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Nonlinear analysis of Type 1 Diabetes Models by Differential Geometric Approach ⋆

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Abstract: The control of physiological systems is a highly demanding task. The requirements are strict and there is a little margin of error, since failure can directly endanger the patient's life. In the same time the performance of the available sensors and actuators are limited in most cases, leaving even higher burden on the control algorithm. Finally the models themselves, which can describe the biophysical and biochemical processes that are most significantly linked to the system we wish to regulate, are rather complex and nonlinear in nature. In general, linear model-based approaches are used, but linearization gives a first source of errors in the further development. The aim of this paper is to investigate two frequently used models describing the metabolism of the human body in case of Type 1 Diabetes Mellitus (T1DM) from nonlinear control perspective: the model presented by Magni et al. (2009) and Hovorka et al. (2004). These models will be investigated using differential geometric approach for the first time.

Keywords: Nonlinear control, observability, controllability, relative degree, type 1 diabetes.

1. INTRODUCTION

Glucose is the primary source of energy for the human body. The blood glucose level is maintained through a complex endocrine system of the human body, and kept in a narrow range (70 - 110 mg/dL). Insulin pays a key role in the process, and when insulin secretion or insulin action is impaired (leading constantly to hyperglycemia), diabetes is diagnosed Fonyo and Ligeti (2008). Type 1 Diabetes Mellitus (T1DM) is the former case being characterized by complete pancreatic β-cell insufficiency, and the treatment usually involves glucose concentration measurements, and subcutaneous insulin injections. From an engineering point of view, the treatment of diabetes mellitus is a control problem that aims to realize the "artificial pancreas", an automated system that can replace the partially or totally deficient blood glucose regulation. It has three main components (Cobelli et al. (2009), Harvey et al. (2010)): continuous glucose sensor for measurements, insulin pump for infusion and control algorithm.

Numerous models appeared in the literature to capture the dynamics of the glucose-insulin household (Bergman et al. (1981), Sorensen (1985), among others), some already containing components to represent the subcutaneous route of glucose and insulin (Magni et al. (2009), Hovorka et al. (2004), Palumbo et al. (2011a)), since this is where the commercially available sensors and pumps access the human body in case of a patient not under direct medical supervision (Chee and Fernando (2007)).

The nonlinearity in each of the above mentioned models represent specific control aspects, but the applied control strategies are usually developed for their linearized (i.e. working point based) versions. Considering the strict requirements the controller should meet, it would be advantageous to consider an approach using nonlinear control theory(Isidori (1995)). Differential-geometry based control has already appeared in the literature (Palumbo et al. (2011a), Palumbo et al. (2011b)), but the complexity of these methods applied to systems of 10th order or above (Kovacs et al. (2011)) has so far limited their use on the most frequently used T1DM models.

The current paper investigates two of these models presented by Magni et al. (2009) and Hovorka et al. (2004) (referred as Type 1 Meal model and Hovorka model), using differential-geometry based control techniques. The results presented may further the efforts in controller development, leading to more effective control laws. The paper is structured as follows. First, the two models are presented. This is followed by the nonlinear control analysis presenting certain properties of the models, such as controllability, observability and relative degree. Section IV concludes the paper and formulates further research directions.

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2. TYPE 1 DIABETES MODELS

In this Section, the two mostly used T1DM models will be briefly summerized. Both models were restructured, and slightly modified, so that they would only contain continuously differentiable functions. The effect on the model will be insignificant with well chosen parameters.

2.1 The Type 1 Meal model

The 13th-order model presented by Magni et al. (2009) is the following:

