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Induced L_2-norm Minimization of Glucose-Insulin System for Type I Diabetic Patients

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Abstract: Using induced L_2-norm minimization, a robust controller was developed for insulin delivery in Type I diabetic patients. The high-complexity nonlinear diabetic patient Sorensen-model was considered and Linear Parameter Varying methodology was used to develop open loop model and robust controller. Considering the normoglycemic set point (81.1 mg/dL), a polytopic set was created over the physiologic boundaries of the glucose-insulin interaction of the Sorensen-model. In this way, Linear Parameter Varying model formalism was defined. The robust control was developed considering input and output multiplicative uncertainties with two additional uncertainties from those used in the literature: sensor noise and worst case design for meal disturbance (60 g carbohydrate).

Keywords: Type I diabetes, robust control, LPV, polytopic set, uncertainty.

1. INTRODUCTION

Diabetes mellitus is one of the most serious diseases which need 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 (Wild et al. 2004). This warns that diabetes could be the "disease of the future", especially in the developing countries (due to the stress and the unhealthy lifestyle).

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 consequences of diabetes are mostly long-term; among others, diabetes increases the risk of cardiovascular diseases, neuropathy and retinopathy (Fonyo and Ligeti 2008). As a result, diabetes mellitus is a serious metabolic disease, which should be artificially regulated.

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.

Type I (also known as insulin dependent diabetes mellitus) 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 (Fonyó and Ligeti 2008). As a result, the only treatment of patients is 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. 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 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 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 and Doyle 2005), (Ruiz-Velazques et al. 2004), 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. In the last decades several models appeared for Type I diabetes patients (Chee and 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. 1979). However, the simplicity of the model proved to be its disadvantage too, whereas in its formulation a lot of components of the glucose-insulin interaction were neglected.

Beside the Bergman-model other more general, but more complicated models appeared in the literature (Cobelli et al. 1982), (Sorensen 1985), (Hovorka et al. 2002). The most complex one proved to be the 19th order Sorensen-model (Sorensen 1985) (the current paper focuses on a modification of it, developed by (Parker et al. 2000)). 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.

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 and Puebla 2006)), to soft-computing techniques (ex. neural networks (Mougiakakou et al. 2006)), adaptive (Lin et al. 2004), model predictive (MPC) (Hernjak and 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). 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 (Wu et al. 2000), (Balas 2002), (Kulcsar 2005).

2. LPV MODELLING USING POLYTOPIC DESCRIPTION

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.

2.1 LPV system definition

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, while the measured parameters assure describing the whole working domain of the designed controller. 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 $\rho(t)$ 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).

Consequently, the polyopic LPV model is valid only inside the polytopic region. 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

Definition 2. 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):

$$\left\| G_\mathcal{P} \right\|_{\mathcal{L}_2 \leftarrow \mathcal{L}_2} = \sup_{\rho\in\mathcal{P}} \sup_{\substack{\|d\|_2 \neq 0 \\ d\in\mathcal{L}_2}} \frac{\|e\|_2}{\|d\|_2} \tag{3}$$

As a result, $\left\| G_\mathcal{P} \right\|_{\mathcal{L}_2 \leftarrow \mathcal{L}_2}$ 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 $X \in \mathbf{R}^{n\times n}$, $X = X^T > 0$ such that for all $\rho \in \mathcal{P}$.

$$\mathcal{L} = \begin{pmatrix} A^T(\rho)X + XA(\rho) & XB(\rho) & \gamma^{-1}C^T(\rho) \\ B^T(\rho)X & -I & \gamma^{-1}D^T(\rho) \\ \gamma^{-1}C(\rho) & \gamma^{-1}D(\rho) & -I \end{pmatrix} < 0 \qquad (4)$$

Then:

1. The function A is quadratically stable over $\mathcal{P}$.
2. There exists a $\beta < \gamma$ such that $\|G_{\mathcal{P}}\|_{\mathcal{L}_2 \leftarrow \mathcal{L}_2} \leq \beta$.

