Robust Tight Glycaemic Control of ICU patients

Levente Kovács*, Péter Szalay*, Balázs Benyó*, J. Geoffrey Chase**

*Budapest University of Technology and Economics, Dept. of Control Engineering and Information Technology
Magyar tudósok krt. 2, Budapest, H-1117 Hungary (Tel: +36-1-463-4027; e-mail: {lkovacs, szalaip, bbenyo}@iit.bme.hu)
** Dept. of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury,
Christchurch, New Zealand (e-mail: geoff.chase@canterbury.ac.nz)

Abstract: Intensive care is one of the most challenging areas of modern medicine. Maintenance of glucose levels in intensive care unit (ICU) patients via control of insulin inputs is currently an active research field. The current paper presents the analysis of postmodern and nonlinear control methods for tight glycaemic control (TGC) under intensive care. Using a clinically validated ICU metabolic system model's redefined version, an H_∞-type robust controller is proposed and compared with a non-conservative complex μ-synthesis method, where robust stability and nominal performance is met under multiplicative uncertainty. The model is rewritten in affine parameter varying form by choosing scheduling parameters and a quasi Affine Linear Parameter Varying (qALPV) controller is designed assuring performance and stability requirements. Closed loop simulation results are tested under MATLAB.

Keywords: diabetes, tight glycaemic control, H_∞ control, μ-synthesis, qALPV.

1. INTRODUCTION

Critically ill patients admitted to the Intensive Care Unit (ICU) often display hyperglycaemia and insulin resistance associated with adverse outcomes (Krinsley (2004)), which are associated with increased morbidity and mortality (Capes et al. (2000)). Tight glycaemic control (TGC) can reduce these adverse outcomes (Chase et al. (2008)), as well as reducing economic costs (Van den Berghe (2006)). The goal of such a control can be realized by automated or semi-automated treatments and, in this way, good outcome can be achieved with minimal extra clinical effort (Chase et al. (2006)).

Several studies have shown that TGC can reduce mortality (Chase et al. (2008)), but several others have reported difficulty repeating these results (Griesdale (2009)). This difficulty is caused in large part due to the significant metabolic variability of ICU patients (Lin et al. (2008)). It presents an ideal application for model-based automation of insulin infusions for TGC.

Accurate metabolic system models are a critical element. The best known model is the minimal model of Bergman et al. (1981), used primarily for clinical research studies. However, the model's simplicity is a disadvantage, with significant components of glucose-insulin interaction neglected in its formulation, as they are not required or are managed in clinical experiments.

Consequently, different models were derived from the minimal model, trying to generalize it to the ICU case. Wong et al. (2006) and Lotz et al. (2006) presented a third order model that better captured insulin losses and saturation dynamics. Van Herpe et al. (2007) created a fourth order model that accounted for further typical features of the ICU patient, although basic structure was retained. Pielmeier et al. (2009) created the 'Glucosafe' model that integrates a range of physiological models and parameters and accounts for the reduced rate of glucose gut absorption and saturation of insulin action in patients with reduced insulin sensitivity.

Of these models, only Wong et al. (2006) and Lotz et al. (2006) (named in the followings as Canterbury-model) have been clinically applied and validated in TGC for ICU patients, as well as in other clinical experiments. An updated version of this model has recently appeared (Suhaimi et al. (2010)).

Regarding the applied control strategies, it was proven that modeling and control are two tightly connected problems. However, most of the applied control methods in ICU focused on the minimal model (Makroglou et al. (2006)).

Using the model of Suhaimi et al. (2010) the aim of the current paper is to develop modern robust control strategies for TGC. The authors focused on the optimization of the amount of insulin under exogenous disturbance and mismatch. Parameter variance is taken into account using H_∞ and μ-synthesis robust linear control methods, but nonlinear model-based linear parameter varying (LPV) technique is also applied.

The paper is structured as follows: first a brief description of the model is given, and then the applied control strategies are described. Robust controller design is followed presenting simulation results on the original nonlinear system. The comparison differences between the linear and nonlinear model based robust control methods are also revealed.