$$
\begin{aligned}
&\dot{x}_1(t) = f_1(\mathrm{x}(t)) = -k_{sc}x_1(t) + \frac{k_{sc}}{V_G}x_2(t)\\
&\dot{x}_2(t) = f_2(\mathrm{x}(t)) = -k_1x_2(t) + k_2x_3(t) + \frac{k_{abs}f_{gut}x_{13}(t)}{BW} -\\
&-U_{ii} + \Big(k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t)\Big)\cdot\\
&\cdot\left(\frac{1}{2} + \frac{1}{\pi}atan\Big(M(k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t))\Big)\right) -\\
&-k_{e1}\Big(x_2(t) - k_{e2}\Big)\left(\frac{1}{2} + \frac{1}{\pi}atan\Big(M(x_2(t) - k_{e2})\Big)\right)\\
&\dot{x}_3(t) = f_3(\mathrm{x}(t)) = k_1x_2(t) - k_2x_3(t) - \frac{V_{mx}x_3(t)x_4(t)}{K_m + x_3(t)} -\\
&-\frac{V_{m0}x_3(t)}{K_m + x_3(t)}\\
&\dot{x}_4(t) = f_4(\mathrm{x}(t)) = -p_2x_4(t) + \frac{p_2}{V_i}x_7(t) - p_2I_b\\
&\dot{x}_5(t) = f_5(\mathrm{x}(t)) = -k_ix_5(t) + k_ix_6(t)\\
&\dot{x}_6(t) = f_6(\mathrm{x}(t)) = -k_ix_6(t) + \frac{k_i}{V_i}x_7(t)\\
&\dot{x}_7(t) = f_7(\mathrm{x}(t)) = -(m_2 + m_4)x_7(t) + m_1x_8(t)\\
&+k_{a2}x_9(t) + k_{a1}x_{10}(t)\\
&\dot{x}_8(t) = f_8(\mathrm{x}(t)) = m_2x_7(t) - (m_1 + m_3)x_8(t)\\
&\dot{x}_9(t) = f_9(\mathrm{x}(t)) = -k_{a2}x_9(t) + k_dx_{10}(t)\\
&\dot{x}_{10}(t) = f_{10}(\mathrm{x}(t)) + \frac{u(t)}{BW} = -(k_{a1} + k_d)x_{10}(t) + \frac{u(t)}{BW}\\
&\dot{x}_{11}(t) = f_{11}(\mathrm{x}(t)) + d(t) = -k_{gri}x_{11}(t) + d(t)\\
&\dot{x}_{12}(t) = f_{12}(\mathrm{x}(t)) = -k_{empt}(t)x_{12}(t) + k_{gri}x_{11}(t)\\
&\dot{x}_{13}(t) = f_{13}(\mathrm{x}(t)) = -k_{abs}x_{13}(t) + k_{empt}(t)x_{12}(t)
\end{aligned}
\tag{1}
$$

where the state variables are: $x_1(t)$ subcutaneous glucose concentration [mg/dL], which represents also the output of the system, $x_2(t)$ and $x_3(t)$ glucose in plasma and rapidly equilibrating tissues, and slowly equilibrating tissues respectively [mg/kg], $x_4(t)$ insulin in interstitial fluid [pmol/L], $x_5(t), x_6(t)$ state variables of the delayed insulin signal [pmol/L], $x_7(t)$ and $x_8(t)$ insulin mass in plasma and liver [pmol/kg], $x_9(t)$ monomeric insulin in the subcutaneous tissue [pmol/kg], $x_{10}(t)$ polymeric insulin in the subcutaneous tissue [pmol/kg], $x_{11}(t)$ amount of solid phase glucose in stomach [mg], $x_{12}(t)$ amount of liquid phase glucose in stomach [mg], $x_{13}(t)$ glucose mass in the intestine [mg]. $u(t)$ injected insulin flow [pmol/min] is the input of the system, while $d(t)$ amount of ingested glucose [mg/min] is considered as disturbance. The parameters of the model are k_{sc} rate parameter [1/min], V_G distribution volume of glucose [mg/dL], k_1, k_2 rate parameters [1/min], k_{abs} rate constant of intestinal absorption [1/min], f_{gut} fraction of intestinal absorption which actually appears in plasma [-], BW body weight [kg], EGP_b basal value of endogenous glucose production [mg/kg/min], U_{ii} insulin-dependent glucose utilization [mg/kg/min], k_{p2} liver glucose effectiveness [1/min], k_{p3} indicator of effect of a delayed insulin signal $\left[\frac{mg\cdot L}{kg\cdot pmol\cdot min}\right]$, G_{pb} basal value of glucose mass in plasma and rapidly equilibrating tissues [mg/kg], I_{db} basal value of delayed insulin signal [pmol/L], k_{e1} renal glomerular filtration rate [1/min], k_{e2} renal threshold [mg/kg], K_{m0}, V_{m0}, V_{mx} model parameters for insulin-dependent glucose utilization, k_{gri} rate of grinding [1/min], $k_{empt(t)}$ rate of gastric emptying [1/min], p_2 rate constant of insulin action [1/min], V_I insulin distribution volume [L/kg], k_i model parameter of the delayed insulin signal [1/min], $m_1, \ldots, m_4$ rate parameters of the insulin subsystem [1/min], k_{a1}, k_{a2} absorption constants [1/min] and k_d degradation constant. The parameter $k_{empt}(t)$ is time-varying, and can be computed from:

