Past and Present of Automatic Glucose-Insulin Control Research at BME

Levente Kovács[1], Balázs Benyó[1], Zoltán Benyó[1], Adalbert Kovács[2]

[1] Department of Control Engineering and Information Technology, Faculty of Electrical Engineering and Informatics, Budapest University of Technology and Economics, H-1117 Budapest, Magyar Tudósok krt. 2, Hungary; lkovacs@iit.bme.hu

[2] Dept. of Mathematics, University "Politehnica" of Timisoara
RO-300006 Timişoara Romania, P-ta Victoriei Nr. 2, profdrkovacs@yahoo.com

Abstract: The paper reviews the research results in the field of automatic control of Type I diabetes mellitus obtained by the Biomedical Engineering laboratory of the Control Engineering and Inforamtion Technology Department, Budapest University of Technology and Economics (BME) in the last years. Beside the past, the present and the future ideas are also numbered.

Keywords: diabetes mellitus, glucose-insulin control, modern robust control, LPV control.

1 Introduction

The normal blood glucose concentration level in the human body varies in a narrow range (70 - 110 ml/dL). If for some reasons the human body is unable to control the normal glucose-insulin interaction (e.g. the glucose concentration level is constantly out of the above mentioned range), diabetes is diagnosed. The phenomena can be explained by several causes, most important ones are stress, obesity, malnutrition and lack of exercise.

The consequences of diabetes are mostly long-term; among others, diabetes increases the risk of cardiovascular diseases, neuropathy and retinopathy [1]. Consequently, diabetes mellitus is a serious metabolic disease, which should be artificially regulated. This metabolic disorder was lethal until 1921 when Frederick G. Banting and Charles B. Best discovered the insulin. Today the life quality of diabetic patients can be enhanced though the disease is still lifelong.

Nowadays health experts refer to diabetes mellitus as the disease of the future. According to the statistics of the World Health Organization (WHO) an increase of the adult diabetes population from 4% (in 2000, meaning 171 million people) to 5.4% (366 million worldwide) is predicted by the year 2030, [2].

From engineering point of view, the treatment of diabetes mellitus can be represented by an outer control loop, to replace the partially or totally deficient blood-glucose-control system of the human body. However, the blood-glucose control is a diffcult problem to be solved. 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, 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 [3], [4], 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.

To design an appropriate control, an adequate model is necessary. The mathematical model of a biological system, developed to investigate the physiological process underling a recorded response, always requires a trade off between the mathematical and the physiological guided choices. In the last decades several models appeared for Type I diabetes patients [5].

The mostly used and also the simplest one proved to be the minimal model of Bergman [6] for Type I diabetes patients under intensive care, and its extension, the three-state minimal model [7]. However, the simplicity of the model proved to be its disadvantage too, as it is very sensitive to parameters variance, the plasma insulin concentration must be known as a function of time and in its formulation a lot of components of the glucose-insulin interaction were neglected.

Therefore, extensions of this minimal model have been proposed [8], [9], [10], [11], trying to capture the changes in patient dynamics of the glucose-insulin interaction, particularly with respect to insulin sensitivity, or even the mixed meal characteristics [12].

Beside the Bergman-model other more general, but more complicated models appeared in the literature [5], [13]. The most complex one proved to be the 19th order Sorensen-model [14]. 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).

Regarding the applied control strategies, the palette is very wide [15]. Starting from classical control strategies (ex. PID control [16]) to soft-computing techniques (ex. neuro-fuzzy methods [17]), adaptive [18], [19], model predictive [13], 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 [4], 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.

In this paper, a review is given on the research results obtained by the Biomedical Engineering laboratory of the Control Engineering and Inforamtion Technology Department, Budapest University of Technology and Economics in the field of automatic control of Type I diabetes mellitus. Most of the results are summerized in the PhD dissertation of the frst author of the current paper [20], but also newer results are discuessed. Moreover, forthcomning research ideas are breifly numbered.

2 Review of Obatined Research Results

2.1 New Modelling Concepts for Type I Diabetes

The model investigation were focused on the extremities of the above mentioned model set: the Bergman-model and the Sorensen-model. Analytical investigation of the high complexity Sorensen-model and the extension of the modified Bergman minimal model was carried out.

In this way, the proposed approximations are indicating numerical algorithmization for complex optimal control strategies focusing to cover a bigger diabetes population.

For the extension of the modified minimal Bergman-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 [21].

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 [22].