2. THE CANTERBURY-MODEL

Wong et al. (2006) developed a series of models based on a fundamental system with three compartments (Wong et al. (2006), Lin et al. (2008)) with recent redefinition in Suhaimi et al. (2010):

$$\dot{G}(t) = -p_G G(t) - S_I(t)\frac{G(t)Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP_b - CNS}{V_G} \quad (1/a)$$

$$\dot{Q}(t) = kI(t) - kQ(t) \quad (1/b)$$

$$\dot{I}(t) = -\frac{nI(t)}{1+\alpha_I I(t)} + \frac{u_{ex}(t)}{V} + \frac{u_{end}(t)}{V} \quad (1/c)$$

$$\dot{P}_1(t) = D(t) - d_1 P_1(t) \quad (1/d)$$

$$\dot{P}_2(t) = d_1 P_1(t) - min\{d_2 P_2(t), P_{max}\} \quad (1/e)$$

$$P(t) = min\{d_2 P_2(t), P_{max}\} \quad (1/f)$$

$$u_{end}(t) = k_1 \, exp\left(\frac{-k_2 I(t)}{k_3}\right), \quad (1/g)$$

where the parameters are defined in Table 1, including typical values assigned to population constants.

This model (as well as its earlier versions) was mainly based on the minimal model of Bergman et al. (1981). The Canterbury-model was first extended with one state variable to represent insulin bounded to interstitial sites, like the one presented in Wong et al. (2006):

$$\dot{G}(t) = -p_G G(t) - S_I(t)(G(t)+G_E)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)}{V_G} \quad (2/a)$$

$$\dot{Q}(t) = kI(t) - kQ(t) \quad (2/b)$$

$$\dot{I}(t) = -\frac{nI(t)}{1+\alpha_I I(t)} + \frac{u_{en}(t)}{V}. \quad (2/c)$$

The model captures insulin losses to the liver and kidneys (Lotz et al. (2006)) and saturation dynamics through the use of Michaelis-Menten functions. All models have their unique insulin sensitivity metric, with the aim to correlate the value derived from the gold-standard euglycaemic clamp method (Lotz et al. (2006)). Contrary to the earlier models, where both insulin sensitivity $S_I(t)$ and glucose clearance $p_G(t)$ were time-varying parameters, in Suhaimi et al. (2010) only $S_I(t)$ is time-varying (Hann et al. 2005).

The insulin sensitivity metric is identified in real-time from data, and various methods have been examined in order to find the most accurate, but also computation time and cost efficient way including integral-based (Hann et al. (2005)) and stochastic (Lin et al. (2008)) parameter identification.

In Suhaimi et al. (2010) the basal value of plasma glucose concentration G_E was eliminated and replaced with two parameters representing endogenous glucose production EGP_b and the glucose demand of the central nervous system CNS. Both of these values are considered constant. However, two additional states were added to capture the delay resulting from glucose absorption during enteral feeding with a second-order system. Saturation was added to keep the states within physiologically acceptable ranges. In real-life applications these limits are not often reached, therefore the gastric absorption system (1/d)-(1/f) can be considered linear and time-invariant.

Furthermore, endogenous insulin production is included. However, no separate state variable was introduced. In earlier model versions, endogenous insulin production depended on exogenous insulin (Hann et al. (2005)) and plasma insulin. Recent (yet unpublished) results show that the suppression of endogenous insulin secretion seen in normal and healthy diabetic individuals is not effective in critical illness. Hence u_{end} can be considered constant ($u_{end} = u_{enb}$), negating (1/g).

Table 1. Variables used in the Canterbury-model.

Notation	Unit	Description	Value
State variables			
G	mmol/L	Plasma glucose concentration	-
Q	mU/L	Concentration of insulin bounded to interstitial sites	-
I	mU/L	Plasma insulin concentration	-
Model inputs			
D	mmol/min	Enteral glucose nutrition	
P	mmol/min	Glucose transfer from the gut to the bloodstream	-
u_{ex}	mU/min	External insulin	-
u_{end}	mU/min	Endogenous insulin production	-
Parameters			
p_G	1/min	Endogenous glucose clearance	0.006
S_I	L/mU/min	Insulin sensitivity	2.25e-4
α_G	L/mU	Insulin effect	1/65
EGP_b	mmol/min	Endogenous glucose production	1.16
CNS	mmol/min	Central nervous system glucose uptake	0.3
V_G	L	Insulin distribution volume	13.3
k	1/min	Effective life of insulin in the compartment	0.0198
n	1/min	First order decay rate from plasma	0.16
α_I	L/mU	Plasma insulin disappearance	0.0017
V_I	L	Insulin distribution volume	3.15
k_1	mU/min	Endogenous insulin production base rate	4.79
k_2	-	Generic constant	1.5
k_3	-	Generic constant	1000
u_{enb}	mU/min	Basal endogenous insulin production	4.7221
d_1	1/min	Transport rate between stomach and gut	0.0347
d_2	1/min	Transport rate between gut and plasma	0.0069
P_{max}	mmol/min	Glucose flux saturation	6.11

