} \frac{dG(t)}{dt} & = -K_{xgi} G(t) I(t) + \frac{T_{gh}}{V_G}, \\ \frac{dI(t)}{dt} & = -K_{xi} I(t) + \frac{T_{iGmax}}{V_I} h\big(G(t)\big) + u(t), \end{cases} \qquad t \geq 0 \tag{11}$$

with initial conditions $G(0) = G_0$, $I(0) = I_0$, where:

- $G(t)$ is the Plasma Glycemia at time t $[mM]$;
- $I(t)$ is the Plasma Insulinemia at time t $[pM]$;
- K_{xgi} is the rate of (insulin-dependent) glucose uptake by tissues per unit of plasma insulin concentration $[min^{-1} pM^{-1}]$;
- T_{gh} is the net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake $[min^{-1}(mmol/KgBW)]$;
- V_G is the apparent distribution volume for glucose $[L/kgBW]$;
- K_{xi} is the apparent first-order disappearance rate constant for insulin $[min^{-1}]$;
- T_{iGmax} is the maximal rate of second-phase insulin release $[min^{-1}(pmol/kgBW)]$;
- V_I is the apparent distribution volume for insulin $[L/kgBW]$;
- $h(\cdot)$ is a nonlinear map modeling the endogenous pancreatic Insulin Delivery Rate (IDR) as

  $$h(G) = \frac{(G/G^*)^\gamma}{1 + (G/G^*)^\gamma},$$

  where γ (dimensionless) is the progressivity with which the pancreas reacts to circulating glucose concentrations and G^* [mM] is the glycemia at which the insulin release reaches half of its maximal rate;

- $u(t)$ is the exogenous intra-venous insulin delivery rate at time t, i.e. the control input $[pM/min]$.

The model in (11) enjoys some interesting properties:

- it is statistically robust, in that its parameters are statistically identifiable with very good precision by means of standard perturbation experiments, such as the Intra-Venous Glucose Tolerance Test (IVGTT) [6, 12];
- it is a compact model, in the sense that according to a "minimal" set of independent parameters, it allows to very well resemble the physiology of the glucose/insulin kinetics [6];
- it is mathematically consistent, in that exhibits satisfactory properties of the solutions [7]; in particular: positivity, boundedness, and a unique positive stable equilibrium.

The interested reader is referred to [6] for further identification issues and statistical robustness of this model and to [7] for details on its mathematical properties and qualitative behavior.

4 The artificial pancreas

We now apply the control design methodology illustrated in Section 2 to the glucose-insulin model described in Section 3. By collecting the state variables within the state vector $x(t) = [x_1(t), x_2(t)]^T = [G(t), I(t)]^T$, equations (10)–(11) can be rewritten in the compact form (1):

$$\begin{cases} \dot{x}(t) & = f(x(t)) + Bu(t), \qquad t \geq 0 \\ y(t) & = Cx(t - \delta(t)), \qquad t \geq \Delta \\ \delta(t) & = t - t_i, \quad t \in [t_i, t_{i+1}), \quad i = 0, 1, \ldots \end{cases} \tag{12}$$

with

$$f(x) = \begin{bmatrix} f_1(x) \\ f_2(x) \end{bmatrix} = \begin{bmatrix} -K_{xgi} x_1 x_2 + \frac{T_{gh}}{V_G} \\ -K_{xi} x_2 + \frac{T_{iGmax}}{V_I} h(x_1) \end{bmatrix},$$

$$\delta(t) \in [0, \Delta], \qquad B = [0 \quad 1]^T, \qquad C = [1 \quad 0].$$

The drift-observability map $z = \phi(x)$ is

$$z = \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} = \phi(x) := \begin{bmatrix} Cx \\ Cf(x) \end{bmatrix} = \begin{bmatrix} x_1 \\ f_1(x) \end{bmatrix} = \begin{bmatrix} x_1 \\ -K_{xgi} x_1 x_2 + \frac{T_{gh}}{V_G} \end{bmatrix} \tag{13}$$

and its Jacobian

$$Q(x) := \frac{\partial \phi(x)}{\partial x} = \begin{bmatrix} 1 & 0 \\ -K_{xgi} x_2 & -K_{xgi} x_1 \end{bmatrix} \tag{14}$$

is non-singular for $x_1 \neq 0$.

