Luenberger-like Observers for Nonlinear Time-Delay Systems with Application to the Artificial Pancreas

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Analysis and control of time-delay systems has gained increasing interest in the last decades, due to the effectiveness of delay-differential equations in modeling a wide range of physical and engineering frameworks, such as ecological systems, industrial processes, telerobotic systems, earth controlled satellite devices and biomedical engineering. A further great impulse has been recently given by networked and distributed control, which may naturally induce non-negligible and possibly time-varying delays in the input/output channels. As in the case of systems described by ordinary differential equations, a crucial point in most advanced control approaches, such as optimal and robust control, is the possibility to solve the so-called *observer problem*, that is the design of algorithms that provide full information on the state of the system by real-time processing of few measurements. The reader can refer to the recent edited book on nonlinear delay systems and references therein [1].

Nonlinear time-delay systems are characterized by the presence of one or multiple delays in the input, state, or measurement equations. In particular, delays in the state equations occur in the modeling of many physical systems, whereas output delays account for both actual measurement lags and sampled observations. In the first part of this article, the most important results in the area of observers for nonlinear systems with state and output delays are reviewed. Although this topic has been extensively investigated in the literature, from both a theoretical and a practical perspective (see the papers [19]–[25] and [28]–[32]), only the most important results provided by the authors in the last 20 years are reported here, based on the so-called *Luenberger-like* observers, in praise of Luenberger seminal work [2]. The delay free case was originally proposed in [3], [4] and it has been subsequently extended to the case of large constant output delays [5], bounded [6] or unbounded [7] time-varying output delays, and also to systems with state delays [8], [9].

Tools based on differential geometry, as developed in [10], [11], are widely exploited, and it is also considered the control problem of using the real-time estimates provided by the observer to implement a control law, which is common in the applications.

The second half of the work is devoted to investigate the applicability of the proposed observer results to a time-delay model of the glucose-insulin system, within the framework of the Artificial Pancreas (AP), a term referring to the set of glucose control strategies required for diabetic people and delivered by means of exogenous insulin administration, usually via subcutaneous or intravenous infusions. From a control engineering perspective, real-time predictions of both glucose and insulin blood concentrations (glycemia and insulinemia, respectively) are of great importance for the AP, since they could be required in closed-loop algorithms whenever the complete knowledge of the state of the system is needed to implement the control law. Differently from insulinemia, plasma glucose measurements are currently affordable with relatively low cost devices and effective algorithms, thus the control problem of designing suitable closed-loop regulators by means of only glucose measurements is well posed, and the use of a state observer to compensate for the lack of direct insulin measurements deserves interest in the AP community [14].

As shown in [12], [13], Delay-Differential Equations (DDE) provide a better representation of the pancreatic insulin delivery rate, with respect to Ordinary Differential Equations (ODE), both for healthy subjects and for patients affected by Type 1 or Type 2 Diabetes Mellitus (denoted T1DM and T2DM patients, respectively, throughout the paper). In [17] and [18] effective observer-based glucose control strategies have been developed using DDE models for both T1DM and T2DM patients.

The aim of this paper is to show the good performances of the state-observer applied to a DDE model of the glucose-insulin system recently exploited in the AP framework. Validation is carried out on the ground of real clinical measurements available from 20 healthy subjects who underwent an Intra-Venous Glucose Tolerance Test (IVGTT). Results show that the observer behavior is robust with respect to the initial conditions, that have been set according to a pair of very critical cases of under- and over-estimation. Also the robustness of the observer with respect to some model parameters, such as the delay in the pancreatic insulin production, is discussed.

Like most of clinical/medical applications, the AP usually faces the problem of dealing with continuous-time models and discrete-time measurements, whose sampling rate depends on the device used. It is shown that a state-observer for systems with output delays can be effectively used in this case, by exploiting the artifice of modeling the discrete-time measurements as a continuous output affected by a piecewise-linear time-varying delay.

This note is ideally divided in 2 parts. The first part is devoted to review most important results on Luenberger-like observers over the last 20 years: besides a preliminary Section involving delayless nonlinear systems, the following two Sections deal with the extension of the observers theory to nonlinear systems with state or output delays. The second part is inspired by recent results in the application of observer-based control laws in the AP biomedical applications, and aims at evaluating the efficacy of the Luenberger-like observers if applied to DDE models of the glucose-insulin system. Validation is carried out on the ground of real clinical measurements available from 20 healthy subjects who underwent an IVGTT.

A Luenberger-like observer for nonlinear systems

In this section the Luenberger-like observer proposed in [3] for single-input-single-output (SISO) delayless systems is presented as a starting point for the development of observers for multi-input-multi-output systems (MIMO) [4], and of observers for delay systems [8], [9] or for systems with delayed measurements [5],[6],[7]. The presentation has been limited to the SISO case in order to have simpler notations. Indeed, the required notations (additional subscripts and block structure of vectors and matrices involved), necessary for the presentation of the results for the MIMO case, is rather complicated and may distract the reader from the essential concepts (see “Observer for MIMO systems”).

Consider a smooth nonlinear system described by the equations

$$\dot{x}(t) = f(x(t)) + g(x(t))u(t), \qquad x(0) = x_0, \tag{1}$$

$$y(t) = h(x(t)), \qquad t \geq 0, \tag{2}$$

where $x(t) \in I\!R^n$ is the state, $u(t) \in I\!R$ is the input function , $y(t) \in I\!R$ is the measured output,

$x_0 \in I\!\!R^n$ is the initial state. $g(x)$ and $f(x)$ are C^∞ vector fields and $h(x)$ is a C^∞ function. The term $f(x)$ of the differential equation (1) that governs the state transition when $u(t) \equiv 0$ is called is called *drift*.

The problem of asymptotic state observation consists in finding a causal system, denoted asymptotic observer, that, when driven by the pair $(u(t), y(t))$, produces a vector variable $\hat{x}(t)$ (observed state) that asymptotically converges to the state $x(t)$, that is $\|x(t) - \hat{x}(t)\| \to 0$.

For the theoretical definition of the state-observability property of a system (1)–(2) and for the construction of an asymptotic state-observer, a square map $\phi : I\!\!R^n \to I\!\!R^n$, denoted *drift-observability map*, is needed. Such map is constructed by stacking the first n Lie derivatives (from 0 to $n-1$) of the output function $h(x)$ along the drift vector field $f(x)$:

$$\phi(x) \triangleq \begin{bmatrix} h(x) \\ L_f h(x) \\ \cdots \\ L_f^{n-1} h(x) \end{bmatrix}. \tag{3}$$

For more details on Lie derivatives and their use see “Lie-derivatives, relative degree, and observability”.

Denoting with Y_n the vector of the first n output derivatives (from 0 to $n-1$) of system (1)–(2)

$$Y_n(t) = \left[\; y(t) \;\; \dot{y}(t) \;\; \ldots \;\; y^{(n-1)}(t) \;\right]^T, \tag{4}$$

it is easy to verify by means of the chain rule that, when $u(t) \equiv 0$,

$$Y_n(t) = \phi\big(x(t)\big). \tag{5}$$

Thus, if the map $Y_n = \phi(x)$ is invertible, then the computation of the state $x(t)$ as a function of the output $y(t)$ and of its first $n-1$ derivatives is *theoretically* possible as a simple map inversion: $x(t) = \phi^{-1}(Y_n(t))$. This property justifies the following definition.

Definition 1: If the drift-observability map $\phi(x)$ is a diffeomorphism from an open set $\Omega \subseteq I\!R^n$ in $\phi(\Omega)$, then the system (1)–(2) is said to be *drift-observable* in Ω. If $\Omega \equiv I\!R^n$, then the system (1)–(2) is said to be *globally drift-observable*.

Note that the formula $x(t) = \phi^{-1}(Y_n(t))$ cannot be used in practice for the state reconstruction from measurements, even in the case $u(t) \equiv 0$, because only the first component of $Y_n(t)$ is the available output measurement and, in addition, in most cases nonlinear maps do not have a closed form inverse $\phi^{-1}(\cdot)$.

A consequence of the drift-observability property of Definition 1 is that the Jacobian of the map $z = \phi(x)$, denoted $Q(x)$ and defined as

$$Q(x) \triangleq \frac{d\phi(x)}{dx}, \tag{6}$$

is nonsingular in Ω, and the inverse map of $z = \phi(x)$ exists in $\phi(\Omega)$. Even if the inverse map is not known in closed form, its Jacobian can be easily computed at $z = \phi(x)$ as

$$\left.\frac{d\phi^{-1}(z)}{dz}\right|_{z=\phi(x)} = Q^{-1}(x). \tag{7}$$

Definition 2: A system is said to be *Uniformly Lipschitz Drift-Observable* (ULDO) in a set $\Omega \subseteq I\!R^n$ if it is drift-observable in Ω and the maps $\phi(\cdot)$ and $\phi^{-1}(\cdot)$ are uniformly Lipschitz in Ω and $\phi(\Omega)$, respectively. If $\Omega \equiv I\!R^n$ the system is said *Globally Uniformly Lipschitz Drift-Observable* (GULDO).

When a nonzero input $u(t)$ is present in (1)–(2), it is useful to define U_σ, the vector of the first σ time-derivatives of the input (from 0 to $\sigma - 1$), when existing:

$$U_\sigma \triangleq \left[u \ \dot{u} \ \ldots \ u^{(\sigma-1)} \ \right]^T. \tag{8}$$

It can be easily proven that taking $\sigma = n - r$, where r is the relative degree of system (1)–(2) (see "Lie-derivatives, relative degree, and observability") a vector function $\Psi(x, U_\sigma)$ exists such that

$$Y_n(t) = \phi\big(x(t)\big) + \Psi\big(x(t), U_\sigma(t)\big), \tag{9}$$

with the property $\Psi(x, 0) = 0$ for any $x \in I\!R^n$. In general, the drift-observability of the system (1)–(2) does not imply that (9) can be solved for $x(t)$, because the invertibility of (9) for x may depend on the input, through the vector U_σ. However, when $r = n$, that implies $\sigma = 0$, then $\Psi \equiv 0$ (see "Canonical Observable form of systems" for details) and drift-observability is sufficient to guarantee state reconstructability for any bounded input.

