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Nonlinear Control Analysis of an ICU Model for Tight Glycaemic Control

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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 an active research field. Accurate metabolic system models are a critical element of automatic control. Different ICU models appeared in the literature some of them already validated in clinical trials. The current paper analyzes and gives a nonlinear synthesis of a frequently used ICU metabolic system model's redefined version. The model has been already validated in clinical trials. Global control characteristics are determined using nonlinear analysis. Results of reachability and observability are explained regarding physiological meanings, and then exact linearization is computed. Finally, quasi affine linear parameter varying (qALPV) modeling methodology is applied and compared with results obtained by exact linearization. It is demonstrated that inside the chosen scheduling parameters' vertex the qAPLV model represents the nonlinear system itself without any approximation. Conclusions are drawn from this analysis for further robust nonlinear model based controller design.

Keywords: Intensive Care Unit, tight glycaemic control, nonlinear analysis, exact linearization, qALPV, scheduling parameter.

1. INTRODUCTION

Critically ill patients admitted to the Intensive Care Unit (ICU) often display hyperglycaemia and insulin resistance (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)). Hence, TGC using model-based methods has become an active research field (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 important components of glucose-insulin interaction neglected in its formulation. Consequently, different models were derived to generalize 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. Pielmeier et al. (2009) created the 'Glucosafe' model that integrates a range of physiological models and parameters. 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)).

The goal of this paper is to make a nonlinear control analysis and synthesis on this modified Canterbury-model and compare the results with the qALPV nonlinear model-based methodology for the same model.

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):

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
$EGPb$	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

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

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

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

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).

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 input (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 and equal with basal endogenous insulin production, u_{enb}, negating (1/g).

3. NONLINEAR ANALYSIS

In this section, global characteristics of the model presented are examined, including reachability, observability and exact linearization, using the nonlinear analysis of Isidori (1995). The nonlinear systems are considered to be in the form:

$$\begin{aligned} \dot{x} &= f(x) + \sum_{i=1}^{m} g_i(x)u_i \\ y_i &= h_i(x) \qquad i = 1,2,\ldots,m \end{aligned} \quad . \quad (3)$$

It can be seen that the system is considered to be input affine. Let x denote that state vectors, u_i the inputs and y_i the outputs of the model.

3.1 Reachability

Let Δ^C be a nonsingular involutive distribution of dimension d and assume that Δ^C is invariant under the vector fields $f, g_1, g_2, \ldots, g_m$.

Moreover, suppose that the distribution $span\{g_1,\ldots,g_m\}$ is contained in Δ^C. Then, for each point x^0 it is possible to find a neighbourhood U^0 of x^0 and a local coordinate transformation $z=\Psi(x)$ defined on U^0 such that, in the new coordinates, the control system (3) is represented by equations of the form:

$$\begin{aligned}\dot{\varsigma}_1 &= f_1(\varsigma_1,\varsigma_2)+\sum_{i=1}^{m} g_{1i}(\varsigma_1,\varsigma_2)u_i \\ \dot{\varsigma}_2 &= f_2(\varsigma_2) \\ y_i &= h_i(\varsigma_1,\varsigma_2) \quad i=1,2,\ldots,m\end{aligned}, \tag{4}$$

where $\varsigma_1=(z_1,z_2,\ldots,z_d)$ and $\varsigma_2=(z_{d+1},z_{d+2},\ldots,z_n)$. In this manner, the state vector ς_1 is locally reachable, whereas ς_2 cannot be controlled (Isidori (1995)).

To construct the Δ^C distribution, initialization is defined:

$$\Delta_0^C = span\{g_1,\ldots,g_m\}. \tag{5}$$

Then, until $rank\,\Delta_k^C$ increases, the following iteration should be done:

$$\Delta_{k+1}^C = \Delta_k^C + \sum_{i=1}^{q}\left[\tau_i,\Delta_k^C\right], \text{ where } \tau_i\in\Delta_k^C \tag{6}$$

The number of local reachable state variables represents the rank of Δ^C (Isidori (1995)).

In other words, determining the degree of reachability means that new vectors have to be determined using Lie-derivatives, and the dimension that the extended vector field spans represents the number of local reachable state variables.

3.2 Observability

Let $d\Delta^O(x)\subset\left(R^n\right)^*$ denote the subspace containing $d\alpha(x)$ row vectors, where $\alpha\in O$ (observation space).

