

DISTRIBUTED-DELAY MODELS OF THE GLUCOSE-INSULIN HOMEOSTASIS AND ASYMPTOTIC STATE OBSERVATION ¹

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Abstract: In this paper the problem of the real-time reconstruction of plasma insulin concentration by using only blood glucose measurements is investigated. This is an interesting problem because the knowledge of the time course of the glucose and insulin concentrations in an individual provides precious informations concerning its health state, and may assume the role of a clinical instrument. For the purpose of the reconstruction of the insulinemia a dynamical model of the glucose-insuline homeostasis is required. The present work considers distributed delay models. Such models have been preferred in recent papers with respect to the standard Minimal Models, available in literature from 70's, because they allow to couple the glucose and insulin dynamics in a unique extended system, whose solutions have been proven to be positive, bounded, and globally asymptotically stable around the basal values of the equilibrium point. Data are acquired according to the Intra Venous Glucose Tolerance Test (IVGTT). Simulation results are reported in order to validate the developed theory. *Copyright*©2005 *IFAC*

Keywords: Nonlinear systems, biomedical systems, state observers, state estimation

1. INTRODUCTION

Glycemia and insulinemia, i.e. glucose and insulin blood concentrations, are important variables in diabetic individuals, and in serious cases require fre-

quent measurements. Glycemia can be readily measured with low-cost devices. On the other hand, the measurement of insulinemia is expensive and not immediate. This fact stimulates the study of algorithms capable of providing the insulin blood concentration by processing a stream of glycemia measurements. Algorithms of this kind, in the control systems literature, are called *state observers*, and are aimed to recon-

¹ Work partially supported by FIRB-MIUR Project "Metodi dell'Analisi Matematica in Biologia, Medicina e Ambiente" and INFN (Italian National Institute of Nuclear Physics).

struct the state of a dynamic system by processing the available measurements. The observer design requires a dynamical model of the system under investigation. Many authors in the last decades proposed and studied different models for the glucose-insulin homeostasis (Bergman *et al.*, 1979; Toffolo *et al.*, 1980; Pacini and Bergman, 1986; Fisher and Teo, 1989; Fisher, 1991; De Gaetano and Arino, 2000; Mukhopadhyay *et al.*, 2004). The models here adopted to estimate the time course of the plasma insulin concentration are families of distributed delay models with single and double kernel (Mukhopadhyay *et al.*, 2004). Such models allow to couple the dynamics of both glucose and insulin kinetics in a unique extended system, whose solutions have been proven to be positive, bounded, and globally asymptotically stable around the basal values of the equilibrium point (De Gaetano and Arino, 2000). The choice of the model in the family to whom it belongs is left to the researcher, based upon theoretical or numerical grounds; from a mathematical point of view different choices are due to different shapes of the delay-kernels characterizing the model. This way, a wide frame of circumstances may be described. The model parameters have been previously identified according to the Intra Venous Glucose Tolerance Test (IVGTT), an experimental procedure easy to perform, minimal invasive, yielding a rich data set. It consists of an intra venous injection in a subject at rest of an impulsive amount of glucose: then, the blood glucose and insulin concentrations are repeatedly sampled over a typical period of three hours.

According to the nonlinear feature of the model for the glucose-insulin homeostasis, the nonlinear observer presented in (Dalla Mora *et al.*, 2000) has been chosen to solve the problem of insulin reconstruction from glucose measurements. It is a powerful tool which asymptotically estimate the state of a nonlinear system from a drift observability property. Such an observer has been already used for the insulin estimate (De Gaetano *et al.*, 2003), where a modified version of the Minimal Model (Bergman *et al.*, 1979; Toffolo *et al.*, 1980; Pacini and Bergman, 1986) had been adopted.