The Luenberger-like observer proposed in [3] is the following dynamic system

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + g(\hat{x}(t))u(t) + Q^{-1}(\hat{x}(t))K\Big(y(t) - h(\hat{x}(t))\Big). \tag{10}$$

(10) is said to be a global exponential observer for the system (1)–(2) if, for some gain vector K there exist $\mu > 0$ and $\alpha > 0$ such that

$$\|x(t) - \hat{x}(t)\| \leq \mu\, e^{-\alpha t} \|x(0) - \hat{x}(0)\|, \tag{11}$$

for any $x(0)$ and $\hat{x}(0)$ in $I\!R^n$ and input u in some class $\mathcal{U}$ (as it will be seen below, some conditions on the input must be satisfied in order to have global exponential convergence).

The following theorem merges the results in [3] with those of [4]:

Theorem 1: For the system (1)–(2) assume that the following hypotheses hold:

1) The system is GULDO (see Definition 2) (γ_ϕ and $\gamma_{\phi^{-1}}$ denote the Lipschitz coefficients of ϕ and ϕ^{-1}, respectively);
2) the functions $\overline{H}(z)$ and $\overline{\Gamma}(z)$ defined in (S11), are uniformly Lipschitz in $I\!R^n$, with Lipschitz coefficients $\gamma_{\overline{H}}$ and $\gamma_{\overline{\Gamma}}$ respectively;
3) there exists a uniform bound $u_M > 0$ on the input function: $|u(t)| \leq u_M$, $\forall t \geq 0$.

Then, the following statements are true:

- if $r = n$ (full relative degree), then *for any* given bound u_M on the input function and *for any* chosen $\alpha > 0$ *there exists* a gain vector $K \in I\!R^n$ such that (11) holds true for some $\mu > 0$;

- if $r < n$ (non-full relative degree), then *for any* chosen $\alpha > 0$ *there exist* a bound $u_M > 0$ on the input function, and a gain vector $K \in I\!R^n$ such that (11) holds true for some $\mu > 0$.

Note that in the case of $r = n$ the bound u_M on the input can be any, that means arbitrarily large, and the choice of the gain vector K that ensures converence strongly depends on the size of u_M. On the contrary, when $r < n$ the convergence of the observation error to zero at the desired rate α can be achieved only if the bound u_M is sufficiently small.

The proof of Theorem 1, available in [4], takes advantage of the form of the observer equation after the change of coordinates $z = \phi(x)$, that is the form (S14). From this, together with the system representation (S10), the error dynamics in z-coordinates ($e_z = z - \hat{z}$) is obtained

$$\dot{e}_z(t) = (A - KC)e_z(t) + B\left(\overline{\Gamma}\big(z(t)\big) - \overline{\Gamma}\big(\hat{z}(t)\big)\right) + F_r\left(\overline{H}\big(z(t)\big) - \overline{H}\big(\hat{z}(t)\big)\right)u(t), \qquad (12)$$

which is a linear system with nonlinear Lipschitz perturbations. The convergence proof consists in showing that for any given α, an observer gain K can be found such to guarantee the exponential convergence of $e_z(t)$ in spite of the Lipschitz perturbations.

Remark 1: The constant μ in (11) depends on the bound u_M on the input function, on the desired exponential rate α and on the Lipschitz constants $\gamma_\phi, \gamma_{\phi^{-1}}, \gamma_{\overline{H}}, \gamma_{\overline{\Gamma}}$.

Remark 2: The GULDO and the *global* uniformly Lipschitz assumption for the functions $\bar{\Gamma}$ and $\overline{H}$ in many applications is too strong and not necessary. When the ULDO and the uniform Lipschitz property for $\bar{\Gamma}$ and $\overline{H}$ are verified only *locally*, that means in bounded subsets of $I\!R^n$, semiglobal convergence results can be proved for the observer (10) under the additional assumption of Bounded-Input Bounded-State (BIBS) stability of system (1)–(2). To be more specific, if for any open bounded set $\Omega \subset I\!R^n$, where the state of a BIBS system is confined (invariant set), a gain K can be found that ensures the convergence to zero of the observation error, then (10) is called a *semiglobal observer*. For further details see [4], where the semiglobal version of Theorem 1 is reported.

Luenberger-like observers for nonlinear systems with state delays

It is a fact that the state space of systems with delays involving the internal variables has infinite dimension, and this leads to difficulties not only in the system analysis and in the synthesis of controllers and/or observers, but also on their physical implementation. In the case of linear delay systems, the state observation problem has been extensively studied (see, for instance, [20], [21], [22], [23] and the references therein). Further difficulties arise in dealing with nonlinear time-delay systems, due to the nonlinear differential description of the dynamics, in an infinite dimensional space. The observation problem in the nonlinear case has been addressed for classes of systems and with different approaches in [24], [8], [9],[25], [28], [29], [30], [31], [32]. In this section the results in [9], based on tools of differential geometry, are briefly summarized, providing nonlinear observer algorithms for a significant class of nonlinear time-delay systems. The observer in [9] has been successfully used in artificial pancreas and other general glucose control frameworks, such as the clinical experiment of CLAMP (see [17], [18]).

An observer for a class of nonlinear systems affected by multiple discrete and distributed delays

Consider the following system

$$\begin{aligned} \dot{x}(t) &= f(x(t)) + g(x(t)) \cdot p(x_t, u(t)), \\ y(t) &= h(x(t)), \qquad t \geq 0, \quad x_t(\tau) = x(t+\tau), \tau \in [-\Delta, 0], \end{aligned} \tag{13}$$

where $x, u, f, g,$ and h are as in (1)–(2), $x_t \in PC([-\Delta, 0]; I\!R^n)$ (here PC denotes the set of bounded, piecewise continuous functions), $\Delta > 0$ is the maximum delay, p is a functional from $PC([-\Delta, 0]; I\!R^n) \times I\!R$ to $I\!R$, and the initial conditions $x_0 \in PC([-\Delta, 0]; I\!R^n)$.

Assumption 1: The triple (f, g, h) has full observation relative degree (see Definition 3) in all $I\!R^n$, and the map (3) $z = \phi(x)$ is a diffeomorphism in $I\!R^n$.

Considering the vector $Y_n(t)$ of output derivatives defined in (4) and the drift-observability map defined in (3), let

$$z(t) = Y_n(t), \; t \geq 0, \qquad z(\tau) = \phi(x_0(\tau)), \quad \tau \in [-\Delta, 0]. \tag{14}$$

Following the same steps that led to (S10), and noting that in the case of full relative degree $F_n = B$, the system (13) can be rewritten as

$$\begin{aligned} &\dot{z}(t) = Az(t) + B\big(\bar{\Gamma}(z(t)) + \overline{H}(z(t))p(\Phi^{-1}(z_t), u(t))\big), \\ &y(t) = Cz(t), \qquad\qquad t \geq 0, \\ &z(\tau) = \phi(x_0(\tau)), \quad \tau \in [-\Delta, 0], \end{aligned} \tag{15}$$

where: $z_t : [-\Delta, 0] \to R^n$ is defined as $z_t(\tau) = z(t+\tau),\ \tau \in [-\Delta, 0],\ t \geq 0$; (A, B, C) have the Brunowsky canonical form (S5), the maps Φ and Φ^{-1} from $PC([-\Delta, 0]; I\!R^n)$ to itself are defined as

$$\begin{aligned} &\Phi(\psi)(\tau) = \phi(\psi(\tau)), \\ &\Phi^{-1}(\psi)(\tau) = \phi^{-1}(\psi(\tau)), \end{aligned} \qquad \psi \in PC([-\Delta, 0]; I\!R^n), \qquad \tau \in [-\Delta, 0]. \tag{16}$$

Note that by the Assumption 1 the Jacobian Q defined in (6) is invertible in all $I\!R^n$.

The observer presented in [9] for nonlinear delay systems with structure (13) is the following

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + g(\hat{x}(t)) \cdot p(\hat{x}_t, u(t)) + Q^{-1}(\hat{x}(t))K(y(t) - h(\hat{x}(t)), \qquad t \geq 0, \tag{17}$$

with initial conditions $\hat{x}_0 \in PC([-\Delta, 0]; I\!R^n)$. As usual, $\hat{x}_t(\tau) = \hat{x}(t+\tau)$, $\tau \in [-\Delta, 0]$.

Theorem 2: Let the system (13) satisfy the Assumption 1, and suppose there exists u_M such that $|u(t)| \leq u_M$ $\forall t \geq 0$. Moreover assume the following Lipschitz hypotheses:

H1) there exist positive constants $\gamma_1, \gamma_2, \gamma_3$ such that, for all $v_1,\ v_2 \in I\!R^n$ and for all $\psi_1, \psi_2 \in PC([-\Delta, 0]; I\!R^n)$,

$$|\bar{\Gamma}(v_1) - \bar{\Gamma}(v_2)| \leq \gamma_1 \|v_1 - v_2\|, \tag{18}$$

$$\sup_{\|u\| \leq u_M} |\overline{H}(v_1)\, p(\Phi^{-1}(\psi_1), u) - \overline{H}(v_2)\, p(\Phi^{-1}(\psi_2), u)| \leq \gamma_2 \|v_1 - v_2\| + \gamma_3 \|\psi_1 - \psi_2\|_\infty; \tag{19}$$

H2) the maps $\phi(\cdot)$ and $\phi^{-1}(\cdot)$ are Lipschitz in all $I\!R^n$ with Lipschitz constants γ_ϕ and $\gamma_{\phi^{-1}}$.

