We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

11

Robust and Optimal Blood-Glucose Control in Diabetes Using Linear Parameter Varying paradigms

Levente Kovács* and Balázs Kulcsár**
**Dept. of Control Engineering and Information Technology, Budapest University of Technology and Economics, Hungary.*
***Delft Centre for Systems and Control Delft University of Technology, Netherlands.*

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 (Fonyo & Ligeti, 2008). 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. Nowadays the life quality of diabetic patients can be enhanced though the disease is still lifelong.
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 (Wild et al., 2004). This warns that diabetes could be the "disease of the future", especially in the developing countries (due to stress and unhealthy lifestyle).
Type I (also known as insulin dependent diabetes mellitus (IDDM)) is one of the four classified types of this disease (Type II, gestational diabetes and other types, like genetic deflections are the other three categories of diabetes), and is characterized by complete pancreatic β-cell insufficiency (Fonyo & Ligeti, 2008). As a result, the only treatment of Type I diabetic patients is based on insulin injection (subcutaneous or intravenous), usually administered in an open-loop manner.
Due to the alarming facts of diabetes, the scientific community proposed to improve the treatment of diabetes by investigating the applicability of an external controller. 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 automated. 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.
However, 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 often 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 hypoglycaemia (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 1960s lot of researchers have investigated the problem of the glucose-insulin interaction and control. The closed-loop glucose regulation, as it was several times formulated (Parker et al., 2000), (Hernjak & Doyle, 2005), (Ruiz-Velazques et al., 2004), requires three components:

- glucose sensor;
- insulin pump;
- a control algorithm, which based on the glucose measurements, is able to determine the necessary insulin dosage.

1.1 Modelling diabetes mellitus

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 (Chee & Tyrone, 2007).
The mostly used and also the simplest one proved to be the minimal model of Bergman (Bergman et al., 1979) for Type I diabetes patients under intensive care, and its extension, the three-state minimal model (Bergman et al., 1981).
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 (Hipszer, 2001), (Dalla Man et al., 2002), (Benett & Gourley, 2003), (Lin et al., 2004), (Fernandez et al., 2004), (Morris et al., 2004), (de Gaetano & Arino, 2000), (Chbat & Roy, 2005), (Van Herpe et al., 2006) trying to capture the changes in patient dynamics of the glucose-insulin interaction, particularly with respect to insulin sensitivity or the time delay between the injection and absorption. Other approximations proposed extensions based on the meal composition (Roy & Parker, 2006a), (Roy & Parker, 2006b), (Dalla Man et al., 2006a) , (Dalla Man et al., 2006b).
Beside the Bergman-model other more general, but more complicated models appeared in the literature (Cobelli et al., 1982), (Sorensen, 1985), (Tomaseth et al., 1996), (Hovorka et al., 2002), (Fabietti et al., 2006).

1.2 The Sorensen-model

The most complex diabetic model proved to be the 19th order Sorensen-model (Sorensen, 1985) (the current work focuses on a modification of it, developed by (Parker et al., 2000)), which is based on the earlier model of (Guyton et al., 1978). Even if the Sorensen-model describes in a very exact way the human blood glucose dynamics, due to its complexity it was rarely used in research problems.

The model was created with a great simplification: glucose and insulin subsystems are disconnected in the basal post absorptive state, which can be fulfilled with no pancreatic insulin secretion. Nomenclature and equations can be found in the Appendix of the current book chapter.

The Sorensen-model can be divided in six compartments (brain, heart and lungs, liver, gut, kidney, periphery), and its compartmental representation is illustrated by Fig. 1.

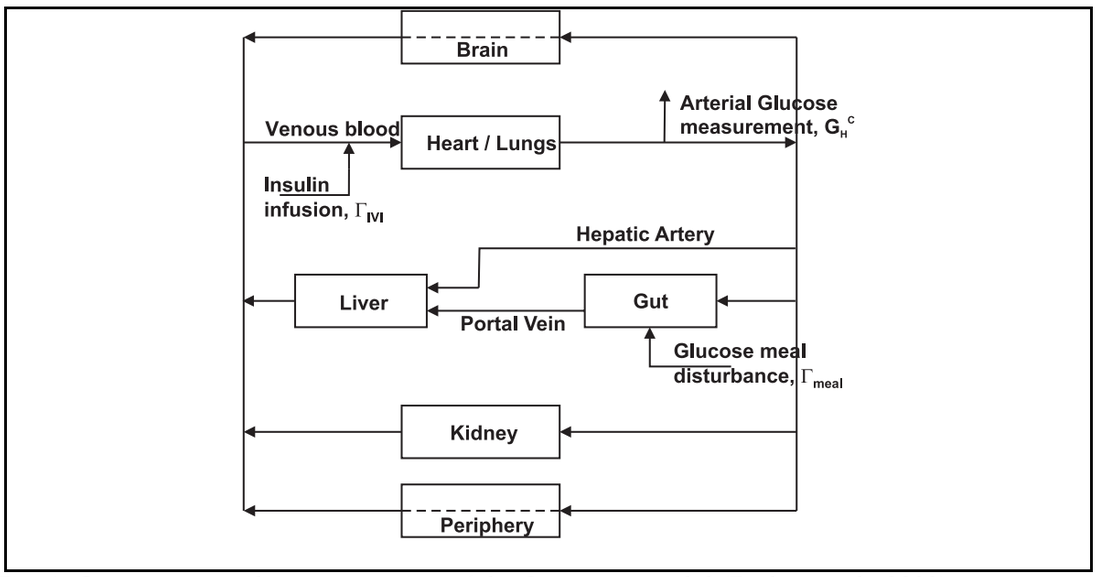

Fig. 1. Compartmental representation of the Sorensen model (Parker et al., 2000).

Transportation is realized with blood circulation assuming that glucose and insulin concentrations of the blood flow leaving the compartment are equal to the concentrations of the compartment. The compartments can be divided into capillary and tissue subcompartments, since glucose and insulin from the blood flow entering the compartment are either utilized or transported by diffusion. In compartments with small time constant or with no absorption the division into subcompartments is unnecessary.

1.3 Control of diabetes mellitus

Regarding the applied control strategies for diabetes mellitus, the palette is very wide (Parker et al., 2001).

Starting from classical control strategies (PID control (Chee et al., 2003), cascade control (Ortis-Vargas & Puebla, 2006)), to soft-computing techniques (fuzzy methods (Ibbini, 2006), neural networks (Mougiakakou et al., 2006), neuro-fuzzy methods (Dazzi et al., 2001)), adaptive (Lin et al., 2004), model predictive (MPC) (Hernjak & Doyle, 2005), (Hovorka et al.,

2004), or even robust H_∞ control were already applied (Parker et al., 2000), (Ruiz-Velazques et al., 2004), (Kovacs et al., 2006), (Kovacs & Palancz, 2007), (Kovacs et al., 2008).
Most of the applied control methods were focused on the Bergman minimal model (and so the applicability of the designed controllers was limited due to excessive sensitivity of the model parameters). On the other hand, for the Sorensen-model, only linear control methods were applied (H_∞ (Parker et al., 2000), (Ruiz-Velazques et al., 2004), MPC (Parker et al., 1999)). An acceptable compromise between the model's complexity and the developed control algorithm could be the parametrically varying system description (Shamma & Athans, 1991), identification (Lee, 1997), optimal control (Wu et al., 2000), (Balas, 2002) and diagnosis (Kulcsar, 2005).

1.4 The aim of the current work

The main contribution of the present work is to give a possible solution for nonlinear and optimal automated glucose control synthesis.
Considering the high-complexity nonlinear Sorensen-model a nonlinear model-based methodology, the LPV (Linear Parameter Varying) technique is used to develop open-loop model and robust controller design based on H_∞ concepts. The results are continuously compared with those obtained by (Parker et al., 2000) where a linear model based robust control algorithm was used (see section 1.5).
The validity of the Sorensen model is caught inside a polytopic region and the model is built up by a linear combination of the linearized models derived in each polytopic point (covering the physiologic boundaries of the glucose-insulin interaction of the Sorensen-model).
Finally, using induced L_2-norm minimization technique, a robust controller is developed for insulin delivery in Type I diabetic patients. The robust control was developed taking input and output multiplicative uncertainties with two additional uncertainties from those used by (Parker et al., 2000). Comparative results are given and closed-loop simulation scenarios illustrate the applicability of the robust LPV control techniques.

