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Analysis of three T1DM simulation models for evaluating robust closed-loop controllers

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ABSTRACT

This work compares three well-known models and simulators in terms of their use in the analysis and design of glucose controllers for patients with Type 1 Diabetes Mellitus (T1DM). The objective is to compare them in practical scenarios which include: model uncertainty, time variance, nonlinearities, glucose measurement noise, delays between subcutaneous and plasma levels, pump saturation, and real-time controller implementation. The pros and cons of all models/simulators are presented. Finally, the simulators are tested with different robust controllers in order to identify the difficulties in the design and implementation phases. To this end, three sources of uncertainty are considered: nonlinearities, time-varying behavior (intra-patient) and inter-patient differences.

1. Introduction

The artificial automatic control of glucose for patients with Type 1 Diabetes Mellitus has been a long-standing objective since the creation of continuous glucose monitors and insulin pumps [1]. The Artificial Pancreas Project launched by the Juvenile Diabetes Research Foundation (JDRF) in 2005 generated a great deal of research in this area in the last few years.

In order to design an automatic controller that may connect a glucose monitor and an insulin pump, a model of the underlying dynamics is generally necessary. To verify the effectiveness of the controller before clinical tests, several *in silico* evaluations should be performed. To this end, a more elaborate dynamic model which includes not only the glucose–insulin behavior, but also many other practical issues (insulin pump constraints, glucose monitor errors, interstitial-plasma delays) should be implemented as a simulator.

A few models based upon ordinary differential equations (ODE) have been used for simulation and control design purposes [2,3,1,4]. Among the initial ones we can mention Sorensen's 19th order model [5] and Bergman's 3rd. order model [6]. One of the first control algorithms was presented in 1991 by Fisher [7] and was based on [6], and more sophisticated models and controllers have been developed since then. Many of them are instrumental for patient analysis, like the AIDA freeware available at http://www.2aida.org/aida/intro.htm [8], while others are also used for automatic controller design and testing. The aim of this work is to present a comparison between the most relevant models in this last group, which can be considered to be the standards in terms of controller performance analysis.

Controller design for this process has been approached in different ways using different models (see [1] for a survey). Solutions go from simple PID control to heuristic fuzzy-logic procedures or parametric-programming [9]. The

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aforementioned models present significant sources of uncertainty that are worth considering. Robust Control Theory [10–12] has been applied to this problem, centered on the uncertainty issue. Also, a Linear Parameter Varying (LPV) model has been derived in [13] based on Sorensen's model and controlled by an H_∞ linear time invariant (LTI) control in [14,15]. In addition, due to the nature of the dynamics in all models, MPC [16–18], nonlinear control design methods [19,20], LPV and Unfalsified control (UC) [21,22], have also been applied. Based on the latter, attention should be paid to all of the following issues:

- Model uncertainty (dynamics, intra- and inter-patient).
- Nonlinear phenomena.
- Time delays, actuator saturation, measurement noise.
- Real-time implementation.

The objective of this work is to compare the three main models which are used in controller (closed-loop) testing: Sorensen's 19th order model [5], the model developed by the Universities of Virginia and Padova (UVa/Padova) [23] and the Cambridge model [18]. The two latter ones have been implemented in the form of simulators as well. As a byproduct of our research, several errors in the literature have been found and are pointed out in order to help the practitioner when programming these models [12].

Another important point is their use in controller synthesis and implementation in practical situations which should include all the issues mentioned previously. In particular, robust controllers should cope with model uncertainty. Hence, three sources of uncertainty (nonlinearities, inter- and intra-patient variations) are considered. The first is interpreted as model variations among different linearization points. The last one considers the time-varying behavior within a certain patient. The time delays, actuator saturation and measurement noise will be included in the design as part of the synthesis weights and also in the closed-loop simulation tests.

The paper is organized as follows. Sections 2–4 describe the three aforementioned dynamic models and simulators, respectively. Section 5 compares them from different points of view. Section 6 is devoted to the application of these models/simulators to controller design and to performance results obtained from these robust controllers. Final conclusions are drawn in Section 7.

2. Sorensen's model

Sorensen's mathematical model is an explanatory physiological mechanism of the glucose metabolism in a normal average man. It divides the body into six compartments: (1) brain, representing the central nervous system; (2) heart and lungs; (3) gut; (4) liver; (5) kidneys and (6) muscular skeleton and adipose tissue (peripheral). In addition, each compartment is composed of three spaces: (1) blood capillary, fed by the arterial blood and evacuated by the venous one; (2) interstitial and (3) intracellular. Nevertheless, the number of spaces can be reduced to two or to one, depending on the permeability of the membranes in each compartment.

In Sorensen's formulation three models interact: glucose, insulin and glucagon. In order to obtain a mathematical representation, a mass balance is performed in each physiological compartment. As a consequence, 12 nonlinear ordinary differential equations are obtained for the glucose (three associated to non dimensional variables) and glucagon dynamics and seven linear ones for the insulin. It is important to note that the linearity in the insulin model is due to the fact that diabetes type I is considered. This assumption not only induces linearity, but also decouples the insulin dynamics from the others. The glucose absorption model in [8] is used by several other authors [11,13–15], as well as in the AIDA simulator, instead of the original one employed in [5]. A close analysis of the dynamic equations (see Appendix A) indicates several inconsistencies with respect to the models presented in previous works (see also [12]). For example in [13], variable A_{IHGU} is confused with A_{IHGP} in Eq. (4). In the same work, there are no parenthesis in Eq. (3) and there are numerical differences in Eq. (7). Also in Eq. (5) the denominator should read T_P^I/V_P^T instead of $1/T_P^I V_P^T$. These last three errors are also present in [11]. In Eq. (2) of [10], instead of V_P^C we find V_P^T, which does not allow its simplification. All these can always be interpreted as typing errors. Nevertheless, there is a common error in all of these works and also in [1] which concerns Eq. (6). The variable which should be there is not I_K^C, but I_H^C instead. This error already appears in the original work [5] in the section where the complete model is presented (pages 213–222), but the correct variable can be identified through the analysis of page 134 over Γ_{KC}, where the article [24] is referenced. The latter can be also ratified by the programming instructions of the model in [5] on page 535.

3. UVa/Padova's model/simulator

This model is presented in [25] and divides the body into two subsystems: glucose and insulin, each divided into two compartments. The parameter adjustment is based on experiments over 204 normal subjects in order to obtain a non-diabetic model (a type 2 diabetic model is also obtained with another database). The GIM simulator [26] adapts the previous non-diabetic model in order to simulate a type 1 diabetic subject which includes a model of subcutaneous (s.c.) insulin kinetics. The glucose absorption model used in [25,26,23] is the one described in [27]. The complete model equations used in GIM are presented in Appendix B.

The UVa/Padova Type 1 Diabetes Mellitus Simulator (T1DMS), which is based on the previous model, is presented in [23]. Its distributed version can be obtained through the UVa/Padova organization, enhanced by models of insulin pumps and glucose monitors, both considered subcutaneous. The aforementioned distributed version has a cohort of 30 virtual[3] patients (10 adults, 10 adolescents, 10 children). A more elaborate model with a cohort of 300 patients and

[3] By virtual we mean a synthetic patient which has been designed by combining different parameters in the simulator.