Then, given any $\alpha > 0$, there exists a gain K for the observer (17), such that

$$\|x(t) - \hat{x}(t)\| \leq e^{-\alpha t}\, \gamma_\phi \gamma_{\phi^{-1}} \|V^{-1}(\lambda)\| \|V(\lambda)\| \|x_0 - \hat{x}_0\|_\infty, \tag{20}$$

where λ is the set of distinct eigenvalues of $A - KC$, and $V(\lambda)$ is the Vandermonde Matrix (S13).

The proof of this Theorem can be found in [9].

Remark 3: As in the case of observer for delay-free systems of the previous section, if the Lipschitz conditions do not hold globally, then semiglobal convergence can be proved by assuming BIBS stability of the system. The relevant convergence Theorem can be found in [9].

Remark 4: As far as the selection of the gain vector $K \in I\!R^n$ is concerned, a longstanding experience on many practical systems including chemical reactors, electrical machines and biological systems, suggests to simply make the choice on the basis of trials by simulations on the system at hand, always guaranteeing the Hurwitz property of the matrix $A - KC$ (see (S5)). A mathematical procedure for the selection of the gain vector K which guarantees the result of Theorem 2 is given below, inspired by the convergence proof reported in [9], on the basis of results provided in [3]. For a given positive real ρ, let $\lambda(\rho) = [-\rho \quad -\rho^2 \quad \cdots \quad -\rho^n]^T$ be a parametrized set of eigenvalues. Then, it is easily proved that, for a chosen converge rate α, there exists $\rho^* > 0$ such that the following inequality holds

$$\sqrt{n}\gamma \left(1 + e^{\alpha\Delta}\right) \|V^{-1}(\lambda(\rho))\| \leq \rho - \alpha, \quad \forall \rho \geq \rho^*, \tag{21}$$

where $\gamma = \max\{\gamma_1 + \gamma_2, \gamma_3\}$. This results holds simply because $\lim_{\rho\to+\infty} \|V^{-1}(\lambda(\rho))\| = 1$ (see

[3]). Then, a gain K that guarantees the convergence (20) of Theorem 2 is any one that assigns the eigenvalues $\lambda(\overline{\rho})$ to the matrix $A - KC$, with $\overline{\rho} \geq \rho^*$. Note that in practical applications it can be difficult to evaluate the coefficient γ in (21). However, the structure of the eigenvalues set $\lambda(\rho)$ gives a precise guideline for the choice of eigenvalues by performing trials by means of computer simulations, gradually increasing ρ until the convergence is reached. Other procedures of gain selection, including one similar to the procedure described above, also based on Linear Matrix Inequalities, are discussed in [17] for the construction of a local observer-based controller for the glucose-insulin system.

A Luenberger-like observer for nonlinear systems with delayed measurements

The problem of state estimation when output measurements are available after some delay arises frequently in engineering applications, for example when the system is controlled or monitored by a remote device through a communication channel, or when the measurement process intrinsically causes a non negligible time delay, for example in biochemical reactors. Time-varying delays in the output are a tool to model also other situations occurring in the measurement process, such as sampling, buffering, and data loss (see "Modeling the measurements through time-varying delays") For this reason the issue of state reconstruction in the presence of output time-delays has been widely investigated in recent years.

A nonlinear system affine in the input and affected by output delays is represented as

$$\dot{x}(t) = f(x(t)) + g(x)u(t), \quad t \geq 0, \quad x(0) = \bar{x} \in I\!R^n, \tag{22}$$

$$y(t) = h(x(t - \delta(t))), \quad t \geq \Delta, \tag{23}$$

where x, u, f, g, h are as in (1)–(2), $y(t)$ is the scalar measurement available at time t, and $\delta(t) \in [0, \Delta]$ is the known time-varying measurement delay of the output. System (22) is an ordinary finite-dimensional system without delay, but the corresponding observer contains $y(t)$ that refers to a past state value. Consequently, the dynamics of the observer and of the estimation error is ruled by a DDE.

The Luenberger-like observer for (22) must rely on past observations in the correction term and it is defined for $t \geq \delta$ by

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + g(\hat{x}(t))u(t) + Q^{-1}(\hat{x}(t))K(\delta(t))\big\{y(t) - h(\hat{x}(t-\delta(t)))\big\}, \tag{24}$$

$$\hat{x}(\tau) = \phi(\tau), \qquad \tau \in [0,\, \Delta], \tag{25}$$

$$K(\delta(t)) = e^{-\eta\delta(t)}K_0. \tag{26}$$

where K_0 is chosen as in the delay-free case to assign eigenvalues to $(A - K_0C)$, and $\eta > 0$ is a further design parameter, whose function is to give more weight to recent measurements than to the old ones. Note that when $\delta(t) = 0$, (24) reduces to the Luenberger-like observer (10) for the delay-free case.

The introduction of a delay-dependent gain guarantees, under the same hypotheses of the delay-free case, the exponential convergence to 0 with rate η of the estimation error when the output delays are time-varying [7].

Theorem 3: Consider system (22)-(23), with $\delta(t) \in [0, \Delta]$, under the same assumptions of Theorem 1. Then, for any assigned $\eta > 0$, there exists K_0 and a positive $\bar{\Delta}$ such that, if $\Delta < \bar{\Delta}$, then (24)–(26) is a global exponential observer for system (22)-(23) such that η is the decay rate of the estimation error (that is, eq. (11) is verified for some $\mu > 0$ and $\alpha = \eta$).

Remark 5: When the Lipschitz Assumptions of Theorem 1 are locally satisfied, and the system is BIBS stable, so that open invariant sets Ω exists when the input u is bounded, on which the drift-observability map is invertible, semiglobal convergence results can be proved, as explained in Remark 2 for the case of delayless output [7].

It is worth noting that Theorem 3 states sufficient conditions for the convergence of the observer (24)–(26) that depend only on the bound of the delay. No other restrictions are placed over the delay function $\delta(t)$, that can be non-differentiable or even discontinuous. Consequently, the observer (24) can be used also in the case of sampled measurements, as long as the sampling interval is less than $\bar{\Delta}$, because sampled measurements can be easily modeled using a discontinuous time-varying delay $\delta(t)$ (piecewice linear function of t). The bound $\bar{\Delta}$ in Theorem 3 depends on the Lipschitz constants of system (22) and on the desired convergence rate η. In the general case, this dependency is complicated to express but it can nevertheless be approximated to derive sufficient conditions for the delay bound [7]. Roughly speaking, the gain K_0, as in the delay-free case, should be large enough to overcome the system nonlinearities, represented by the Lipschitz constants, and to achieve the desired convergence rate η. On the other hand a large gain K_0 reduces the maximal delay $\bar{\Delta}$, because K_0 multiplies delayed error terms, and the result is likely to destabilize the error system if the gain is too high and the delay too large. This explains why a gain K_0 too high reduces the maximal delay $\bar{\Delta}$. The delay dependent coefficient $e^{-\eta\delta(t)}$ is beneficial in expanding the maximum delay $\bar{\Delta}$, but can not manage delays of any size.

When the output delay exceeds the bound $\bar{\Delta}$ it is possible to resort to a cascade of observers (chain observer). The idea is to have an array of observers, each one in charge of a fraction of the total delay. This approach was originally pursued for constant delays [5], [19]. The extension to time-varying delays [7] is not trivial and requires additional hypotheses on the delay function $\delta(t)$. Many results about chain observers in the case of large time-varying delays can be found in [7].

Remark 6: All the variants of the Luenberger-like observer presented until this point for the different types of dynamic systems considered (without delays, with delays in the state variables or in the measurements, constant or time-varying delays) are strongly based on the knowledge of the dynamic model of the measured process. It can be said that the task of the observer is to compute in real-time a state trajectory that is in agreement with both the model and the measurements. The observability assumption on the system (invertibility of the observability map) ensures that there exists only one state trajectory that is in perfect agreement with a given output trajectory, and therefore the observer asymptotically returns the true state. From these considerations it is natural to ask what happens if the model used for the observer construction, denoted the *nominal model*, is different from the *true model*, that is the model that generates the measurements processed by the observer. In this case the task of the observer becomes the one of computing a state trajectory that is consistent with both the *nominal model* and the measurements. It is clear that the reconstructed state now is in agreement with the nominal model, and not with the true model. As a general qualitative rule, it can be said that the closer is the nominal model to the true model, the closer is the reconstructed state trajectory to the true state. As a consequence, a *good* observer constructed exploiting a *bad* model (that means significantly different from the true model) is expected to return a state trajectory significantly different from the true state.

Observers as real-time estimators for the Artificial Pancreas

The Artificial Pancreas (AP) refers to the set of glucose control strategies required for diabetic people and delivered by means of exogenous insulin administration, usually via subcutaneous or intravenous infusions. The increasing number of diabetic patients, along with the rising costs of care treatments, has gathered efforts from many diverse areas ranging from medicine to mathematical modeling of the glucose-insulin system, including computer science and control engineering, aiming at containing the disease and improving the wellness according to wearable and as little invasive as possible devices (see for instance [33] and references therein).

