New Principles and Adequate Control Methods for Insulin Dosage in Case of Diabetes

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Abstract. The paper is a short summary of the author's PhD dissertation with the same title [1], submitted at the Budapest University of Technology and Economics in November 2007. The thesis is a multidisciplinary work including physiological modelling and control, control engineering and informatics and the new scientific results are structured on three parts: modelling concepts of Type I diabetes, robust control methods for optimal insulin dosage and symbolic computation-based robust algorithms using *Mathematica*.

Keywords: diabetes mellitus, glucose-insulin control, minimal-model, Sorensen-model, robust control, LPV control, *Mathematica*.

1 Introduction

Diabetes mellitus is one of the most serious diseases which need to be artificially regulated. The statistics of the World Health Organization (WHO) predate an increase of adult diabetes population from 4% (in 2000, meaning 171 million people) to 5,4% (366 million worldwide) by the year 2030 [2]. This warns that diabetes could be the "disease of the future", especially in the developing countries (due to the stress and the unhealthy lifestyle).

In many biomedical systems, external controller provides the necessary input, because the human body could not ensure it. The outer control might be partially or fully automatized. The self-regulation has several strict requirements, but once has been designed it permits not only to facilitate the patient's life suffering from the disease, but also to optimize (if necessary) the amount of the used dosage.

The blood-glucose control is one of the most difficult control problems to be solved in biomedical engineering. One of the main reasons is that patients are extremely diverse in their dynamics and in addition their characteristics are time varying. Due to the inexistence of an outer control loop, replacing the partially or totally deficient blood-glucose-control system of the human body, patients are regulating their glucose level manually. Based on the measured glucose levels (obtained from extracted blood samples), they decide on their own what is the necessary insulin dosage to be injected. Although this process is supervised, mishandled situations often appear. Hyper- (deviation over the basal glucose level) and hypoglycemia (deviation under the basal glucose level) are both dangerous cases, but on short term the latter is more dangerous, leading for example to coma.

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Starting from the Seventies lot of researchers investigate the problem of the glucose-insulin interaction and control. The closed-loop glucose regulation as it was several times formulated [3, 4, 5], requires three components: glucose sensor, insulin pump, and a control algorithm, which based on the glucose measurements, is able to determine the necessary insulin dosage.

The author's PhD dissertation [1], focused on the last component and analyzed robust control aspects of optimal insulin dosage for Type I diabetes patients.

To design an appropriate control, an adequate model is necessary. In the last decades several models appeared for Type I diabetes patients. The mostly used and also the simplest one proved to be the minimal model of Bergman [6] and its extension, the three-state minimal model [7]. However, the simplicity of the model proved to be its disadvantage too, while in its formulation a lot of components of the glucose-insulin interaction were neglected. Therefore, the model is valid only for Type I diabetes patients under intensive care. The dynamic characteristics of the model are created by artificially dosed glucose input. As a result, the model can simulate only a 3 hours period. Furthermore, it was demonstrated, that the model control possibilities are limited, while it is very sensitive to its parameters variance.

Henceforward, extensions of this minimal model have been proposed [8, 9, 10, 11], trying to capture the changes in patients' dynamics, particularly with respect to insulin sensitivity, Also with respect to the meal composition, minimal model extensions were created [12, 13]. In the PhD thesis cited by the current paper [1], the author used the modified minimal model of Bergman proposed by [11], as well as the extended three-state minimal model [7].

Beside the Bergman-model other more general, but more complicated models appeared in the literature [14, 15]. The most complex one proved to be the 19th order Sorensen-model [15]. Even if the model describes in the most exact way the human blood glucose dynamics, its complexity made it to be rarely used in research problems. Nowadays, it is again more often investigated (due to its general validity), therefore the second model considered by the author in his PhD thesis is the Sorensen-model.

