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Investigating a Novel Model of Human Blood Glucose System at Molecular Levels from Control Theory Point of View

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Abstract: According to the data provided by the World Health Organization (WHO) diabetes has become an endemic of these days. There are several nonlinear models describing the dynamic of glucose-insulin of diabetes mellitus, like the simplest one with only three state variables, also known as the model of Bergman, and the most complex with 19 state variables, the model of Sorensen. Their common characteristic is that they describe type 1 diabetes physiologically. A recently published theoretical model [1] is capable of describing human blood glucose system at molecular levels. This paper is based on its analysis from a control theory point of view with multiple purposes: nonlinear analysis, rank reduction possibilities with physiological explanations, defining physiological working points for further polytopic modeling, analyzing control properties of the linear systems in the defined working points.

Keywords: Diabetes, nonlinear analysis, model reduction, physiologic working points.

1. 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: among others, diabetes increases the risk of cardiovascular diseases, neuropathy and retinopathy. Four

types of diabetes are known: type 1 (also known as insulin-dependent diabetes mellitus), type 2 (or insulin- independent diabetes mellitus), gestational diabetes and other special types, like genetic deflections. Consequently, diabetes mellitus is a serious metabolic disease, which should be artificially regulated.

The newest statistics of the World Health Organization (WHO) predate an increase of adult diabetes population from 4% (in 2000, meaning 171 million people) to 5.4% (366 million worldwide) by the year 2030 [2]. This is a warning that diabetes could be the "disease of the future", especially in developing countries (due to stress and unhealthy lifestyle).

To design an appropriate control, an adequate model is necessary. In the last decades several models appeared for type 1 diabetic patients [3]. The most widely used and also the simplest one proved to be the minimal model of Bergman [4], for type 1 diabetic patients under intensive care, and its extension, the three-state minimal model [5]. However, the simplicity of the model proved to be its disadvantage too, since in its formulation a lot of components of the glucose-insulin interaction were neglected.

Besides the Bergman-model other models appeared in the literature [6]-[8], which are more general, but more complicated. The most complex one proved to be the 19^{th} order Sorensen-model [6], which is based on the earlier model of [8]. Even if the Sorensen-model describes the human blood glucose dynamics in a very exact way, it is rarely used in research problems due to its complexity.

2. The molecular model

In contrast with the earlier phenomenological aspect, the model applies a more accurate approach [1] published in 2008; it describes the human blood glucose system at molecular levels. Consequently, the cause-effect relations are more plausible and different functions and processes can be separated. The considered model is approximately halfway from Bergman's model [4]-[5] to Sorensen's [6] with its 8 state variables and it can be naturally divided into three subsystems: the transition subsystem of glucagon and insulin, the receptor binding subsystem and the glucose subsystem. Parameters of the model can be found in [1].

A. Transition subsystem

We assume that plasma insulin does not act directly on glucose metabolism but through cellular insulin [9]. Let s_1^p and s_2^p denote concentrations of plasma glucagon and insulin, respectively. Complementing equations of [10] with transition delay the subsystem can be described with

$$\frac{ds_j^p}{dt} = -\left(k_{j,1}^p + k_{j,2}^p\right)s_j^p + w_j \qquad j = 1,2 \tag{1}$$

where w_1 and w_2 stand for glucagon and insulin produced by the pancreas. The equations show that the hormones of pancreas have a positive effect on their plasma concentrations, while the hormones in plasma can be interpreted as a negative feedback.

The positive constants $k_{j,1}^p$ denote transition rates and $k_{j,2}^p$ the degradation rates (j=1,2). Contrary to [10], we suppose that intracellular insulin cannot go back to plasma, which is in harmony with Bergman's minimal model [4]-[5].

