Robust Control of Type 1 Diabetes using μ-synthesis

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Abstract: Robust servo control of type 1 diabetes is presented from a control theoretic perspective in this paper. Using a recently published glucose-insulin model, first the transformation of the model to the type 1 diabetes case is performed. Then, by parametric nonlinear model sensitivity analysis using a gridding method, the uncertainty around the nominal model is characterized. The viability of the robust servo, linear μ-control algorithm tested in highly nonlinear closed-loop simulation environment is realized by a two degree-of-freedom robust controller. Robust performance requirements are achieved and glucose level tracking is ensured under unknown and realistic exogenous meal disturbance.

Keywords: Type 1 diabetes, robust control, μ-synthesis, glucose tracking, uncertainty.

1. INTRODUCTION

The normal blood glucose concentration level in the human body varies in a narrow range (80 - 120 mg/dL). Diabetes appears if for some reason the human body is unable to control the normal glucose-insulin interaction (e.g. the glucose concentration level is often out of the normal range). The consequences of diabetes are diverse and mostly long-term, as diabetes increases the risk of cardiovascular diseases, neuropathy and retinopathy, Fonyó and Ligeti (2008).

Among the four types of diabetes (type 1 or insulin-dependent diabetes mellitus (IDDM), type 2 or insulin-independent diabetes mellitus (IIDM), gestational diabetes and other special types, like genetic deflections), type 1 can be characterized as a standard clinical picture: the β cells responsible for insulin production are completely destroyed. Accordingly, there is no human insulin production and artificial insulin source has to be applied.

The treatment of diabetes in this case can be controlled by an outer loop Cobelli and Mari (1985), Doyle III et al. (1995), Parker et al. (2000), Hovorka et al. (2004), Lee et al. (2009), replacing the human glucose-insulin equilibrium system, if needed. This replacement, the outer control, might be partially or fully automated. Self-regulation has several strict requirements, but once it has been designed it facilitates an optimal insulin dose, which, over time, can mitigate the negative effects of type 1 diabetes mellitus (T1DM).

Blood glucose control is one of the most difficult control problems to be solved. One of the main reasons is that patients are extremely diverse in their dynamics and their characteristics are time varying. Modeling the system and controlling its behavior are two tightly connected questions. Hence, the problems cannot be discussed separately. As a result of numerous researches, two main aspects were proposed, Chee and Fernando (2007): model-less (empirical) and model-based approaches.

The mathematical description of the glucose-insulin system of T1DM patients is usually just an approximation (e.g. the novel glucose-insulin model, Liu and Tang (2008)), and consequently it contains neglected static and dynamic components. Furthermore, model parameters can vary significantly between patients and over time. Therefore, in this paper we take robust control algorithm into account.

The paper presents a robust servo linear μ-control algorithm application on the novel glucose-insulin model of Liu and Tang (2008), transformed to describe the T1DM individual. Giving a general overview of the robust control methodology, sensitivity analysis in frequency domain is performed to determine the nonlinear model uncertainty for control design. Controller design, the explanation of the weighting functions used, the results of design iterations, and the simulation results of the obtained controller (on the nonlinear model) are presented in the Results section, followed by Conclusions.

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2. BRIEF REVIEW OF THE LIU-TANG MODEL

In contrast with most of the earlier models the model of Liu and Tang (2008) applies a different approach: it considers enzyme activity of glucose-glycogen and glycogen-glucose conversion and glucose utilization dynamics. However, it is not purely a molecular model. Consequently, the cause-effect relations are more plausible and different functions and processes can be separated. However, it has to be noted that the model has not yet been validated with experiments. Since the model has been published recently and is not widely used yet, a brief review is presented here. Numerical values of the model parameters can be found in Liu and Tang (2008), Kovács et al. (2009a).

2.1 Transition subsystem

Let x_1 and x_2 denote concentrations of plasma glucagon and insulin, respectively. Complementing equations of Sturis et al. (1991) with transition delay of the subsystem can be described with:

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -k^p_{1,1}x_1 - k^p_{1,2}x_1 + w_1, \tag{1}$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = -k^p_{2,1}x_2 - k^p_{2,2}x_2 + w_2, \tag{2}$$

where w_1 and w_2 stand for concentrations of glucagon and insulin produced by the pancreas - for more detailed explanation see Equations (12)-(13), other parameters can be found in Liu and Tang (2008).