The observer in (4) takes the following form:

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + Bu(t) + e^{-\eta\delta(t)} Q^{-1}(\hat{x}(t)) K\big\{y(t) - C\hat{x}(t-\delta(t))\big\}, \tag{15}$$

where $K = \begin{bmatrix} -(\lambda_1+\lambda_2) \\ \lambda_1\lambda_2 \end{bmatrix}$ assigns the eigenvalues $\lambda_1 < 0$, $\lambda_2 < 0$ of $(A-KC)$ to obtain convergence to zero of the estimation error $x(t) - \hat{x}(t)$, with $A = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}$.

By recalling $\hat{x}(t) = [\hat{x}_1(t), \hat{x}_2(t)]^T = [\hat{G}(t), \hat{I}(t)]^T$, the explicit form of the observer (4), for $t \in [t_i, t_{i+1})$, for $i = 0, 1, ...$, is the following:

$$\begin{cases} \frac{d\hat{G}(t)}{dt} = -K_{xgi}\hat{G}(t)\hat{I}(t) + \frac{T_{gh}}{V_G} + e^{-\eta\delta(t)}(\lambda_1+\lambda_2)(G(t_i) - \hat{G}(t_i)), \\ \frac{d\hat{I}(t)}{dt} = -K_{xi}\hat{I}(t) + \frac{T_{iGmax}}{V_I} h\big(\hat{G}(t)\big) + u(t) + e^{-\eta\delta(t)} \frac{K_{xgi}(\lambda_1+\lambda_2)\hat{I}(t) - \lambda_1\lambda_2}{K_{xgi}\hat{G}(t)} (G(t_i) - \hat{G}(t_i)) \end{cases} \tag{16}$$

The technical hypotheses of Theorem 1 hold for the glucose-insulin system in (10)–(11) (see also the assumptions in [8] for the more general DDE case), guaranteeing the exponential convergence to zero of the observation error.

We now detail the glucose control algorithm. The dynamics of the observability map in (13) is the following:

$$\begin{aligned} \dot{z} = \begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} &= \frac{\partial\phi(x)}{\partial x}\dot{x} = Q(x)(f(x) + Bu) \\ &= \begin{bmatrix} 1 & 0 \\ -K_{xgi}x_2 & -K_{xgi}x_1 \end{bmatrix} \begin{bmatrix} f_1(x) \\ f_2(x) + u \end{bmatrix} \\ &= \begin{bmatrix} 1 & 0 \\ -K_{xgi}x_2 & -K_{xgi}x_1 \end{bmatrix} \begin{bmatrix} z_2 \\ -K_{xi}x_2 + \frac{T_{iGmax}}{V_I} h(x_1) + u \end{bmatrix}, \end{aligned} \tag{17}$$

from which one gets

$$\begin{cases} \dot{z}_1 = z_2, \\ \dot{z}_2 = -K_{xgi}x_2\Big(-K_{xgi}x_1x_2 + \frac{T_{gh}}{V_G}\Big) + K_{xgi}x_1\Big(K_{xi}x_2 - \frac{T_{iGmax}}{V_I}h(x_1)\Big) - K_{xgi}x_1u. \end{cases} \tag{18}$$

By imposing $\dot{z}_2 := v$, we get the linearizing feedback as

$$u = K_{xi}x_2 - \frac{T_{iGmax}}{V_I}h(x_1) - \frac{v + K_{xgi}x_2(-K_{xgi}x_1x_2 + \frac{T_{gh}}{V_G})}{K_{xgi}x_1} \tag{19}$$

which is computable for positive values of the glycemia x_1, consistently with the fact that in those cases the Jacobian matrix $Q(x)$ in (14) is non-singular.