B. Receptor binding subsystem

Let s_1 and s_2 denote intracellular concentrations of glucagon and insulin, whereas r_1 and r_2 stand for concentrations of glucagon- and insulin-bound receptors, respectively. Assuming that the receptor recycling system is closed intracellular concentrations can be described with

$$\frac{ds_j}{dt} = -k_{j,1}^s s_j\left(R_j^0 - r_j\right) - k_{j,2}^s s_j + k_{j,1}^p s_j^p V_p V^{-1} \qquad j = 1,2\,, \tag{2}$$

$$\frac{dr_j}{dt} = k_{j,1}^s s_j\left(R_j^0 - r_j\right) - k_j^r r_j \qquad j = 1,2 \tag{3}$$

where R_1^0 and R_2^0 denote total concentrations of receptors, $k_{j,1}^s$ stand for the hormone-receptor association rates, $k_{j,2}^s$ the degradation rates, k_j^r the inactivation rates (j=1,2). V_p is plasma volume, whereas V is intracellular volume.

C. Glucose subsystem

Blood glucose has two sources: endogenous hepatic production with glycogen transformation and exogenous meal intake. Glucose utilization can be divided into two groups: insulin-independent (brain and nerve cells) and insulin-dependent (muscle and adipose tissues).

Insulin-independent part [12] can be modelled by

$$f_1(g_2) = U_b\left(1 - e^{-\frac{q_2}{C_2}}\right) \tag{4}$$

that saturates at 500 mg/l (q_2 denotes glucose concentration).

Insulin-dependent part can be calculated by the product

$$f_2(q_2)f_3(s_2)=\frac{q_2}{C_3}\left\{U_0+(U_m-U_0)\left(\frac{s_2}{C_4}\right)^{\beta}\left[1+\left(\frac{s_2}{C_4}\right)^{\beta}\right]^{-1}\right\} \tag{5}$$

which was originally used in [13]. $f_3(s_2)$ saturates at insulin concentration 500 mU/l.

Concluding the assumptions the glucose subsystem can be described with

$$\frac{dq_1}{dt}=\frac{k_1r_2}{1+k_2r_1}\frac{V_{\max}^{gs}q_2}{K_m^{gs}+q_2}-k_3r_1\frac{V_{\max}^{gp}q_1}{K_m^{gp}+q_1}, \tag{6}$$

$$\frac{dq_2}{dt}=-\frac{k_1r_2}{1+k_2r_1}\frac{V_{\max}^{gs}q_2}{K_m^{gs}+q_2}+k_3r_1\frac{V_{\max}^{gp}q_1}{K_m^{gp}+q_1}-f_1(q_2)-f_2(q_2)f_3(s_2)+G_{in}, \tag{7}$$

where q_1 and q_2 denote glycogen and glucose concentration, v^{gp} and v^{gs} stand for reaction rate of glycogen phosphorylase and glycogen synthase, respectively. $V_{\max}^{gp}$ and $V_{\max}^{gs}$ are maximal reaction rates of the enzymes whereas K_m^{gp} and K_m^{gs} are their Michaelis-Menten constants. Exogenous glucose intake is denoted by G_{in}.

D. Pancreatic control

Hormones of the pancreas have a cardinal role in blood glucose regulation and homeostatic stability, since negative feedback of glucagon and insulin assures controllability. Control mechanism of the pancreas [9] is described with

$$w_1(q_2)=\frac{G_m}{1+b_1e^{a_1(q_2-C_5)}}, \tag{8}$$

$$w_2(q_2)=\frac{R_m}{1+b_2e^{a_2(C_1-q_2)}}, \tag{9}$$

where w_1 and w_2 denote glucagon (GIR) and insulin infusion rates (IIR), respectively.

E. Aspect of control theory

As for inputs, exogenous insulin (u_1) is completely disposable, since it is in daily use in the form of injection (type 1 diabetes is treated this way). Glucose

taken as meal (G_{in}) represents disturbance for the model, but as a result of more profound consideration it can be regarded as control input. Healthy people use it more or less to regulate their blood glucose level, but in case of diabetic patients the situation is crystal clear: it is strictly prescribed for them what to eat and when to eat, so exogenous glucose is treated as a second control input henceforward (u_2). In order to analyze the model in a quantitative manner, a physiologically correct exogenous glucose input has to be defined. According to the literature a widely used absorption curve is applied which was recorded under extremely strict and precise conditions [14].