1.5 Brief review of the article published by (Parker et al., 2000)

As in the current chapter a continuous comparison of the obtained results will be done with those obtained by (Parker et al., 2000), we considered useful to briefly summarize the mentioned article.
Although the first application of the H_∞ theory on the field of diabetic control was that of (Kienitz & Yoneyama, 1993), the publication of (Parker et al., 2000) can be considered a pioneer work in applying the H_∞ method for glucose-insulin control of Type I diabetic patients using the fundamental nonlinear Sorensen-model.
In (Parker et al., 2000) uncertainty in the nonlinear model was characterized by up to ±40% variation in eight physiological parameters and by sensitivity analysis it was identified that three-parameter set have the most significant effect on glucose and insulin dynamics. Controller performance was designed to track the normoglycemic set point (81.1 mg/dL) of the Sorensen-model in response to a 50 g meal disturbance (using the six hour meal disturbance function of (Lehmann & Deutsch, 1992)). By this way, glucose concentration was maintained within ±3.3 mg/dL of set point.

The results were compared to the results of (Kienitz & Yoneyama, 1993), who developed an H_∞ controller based on a third order linear diabetic patient model. Performance of (Kienitz & Yoneyama, 1993)'s controller in response to a meal disturbance was quantitatively similar to the nominal controller obtained by (Parker et al., 2000). However, the uncertainty-derived controller of (Parker et al., 2000) was tuned to handle significantly more uncertainty than that of (Kienitz & Yoneyama, 1993).
On the other hand, (Parker et al., 2000) underlined that a significant loss in performance appeared applying the potential uncertainty in the model in comparison to the nominal case. This could be mostly exemplified by the near physiologically dangerous hypoglycaemic episode, typically characterized as blood glucose values below 60 mg/dL (see Fig. 9 and Fig. 10 of (Parker et al., 2000) also captured by Fig. 2 of the current work).
Therefore, our goal was dual: applying nonlinear model-based LPV control methodology to design robust controller for Type I diabetic patients and to design a robust controller by taking into account two additional uncertainties from those used in (Parker et al., 2000), namely sensor noise and worst case design for meal disturbance presented in (Lehmann & Deutsch, 1992) (60 g carbohydrate).

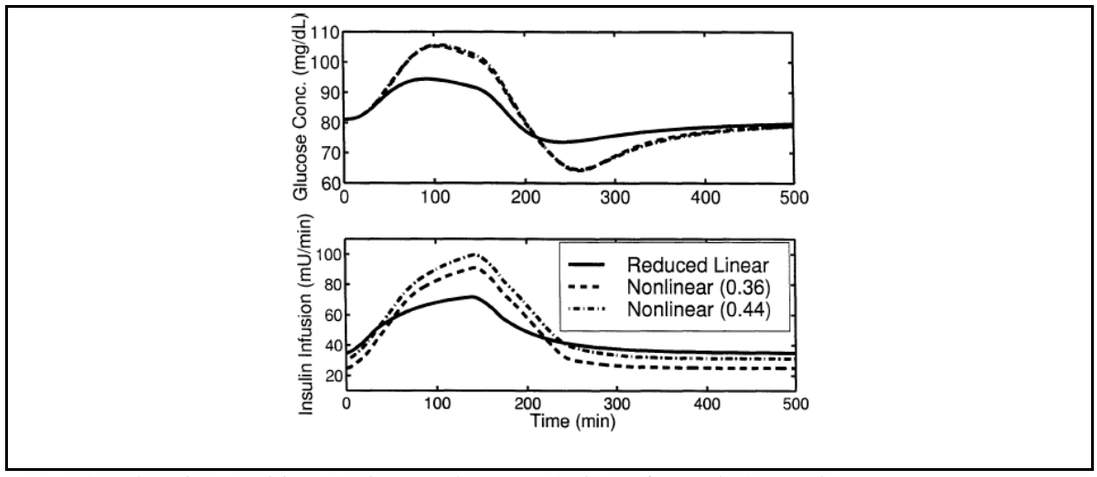

Fig. 2. Results obtained by (Parker et al., 2000) (taking from their work).

2. LPV modelling using polytopic description

The chapter suggests using Linear Parameter concepts with optimal and robust control scheme in order to show a candidate for diabetes Type I closed-loop control. First, the most important control related definition of such a system class is given. Solution of the robust control synthesis by Linear Matrix Inequalities (LMI) is briefly summarized.

2.1 LPV system definition

Linear Parameter Varying (LPV) system is a class of nonlinear systems, where the parameter could be an arbitrary time varying, piecewise-continuous and vector valued function denoted by $\rho(t)$, defined on a compact set $\mathcal{P}$. In order to evaluate the system, the parameter trajectory is requested to be known either by measurement or by computation. A formal definition of the parameter varying systems is given below.

Definition 1. For a compact $\mathcal{P} \subset \mathbf{R}^s$, the parameter variation set $F_{\mathcal{P}}$ denotes the set of all piecewise continuous functions mapping $\mathbf{R}^+$ (time) into $\mathcal{P}$ with a finite number of discontinuities in any interval. The compact set $\mathcal{P} \subset \mathbf{R}^s$ along with the continuous functions A: $\mathbf{R}^s \to \mathbf{R}^{n\times n}$, B: $\mathbf{R}^s \to \mathbf{R}^{n\times n_u}$, C: $\mathbf{R}^s \to \mathbf{R}^{n_y\times n}$, D: $\mathbf{R}^s \to \mathbf{R}^{n_y\times n_u}$ represent an n^{th} order LPV system whose dynamics evolve as:

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

with $\rho(t) \in F_{\mathcal{P}}$ (Wu et al., 2000).

As a result, it can be seen that in the LPV model, by choosing parameter variables, the system's nonlinearity can be hidden. This methodology is used on different control solutions, like (Balas, 2002), which gave also a solution of the problem.

There are different descriptions of the LPV systems (Kulcsar, 2005). In the affine description possibility, a part of the x(t) states are equal with the ρ(t) parameters. However, due to the complexity of the Sorensen model, this representation is impossible to be developed.

Polytopic representation could be another description of the LPV systems. In this case, the validity of the model is caught inside a polytopic region and the model is built up by a linear combination of the linearized models derived in each polytopic point ($\Sigma_i = \begin{bmatrix} A_i & B_i \\ C_i & D_i \end{bmatrix}$) (Kulcsar, 2005):

$$\Sigma(t) \subset \{\Sigma_1, \ldots, \Sigma_2\} = \left\{ \sum_{i=1}^{j} \alpha_i \Sigma_i : \alpha_i \geq 0, \sum_{i=1}^{j} \alpha_i = 1 \right\} \tag{2}$$

Hence, the LPV system is given by the complex combination of the positive coefficients and the system Σ-s. The polytopic LPV model can be thought as a set of linear models on a vertex (a convex envelope of LTI systems), where the grid points of the description are LTI systems. The generation of a polytopic model is the derivation around an operating point of the general nonlinear state-space representation. The LPV polytopic model is valid only in a restricted domain, characterized by the range of the polytope (Kulcsar, 2005).

Therefore, the correct definition of the polytopic region (which is capable to describe the whole working area of the system) is a key point in this methodology.

2.2 Induced L_2 performance objective of LPV systems region

For a given compact set $\mathcal{P} \subset \mathbf{R}^s$ and a continuous bounded matrix function A: $\mathbf{R}^s \to \mathbf{R}^{n\times n}$ which describes the $\dot{x}(t) = A(\rho(t))x(t)$ LPV system ($\rho(t) \in \mathcal{P}$) and for a V Lyapunov function candidate, it can be written that the time derivative of V(x) (for $\forall \rho \in \mathcal{P}$ along the LPV system trajectories) is (Tan, 1997):

$$\frac{d}{dt} V(x(t)) = x^T(t)\left[A^T(\rho(t))P + PA(\rho(t))\right]x(t) \tag{3}$$

Defintion 2. Function A is quadratically stable over $\mathcal{P}$ if there exists a $P \in \mathbf{R}^{n\times n}$, $P = P^T > 0$ positive definite matrix, such that for $\forall \rho \in \mathcal{P}$ (Wu et al., 2000):

$$A^T(\rho(t))P + PA(\rho(t)) < 0 \tag{4}$$

It can be seen that the quadratic stability is a strong form of the robust stability with respect to time varying parameters as it is true for quick changes of the ρ(t) parameter trajectory and for its definition it is enough a single quadratic Lyapunov-function.