The matrix inequality (4) can be rewritten in the more familiar Riccati inequality by taking Schur components (Tan 1997):

$$A^T(\rho)X + XA(\rho) + \gamma^{-2}C^T(\rho)C(\rho) + \left(XB(\rho) + \gamma^{-2}C^T(\rho)D(\rho)\right)\cdot$$
$$\cdot\left(I - \gamma^{-2}D^T(\rho)D(\rho)\right)^{-1}\left(B^T(\rho)X + \gamma^{-2}D^T(\rho)C(\rho)\right) < 0 \qquad (5)$$

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

$$\mathcal{L}_{\gamma^2} = \begin{pmatrix} A^T(\rho)X + XA(\rho) & XB(\rho) & C^T(\rho) \\ B^T(\rho)X & -I & 0 \\ C(\rho) & 0 & -\gamma^2 I \end{pmatrix} < 0 \qquad (6)$$

3. RESULTS

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

The publication of (Parker et al. 2000) was one of the first pioneer works in applying the H_∞ method for glucose-insulin control of Type I diabetic patients using the fundamental nonlinear Sorensen-model. 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) in response to a 50 g meal disturbance (using the six hour meal disturbance function of (Lehmann and 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 and Yoneyama 1993), who developed an H_∞ controller based on a third order linear diabetic patient model. Performance of (Kienitz and 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 and Yoneyama 1993).

However, (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 hypoglycemic episode, typically characterized as blood glucose values below 60 mg/dL (see Fig. 9 and Fig. 10 of (Parker et al. 2000)).

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 and Deutsch 1992) (60 g carbohydrate).

3.2 Covering the Sorensen-model with a polytopic region

The 19th order Sorensen model is structured in six compartments (Fig. 1). The model has two inputs: Γ_{meal} (meal disturbance) and Γ_{IVI} (injected insulin amount), and one output, the capillary heart-lungs glucose concentration, G_H^C . However, we have considered also the peripheric insulin concentration in the capillaries, I_P^C as an additional 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 $I_{P\ init}^C$ = 26.65 mU/L), while the others were deflections from this point (given below in %) (Kovacs 2008):

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

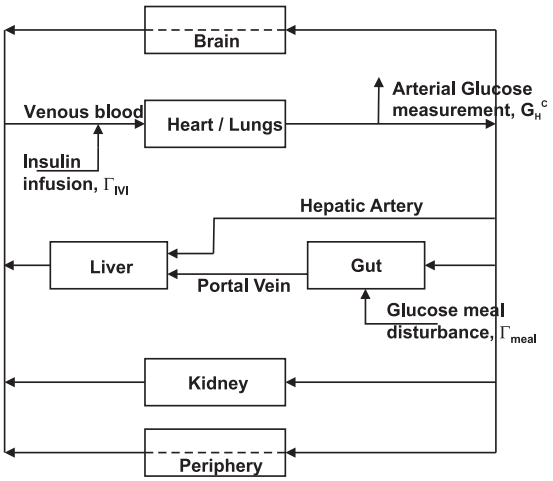

Fig. 1. Compartmental representation of the Sorensen model (Parker et al. 2000).

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

In the points of the so generated polytopic region (48 points) we have determined one by one a linearized model and we have proved their stability, and partial observability and controllability (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 published in (Parker et al. 2000). Results proved to be similar (Fig. 2). It can be seen that the LPV model remains inside the considered polytopic region and approximates with an acceptable error the nonlinear system (below 10%). As we have mentioned earlier, for meal disturbance we have used the same six hour meal disturbance function of (Lehmann and Deutsch 1992), 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.

3.3 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 hypoglycemic situation appears for the considered uncertainties. In case of a diabetic patient this could be a dangerous situation.

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_P.

$$\min_K \|G\| = \min_K \sup_{\rho \in F_p} \sup_{\|d\| \neq 0} \frac{\|z_{y1}\|}{\|d\|} \tag{7}$$

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

In our situation starting from the same situation presented in (Parker et al. 2000), we have reproduced the same results obtained by (Parker et al. 2000) with the dangerous near hypoglycemic episode (dashed line) (Fig. 3), but using the LPV methodology. This point meant the staring point of our control problem.

However, as we mentioned above, we have considered two additional types of multiplicative uncertainties for the system: output (neglected in (Parker et al. 2000), by considering it a 1/10000 value) and input one. In case of sensor noise, we have considered that for insulin measurements a 5% error, while for glucose measurements a 2% error is tolerable (values taken from clinical experience). For meal disturbances (Parker et al. 2000) considered the design for 50 g carbohydrate, while our situation focused on the worst case of (Lehmann and Deutsch 1992), a 60 g carbohydrate intake.