Then, for each point x^0 it is possible to find a neighbourhood U^0 of x^0, where $d\Delta^O(x)=d<n$ for $\forall x\in U^0$ and a local coordinate transformation $z=\Psi(x)$ defined on U^0 such that, in the new coordinates, the control system (3) is represented by equations of the form:

$$\begin{aligned}\dot{\varsigma}_1 &= f_1(\varsigma_1)+\sum_{i=1}^{m} g_{1i}(\varsigma_1)u_i \\ \dot{\varsigma}_2 &= f_2(\varsigma_1,\varsigma_2)+\sum_{i=1}^{m} g_{2i}(\varsigma_1,\varsigma_2)u_i \\ y_i &= h_i(\varsigma_1) \quad i=1,2,\ldots,m\end{aligned}, \tag{7}$$

where $\varsigma_1=(z_1,z_2,\ldots,z_d)$ and $\varsigma_2=(z_{d+1},z_{d+2},\ldots,z_n)$, and the system is considered to be input affine. Consequently, state vector ς_1 is locally observable, whereas ς_2 cannot be observed (Isidori (1995)).

To construct the $d\Delta^O$ codistribution, the O observation space has to be extended with Lie-derivatives of h_i, until $rank\,d\Delta^O$ increases. The number of local observable state variables represents the rank of $d\Delta^O$ (Isidori (1995)).

In other words, similar to the previous case, determining the degree of observability means that new covectors have to be determined (using Lie-derivatives), and the dimension that the extended covector field spans represents the number of local observable state variables.

3.3 Exact Linearization of Single-Input Systems

The $\dot{x}=f(x)+g(x)u$, $y=h(x)$ single-input single-output nonlinear system defined on an open and dense subset, U, is said to have relative degree r on U if:

$$L_g L_f^k h(x)=0 \text{ for all } x\in U \text{ and all } k<r-1 \tag{8/a}$$

$$L_g L_f^{r-1} h(x)\neq 0 \tag{8/b}$$

Any nonlinear system with the relative degree $n=dim(x)$ at some x_0 point can be transformed into a system through Static State Feedback Control, which in a neighbourhood of $z_0=\Phi(x_0)$ is linear and controllable, where $z=\Phi(x)$ is a nonlinear coordinate transformation with non-singular Jacobian matrix at x_0.

The coordinate transformation must be defined:

$$\Phi(x)=\begin{pmatrix}h(x) & L_f h(x) & \cdots & L_f^{n-1}h(x)\end{pmatrix}^T \tag{9}$$

Moreover, the following state feedback law shall be used: $u=\frac{1}{\beta(z)}(-\alpha(z)+v)$, where v is the external reference input, $\alpha(z)=L_f^n h\left(\Phi^{-1}(z)\right)$ and $\beta(z)=L_g L_f^{n-1}h\left(\Phi^{-1}(z)\right)$.

In this way, the resulting linear system is a series of n integrators $y^{(n)}=v$ (Isidori (1995)).

3.4 Results of Nonlinear Analysis

In the following, results of the nonlinear analysis on the Canterbury model are presented.

The number of reachable state variables is 3, which corresponds with reality. The two components of the model representing gastric emptying ($P_1(t)$, $P_2(t)$) only depend from the meal input, and have no feedback from the three other states of the model ($G(t)$, $Q(t)$, $I(t)$). Hence, $P_1(t)$ or $P_2(t)$ cannot be influenced by the external insulin input. Consequently, from a control viewpoint we can reach all "important" state variables ($G(t)$, $Q(t)$, $I(t)$).

The model is only partially observable with two observable state variables, which is also in accordance with physiological considerations. Plasma glucose ($G(t)$) can be easily measured, while plasma insulin ($I(t)$) can be estimated

(if it is necessary) by knowing the insulin input. It can also be measured, although not in clinical useful timeframes for real-time control.

Observability would increase if C-peptid levels would be measured as well, just like presented by Docherty et al. (2009), but it would take days and adequate laboratory equipment to process C-peptid samples, therefore cannot be used in real-life applications. As for exact linearization, the relative degree is found to be 3.

Since enteral glucose nutrition ($D(t)$) is treated as noise or a disturbance, the corresponding input and state variables can be discarded, resulting in a simpler model similar to the earlier versions presented beforehand. Further modifications can be made by eliminating the state variable representing concentration of insulin bounded to interstitial sites, $Q(t)$ (Kovacs et al. (2010)). The value of this compartment cannot be measured directly. Moreover, it can be considered as a slow variable (Lehmann and Deutsch (1992)). In this way, $\dot{Q}(t) \approx 0$ and $Q(t) = I(t)$. As a result, $Q(t)$ can be eliminated by substituting it into (1/a) and (1/c), thus resulting in the following system:

$$\dot{G}(t) = -p_G G(t) - S_I(t)\frac{G(t)I(t)}{1+\alpha_G I(t)} + \frac{P(t) + EGP_b - CNS}{V_G} \quad (10/a)$$

$$\dot{I}(t) = -\frac{nI(t)}{1+\alpha_I I(t)} + \frac{u_{ex}(t)}{V_I} + \frac{u_{enb}}{V_I} \quad (10/b)$$

The effect of the state elimination was examined by comparing the output of the two models (Fig. 1).