From a control engineering perspective, glucose and insulin real-time predictions are of great importance for the AP, since they could be required in closed-loop algorithms whenever the complete knowledge of the state of the system is needed to design the control law [14]. Differently from plasma glycemia, which can be straightforwardly measured with relatively low cost devices and affordable algorithms, plasma insulinemia is slower and more cumbersome to obtain, more expensive and also less accurate. This fact has stimulated the investigation of algorithms capable of providing in real-time the plasma insulin concentration by processing a stream of glycemia measurements, that with the current technology are available with a sampling period of 5min or less [33]. The importance of state-estimation algorithms is due to the great variety of observer-based control laws applicable, at least in theory, to the glucose control problem, with exogenous insulin administration playing the role of control input. Observer-based control laws belong to the field of *model-based* strategies, when the regulator is synthesized by explicitly exploiting the structure of the model equations. To this aim, small-scale *minimal models* are usually preferred since they allow to provide the analytical solution to the control problem under investigation

[37].

In this framework, the DDE minimal model exploited in [17] to track plasma glycemia down to a safe euglycemic level for a Type 2 diabetic patient is considered. It is a short-term glucose-insulin model, originally exploited to investigate Intra-Venous Glucose Tolerance Tests (IVGTT), see the sidebar “The IVGTT clinical protocol”. Its applicability to the Artificial Pancreas is clearly limited to a short time period, during which the only perturbation is provided by the exogenous insulin infusion (the control input): short-term models allow to investigate the transient of closed-loop glucose control strategies, pointing out criteria for safety and efficacy related to the feedback control [18].

Differently from Type 1 diabetic patients (they will be denoted by T1DM and T2DM shortly), for whom there is no endogenous insulin release at all, in T2DM exogenous insulin administration complements the endogenous insulin production, thus making unavoidable the modeling of the pancreatic Insulin Delivery Rate (IDR). This fact motivates the use of DDE models when seeking model-based glucose control laws applicable not only to T1DM, but also to T2DM (the great majority of people suffering from Diabetes Mellitus) as well as to healthy subjects undergoing clinical experiments where glucose control is presently manually regulated by a physician (this is the case of the Euglycemic Hyperinsulinemic Clamp, [34]). Indeed, DDE models have been shown to properly (and better than standard ODE models) account for irregularly varying pancreatic IDR (see for instance [12], [13] and references therein).

The DDE model here investigated has been employed in the recent literature to desgn a model-based glucose control law, which properly exploits insulin estimates achieved by means of a state observer for DDE nonlinear systems. Besides theoretical results highlighted in [17], the validity of the observer-based glucose control strategies has been recently evaluated by closing the loop on a population of virtual patients, generated by a different, “maximal”, multi-compartmental model accepted by the Food and Drug Administration (FDA) as an alternative to animal trials for the preclinical testing of control strategies in AP [18]. In [18] exogenous insulin was supposed to be administered intravenously, thus accounting for AP strategies directly applicable to problems of glycemia stabilization in critically ill subjects, such as in surgical Intensive Care Units after major procedures [35]. Analogous results have been also obtained for the Clamp experiment, [26], [27], with the same DDE model exploited in a completely different clinical framework. In both cases pancreatic IDR could not be neglected.

In the following, the performances of the observer for the aforementioned DDE model of the glucose-insulin system are analyzed and further evaluated in open-loop, on the ground of real measurements available from 20 healthy subjects who underwent an IVGTT. These data have already been acquired and used in [15] for a different purpose. The model equations are reported below, with $G(t)$, [mM], and $I(t)$, [pM], denoting plasma glycemia and insulinemia, respectively:

$$\begin{aligned} \frac{dG(t)}{dt} &= -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G}, \\ \frac{dI(t)}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}\xi\big(G(t-\tau_g)\big), \end{aligned} \tag{27}$$

where $\xi(\cdot)$ is a nonlinear map of the type

$$\xi(G) = \frac{(G/G^*)^\gamma}{1+(G/G^*)^\gamma}, \tag{28}$$

that models the endogenous pancreatic IDR. In [16] it has been proven that the system is invariant in $\mathbb{R}^2_+$, the open positive orthant of $\mathbb{R}^2$, that means that the time-evolution of glucose and insulin concentrations are proven to be greater than a strictly positive value for any positive initial condition (see the sidebar "DDE glucose-insulin model parameters" for further details on the model parameters, their physiological meaning and measurement units, and see [16] for further details on the model mathematical coherence and [15] for identification issues and statistical robustness).

To formalize the problem to estimate plasma insulin concentration from only glucose measurements, define the state $x = (G, I) \in \mathbb{R}^2$. Then, model (27)-(28) endowed with the measurement equation $y(t) = G(t)$ can be restated according to (13) where $u(t) \equiv 0$ (because no glucose or insulin inputs are modeled for the open-loop system) and functions $f(\cdot)$, $g(\cdot)$, $p(\cdot)$ and $h(\cdot)$ are defined as follows:

$$f(x) = \begin{bmatrix} -K_{xgi}x_1x_2 + \frac{T_{gh}}{V_G} \\ -K_{xi}x_2 \end{bmatrix} \qquad g(x) = \begin{bmatrix} 0 \\ \frac{T_{iGmax}}{V_I} \end{bmatrix} \qquad p(x_t, 0) = \begin{bmatrix} 0 \\ \xi(x_{1t}) \end{bmatrix} \qquad h(x) = x_1. \tag{29}$$

The full observation relative degree is readily verified by the triple (f, g, h), with the observability map

$$\phi(x) = \begin{bmatrix} h(x) \\ L_f h(x) \end{bmatrix} = \begin{bmatrix} x_1 \\ -K_{xgi}x_1x_2 + \frac{T_{gh}}{V_G} \end{bmatrix} \tag{30}$$

being a diffeomorphism in $\mathbb{R}^2_+$, therefore the diffeomorphism holds true for all meaningful cases. The observer equations for model (27) are:

$$\begin{bmatrix} \frac{d\widehat{G}(t)}{dt} \\ \frac{d\widehat{I}(t)}{dt} \end{bmatrix} = \begin{bmatrix} -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \frac{T_{gh}}{V_G} \\ -K_{xi}\widehat{I}(t) + \frac{T_{iGmax}}{V_I}\xi\big(\widehat{G}(t-\tau_g)\big) \end{bmatrix} + Q\big(\widehat{G}(t), \widehat{I}(t)\big)^{-1} K(G(t) - \widehat{G}(t)) \tag{31}$$

where Q is the Jacobian of the observability map ϕ defined in (30), invertible in $\mathbb{R}^2_+$. Assumption 1 and hypotheses H1 and H2 of Theorem 2 are locally (not globally) satisfied, therefore semiglobal results are ensured, by virtue of Remark 3, since the system is BIBS (for the open loop case under investigation it is stable with null input). The selection of the gain vector K determines the observer convergence. Though a mathematical procedure is available (Remark 4) the choice of the eigenvalues, and thus of the gain vector K, has been set by simulation trials, according to a tradeoff providing the Hurwitz property of matrix $A - KC$ with a not too large gain K, which may arise numerical problems in the observer implementation.

The procedure to evaluate the quality of the observer performances is based on a twofold use of the IVGTT protocol: the IVGTT will be first exploited *in vivo* to identify the DDE model parameters by means of real data (glucose and insulin measurements) previously collected by the 20 healthy subjects; then, the IVGTT will be exploited *in silico* to simulate a perturbation of the initial state and then apply the observer methodology (properly tuned on the individual parameter estimates) to infer plasma insulin concentration from glucose measurements. A couple of indexes will be as well introduced to measure and compare each other the individual observer error.

According to the IVGTT procedure, see the sidebar "The IVGTT clinical protocol", the bolus D_g is fixed to 1.83 mg/kgBW for the *in vivo* experiments. The identification task is performed by Generalized Least Square method [15]. The basal values of glycemia and insulinemia, G_b and I_b, enter the identification scheme as covariates, and are measured before the experiments. Regarding the other model parameters, $V_I = 0.25$L/kgBW and $G^{\star} = 9$mM are fixed by the investigator and kept constant, V_G, τ_g, K_{xgi}, K_{xi}, γ, I_{Δ} are free model parameters to be estimated and T_{iGmax}, T_{gh} are determined from the other parameters according to the algebraic steady-state conditions.

This way the 20 sets of data (both glucose and insulin measurements) allow to identify the parameters of the DDE models associated to each real subject. Successively, each of the 20 DDE models will be exploited to design the observer: in other words the observer is synthesized by means of a DDE model *tailored* to the subject, in the spirit of *personalized medicine*. Simulations will be carried out by implementing *in silico* a different IVGTT experiment, according to a double amount of the glucose bolus $D_g = 3.66$ instead of 1.83 mg/kgBW. As previously stated, the observer equations are reported in (31), with the observer gain K designed to provide the same eigenvalues (set equal to $\{-0.2, -0.3\}$) to matrix $A - KC$, (S12), for all subjects. The fact that a unique value of the gain K is able to cope with the different subjects under investigation may be interpreted as a sign of a rather homogeneity in the population of 20 individuals. As far as the observer initial conditions are concerned, a pair of critical worst cases are considered. One case refers to an underestimate that completely neglects the insulin first phase in (S15), thus $\widehat{I}(0) = I_b$; the other case refers to an overestimate of the first phase corresponding to 1000 times as much as the basal insulinemia: $\widehat{I}(0) = 1000 I_b$.