Regarding the applied control strategies, the palette is very wide [16]. Starting from classical control strategies (ex. PID control [17]) to soft-computing techniques (ex. neuro-fuzzy methods [18]), adaptive [11], model predictive [3, 19], or even robust H_∞ control were already applied [4, 5]. However, due to the excessive sensitivity of the model parameters (the control methods were applied mostly on the Bergman minimal model), the designed controllers were true only for one (or in best way for few) patient(s).

As a result, investigations demonstrated [3, 5], that even if the best way to approach the problem is to consider the system model and the applied control technique together, if high level of performance is desired, a low complexity control (like PID) is not effective. Therefore, the literature has oriented in two directions: adaptive control and robust control techniques.

The advantage of the adaptive control is the retuning possibility of the controller even in its working conditions. However, its disadvantage appeared if the complexity of the diabetes model was grown. Robust control adjusted the disadvantages of the adaptive control technique, but the designing steps are more difficult. Due to the fact that the literature has clearly presented the adaptive control possibilities of the glucose-insulin control, the PhD dissertation of the author [1], focuses on the robust control methodology.

2 New Modelling Concepts for Type I Diabetes

The proposed modeling formalisms cover the analytical investigation of the high complexity Sorensen-model and the extension of the modified Bergman minimal model. In this way, the proposed approximations are indicating numerical algorithmization for complex optimal control strategies while cover a bigger diabetes population.

For the extension of the modified minimal model, an internal insulin device was proposed. In this way, without damaging the simple structure of the Bergman model it was possible to model not only the Type I intensive care situation, but also the physiological variation of the interstitial insulin.

In case of the Sorensen-model, for an easier handling, inside the physiological boundaries, an LPV (Linear Parameter Varying) modeling formalism was proposed. In this way the model is possible to be reduced to a corresponding degree and consequently to ease the control possibilities and the applicability of the Sorensen-model.

3 Robust Control Methods for Optimal Insulin Dosage in Case of Type I Diabetic Patients

The proposed robust control methods for insulin dosage were structured on the two considered models.

Firstly, the modified minimal model of Bergman was investigated. The mini-max control method was developed comparing it with the classical LQ method. Furthermore, using the μ-synthesis method, parameter uncertainty was taken into account, which supplements the H_∞ method in guaranteeing the robust performance requirements. Moreover, with suitable parameterization, a quasi-Affine Linear Parameter Varying system-set have been defined and exploiting this result a (nonlinear) controller was designed ensuring quadratic stability.

Regarding the Sorensen-model, using the normoglycaemic insulin input, the high complexity Sorensen-model was parameterized and described with politopic LTI (Linear Time Invariant) systems. With the so built LPV model a corresponding controller using induced L_2 norm minimization was designed. Finally, with the nonlinear (LPV) controller the nonlinear Sorensen-model was controlled guaranteeing γ performance level.

4 Symbolic Computation-Based Robust Algorithms with *Mathematica*

To ease the applicability of the applied robust methods, user-friendly symbolic algorithms were developed under *Mathematica*, which help the introduction of the so developed insulin dosage algorithms in therapeutics as well as in education.

Firstly, the extended LQ (minimax) method was symbolically implemented under *Mathematica*. It was shown how MATLAB selects its own solution (from the two resulting solutions), and a general formula was determined for the worst-case result in case of the modified minimal model of Bergman.

Secondly, regarding the modified minimal model of Bergman it was shown, that the applicability of the minimax method has practical limitations. Therefore, for the modified minimal model of Bergman a solution was proposed, using Gröbner-bases, which spans these limitations. In this way, even if the worst case solution cannot be achieved, it is possible to obtain a better solution than the classical LQ one.

Finally, the graphical interpretation of the H_∞ method implemented under *Mathematica* uses a requirement envelope. For the disturbance rejection criteria the author formulated and extended the requirement envelope's criterion-set with another criterion. The correctness of this „plus" criterion was demonstrated on the extended minimal model of Bergman, and it was compared with literature results. It was presented that the constant used in the proposed plus criteria can be connected with the sensor noise weighting function used under MATLAB.

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