Defintion 3. For a quadratically stable LPV system $\Sigma_{\mathcal{P}}$ and for zero initial conditions, the induced L_2-norm of an LPV system is defined as follows (Tan, 1997):

$$\left\|G_P\right\|_2 = \sup_{\rho\in P}\ \sup_{\substack{\|d\|_2\neq 0\\ d\in L_2}} \frac{\|e\|_2}{\|d\|_2} \tag{5}$$

As a result, $\left\|G_P\right\|_2$ represents the largest disturbance to error over the set of all causal linear operators described by $\Sigma_{\mathcal{P}}$.

Corollary 1. (Tan, 1997) Given the LPV system $\Sigma_{\mathcal{P}}$ and $\gamma > 0$ a positive scalar, if there exists an $X \in R^{n\times n}$, $X = X^T > 0$ such that for all $\rho \in \mathcal{P}$.

$$L = \begin{pmatrix} A^T(\rho)X + XA(\rho) & XB(\rho) & \gamma^{-1}C^T(\rho) \\ B^T(\rho)X & -I & \gamma^{-1}D^T(\rho) \\ \gamma^{-1}C(\rho) & \gamma^{-1}D(\rho) & -I \end{pmatrix} < 0 \tag{6}$$

then:

1. The function A is quadratically stable over $\mathcal{P}$.
2. There exists a $\beta < \gamma$ such that $\left\|G_P\right\|_2 \le \beta$.

The matrix inequality (6) can be rewritten in the more familiar Riccati inequality by taking Schur components (Tan, 1997):

$$\begin{aligned} &A^T(\rho)X + XA(\rho) + \gamma^{-2}C^T(\rho)C(\rho) + \left(XB(\rho) + \gamma^{-2}C^T(\rho)D(\rho)\right)\cdot \\ &\cdot\left(I - \gamma^{-2}D^T(\rho)D(\rho)\right)^{-1}\left(B^T(\rho)X + \gamma^{-2}D^T(\rho)C(\rho)\right) < 0 \end{aligned} \tag{7}$$

As a result, the aim of the induced L_2 performance minimization is to find $\min_X \gamma$, with $L_{\gamma^2} < 0$, $X > 0$ and $\gamma > 0$ constraints, where L_{γ^2} can be derived from (6):

$$L_{\gamma^2} = \begin{pmatrix} A^T(\rho)X + XA(\rho) & XB(\rho) & C^T(\rho) \\ B^T(\rho)X & -I & 0 \\ C(\rho) & 0 & -\gamma^2 I \end{pmatrix} < 0 \tag{8}$$

3. Results

Open- and closed-loop LPV results are shown to describe the Sorensen-model. First, a polytopic gridding method is provided, second a robust control design is performed subjected to the uncertain open-loop LPV system and additional frequency weightings.

3.1 Covering the Sorensen-model with a polytopic region

In case of the 19th order Sorensen model (Fig. 1) two inputs: Γ_{meal} (meal disturbance), Γ_{IVI} (injected insulin amount), and one output, the capillary heart-lungs glucose concentration, G_H^C can be delimited. However, we have considered also the peripheral insulin concentration in the capillaries, I_P^C as an additionally output.

Due to the high complexity of the Sorensen-model it was hard to investigate the global stability of the system (the Lyapunov function is a real function with 19 variables). Therefore, a solution could be to cover the working region with a set of linear systems and in this way to investigate the local stability of them.
Choosing the polytopic points we have restricted to the physiological meanings of the variables. The first point was the normoglycaemic point (glucose concentration $y = G_H^C$ = 81.1 mg/dL and calculated insulin concentration $I_{P\,init}^C$ = 26.6554 mU/L), while the others were deflections from this point (given below in %):

- glucose concentrations: 25%, 50%, 75%, 100%, 150%, 200%;
- insulin concentrations: 0%, 25%, 50%, 100%, 150%, 200%.

The glucagon and the additional values were kept at their normoglycaemic value.
In the points of the so generated polytopic region (36 points) we have determined one by one a linearized model and we have analyzed the stability, observability and controllability properties of them. Each system proved to be stable, and partially observable and controllable (the rank of the respective matrices were all 15 and 14 respectively) (Kovacs, 2008). Finally, we have simulated the so developed polytopic LPV system of the Sorensen model, and we have compared the results with those obtained by (Parker et al., 2000). After comparing the results it can be seen (Fig. 3) that the LPV model is approximating with an acceptable error the nonlinear system. However, it can be also observed that without an insulin injection the glucose concentration reaches an unacceptable value for a diabetic patient. Moreover, for the considered polytope the LPV system is stepping out from the defined region being unable to handle the uncovered region.

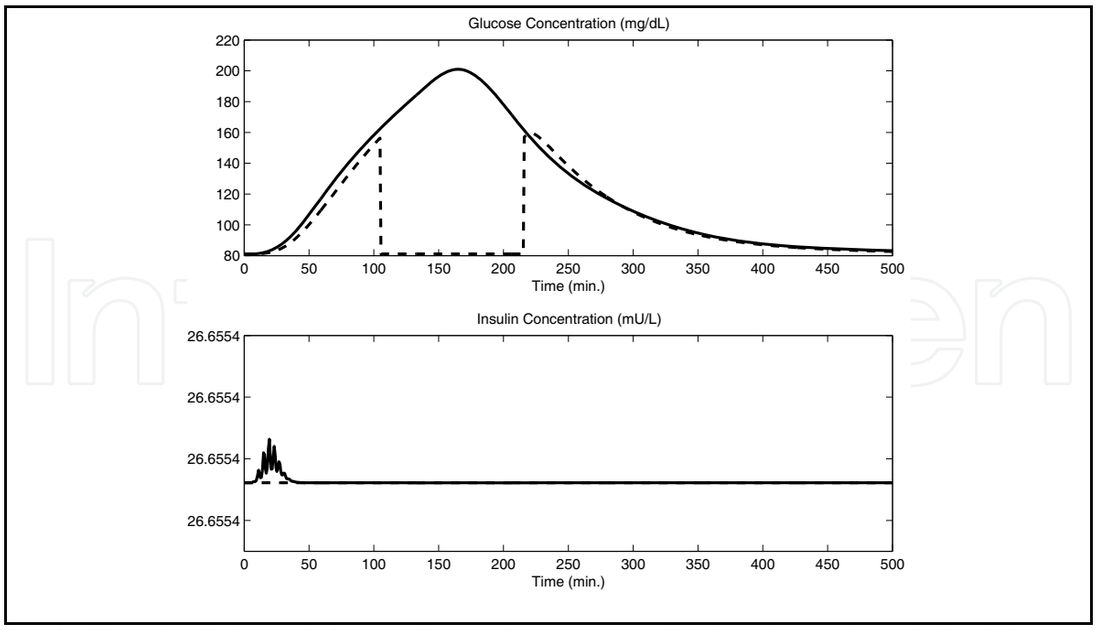

Fig. 3. The simulation of the nonlinear Sorensen model (continuous) and the 36 points polytope region (dashed).

Therefore, we had to extend the glucose concentration region of the considered polytope considering other grid points too, while the insulin concentration grid remained the same:

- glucose concentrations: 25%, 50%, 75%, 100%, 150%, 200%, 300%, 400%;
- insulin concentrations: 0%, 25%, 50%, 100%, 150%, 200%.

Using the newly generated polytopic region (48 points) and after the same investigation of each linear model (obtaining the same results: each system proved to be stable and partially observable and controllable) it can be seen that the LPV model remains inside the considered polytopic region (Fig. 4) and approximates with an acceptable error the nonlinear system (Kovacs, 2008).
For meal disturbance we have used the same six hour meal disturbance function of (Lehmann & Deutsch, 1992) (Fig. 5), filtered with a $\frac{1/60}{s+1/60}$ first order lag used by (Parker et al., 2000), while the insulin input was considered zero.
It can be seen, that in absence of control the open-loop simulation is going up to a very high glucose concentration value, unacceptable for a Type I diabetic patient.