To assess the goodness of the observer-based insulin estimate $\widehat{I}$ a pair of indexes related to the accuracy of the observed insulin and efficacy of the method are defined. The former is evaluated in terms of the *Normalized Integral Error, NIE* over the 180 minutes of the simulated experiment

$$NIE = \frac{\sqrt{\frac{1}{T_{fin}} \int_0^{T_{fin}} \left| I(t) - \widehat{I}(t) \right|^2 dt}}{\left| I(0) - \widehat{I}(0) \right|}, \qquad T_{fin} = 180\text{min}; \tag{32}$$

the latter is evaluated in terms of the time instant t_{min} according to which the observer error is definitely below a given fraction of insulinemia

$$|I(t) - \widehat{I}(t)| < pI(t) \qquad \forall t \geq t_{min} \qquad p \in (0, 1) \tag{33}$$

Index NIE will be exploited to compare the performances of different observers, whilst index t_{min} allows to evaluate the efficacy of any single observer run. In the spirit of observer-based control laws, in absence of a separation principle for nonlinear systems, the faster the observer matches the real state, the better performances are expected from the closed-loop system. It has to be stressed that the time an AP takes to track a desired glucose level cannot be excessively short (say, smaller than 5 minutes) because this might involve excessively high (and potentially dangerous) serum insulin concentrations. Instead, AP algorithms use to take 2–3 hours to make a smooth variation from a hyperglycemic level down to a safe euglycemic one [17]. In this framework, an observer that provides an almost exact insulin estimate within 20–30 minutes (which is 10–25% of the whole expected control period) should be considered a good observer.

Figure 1 reports the performances of the observer with t_{min} computed according to $p = 0.15$ and $p = 0.05$ respectively. We point out that both choices are nontrivially demanding, if compared to standard insulin sensors providing plasma insulinemia (for example for IVGTT, and not in real-time) with a coefficient of variation of about 7% [15]. It is apparent that an underestimation (at least such a coarse under-estimation) provides a worse accuracy in terms of a larger average NIE with a larger variability. As far as the efficacy, both cases of $p = 0.15$ and $p = 0.05$ provide very good results with t_{min} easily below 30min (and in case of $p = 0.15$ also below 20min). In other words, no matter how *bad* is the initial estimate, no matter if it is an over- or an under-estimate: the observer is able to track successfully the correct insulinemia within 20/30 minutes. Fig. 3 shows the time course of one of the subjects' insulinemia (left panel) and observer error (right panel) to better appreciate the goodness of fit of the observer curve to real insulinemia.

As previously stressed in Remark 6, the knowledge of the dynamic model is unavoidable

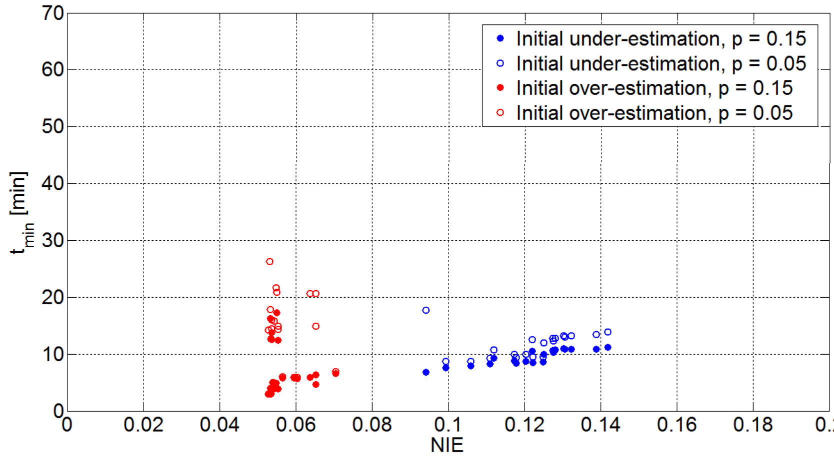

Figure 1: Accuracy/efficacy performance grid for $p = 0.15$ (full circles) and $p = 0.05$ (empty circles). Each circle refers to a pair of (NIE, t_{min}). Blue color refers to the underestimated case, red color refers to the overestimated case.

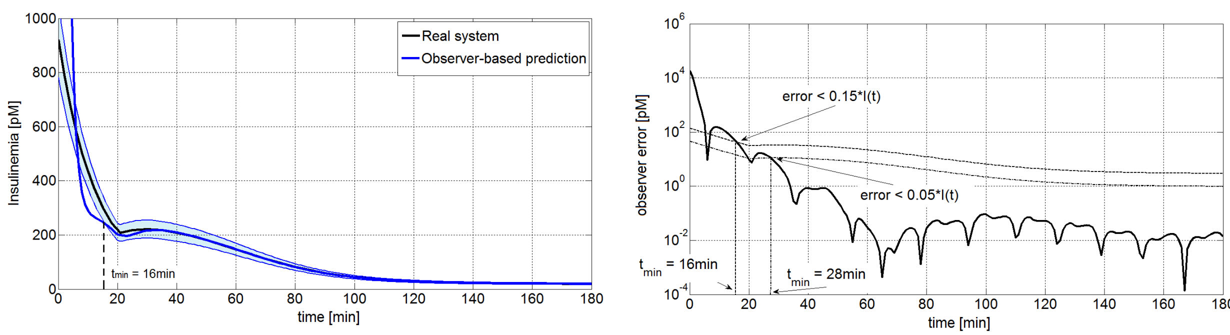

Figure 2: Left panel: time course of observed insulin concentration (blue line) of one of the 20 Subjects compared to the real insulinemia (black line). The cyan zone around real insulinemia highlights the region on to which the estimation must be definitely constrained to define t_{min} for $p = 0.15$. Right panel: time course of observed insulin error (absolute value).

to guarantee the coherence of the observer. This fact clearly holds true also for medical applications like the one under investigation, where the model identification usually requires nontrivial (and sometimes invasive) perturbation experiments, carried out under the supervision of a physician. A robustness analysis of the observer performances has been done in closed-loop frameworks like the ones investigated in [17] where the designed observer was applied in closed-loop on a model whose parameters had been allowed to change according to given coefficients of variations; or in [18] where a different dynamical model was exploited to validate the observer-based control law. In both cases the aim of the robustness analysis was focused on the safety ("is plasma glycemia always greater than a safe hypoglycemic level?") and on the efficacy of the therapy ("does the closed-loop insulin administration track a euglycemic level of glycemia within a limited time from the beginning of the therapy?").

Here the aim is to exploit the available data to investigate the open-loop performances of the observer. For instance, it can be thought to construct a *mean model*, that is a model with the structure of (27), whose parameters are calibrated on data coming from the whole population of 20 individuals, and to exploit it to design the observer on a subject supposed to be consistent with (but not belonging to) the population used for the observer calibration. No perturbation experiments are designed to properly identify the DDE model associated to the observed subject. In the spirit of Remark 6, by assuming that the observer is successfully designed to track the trajectory associated to the mean model, the goodness of the state estimate is all a matter of how representative the mean model is for the population (or, in particular, how close the observed subject is to the mean model). For instance, consider as the observed subject the one reported in Fig. 2 and exploit the other 19 sets of data to infer the mean model according to the following procedure: (i) normalize the other 19 subjects streams of glucose-insulin data with respect to the observed subject basal values (this fact guarantees at least the convergence to zero of the estimation error, since the observed subject and the mean model share the same unique equilibrium point given by the basal values; unfortunately, it does not guarantee the correct transient); (ii) identify the mean model by averaging the normalized set of data. Fig. 3 shows the performances of the observer designed by means of the mean model, and applied to the observed subject. Both the initial under- and over-estimate are considered: it can

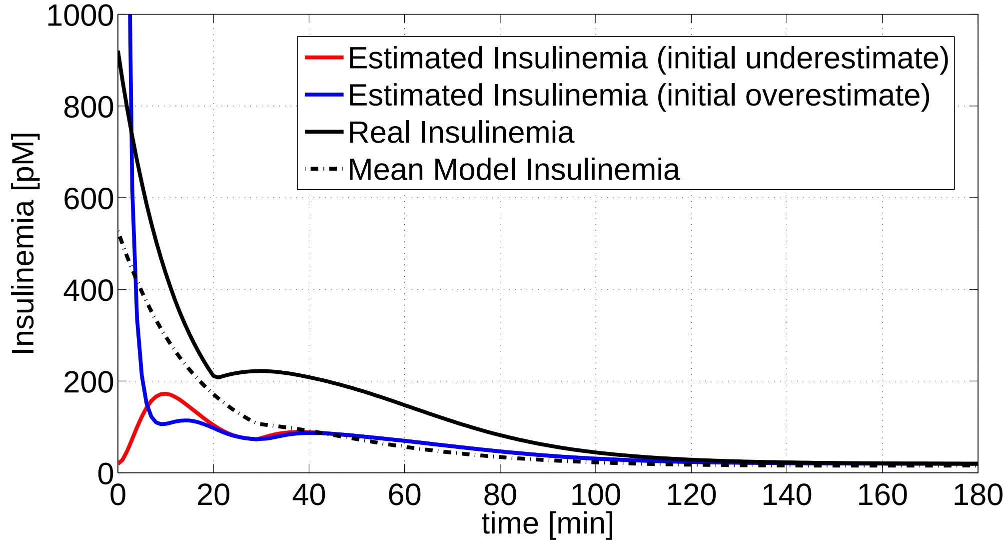

Figure 3: Observer applied to one of the subject individuals, synthesized according to the mean model associated to the population.

be appreciated how these curves confuse each other after about 20 minutes (the same average error transient emerging from Fig. 1); they both converge to the mean model trajectory, which is, unfortunately, markedly different from the one related to the observed subject (though sharing the same qualitative behavior).