The nonlinear analysis indicated that this reduced model is now fully reachable and observable through the external insulin input. The relative degree is the same as the number of state variables.

Therefore, we can turn this simplified system into a linear system via Static State Feedback Control (Fig. 2). After computing the necessary Lie derivates, the resulting feedback rule can be expressed in the following symbolic form:

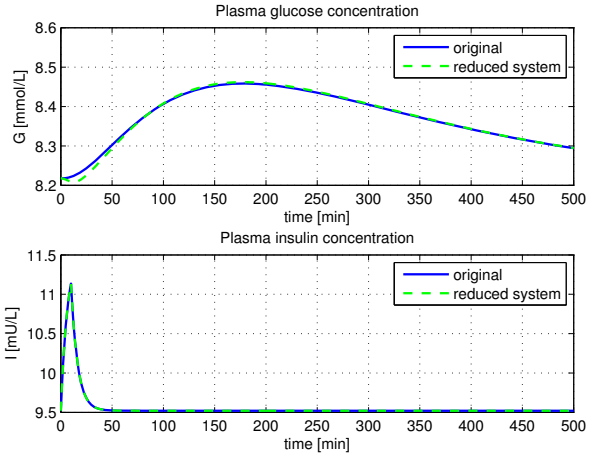

Fig. 1. Comparison of original and simplified model.

$$a(x) = L_f^2 h(x) =$$

$$= \left(\left(\frac{S_I I \alpha_G}{(1+\alpha_G I)^2} - \frac{S_I}{1+\alpha_G I}\right)\left(u_{enb} - \frac{nI}{1+\alpha_I I}\right) - \left(p_G + \frac{S_I I}{1+\alpha_G I}\right)^2\right) G -$$

$$- \left(p_G + \frac{S_I I}{1+\alpha_G I}\right)\left(\frac{EGB_b + CNS}{V_G}\right) \quad (11)$$

$$b(x) = L_g L_f^1 h(x) = \frac{-S_I G}{(1+\alpha_G I)^2 V_I} \quad (12)$$

$$u_{ex} = \frac{1}{b(x)}(u - \alpha(x)) \quad (13)$$

The output of the second order system when u_{ex} external insulin input was determined in the earlier presented manner, and, in the case of an ideal state observer, was identical with a linear time invariant system consisting of two integrators. Naturally, a different second order system could be realized with the same method (Isidori (1995)).

The analysis was performed when endogenous insulin production was not constant, but an exponential function of I. It yields the same results and slightly more complex function for the static state feedback. Hence, the overall approach is still valid in that case as well.

4. qALPV DESCRIPTION AND MODELLING

Linear Parameter Varying (LPV) systems are 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)):

$$\begin{aligned} \dot{x}(t) &= A(\rho)x(t) + B(\rho)u(t) \\ y(t) &= C(\rho)x(t) + D(\rho)u(t) \end{aligned}, \quad (14)$$

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.

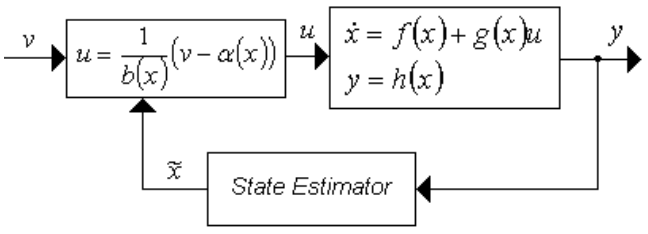

Fig. 2. Static State Feedback Control.

4.1 qALPV Modeling

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 (14) with $dim(\rho(t)) = N$ means:

$$\begin{aligned} A(\rho) &= A_0 + \rho_1 A_1 + \ldots + \rho_N A_N \\ B(\rho) &= B_0 + \rho_1 B_1 + \ldots + \rho_N B_N \\ C(\rho) &= C_0 + \rho_1 C_1 + \ldots + \rho_N C_N \\ D(\rho) &= D_0 + \rho_1 D_1 + \ldots + \rho_N D_N \end{aligned} . \tag{15}$$

Hence, the affine LPV system can be written as:

$$\Sigma(t) = \left\{ \Sigma_0 + \sum_{i=1}^{N} \rho_i \Sigma_i : \rho_i \in \left[\underline{\rho}_i \ \overline{\rho}_i\right], \dot{\rho}_i \in \left[\underline{\dot{\rho}}_i \ \overline{\dot{\rho}}_i\right] \right\}, \tag{16}$$

with $\Sigma_i = \begin{bmatrix} A_i & B_i \\ C_i & D_i \end{bmatrix}$, and $i = 1,2,\ldots,n$. In (16) the parameters are varying between known minimal ($\underline{\rho}_i$) and maximal ($\overline{\rho}_i$) bounds, which are respectively the limits of their known rates.