3.2 LPV based robust control of the Sorensen-model

In case of robust control design, the results presented in (Parker et al., 2000) showed that a near hypoglycaemic situation appears for the considered uncertainties (Fig. 2). In case of a diabetic patient this could be also a dangerous situation (not only hyperglycaemia).
The aim of the control design is to minimize the meal disturbance level over the performance output for all possible variation of the parameter within the polytope $F_{\mathcal{P}}$.

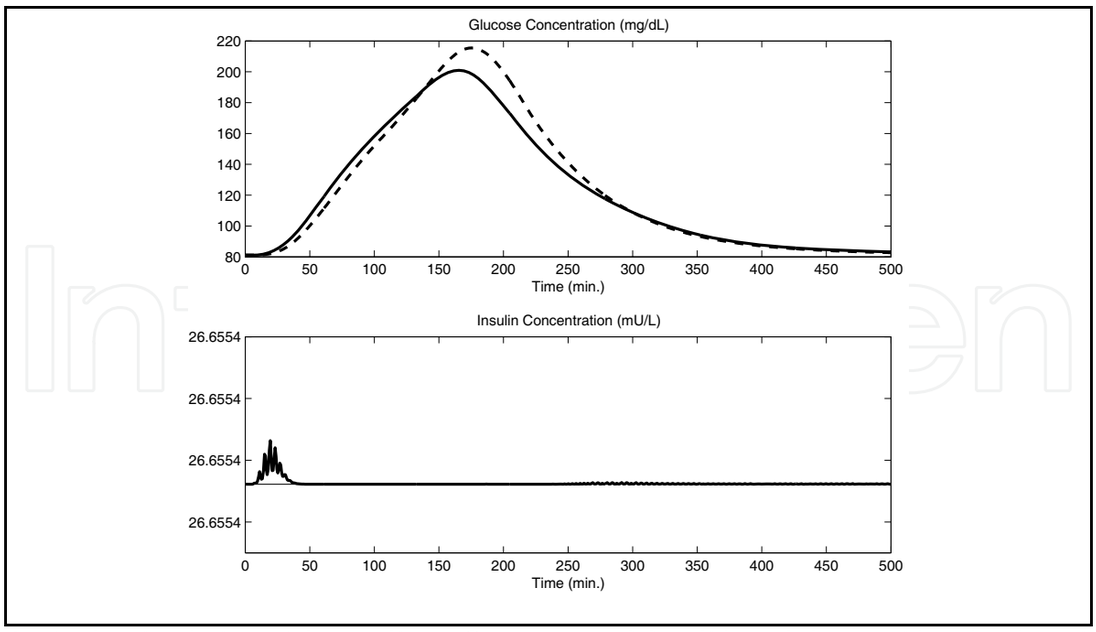

Fig. 4. The simulation of the nonlinear Sorensen model (solid) and the considered polytopic region (dashed).

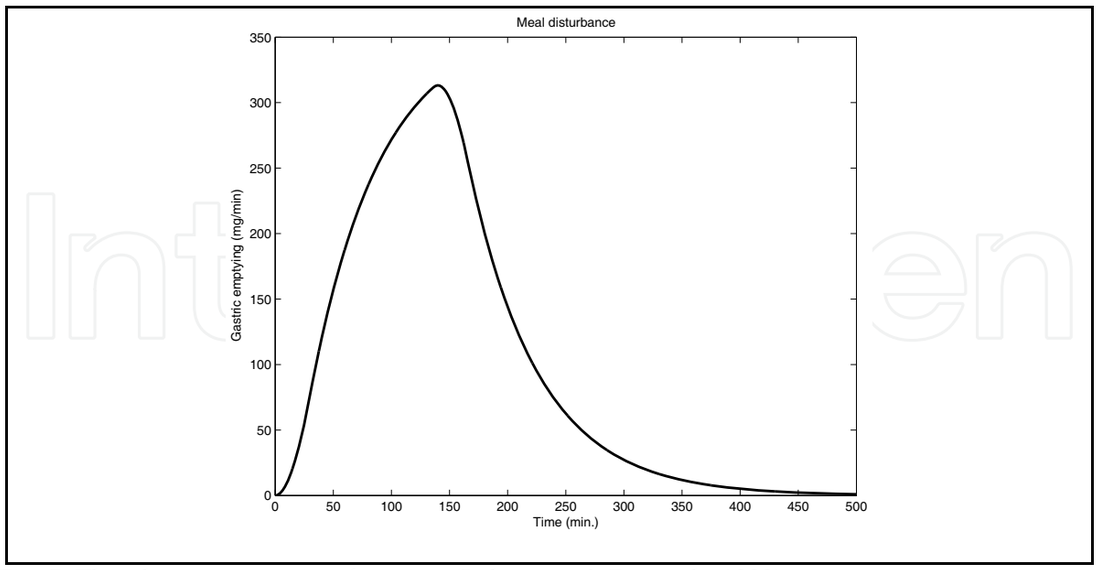

Fig. 5. The glucose emptying function (Lehmann & Deutsch, 1992).

$$\min_{K}\|G\| = \min_{K}\sup_{\rho\in F_p}\sup_{\|d\|\neq 0}\frac{\|z_{y1}\|}{\|d\|} \tag{9}$$

where d denotes the meal disturbance input and z describes the glucose variation. Priory information is injected to the controller throughout the augmentation of the nominal plant with extra dynamics, called weighting functions.

Therefore, the starting point of the control design was the appropriate choice of the weighting functions. Firstly, we have reproduced the results obtained by (Parker et al., 2000) with the dangerous near hypoglycemic episode, but using the LPV methodology (on the polytopic region presented in the previous section). Consequently, the weighting functions used were the followings:

- The multiplicative uncertainty of the insulin input, $W_i = \frac{s^2 + 0.47s + 0.015}{s^2 + 0.29s + 0.022}$;
- The multiplicative uncertainty of the glucose input, $W_{im} = \frac{1.63s^2 + 0.21s + 0.007}{s^2 + 0.52s + 0.010}$;
- The performance weighting function, $W_{perf} = \frac{\frac{1}{1.2}s + 0.25}{s + 0.01 * 0.25}$;
- The disturbance (glucose) input weighting function, $W_m = \frac{1}{6s+1}$.

However, as we mentioned above, we have additionally taken into account sensor noise too (neglected in (Parker et al., 2000), by considering it a 1/10000 value). We have considered that for insulin measurements a 5% error, while for glucose measurements a 2% error is tolerable (values taken from clinical experience).

As a result, the considered closed-loop interconnection of system can be illustrated by Fig. 6, while the obtained results obtained on the original nonlinear Sorensen-model can be seen in

Fig. 7. By the reproduced results of (Parker et al., 2000) we have proved that the obtained controller (designed for the created LPV model) works correctly.
Now, we have redesigned the control problem, to minimize the negative effects obtained by (Parker et al., 2000). Moreover, for meal disturbances we focused on the worst case of the (Lehmann & Deutsch, 1992) absorption taking into account a 60 g carbohydrate intake (in comparison with the 50 g carbohydrate considered by (Parker et al., 2000)).
To avoid the hypoglycaemic situation and take into account the two additional uncertainties mentioned above, we have extended the control loop with a weighting function for the control signal and an output uncertainty block (Fig. 8).

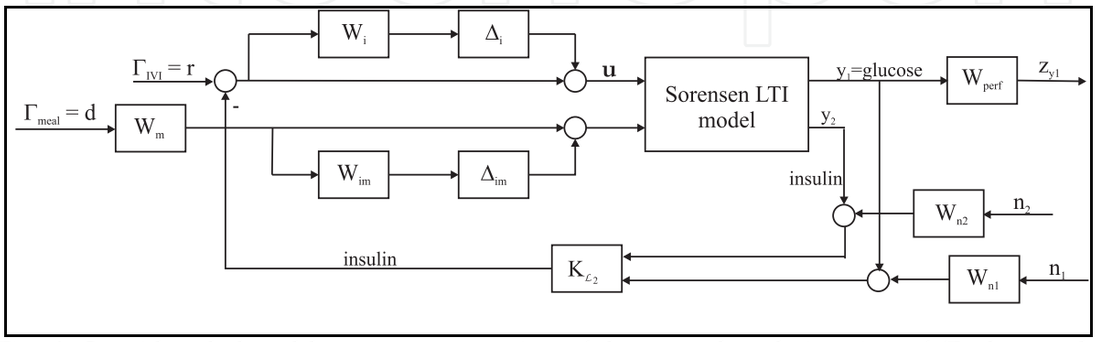

Fig. 6. Considered closed-loop interconnection of the reproduced situation of (Parker et al., 2000) extended with additionally considered sensor noise weighting functions.

