DDE Models of the Glucose-Insulin System: A Useful Tool for the Artificial Pancreas

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Abstract Delay differential equations are widely adopted in life sciences: including delays explicitly in mathematical models allows to simulate the systems under investigation more accurately, without the use of auxiliary fictitious compartments. This work deals with Delay Differential Equation (DDE) models exploited in the specific framework of the glucose-insulin regulatory system, and a brief review of the DDE models available in the literature is presented. Furthermore, recent results on the closed loop control of plasma glycemia, based on DDE models of the individual glucose-insulin system are summarized. Indeed, DDE models revealed to be particularly suited to simulate the pancreatic insulin delivery rate, thereby allowing to treat in a unified fashion both Type 1, where no endogenous insulin release is available, and Type 2 diabetic patients, where the exogenous insulin administration adds up to the endogenous insulin production.

Keywords Glucose-insulin system · Delay differential equation models · Artificial pancreas

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1 Introduction

Diabetes Mellitus comprises a group of metabolic diseases characterized by hyperglycemia. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially eyes, kidneys, nerves, heart, and blood vessels. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular diseases. Diabetes a very high incidence: the number of diabetic patients is expected to double by the year 2030, compared to 2000 data [1]. Hence, diabetes management has a heavy impact on many national public health budgets.

In a healthy person, the blood glucose is maintained between 3.9 and 6.9 mmol/L by means of a complex control system which ensures a balance between glucose entering the bloodstream after liver gluconeogenesis and intestinal absorption following meals, and glucose uptake from the peripheral tissues. This balance is regulated mainly by the insulin, a hormone produced by the β-cells of the pancreas when properly stimulated by the level of plasma glycemia: indeed, insulin enhances the glucose uptake in the muscles and the adipose tissues as well as it promotes the stocking of circulating glucose in excess to the liver.

A pathological increase in blood glucose concentration (hyperglycemia) results from defects in insulin secretion, insulin action, or both. In case of an absolute deficiency of insulin secretion, caused by an autoimmune destruction of the pancreatic β cells, Type 1 diabetes occurs: these patients require exogenous insulin administration for survival. On the other hand, in case of hyperglycemia caused by a combination of resistance to insulin action and inadequate compensatory insulin secretory response, Type 2 diabetes occurs: these patients have therefore insulin resistance and usually also a relative (rather than absolute) insulin deficiency, in the face of increased levels of circulating glucose.

The basic therapeutic procedure for diabetes is the exogenous administration of insulin. This compensation could be accomplished by means of a variety of schemes, depending on the *a priori* knowledge of the patient's glucose-insulin homeostasis and on the technology available for actuating the designed control law. In most widespread cases, glucose control strategies are mainly actuated by subcutaneous administration of insulin, with the dose adjusted by the patients themselves, on the basis of capillary plasma glucose concentration measurements. On the other hand, a real-time closed-loop control scheme would require an algorithm that provides the proper dose of the hormone independently of any action on the patient, and is robust with respect to the many sources of perturbation of the glucose-insulin system like meal ingestion, physical exercise or trivially, malfunctioning of the artificial pancreas devices. To this aim, the use of a mathematical model of the patient's glucose-insulin system would allow to exploit individual optimal strategies to synthesize the exogenous insulin administration. Clearly, the more accurate the model, the more efficient will the control law be.

The modeling of the glucose-insulin system is an appealing and challenging topic in biomathematics and many different models have been presented in the last decades

(see e.g. [2, 3] and references therein). Section 2 provides a brief review on Delay Differential Equation (DDE) models of the glucose-insulin system, and aims to motivate the reason because so many DDE models appeared in the literature along the past decade; Sect. 3 presents recent results on DDE-model-based control laws for the artificial pancreas, focusing on the state of the art, main results obtained and future developments.

2 DDE Models of the Glucose-Insulin System

Most of the available glucose-insulin models are strongly related to the experimental framework they want to replicate and can be roughly split into two main branches: the ones concerning short period experiments like, e.g., the IntraVenous/Oral Glucose Tolerance Test (IVGTT/OGTT), that last no more than 5/6 h, and the others related to long period experiments, mainly concerning the glucose/insulin ultradian oscillations, that usually last 24 h.