As for outputs, blood glucose level (q_2) is essential to characterize the system (in addition it can be measured easily). Concentration of plasma insulin (s_2^p) is only measurable under laboratory conditions, but any controller designed to regulate pathologic blood glucose system has to be qualified by the amount of injected insulin. Summarizing the considerations, the outputs of the model are plasma insulin (y_1) and blood glucose level (y_2).

3. Nonlinear analysis

In this section global characteristics of the molecular model are observed from a differential geometric point of view. Differential geometry deals with differential equations defined over differentiable manifolds, hence dynamic systems and their trajectories can be analyzed. Main definitions and ideas of differential geometry can be found in [15].

A. Nonlinear model

The molecular model presented in Section 2 has to be formulated exactly. Let f, g_1 and g_2 denote vector fields over an eight dimensional manifold, h_1 and h_2 stand for real-valued functions. In this case, the input-affine nonlinear system Σ can be described with

$$\begin{aligned} \dot{x} &= f(x) + \sum_{i=1}^{2} u_i g_i(x) \\ y_i &= h_i(x) \qquad i = 1,2 \end{aligned}, \tag{10}$$

where

$$f = \begin{bmatrix} -\left(k_{11}^{p} + k_{12}^{p}\right)x_1 + w_1 \\ -\left(k_{21}^{p} + k_{22}^{p}\right)x_2 + w_2 \\ -k_{11}^{s}x_3\left(R_1^0 - r_1\right) - k_{12}^{s}x_3 + k_{11}^{p}x_1\dfrac{V_p}{V} \\ -k_{21}^{s}x_4\left(R_2^0 - r_2\right) - k_{22}^{s}x_4 + k_{21}^{p}x_2\dfrac{V_p}{V} \\ k_{11}^{s}x_3\left(R_1^0 - x_5\right) - k_1^{r}x_5 \\ k_{21}^{s}x_4\left(R_2^0 - x_6\right) - k_2^{r}x_6 \\ \dfrac{k_1x_6}{1+k_2x_5}\dfrac{V_{\max}^{gs}x_8}{K_m^{gs}+x_8} - k_3x_5\dfrac{V_{\max}^{gp}x_7}{K_m^{g1}+x_7} \\ -\dfrac{k_1x_6}{1+k_2x_5}\dfrac{V_{\max}^{gs}x_8}{K_m^{gs}+x_8} + k_3r_1\dfrac{V_{\max}^{gp}x_7}{K_m^{g1}+x_7} - f_1\left(x_8\right) - f_2\left(x_8\right)f_3\left(x_4\right) \end{bmatrix}, \tag{11}$$

$$g = \begin{bmatrix} g_1 & g_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}^T, \tag{12}$$

$$h = \begin{bmatrix} h_1 \\ h_2 \end{bmatrix} = \begin{bmatrix} s_2^p \\ g_2 \end{bmatrix}. \tag{13}$$

B. 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 neighborhood U_0 of x_0 and a local coordinate transformation $z = \Psi(x)$ defined on U_0 in such a way that in the new coordinates, the control system Σ is represented by equations of the form

$$\begin{aligned} \dot{\varsigma}_1 &= f_1\left(\varsigma_1, \varsigma_2\right) + \sum_{i=1}^{m} g_{1i}\left(\varsigma_1, \varsigma_2\right)u_i \\ \dot{\varsigma}_2 &= f_2\left(\varsigma_2\right) \\ y_i &= h_i\left(\varsigma_1, \varsigma_2\right) \end{aligned}, \tag{14}$$

where $\varsigma_1 = \left(z_1, z_2, \ldots, z_d\right)$ and $\varsigma_2 = \left(z_{d+1}, z_{d+2}, \ldots, z_n\right)$ [15].

In this case ς_1 is locally reachable, since it can be manipulated by the inputs of Σ while ς_2 cannot be controlled. Consequently, the number of reachable states is equal to the rank of distribution Δ^C.