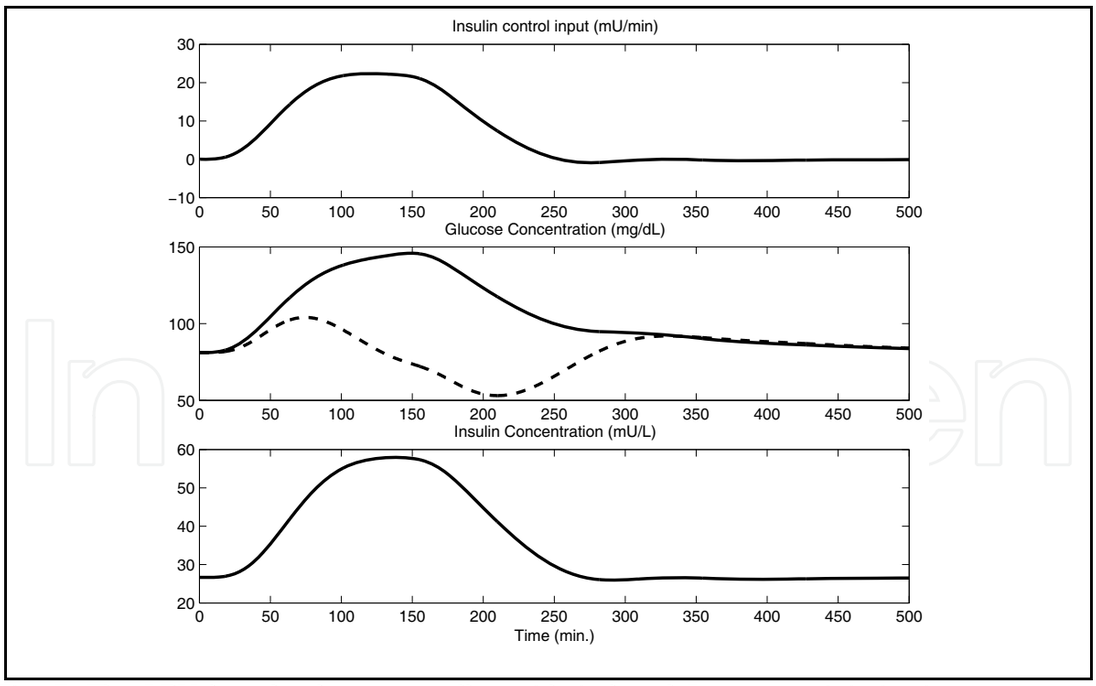

Fig. 7. The LPV based robust controller with induced L_2-norm minimization guarantee, using the same weighting functions as in (Parker et al., 2000): in case of the original nonlinear Sorensen model (solid) and the considered polytopic region (dashed) controller.

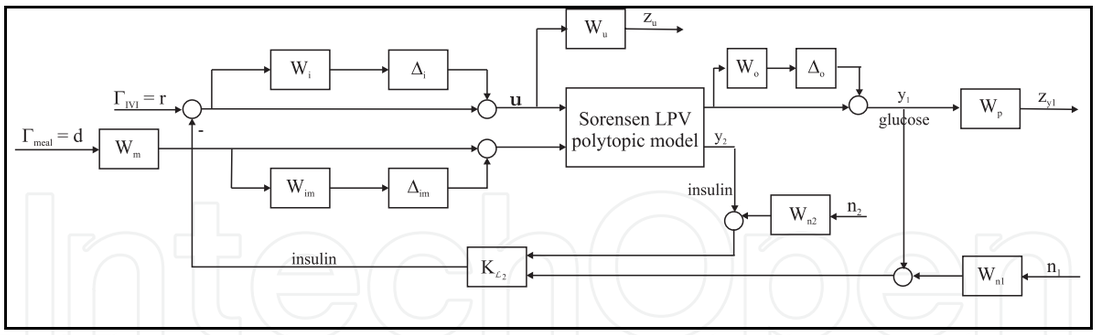

Fig. 8. The augmented system structure using the additional restrictions from those published in (Parker et al., 2000).

As a result, regarding the weighting functions used in (Parker et al., 2000), we have modified only the multiplicative uncertainty weighting functions (W_{im}, W_i) and the performance weighting function W_{perf}, while these were chosen only from engineering point of view. Now physiological aspects were taken also into account. The frequency response of the weighting functions can be seen in Fig. 9.
During the robust control design, a $\gamma = 1.0096$ solution was obtained. It can be seen (Fig. 10) that the hypoglycaemic situation is avoided and the glucose level is kept inside the normal 80-120 mg/dL range. Testing the controller on the original nonlinear Sorensen-model results are good too. Although in this case the glucose results are stepping out the normal range (160 mg/dL) this is acceptable (and similar to the healthy subjects).

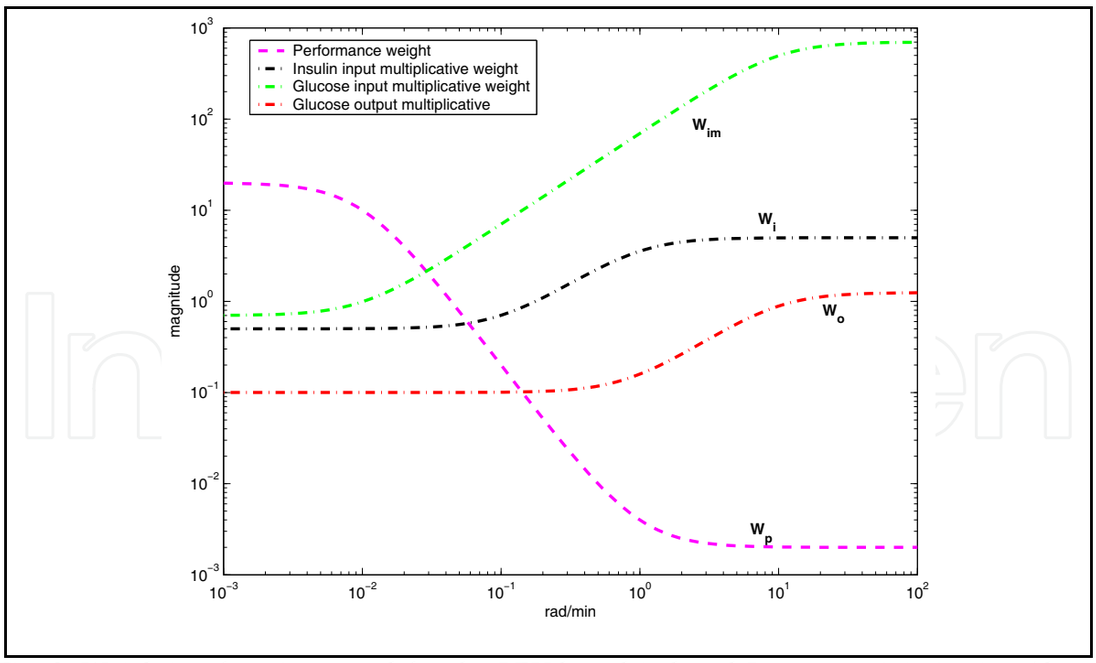

Fig. 9. Weighting functions used for the LPV-based induced L_2-norm minimization (those which have been modified from (Parker et al., 2000)).

