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NEW PRINCIPLES AND ADEQUATE CONTROL METHODS FOR INSULIN DOSAGE IN CASE OF DIABETES

Summary of PhD thesis

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1. Introduction

Diabetes mellitus is one of the most serious diseases which needs to be artificially regulated. The newest 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 [1]. 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 it 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 by doctors (diabetologists), 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.

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 [2], [3], [4], requires three components:

- Glucose sensor (already realized even for 10 min. frequent readings: MiniMed [5], Glucowatch [6]);
- Insulin pump, for insulin injection (MiniMed [7], Disetronic [8]);
- Control algorithm, which based on the glucose measurements, is able to determine the necessary insulin dosage.

The current dissertation focuses on the last component and analyzes 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 [9] and its extension, the three-state minimal model [10]. 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 true 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 [11], [12], [13], [14], [15], trying to capture for the glucose-insulin interaction the changes in patients' dynamics, particularly with respect to insulin sensitivity, Also with respect to the meal composition, minimal model extensions were created [16], [17]. The current PhD thesis uses the modified minimal model of Bergman proposed by [15], as well as the extended three-state minimal model [10].

Beside the Bergman-model other more general, but more complicated models appeared in the literature [18], [19], [20], [21]. The most complex one proved to be the 19th order Sörensen-model [21], which is an improvement of an earlier model [22]. Even if the model describes in the most exact way the human blood glucose dynamics, its complexity made to be used rarely in research problems. Nowadays, it is often used again (due to its general validity), therefore the second model of my investigations is represented by the Sörensen-model.

Regarding the applied control strategies, the palette is very wide [23]. Starting from classical control strategies (PID control [24], cascade control [25], optimal control [26]), to soft-computing techniques (fuzzy methods [27], neural networks [28], neuro-fuzzy methods [29]), adaptive [11], [15], [30], [31] model predictive [2], [32], [33], or even robust H_∞ control were already applied [3], [4]. 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 [2], [4], that even if 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 has grown. Robust control adjusted the disadvantages of the adaptive control technique, but the designing steps are difficult. Due to the fact that the literature has clearly presented the adaptive control possibilities of the glucose-insulin control, what's more, even in the BUTE Biomedical Engineering laboratory such a PhD thesis appeared ten years ago [15], the current dissertation focuses on the robust control methodology.

2. Summary of new scientific results

1st Thesis Group – New modeling principles for Type I diabetes

I have formulated new modeling principles in case of Type I diabetes mellitus. My modeling formalisms are extended on the analytical investigation of the modified minimal model of Bergman and on the high complexity Sörensen-model. Furthermore, the proposed approximations are indicating numerical algorithmization for complex optimal control strategies as well as for covering a bigger diabetes population.

Publications related to this thesis group: [K-3], [K-5], [K-8], [K-18], [K-29], [K-30], [K-31].

1.1. Extension of the modified minimal model of Bergman.

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

1.2. LPV modeling of the Sörensen-model.

For an easier handling, inside the physiological boundaries I have proposed for the Sörensen-model an LPV (Linear Time Varying) modeling formalism. 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 Sörensen-model.

2nd Thesis Group – Robust control methods for optimal insulin dosage

I have developed robust control methods for insulin dosage of Type I diabetes patients.

Publications related to this thesis group: [K-6], [K-7], [K-9], [K-15], [K-16], [K-19], [K-22].

2.1. Robust control methods for the modified minimal model of Bergman.

I have developed the minimax control method for the modified minimal model (comparing it with the classical LQ method).

Furthermore, using the μ-synthesis method, I have taken into account parameter uncertainty, which is supplementing the H_∞ method in guaranteeing the robust performance requirements.

With suitable parametrization, I have defined a quasi-Affine Linear Time Varying system-set and exploiting this result I have designed a (nonlinear) controller ensuring quadratic stability.

2.2. LPV type robust control for the Sörensen-model.

Using normoglycaemic insulin input, I have parametrized the high complexity Sörensen-model and described it with politopic LTI (linear time invariant) systems. With the so built LPV model, I have designed a corresponding controller using induced $\mathcal{L}_2$ norm minimization. Finally, with the nonlinear (LPV) controller, I have regulated the nonlinear Sörensen-model guaranteeing γ performance level.

3rd Thesis Group – Symbolic computation-based robust algorithms with *Mathematica*

In an innovative way, to ease the applicability of the applied robust methods, I have developed under Mathematica user-friendly symbolic algorithms, which help the introduction of the so developed insulin dosage algorithms in therapeutics.

From control system point of view, I have extended with another criterion the graphical H_∞ method, I have proposed a solution spanning the minimax control limitations and I have coupled the robust method approaches under Mathematica and MATLAB.

Publications related to this thesis group: [K-1], [K-2], [K-4], [K-10]-[K-14], [K-16], [K-17], [K-20], [K-21], [K-23]-[K-28].

