Analyzing a Novel Model of Human Blood Glucose System at Molecular Levels

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Abstract—**Blood glucose system is one of the most important systems of the human body, since energy transport is fulfilled through this complex endocrine control process. Because of great importance (in case of failure, its primary consequence is diabetes mellitus), many models were published, most of them with phenomenological approach. The aim of the current paper is to analyze a new molecular model published recently [1]. Global control theoretical characteristics are determined with nonlinear analysis. Physiological working points are defined for further polytopic modeling with linearization and model reduction is discussed and presented based on medical principles.**

I. Introduction

THE normal blood glucose concentration level in the human body varies in a narrow range (70 - 110 mg/dL). If for some reason 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: it increases the risk of cardiovascular diseases, neuropathy and retinopathy [2]. The newest statistics of the World Health Organization (WHO) predate an increase of adult diabetic population from 4% (in 2000, meaning 171 million people) to 5.4% (366 million worldwide) by the year 2030 [3]. This warns that diabetes could be the "disease of the future", especially in developing countries (because of stress and unhealthy lifestyle).

Due to the alarming facts of diabetes, the scientific community proposed to improve the treatment of diabetes by investigating the applicability of an external controller. In many biomedical systems, external controller provides the necessary input, because the human body could not ensure it. The 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.

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. Starting from the 1970s 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 [4]-[7] requires three components: glucose sensor, insulin pump and a control algorithm (based on the glucose measurements), which 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 diabetic patients [7]. The most widely used and also the simplest one proved to be the minimal model of Bergman [8] while the most complex one is represented by the 19th order Sorensen-model [9]. Regarding the applied control strategies for diabetes mellitus, the palette is very wide [10]. Starting from classical control strategies (PID control [11], cascade control [12]), to soft computing techniques [13]-[15], adaptive [16], model predictive (MPC) [5], [17], or even robust H_∞ control were already applied [4], [6], [18] and [19]. 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_∞ [4], [6], MPC [20]).

The current paper focuses on a newly appeared and promising model [1], which describes the human blood glucose system in general at molecular level. Our aim was to analyze the model's possibilities for a future robust controller design.

The paper is organized as follows: in Section II, the new molecular model is explained, whereas Section III provides information on global control theoretical characteristics of the model based on nonlinear analysis. In Section IV, model linearization is carried out, followed by defining physiological working points for further polytopic modeling. This section also examines reduction possibilities of the considered model based on medical principles. Finally, conclusions are drawn in Section V.

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II. Molecular Model

The considered model [1] has eight state variables, which is approximately halfway from the model of Bergman [8] to the model of Sorensen [9]. The new, molecular approach provides more plausible explanations because of biochemical principles. The model can be naturally divided into three subsystems: the transition subsystem of glucagon and insulin, the receptor binding subsystem and the glucose subsystem. These are described briefly below (the model constants are summarized in Table I).

A. Transition subsystem of glucagon and insulin

The first subsystem can be described with

$$\dot{x}_1 = -\left(k_{11}^p + k_{12}^p\right)x_1 + w_1, \tag{1}$$

$$\dot{x}_2 = -\left(k_{21}^p + k_{22}^p\right)x_2 + w_2 + u_1, \tag{2}$$

where x_1 and x_2 stand for the concentrations of glucagon and insulin in the plasma. Let w_1 and w_2 denote glucagon and insulin production rates by pancreas, whereas u_1 is the rate of intravenous insulin injected. The transitional rates are k_{j1}^p, whereas the degradation rates are k_{j2}^p (j = 1,2).