$$
\begin{aligned}
&k_{empt}(t) = k_{min} + \frac{k_{max} + k_{min}}{2}\cdot\\
&\cdot\Big(tanh(\alpha(x_{11}(t) + x_{12}(t) - b\cdot D) + 1\Big)
\end{aligned}
\tag{2}
$$

where k_{min} and k_{max} stand for the minimal and the maximal value of $k_{empt}(t)$ respectively. D is the total amount of carbohydrate the meal contained [mg]. The rate of gastric emptying is on its minimal value when the amount of ingested glucose $(x_{11}(t) + x_{12}(t))$ is zero, but as it increases, $k_{empt}(t)$ starts rising with the rate α and reaches the value $(k_{min} + k_{max})/2$ at the b percentage of D. Finally $k_{empt}(t) = k_{max}$ if $x_{11}(t) + x_{12}(t) = D$.

2.2 The Hovorka model

The 11-th order model presented by Hovorka et al. (2004), and later updated by Wilinska et al. (2010), can be described by the following differential equations:

$$
\begin{aligned}
&\dot{x}_1(t) = f_1(\mathrm{x}(t)) = -k_{a,int}x_1(t) + \frac{k_{a,int}}{V_G}x_2(t)\\
&\dot{x}_2(t) = f_2(\mathrm{x}(t)) = -\left(\frac{F^s_{01}}{x_2(t) + V_G} + x_4(t)\right)x_2(t) +\\
&+k_{12}x_3(t) + \frac{x_{10}(t)}{t_{max}} - Phy(t) - R_{cl}(x_2(t) -\\
&-R_{thr}V_G)\left(0.5 + \frac{1}{\pi}atan\Big(M(x_2(t) - R_{thr}V_G)\Big)\right) +\\
&+EGP_0(1 - x_6(t))\left(0.5 + \frac{1}{\pi}atan\Big(M(1 - x_6(t))\Big)\right) +\\
&+\left(U_G - \frac{x_{10}(t)}{t_{max}}\right)\omega_1(t)\\
&\dot{x}_3(t) = f_3(\mathrm{x}(t)) = x_4(t)x_2(t) - \Big(k_{12} + x_5(t)\Big)x_3(t)\\
&\dot{x}_4(t) = f_4(\mathrm{x}(t)) = -k_{b1}x_4(t) + S_{IT}k_{b1}x_7(t)\\
&\dot{x}_5(t) = f_5(\mathrm{x}(t)) = -k_{b2}x_5(t) + S_{ID}k_{b2}x_7(t)\\
&\dot{x}_6(t) = f_6(\mathrm{x}(t)) = -k_{b3}x_6(t) + S_{IE}k_{b3}x_7(t)\\
&\dot{x}_7(t) = f_7(\mathrm{x}(t)) = \frac{k_a}{V_I}x_8(t) - k_ex_7(t)\\
&\dot{x}_8(t) = f_8(\mathrm{x}(t)) = -k_ax_8(t) + k_ax_9(t)\\
&\dot{x}_9(t) = f_9(\mathrm{x}(t)) + u(t) = -k_ax_9(t) + u(t)\\
&\dot{x}_{10}(t) = \left(U_G\left(\frac{x_{11}(t)}{x_{10}(t)} - 1\right) - \frac{x_{11}(t) - x_{10}(t)}{t_{max}}\right)\cdot\\
&\cdot\omega_1(t) + \frac{x_{11}(t) - x_{10}(t)}{t_{max}}\\
&\dot{x}_{11}(t) = f_{11}(\mathrm{x}(t)) + Bio\cdot D(t) = Bio\cdot D(t) -\\
&-\frac{x_{11}(t)}{t_{max}} - \left(U_G\frac{x_{11}(t)}{x_{10}(t)} - \frac{x_{11}(t)}{t_{max}}\right)\omega_1(t)
\end{aligned}
\tag{3}
$$