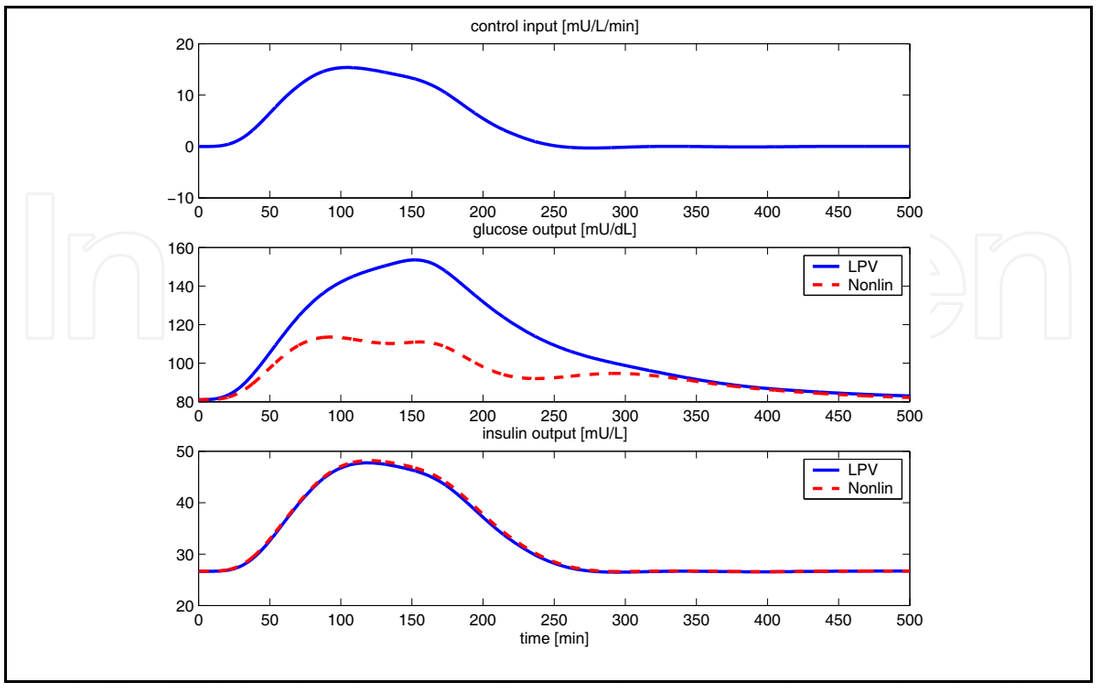

Fig. 10. The LPV based robust controller (for the case of the considered additional uncertainties) with induced L_2-norm minimization guarantee in case of the original nonlinear Sorensen model (solid) and the considered polytopic region (dashed).

4. Conclusions

In the current work a nonlinear model-based LPV control method was applied to design a robust controller for the high complexity Sorensen-model. The used methodology is more general than the classical linear H_∞ method as it deals directly with the nonlinear model itself. From the different descriptions of the LPV systems, polytopic representation was used, where the validity of the model was captured inside a polytopic region. In this way the model was built up by a linear combination of the linearized models derived in each considered polytopic point.

Using induced L_2-norm minimization technique, a robust controller was developed for insulin delivery in Type I diabetic patients. Considering the normoglycaemic set point (81.1 mg/dL), a polytopic set was created over the physiologic boundaries of the glucose-insulin interaction of the Sorensen-model.

The robust control was developed taking into account input and output multiplicative uncertainties, sensor noise and worst case meal disturbance (as additional restrictions from those applied in (Parker et al., 2000)). The obtained results showed that glucose level can be kept inside a normal range, avoiding hypoglycaemic episode (which was not possible with the control formalism applied in (Parker et al., 2000)). By the given comparative results and closed-loop simulation scenarios it was illustrated the applicability of the robust LPV control techniques.

Parameter dependency of the considered weighting functions could be considered in the future, which gives additional design freedom.

5. Acknowledgment

This research has been supported by Hungarian National Scientific Research Foundation, Grants No. OTKA T69055.

6. References

Balas, G.J. (2002). Linear, Parameter-Varying Control and Its Application to a Turbofan Engine. *International Journal of Robust and Nonlinear Control*, vol. 12, no. 9, pp. 763-796.

Benett, D.L. and Gourley, S.A. (2003). Asymptotic properties of a delay differential equation model for the interaction of glucose with plasma and interstitial insulin. *Applied Mathematics and Computation*, vol. 151, no. 1, pp. 189-207.

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

Bergman, R.N., Philips, L.S. and Cobelli, C. (1981). Physiologic evaluation of factors controlling glucose tolerance in man. *Journal of Clinical Investigation*, vol. 68, pp. 1456-1467.

Chbat, N.W. and Roy, T.K. (2005). Glycemic Control in Critically Ill Patients – Effect of Delay in Insulin Administration. in *Proc. of 27th IEEE EMBS Annual International Conference*, Shanghai, China, pp. 2506-2510.

Chee, F., Fernando, T.L., Savkin, A.V. and van Heeden, V. (2003). Expert PID control system for blood glucose control in critically ill patients. *IEEE Transactions on Information Technology in Biomedicine*, vol. 7, no. 4, pp. 419-425.

Chee, F. and Tyrone, F. (2007). *Closed-loop control of blood glucose*. Lecture Notes of Computer Sciences 368, Springer-Verlag, Berlin.

Cobelli, C., Federspil, G., Pacini, G., Salvan, A. and Scandellari, C. (1982). An integrated mathematical model of the dynamics of blood glucose and its hormonal control. *Mathematical Biosciences*, vol. 58, pp. 27-60.

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

Dalla Man, Ch., Caumo, A. and Cobelli, C. (2002). The Oral Glucose Minimal Model: Estimation of Insulin Sensitivity From a Meal Test. *IEEE Transactions on Biomedical Engineering*, vol. 49, no. 5, pp. 419-429.

Dalla Man, Ch., Toffolo, G., Basu, R., Rizza, R.A. and Cobelli, C. (2006a). A Model of Glucose Production During a Meal. in *Proc. of 28th IEEE EMBS Annual International Conference*, New York City, USA, pp. 5647-5650, 2006.

Dalla Man, Ch., Rizza, R.A. and Cobelli, C. (2006b). Mixed Meal Simulation Model of Glucose-Insulin System. in *Proc. of 28th IEEE EMBS Annual International Conference*, New York City, USA, pp. 307-310.

Fabietti, P.G., Canonico, V., Orsini Federici, M., Massi Benedetti, M. and Sarti, E. (2006). Control oriented model of insulin and glucose dynamics in type 1 diabetics. *Medical and Biological Engineering and Computing*, vol. 44, pp. 69–78.

Fernandez, M., Acosta D., Villasana M. and Streja, D. (2004). Enhancing Parameter Precision and the Minimal Modeling Approach in Type I Diabetes", in *Proc. of 26th IEEE EMBS Annual International Conference*, San Francisco, USA, pp. 797–800.

Fonyo, A. and Ligeti, E. (2008). *Physiology* (in Hungarian). 3rd ed., Ed. Medicina, Budapest.

de Gaetano, A. and Arino, O. (2000). Some considerations on the mathematical modeling of the Intra-Venous Glucose Tolerance Test. *Journal of Mathematical Biology*, vol. 40, pp. 136-168.

Guyton, J.R., Foster, R.O., Soeldner, J.S., Tan, M.H., Kahn, C.B., Koncz, L. and Gleason, R.E. (1978). A model of glucose-insulin homeostasis in man that incorporates the heterogeneous fast pool theory of pancreatic insulin release. *Diabetes*, vol. 27, pp. 1027.

Hernjak, N. and Doyle III, F.J. (2005). Glucose control design using nonlinearity assessment techniques. *AIChE Journal*, vol. 51, no. 2, pp. 544-554.

Hipszer, B.R. (2001). *A Type 1 Diabetic Model*. Master Thesis, Drexel University, USA, 2001.

Hovorka, R., Shojaee-Moradie, F., Carroll, P.V., Chassin, L.J., Gowrie, I.J., Jackson, N.C., Tudor, R.S., Umpleby, A.M. and Jones, R.H. (2002). Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *American Journal Physiology Endocrinology Metabolism*, vol. 282, pp. 992-1007.

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

Ibbini, M. (2006). A PI-fuzzy logic controller for the regulation of blood glucose level in diabetic patients. *Journal of Medical Engineering and Technology*, vol. 30, no. 2, pp. 83-92.

Kienitz, K.H. and Yoneyama, T. (1993). A Robust Controller for Insulin Pumps Based on H-Infinity Theory. *IEEE Transactions on Biomedical Engineering*, vol. 40, no. 11, pp. 1133-1137.