B. Receptor binding subsystem of glucagon and insulin

Let x_3 and x_4 denote the concentrations of intracellular glucagon and insulin, x_5 and x_6 the concentrations of glucagon- and insulin-bound receptors. The subsystem can be described with

$$\dot{x}_3 = -k_{11}^s x_3\left(R_1^0 - x_5\right) - k_{12}^s x_3 + k_{11}^p x_1 V_p V^{-1}, \tag{3}$$

$$\dot{x}_4 = -k_{21}^s x_4\left(R_2^0 - x_6\right) - k_{22}^s x_4 + k_{21}^p x_2 V_p V^{-1}, \tag{4}$$

$$\dot{x}_5 = k_{11}^s x_3\left(R_1^0 - x_5\right) - k_1^r x_5, \tag{5}$$

$$\dot{x}_6 = k_{21}^s x_4\left(R_2^0 - x_6\right) - k_2^r x_6, \tag{6}$$

where R_1^0 and R_2^0 are the total concentrations of receptors, respectively. Association rates for glucagon and insulin to bind their receptors are k_{j1}^s, whereas k_{j2}^s denote the degradation and k_j^r the inactivation rates (j = 1,2). Plasma insulin volume is V_p, cellular insulin volume is V.

C. Glucose production and utilization subsystem

Plasma glucose production can be classified into two classes: exogenous glucose taken from food and endogenous hepatic glucose by converting glycogen into glucose in liver.

Glucose utilization has two sinks: insulin-independent (brain and nerve cells) and insulin-dependent (fat cells and muscle) part.

To model the insulin-independent part, we consider:

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

where x_8 denotes plasma glucose concentration and U_b stand for maximum velocity of insulin-independent glucose utilization, whereas C_2 is a scaling constant.

Insulin-dependent glucose utilization can be defined as the product of

$$f_2\left(x_8\right) = \frac{x_8}{C_3}, \tag{8}$$

$$f_3\left(x_4\right) = U_0 + \left(U_m - U_0\right)\left(\frac{x_4}{C_4}\right)^{\beta}\left[1 + \left(\frac{x_4}{C_4}\right)^{\beta}\right]^{-1}, \tag{9}$$

where U_0 and U_m denote minimum and maximum velocity of insulin-dependent glucose utilization.

The glucose subsystem can be formulated as follows:

$$f_4 = \frac{k_1 x_6}{1 + k_2 x_5}\frac{V_{\max}^{gs} x_8}{K_m^{gs} + x_8}, \tag{10}$$

$$f_5 = k_3 x_5 \frac{V_{\max}^{gp} x_7}{K_m^{g1} + x_7}, \tag{11}$$

$$\dot{x}_7 = f_4 - f_5, \tag{12}$$

$$\dot{x}_8 = -f_4 + f_5 - f_1 - f_2 f_3 + u_2, \tag{13}$$

where u_2 denotes exogenous glucose input, f_4 and f_5 stand for conversion of glucose into glycogen and conversion of glycogen into glucose, respectively. The feedback gains are k_1, k_2 and k_3.

D. Control mechanism of pancreas

The feedback rates can be modeled by

$$w_1\left(x_8\right) = \frac{G_m}{1 + b_1 e^{a_1\left(x_8 - C_5\right)}}, \tag{14}$$

$$w_2\left(x_8\right) = \frac{R_m}{1 + b_2 e^{a_2\left(C_1 - x_8\right)}}, \tag{15}$$

where w_1 and w_2 stand for glucagon and insulin secretion of pancreas, G_m and R_m are saturation values.

E. Nonlinear model

The molecular model can be regarded as an input-affine nonlinear model:

$$\begin{aligned}\dot{x} &= f(x)+\sum_{i=1}^{2} u_i g_i(x) \\ y_i &= h_i(x) \qquad i=1,2\end{aligned}, \tag{16}$$

where

$$f=\begin{bmatrix} -\left(k_{11}^p+k_{12}^p\right)x_1+w_1 \\ -\left(k_{21}^p+k_{22}^p\right)x_2+w_2 \\ -k_{11}^s x_3\left(R_1^0-r_1\right)-k_{12}^s x_3+k_{11}^p x_1 V_p V^{-1} \\ -k_{21}^s x_4\left(R_2^0-r_2\right)-k_{22}^s x_4+k_{21}^p x_2 V_p V^{-1} \\ k_{11}^s x_3\left(R_1^0-x_5\right)-k_1^r x_5 \\ k_{21}^s x_4\left(R_2^0-x_6\right)-k_2^r x_6 \\ f_4-f_5 \\ -f_5+f_4-f_1-f_2 f_3 \end{bmatrix}, \tag{17}$$