2.1 Short Period DDE Models

As far as short period experiments are concerned, models have been proposed mainly with the purpose of estimating the individual insulin sensitivity of tissues in order to predict a possible diabetes progression. In this framework, the mostly used model in physiological research of the glucose metabolism is the Minimal Model [4, 5], proposed for the interpretation of the IVGTT. It consists of three coupled ordinary differential equations, one for the insulin and two for the glucose dynamics, modeling the apparent delay of insulin action on the insulin-dependent glucose uptake by means of an auxiliary remote compartment. The Minimal Model played a crucial role in modeling the glucose-insulin system, mainly because it provided the insulin sensitivity as a combination of the model parameter, thus coming out as a by-product of the model identification procedure. However, some criticisms have been raised in the last decade, mainly related to the mathematical coherence of the model (the coupled equations do not ensure bounded solutions, nor a steady-state equilibrium) and to the lack of apparent validity besides the IVGTT experimental framework.

First DDE models of the glucose-insulin system have been actually proposed to overcome these drawbacks. In [6] the Authors deleted the remote compartment in the glucose dynamics and introduced a distributed delay for the glucose-dependent Insulin Delivery Rate (IDR). Besides being mathematically coherent and more versatile to different sets of experiments apart from the IVGTT, such a DDE model has also been validated on real data and, moreover, it provides the insulin sensitivity by the estimate of a single parameter. Thereafter, there has been a widespread development of DDE models, which revealed to be particularly suitable to replicate the IDR. For instance families of DDE models have been proposed, where general delays are

introduced both in the insulin action on tissue glucose uptake and in the glucose action on pancreatic insulin secretion, [7, 8].

Despite the development of different DDE models of the glucose-insulin system, they have not been adopted in a model-based framework for the artificial pancreas, since [9]. This is because most of the efforts in this research area have been mainly devoted to Type 1 diabetic patients, in whom the absence of a pancreatic IDR motivates urgent research efforts in closed-loop exogenous insulin infusion therapies, and weaken the necessity of preferring DDE models instead of ODE ones. On the other hand, the ability of time-delay systems to better model the endogenous IDR makes it so that DDE-model-based approaches could reveal to be very effective for treating the much more prevalent category of Type 2 diabetic patients.

Below are reported the equations of a DDE model recently exploited for theoretical research in artificial pancreas [10]

$$\begin{aligned} \frac{dG(t)}{dt} &= -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G}, \\ \frac{dI(t)}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g)), \qquad f(G) = \frac{(\frac{G}{G^*})^\gamma}{1+(\frac{G}{G^*})^\gamma}. \end{aligned} \tag{1}$$

where $G(t)$, [mM] and $I(t)$, [pM], denote plasma glycemia and insulinemia. K_{xgi}, [$\text{min}^{-1}\,\text{pM}^{-1}$], is the rate of glucose uptake by insulin-dependent tissues 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; V_G and V_I, [L/kgBW], are the apparent glucose and insulin distribution volume; 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; 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 and G^*, [mM], is the glycemia at which the insulin release is half its maximal rate.

Mathematical coherence has been proven in [8], where the model has been shown to provide positive and bounded solutions, and is endowed with a unique asymptotically stable equilibrium point (for basal glycemia and insulinemia). Sufficient conditions are also given for global stability, that has been investigated in further papers [11, 12].

2.2 Long Period DDE Models

Long-term models of the glucose-insulin system are mainly motivated to reproduce the phenomenon of sustained, apparently regular, long period oscillations of glycemia and insulinemia, known as *ultradian* oscillations. A pioneering work in such a framework has been the paper of Sturis et al. in 1991 [13], a sixth order nonlinear ODE

model according to which the Authors proposed a plausible mechanism for the genesis of the oscillations, suggesting they could originate from the glucose-insulin reciprocal interaction without postulating an intra-pancreatic pacemaker for their existence. In fact, the model presents two delays, both realized by means of additional fictitious compartments: one delay is associated to the suppression of glucose production by insulin (two-compartment model for the insulin kinetics), while the other is related to the effect of insulin on glucose production (four compartment model for the glucose kinetics). The model of Sturis et. al. has been the starting point for many further DDE models, aiming to replicate the occurrence of long period oscillations as coming from a Hopf bifurcation point (see, e.g. [14–18]). It has to be stressed that though the model of Sturis et. al. and its DDE versions have been used, especially in recent years, to study the effect of pulsatile insulin profiles in (pre)-diabetic patients [19–23], to the best of the authors' knowledge, they have not yet been adopted to synthesize a model-based control law for insulin therapy.

3 DDE Model Based Control

First results on DDE-model-based control of the glucose-insulin system can be found in [9, 24], where the DDE model described in (1) was considered for a possible intravenous (iv) administration of the insulin therapy. To this aim the insulin equation in (1) is endowed with an additive control input $u(t)$. Compared to the usual subcutaneous insulin injection, the use of iv insulin administration, delivered by automatic, variable speed pumps provides a wider range of possible strategies and ensures a rapid delivery with negligible delays. As a matter of fact, control algorithms based on iv insulin administration are directly applicable so far only to problems of glycemia stabilization in critically ill subjects, such as in surgical intensive care units after major procedures.

In [9, 24] the input-output linearization with delay cancelation is achieved, by means of suitable inner and outer feedback control laws, with guaranteed internal stability. In particular, a reliable, causal state feedback which allows to reduce a high basal plasma glucose concentration to a lower level, according to a smooth reference glucose trajectory $G_{\mathrm{ref}}(t)$, is designed with:

$$u(t) = \frac{S(G(t), I(t), G(t-\tau_g)) - v(t)}{K_{xgi} G(t)} \tag{2}$$

where

$$\begin{aligned} S(G(t), I(t), G(t-\tau_g)) = & -K_{xgi} I(t) \left(-K_{xgi} I(t) G(t) + \frac{T_{gh}}{V_G} \right) \\ & -K_{xgi} G(t) \left(-K_{xgi} I(t) + \frac{T_{iGmax}}{V_I} f(G(t-\tau_g)) \right) \end{aligned} \tag{3}$$

and $v(t) = \ddot{G}_{ref}(t) + Re(t)$, with $R \in \mathbb{R}^{1\times 2}$ a matrix such that

$$H = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} R \tag{4}$$

has prescribed eigenvalues with negative real part and $e(t) = Z(t) - Z_{\text{ref}}(t)$, with

$$Z(t) = \begin{bmatrix} z_1(t) \\ z_2(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ -K_{xgi} G(t) I(t) + \frac{T_g h}{V_G} \end{bmatrix}, \qquad Z_{\text{ref}}(t) = \begin{bmatrix} G_{\text{ref}}(t) \\ \dot{G}_{\text{ref}}(t) \end{bmatrix} \tag{5}$$

The glucose reference signal to be tracked, $G_{\text{ref}}(t)$, is supposed to be bounded, twice continuously differentiable, with bounded first and second derivatives. Such a closed-loop control law ensures input-to-state stability of the closed loop error system with respect to disturbances occurring in the insulin dynamics, such as insulin actuator malfunctions.

The main drawback concerns the necessity to exploit both glucose and insulin measurement at the present and at a delayed time: insulin measurements are slower and more cumbersome to obtain, more expensive, and also less accurate than glucose measurements. A need exists, therefore, to design a control law avoiding real-time insulin measurements. To this aim, in order to close the loop by means of only glucose measurements, a state observer for the DDE system (1) has been proposed in [25, 26]. By suitably exploiting the state observer theory for nonlinear time delay systems (see [27]), the observer equations for the estimates of glycemia and insulinemia , $\hat{G}(t)$, and $\hat{I}(t)$ respectively, are given by

$$\begin{bmatrix} \frac{d\hat{G}(t)}{dt} \\ \frac{d\hat{I}(t)}{dt} \end{bmatrix} = \begin{bmatrix} -K_{xgi} \hat{G}(t) \hat{I}(t) + \frac{T_{gh}}{V_G} \\ -K_{xi} \hat{I}(t) + \frac{T_{iGmax}}{V_I} f\left(\hat{G}(t - \tau_g)\right) + u(t) \end{bmatrix} + Q^{-1}(\hat{G}(t), \hat{I}(t)) W (G(t) - \hat{G}(t)), \tag{6}$$

where $Q^{-1} \in \mathbb{R}^{2\times 2}$ is the inverse matrix of the Jacobian of the observability map (see [28]), here given, for $\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \in \mathbb{R}^2$, by $\begin{bmatrix} x_1 \\ -K_{xgi} x_1 x_2 + \frac{T_{gh}}{V_G} \end{bmatrix}$. The gain matrix $W \in \mathbb{R}^{2\times 1}$ is chosen in order to assign suitable eigenvalues to matrix $\hat{H}$, defined by means of the Brunowski pair (A_b, C_b) as

$$\hat{H} = A_b - W C_b, \quad \text{where} \quad A_b = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}, \quad C_b = \begin{bmatrix} 1 & 0 \end{bmatrix}. \tag{7}$$

In order to close the loop from the observed state, the control law (2)–(5) suitably exploits the estimates $\hat{G}$ and $\hat{I}$ as follows

$$u(t) = \frac{S(\hat{G}(t), \hat{I}(t), \hat{G}(t - \tau_g)) - v(t)}{K_{xgi} \hat{G}(t)}, \quad t \geq 0 \tag{8}$$

with $v(t) = \ddot{G}_{\text{ref}}(t) + R\hat{e}(t)$, $\hat{e}(t) = \hat{Z}(t) - Z_{\text{ref}}(t)$, and

$$\hat{Z}(t) = \begin{bmatrix} \hat{z}_1(t) \\ \hat{z}_2(t) \end{bmatrix} = \begin{bmatrix} \hat{G}(t) \\ -K_{xgi}\hat{G}(t)\hat{I}(t) + \frac{T_g h}{V_G} \end{bmatrix} \tag{9}$$

Such a control law has been proven to ensure the local convergence of the tracking error to zero. Simulations that validated the theoretical results were also performed in a virtual environment, showing that the results are robust with respect to a wide range of parameter uncertainties or device malfunction. Additionally, the control law has been further evaluated by closing the loop on a *virtual patient*, whose model equations are different from the ones used to synthesize the control law [29]. That means: a minimal model of the glucose-insulin system to design the insulin therapy, and a different, more detailed, comprehensive model to test in silico the control scheme. Such a chosen *maximal* model for the virtual patient, [30], has been recently accepted by the Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas.

Further developments on such a research line involve subcutaneous insulin administration, instead of intravenous infusions, that are usually provided under the direct supervision of a physician. To this aim, in [31–33], the model Eq. (1) are coupled to simple linear model of the insulin absorption from the subcutaneous depot, already exploited with the aim of glucose control in [34]:

$$\begin{aligned} \frac{dG}{dt} &= -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G}, \\ \frac{dI}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I} f\big(G(t-\tau_g)\big) + \frac{S_2(t)}{V_I t_{max,I}}, \\ \frac{dS_2}{dt} &= \frac{1}{t_{max,I}} S_1(t) - \frac{1}{t_{max,I}} S_2(t), \\ \frac{dS_1}{dt} &= -\frac{1}{t_{max,I}} S_1(t) + u(t), \end{aligned} \tag{10}$$

with $t_{max,I}$, [min], the time-to-maximum insulin absorption. The same ideas based on the input/output feedback linearization are applied in this framework with, however, much more complicated formulas to synthesize the control law: preliminary results can be found in [32] where the control law is synthesized by assuming a complete knowledge of the state of the system (i.e. glucose and insulin real-time measurements), and local convergence to zero of the tracking error $G(t) - G_{\text{ref}}(t)$ is proven. In [33] the same convergence results are obtained by means of a state observer for the intravenous and subcutaneous insulin values, and the convergence to zero of the tracking error is proven in [31].

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