2.2 Receptor binding subsystem

Let x_3 and x_4 stand for intracellular concentrations of glucagon and insulin, where x_5 and x_6 denote concentrations of glucagon- and insulin-bound receptors, respectively:

$$\frac{\mathrm{d}x_3}{\mathrm{d}t} = -k^s_{1,1}x_3\left(R^0_1 - x_5\right) - k^s_{1,2}x_3 + \frac{k^p_{1,1}x_1V_p}{V}, \tag{3}$$

$$\frac{\mathrm{d}x_4}{\mathrm{d}t} = -k^s_{2,1}x_4\left(R^0_2 - x_6\right) - k^s_{2,2}x_4 + \frac{k^p_{2,1}x_2V_p}{V}, \tag{4}$$

$$\frac{\mathrm{d}x_5}{\mathrm{d}t} = k^s_{1,1}x_3\left(R^0_1 - x_5\right) - k^r_1x_5, \tag{5}$$

$$\frac{\mathrm{d}x_6}{\mathrm{d}t} = k^s_{2,1}x_4\left(R^0_2 - x_6\right) - k^r_2x_6, \tag{6}$$

other parameters can be found in Liu and Tang (2008).

2.3 Glucose subsystem

Blood glucose has two sources: endogenous hepatic production from glycogen and appearance from exogenous meal intake. Let x_7 and x_8 denote glycogen and glucose concentrations, with exogenous glucose intake denoted by G_{in}.

Glucose utilization can be divided into two groups: insulin-independent (brain and nerve cells) and insulin-dependent (muscle, liver and adipose tissues).

The insulin-independent part is modeled by:

$$f_1 = U_b\left(1 - e^{-\frac{x_8}{C_2}}\right), \tag{7}$$

while the insulin-dependent part can be calculated by:

$$f_2 = \frac{x_8}{C_3}\left[U_0 + \frac{(U_m - U_0)\left(\frac{x_4}{C_4}\right)^\beta}{1 + \left(\frac{x_4}{C_4}\right)^\beta}\right]. \tag{8}$$

For the sake of simplicity, let:

$$f_3 = \frac{k_1x_6}{1 + k_2x_5}\frac{V^{gs}_{max}x_8}{K^{gs}_m + x_8} - k_3x_5\frac{V^{gp}_{max}x_7}{K^{gp}_m + x_7}, \tag{9}$$

which describes the glucose-glycogen and glycogen-glucose conversions, respectively, based on the Michaelis-Menten equation.

By modeling glucose-glycogen and glycogen-glucose conversions the glucose subsystem can be described with:

$$\frac{\mathrm{d}x_7}{\mathrm{d}t} = f_3, \tag{10}$$

$$\frac{\mathrm{d}x_8}{\mathrm{d}t} = -\left(f_1 + f_2 + f_3\right) + G_{in}. \tag{11}$$

2.4 Pancreatic control

Hormones of the pancreas play the leading role in normal blood glucose regulation and homeostatic stability since negative feedback of glucagon and insulin through blood glucose level assures controllability (in medical sense):

$$w_1\left(x_8\right) = \frac{G_m}{1 + b_1e^{a_1(x_8 - C_5)}}, \tag{12}$$

$$w_2\left(x_8\right) = \frac{R_m}{1 + b_2e^{a_2(C_1 - x_8)}}, \tag{13}$$

where $w_1\left(x_8\right)$ and $w_2\left(x_8\right)$ denote glucagon and insulin release rates (total amount of secreted hormone by the pancreas).

2.5 Model transformation

The real purpose of the research is to regulate the pathologic system. To fulfill this objective, the model has to be transformed to describe T1DM.

In T1DM insulin secretion of the pancreas becomes insufficient to regulate blood glucose. Due to the fact that (13) describes the insulin infusion rate (IRR) of the pancreas, where R_m denotes saturation value of pancreatic insulin secretion, in order to model T1DM R_m has to be decreased resulting in unsatisfactory pancreatic insulin secretion, Kovács et al. (2009a). However, it has to be noted that the transformed model has not yet been validated by experiments.