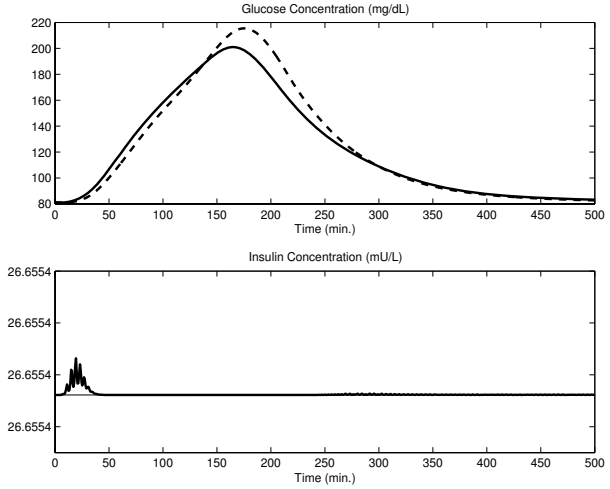

Fig. 2. The simulation of the nonlinear Sorensen model (solid) and the considered polytopic region (dashed).

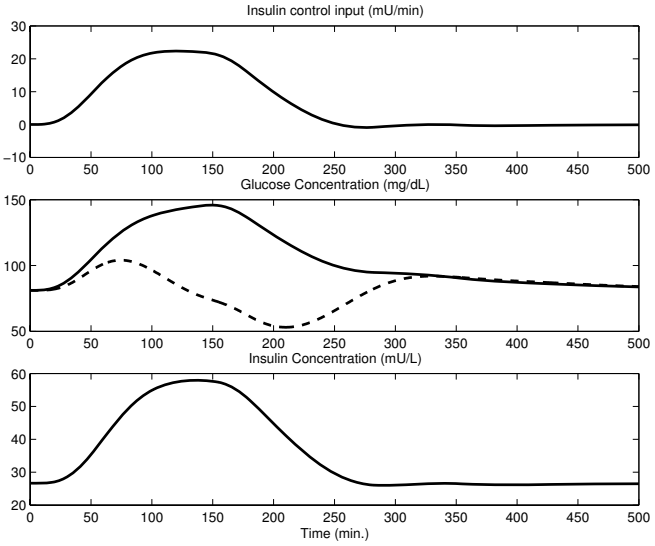

Fig. 3. The LPV based robust controller with induced L_2-norm minimization guarantee, using the same weighting functions as in (Parker et al. 2000): in case of the original nonlinear Sorensen model (solid) and the considered polytopic region (dashed).

To avoid the hypoglycemic situation and take into account the two additional uncertainties, we have extended the control loop with a weighting function for the control signal and an output uncertainty block (Fig. 4).

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_p, while these were chosen only from engineering point of view. Now physiological aspects were taken also into account (Fig. 5) by considering the polytopic points' model. The shape of the determined uncertainty functions are in accordance with those obtained by (Parker et al. 2000); however in the current situation first order transfer functions were obtained.

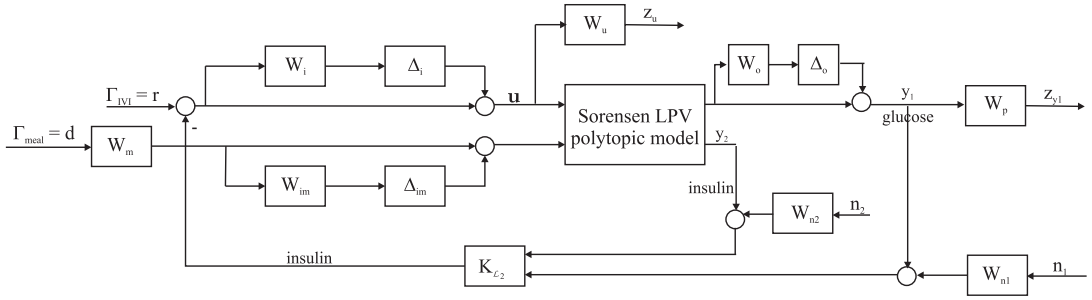

Fig. 4. The augmented system and the controller.