3. ROBUST CONTROL DESIGN USING COMPLEX μ SYNTHESIS

Linear H_∞, respectively μ control syntheses are promising methods on the palette of the 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 soft- and hardware, (Balas et al. (1991), Zhou (1996)). One of the biggest advantages of these methodologies (beyond the well defined mathematical backgrounds) might be the robustness itself. Robustness against model mismatches, against disturbances.

For robust control synthesis, let us consider the augmented system drawn in the Fig. 1. It 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 (insulin inlet), y is the output (glucose and insulin levels), d is the disturbance (glucose), 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: $K = [K_r\ K_y]$, where K_y is the feedback part of the controller and K_r is the pre-filter part.

One widespread approach of describing uncertainties is the unstructured formulation. Even if the precise uncertainty dynamics are unknown, usually an upper bound could be defined in frequency domain in order to characterize the mismatch. Complex uncertainties, neglected dynamics, respectively their (frequency depending) bounds could be classified into several groups.

In our case, the 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 is represented with W_m and $\varDelta_m$. W_m is assumed to be known, and it presents all a priori information about the neglected dynamics. The transfer function $\varDelta_m$ is assumed to be stable and unknown with the norm condition, $\|\varDelta_m\|_\infty < 1$. The formal definition of the multiplicative uncertainty is given by:

$$M(G_n,W_m) := \left\{ G : \left| \frac{G(i\omega)-G_n(i\omega)}{G_n(i\omega)} \right| \le |W_m r(i\omega)| \right\} . \qquad (3)$$
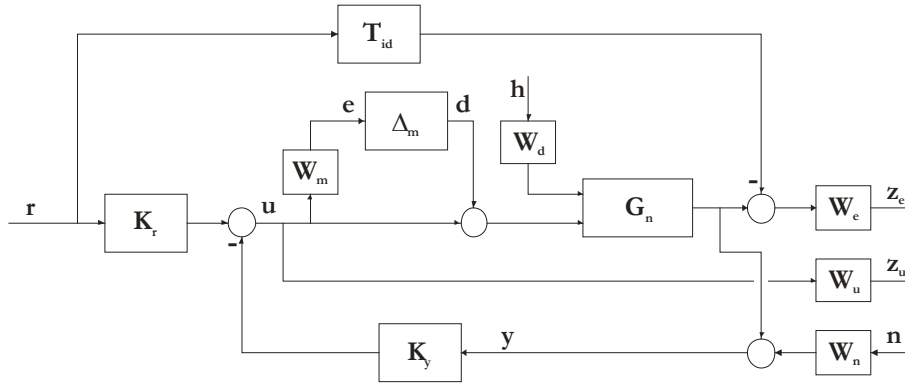
Necessary and sufficient conditions for robust stability and robust performance can be formulated in terms of the structured singular value denoted as μ, (Zhou (1996)). By introducing the so called linear fractional transformation (LFT) of the (P, K) pair one gets back the so-called the $\Delta - M$ 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:

$$\begin{bmatrix} e \\ \tilde{z} \end{bmatrix} = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix} \begin{bmatrix} d \\ \tilde{w} \end{bmatrix} , \qquad (4)$$

where $\tilde{w} = \begin{bmatrix} r & n & h \end{bmatrix}^T$, $\tilde{z} = \begin{bmatrix} z_e & z_u \end{bmatrix}^T$.