Construction of distribution Δ^C:

- initialization $\Delta_0^C = span\{f, g_1, \ldots, g_m\}$,
- expansion of distribution Δ^C

$$\Delta_{k+1}^C = \Delta_k^C + \sum_{i=1}^{q} [\tau_i, \Delta_k^C], \tag{15}$$

until rank Δ_{k+1}^C >rank Δ_k^C, where $\tau_i \in \Delta_k^C$, $i = 1,2,\ldots,q$ ($\dim \Delta_k^C = q$).

C. Observability

Let $d\Delta^O(x) \subset (R^n)^*$ denote the subspace containing the row vectors $d\alpha(x)$ for $\forall x \in X$, where $\alpha \in O$ (observation space). Moreover, suppose that for each point x_0 it is possible to find a neighborhood U_0 of x_0 so that $d\Delta^O(x) = d < n$, $\forall x \in U_0$. In this case a local coordinate transformation $z = \Psi(x)$ defined on U_0 transforms the control system Σ to the form

$$\begin{aligned} \dot{\varsigma}_1 &= f_1(\varsigma_1) + \sum_{i=1}^{m} g_{1i}(\varsigma_1) u_i \\ \dot{\varsigma}_2 &= f_2(\varsigma_1, \varsigma_2) + \sum_{i=1}^{m} g_{2i}(\varsigma_1, \varsigma_2) u_i \\ y_i &= h_i(\varsigma_1) \end{aligned} \tag{16}$$

where $\varsigma_1 = (z_1, z_2, \ldots, z_d)$ and $\varsigma_2 = (z_{d+1}, z_{d+2}, \ldots, z_n)$ [15].

In this case ς_1 is locally observable since it appears in the outputs of Σ, while ς_2 cannot be observed because it does not show up either in the outputs of Σ or in ς_1. Consequently, the number of observable states is equal to the rank of codistribution $d\Delta^O$.

Construction of codistribution $d\Delta^O$: expansion of observation space O with Lie-derivatives until the rank of $d\Delta^O$ increases.

C. Input-output linearization

If there is a relative degree vector $r = (r_1, r_2, \ldots, r_m)$, open set $U(x_0)$, assignment $v = q(x) + S(x)u$, smooth function $q: U \to R^m$ and $S: U \to R^{m \times m}$ where $\det S(x_0) \neq 0$ for the nonlinear system Σ so that $y_i^{(r_i)} = v_i$, $i = 1,2,\ldots,m$,

then the system can be decomposed into *m* subsystems with r_i integrators in the i^{th} subsystem [15].

If there is no zero dynamics, the system can be input-output linearized with the static feedback $u(x) = -S^{-1}(x)q(x) + S^{-1}(x)v$ where v is the new input vector, q is feedback, so the linearized system can be transformed into Brunovsky-form.

D. Global control characteristics

To be able investigating the global control characteristics of the molecular model we have implemented under MATLAB the algorithms presented above (sections 3.A and 3.B). The following results were obtained:

- completely reachable system, since $rank\,\Delta^C = 8$,
- number of the observable states of the model is 4, since $rank\,d\Delta^O = 4$,
- static feedback results in such complex vector fields that MATLAB is unable to handle them (manually it is also too complex), so this question cannot be answered this way. Linearization with dynamic feedback (dynamic extension, Cartan fields) has the same problem.

4. Linear analysis

Global characteristics of the molecular model are examined in Section 3 and led to the conclusion that despite the great importance of the achieved results practical application is very difficult because of the extreme complexity of the generated vector fields. Furthermore, ulterior aim of the research is polytopic modeling of the system, hence linearization and model reduction possibilities are observed in this section. In this manner local characteristics of the molecular model can be determined.