2. SINGLE-KERNEL DELAY MODELS

This section is devoted to present a family of single-kernel distributed-delay differential models for the glucose-insulin homeostasis, (Mukhopadhyay *et al.*, 2004) (the name of the system parameters are the same adopted in (Mukhopadhyay *et al.*, 2004) where also their meaning is explained):

$$\dot{G}(t) = -b_1 G(t) - b_4 I(t) G(t) + b_7, \quad (1)$$

$$\dot{I}(t) = -b_2 I(t) + b_6 \int_0^\infty \omega(s) G(t-s) ds, \quad (2)$$

with initial conditions

$$G(t) \equiv G_b \quad \forall t \in (-\infty, 0), \quad G(0) = G_b + b_0 \quad (3)$$

$$I(t) \equiv I_b \quad \forall t \in (-\infty, 0), \quad I(0) = I_b + b_3 b_0. \quad (4)$$

The weight function $\omega(t)$ is a non negative square integrable function defined on $\mathbb{R}^+ = [0, \infty)$ such that:

$$\int_0^\infty \omega(t) dt = 1, \quad \int_0^\infty t \omega(t) dt < +\infty. \quad (5)$$

The finite quantity $\Delta_a = \int_0^\infty t \omega(t) dt$ has the meaning of an average time delay.

Equation (1) refers to the glucose kinetics: the first term models the constant rate spontaneous glucose decay, the second term models the insulin-dependent glucose disappearance rate, while the third term is necessary in order to have an asymptotic decay to the basal glycemia level. Equation (2) describes the variation of the insulin plasma concentration as a function of two terms: the first models the insulin catabolism (constant rate insulin decay), the second models the pancreatic insulin secretion as an integral function of the past glycemia. Physiologically, the delay integral kernel of equation (2) accounts for the sensitivity of the pancreas to the concentration of blood glucose: the pancreas output insulin at a given instant is proportional to a suitably weighted average of the past blood glucose concentrations. A liver first-pass effect is taken into account in the second of equations (4), where an instantaneous insulin release at time 0 is assumed, proportional to the equivalent concentration of the glucose bolus b_0 .

Seven parameters are present in the model (1)-(4) (from b_0 to b_7 , b_5 is missing). However, there are only five free parameters. Assuming the subject at equilibrium ($G(t) \mapsto G_b$, $I(t) \mapsto I_b$) for a sufficient long time ($t \mapsto +\infty$), the following two conditions are obtained from equations (1)-(2)

$$\begin{aligned} 0 &= -b_1 G_b - b_4 I_b G_b + b_7 \\ 0 &= -b_2 I_b + b_6 G_b. \end{aligned} \quad (6)$$

Taking b_0, b_1, b_2, b_3, b_4 as free parameters, b_6 and b_7 are given by:

$$b_6 = b_2 \frac{I_b}{G_b}, \quad b_7 = b_1 G_b + b_4 I_b G_b. \quad (7)$$

As far as what concern the weighting function $\omega(t)$ in the integral in equation (2), its shape characterizes the choice of the model according to the features of individuals to whom it is related. For instance, normal individuals, showing a prompt and appropriate insulin response to hyperglycemic stimuli, will likely have a promptly rising and falling ω curve. NIDDM (Non Insulin Dependent Diabetes Mellitus) subjects, presenting a sustained insulin response to moderately hyperglycemic stimuli, will likely have persistently elevated ω for long times in the past; while IDDM subjects, with almost absent pancreatic response to circulating glucose, will show ω small for long times.

These examples suggest to choose for the kernel ω a class of functions that is flexible enough: ω should be suitably parameterized to give the possibility of distinguishing between patient populations (the correct values of the parameters for a given individual should be obtained through experimental parameter identification). The requirement for $\omega(t)$ to be non-negative and square-integrable over $[0, \infty)$ implies asymptotic decay to zero. Moreover, the shape of $\omega(t)$ should be such to give zero weight to recent glucose concentration measurements and maximum weight to measurements at a given delay Δ_m . This implies that $\omega(0) = 0$, then $\omega(t)$ increases to reach a maximum in $t = \Delta_m$, and then asymptotically decreases to zero. In this work, the following shape is chosen for ω :

$$\omega(t) = \gamma^2 t e^{-\gamma t}, \quad (8)$$

identified uniquely by its parameter γ . The maximum of $\gamma^2 t e^{-\gamma t}$ is at $\Delta_m = 1/\gamma$, while the average delay is $\Delta_a = 2/\gamma$.