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 perturbation 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 $1/\mu_\Delta(M)$ is the "size" of the smallest perturbation Δ, measured by its maximum singular value. As a result the robust stability can be reformulated as:

$$\sup_\omega \mu(M_{11}) < 1 \Leftrightarrow \|\mu(M_{11})\|_\infty < 1 . \qquad (5)$$

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

$$\sup_\omega \mu(M) < 1 \Leftrightarrow \|\mu(M)\|_\infty < 1 . \qquad (6)$$

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)).

By adding other weighting functions, the degree of the H_∞ controller will increase. To achieve RP the tuning of the additional considered weighting functions should be necessary. In other words, RP is guaranteed only for planned / scheduled uncertainty. Therefore, it could be more practical to make investigations in the direction of non-linear control.

Fig. 1. Augmented closed loop interconnection.

4. LPV MODELLING AND QALPV DESCRIPTION

The H$_\infty$ and μ-synthesis method presented above was questioned over the linearized mathematical model of the glucose-insulin system. However, model-based controller design needs non-linear control strategies, to have a more closely behaviour to the real situation. This question is connected to the initial value problem and the answer is given by simulation results and by their evaluation in the followings.

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 $\mathcal{P}$ (Lee (1997)):

$$\dot{x}(t) = A(\rho)x(t) + B(\rho)u(t)$$
$$y(t) = C(\rho)x(t) + D(\rho)u(t) \qquad (7)$$

Consequently, LPV systems provide a model paradigm that goes beyond the classical representation of nonlinear and linear systems (Lee (1997)). Basically, LPV systems can be seen as an extension of linear time-invariant (LTI) systems, where the relations are considered to be linear, but model parameters are assumed to be functions of a time-varying signal.

To evaluate the system, the parameter trajectory is required to be known, either by measurement or by computation. Hence, by choosing parameter variables the system's nonlinearity can be hidden, while the measured parameters describe the whole working domain of the designed controller. This methodology is used on different control solutions (Balas (2002)), which gave also a solution of the problem.

4.1 qALPV modelling

There are different descriptions of LPV systems (Lee 2005). In the quasi-affine description, a part of the state vector $x(t)$ is equal with the $\rho(t)$ scheduling parameters. The affine dependency of (7) with $dim(\rho(t)) = N$ means:

$$A(\rho) = A_0 + \rho_1 A_1 + \ldots + \rho_N A_N$$
$$B(\rho) = B_0 + \rho_1 B_1 + \ldots + \rho_N B_N$$
$$C(\rho) = C_0 + \rho_1 C_1 + \ldots + \rho_N C_N \qquad (8)$$
$$D(\rho) = D_0 + \rho_1 D_1 + \ldots + \rho_N D_N$$

Hence, the affine LPV system can be written as:

$$\Sigma(t) = \left\{ \Sigma_0 + \sum_{i=1}^{N} \rho_i \Sigma_i : \rho_i \in \left[\underline{\rho}_i \ \overline{\rho}_i \right], \dot{\rho}_i \in \left[\underline{\dot{\rho}}_i \ \overline{\dot{\rho}}_i \right] \right\}, \qquad (9)$$

with $\Sigma_i = \begin{bmatrix} A_i & B_i \\ C_i & D_i \end{bmatrix}$, and $i = 1,2,\ldots,n$.

In (9) the parameters are varying between known minimal ($\underline{\rho}_i$) and maximal ($\overline{\rho}_i$) bounds (respectively the limits of theirs rates are known).

4.2 qALPV modelling of the Canterbury Model

Kovács et al. (2010) investigated qALPV modelling possibility of the model presented in Wong et al. (2006). It was demonstrated that time dependent variation of the $S_I(t)$ insulin sensitivity and the fractional nonlinear form in (2/a) and (2/c) can be captured in the scheduling parameters $\rho(t)$ and qALPV form can be realized. Moreover, the model can be reduced to a second order system (Kovács et al. (2010)).