2.6 Open-loop simulation

By setting $R_m = 0$ T1DM can be modeled. Applying the glucose input presented in Korach-Andre et al. (2004), open-loop simulation can be realized (Fig. 1). Initial conditions are adapted from Liu and Tang (2008), where $x_2(0) = 2mU/l$. Hence, plasma insulin is present at the beginning of the simulation assumed due to prior insulin therapy. Observing Fig. 1 it can be seen that with no insulin secretion (open-loop simulation, no feedback is applied) blood glucose levels increase for about 360 minutes

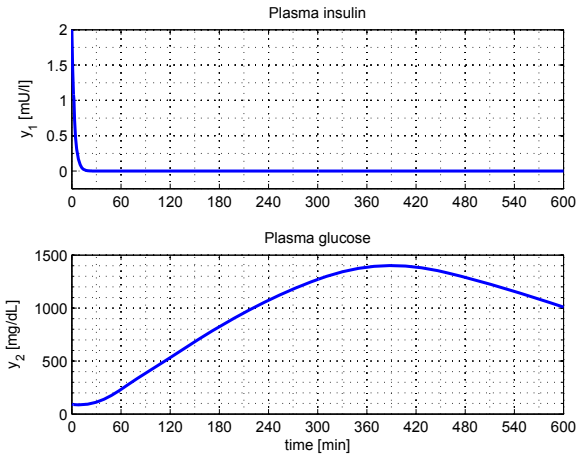

Fig. 1. Responses of the transformed type 1 diabetic Liu-Tang model.

to 1500 mg/dl (which is lethal) then decreases as a result of the delayed effect of low level of insulin. Consequently, T1DM conditions can be created.

It has to be remarked that plasma insulin is not an actual, realistic output, but in order to answer performance questions regarding control methods, it is considered to be a measureable output, however, it is not used in the controller method itself.

3. ROBUST CONTROL DESIGN USING COMPLEX μ-SYNTHESIS

Linear $\mathcal{H}_\infty$ and μ control synthesis are promising methods on the palette of robust control systems. These postmodern techniques date back to around two decades, Doyle et al. (1989). Progressively it gains ground by the more and more powerful computational software and hardware, Zhou (1996), Balas et al. (1991). Necessary and sufficient conditions for robust stability and robust performance can be formulated in terms of the structured singular value denoted as μ, Zhou (1996).

Consider the closed-loop system drawn in Fig. 2, which includes the feedback structure of the model G_n and controller K, and elements associated with the uncertainty models and performance objectives. In the diagram, r is the reference, u is the control input, y is the output, n is the measurement noise, and z_e is the deviation of the output from the required one. The structure of the controller K may be partitioned into two parts: $K = [K_r \quad K_y]$, where K_y is the feedback part of the controller and K_r is the prefilter part. The augmented P-K structure can be created by applying the weighting functions given above and the inputs can be written as:

$$\tilde{w} = [r \;\; n \;\; h]^T, \quad \tilde{z} = [z_e \;\; z_u]^T. \tag{14}$$

By introducing the so called linear fractional transformation (LFT) of the (P, K) pair Zhou (1996), one gets back the $\Delta - M$ structure, Zhou (1996). In order to analyze the performance and robustness requirements, the closed loop system is expressed by the lower LFT of partition blocks M:

$$\begin{bmatrix} e \\ \tilde{z} \end{bmatrix} = \left[\begin{array}{c|c} M_{11} & M_{12} \\ \hline M_{21} & M_{22} \end{array}\right] \begin{bmatrix} d \\ \tilde{w} \end{bmatrix}. \tag{15}$$

The robust stability (RS) can be guaranteed when the closed-loop system is internally stable. The internal stability means that from all inputs to all outputs the created transfer function is stable. As a result $\|M_{11}\|_\infty < 1$.

This condition might be conservative, while the set of perturbations Δ is member of a bounded subset, Zhou (1996). A less conservative solution of the problem is to structure uncertainties. This is the structured singular value μ and in this way $1/\mu_{\mathbf{\Delta}}(M)$ is the "size" of the smallest perturbation Δ, measured by its maximum singular value. As a result, the robust stability can be reformulated as:

$$\sup_\omega \mu(M_{11}) < 1 \Longleftrightarrow \|\mu(M_{11})\|_\infty < 1. \tag{16}$$

The main goal of our synthesis is to guarantee robust performance (RP). The closed-loop system achieves robust performance if the following performance objective is met, Zhou (1996):

$$\sup_\omega \mu(M) < 1 \Longleftrightarrow \|\mu(M)\|_\infty < 1. \tag{17}$$

Using μ it is possible to test both robust stability and robust performance in a non-conservative manner. Computation of μ can be done by D-K iteration, Gu et al. (2005).

4. RESULTS

In this section, the robust servo glucose-insulin controller is designed and applied through the model-based diabetic patient system based on the principles described in the previous section. Due to the fact that perfect fitting of a model-real plant does not exist, the model (or nominal plant) always contains neglected dynamics of the real world. The nominal plant is usually a lower order system than the real plant, because highly complicated components are neglected rather than modeled.