The reference signal for the glucose is chosen as

$$y_{ref}(t) = G_{ref}(t) = G_d + (G_b - G_d)e^{-\lambda t},$$

with $\lambda > 0$, which aims at driving the basal glycemia G_b of a subject to a desired value G_d. By setting

$$z_{ref} = \begin{bmatrix} z_{1,ref} \\ z_{2,ref} \end{bmatrix} := \begin{bmatrix} y_{ref} \\ \dot{y}_{ref} \end{bmatrix},$$

one easily obtains

$$\dot{z}_{ref}(t) = \begin{bmatrix} \dot{z}_{1,ref}(t) \\ \dot{z}_{2,ref}(t) \end{bmatrix} = \begin{bmatrix} z_{2,ref}(t) \\ \dot{z}_{2,ref}(t) \end{bmatrix} = \begin{bmatrix} -\lambda(G_b - G_d)e^{-\lambda t} \\ \lambda^2(G_b - G_d)e^{-\lambda t} \end{bmatrix}.$$

The error dynamics $e := z - z_{ref}$ is

$$\dot{e} = \begin{bmatrix} \dot{z}_1 - \dot{z}_{1,ref} \\ \dot{z}_2 - \dot{z}_{2,ref} \end{bmatrix} = \begin{bmatrix} z_2 - z_{2,ref} \\ v - \dot{z}_{2,ref} \end{bmatrix} = Ae + B(v - \dot{z}_{2,ref}).$$

We finally impose

$$v = He + \dot{z}_{2,ref} \tag{20}$$

to obtain the convergence to zero of the linearized error dynamics, where $H = \begin{bmatrix} -\lambda_3\lambda_4 \\ (\lambda_3 + \lambda_4) \end{bmatrix}^T$ assigns the eigenvalues $\lambda_3 < 0$, $\lambda_4 < 0$ of matrix $(A + BH)$.

As discussed at the end of Section 2, in the spirit of separation principle, we restate the control law in (19)–(20) in terms of a feedback from the reconstructed state, which leads to the following continuous control law

$$u = \max\left\{0, K_{xi}\hat{x}_2 - \frac{T_{iGmax}}{V_I}h(\hat{x}_1) - \frac{H(\hat{z} - z_{ref}) + \dot{z}_{2,ref} + K_{xgi}\hat{x}_2(-K_{xgi}\hat{x}_1\hat{x}_2 + \frac{T_{gh}}{V_G})}{K_{xgi}\hat{x}_1}\right\} \tag{21}$$

where $\hat{z} := \begin{bmatrix} \hat{x}_1 \\ f_1(\hat{x}) \end{bmatrix}$, and $\hat{x} = \begin{bmatrix} \hat{x}_1 \\ \hat{x}_2 \end{bmatrix} = \begin{bmatrix} \hat{G} \\ \hat{I} \end{bmatrix}$ is the observer output in (16). Note that in (21) we explicitly prevent the possibility of a negative exogenous insulin rate.

5 In-silico evaluation

We here evaluate the performance of the algorithm developed in the previous sections in a non-ideal experimental setting. We start from the data coming from 3 healthy subjects, whose glucose and insulin samples are a subset of the data collected in [6]. Such patients underwent an Intra-Venous Glucose Tolerance Test (IVGTT), which is a perturbation experiment consisting in administering intra-venously

Parameter	Patient 1	Patient 2	Patient 3
G_b	8.96	8.78	8.44
I_b	27.82	24.04	7.04
K_{xgi}	$7.45 \cdot 10^{-5}$	$9.96 \cdot 10^{-5}$	$5.39 \cdot 10^{-5}$
T_{gh}	0.0025	0.0027	0.0003
V_G	0.13	0.13	0.10
K_{xi}	0.10	0.06	0.25
T_{iGmax}	1.39	0.75	0.94
V_I	0.24	0.25	0.25
γ	2.30	2.52	1.52
G^*	9	9	9

Table 1
Numerical values of the model parameters (in the respective units of measurement) for the 3 patients considered.

a glucose bolus after an overnight fasting period and then sampling plasma glucose and serum insulin concentration during the following 3 hours, with varying sampling time. IVGTT is also considered among the most affordable and commonly used perturbation procedures used to estimate insulin sensitivity. Glucose and insulin measurements from this experiment are used to identify the parameters of the ODE model (11), which is coincident with the DDE model in [6], [7] in the particular case $\tau_g = 0$. In fact, as already mentioned at the beginning of Section 3, we consider the subjects for which the delay in the glucose action on pancreatic IDR is negligible, since the sample-based observer illustrated in Section 2 follows the approach in [17] and, unfortunately, there are no theoretical results on such a method applied to systems with state delays.