Consequently, for the updated Canterbury-model (Suhaimi et al. (2010)) of (1) the scheduling parameters can be also defined for qALPV description:

$$\rho(t) = \begin{bmatrix} \rho_1(t) \\ \rho_2(t) \end{bmatrix} = \begin{bmatrix} S_I(t)\dfrac{I(t)}{1+\alpha_G I(t)} \\ \dfrac{1}{1+\alpha_I I(t)} \end{bmatrix}. \qquad (10)$$

Hence, in (7) the parameter matrices become:

$$A(\rho(t)) = A_0 + A_1\rho_1(t) + A_2\rho_2(t) =$$
$$= \begin{bmatrix} p_G & 0 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} -1 & 0 \\ 0 & 0 \end{bmatrix}\rho_1(t) + \begin{bmatrix} 0 & 0 \\ 0 & -n \end{bmatrix}\rho_2(t) \qquad (11)$$

$$B = \begin{bmatrix} B_1 & B_2 \end{bmatrix}, B_1 = \begin{bmatrix} 0 \\ \dfrac{1}{V} \end{bmatrix}, B_2 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, C = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}.$$

The vertex defined by the scheduling parameters is presented in Fig. 2. It can be seen the parameters are upper and lower bounded (Table 2) satisfying the qALPV modeling condition.
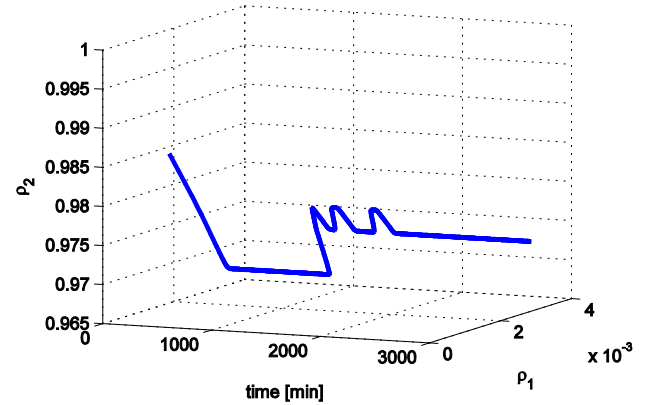

Fig. 2. Vertex defined by the scheduling parameters (ρ_1, ρ_2).

Table 2. Bounds of scheduling parameters.

		By measurement	Theoretical bound
ρ_1	$\underline{\rho}_1$	0.0019	0 (if I → 0)
	$\overline{\rho}_1$	0.0034	0.0146 (if I → ∞)
ρ_2	$\underline{\rho}_2$	0.9672	0 (if I → ∞)
	$\overline{\rho}_2$	0.9841	1 (I → 0)

4.3 Question of stability

The stability requirements are treated in the sequel. The insulin inlet uses a parameter dependent gain. Therefore:

$$A_{cl}(\rho) = A(\rho) + B_2 K(\rho) \tag{12}$$

$$K(\rho) = K_0 + \rho_1 K_1 + \rho_2 K_2 \tag{13}$$

$A_{cl}(\rho)$ is the closed loop parameter varying matrix and $K(\rho)$ is the state feedback term. As a result, the quadratically stabilizing parameter dependent Lyapunov criterion is::

$$A_{cl}(\rho)Q + QA_{cl}(\rho) = (A(\rho) + B_2 K(\rho))^T Q +$$
$$+ Q(A(\rho) + B_2 K(\rho)) < 0 \tag{14}$$

where Q is the solution matrix.

5. RESULTS

The robust TGC ICU controller is designed and applied through the model-based diabetic patient system (1).

Regarding the choice of the weighting functions, the input multiplicative weight W_m, comprehends the neglected actuator dynamics. At low frequency, where the linear model is supposed to be satisfactory, the relative mismatch was adjusted to 10%. Moreover, above 1 rad/min it starts to grow up (the cross over frequency is about 30 rad/min) and at higher frequency shape the linear model is fully uncertain, the weight is over 100%. To assure the good tracking performance W_e was increased at lower frequency up to 100. Based on the small gain theorem (Zhou (1996)) the permitted tracking error in this range is over 0.01 μU/ml. More the weight is decreased in frequency, more the tracking slip is. Uncertain system can not be forced to properly follow the reference signal. A slightly damped dynamic input weight is applied to filter the disturbance input, the glucose inlet. The cut off frequency of the W_d is around 20 rad/min. Usually, measurement noise corrupts the outputs. The general percentage of the incorporating noise, by channel, might not be over 2–5%. During the design process W_n anticipates 5% measurement noise. The synthesis is high sensitive even for a moderated change in the error term of insulin noise. The control input, i.e. the insulin inlet was maximized, because one can not use as many control energy as desired. The input inverse scale W_u permits to use a maximal, normalized and constant control input 38.525 μU/min (Parker et al. (2000)). Fig.3 plots the weighting functions used in Fig.1.