where the state variables are: $x_1(t)$ glucose concentration in the subcutaneous tissue [mmol/L] representing also the

output of the system, $x_2(t)$ and $x_3(t)$ represent the masses of glucose in accessible and non-accessible compartments [mmol], $x_4(t)$, $x_5(t)$ and $x_6(t)$ remote effect of insulin on glucose distribution, disposal and endogenous glucose production respectively, $x_7(t)$ insulin concentration in plasma [mU/L], $x_9(t)$ and $x_8(t)$ insulin masses in the accessible and non-accessible compartments [mU], $x_{10}(t)$ and $x_{11}(t)$ glucose masses in the non-accessible and accessible compartments of the gut [mmol]. $u(t)$ injected insulin flow of rapid-acting insulin [mU/min] is the input of the system, while $D(t)$ amount of ingested carbohydrates [mmol/min] is considered as disturbance. $Phy(t)$ effect of physical activity [mmol/min] does also act as a disturbance, but will be considered as a slowly changing time-variant parameter. The parameters of the model are $k_{a,int}$ transfer rate constant between the plasma and the subcutaneous compartment [1/min], V_G distribution volume of glucose in the accessible compartment [L], F_{01}^s parameter of the total non-insulin dependent glucose flux [mmol/min], k_{12} transfer rate constant from the non-accessible to the accessible compartment [1/min], R_{cl} renal clearance constant [1/min], R_{thr} glucose threshold [mmol/L], EGP_0 endogenous glucose production extrapolated to the zero insulin concentration [mmol/min], t_{max} time-to-maximum appearance rate of glucose in the accessible compartment [min], U_G maximum glucose flux from the gut [mmol/kg/min], k_{b1} and k_{b2} deactivation rate constants $[\frac{min^{-2}}{mU/L}]$, k_{b3} deactivation rate constant for the insulin effect on endogenous glucose production $[\frac{min^{-1}}{mU/L}]$, k_{a1}, k_{a2} and k_{a3} activation rate constants [1/min], $S_{IT} = k_{a1}/k_{b1}$, $S_{ID} = k_{a2}/k_{b2}$ and $S_{IE} = k_{a3}/k_{b3}$ insulin sensitivities for transport, distribution and endogenous glucose production $[\frac{10^{-4}min^{-1}}{mU/L}]$ and $[\frac{10^{-4}}{mU/L}]$, k_a insulin absorption rate constant [1/min], V_i volume of distribution of rapid-acting insulin [L], k_e fractional elimination rate from plasma [1/min], Bio carbohydrate bioavailability of the meal [-]. $\omega_1(t)$ denotes $\left(0.5 + \frac{1}{\pi} atan\Big(M(x_{10}(t) - U_G t_{max})\Big)\right)$.

For both models a second order linear system has been added (4) to the meal intake input, with adequately fast dynamics (faster than the rest of the systems), that must be treated as unknown when designing a controller. It will have significance when determining the relative degree of each model. This is justified by the fact that there are several processes during a meal intake, that for practical reasons were not considered while formulating the above presented models (chewing, swallowing, etc.). It is also encouraging, that the same model can be used for both systems. In equation (4), n stands for the order of the investigated T1DM model, $\hat{y}(t)$ is the glucose flux that will provide the amount of ingested glucose/amount of ingested carbohydrates input for the models in the prescribed units. The $\hat{u}(t)$ input of the added dynamics has the same units as the output $\hat{y}(t)$. The p_r parameters represent rate transitions [1/min].

$$\begin{pmatrix} \dot{x}_{n+1}(t) \\ \dot{x}_{n+2}(t) \end{pmatrix} = \begin{bmatrix} -p_r & p_r \\ 0 & -p_r \end{bmatrix} \begin{pmatrix} x_{n+1}(t) \\ x_{n+2}(t) \end{pmatrix} + \begin{pmatrix} 0 \\ 1 \end{pmatrix} \hat{u}(t) \quad (4)$$
$$\hat{y} = p_r x_{n+1}(t)$$

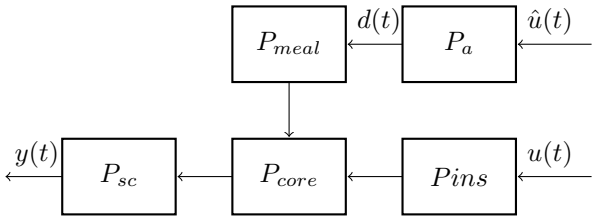

Fig. 1. Structure of the investigated models

3. CONTROLLABILITY AND OBSERVABILITY

Both model can be divided into 5 subsystems: P_{core} core glucose dynamics, P_{ins} - insulin subsystem, P_{meal} - meal ingestion/absorption subsystem, P_{sc} - subcutaneous glucose dynamics subsystem and P_a - added meal intake dynamics. This structure is displayed in Fig. 1.