After the preliminary identification, since the considered subjects are not diabetic (but some of them are pre-diabetic), we consider a perturbation of the parameters that simulates a natural progression of the disease towards diabetes (see also [8]). In particular, we reduced the insulin resistance (up to values $K_{xgi} < 10^4$) as well as the pancreatic glucose sensitivity T_{iGmax}, and then recomputed consistently (via the algebraic steady-state conditions obtained from the model in Eq. (11)) some of the other parameters, in particular the basal values of glycemia G_b and insulinemia I_b, which constitute the equilibria of (11) in absence of exogenous insulin administration ($u = 0$):

$$\begin{cases} K_{xgi} V_G G_b I_b &= T_{gh}, \\ K_{xi} V_I I_b &= T_{iGmax} h\big(G_b\big). \end{cases}$$

The values of the parameters for the three individuals are summarized in Table 1. In the spirit of *personalized medicine*, the parameters of each model are assumed to be known (up to some uncertainty) in the design of the artificial pancreas *tailored* to the particular subject.

On top of the assumptions considered so far, we build a more realistic simulation setup by imposing a quantization error both in the sampling and in the actuation,

accounting for the processes of analog-to-digital and digital-to-analog conversion in digital devices. We consider a quantization step of 0.1 mM for the glycemia measurements and $20pM/min$ for the exogenous Insulin Delivery Rate (IDR). As a consequence, the observer-based controller is initialized with quantization errors.

Regarding the sampling time of the glucose measurements, we impose a constant sampling time $t_{i+1} - t_i = \Delta$, for all i. So we can write more simply $t_i = i \cdot \Delta$, with $\Delta = 5$ [min]. This choice is consistent with many Continuous-Glucose-Monitoring (CGM) devices currently on the market [21]. We assume that each control sample is held for the same interval.

Simulations have been carried out by designing the AP for each of the three subjects, but considering an additional random uncertainty (up to $\pm 5\%$) with respect to the correct model parameters in Table 1. The observer gain K in (4) and the control gain H in (21) are set to obtain the same closed-loop eigenvalues for all patients: $\lambda_1 = -0.8$, $\lambda_2 = -1.6$, $\lambda_3 = -1$, $\lambda_4 = -0.5$. The parameter η in (16) is set equal to 5, the target glycemia is equal to $G_d = 5$ mM, the decay rate is $\lambda = 1/30$.

The results are shown in Figures 1–2 in terms of glucose-insulin behavior, glucose percent error and IDR input. We note that the glucose trajectory (Fig. 1, top panel) monotonically decreases towards the target value G_d, which is approached in the three subjects within the considered time horizon of 3 hours. Correspondingly, the insulinemia trajectory (Fig. 1, bottom panel) shows an initial peak (exceeding 150 pM for the three patients), to then recover towards levels below the 50-pM value. Higher values of insulinemia (patient 3) correspond to higher exogenous insulin infusions (Fig. 2, bottom panel). In spite of the different parameters and initial conditions, the error falls below 10% (with respect to the target glycemia G_d) within about 1 hour for all the patients (Fig. 2, top panel), due to the common choice of the closed-loop eigenvalues.

6 Discussion and further work

In this work, we addressed a glucose control problem with incomplete/inaccurate information, in the direction of the development of the so-called Artificial Pancreas. Starting from a compact ODE model, well representing the dynamic behavior of the glucose-insulin system in the individuals showing a negligible delay in the pancreatic second-phase insulin secretion, we first designed an observer reconstructing the full glucose-insulin dynamics from sparse glucose samples. Then, the loop was closed by designing a feedback control law in terms of exogenous insulin delivery (based on the reconstructed state), with the goal of tracking a desired behavior of glycemia. A preliminary in-silico evaluation of the proposed methods has been performed on virtual patients whose parameters have been computed starting from real data, in a non-ideal simulation setting including quantization and parameter variations. The obtained results show that the approach can constitute a promising tool for studying the Artificial Pancreas in more realistic scenarios. In view of this goal, future research effort will be devoted to the validation of the techniques illustrated in this paper in the context of more comprehensive models (such as [14]), to better