One can easily understand, by adopting the H_∞ synthesis method (e.g. γ-iteration), that the robust performance prescription can not be achieved (Table 3). By μ-synthesis a less conservative solution can be given. The final D scale assures the robust stability (the value of μ is under 1). Consequently, robust performance is met. However, the controller degree increased significantly.

In case of qALPV method by the bounded scheduling parameters the nonlinear control input can be calculated, obtaining:
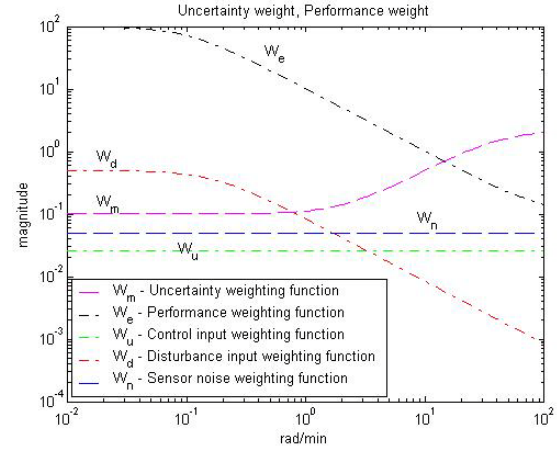
$$u_{qALPV} = -0.48x_2 + x_1x_2 - 0.72 \tag{15}$$

Fig. 3. The frequency response of some weighting functions in case of the model of Suhaimi et al. (2010).

Table 3. D-K iteration summary.

Iteration	1	2	3
Controller order	6	12	12
D-scale order	0	6	6
Gamma	1.563	1.115	1.018
Peak value of μ	1.099	1.006	0.997

For a theoretical food intake scenario (Kovács et al (2005)):

$$h(t) = 0.05 \cdot e^{-\frac{(t-10)^2}{45}} \tag{16}$$

glucose output concentration can be seen Fig. 4.

Here one can see a comparison of linear and nonlinear model-based control strategies too. In the mixed μ case the tracking error is lower than in the qALPV control system, but one needs to emphasize that the linear control is working properly around the operating point with the uncertainty and other weights previewed. However, the LPV system is valid for the whole working domain being equal with the original nonlinear system.
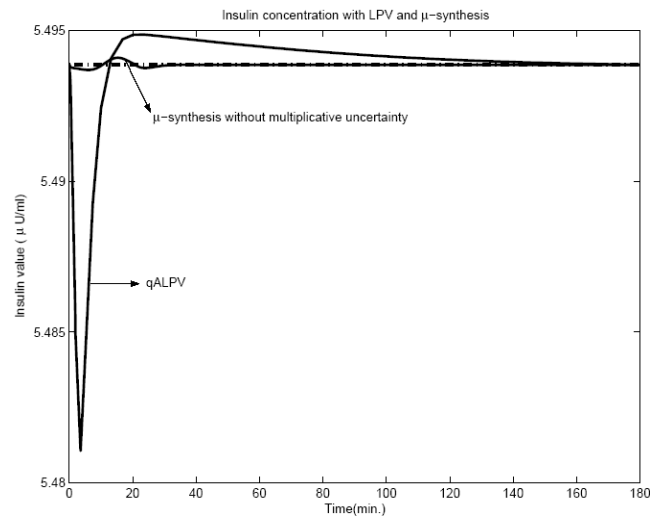

Fig. 4. Variation of glucose concentration in case of LPV and μ-synthesis methods.

6. CONCLUSIONS

Linear robust μ-synthesis design (assuring RP with structuring the uncertainty description) and nonlinear qALPV method were applied on a frequently used ICU metabolic model validated in clinical trials. The μ-synthesis (D-K iteration) method proved to guarantee robust performance if one remains in the given interval of the planned uncertainty. However, if one steps out from these bounds LPV control could be more efficient. The paper presents also the closed, glucose-insulin loop qALPV problem. The nonlinear problem was transformed into linear, but parameter dependent form. Further research will be done on simulating the designed controllers on real ICU data of different patients. Other clinically validated ICU models will be also investigated.

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