To determine the controllability and observability of linear systems, examining the rank of $\mathbf{M}_c = [\,\mathbf{A}^0\mathbf{B}\ \cdots\ \mathbf{A}^{n-1}\mathbf{B}\,]$ and $\mathbf{M}_o = [\,(\mathbf{A}^T)^0\mathbf{C}^T\ \cdots\ (\mathbf{A}^T)^{n-1}\mathbf{C}^T\,]^T$ controllability and observability matrices are enough. In case of a nonlinear model (5), where $\mathrm{f(x)} = (\,f_1(\mathrm{x})\ \cdots\ f_n(\mathrm{x})\,)^T$ vector-space consists of $f_1(\mathrm{x})\ \cdots\ f_n(\mathrm{x})$ smooth scalar-valued functions, $h(\mathrm{x})$ is a smooth scalar valued function, furthermore $\mathrm{g(x)}$ and $\mathrm{h_d(x)}$ are smooth vector-spaces, the rank of the smallest f-involutive distribution, containing $\mathrm{g(x)}$ and $\mathrm{h}_d(\mathrm{x})$ must be investigated for reachability, and the rank of distribution (6) to determine local observability, where $\mathcal{L}_f^j h(\mathrm{x})$ notes the j-th Lie-derivative of $h(\mathrm{x})$ scalar-valued function along the vector space $\mathrm{f(x)}$ (Isidori (1995)).

$$\begin{aligned} \dot{\mathrm{x}}(t) &= \mathrm{f(x}(t)) + \mathrm{g(x}(t))u(t) + \mathrm{h}_d(\mathrm{x}(t))u(t) \\ y(t) &= h(\mathrm{x}(t)) \end{aligned} \quad (5)$$

$$\Delta_o(\mathrm{x}) = \begin{bmatrix} \dfrac{\partial h(\mathrm{x})}{\partial x_1} & \dfrac{\partial h(\mathrm{x})}{\partial x_2} & \cdots & \dfrac{\partial h(\mathrm{x})}{\partial x_n} \\ \dfrac{\partial \mathcal{L}_f h(\mathrm{x})}{\partial x_1} & \dfrac{\partial \mathcal{L}_f h(\mathrm{x})}{\partial x_2} & \cdots & \dfrac{\partial \mathcal{L}_f h(\mathrm{x})}{\partial x_n} \\ \vdots & \vdots & & \vdots \\ \dfrac{\partial \mathcal{L}_f^{n-1} h(\mathrm{x})}{\partial x_1} & \dfrac{\partial \mathcal{L}_f^{n-1} h(\mathrm{x})}{\partial x_2} & \cdots & \dfrac{\partial \mathcal{L}_f^{n-1} h(\mathrm{x})}{\partial x_n} \end{bmatrix} \quad (6)$$

Another important attribute of nonlinear and linear systems is their relative degree (Isidori (1995)). This property tells that when investigating the time derivatives of the output of a system, in which order of derivative does the input signal appear. Let us assume that the system is given in the form of (5), and its relative degree is r. Then the following statements apply (Isidori (1995)):

- $\mathcal{L}_g \mathcal{L}_f^i h(\mathrm{x}) = 0$ for every $i < r - 1$
- $\mathcal{L}_g \mathcal{L}_f^{r-1} h(\mathrm{x}) \neq 0$

In order to determine the reachability, observability and relative degree of the systems, a few things must be considered:

- Both models are rather complex and nonlinear. Using the above mentioned methods directly might be too difficult to handle.
- The series of reachable and observable nonlinear SISO systems form a reachable system from the input of the first system to the output of the last system. This can be proven in the following way: if a system

is reachable, then all of its state variables can be influenced through its input, and they can be driven to a $\mathrm{x}(t)$ desired value from any given $\mathrm{x}_0(\tau)$ point of the state-space under finite $t-\tau$ time with adequately chosen $u(.)$ function as input. All of these state variables have distinguishable effect on the output of the system due to its observability. If this output provides input for a second reachable and observable system, then all state variables of the second system can be influenced through the output of the first system. Through iteration, all state variables of all the nonlinear systems of the series can be reached.