$$g=\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^T, \tag{18}$$

$$h=\begin{bmatrix} x_2 & x_8 \end{bmatrix}^T. \tag{19}$$

F. Open-loop simulation

Open-loop simulation results can be seen in Fig. 1: exogenous glucose input is adapted from [21], whereas concentrations of plasma insulin and plasma glucose are the outputs of the model. From the aspect of human physiology the results are correct, since healthy regulation contains two significantly different phases: a short and intense period (preparation phase) which is followed by a long-drawn-out tranquility phase.

III. Nonlinear Analysis

In order to examine global control characteristics of the molecular model, we have performed a nonlinear analysis first [22], [23]. Reachability, observability and input-output linearization were checked and results are summarized in this chapter. The nonlinear system is in the form of (16).

A. Reachability

Nonlinear systems can be transformed into the form of

$$\begin{aligned}\dot{\varsigma}_1 &= f_1(\varsigma_1,\varsigma_2)+\sum_{i=1}^{m} g_{1i}(\varsigma_1,\varsigma_2)u_i \\ \dot{\varsigma}_2 &= f_2(\varsigma_2) \\ y_i &= h_i(\varsigma_1,\varsigma_2) \qquad i=1,2,\ldots,m\end{aligned}, \tag{20}$$

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, state vector ς_1 is locally reachable [22].

In order to construct the reachability distribution Δ^C, initialization is $\Delta_0^C=span\{g_1,\ldots,g_m\}$. Then, until $rank\,\Delta_k^C$ increases:

TABLE I
Parameters of Model

Symbol	Value	Unit
k_{11}^p, k_{21}^p	0.14	1/min
k_{12}^p	0.3	1/min
k_{22}^p	0.167	1/min
k_{11}^s	$6\cdot10^7$	1/M/min
k_{21}^s	$4.167\cdot10^{-4}$	1/(mU/l)/min
k_{12}^s, k_{22}^s	0.01	1/min
k_1^r, k_2^r	0.2	1/min
R_1^0	$9\cdot10^{-13}$	M
R_2^0	0.52	mU/l
$V_{\max}^{gp}$	80	mg/l/min
K_m^{gp}	600	mg/l
$V_{\max}^{gs}$	$3.87\cdot10^{-4}$	mg/l/min
K_m^{gs}	67.08	mg/l
k_1	$8\cdot10^5$	1/(mU/l)
k_2	10^{12}	1/M
k_3	$4\cdot10^{12}$	1/M
V	11	l
V_p	3	l
U_b	7.2	mg/l/min
U_0	4	mg/l/min
U_m	94	mg/l/min
G_m	$2.23\cdot10^{-10}$	M/min
R_m	70	mU/l/min
C_1	2000	mg/l
C_2	144	mg/l
C_3	1000	mg/l
C_4	80	mg/l
C_5	1000	mg/l
β	1.77	-
a_1	$5\cdot10^{-3}$	1/(mg/l)
a_2	$3.33\cdot10^{-3}$	1/(mg/l)
b_1	10	-
b_2	1	-

$$\Delta_{k+1}^C=\Delta_k^C+\sum_{i=1}^{q}\left[\tau_i,\Delta_k^C\right], \tag{21}$$

where $\tau_i\in\Delta_k^C$, $i=1,2,\ldots,q$ ($\dim\Delta_k^C=q$). The number of local reachable state variables is the rank of Δ^C. Checking our system (16), it proved to be completely reachable, since $rank\,\Delta^C=8$.