In order to solve the state estimation problem, a first order differential system has to be achieved from (1)-(2). Such a purpose is obtained by suitably defining the extended state component:

$$\eta(t) = \int_0^\infty \omega(s) G(t-s) ds = \int_{-\infty}^t \omega(t-\tau) G(\tau) d\tau \quad (9)$$

with $\tau = t - s$. Then:

$$\dot{\eta}(t) = \omega(0)G(t) + \int_{-\infty}^t \frac{d\omega(t-\tau)}{dt} G(\tau) d\tau. \quad (10)$$

According to (8) $\omega(0) = 0$, so that:

$$\dot{\eta}(t) = \int_{-\infty}^t \frac{d\omega(t-\tau)}{dt} G(\tau) d\tau. \quad (11)$$

Since:

$$\frac{d\omega(t)}{dt} = -\gamma\omega(t) + \gamma^2 e^{-\gamma t} \quad (12)$$

it follows:

$$\dot{\eta}(t) = -\gamma\eta(t) + \gamma^2 \int_{-\infty}^t e^{-\gamma(t-\tau)} G(\tau) d\tau. \quad (13)$$

By defining a further state component

$$\xi(t) = \int_{-\infty}^t e^{-\gamma(t-\tau)} G(\tau) d\tau \quad (14)$$

with:

$$\dot{\xi}(t) = -\gamma\xi(t) + G(t). \quad (15)$$

equation (13) becomes:

$$\dot{\eta}(t) = -\gamma\eta(t) + \gamma^2\xi(t). \quad (16)$$

Finally, according to the positions:

$$x(t) \stackrel{\text{def}}{=} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ I(t) \\ \eta(t) \\ \xi(t) \end{bmatrix} \in \mathbb{R}^4 \quad (17)$$

the following system is obtained:

$$\dot{x}_1(t) = -b_1 x_1(t) - b_4 x_2(t) x_1(t) + (b_1 + b_4 I_b) G_b, \quad (18)$$

$$\dot{x}_2(t) = -b_2 x_2(t) + b_2 \frac{I_b}{G_b} x_3(t), \quad (19)$$

$$\dot{x}_3(t) = -\gamma x_3(t) + \gamma^2 x_4(t), \quad (20)$$

$$\dot{x}_4(t) = -\gamma x_4(t) + x_1(t), \quad (21)$$

with the initial conditions:

$$x_1(t) \equiv G_b \quad \forall t < 0, \quad x_1(0) = G_b + b_0 \quad (22)$$

$$x_2(t) \equiv I_b \quad \forall t < 0, \quad x_2(0) = I_b + b_3 b_0 \quad (23)$$

and $x_3(0) = G_b$, $x_4(0) = G_b/\gamma$, in that:

$$x_3(0) = \int_{-\infty}^0 \omega(-\tau) G(\tau) d\tau = G_b \int_{-\infty}^0 \omega(-\tau) d\tau \quad (24)$$

$$x_4(0) = \int_{-\infty}^0 e^{\gamma\tau} G(\tau) d\tau = G_b \int_{-\infty}^0 e^{\gamma\tau} d\tau \quad (25)$$

Assuming that the measurements are just blood glucose concentration, the output equation is simply:

$$y(t) = x_1(t). \quad (26)$$

3. DOUBLE-KERNEL DELAY MODEL

In the present section a double-kernel distributed-delay model is investigated, which differs from model (1)-(2) only in the equation describing the time course of blood glucose concentration, where a delay kernel is also present. Retaining the same names for the parameters used in the previous section, the model equations are the following:

$$\dot{G}(t) = -b_1 G(t) - b_4 G(t) \int_0^\infty \omega_I(s) I(t-s) ds + b_7 \quad (27)$$

$$\dot{I}(t) = -b_2 I(t) + b_6 \int_0^\infty \omega_G(s) G(t-s) ds, \quad (28)$$

with the same initial conditions stated in (3)-(4).

