Biomedical Signal Processing and Control 40 (2018) 204–213

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Linear parameter-varying model to design control laws for an artificial pancreas

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ARTICLE INFO

Article history:
Received 21 February 2017
Received in revised form 20 August 2017
Accepted 16 September 2017

Keywords:
LPV model
Controller synthesis
Type 1 diabetes
Artificial pancreas
ν-gap metric

ABSTRACT

The contribution of this work is the generation of a control-oriented model for insulin-glucose dynamic regulation in type 1 diabetes mellitus (T1DM). The novelty of this model is that it includes the time-varying nature, and the inter-patient variability of the glucose-control problem. In addition, the model is well suited for well-known and standard controller synthesis procedures. The outcome is an average linear parameter-varying (LPV) model that captures the dynamics from the insulin delivery input to the glucose concentration output constructed based on the UVA/Padova metabolic simulator. Finally, a system-oriented reinterpretation of the classical *ad-hoc* 1800 rule is applied to adapt the model's gain.

The effectiveness of this approach is quantified both in open- and closed-loop. The first one by computing the root mean square error (RMSE) between the glucose deviation predicted by the proposed model and the UVA/Padova one. The second measure is determined by using the ν-gap as a metric to determine distance, in terms of closed-loop performance, between both models. For comparison purposes, both open- (RMSE) and closed-loop (ν-gap metric) quality indicators are also computed for other control-oriented models previously presented.

This model allows the design of LPV controllers in a straightforward way, considering its affine dependence on the time-varying parameter, which can be computed in real-time. Illustrative simulations are included. In addition, the presented modeling strategy was employed in the design of an artificial pancreas (AP) control law that successfully withstood rigorous testing using the UVA/Padova simulator, and that was subsequently deployed in a clinical trial campaign where five adults remained in closed-loop for 36 h. This was the first ever fully closed-loop clinical AP trial in Argentina, and the modeling strategy presented here is considered instrumental in resulting in a very successful clinical outcome.

1. Introduction

An artificial pancreas (AP) is a system that automatically controls glycemia in controls glycemia in type 1 diabetes mellitus (T1DM) patients by infusing an adequate amount of insulin, according to the measured glucose level. The decision of how much insulin to infuse is made by a control algorithm. In general, this algorithm is based on a mathematical model that is required to suitably describe the insulin-glucose dynamics. Thus, the model constitutes a key element in the development of a reliable AP.

Several simulation models have been proposed since the late 1970s [1–4]. They have been used to perform a vast amount of *in silico* studies, giving an affordable and safe means of testing glucose controllers. Thus, the use of computer simulation has accelerated the development of AP [5].

The main goal of simulation models is to provide a blood glucose prediction as close as possible to a real situation. However, this class of models is not generally used for controller synthesis, due to its excessive mathematical complexity. Therefore, simplifications of these models are generally considered at the controller design phase, because most of the well established theory of control law design accommodates only simpler models that are normally referred to as control-oriented models. Thus, although control-oriented models have to represent the underlying dynamics to some degree, they are mainly obtained for synthesis purposes and have a much simpler mathematical formulation.

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http://dx.doi.org/10.1016/j.bspc.2017.09.021
1746-8094/

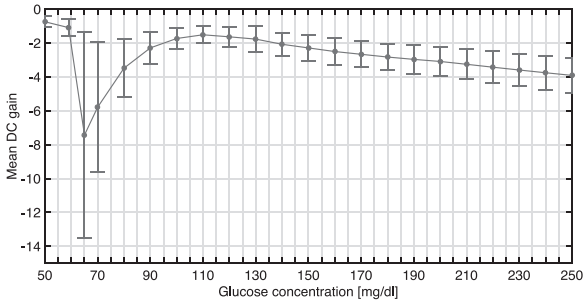

Fig. 1. Mean DC gain for the adult patients of the distribution version of the UVA/Padova simulator, linearized at different glucose concentrations. The mean ±1 STD values are represented by vertical bars.

Another aspect that is worth considering in designing glucose controllers is that most metabolic parameters related to the insulin-glucose system are not easily identifiable in practice, and finding each parameter of a complex and time-varying model is intractable. Therefore, some tuning based on only a small number of easily obtainable patient-specific characteristics is required in practice for a safe and effective AP [6]. Consequently, a few works have been focused on such personalization [7–11].