A. Steady state linearization

Linearization is carried out by applying Jacobian matrices in a steady state. The linearized form of system

$$\begin{aligned} \dot{x} &= f(x,u) \\ y &= h(x,u) \end{aligned} \tag{17}$$

in steady state (x_0, u_0) with output y_0 is

$$\begin{aligned} \dot{\tilde{x}} &= A\tilde{x} + B\tilde{u} \\ \tilde{y} &= C\tilde{x} + D\tilde{u} \end{aligned}, \tag{18}$$

where

$$\begin{aligned} \tilde{x} &= x - x_0 \\ \tilde{u} &= u - u_0 \\ \tilde{y} &= y - y_0 \end{aligned} \tag{19}$$

and

$$A = \left.\frac{\partial f}{\partial x}\right|_{(x_0,u_0)}, \tag{20}$$

$$B = \left.\frac{\partial f}{\partial u}\right|_{(x_0,u_0)}, \tag{21}$$

$$C = \left.\frac{\partial h}{\partial x}\right|_{(x_0,u_0)}, \tag{22}$$

$$D = \left.\frac{\partial h}{\partial u}\right|_{(x_0,u_0)}. \tag{23}$$

B. Corner points

Observing simulation results it can be seen that blood glucose varies between 700-1800 mg/l. An obvious choice could be searching for steady points within this range and approximating the nonlinear model with these steady states. With a resolution of 100 mg/l the twelve determined steady states (in our terms corner points) are stable, completely controllable and completely observable.

In order to approximate the nonlinear system third degree polynomial functions can be fit to the corner points interpolating the non-determined steady states. Applying the glucose and insulin input presented in Section 2 to the system that is determined by linearizing the nonlinear model along the approximation function in each variable, the system becomes instable and its responses are meaningless. This is because linearization is only precise in the neighborhood of the actual steady state, but the presented method tries to describe the system in distant regions of the state space with only one variable (blood glucose) which is far too imprecise. Consequently, another method has to be chosen in order to reduce complexity of the nonlinear model.

C. Physiologic working points and further LPV modeling

Polytopic approach of LPV modeling can only be applied if the linear models are stable and cover the operating area in a more or less uniform way. In order to fulfill these conditions physiologic working points (PWPs) are defined: these are state vectors that are not exact solutions of the differential equations describing the molecular model but derived from a steady state.

Applying only five different values for each state variable (which is a rather rough quantization) almost 400000 PWPs should be considered. Exponential explosion is down-to-earth, hence complexity reduction is crucial.

Normalization of the trajectories of the molecular model (see *Fig. 1 and Fig. 2*) to [0,1] results in a valuable experiment: variables can be divided into two groups. One of them is the glucagon-type variables (see *Fig. 1*) whereas the other is the group of insulin-type variables (see *Fig. 2*). Glycogen is the only variable that does not fit perfectly into either group (but it can be categorized as an insulin-type variable), which is not surprising, since glycogen is the stored form of glucose that can be interpreted as the integral of the glucose excess (saturation can be remarked after linear phase).

As a result of biochemical and physiological considerations variables are divided into two groups: glucagon- and insulin-type. PWPs are generated by multiplying the normoglycaemic values [1] by [0.25 0.5 0.75 1 1.25 1.5 2 4] in case of both group, value of glycogen is not modified. The created 64 PWPs are stable, completely controllable and observable, hence further polytopic modeling can be fulfilled.

D. Model reduction

Considering the results it is probable that the complexity of the model can be reduced since variables are not independent in a physiologic sense. Many methods have been published in the subject of linear model reduction, one of the most widely used is based on state space transformation and projection to a subspace [16].

The aim is to determine a minimal set of state variables producing almost the same input-output behavior as the original system. Input-output behavior of a linear, autonomous system remains unchanged after a linear, nonsingular state space transformation.