Note that a subscript has been added to the weighting functions ω to distinguish between glucose and insulin kinetics. The properties of the two kernels ω_I and ω_G are similar; in particular conditions (5) are both true. That means, a unique equilibrium point (G_b, I_b) exists for model (27)–(28), satisfying the same conditions of (6), from which (7) are straightforward. Physiological considerations, analogous to those made for the kernel $\omega(t)$ in (2), suggest the following forms for the two kernels in (27)–(28)

$$\omega_I(t) = \gamma_I^2 t e^{-\gamma_I t}, \quad \omega_G(t) = \gamma_G^2 t e^{-\gamma_G t}. \quad (29)$$

In this work the assumption that $\omega_G(t) \equiv \omega_I(t) \equiv \omega(t)$ as in (8) is considered, that means $\gamma_I = \gamma_G = \gamma$, according to (29). By introducing the following further state components as in (9)-(14):

$$\eta_G(t) = \int_0^\infty \omega(s) I(t-s) ds, \quad (30)$$

$$\xi_G(t) = \int_{-\infty}^t e^{-\gamma(t-s)} I(s) ds, \quad (31)$$

$$\eta_I(t) = \int_0^\infty \omega(s) G(t-s) ds, \quad (32)$$

$$\xi_I(t) = \int_{-\infty}^t e^{-\gamma(t-s)} I(s) ds, \quad (33)$$

the following 6-th order nonlinear system is obtained:

$$\dot{x}_1(t) = -b_1 x_1(t) - b_4 x_1(t) x_3(t) + (b_1 + b_4 I_b) G_b, \quad (34)$$

$$\dot{x}_2(t) = -b_2 x_2(t) + b_2 \frac{I_b}{G_b} x_5(t), \quad (35)$$

$$\dot{x}_3(t) = -\gamma x_3(t) + \gamma^2 x_4(t), \quad (36)$$

$$\dot{x}_4(t) = -\gamma x_4(t) + x_2(t), \quad (37)$$

$$\dot{x}_5(t) = -\gamma x_5(t) + \gamma^2 x_6(t), \quad (38)$$

$$\dot{x}_6(t) = -\gamma x_6(t) + x_1(t), \quad (39)$$

where it has been posed:

$$x(t) \stackrel{\text{def}}{=} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \\ x_5(t) \\ x_6(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ I(t) \\ \eta_G(t) \\ \xi_G(t) \\ \eta_I(t) \\ \xi_I(t) \end{bmatrix} \in \mathbb{R}^6. \quad (40)$$

The initial conditions for x_1, x_2 are the same as in (22)-(23); the initial conditions for the other state components are:

$$x_3(0) = I_b, \quad x_4(0) = I_b/\gamma, \quad (41)$$

$$x_5(0) = G_b, \quad x_6(0) = G_b/\gamma, \quad (42)$$

as it easily comes according to (24)-(25). The output equation is still (26).

4. STATE OBSERVERS FOR NONLINEAR SYSTEMS

In this section the observer for nonlinear systems presented in (Dalla Mora *et al.*, 2000) is applied to (18)-(21) and to (34)-(37) with (26) as available measurements. Note that both the models are stationary autonomous nonlinear systems, that means they are described by the following equations:

$$\dot{x}(t) = f(x(t)), \quad x(0) = x_0, \quad (43)$$

$$y(t) = h(x(t)) \quad (44)$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $y(t) \in \mathbb{R}$ is the scalar output (glucose measurements). f, h are analytical vector field, with $h(x) = x_1$.

The observer presented in (Dalla Mora *et al.*, 2000) is a dynamic system with the following structure (identity observer):

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + H(\hat{x}(t)) (y(t) - h(\hat{x}(t))). \quad (45)$$

The design of the observer gain $H(\cdot)$ is fundamental to ensure the exponential decay to zero of the observation error $e(t) = x(t) - \hat{x}(t)$. The construction of

$H(\cdot)$ according to the theory presented in (Dalla Mora *et al.*, 2000) is illustrated below. First, the definition of repeated Lie derivatives is reported for the easy of the reader:

$$L_f^0 h(x) = h(x) \quad (46)$$

$$L_f^s h(x) = \frac{\partial L_f^{s-1} h(x)}{\partial x} f(x). \quad (47)$$

The following definition formalizes a necessary condition for the construction of the observer and for its convergence:

Definition 1. (Dalla Mora *et al.*, 2000) A system of the type (43)-(44) is said to be **drift observable** in $\Omega \subseteq \mathbb{R}^n$ if the observability map defined as

$$\Phi(x) = \begin{bmatrix} L_f^0 h(x) \\ L_f^1 h(x) \\ \vdots \\ L_f^{n-1} h(x) \end{bmatrix} \quad (48)$$

is a diffeomorphism in an open set that contains or coincides with Ω .