Both the linear and the nonlinear descriptions have two inputs. One of them is the control input, the other is assumed to be disturbance. The control input is the insulin input, the disturbance arises from glucose intake. The measured quantities are considered to be both the plasma insulin and glucose concentrations (however, one would not be able to measure plasma insulin in real time, but can estimate it knowing the insulin input).

The aim of the robust control under model mismatch is the disturbance rejection on the glucose and the tracking of a predefined glucose concentration level reference. During the synthesis one takes the input weighting into account in order to force the designed control input signal to stay in an acceptable magnitude domain, and the controller will be tested on the nonlinear plant with noise corrupted measurements. One of the biggest advantages of postmodern linear $\mathcal{H}_\infty$, respectively μ control syntheses (beyond the well defined mathematical backgrounds) might be the robustness itself: robustness against model mismatches, as well as against disturbances, Zhou (1996).

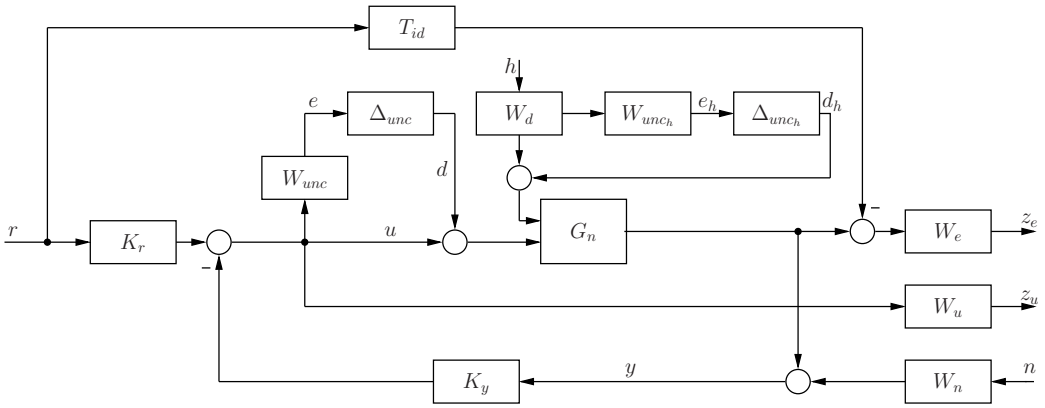

Fig. 2. Augmented closed loop interconnection.

4.1 Uncertainty analysis and controller design

One widespread approach of describing uncertainties is the unstructured formulation. Even if the precise uncertainty dynamics are unknown, usually an upper bound can be defined in the frequency domain to characterize the mismatch. Complex uncertainties and neglected dynamics can be classified into several groups. Two major types (not counting the more complicated structures) of complex uncertainty are distinguished: the additive and the multiplicative blocks (at the plant output or input for MIMO systems). This choice always requires a certain amount of a priori information. For robust control of T1DM, the uncertainty formulation has always been a great challenge. One of the earliest solutions can be found in Parker et al. (2000) for the model of Sorensen. Moreover, further improvements of the original idea from a physiological point of view can be found in Kovács et al. (2009b).

In our case, input multiplicative uncertainty is preferred because it specifies the digression, the frequency depending difference (in percentage) between the nominal and the actual plant. The uncertainties between the nominal model and the real plant with W_{unc} and Δ_{unc} (for the insulin control input part), and W_{unc_h} and Δ_{unc_h} (for glucose disturbance part) is assumed to be known, and it presents all a priori information about the neglected dynamics. In the following, we neglect the actuator dynamics and high frequency behavior of the nonlinear plant by means of multiplicative description.

Starting from the formal definition of the multiplicative uncertainty:

$$M := \left\{ G : \left| \frac{G(i\omega) - G_n(i\omega)}{G_n(i\omega)} \right| \leq |W_{mr}(i\omega)| \right\}, \qquad (18)$$

where G and G_n are the transfer function of the plant and the nominal plant, respectively, a parametric sensitivity analysis was performed on the nonlinear model to determine W_{unc} and W_{unc_h}. The shape of the input multiplicative uncertainty is defined in two steps. First, the low frequency part, i.e. steady state modeling error is determined by sensitivity analysis. Second, the high frequency part is defined to cover neglected nonlinear and actuator dynamics.