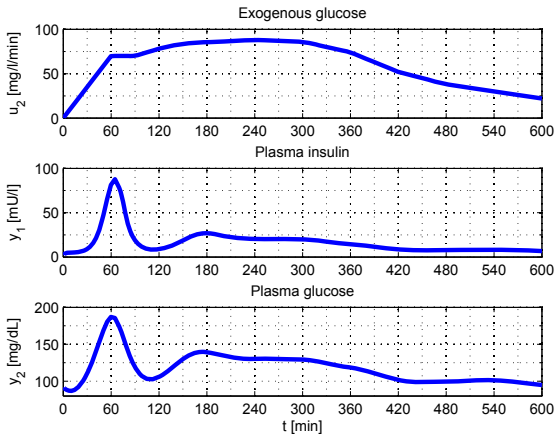

Fig. 1. Open-loop simulation results.

B. *Observability*

In order to examine observability, the nonlinear system has to be transformed into the form of

$$\begin{aligned}\dot{\varsigma}_1 &= f_1(\varsigma_1)+\sum_{i=1}^{m} g_{1i}(\varsigma_1)u_i \\ \dot{\varsigma}_2 &= f_2(\varsigma_1,\varsigma_2)+\sum_{i=1}^{m} g_{2i}(\varsigma_1,\varsigma_2)u_i \\ y_i &= h_i(\varsigma_1) \qquad i=1,2,\ldots,m\end{aligned}, \tag{22}$$

where $\varsigma_1=(z_1,z_2,\ldots,z_d)$ and $\varsigma_2=(z_{d+1},z_{d+2},\ldots,z_n)$. Consequently, state vector ς_1 is locally observable [22].

In order to construct the observability codistribution $d\Delta^O$, 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 is the rank of $d\Delta^O$. System (18) has four local observable state variables, since *rank* $d\Delta^O=4$.

C. *Input-output linearization*

If there exist for the system (16) the relative degree $r=(r_1,r_2,\ldots,r_m)$, neighborhood $U(x_0)$ and $v=q(x)+S(x)u$, where $q:U\to R^m$ and $S:U\to R^{m\times m}$ are smooth mappings with $\det S(x_0)\neq 0$ and

$$S(x)=\begin{bmatrix} L_{g_1}L_f^{r_1-1}h_1 & L_{g_2}L_f^{r_1-1}h_1 & \cdots & L_{g_m}L_f^{r_1-1}h_1 \\ L_{g_1}L_f^{r_2-1}h_2 & L_{g_2}L_f^{r_2-1}h_2 & \cdots & L_{g_m}L_f^{r_2-1}h_2 \\ \vdots & \vdots & \ddots & \vdots \\ L_{g_1}L_f^{r_m-1}h_m & L_{g_2}L_f^{r_m-1}h_m & \cdots & L_{g_m}L_f^{r_m-1}h_m \end{bmatrix}, \tag{23}$$

then $y_i^{(r_i)}=v_i \quad i=1,2,\ldots,m$ [22].

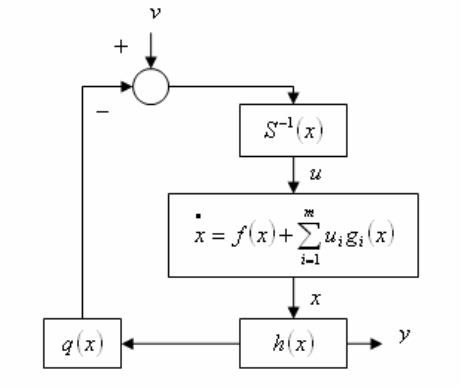

Fig. 2. Input-output linearizaton.