One interesting approach to obtain a personalized control-oriented model is to adapt a low-order model structure based on *a priori* patient information. For example, given the patient's total daily insulin (TDI), an insulin sensitivity factor can be obtained using the so-called 1800 rule (1800/TDI) that is suggested in the medical care literature [12]. From the medical point of view, the 1800 rule indicates the maximum drop in glucose concentration, measured in mg/dl, after a 1 U injection of rapid-acting insulin. Since the work in [13], that rule has been used in several studies, both clinical and *in silico*, to tune the gain of a linear time invariant (LTI) model to a particular patient [14–19]. Nevertheless, the 1800 rule is an empirical rule, and the clinical literature does not advise at which glucose concentration it works best, or is most appropriate. This is important because the patient's insulin sensitivity depends, amongst other factors (see [20,21]), on the glucose concentration, meaning that an (LTI) representation of the insulin-glucose system is not enough to totally describe it. This nonlinear behavior is illustrated in Fig. 1, where the mean DC gain for all the *in silico* adults of the UVA/Padova metabolic simulator [22,23] linearized at several glucose concentrations is depicted. Steady-state glucose concentrations were achieved by only adapting the insulin infusion rate, i.e., the higher the insulin infusion rate, the lower the steady-state glucose concentration, and vice versa. Therefore, the hypoglycemic region presented in Fig. 1 actually represents a hypoglycemic/hyperinsulinemic region, and the hyperglycemic region actually represents a hyperglycemic/hypoinsulinemic region. In order to understand the shape of that figure, both regions can be analyzed separately as follows.

Concerning the hypoglycemic/hyperinsulinemic region, it can be seen from Fig. 1 that there is an increase in insulin sensitivity when glucose decreases below approximately 120 mg/dl. In the UVA/Padova model, it is assumed that the insulin-dependent utilization increases when glucose decreases below its basal value, which is 120 mg/dl on average. This coincides with clinical knowledge [24,25]. The loss of insulin sensitivity when glucose decreases below very low concentrations can be explained in the following way. On the one hand, the insulin-dependent utilization in the UVA/Padova model is described considering a "risk" function that increases when glucose decreases below its basal value (the lower the glucose value, the higher the risk), and saturates when glucose reaches 60 mg/dl. On the other hand, there is a counterregulatory response due to the glucagon action. The static secretion of glucagon increases when glucose decreases below its basal value. Together, the increase in glucagon secretion and the saturation of the "risk" function related to the insulin-dependent utilization make the region on the left of Fig. 1 (glucose from 50 to 60 mg/dl) less sensitive to insulin.

Concerning the hyperglycemic/hypoinsulinemic region, we are aware of the basic clinical knowledge that indicates a loss of insulin sensitivity in hyperglycemia. However, it should be considered that such knowledge is generally based on hyperinsulinemic clamps [26,27], and that a hyperglycemic/hypoinsulinemic event is quite different to many, but not all, real-world hyperglycemic events, which are usually induced by meal intake and are accompanied by prolonged glucose appearance and increased insulin infusion. For example, hyperinsulinemia is associated with insulin receptor deficiency [28,29], and several works suggest that it is the main inducer of insulin resistance, and not hyperglycemia *per se* [30–32]. In addition, basing a control law on this case may be safer than basing it on the expectation of reduced insulin sensitivity, because doing so may result in elevated insulin delivery and thus may lead to postprandial hypoglycemia.

Multiple linear parameter-varying (LPV) models have been proposed in the past [33–38]. An LPV model is a family of linear time-varying systems described in standard state-space form, with matrices (A, B, C, D) depending on a time-varying parameter vector $\rho(t)$, measured in real time:

$$\begin{aligned} \dot{x}(t) &= A(\rho)x(t) + B(\rho)u(t) \\ y(t) &= C(\rho)x(t) + D(\rho)u(t). \end{aligned} \tag{1}$$

LPV models were introduced in the control community in the early 1990s. The first significant results in terms of analysis and controller synthesis can be found in [39–42]. It is a good way to represent a large class of nonlinear models, and particularly, to apply gain-scheduling control in a systematic way, with theoretical guarantees of performance and stability [43]. While in traditional gain-scheduling the gain of a linear controller is adjusted as the operating condition changes (something typically used in aircraft control), in LPV control, a smooth real-time adaptation of the controller to the operating condition is provided. In addition, but at the cost of conservatism, the approach can be applied to an even wider range of systems known as *quasi*-LPV systems. In this case, the time-varying parameter can be one of the states of the model, in particular the output. Further comments on *quasi*-LPV models can also be found in [39,44]. In [33] and [34], the Bergman minimal model [1] was considered and transformed into a *quasi*-LPV model by an appropriate choice of parameters. In [35–37], the Sorensen compartmental model [2] was linearized at different points, which were defined as the vertexes of an affine-LPV model that covers the original nonlinear one. This model was used as an uncertainty LTI model set, and an $\mathcal{H}_\infty$ controller was designed to control it, hence, the time-varying characteristics were not exploited. Finally, in [38], an LPV approach using the Cambridge model [4] was developed.

In this work, the discussion presented in [45] is considered and adapted to the AP application. There, it is explained that the use of complex, high-order models for synthesis is not necessarily related to better closed-loop performance. In that sense, a simple third-order LPV model from the insulin delivery input to the glucose deviation output is proposed here, and personalized by a system-oriented reinterpretation of the 1800 rule. Thus, a combination of the model personalization using *a priori* patient-specific characteristics with the time-varying description of the dynamics by means of an LPV system representation, is achieved. Due to the fact that this modeling strategy is intended mainly for controller design, the ν-gap metric δ_ν (see [46,47]) is employed to quantify the quality of achievable closed-loop performance afforded by the control-oriented model. Model identification and tuning are per-