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.

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

$$\rho(t) = \begin{bmatrix} \rho_1(t) \\ \rho_2(t) \end{bmatrix} = \begin{bmatrix} S_I(t) \dfrac{I(t)}{1+\alpha_G I(t)} \\ \dfrac{1}{1+\alpha_I I(t)} \end{bmatrix}. \tag{17}$$

Hence, in (14) the parameter matrices become:

$$\begin{aligned} &A(\rho(t)) = A_0 + A_1\rho_1(t) + A_2\rho_2(t) = \\ &= \begin{bmatrix} p_G & 0 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} -1 & 0 \\ 0 & 0 \end{bmatrix}\rho_1(t) + \begin{bmatrix} 0 & 0 \\ 0 & -n \end{bmatrix}\rho_2(t) \\ &B = \begin{bmatrix} B_1 & B_2 \end{bmatrix}, B_1 = \begin{bmatrix} 0 \\ \dfrac{1}{V} \end{bmatrix}, B_2 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, C = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}. \end{aligned} \tag{18}$$

It should be mentioned that in the $u_1(t)$ input a continuously added constant (offset) modifies the $P(t)$ value (the glucose transfer from the gut to the bloodstream) defined:

$$u_1(t) = \frac{1}{V_G} P(t) + \frac{EGP_b - CNS}{V_G}. \tag{19}$$

The vertex defined by the scheduling parameters (ρ_1, ρ_2) of (17) is presented in Fig. 3. It can be seen the parameters are upper and lower bounded reflected also by Table 2, satisfying the qALPV modeling condition. The created qAPLV model perfectly matches the original nonlinear system (Fig. 4) demonstrating that inside the scheduling parameters' vertex the qAPLV model represents the nonlinear system itself without any approximation.

5. CONCLUSIONS

The current paper gave a nonlinear control analysis roadmap for a frequently used and clinically validated ICU metabolic model. First, global control theoretical characteristics were determined using nonlinear analysis. Results of reachability and observability were explained regarding physiological meanings, then exact linearization was computed. Quasi-affine linear parameter varying (qALPV) modelling methodology was then used and compared with results obtained by exact linearization. It was demonstrated that inside the chosen scheduling parameters' vertex the qAPLV model represents the nonlinear system itself without any approximation. Further research will be done on robust LPV controller design, with simulations on real-data as well as combining the methodology with stochastic aspects (Pozna et al. (2010)).

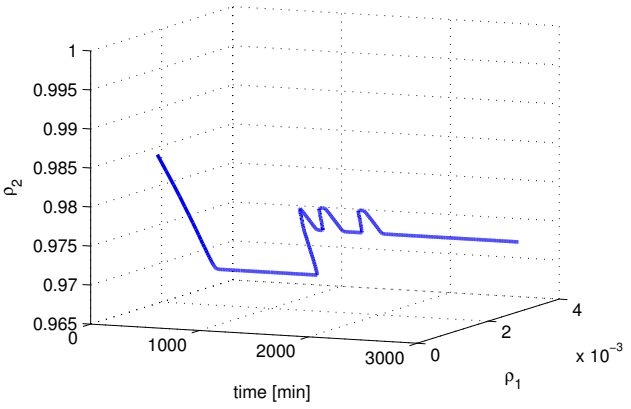

Fig. 3. Vertex defined by the scheduling parameters (ρ_1, ρ_2).

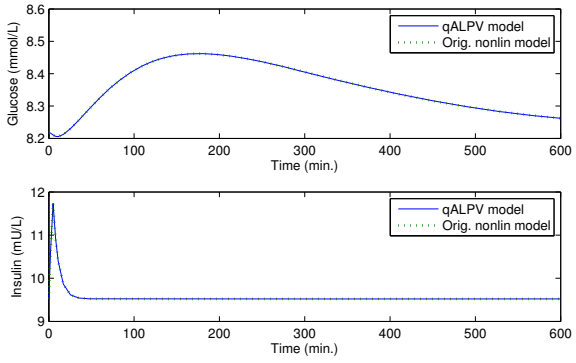

Fig. 4. Comparison of original nonlinear and qALPV model.

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)

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