In this manner, the system is the composition of m unconnected rows of integrators and the zero dynamics. If there is no zero dynamics, the system (16) can be input-output linearized with the static feedback

$$u(x)=-S^{-1}(x)q(x)+S^{-1}(x)v\,, \tag{24}$$

where v is the new input vector, q is feedback, so the linearized system can be transformed into Brunovsky-form:

$$\begin{aligned}\frac{dz_i}{dt} &= A_i z_i + b_i v_i \\ y_i &= c_i z_i\end{aligned}, \tag{25}$$

where z_i are the transformed state variables (see Fig. 2).

With this approach, the complexity of the constructed vector fields is too great, hence MATLAB can not handle it. Linearization via static feedback can not be fulfilled because of lack of computational capacity. Dynamic feedback methods, like Cartan-fields or dynamic extension can not be applied either because of great complexity. Since nonlinear control design is much more complicated than linear another aspect has to be taken into account in order to handle the model and design appropriate controller.

IV. Linear Analysis

In this section, local characteristics of the linearized model are examined like stability, controllability and observability. Although these characteristics are valid only in the vicinity of the considered working point, there are techniques which are able to combine local characteristics with global ones e.g. Linear Parameter Varying (LPV) modeling.

LPV methodology is useful if an acceptable compromise between the model's complexity and the developed control algorithm is searched. LPV system is a class of nonlinear systems, where the parameter could be an arbitrary time varying, piecewise-continuous and vector valued function. The changing scheduling parameter has to be measured or

computed. In this way, the system's nonlinearity can be hidden, while the measured parameters ensure describing the entire validity region both for model and controller [24].

There are different descriptions of LPV systems [25]. According to polytopic representation, 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.

As a result, our aim was to create the valid polytopic region of the investigated model by selecting physiologically valid working points for further Linear Parameter Varying (LPV) modeling. Furthermore, model reduction analysis is presented based on physiological principles.

A. Normoglycemic steady point

The totally controllable, totally observable and stable normoglycemic steady point is defined in this chapter at 100 mg/dL [1], where the state variables are:

$$\begin{aligned} x_1^{NormoGly} &= 4.61\cdot 10^{-11}\ (M) & x_2^{NormoGly} &= 7.86\ (mU/l) \\ x_3^{NormoGly} &= 1.75\cdot 10^{-10}\ (M) & x_4^{NormoGly} &= 29.42\ (mU/l) \\ x_5^{NormoGly} &= 4.50\cdot 10^{-14}\ (M) & x_6^{NormoGly} &= 0.03\ (mU/l) \\ x_7^{NormoGly} &= 829.68\ (mg/l) & x_8^{NormoGly} &= 100\ (mg/dL) \end{aligned} \quad (26)$$

B. Physiological working points

For further LPV modeling stable working points are required covering the total working space. Concerning biochemical principles, the state variables are not totally independent from medical approach. Normalizing the trajectories to [0,1] for input adapted from [21], two significant classes can be formulated: insulin type (x_2, x_4, x_6 and x_8 in Fig. 3) and glucagon type (x_1, x_3 and x_5 in Fig. 4) variables. Glycogen (x_7) is the only variable that does not fit perfectly, since it is the integrated form of glucose excess.

Definition of the working space is based on physiological data: variables vary in the range of [0.25 ... 4] times of the normoglycemic steady point. Consequently, physiological working points can be defined by multiplying the normoglycemic values for each class with [0.25 0.5 0.75 1 1.25 1.5 2 4], whereas x_7 is constant. In this manner, we create 64 totally controllable, totally observable and stable working points. It has to be noted that physiological working points are not analytical solutions of the nonlinear model, but they can be used for further polytopic modeling.

C. Model reduction

Since state variables are connected, it is probable that the rank of the model can be reduced. In order to perform this, we use state space transformation and projection.