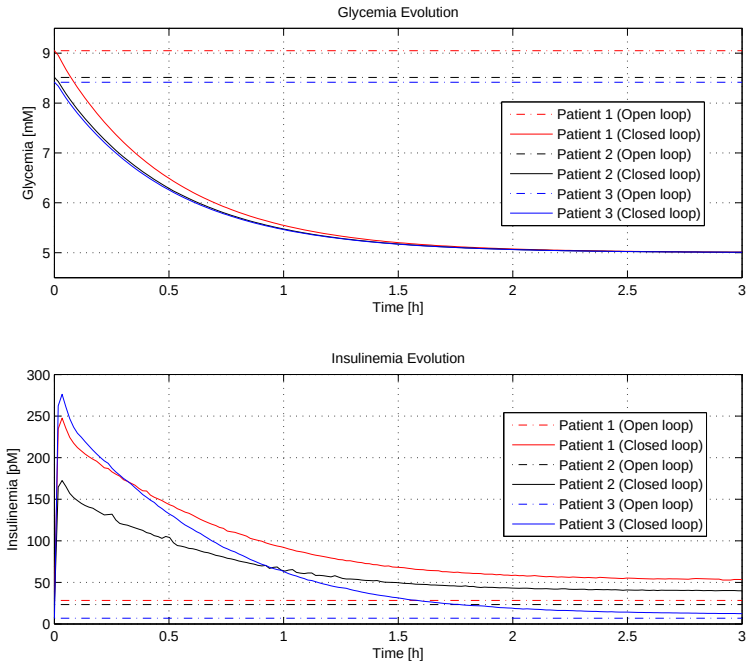

Figure 1
Time course of glucose concentration (top panel) and insulin concentration (bottom panel) for the 3 virtual patients considered. The dash-dotted lines represent the basal values of glycemia and insulinemia, while the solid lines are obtained by closing the loop by means of the Artificial Pancreas.

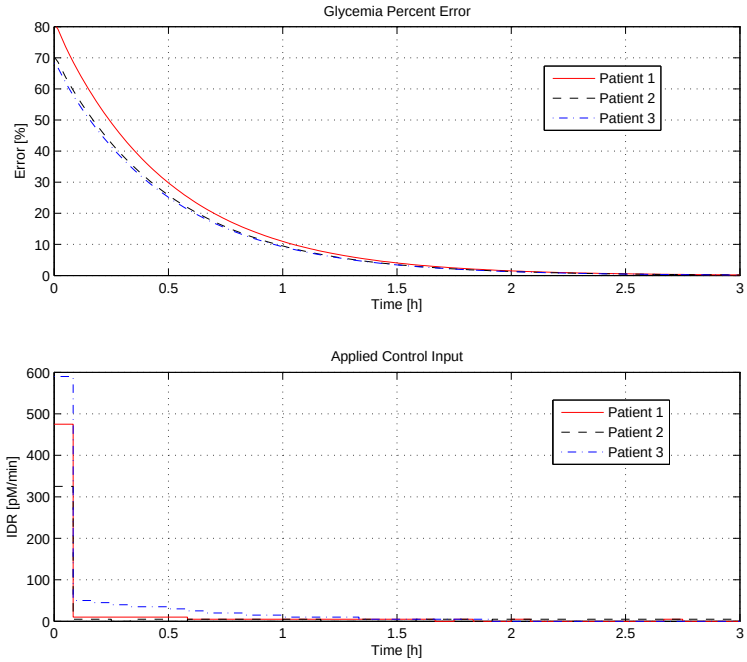

Figure 2
Glycemia percent error (top panel) and applied control input in terms of exogenous Insulin Delivery Rate (bottom panel) for the 3 virtual patients considered.

understand the way a real patient would react to the proposed treatment. In addition, formal extensions of the observer-based control to the more general cases of state delays and quantized inputs and outputs are under investigation.

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