Kovacs, L., Palancz, B., Benyo, B, Torok, L. and Benyo, Z. (2006). Robust blood-glucose control using Mathematica. in *Proc. of 28th EMBS Annual International Conference*, New York, USA, pp. 451-454.

Kovacs, L. and Palancz, B. (2007). Glucose-insulin control of Type1 diabetic patients in H_2/H_∞ space via Computer Algebra. *Lecture Notes in Computer Science*, vol. 4545, pp. 95–109.

Kovacs L., Kulcsar B., Bokor, J. and Benyo, Z. (2008). Model-based Nonlinear Optimal Blood Glucose Control of Type 1 Diabetes Patients. in *Proc. 30th IEEE EMBS Annual International Conference*, Vancouver, Canada, pp 1607-1610.

Kovacs, L. (2008). *New principles and adequate control methods for insulin dosage in case of diabetes*. PhD dissertation (in Hungarian). Budapest University of Technology and Economics, Budapest, Hungary.

Kulcsar, B. (2005). *Design of Robust Detection Filter and Fault Correction Controller*. PhD dissertation, Budapest University of Technology and Economics, Budapest, Hungary.

Lee, L.H. (1997). *Identification and Robust Control of Linear Parameter-Varying Systems*. PhD dissertation, University of California at Berkeley, USA.

Lehmann, E.D. and Deutsch, T.A. (1992). A physiological model of glucose-insulin interaction in Type1 diabetes mellitus. *Journal of Biomedical Engineering*, vol. 14, pp. 235-242.

Lin, J., Chase, J.G., Shaw, G.M., Doran, C.V., Hann, C.E., Robertson, M.B., Browne, P.M., Lotz, T., Wake, G.C. and Broughton, B. (2004). Adaptive bolus-based set-point regulation of hyperglycemia in critical care. in *Proc. of 26th IEEE EMBS Annual International Conference*, San Francisco, USA, pp. 3463-3466.

Morris, H.C., O'Reilly, B. and Streja, D. (2004). A New Biphasic Minimal Model. in *Proc. of 26th IEEE EMBS Annual International Conference*, San Francisco, USA, pp. 782–785.

Mougiakakou, S.G., Prountzou, A., Iliopoulou, D., Nikita K.S., Vazeou, A. and Bartsocas, Ch.S. (2006). Neural network based glucose – insulin metabolism models for children with type 1 diabetes. in *Proc. of 28th IEEE EMBS Annual International Conference*, New York, USA, pp. 3545-3548.

Ortiz-Vargas, M. and Puebla, H. (2006). A cascade control approach for a class of biomedical systems. in *Proc. of 28th IEEE EMBS Annual International Conference*, New York, USA, pp. 4420-4423.

Parker, R.S., Doyle III, F.J. and Peppas, N.A. (1999). A Model-Based Algorithm for Blood Glucose Control in Type I Diabetic Patients. *IEEE Transactions on Biomedical Engineering*, vol. 46, no. 2, pp. 148-157.

Parker, R.S., Doyle III, F.J., Ward, J.H. and Peppas, N.A. (2000). Robust H_∞ Glucose Control in Diabetes Using a Physiological Model. *AIChE Journal*, vol. 46, no. 12, pp. 2537-2549.

Parker, R.S., Doyle III, F.J. and Peppas, N.A. (2001). 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*, vol. 20, no.1, pp. 65-73.

Roy, A. and Parker, R.S. (2006a). Dynamic Modeling of Free Fatty Acid, Glucose, and Insulin: An Extended "Minimal Model". *Diabetes Technology & Therapeutics*, vol. 8, pp. 617-626.

Roy, A. and Parker, R.S. (2006b). Mixed Meal Modeling and Disturbance Rejection in Type I Diabetic Patients. in *Proc. of 28th IEEE EMBS Annual International Conference*, New York City, USA, pp. 323-326.

Ruiz-Velazquez, E., Femat, R. and Campos-Delgado, D.U. (2004). Blood glucose control for type I diabetes mellitus: A robust tracking H_∞ problem. *Elsevier Control Engineering Practice*, vol. 12, pp. 1179-1195.

Shamma, J. and Athans, M. (1991). Guaranteed properties of gain scheduled control for linear parameter varying plants. *Automatica*, vol. 27, no. 3. pp. 559-564.

Sorensen, J.T. (1985). *A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes*. PhD Thesis, Dept. of Chemical Eng. Massachusetts Institute of Technology, Cambridge, USA.

Tan, W. (1997). *Applications of Linear Parameter-Varying Control Theory*. MsC. thesis, University of California at Berekley, USA.

Thomaseth, K., Kautzky-Willer, A., Ludvik, B., Prager, R. and Pacini, G. (1996). Integrated mathematical model to assess β -cell activity during the oral glucose test. *Modeling in Physiology*, pp. 522-531.

Van Herpe, T., Pluymers, B., Espinoza, M., Van den Berghe, G. and de Moor, B. (2006). A minimal model for glycemia control in critically ill patients. in *Proc. 28th of IEEE EMBS Annual International Conference*, New York, USA, pp. 5432-5435.

Wild, S., Roglic, G., Green, A., Sicree, R. and King, H. (2004). Global prevalence of diabetes - Estimates for the year 2000 and projections for 2030. *Diabetes Care*, vol. 27, no. 5, pp. 1047-1053.

Wu, F., Grigoriadis, K.M. and Packard, A. (2000). Anti-windup controller design using linear parameter varying control methods. *International Journal of Control*, vol. 73, no. 12, pp. 1104-1114.

7. Appendix

7.1 Nomenclature and constants used in the Sorensen-model

In the current work the same nomenclature was used as it can be found in (Parker et al., 2000). The notations of the indexes used in the equations given below are:

- A - hepatic artery
- B - brain
- BU - brain uptake
- C - capillary space
- G - glucose
- H - heart and lungs
- HGP - hepatic glucose production
- HGU - hepatic glucose uptake
- I - insulin
- IHGP - insulin effect on HGP
- IHGU - insulin effect on HGU
- IVI - intravenous insulin infusion
- K - kidney
- KC - kidney clearance
- KE - kidney excretion
- L - liver
- LC - liver clearance
- N - glucagon
- NHGP - glucagon effect on HGP
- P – periphery (muscle / adipose tissue).
- PC - peripheral clearance
- PGU - peripheral glucose uptake
- PIR - pancreatic insulin release
- PNC - pancreatic glucagon clearance
- PNR - pancreatic glucagon release (normalized).
- RBCU - red blood cell uptake
- S – gut (stomach / intestine).
- SIA - insulin absorption into blood stream from subcutaneous depot
- SU - gut uptake
- T - tissue space

while the model variables notations are:

- A - auxiliary equation state (dimensionless).
- B - fractional clearance (I, dimensionless; N, L/min).
- G - glucose concentration (mg/dL).
- I - insulin concentration (mU/L).
- N - glucagon concentration (normalized, dimensionless).
- Q - vascular plasma flow rate (L/min).
- q - vascular blood flow rate (dL/min).
- T - transcapillary diffusion time constant (min).
- V - volume (L).
- v – volume (dL).
- Γ - metabolic source or sink rate (mg/min or mU/min).

The values of the used constants can be seen in Table 1.

[dL]	[L]	[dL/min]	[L/min]	[L/min]	[min]
$v_B^C = 3.5$	$V_B^C = 0.265$	$q_B = 5.9$	$Q_B = 0.45$	$F_{PNC} = 0.91$	$T_B = 2.1$
$v_B^T = 4.5$	$V_H^C = 0.985$	$q_H = 43.7$	$Q_H = 3.12$	$F_{LC} = 0.4$	$T_P^G = 5.0$
$v_H^C = 13.8$	$V_S^C = 0.945$	$q_S = 10.1$	$Q_S = 0.72$	$F_{KC} = 0.3$	$T_P^I = 20$
$v_S^C = 11.2$	$V_L^C = 1.14$	$q_L = 12.6$	$Q_L = 0.9$	$F_{PC} = 0.15$	
$v_L^C = 25.1$	$V_K^C = 0.505$	$q_A = 2.5$	$Q_A = 0.18$		
$v_K^C = 6.6$	$V_P^C = 0.735$	$q_K = 10.1$	$Q_K = 0.72$		
$v_P^C = 10.4$	$V_P^T = 6.3$	$q_P = 15.1$	$Q_P = 1.05$		
$v_P^T = 67.4$	$V_N = 9.93\ l$				

Table 1. Parameter values for the Sorensen-model (Parker et al., 2000).