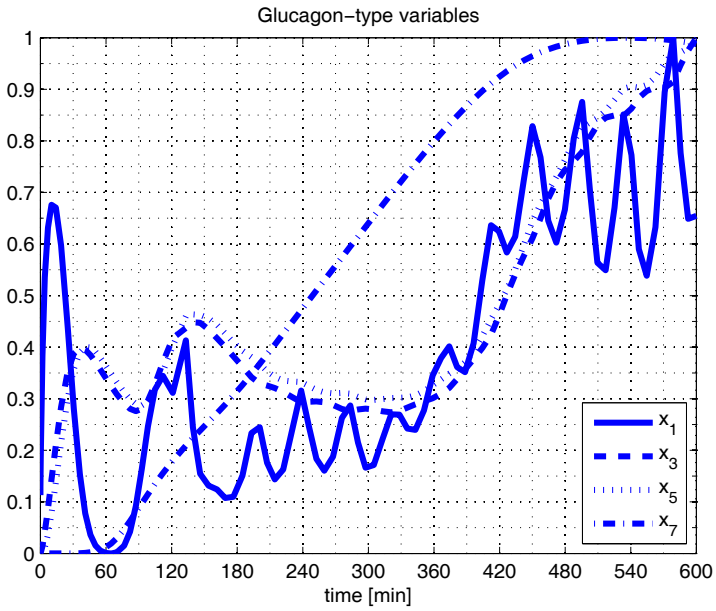

Figure 1: Glucagon-type variables.

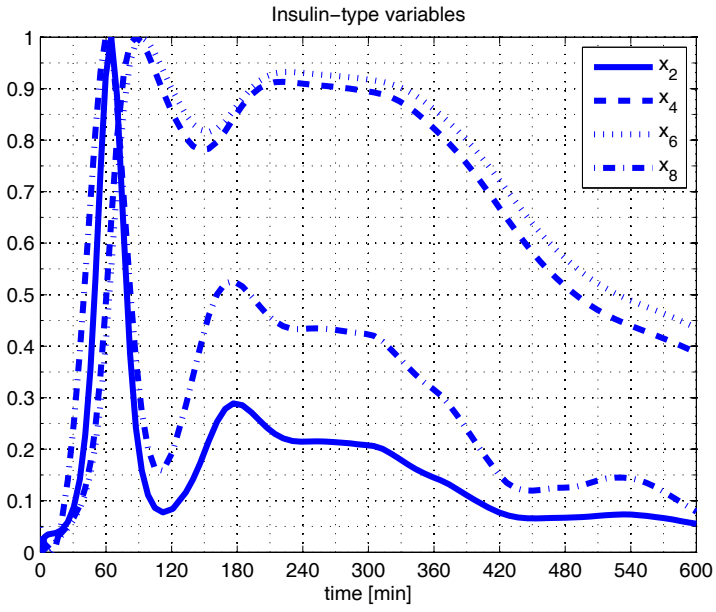

Figure 2: Insulin-type variables.

The method is supported by MATLAB Control System and Robust Toolbox. In case of linearized systems model reduction can be realized as follows: numeric conditioning (ssbal), input-output balancing (obalreal), model reduction based on frequency domain (modred) and determination of state space transformation.

Function balmr() of the MATLAB Robust Control toolbox executes model reduction by minimizing the difference between the H_∞ norms of the original and the reduced systems in frequency domain, but information on state space transformation is lost. This information can be gathered by applying the above-mentioned algorithm.

As a result of reduction Hankel Singular Values of the transformed system Ξ (obtained by MATLAB) 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 $1.31 \cdot 10^{-6}$. Hankel Singular Values represent the relative importance of the state variables independently from realization. Consequently, model reduction can be fulfilled by omitting the state variables with small Hankel Singular Values. It can be seen that the structure of the state variables is the same as in the previous subsection: the first two Hankel Singular Values are much greater than the others validating the considerations applied in case of determination of PWPs.

E. Analyzing the results of reduction

Linearized model in the normoglycaemic state is reduced with different ranks. Responses of the reduced models for 5% perturbation in the initial conditions can be seen in *Fig. 3* and *Fig. 4*. Observing the trajectories it can be seen that the structure described above is plausible since the behavior of the original model can be more or less imitated with only two state variables and with the model of rank four no significant development is achieved.