- Only the reachability of the subsystem consisting of P_{ins}, P_{core}, and P_{sc}, is necessary for blood glucose control. This is a series of SISO systems.
- The arctan ($atan(.)$) functions in (1) and (3) cause a "switching" effect, which must be treated directly when controlling the system, but from observability point of view one need only to determine observability between the switches. This way four and eight different nonlinear systems can be distinguished for each models respectively, which are easier to handle.
- The state variables of subsystem P_a cannot be observed, since it is considered as unknown dynamics.

3.1 Analysis of the Type 1 Meal model

Let us investigate each subsystem separately. The additional component of the meal intake was chosen to be controllable and observable. The first order system of the subcutaneous glucose dynamics is also controllable and observable. The third investigated model is the insulin subsystem with linear dynamics (7). It contains the equations belonging to state variables $x_7(t), \ldots, x_{10}(t)$.

$$\begin{aligned}\dot{\mathrm{x}}(t) &= \begin{bmatrix} -(m_2+m_4) & m_1 & k_{a2} & k_{a1} \\ m2 & -(m_1+m_3) & 0 & 0 \\ 0 & 0 & -k_{a2} & k_d \\ 0 & 0 & 0 & -(k_{a1}+k_d) \end{bmatrix}. \\ &\mathrm{x}(t) + \begin{pmatrix} 0 & 0 & 0 & BW^{-1} \end{pmatrix}^T u(t) \\ y(t) &= \begin{pmatrix} 1 & 0 & 0 & 0 \end{pmatrix} \mathrm{x}(t)\end{aligned} \tag{7}$$

The M_c controllability matrix of the subsystem has full rank as long as $|M_c|$ (8) does not equals zero. The M_o observability matrix of the subsystem has full rank as long as $|M_o|$ (8) does not equals zero.

$$\begin{aligned}|M_c| &= -\frac{k_d m_2}{BW}(k_{a2}^2(k_{a1}+k_d)^2 - k_{a1}k_{a2}(k_{a1}+k_d)\cdot \\ &\cdot(m_1+m_2+m_3+m_4) + k_{a1}^2(m_1m_4+m_2m_3+m_3m_4)) \\ |M_o| &= k_{a2}m_1(k_{a1}+k_d)(k_{a1}-k_{a2})(m_1-k_{a2}+m_3)\cdot \\ &\cdot(k_{a1}+k_d-m_1-m_3)\end{aligned} \tag{8}$$

$$\begin{aligned}|\Delta_c(\mathrm{x})| &= \frac{k_i^3 p_2 (k_i-p_2)^2}{V_i^3}\Big(\Big(\Delta_{c,(1,4)}\Delta_{c,(2,3)}(3k_i^2+2k_ip_2+ \\ &+p_2^2) + \Delta_{c,(1,5)}\Delta_{c,(2,3)}(2k_i+p_2) - \Delta_{c,(1,4)}\Delta_{c,(2,5)} + \\ &+\Delta_{c,(1,5)}\Delta_{c,(2,4)}\Big) - \Big(\Big(k_i^2\frac{\partial f_2(\mathrm{x})}{\partial x_5} + k_2p_2\frac{\partial f_3(\mathrm{x})}{\partial x_4}\Big)\cdot \\ &\cdot\Big(\Delta_{c,(2,4)}(3k_i^2+2k_ip_2+p_2^2) + \Delta_{c,(2,5)}(p_2+2k_i)\Big) - \\ &- \frac{k_ip_2}{V_i}\frac{\partial f_3(\mathrm{x})}{\partial x_4}\Big(2\Delta_{c,(1,4)}(k_i+p_2)^2 + \Delta_{c,(1,5)}(2p_2+k_i)\Big)\Big) \\ &+ \frac{k_i^2p_2}{V_i^2}\frac{\partial f_3(\mathrm{x})}{\partial x_4}\Big(k_i^2\frac{\partial f_2(\mathrm{x})}{\partial x_5} + k_2p_2\frac{\partial f_3(\mathrm{x})}{\partial x_4}\Big)\cdot \\ &\cdot(k_i^2+2k_ip_2+3p_2^2)\Big)\end{aligned} \tag{9}$$