A different kind of simulations is set up in order to evaluate the robustness of the observer performances with respect to a single parameter uncertainty. To this end we have chosen the most representative parameter for a DDE model, that is the state delay τ_g. This would create some sort of systematic error in the transient, but not in the asymptotic behavior, since a different delay would not change the basal values of glycemia and insulinemia. The observer performances will be evaluated according to the t_{min} index, to best represent how fast the insulin estimate is sufficiently close to the real one, in spite of the uncertainty on the delay. The following campaign of simulations has been run: for each individual, and for both the initial critical worst cases (under- and overestimate of initial insulinemia) simulations have been run with the

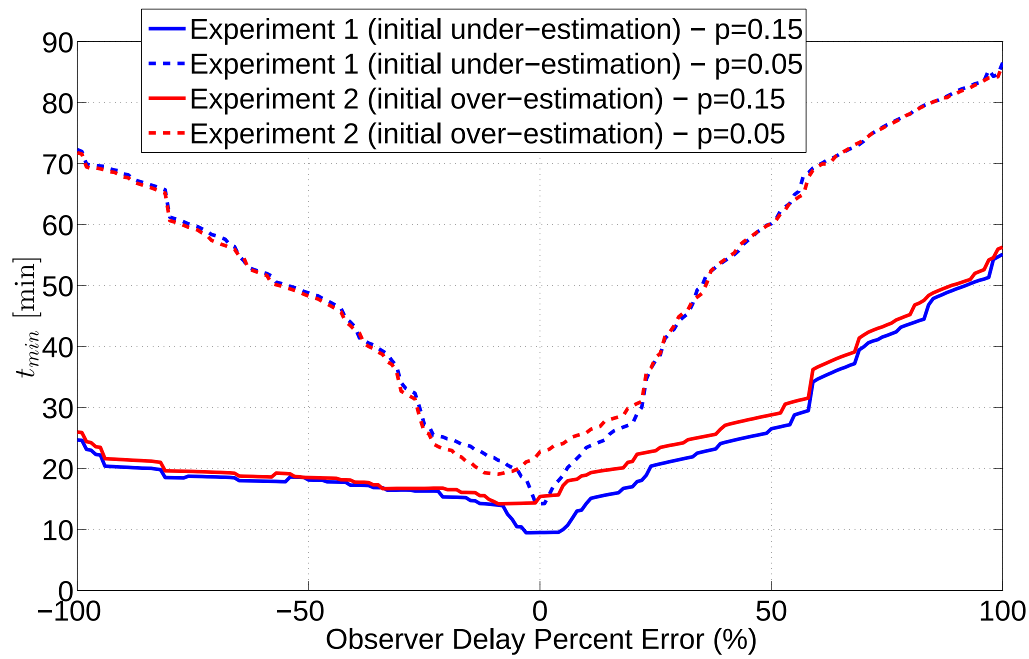

Figure 4: t_{min} mean curve (over the considered population of 20 individuals) for different percent errors of the observer delay with respect to the model delay.

observer synthesized according to a delay whose value varies within 0% of uncertainties (that means that the observer is synthesized according to the correct value of the delay) and $\pm 100\%$ of uncertainties (-100% meaning $\tau_g = 0$ and +100% meaning a double value for τ_g) with a step of 1% variation. According to results reported in Fig. 4 it is apparent that, according to a looser target observer performance ($p = 0.15$), we can still trust the observer performances, at least for underestimates of the delay, since even a total neglection of the delay does not produce a t_{min} greater, in average, than 30min; instead, an overestimate of the delay would provide a t_{min} greater than 30min for delays overestimated more than 50%. As far as a tighter target observer performance ($p = 0.05$), the t_{min} curve is more pronounced (t_{min} becomes greater than 30min for delay underestimates greater than 30% and overestimates greater than 20%), though it keeps the same qualitative behavior of the case $p = 0.15$.

Observer in case of sampled measurements

Like most of clinical/medical applications, the AP usually faces the problem of dealing with continuous-time models and discrete available measurements, whose sampling rate strongly depends on the kind of the exploited device. In this framework, observers will be considered, whose correction terms only exploit glucose discrete samples. Though measurements are acquired at discrete sampling times, the output can be modeled by the time-delay continuous function reported in (23), with $\delta(t)$ defined within any two consecutive sampling instants t_i, t_{i+1} as $\delta(t) = t - t_i$, $t \in [t_i, t_{i+1})$ (see also the sidebar "Output delays as tool to model features of the measurement process").

Unfortunately the observer equations reported in (24)-(26) do not straightforwardly apply to the present case, since they hold true for ODE systems with delayed outputs. For these reasons, only those subjects will be considered, for whom the apparent delay is negligible. It comes out to have 3 of such subjects with an estimated $\tau_g < 1$ min, whose model parameters have been re-calibrated by imposing $\tau_g = 0$min in the identification procedure. As a matter of fact the glucose-insulin system (27) is reformulated with $\tau_g = 0$min in the shape of equations (22)-(23) with $u(t) \equiv 0$ and

$$f(G,I) = \begin{bmatrix} -K_{xgi}GI + \frac{T_{gh}}{V_g} \\ -K_{xi}I + \frac{T_{iGmax}}{V_i}\xi(G) \end{bmatrix} \qquad h\big(G(t-\delta(t))\big) = G(t-\delta(t)) \tag{34}$$

It readily comes that the system shares the same observability map of (30), thus locally satisfying the ULDO hypotheses in Definition 1. As a matter of fact, according to uniformly bounded delays $\delta \in [0 \quad \Delta]$, Theorem 3 holds true (in its weaker form stressed by Remark 5), therefore there exists an observer gain K_0 such that local convergence of the state observer (24)-(26) is ensured with a rate η compatible with the choice of the bound Δ given by the sampling time of the measurements acquiring system. Similarly to the previous subsection, the observer gain K_0 has been set (by simulations) to obtain eigenvalues $\lambda = \{-0.2, -0.3\}$ for $A - K_0 C$, whilst the choice of $\eta = 5$ revealed to be (by simulations) compatible with a sampling period smaller than 10 minutes.

Simulations have been carried out by designing the observer for each of the three subjects by properly exploiting the correct model parameters. The same accuracy/efficacy indexes defined in (32)-(33) are here exploited. Different constant sampling periods Δ are investigated in simulation, with $\Delta \in \{2, 5, 10\}$ min. Results are reported in Fig. 5, where different symbols (circles, squares and diamonds) refer to different sampling periods. Each line refers to a subject with different sampling period: the continuous and dotted lines refer to t_{min} computed according to $p = 0.15$ and $p = 0.05$ respectively. The same grid of the previous picture is exploited. This time colored zones have been added to improve the readability: the green zone refers to very good results for t_{min}, that means below 30 min; the yellow zone refers to satisfactory results, with t_{min} below 60 min; the other colors refer to an observer that takes too time to converge. From the grid it is apparent that the case of $\Delta = 10$ min and $p = 0.05$ provides the greatest increase in t_{min}, thus worsening the observer performances: this is intuitive, since (i) $\Delta = 10$ min refers to the largest sampling time considered in simulations, therefore the observer benefits of a less frequent correction term, and (ii) $p = 0.05$ requires a tighter convergence of the state estimate (with respect to the case of $p = 0.15$). On the other hand, simulations highlight a trend which is not foreseeable in principle: underestimating the initial insulinemia provides better results; for instance, considering such initialization and a t_{min} computed with $p = 0.15$ always leads to satisfactory performances for the observer, with two (out of three) subjects in the green zone.

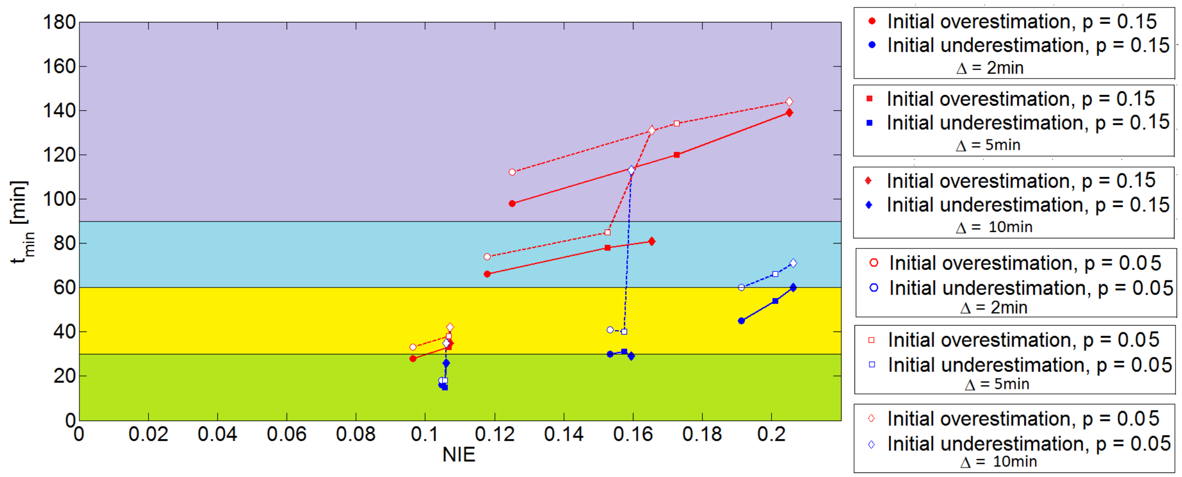

Figure 5: Accuracy/efficacy performance grid: the case of discrete glucose measurements. Three subjects with negligible delay τ_g are considered. Circles, squares and diamonds are referred to different sampling periods $\Delta \in \{2, 5, 10\}$ min, respectively. Full (resp. empty) symbols represent the case $p = 0.15$ (resp. $p = 0.05$). Red (resp. blue) symbols denote the case of initial overestimation (resp. underestimation). Solid/dashed lines link the full/empty symbols referred to the same patient.