This idea was partially adapted and then modified from Parker et al. (2000). The idea is to take uncertain parameters in the nonlinear model. Ranges are associated to these selected parameters. Then, taking every single extremal combination of the parameters, linearization is performed. Finally, the frequency content of the perturbed and linearized model is compared and relative differences are computed. Instead of using the extremal values, a gridding technique is proposed in this study.

Due to the fact that no physical data was available from which to identify ranges of parametric uncertainty, a $\pm 10\%$ variability of the insulin subsystem and a $\pm 10\%$ variability of the glucagon/glucose subsystem was assumed based on Liu and Tang (2008). The sensitivity was performed regarding the $k^p_{1,1}$, $k^p_{1,2}$, $k^p_{2,1}$, $k^p_{2,2}$ (for the plasma transition subsystem), $k^s_{1,1}$, $k^s_{1,2}$, $k^s_{2,1}$, $k^s_{2,2}$ (for the intracellular subsystem) and k_1, k_2, k_3 as well.

For each parameter, a $(+max,\ +1/2max,\ -1/2max,\ -max)$ grid was applied to the 100 mg/dL nominal value of the considered model. For each possible combination, the nonlinear model was linearized and the linear model obtained was used to determine parametric sensitivity by determining $sup\ W_{rel}$ of the relative uncertainty relation $U_{rel}(\omega) = \left| \frac{G_p(\omega) - G(\omega)}{G(\omega)} \right|$, where G_p stands for the perturbed model, and G for the nominal one. The frequency range of interest was $\omega \in [0.001, 0.1] rad/sec$. The final results are:

$$W_{unc} = \frac{15}{s^2 + 10.05s + 1}, \qquad (19)$$

$$W_{unc_h} = \frac{5}{s^2 + 10.05s + 1}. \qquad (20)$$

Other weighting functions were selected for physiological reasons, Kovács et al. (2009b).

Summarizing the iterative steps for the μ-synthesis (Table 1), one can see that by adopting the $\mathcal{H}_\infty$-synthesis method (e.g. γ-iteration), a robust performance prescription cannot be achieved. A less conservative solution might be the μ-synthesis by $D-K$ iteration for complex uncertainty, Balas et al. (1991). The final (frequency dependent) D scale assures robust stability because the computed and scaled μ value is under 1. Consequently, robust performance is met. However, the controller degree increased significantly.

Table 1. Iteration summary of robust control design

Iteration	1	2	3
Controller order	15	19	23
D-scale order	0	4	8
γ archived	1.563	1.021	1.006
Peak value of μ	1.480	0.980	0.962

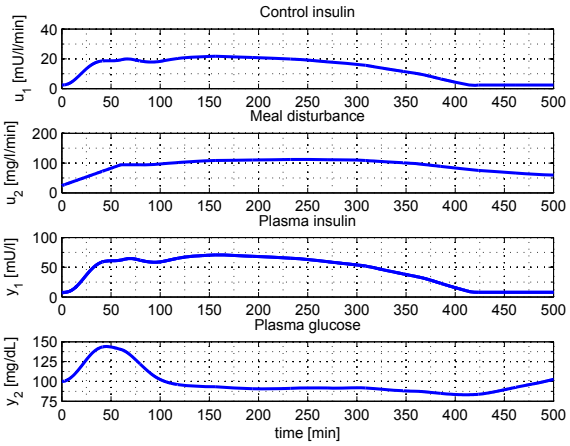

Fig. 3. Closed-loop responses of the μ-synthesis on the nonlinear model.

Testing the robust servo-controller using the food intake profile presented in Korach-Andre et al. (2004), it can be seen in Fig. 3 that the glucose concentration (y_2) stays in the normal 80-120 mg/dl range, while the insulin control input (u_1) is optimized. The glucose concentration is out of the mentioned region (145 mg/dl) only at the beginning of the meal absorbtion (u_2), but this is normal in case of food intake.

Moreover, at the end of the simulation the glucose concentration decreases to 77 mg/dl which can be explained by the mix of the delay of the insulin effect and the high glucose input. Even though, the mentioned period is near the normal range without reaching the upper bound of hypoglycaemia.

4.2 Virtual validation

Given the fact that the required input of the Liu-Tang model is glucose absorption, which is greatly difficult to measure, the only real input data we have is from Korach-Andre et al. (2004). Therefore, the authors generated virtual, but plausible and realistic, absorption profile to test the robustness of the designed controller.