Note that the drift-observability ensures that the Jacobian $\partial\Phi(x)/\partial x$ of the observability map is nonsingular in Ω .

Definition 2. (Dalla Mora *et al.*, 2000) A system of the type (43)-(44) is said to be **uniformly Lipschitz drift-observable (ULDO)** in a set $\Omega \subseteq \mathbb{R}^n$ if it is drift-observable in Ω and both the maps Φ, Φ^{-1} are uniformly Lipschitz in Ω and $\Phi(\Omega)$ respectively. If $\Omega \equiv \mathbb{R}^n$, the system is said **globally-ULDO (GULDO)**.

Theorem 3. (Dalla Mora *et al.*, 2000) Assume that a system of the type (43)-(44) is GULDO and, moreover, that the function

$$L_f^n h(\Phi^{-1}(z)), \quad (49)$$

is uniformly Lipschitz in \mathbb{R}^n . Consider the observer (45) with $H(\hat{x}(t))$ given by:

$$H(\hat{x}(t)) = Q^{-1}(\hat{x}(t)) K \quad (50)$$

with $Q(\hat{x}(t))$ the Jacobian of the observability map $\Phi(x)$

$$Q(\hat{x}(t)) = \frac{\partial\Phi(x)}{\partial x} \quad (51)$$

Then, for any $\alpha > 0$, there exists a choice for the gain vector K such that for any initial condition of the original system x_0 and of the observer \hat{x}_0 the observation error $e(t) = x(t) - \hat{x}(t)$ has an exponential decay to zero at rate α :

$$\|e(t)\| \leq M e^{-\alpha t} \|e(0)\| \quad (52)$$

for some $M > 0$.

The proof is in (Dalla Mora *et al.*, 2000), where also weaker convergence conditions are given. The choice of the gain vector K is strictly related to the desired rate of convergence α and to the Lipschitz constant of the function (49). In practice, the computation of K is made by choosing a set λ of n eigenvalues

$$\lambda = \{\lambda_1, \dots, \lambda_n\},$$

$$\text{with } \lambda_n < \dots < \lambda_2 < \lambda_1 < -\alpha < 0 \quad (53)$$

and finding K such to assign such to the the matrix $A_b - KC_b$, where (A_b, C_b) is an observable Brunovsky pair in \mathbb{R}^n , i.e.

$$A_b = \begin{bmatrix} 0 & 1 & \dots & 0 \\ 0 & 0 & \ddots & \vdots \\ \vdots & \ddots & \ddots & 1 \\ 0 & \dots & 0 & 0 \end{bmatrix}, \quad C_b = [1 \ 0 \ \dots \ 0] \quad (54)$$

The vector K that assigns the set λ of eigenvalues can be easily computed by:

$$K = -V^{-1}(\lambda) \begin{bmatrix} \lambda_1 \\ \vdots \\ \lambda_n \end{bmatrix}, \quad (55)$$

with

$$V(\lambda) = \begin{bmatrix} \lambda_1^{n-1} & \dots & \lambda_1 & 1 \\ \vdots & \ddots & \vdots & \vdots \\ \lambda_n^{n-1} & \dots & \lambda_n & 1 \end{bmatrix} \quad (56)$$

the Vandermonde matrix associated to the set λ of eigenvalues (see also (Dalla Mora *et al.*, 1997) for more details).

5. SIMULATION RESULTS

Simulations have been presented for both the families of models concerning the glucose-insulin homeostasis. In both cases, data are acquired according to the Intra Venous Glucose Tolerance Test (IVGTT), an experimental procedure easy to perform, minimal invasive, yielding a rich data set. It consists of an intra venous injection in a subject at rest of an impulsive amount of glucose: then, the blood glucose and insulin concentrations are repeatedly sampled over a typical period of three hours.