Conclusion

In this article a review of results concerning Luenberger-like observers for nonlinear dynamical systems with state and output delays is reported, and their application to the problem of the real-time reconstruction of the insulinemia in humans from plasma glucose measurements is presented. The problem of obtaining the insulinemia by processing glycemia measurements is very important for the development of the Artificial Pancreas (AP), a device aimed at supporting or replacing the pancreatic activity of insulin production in diabetic individuals. Indeed, glycemia can be accurately, easily, and quickly measured by small, portable, and cheap devices, while insulinemia measurements require large and costly laboratory equipments. Asymptotic state observers can solve the problem of obtaining insulinemia from glycemia by suitably exploiting the mathematical model of insuline-glucose dynamics. A simple and accurate model available in the literature is in the form of Delay-Differential-Equation (DDE), and has already been successfully used for the construction of insulin observers, and also for designing an insulin infusion therapy for both Type 1 and Type 2 patients.

In this work only aspects of observed-based insulin reconstruction have been presented. First, it has been shown how observers can be constructed exploiting the DDE model of glucose-insuline dynamics, by assuming continuous time glucose measurements. Then, an observer has been presented that processes discrete-time glucose measurements and returns, in real-time, the insulinemia in continuous-time. The performances of the observers have been evaluated by considering a set of real measurements coming from 20 healthy subjects who underwent an Intra-Venous Glucose Tolerance Test (IVGTT). The parameters of the DDE model of each individual have been identified and on the basis of the obtained model a *personalized* observer has been constructed for each subject. The performances of the observers have been evaluated and displayed using two quality indicators: one for the average size of the observation error and one for the convergence time. The campaign of simulations has demonstrated the robustness of the observers with respect to the initialization (that is, with respect to the unknown initial value of insulinemia). Some caveats have been addressed concerning the use in the observer design of models whose parameters are significantly different from those of the single subjects. As an example, the 20 IVGTT insulin and glucose data available have been used to identify a kind of mean model, that has been exploited for the construction of an observer. It comes out that for those subjects whose personalized model is significantly different from the mean model, the insulinemia values returned by the observer can be far from the true insulinemia profile of the subject. The last campaign of simulations presented in this work concerns the observer that processes discrete-time (sampled) glycemia measurements and returns a continuous-time insulinemia profile. For this case there not exists in the literature an observer design technique that deals with DDE, and therefore a subpopulation of individuals with negligible delay in the model has been used in the simulation campaign. The performances of the observers have been evaluated and displayed using the previously defined quality indicators in correspondence to different sampling intervals (2, 5 and 10 min). It turns out that in this case an initial underestimation of the insulin plasma concentration level has to be preferred in order to have acceptable convergence times.

As a conclusion, the use of observers as a subsystem in Artificial Pancreas appears to be a promising technique, although some work has still to be done, in particular for the development of observers that deals with DDE models and sampled measurements.

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Lie-derivatives, relative degree and observability

The Lie derivative of a smooth function $h(x)$ along a smooth vector field $f(x)$ is the directional derivative defined as

$$L_f h(x) \triangleq \frac{dh(x)}{dx} f(x). \tag{S1}$$

$L_f^k h(x)$ denotes the k-th order Lie derivative, recursively defined

$$L_f^k h(x) \triangleq L_f L_f^{k-1} h(x) = \frac{dL_f^{k-1} h(x)}{dx} f(x), \quad k \in \mathbb{N}, \tag{S2}$$

with $L_f^0 h(x) = h(x)$. Note that if both $h(x)$ and $f(x)$ are linear, say $h(x) = Cx$ and $f(x) = Ax$, it results $L_f^k h(x) = CA^k x$, and the jacobian $Q(x)$ of the observability map $\phi(x)$ defined in (3) becomes the standard observability matrix for linear systems, and the drift-observability property given in Definition 1 is equivalent to nonsingularity of the observability matrix.

In the state observation problem the following concept is needed:

Definition 3: The system (1)–(2) (or, the triple (f, g, h)) is said to have *observation relative degree* $r \in \mathbb{N}$ in a set $\Omega \in I\!R^n$ if

$$\begin{aligned} &\forall x \in \Omega, \quad L_g L_f^s h(x) = 0, \quad s = 0, 1, \ldots, r-2, \\ &\exists x \in \Omega, : \quad L_g L_f^{r-1} h(x) \neq 0. \end{aligned} \tag{S3}$$

If $r = n$ the system (1)–(2) is said to have *full relative degree*.

This is a weaker version of the concept of *relative degree* (see [36]) used for control purposes: if Ω is an open set and $L_g L_f^{r-1} h(x) \neq 0 \quad \forall x \in \Omega$, then the triple (f, g, h) has relative degree r. For linear systems, where $(f, g, h) = (Ax, B, Cx)$, it is readily seen that $L_g L_f^s h(x) = CA^s B$, so that the relative degree r is the lowest integer such that $CA^{r-1} B \neq 0$, and it coincides with the observation relative degree.

Canonical Observable form of systems

A drift-observable system (1)–(2) can be put in a canonical observable form by using the drift-observability map $z = \phi(x)$ defined in (3) as a change of coordinates. Differentiating both sides of $z(t) = \phi\big(x(t)\big)$, and omitting time dependencies, we get $\dot{z} = Q(x)\dot{x}$ and

$$\dot{z} = Q(x)f(x) + Q(x)g(x)u. \tag{S4}$$

Defining the matrices $A \in I\!R^{n\times n}$, $B \in I\!R^{n}$, $C \in I\!R^{n}$ as

$$\begin{aligned} A &\triangleq \begin{bmatrix} 0_{(n-1)\times 1} & I_{(n-1)\times(n-1)} \\ 0 & 0_{1\times(n-1)} \end{bmatrix}, \quad B \triangleq \begin{bmatrix} 0_{(n-1)\times 1} \\ 1 \end{bmatrix} \\ C &\triangleq \begin{bmatrix} 1 & 0_{1\times(n-1)} \end{bmatrix}, \end{aligned} \tag{S5}$$

which make up a Brunowsky triple of order n, and the function

$$\Gamma(x) \triangleq L_f^n h(x). \tag{S6}$$

we easily get

$$Q(x)f(x) = \begin{bmatrix} L_f h(x) \\ \vdots \\ L_f^n h_j(x) \end{bmatrix} = A\phi(x) + B\Gamma(x), \quad h(x) = C\phi(x). \tag{S7}$$

Moreover, defining $F_r \in I\!R^{n\times n-r+1}$ and $H : I\!R^n \to I\!R^{n-r+1}$ as

$$F_r \triangleq \begin{bmatrix} 0_{(r-1)\times(n-r+1)} \\ I_{n-r+1} \end{bmatrix}, \quad H(x) \triangleq \begin{bmatrix} L_g L_f^{r-1} h(x) \\ \vdots \\ L_g L_f^{n-1} h(x) \end{bmatrix}, \tag{S8}$$

and considering that, by definition of observation relative degree in Ω, so that the first $r-1$ rows of vector $Q(x)g(x)$ are identically zero in Ω, we get

$$Q(x)g(x) = \begin{bmatrix} L_g h(x) \\ \vdots \\ L_g L_f^{n-1} h_j(x) \end{bmatrix} = F\,H(x). \tag{S9}$$

Taking into account (S7) and (S9), equation (S4) takes the form

$$\begin{aligned} \dot{z}(t) &= Az(t) + B\bar{\Gamma}\big(z(t)\big) + F_r\overline{H}\big(z(t)\big)u(t), \\ y(t) &= Cz(t), \end{aligned} \tag{S10}$$

where

$$\bar{\Gamma}(z) = \Gamma\big(\phi^{-1}(z)\big), \qquad \overline{H}(z) = H\big(\phi^{-1}(z)\big). \tag{S11}$$

System (S10) is the canonical observable form of system (1)–(2) and, in the case of linear systems, it coincides with the standard observable canonical form.

The pair (A, C) is observable, and it is an easy matter to assign any set $\lambda = (\lambda_1, \ldots, \lambda_n)$

of eigenvalues to the matrix $A - KC$, that has the companion structure

$$A - KC = \begin{bmatrix} -k_1 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ -k_{n-1} & 0 & \cdots & 1 \\ -k_n & 0 & \cdots & 0 \end{bmatrix}. \tag{S12}$$

The gain associated to the set of eigenvalues λ will be denoted by $K(\lambda)$, and its components are the coefficients of the monic polynomial whose set of roots is λ. If the eigenvalues are distinct, matrix $A - K(\lambda)C$ can be diagonalized by the Vandermonde matrix

$$V(\lambda) = \begin{bmatrix} \lambda_1^{n-1} & \cdots & \lambda_1 & 1 \\ \vdots & \ddots & \vdots & \vdots \\ \lambda_n^{n-1} & \cdots & \lambda_n & 1 \end{bmatrix}, \tag{S13}$$

since it is easily verified that $V(\lambda)\big(A - K(\lambda)C\big) = \mathrm{diag}\{\lambda\}V(\lambda)$.

An observer for the system (S10) is achived by adding a linear output feedback

$$\dot{\hat{z}}(t) = Az(t) + B\overline{\Gamma}\big(z(t)\big) + F_r\overline{H}\big(z(t)\big)u(t) + K\big(y(t) - C\hat{z}(t)\big). \tag{S14}$$

Note that in the case of full relative degree, that is $r = n$, then $F_r = B$ and $H(x) = L_g L_f^{n-1} h(x)$ is scalar.