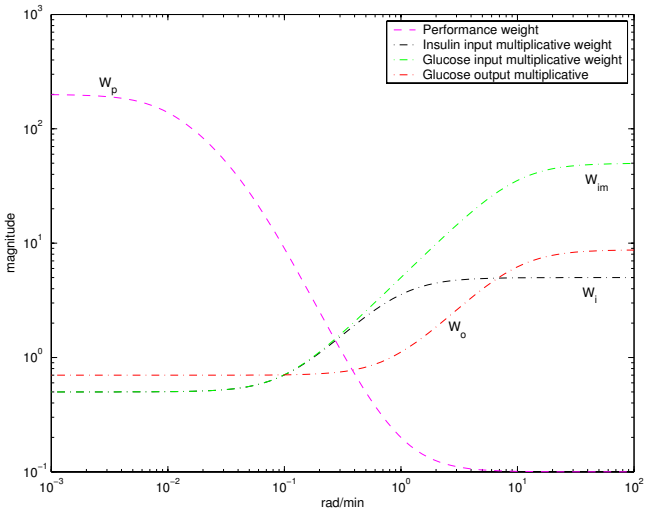

Fig. 5. Weighting functions (W_{im}, W_i, W_p , W_u) used for the LPV-based induced L_2-norm minimization (those which have been modified from (Parker et al. 2000)).

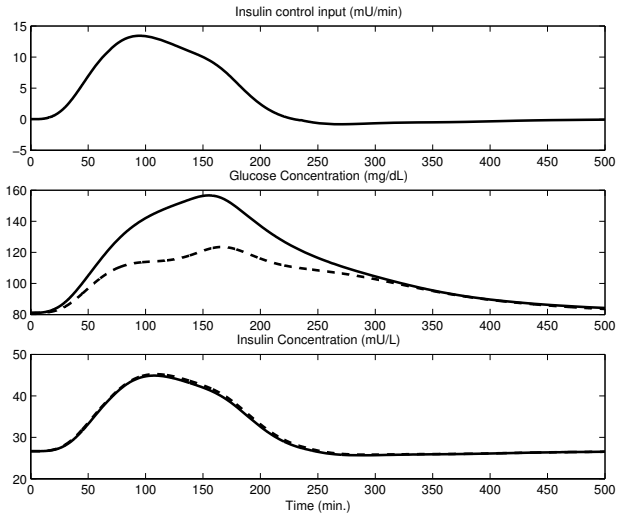

Fig. 6. The LPV based robust controller (for the case of the considered additional uncertainties) with induced L_2-norm minimization guarantee in case of the original nonlinear Sorensen model (solid) and the considered polytopic region (dashed).

Regarding the clinical affect of the uncertainties not only the insulin (as control input), but also the glucose (as disturbance) was more restricted (out of the ordinary case presented in (Ruiz-Velazques et al. 2004)). In this way the glucose input (meal intake) could be considered also as a sensitive input.

During the robust control design, a γ = 1.97 solution was obtained. Results can be seen in Fig. 6. It can be observed that due to the chosen weighting functions the first and second physiological phase of the control input function are not well delimited, but the same control signal shape was obtained as in (Parker et al. 2000) (using now stronger restrictions). It can be also seen that the dangerous hypoglycemic situation is avoided and the glucose level is kept inside the normal 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).

4. CONCLUSIONS

In this paper 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. The validity of the model was captured inside a polytopic region and in this way the model was built up by a linear combination of the linearized models derived in each considered polytopic point.

Sensor noise and worst case meal disturbance were applied in the robust control designing process of the system as well as some weighting functions used in (Parker et al. 2000) were retuned from physiological considerations. The obtained results showed that glucose level can be kept inside the normal range, which was hardly possible with the control formalism applied in (Parker et al. 2000). As a result, the applied control methodology could be a useful help in the investigation of the Sorensen model in control problems.

Parameter dependency of the considered weighting functions could be considered in the future, which gives additional design freedom. Simulation tests on a complete diurnal cycle can be taken into account or the application of the LPV methodology in the problem of glycaemic control can be considered also as a further question to be investigated.

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