A newly appeared molecular model [23], was also examined to describe the human blood glucose system. As a result of the molecular point of view the cause-effect relations are more plausible and the processes can be described in a more exact and precise way. Therefore, our investigations went over this model synthesis too [24]. Global control properties were determined by nonlinear analysis followed by steady state linearization. Corner points were defined, but this approach could not ensure proper approximation of the model, hence phsysiological working points were defined for further LPV modeling. In order to reduce complexity model reduction possibilities were observed with physiological concerns as well as with mathematical ones and the results agreed. Physiological, biochemical and mathematical approaches were applied and conclusions were made by synchronizing the principles of the different fields of study.

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

Robust control algorithms using modern control theory were also developed for Type I diabetes patients. The proposed methods were structured on the Bergman and Sorensen models.

Firstly, the modified minimal model of Bergman was investigated. The minimax control method was developed comparing it with the classical LQ method [25]. Furthermore, using the μ-synthesis, parameter uncertainty was taken into account, which supplements the H_∞ method in guaranteeing the robust performance requirements [26]. 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 [27].

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 [28].

2.2 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.

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

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 [30].

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 [31].

Finally, the graphical interpretation of the H_∞ method implemented under *Mathematica* uses a requirement envelope. For the disturbance rejection criteria the requirement envelope's criterion-set was extended 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 [29].

3 Actual Research Tasks and Further Plans

Actual research tasks are strict related to the already published results:

- Based on the novel molecular-based model robust control design is taken into account.
- Robust control applicability is tested on healty cohort on the considered models.
- A "model-receipt" is under development to give a useful help for those starting to work in this research field.
- Mixed meal model is under development.

Regarding future plans, robust control design is planned for ICU (Intensiv Care Unit) cases; the applied robust control methodology is planned to be validated on diabetic patient scenarios using different clinical data for the considered mathematical models.

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References

[1] Fonyo A. and E. Ligeti: Physiology (in Hungarian). 3rd ed., Ed. Medicina, Budapest, 2008

[2] Wild S., G. Roglic, A. Green, R. Sicree and H. King: Global Prevalence of Diabetes - Estimates for the year 2000 and projections for 2030. Diabetes Care, 2004, vol. 27/5, pp. 1047-1053

[3] Parker R. S., F. J. Doyle III, J. H. Ward and N. A. Peppas: Robust H_∞ Glucose Control in Diabetes Using a Physiological Model, AIChE Journal, 2000, vol. 46/12, pp. 2537-2549

[4] Ruiz-Velazquez E., R. Femat and D. U. Campos-Delgado: Blood glucose control for Type1 diabetes mellitus: A robust tracking H_∞ problem. Control Engineering Practice, 2004, Vol. 12, pp. 1170-1195

[5] Chee F. and F. Tyrone: Closed-loop control of blood glucose. Lecture Notes of Computer Sciences 368, Springer-Verlag, Berlin, 2007

[6] Bergman B. N., Y. Z. Ider, C. R. Bowden and C. Cobelli: Quantitive estimation of insulin sensitivity, American Journal of Physiology, 1979, vol. 236, pp. 667-677

[7] Bergman R. N., L. S. Philips and C. Cobelli: Physiologic evaluation of factors controlling glucose tolerance in man, Journal of Clinical Investigation, 1981, vol. 68; pp.1456-1467

[8] Lin J., J. G. Chase, G. M. Shaw, C. V. Doran, C. E. Hann, M. B. Robertson, P.M. Browne, T. Lotz, G. C. Wake and B. Broughton: Adaptive Bolus-Based Set-Point Regulation of Hyperglycemia in Critical Care, Proc. of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc., San Francisco, USA, 2004, pp. 3463-3466

[9] Fernandez M., D. Acosta, M. Villasana and D. Streja: Enhancing Parameter Precision and the Minimal Modeling Approach in Type I Diabetes, Proc. of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc., San Francisco, USA, 2004, pp. 797-800

[10] Morris H. C., B. O'Reilly and D. Streja: A New Biphasic Minimal Model, Proc of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc., San Francisco, USA, 2004, pp. 782-785

[11] de Gaetano A. and O. Arino: Some considerations on the mathematical modeling of the intra-venous glucose tolerance test. Journal of Mathematical Biology, 2000, Vol. 40, pp. 136-168

[12] Anirban R. and R. S. Parker: Mixed Meal Modeling and Disturbance Rejection in Type I Diabetic Patients, Proc. of the 28th IEEE EMBS Annual International Conference, New York City, USA, 323-326, 2006