Results of the model reduction are examined in time and frequency domain. Since the models have two inputs and two outputs four transfer functions can be defined. In time domain impulse responses of the original, linearized model and the reduced models are compared (see *Fig. 5* for one of the four possible transfer functions), whereas in frequency domain Bode diagrams are collated (see *Fig. 6* for one of the four possible transfer functions).

The investigation is realized in the normoglycaemic steady state, but it should be done in case of any steady state. The important frequency range is 0.0002-0.2 rad/min [17]: noise dominates in higher frequencies and the dynamics of the sensor and the actuator (insulin pump) takes place in this range.

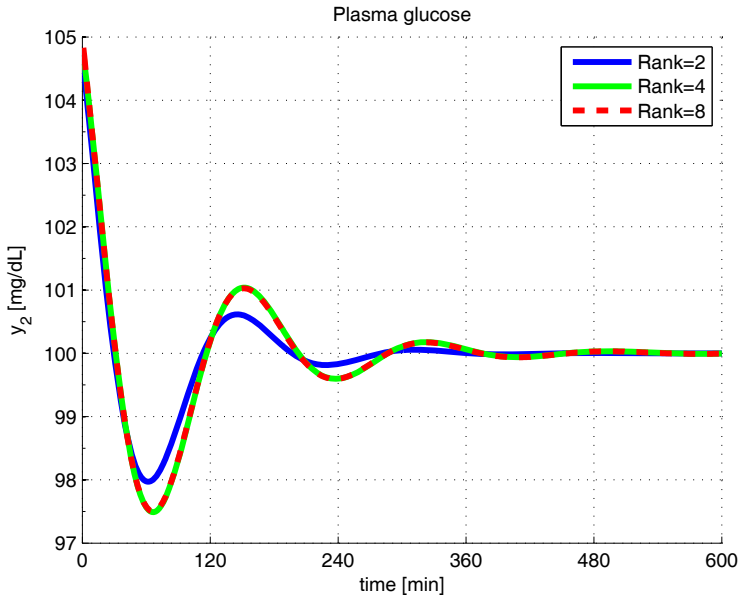

Figure 3: Plasma glucose concentration responses for 5% deviation at the normoglycaemic steady state of the reduced models of different ranks.

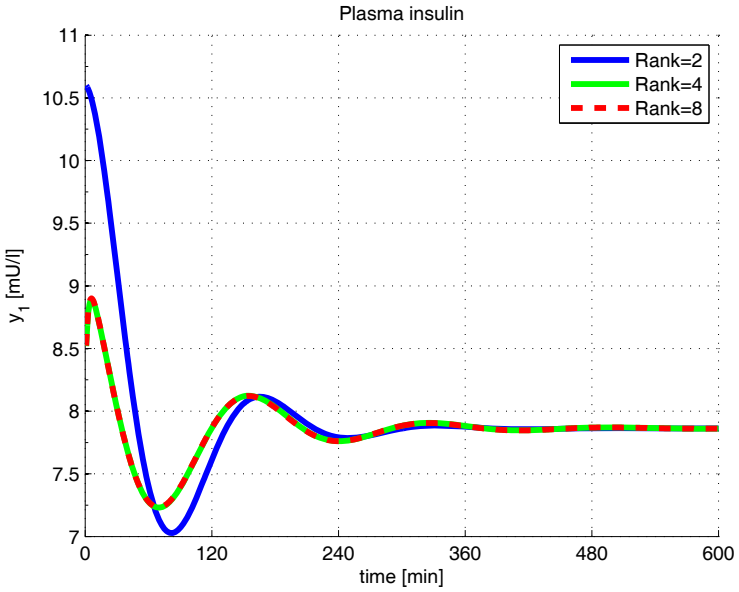

Figure 4: Plasma insulin concentration responses for 5% deviation at the normoglycaemic steady state of the reduced models of different ranks.