3.1. Developing symbolic algorithms.

Under *Mathematica* I have symbolically implemented the extended LQ (minimax) method, I have shown that from the two resulting solutions how is MATLAB selecting its own solution, and I have determined with a general formula the worst-case result for the modified minimal model of Bergman.

3.2. Spanning the minimax method limitations with Gröbner-bases.

Regarding the modified minimal model of Bergman I have shown, that the applicability of the minimax method has practical limitations. Therefore, for the modified minimal model of Bergman I have proposed a solution, 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.

3.3. Extending the robust H_∞ criterion-set under Mathematica.

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

3. Publications related to the PhD thesis

3.1. Journal papers

[K-1] **Kovács L.**, B. Benyó, B. Paláncz and Z. Benyó. A fully symbolic design and modeling of nonlinear glucose control with Control System Professional Suite (CSPS) of *Mathematica*. *Acta Physiologica Hungarica*, 91 (2), 147–156, 2004, ISSN 0231 424 X, IF: 0.2.

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[K-3] **Kovács L.**, K. Papp, B. Vígh, Dr. A. Czinner, Dr. Zs. Almássy, Dr. G. Katona, Dr. Zs. Farkas and Dr. A. Illényi. Medical Information System for Diagnosing Diabetes Mellitus and Hearing Disorder in Children. *Periodica Politechnica, TU Timisoara, Transactions on Automatic Control and Computer Science, papers of CONTI 2004, 6th Int. Conf. on Technical Informatics,* 49 (63 / 2), 37-42, 2004, ISSN 1224-600X.

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[K-8] **Kovács L.** Extension of the Bergman model – possible generalization of the glucose-insulin interaction? *Periodica Politechnica Electrical Engineering*, Budapest, 50 (1-2), 23-32, 2006, ISSN 0324-6000.

[K-9] **Kovács L.**, B. Kulcsár and Z. Benyó. On The Use Of Robust Servo Control In Diabetes Under Intensive Care. *Scientific Bulletin of "Politehnica" University Timisoara, Transactions on Automatic Control and Computer Science*, 51 (65 / 1), 37–42, 2006, ISSN 1224-600X.

[K-10] **Kovács L.** and B. Paláncz. Glucose-insulin control of Type1 diabetic patients in H_2/H_∞ space via Computer Algebra. *Springer Lecture Notes in Computer Science, Proceedings of Second International Conference on Algebraic Biology, Linz, Austria*, 4545, 95–109, 2007, ISSN 0302-9743, IF: 0.402.

[K-11] Paláncz B., **L. Kovács**, B. Benyó and Z. Benyó. Robust Blood-Glucose Control of Type I Diabetes Patients under Intensive Care using *Mathematica*. *Encyclopaedia of Healthcare Information Systems*, IDEA Group (USA), in press.

3.2. International conferences

[K-12] Benyó B., Z. Benyó, B. Paláncz, **L. Kovács** and L. Szilágyi. A fully symbolic design and modeling of nonlinear glucose control with Control System Professional Suite (CSPS) of *Mathematica*. *In Proceedings of World Congress on Medical Physics and Biomedical Engineering (WC2003)*, Sydney, Australia, e-publication #2813, ISSN 1727-1983, ISBN 1 877040 14 2, 2003.

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[K-21] **Kovács L.**, B. Paláncz, B. Benyó, L. Török and Z. Benyó. Robust Blood-Glucose Control using *Mathematica*. *In Proceedings 28th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, New York, USA, 451–454, ISBN 1 4242 0033 3, 2006.

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[K-23] Benyó B., Z. Benyó, B. Paláncz, **L. Kovács** and L. Szilágyi. *A fully symbolic design and modeling of nonlinear glucose control with Control System Professional Suite*

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[K-27] **L. Kovács** – Robust glucose-insulin control of type I diabetes in H_2/H_∞ space using *Mathematica* (in Hungarian), MPV Conference, Oradea, Romania, September 2007.

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[K-29] **L. Kovács** – Extension of the minimal Bergman model. A possible generalization of the glucose-insulin interaction (in Hungarian), Jubilee of 10 years of Biomedical Engineering Education in Hungary, Budapest, Hungary, electronic publication #04, July 2005.

[K-30] **L. Kovács** – Medical Information System for Diagnosing Diabetes Mellitus and Hearing Disorder in Children (in Hungarian), MPV Conference on Informatics, Budapest, Hungary, May 2004.

[K-31] Z. Benyó, **L. Kovács**, Gy. Várallyay Jr., L. Szilágyi – OTKA T042990: Diagnostic-purpose Research of Biological Signals (in Hungarian), XXIII. Centenary Neumann Collokvium, Veszprém, Hungary, November 2003.

3.5. Grants won in the PhD topic

[K-32] OTKA 69055 grant. 2007-2010. *Development of new measurement and control methods, and their bioinformatical applications, for early diagnosis and optimal treatment of metabolic diseases*, Coordinator: Dr. Zoltán Benyó.

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