[13] Hovorka R., V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering and M. E. Wilinska: Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes, Physiological measurement, 2004, Vol. 25, pp. 905-920

[14] Sorensen J. T.: A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes, Ph.D. thesis, Massachusetts Institute of Technology (MIT), 1985

[15] Parker R. S., F. J. Doyle III and N. A. Peppas: The Intravenous Route to Blood Glucose Control. A Review of Control Algorithms for Noninvasive Monitoring and Regulation in Type I Diabetic Patients. IEEE Engineering in Medicine and Biology, 2001, pp. 65-73

[16} Chee F, T. L. Fernando, A. V. Savkin and V. van Heeden: Expert PID Control System for Blood Glucose Control in Critically Ill Patients. IEEE Transactions on Information Technology in Biomedicine, 2003, Vol. 7/4, pp. 419-425

[17] Dazzi D, F Taddei, A Gavarini, E Uggeri, R Negro and A Pezzarossa: The control of blood glucose in the critical diabetic patient: A neuro-fuzzy method. Journal of Diabetes and Its Complications, 2001, Vol. 15, pp. 80-87

[18] Palerm C. C.: Drug Infusion Control: An extended direct model reference adaptive control strategy. PhD thesis, Troy, New York, 2003

[19] Hovorka R.: Management of Diabetes using adaptive control. International Journal of Adaptive Control and Signal Processing, 2004, Vol. 19/5, pp. 309-325

[20] Kovacs L.: New principles and adequte control methods for insulin optimization in case of Type I diabetes mellitus, PhD Thesis (in Hungarian), Budapest University of Technology and Economics, Hungary, 2007

[21] Kovacs L.: Extension of the Bergman model – possible generalization of the glucose-insulin interaction? Periodica Politechnica Electrical Engineering, Budapest, 2006, vol. 50 / 1-2, pp. 23-32

[22] Kovacs L. and B. Kulcsár: LPV modeling of Type 1 Diabetes Mellitus, CINTI 2007 – 8th International Symposium of Hungarian Researchers on Computational Intelligence and Informatics, Budapest, Hungary, 2007, pp. 163-173

[23] Liu W. and T. Fusheng: Modeling a simplified regulatory system of blood glucose at molecular levels. Journal of Theoretical Biology, 2008, vol. 252, pp. 608-620

[24] Kovacs L., A. Gyorgy, Zs. Almassy and Z. Benyo: Analyzing a novel model of human blood glucose system at molecular levels, ECC'09 – 10th European Control Conference, Budapest, Hungary, 2009, pp. 2494-2499

[25] Kovacs L, B. Palancz and Z. Benyo: Classical and Modern Control Strategies in Glucose-Insulin Stabilization. 16th IFAC World Congress, Prague, Czech Republic, electronic publication #04165, 2005

[26] Kovacs L., B. Kulcsar and Z. Benyo. 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, 2006, vol. 51 / 65 (1), pp. 37–42

[27] Kovacs L., B. Kulcsar, J. Bokor and Z. Benyo: LPV Fault Detection of Glucose-Insulin System. Proc. 14th Mediterranean Conference on Control and Automation, Ancona, Italy, e-publication TLA2-4, 2006

[28] Kovacs L., B. Kulcsar, B. Benyo and Z. Benyo: Induced L2-norm Minimization of Glucose-Insulin System for Type I Diabetic Patients, MCBMS'09 – 7th IFAC Symposium on Modelling and Control in Biomedical Systems (including Biological Systems), Aalborg, Denmark, 2009, pp. 55-60

[29] Palancz B., L. Kovacs, B. Benyo and Z. Benyo: Robust Blood-Glucose Control of Type I Diabetes Patients under Intensive Care using Mathematica, in: Encyclopaedia of Healthcare Information Systems, Publ. Medical Information Science Reference, 2008, pp. 1210-1219

[30] Palancz B. and L. Kovacs: Application of Computer Algebra to Glucose-Insulin Control in H2/H∞ space using Mathematica. Periodica Politechnica Electrical Engineering, Budapest, 2006, vol. 50 / 1-2, pp. 33–45

[31] Kovacs L. and B. Palancz: Glucose-insulin control of Type1 diabetic patients in H2/H∞ space via Computer Algebra, Springer Lecture Notes in Computer Science (AB2007 - 2nd International Conference on Algebraic Biology, Linz, Austria), 2007, vol. 4545, pp. 95-109