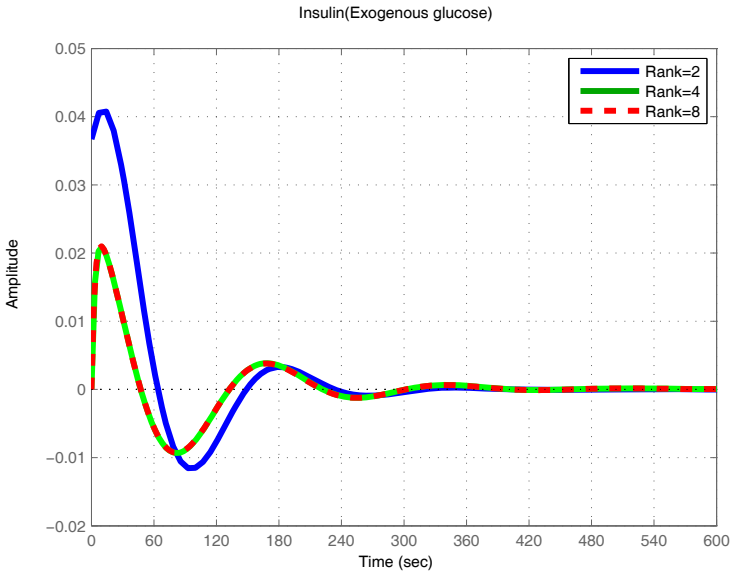

Figure 5: Impulse responses of Insulin(Exogenous glucose) transfer functions of the linearized models of different ranks.

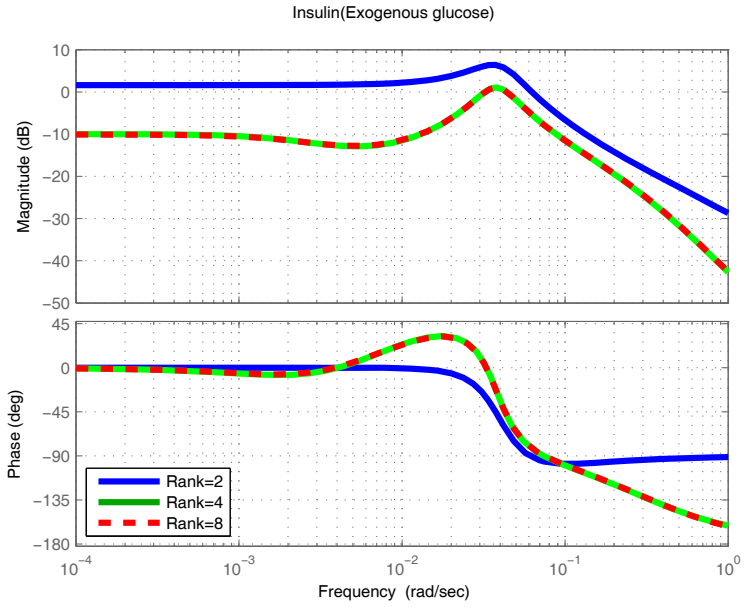

Figure 6: Bode-diagrams of Insulin(Exogenous glucose) transfer functions of the linearized models of different ranks.

Examination results in reassuring observations: the second order model is more or less similar to the original behavior, but the precision is not enough. In contrast with this, the fourth order approximation produces almost identical behavior that the original, linearized model in frequency and time domain as well.

Summarizing the achieved results, we can state that second order approximation is not enough, but fourth order is almost perfect which is not surprising considering biochemical and physiological principles.

5. Conclusion

This paper focused on a novel model offering a radical change in approach. As a result of the applied molecular point of view the cause-effect relations are more plausible and the processes can be described in a more exact and precise way.

After a brief review of the earlier results, the molecular model was presented and described in detail from the aspect of control theory. Global control properties were determined by nonlinear analysis. Nonlinear analysis was followed by steady state linearization. First corner points were defined, but this approach could not ensure proper approximation of the model, hence physiological working points (PWPs) were defined for further LPV modeling. In order to reduce complexity model reduction possibilities were observed with physiological concerns as well as with mathematical ones and the results agreed.

Physiological, biochemical and mathematical approaches were applied and conclusions were made by synchronizing the principles of the different fields of study.

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