7.2 Equations of the Sorensen-model

The equations of the Sorensen-model can be structured in three parts:

- Glucose equations;
- Insulin equations;
- Glucagons production;

The eight equations of the glucose part are given below:

$$\dot{G}_B^C = \left(G_H^C - G_B^C\right)\frac{q_B}{v_B^C} - \left(G_B^C - G_B^T\right)\frac{v_B^T}{T_B v_B^C} \tag{A-1}$$

$$\dot{G}_B^T = \left(G_B^C - G_B^T\right)\frac{1}{T_B} - \frac{\Gamma_{BU}}{v_B^T} \tag{A-2}$$

$$\dot{G}_H^C = \left(G_B^C q_B + G_L^C q_L + G_K^C q_K + G_P^C q_P - G_H^C q_H - \Gamma_{RBCU}\right)\frac{1}{v_H^C} \tag{A-3}$$

$$\dot{G}_S^C = \left(G_H^C - G_S^C\right)\frac{q_S}{v_S^C} + \frac{\Gamma_{meal}}{v_S^C} - \frac{\Gamma_{SU}}{v_S^C} \tag{A-4}$$

$$\dot{G}_L^C = \left(G_H^C q_A + G_S^C q_S - G_L^C q_L\right)\frac{1}{v_L^C} + \frac{\Gamma_{HGP}}{v_L^C} - \frac{\Gamma_{HGU}}{v_L^C} \tag{A-5}$$

$$\dot{G}_K^C = \left(G_H^C - G_K^C\right)\frac{q_K}{v_K^C} - \frac{\Gamma_{KE}}{v_K^C} \tag{A-6}$$

$$\dot{G}_P^C = \left(G_H^C - G_P^C\right)\frac{q_P}{v_P^C} + \left(G_P^T - G_P^C\right)\frac{v_P^T}{T_P^G v_P^C} \tag{A-7}$$

$$\dot{G}_P^T = \left(G_P^C - G_P^T\right)\frac{1}{T_P^G} - \frac{\Gamma_{PGU}}{v_P^T} \tag{A-8}$$

where for simplification $k_B^C = G_B^C \frac{v_B^T}{T_B}$ and $k_B^T = G_B^T \frac{v_B^T}{T_B}$ notations can be introduced.

The seven insulin equations are:

$$\dot{I}_B^C = \left(I_H^C - I_B^C\right)\frac{Q_B}{V_B^C} \tag{A-9}$$

$$\dot{I}_H^C = \left(I_B^C Q_B + I_L^C Q_L + I_K^C Q_K + I_P^C Q_P - I_H^C Q_H + \Gamma_{IVI}\right)\frac{1}{V_H^C} \tag{A-10}$$

$$\dot{I}_S^C = \left(I_H^C - I_S^C\right)\frac{Q_S}{V_S^C} \tag{A-11}$$

$$\dot{I}_L^C = \left(I_H^C Q_A + I_S^C Q_S - I_L^C Q_L\right)\frac{1}{V_L^C} + \frac{\Gamma_{PIR}}{V_L^C} - \frac{\Gamma_{LC}}{V_L^C} \tag{A-12}$$

$$\dot{I}_K^C = \left(I_H^C - I_K^C\right)\frac{Q_K}{V_K^C} - \frac{\Gamma_{KC}}{V_K^C} \tag{A-13}$$

$$\dot{I}_P^C = \left(I_H^C - I_P^C\right)\frac{Q_P}{V_P^C} - \left(I_P^C - I_P^T\right)\frac{V_P^T}{T_P^I V_P^C} \tag{A-14}$$

$$\dot{I}_P^T = \left(I_P^C - I_P^T\right)\frac{1}{T_P^I} + \frac{\Gamma_{SIA}}{V_P^T} - \frac{\Gamma_{PC}}{V_P^T} \tag{A-15}$$

The remaining four equations compose the remaining states of the Sorensen model: the glucagon and three additional (dimensionless) variables. The use of the latter three variables is to highlight the glucagons dependent dynamics of the glycogen (synthesis or glycogenolyzes) which is also dependent by the actual blood glucose and insulin level:

$$\dot{N} = \left(\Gamma_{PNR} - N\right)\frac{F_{PNC}}{V_N} \tag{A-16}$$

$$\dot{A}_{IHGP} = \frac{1}{25}\left[1.2088 - 1.138\tanh\left(1.669\frac{I_L^C}{21.43} - 0.8885\right) - A_{IHGP}\right] \tag{A-17}$$

$$\dot{A}_{NHGP} = \frac{1}{65}\left[\frac{2.7\tanh(0.388N) - 1}{2} - A_{NHGP}\right] \tag{A-18}$$

$$\dot{A}_{IHGU} = \frac{1}{25}\left[2\tanh\left(0.549\frac{I_L^C}{21.43}\right) - A_{IHGU}\right] \tag{A-19}$$

It can be observed, that in the different equations different Γ_i parameters appear. These correspond for the different metabolic source and sinks:

$$\Gamma_{BU} = 70 \tag{A-20}$$

$$\Gamma_{RBCU} = 10 \tag{A-21}$$

$$\Gamma_{SU} = 20 \tag{A-22}$$

$$\Gamma_{HGP} = 155A_{IHGP}\left[2.7\tanh(0.388N) - A_{NHGP}\right]\cdot\left[1.425 - 1.406\tanh\left\{0.6199\left(\frac{G_L^C}{101} - 0.4969\right)\right\}\right] \tag{A-23}$$

$$\Gamma_{HGU} = 20A_{IHGP}\left[5.6648 + 5.6589\tanh\left\{2.4375\left(\frac{G_L^C}{101} - 1.48\right)\right\}\right] \tag{A-24}$$

$$\Gamma_{KE} = \begin{cases} 71 + 71\tanh\left[0.011\left(G_K^C - 460\right)\right] & \text{, if } G_K^C < 460\dfrac{mg}{dl} \\ 0.872G_K^C - 300 & \text{, if } G_K^C \geq 460\dfrac{mg}{dl} \end{cases} \tag{A-25}$$

$$\Gamma_{PGU} = \frac{35G_P^T}{86.81}\left[7.035 + 6.51623\tanh\left\{0.33827\left(\frac{I_P^T}{5.304} - 5.82113\right)\right\}\right] \tag{A-26}$$

$$\Gamma_{LC} = F_{LC}\left(I_H^C Q_A + I_S^C Q_S + \Gamma_{PIR}\right) \tag{A-27}$$

$$\Gamma_{PIR} = 0 \tag{A-28}$$

$$\Gamma_{KC} = F_{KC}I_K^C Q_K \tag{A-29}$$

$$\Gamma_{PC} = \frac{I_P^T}{\dfrac{1 - F_{PC}}{F_{PC}}\dfrac{1}{Q_P} - \dfrac{1}{T_P^I V_P^T}} \tag{A-30}$$

$$\Gamma_{PNR} = \left[1.3102 - 0.61016\tanh\left\{1.0571\left(\frac{I_H^C}{15.15} - 0.46981\right)\right\}\right]\cdot \left[2.9285 - 2.095\tanh\left\{4.18\left(\frac{G_H^C}{91.89} - 0.6191\right)\right\}\right] \tag{A-31}$$

Biomedical Engineering

Edited by Carlos Alexandre Barros de Mello

ISBN 978-953-307-013-1

Hard cover, 658 pages

Publisher InTech

Published online 01, October, 2009

Published in print edition October, 2009

Biomedical Engineering can be seen as a mix of Medicine, Engineering and Science. In fact, this is a natural connection, as the most complicated engineering masterpiece is the human body. And it is exactly to help our “body machine” that Biomedical Engineering has its niche. This book brings the state-of-the-art of some of the most important current research related to Biomedical Engineering. I am very honored to be editing such a valuable book, which has contributions of a selected group of researchers describing the best of their work. Through its 36 chapters, the reader will have access to works related to ECG, image processing, sensors, artificial intelligence, and several other exciting fields.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen