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Model-based control of plasma glycemia: Tests on populations of virtual patients

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ABSTRACT

Closed-loop devices delivering medical treatments in an automatic fashion clearly require a thorough preliminary phase according to which the proposed control law is tested and validated as realistically as possible, before arranging *in vivo* experiments in a clinical setting. The present note develops a virtual environment aiming to validate a recently proposed model-based glucose control law on a solid simulation framework. From a theoretical viewpoint, the artificial pancreas has been designed by suitably exploiting a minimal set of delay differential equations modeling the glucose–insulin regulatory system; on the other hand, the validation platform makes use of a different, multi-compartmental model to build up a population of virtual patients. Simulations are carried out by properly addressing the available technological limits and the unavoidable uncertainties in real-time continuous glucose sensors as well as possible malfunctioning on the insulin delivery devices. The results show the robustness of the proposed control law that turns out to be efficient and extremely safe on a heterogenous population of virtual patients.

1. Introduction

Diabetes Mellitus is a major chronic disease that comprises a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Being definitely deficient of the endogenous pancreatic insulin release, Type 1 diabetic patients require exogenous insulin administration to survive. Another, much more prevalent form of the disease (Type 2 diabetes) is caused by a combination of resistance to insulin action and inadequate compensatory insulin secretory response. These individuals have therefore insulin resistance and usually have relative (rather than absolute) insulin deficiency.

The *Artificial Pancreas* refers to the set of glucose control strategies aiming to cope with most malfunctioning of the endogenous insulin feedback action (in Type 1 diabetes only exogenous insulin is available, while in Type 2 exogenous insulin complements pancreatic production) by means of exogenous insulin administration, usually delivered with subcutaneous or intravenous infusions. The use of intravenous insulin administration, delivered by automatic, variable speed pumps under the direct supervision of a physician, provides a wider range of possible strategies with respect to the subcutaneous route, and ensures a rapid delivery with negligible delays. As a matter of fact, control algorithms based on intravenous infusions (we can cite, among the others, [29,31,4,6,15,14,25]) 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, [33].

In the present paper a virtual environment is developed, aiming to test and validate a recently proposed model-based glucose control law. Closed-loop algorithms for the artificial pancreas can be designed according to a "model-based" or to a "model-less" approach, see e.g. [3]. The former approach properly exploits the chosen mathematical structure of the glucose–insulin system, thus allowing to face the control problem from a mathematical viewpoint. To this aim, small-scale "minimal models", according to which closed-loop control strategies can be found in the literature, are usually preferred (see, e.g. [6,13,25]). Unfortunately, a model-based approach cannot exploit the mathematical structure of a, presumably more realistic, multi-compartmental "maximal model" because of its complexity, unless deciding to make linearization, discretization or model reduction. On the other hand model-less approaches allow to consider "maximal models" straightforwardly

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as virtual patients themselves: the control law is designed by means of optimization algorithms implemented accounting for the input–output time-courses provided by the model, but we give up the opportunity to make proofs of the closed-loop theoretical validity of the chosen insulin infusion therapy. In this framework there can be cited, among the others, [29,11,31,4,20,18,15,14,17]. The present paper aims to bridge the two approaches providing a virtual environment (built up according to a population of virtual patients generated by a "maximal model") to a model-based control strategy synthesized according to a "minimal model". To this end, we make a specific choice (from the recent literature) for both the model-based control law and the "maximal model" of the virtual patients. However, in principle, the philosophy of the paper can be applied to any model-based control law, according to virtual patients generated by any "maximal model".

The model-based control law to be validated in the proposed virtual algorithm has been presented by the authors in the recent literature by suitably exploiting a Delay Differential Equation (DDE) model of the glucose–insulin system [25]. In [25] it has been mathematically proven that the system described by such a DDE model can be controlled to track a desired glucose profile in order to reduce a hyperglycemic basal state down to a safe euglycemic level by means of glucose measurements only, and that such a safe basal level for the closed loop system is asymptotically stable. Differently from other closed-loop approaches, which make use of Ordinary Differential Equation (ODE) models of the glucose–insulin system to design the feedback control law according to many different control strategies (see, e.g. Model Predictive Control in [11,18], Parametric Programming in [6], H_∞ control in [29,15,14], non-standard H_∞ control in [4,31]), a DDE model-based control law is able to take into account irregularly varying pancreatic Insulin Delivery Rate (IDR) (see e.g. [19] and references therein), thus allowing the construction of a control scheme also applicable to Type 2 diabetic patients. Despite the great spread of DDE models of the glucose–insulin system in the last decade, their use in the field of the artificial pancreas has only recently sparked interest, mainly limited to open-loop approaches (see [12] and references therein). Indeed, attempts to design closed-loop ODE model-based glucose controls have been limited so far to Type 1 diabetic patients (who have essentially no endogenous insulin production), circumventing in this way the need to model pancreatic IDR. The DDE model here considered can realistically account for endogenous IDR, thereby modeling in a unified fashion healthy subjects, insulin resistant and insulin-deficient diabetic patients.

The large-scale mathematical model of the virtual patient used in the present work [5] has been chosen because of its widespread use in this field: indeed, a computer simulator of diabetic patients based on this extended model has been the first of its kind to be accepted by the *Food and Drug Administration (FDA)* as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas [16].

The novel contribution of the present work is the construction of the virtual environment making it possible to evaluate whether a model-based theoretical control law, designed according to a parsimonious or compact model of the glucose insulin system, is robust enough to ensure high levels of safety and efficacy also when closed onto a different, multi-compartmental (presumably more realistic) model, in spite of the many unavoidable sources of uncertainties pertaining to a real-time closed-loop setting. A pivotal role in building up the *in silico* environment is played by the identification procedure, necessary to make the two models consistent with each other. This task is accomplished by considering a virtual Intra-Venous Glucose Tolerance Test (IVGTT) generated by the *Average Virtual Patient (AVP)* representative of a population of virtual patients, and by fitting the compact model parameters on the glucose–insulin evolutions given by the AVP. The model-based control law [25] is synthesized by suitably exploiting the identified compact model parameters: to this end the control parameters are tuned by simulations of the compact model, in the same way as it should be done for individualized insulin therapy before applying the control law to a real patient. In this way a fixed, unique insulin infusion therapy scheme is designed, to be administered to a population of virtual patients generated by properly varying the AVP parameters. Uncertainties in blood glucose measurements, as well as malfunctioning of the insulin delivery devices are considered, consistently with current technology, in order to obtain an effective benchmark for the closed-loop control and to show in fact the robustness of the proposed approach. Safety and efficacy criteria will be adopted in order to stress the robustness of the control methodology with respect to a rather heterogeneous population of virtual patients, according to recent literature [2]. A preliminary version of the paper has been presented in [26].

2. Material and methods

The basic idea of the paper is to use a simplified (though accurate) model of the glucose–insulin system to synthesize a model-based glucose control law, and to use a different, more exhaustive, comprehensive model to test the control law on a rather heterogenous population of virtual patients. This idea is developed in this section in two steps: the former is devoted to briefly recap the feedback control scheme adopted for the exogenous insulin administration; the latter deals with the development of the virtual environment in details.

2.1. The model-based control law

The insulin infusion therapy under investigation is the one recently published in [25], whose design principles make use of the following DDE mathematical model of the glucose–insulin system, [22,28]. The equations are written with respect to plasma glycemia, $G(t)$, [mM], and insulinemia, $I(t)$, [pM]:

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

with K_{xgi}, [$\mathrm{min}^{-1}\,\mathrm{pM}^{-1}$], the rate of (insulin-dependent) glucose uptake by tissues per pM of plasma insulin concentration; T_{gh}, [(mmol/kg BW)/min], the net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake; V_G, V_I, [L/kg BW], the apparent distribution volumes for glucose and insulin, respectively; K_{xi}, [min^{-1}], the apparent first-order disappearance rate constant for insulin; T_{iGmax}, [(pmol/kg BW)/min], the maximum rate of second-phase insulin release; τ_g, [min], the apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations.

The nonlinear map $f(\cdot)$ models the endogenous pancreatic insulin delivery rate as:

$$f(G) = \frac{(G/G^*)^\gamma}{1+(G/G^*)^\gamma}, \tag{2}$$

where 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 of its maximum rate.

The signal $u(t)$, [(pmol/kg BW)/min], is the control input, i.e. the exogenous insulin delivery rate.

The subject is supposed to be at rest before the insulin therapy starts, so that the initial conditions are equal to the constant, hyperglycemics basal levels (G_b, I_b):

$$G(\tau) = G_b, \quad I(\tau) = I_b, \quad \tau \in [-\tau_g, 0]. \tag{3}$$

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