Below are reported a pair of significative simulations concerning the observer presented in the previous section applied to both the single and double kernel delay models. In both cases, parameters from b_0 to b_4 are taken from the ones estimated in (De Gaetano and Arino, 2000), even if the models to whom they are referred are slightly different, because they maintain the same physiological meaning. More in details, they are referred for a 25 years old man, height 170cm, body weight 66Kg, basal glycemia $G_b = 87\text{mg/dl}$, basal insulinemia $I_b = 37.9\text{pM}$, with:

$$\begin{aligned} b_0 &= 311\text{mg/dl}, & b_1 &= 1 \cdot 10^{-4}\text{min}^{-1}, \\ b_2 &= 0.2196\text{min}^{-1}, & b_3 &= 0.64\text{pM}/(\text{mg/dl}), \\ b_4 &= 3.73 \cdot 10^{-4} \end{aligned} \quad (57)$$

so that, from (7), it comes:

$$\begin{aligned} b_6 &= 0.096\text{min}^{-1}\text{pM}/(\text{mg/dl}), \\ b_7 &= 1.24(\text{mg/dl})\text{min}^{-1}. \end{aligned} \quad (58)$$

Parameter γ in both the models has been chosen equal to 0.2.

The eigenvalues used for the computation of K are:

$$\lambda = -[10^{-4} \ 0.1 \ 0.2 \ 0.4] \quad (59)$$

for the single-kernel model and

$$\lambda = -[10^{-2} \ 2 \cdot 10^{-2} \ 3 \cdot 10^{-2} \ 0.4 \ 0.6 \ 5] \quad (60)$$

Figures 1-2 show the results of the numerical simulations concerning the measured and estimated plasma insulin concentrations over a one hour time range.

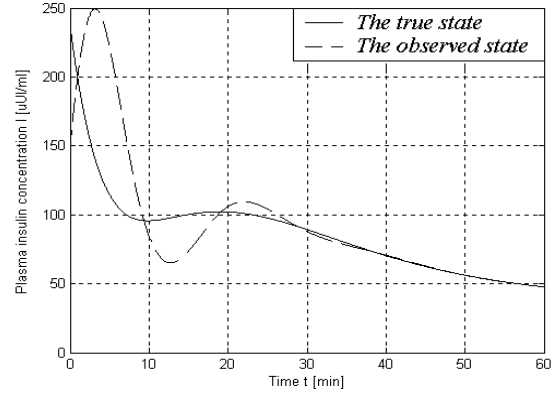


Fig. 1. Observer applied to the single-kernel model

6. CONCLUSIONS AND FUTURE DEVELOPMENTS

Similarly to (De Gaetano *et al.*, 2003), in this work the problem of the state reconstruction, by applying the theory of asymptotic state observation for nonlinear

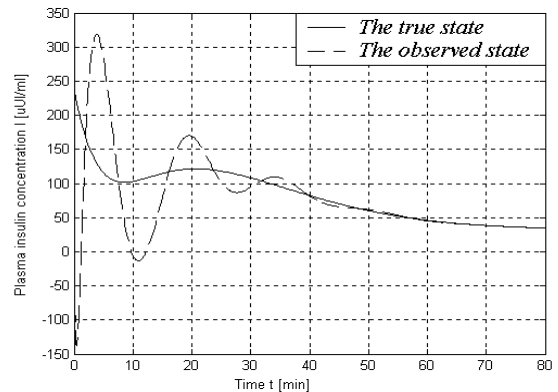


Fig. 2. Observer applied to the double-kernel model

systems, has been explored for distributed-delay kernel models of glucose-insulin homeostasis. The aim is the real-time monitoring of the plasma insulin concentration using only measurements of blood glucose concentration.

An analytic methodology is introduced in order to recast the distributed-delay nonlinear models into a nonlinear systems without delay, in front of an increase of the state space dimension.

The availability of real-time data on the insulin concentration is a prerequisite for the development of an *artificial pancreas* controlling in real time the blood glucose level with optimum insulin infusions from an in vivo pump. Finally, the main aspect, from a biomedical point of view, of the future research is the *clinical validation* of the models used in this paper, based on sets of real measurements of groups.

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