Based on theoretical models of absorption of Piotrovskii (1987), the concentration of glucose absorbed can be considered to follow a Weibull curve as a function of time:

$$g = p_3 \left(\frac{t}{p_1}\right)^{p_2} e^{-\left(\frac{t}{p_1}\right)^{p_2}}. \tag{21}$$

Observing the role of parameters p_1, p_2 and p_3, it can be seen that p_1 corresponds to the input scaling, in other words, it scales the curve along the horizontal axis. Variable p_2 determines the shape of the curve, since it can be interpreted as a time constant of the system; hence it could model patient variability. p_3 scales the curve along the vertical axis. Therefore, it can take into account the amount of the glucose input. It has to be noted that this method is not to create the precise model of glucose absorption (eg. the exact quantitative relation between patient variability and p_2; or meal input and p_3 is not determined, although physiological considerations were taken into account), but to generate plausible absorption curves based on Korach-Andre et al. (2004).

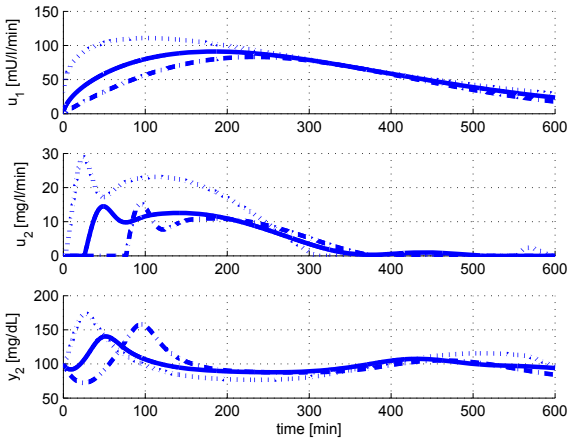

Fig. 4. Closed-loop response of the nonlinear model in case of modified amount of input glucose: $0.8p_2$ – dotted line, p_2 – solid line, $1.2p_2$ – dashed dotted line.

Hence, two simulation scenarios were considered:

(1) modified amount of input glucose: $\pm 20\% p_2$;
(2) modified time constant (patient variability): $\pm 20\% p_3$.

Closed-loop simulation results can be seen in Fig. 4-5. Observing glucose levels, it can be seen that the controller is robust enough in terms of meal disturbance and patient variability, since blood glucose level stays in the desired range. However, it has to be remarked, that blood glucose level is sometimes near to the upper bounds defining hypoglycemia. In these situations, the controller switches off, no insulin is injected, and blood glucose level starts to increase. This is in accordance with literature, Dassau et al. (2010). Later, if blood glucose level is getting too high (Fig. 4, after 550 minutes), the controller switches on again, and blood glucose is regulated by additional insulin injected.

The results are plausible from a physiological perspective, since time delay can be observed between insulin injections and blood glucose level (Fig. 4-5). Additionally, the infused insulin doses are realistic compared to the glucose input.

5. CONCLUSION

Linear robust μ-synthesis design was applied to assure robust performance with structuring the uncertainty description of T1DM model. For the two-degree-of-freedom controller structure presented, the nonlinear model uncertainty was characterized by varying the model parameters and set up for controller design by sensitivity analysis in frequency domain. By the applied non-conservative complex μ-synthesis method, not only robust stability is met,

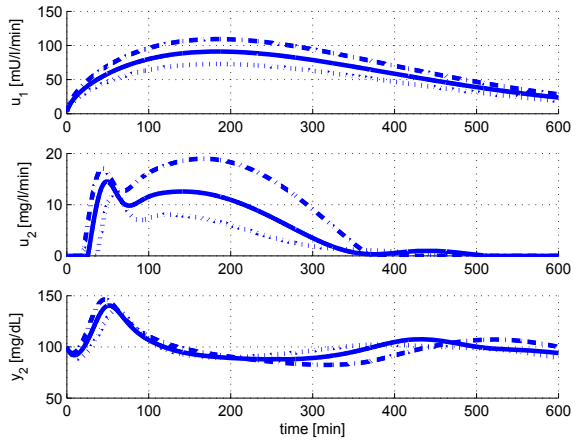

Fig. 5. Closed-loop response of the nonlinear model in case of modified time constant: $0.8p_3$ – dotted line, p_3 – solid line, $1.2p_3$ – dashed dotted line.

but also the nominal performance i.e. disturbance rejection is fulfilled.

It was demonstrated (using glucose absorbtion scenario taken from the literature) that the controller tested on the original nonlinear model keeps blood glucose concentration in the desired range while the insulin amount to be injected is optimized.

Future research can be supported on mixed uncertainties and nonlinear model based robust control methods. Moreover, simulation results should be compared to real experiments and other control methods.

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