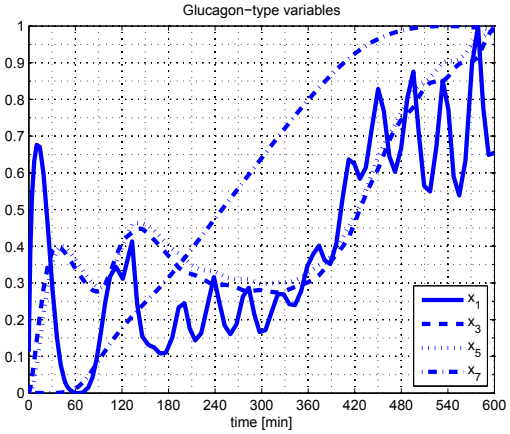

Fig. 3. Glucagon-type state variables.

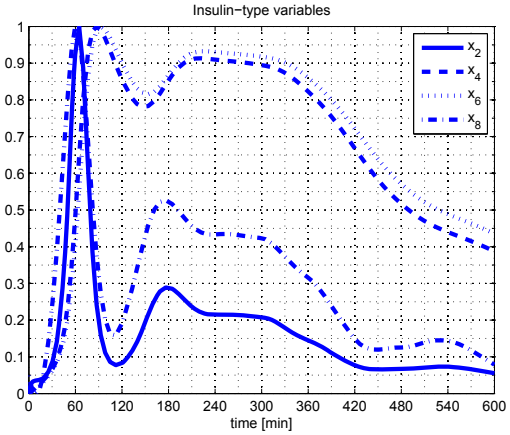

Fig. 4. Insulin-type state variables.

Let W_c and W_o denote the controllability and observability matrices, respectively, and W_{co} their product. Let T be a transformation, where Λ is diagonal in the factorization

$$W_{co} = T\Lambda T^{-1}. \quad (27)$$

In this manner, the transformed W_c and W_o matrices are:

$$\tilde{W}_c = T^{-1} W_c \left(T^{-1}\right)^*, \quad (28)$$

$$\tilde{W}_o = T^* W_o T, \quad (29)$$

and $\tilde{W}_c = \tilde{W}_o = \Xi$, where Ξ is diagonal [26].

The eigenvalues of the transformed system are the Hankel singular values, and the greater the eigenvalue, the higher the importance of the corresponding state variable. Hankel singular values are 9.64, 5.89, 1.37, 1.10, $1.38\cdot 10^{-2}$, $4.32\cdot 10^{-3}$, $7.03\cdot 10^{-5}$ and $1.31\cdot 10^{-6}$ for system (16).

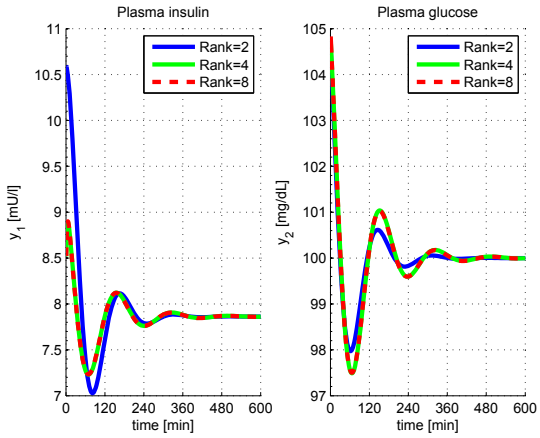

Fig. 5. Model reduction with different ranks. System responses at the normoglycemic steady point while deviation is 5%: a) plasma insulin and b) plasma glucose.

It can be seen that the first two eigenvalues are significant, which is expected after the two classes, and after four singular values the others are minor enough to neglect them, as it can be also seen in Fig. 5. Important frequency range is [0.0002 0.2] rad/min [4], so the effect of model reduction was tested with Bode diagrams in frequency domain and with impulse responses in time domain. System with two state variables is quite inaccurate, whereas with four variables the approximation is almost perfect.

V. Conclusion

In this paper, we examined a new molecular model to describe the human blood glucose system in a more plausible way because of biochemical principles. Nonlinear analysis eventuated in theoretical results of great importance, but from practical aspect their use is difficult because of complexity. Physiological working points are defined for further LPV modeling and model reduction is examined with biological basis.

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