Observer for MIMO systems

The observer construction described in the main text and the global and semiglobal convergence theorems can be extended to the case of Multi-Input-Multi-Output (MIMO) systems [4]. When the output y of system (1)–(2) is a vector in $I\!R^q$ and the input u is in $I\!R^p$, then the observation relative degree is defined as a multiindex $\bar{r} = \{r_1, \ldots, r_q\}$, where each r_j is the lowest among all relative degrees of the output component y_j with respect to each scalar input u_k, $k = 1, \ldots, p$. For each output function $h_j(x)$ a map $z_j = \phi_{s_j}(x)$ is constructed as in (3), stacking in a vector the Lie derivatives $L_f^k h_j(x)$ for $k = 0, \ldots, s_j - 1$, where the q integers $s_j \leq r_j$ must sum up to n. Thus, in general, many choices of drift-observability maps exist, and the invertibility and Lipschitz properties of the map $\phi_{\bar{s}}(x) = \mathrm{col}_{j=1}^q \big\{\phi_{s_j}(x)\big\}$ strongly depend on the choice of the multiindex $\bar{s} = \{s_1, \cdots, s_q\}$. The convergence Theorem 1 is stated in [4] for the MIMO case. It is worth noting that the strong convergence result given in Theorem 1 for the case of full relative degree (that is, $r = n$) of SISO systems, extends to MIMO systems in the case of $\sum_{j=1}^q r_j = n$.

Modeling the measurements through time-varying delays

The features of different measurement acquisition or transmission processes, such as buffering, sampling, data shuffling and data loss, can be modeled through a suitable choice of time-varying output delays. For instance, the case in which during some intervals no measurement is being received by the observer can be modeled by means of an output delay function $\delta(t)$ that increases with time with $\dot{\delta}(t) = 1$. When $\delta(t)$ is not continuous, or $|\dot{\delta}(t)| > 1$, then $t - \delta(t)$ is not necessarily monotone and increasing. In other words, measurements can be received in a different order than the time they have been taken. In this case the observer can either use the most recent measurement available, discarding older measurements, or use the measurements according to their arrival time without discarding anything. In Figure 1 the second option is assumed to illustrate how buffering, sampling, data shuffling and data loss can be uniformly modeled by means of appropriate delay functions. The first alternative can be studied similarly.

In the case of buffering the function $\delta(t)$ is continuous. The vertical segment models the arrival of a packet of output data previously stored in the buffer, thus in reality it has some large but finite slope. In the case of sampling the measurement is received only at discrete time points and the corresponding delay function is $\delta(t) = \mathrm{mod}(t, T)$, where T is the sampling period. The case of shuffling corresponds to a piece-wise constant delay, which in the plot switches among the values 1 and 4. In practical situations this may happen when the data are contained into packets that are sent through a communication channel and received in the wrong order. In the case of data loss, $t - \delta(t)$ becomes flat during the loss periods, that in the plot start at $t = 2$ and $t = 6$. In the loss period the last available measurement is used.

It may be noticed that in the first and third case all the measurements are eventually received, but in the second and fourth they are not. When $\delta(t)$ is continuous no output measurement is lost, and it is easy to prove that all data taken at $\tau \leq t - \delta(t)$ are available at time t. The third plot illustrates how the absence of losses is compatible with a discontinuous $\delta(t)$. Since the output is lost when it is generated at some time τ which is not included in the image of $[\Delta, +\infty)$ under the function $t - \delta(t)$, *loss-less delay functions* are those for which for any time $\tau > \Delta$ it exists $t \geq \tau$ such that $\tau = t - \delta(t)$. For a loss-less delay function all data previous to $t - \Delta$ are available at time t.

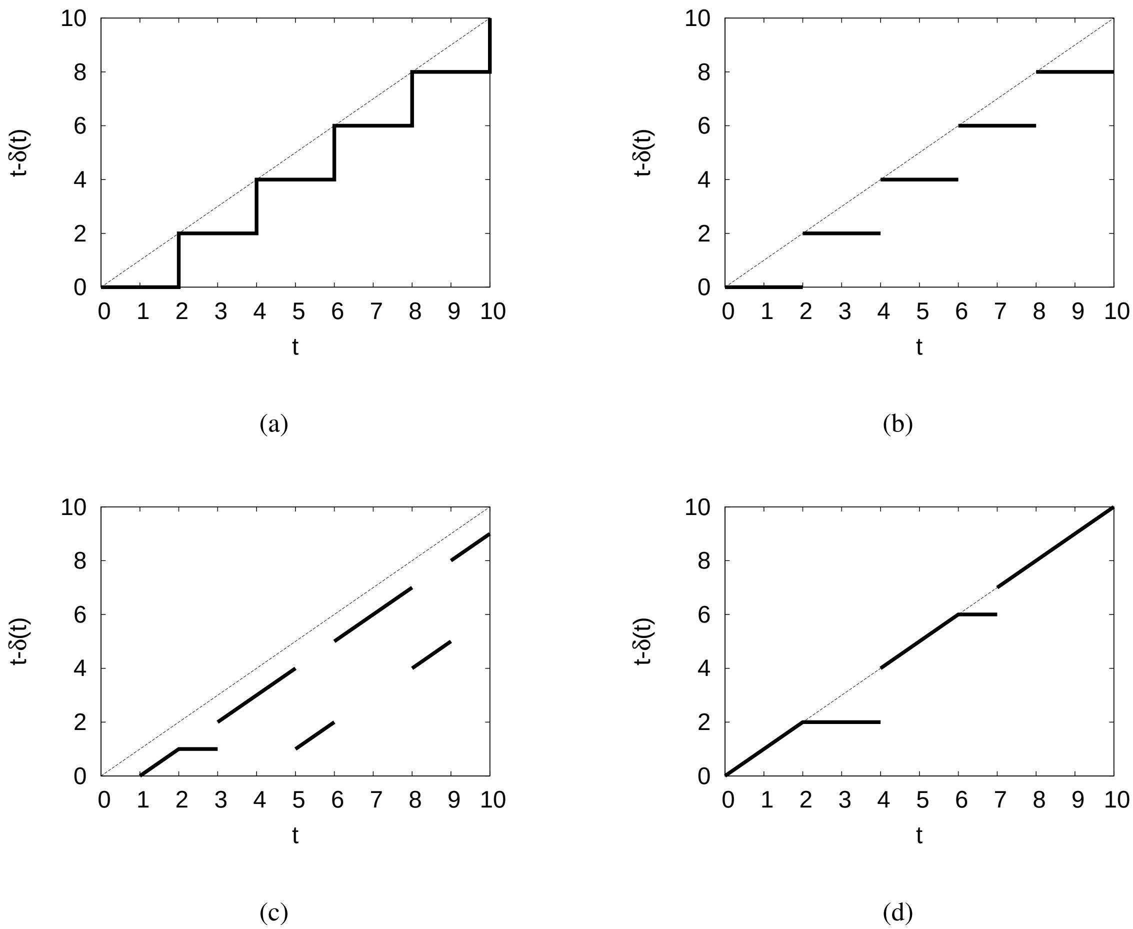

Figure S1: Buffering (a), sampling (b), data shuffling (c) and data loss (d) with the correspondent functions $t - \delta(t)$. The horizontal axis is the time t of the observer. The vertical axis represents the time instant $t-\delta(t)$ at which the output processed at time t has been generated. The situation without delay is represented by the dotted line.

The IVGTT clinical protocol

From a clinical viewpoint, the IVGTT is a perturbation experiment that consists in administering intra-venously a glucose bolus D_g after an overnight fasting period and then sampling plasma glucose and serum insulin concentration during the following 3 hours. The bolus administration at time $t = 0$ produces an instantaneous increase of both plasma glucose and insulin concentration (first phase of insulin release), so that:

$$G(0) = G_b + \frac{D_g}{V_G} \qquad I(0) = I_b + I_\Delta \frac{D_g}{V_G} \tag{S15}$$

with I_Δ a further parameter to be estimated. Blood samples are acquired every 2 min for the first 10-min interval, every 5 min for the next 30-min interval, every 10 min for the next 20-

min interval and finally every 20 min for the last 120-min interval (an overall sampling period of 3 hours). These blood samples are exploited to measure (not in real time) glycemia and insulinemia. Glucose and insulin measurements are used to identify the parameters of the model under investigation. The delay τ_g in the glucose action on pancreatic IDR (27) is necessary to reproduce the second-phase insulin response, showing an evident insulin concentration *hump*, [15].

DDE model parameters

The glucose-insulin model parameters referring to the DDE (27)-(28) are defined as follows, with measurement units chosen as in [15], [16]:

- K_{xgi} $[min^{-1}pM^{-1}]$ is the rate of glucose uptake by tissues (insulin-dependent) per pM of plasma insulin concentration;
- T_{gh} $[min^{-1}(mmol/kgBW)]$ is the net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake (mainly by the brain, supposed constant throughout the experiment);
- V_G $[L/kgBW]$ is the apparent distribution volume for glucose;
- K_{xi} $[min^{-1}]$ is the apparent first-order disappearance rate constant for insulin;
- T_{iGmax} $[min^{-1}(pmol/kgBW)]$ is the maximal rate of second-phase insulin release;
- V_I $[L/kgBW]$ is the apparent distribution volume for insulin;
- τ_g $[min]$ is the apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations;
- γ $[-]$ is the progressivity with which the pancreas reacts to circulating glucose concentrations. If γ were zero, the pancreas would not react to circulating glucose at all; if γ were 1, the pancreas would respond according to a Michaelis-Menten dynamics, where $\widetilde{G}$ is the glucose concentration of half-maximal insulin secretion; when γ is greater than 1 (as is usually the case), the pancreas responds according to a sigmoidal function;
- $\widetilde{G}$ $[mM]$ is the glycemia at which the insulin release is the half of its maximal rate; at a glycemia equal to $\widetilde{G}$ corresponds an insulin secretion equal to $T_{iGmax}/2$.

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