The final subsystem is the core of the model, the glucose dynamics combined with insulin effect subsystem, resulting in a fifth order nonlinear system, since the equations belonging to states $x_2(t), \ldots, x_6(t)$ are used. It has inputs coming from the insulin subsystem (7) and the glucose absorption subsystem. From control point of view, we can only access the signal coming from the insulin subsystem, hence we have to reduce the investigated model into a SISO system. The reachability distribution will not be presented here due to lack of space, but it spans $\mathbb{R}^5$ space if the determinant (9) does not equals zero:

When investigating the global observability of the system, the following four cases must be considered:

(1) $x_2(t) \geq k_{e2},\ k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t) \geq 0,$
(2) $x_2(t) \geq k_{e2},\ k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t) < 0,$
(3) $x_2(t) < k_{e2},\ k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t) \geq 0,$
(4) $x_2(t) < k_{e2},\ k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t) < 0,$

The first inequality ($x_2(t) \geq k_{e2}$) pays little role in observability, it has only significance when certain relations exist between the parameters, which never occurs in practical cases. In case of $k_{p1} - k_{p2}x_2(t) - k_{p3}x_5(t) \leq 0$ however state variables $x_{10}(t), \ldots, x_4(t)$ have no effect on the output of the system if $x_3(t) = 0$. Since $x_3(t)$ corresponds with glucose concentration in slowly equilibrating tissues, this practically never occurs. In general we can conclude, that in practice, with the exception of a finite number of singular points of the state-space, the model is locally observable.

Finally, the relative degree of the model for both input and disturbance is investigated. Let us consider the model without the subcutaneous glucose dynamics, described by the mapping $\tilde{\mathrm{f}}(\mathrm{x}) = (\, f_2(\mathrm{x}) \cdots f_{15}(\mathrm{x})\,)^T$ with $\tilde{h}(\mathrm{x}) = x_2(t)$ as output. The relative degree for both input and disturbance is 5, since:

$$\mathcal{L}_g\mathcal{L}_{\tilde{\mathrm{f}}}^3\tilde{h}(\mathrm{x}) = \mathcal{L}_{h_d}\mathcal{L}_{\tilde{\mathrm{f}}}^3\tilde{h}(\mathrm{x}) = 0 \tag{10}$$

$$\mathcal{L}_g\mathcal{L}_{\tilde{\mathrm{f}}}^4\tilde{h}(\mathrm{x}) = \frac{k_2k_{a1}p_2}{V_iBW}\frac{\partial f_3(\mathrm{x})}{\partial x_4}\frac{k_{a1}k_i^2}{V_iBW}\frac{\partial f_2(\mathrm{x})}{\partial x_5} \tag{11}$$

$$\mathcal{L}_{h_d}\mathcal{L}_{\tilde{\mathrm{f}}}^4\tilde{h}(\mathrm{x}) = \frac{f_{gut}k_{abs}p_r^2}{BW}\frac{\partial f_{11}(\mathrm{x})}{\partial x_{13}} \tag{12}$$

The relative degree of the complete system is therefore 6.

3.2 Analysis of the Hovorka model

Similarly to the Type 1 Meal model, 5 subsystems can be distinguished in a similar manner. The additional component of the meal intake is the same, and the subcutaneous glucose dynamics is a first order linear system as well. However, the insulin subsystem in this case consists of parts of the insulin action subsystem and the subcutaneous insulin absorption/kinetics subsystem, which were presented in Hovorka et al. (2004) and Wilinska et al. (2010). The resulting fifth order system is linear, with 3 outputs (13), constructed by the equations that belong to state variables $x_4(t)$, $x_5(t)$ and $x_7(t), \ldots, x_9(t)$.

$$\dot{\mathrm{x}}(t) = \begin{bmatrix} -k_{b1} & 0 & S_{IT}k_{b1} & 0 & 0 \\ 0 & -k_{b2} & S_{ID}k_{b2} & 0 & 0 \\ 0 & 0 & -k_e & \frac{k_a}{V_I} & 0 \\ 0 & 0 & 0 & -k_a & k_a \\ 0 & 0 & 0 & 0 & -k_a \end{bmatrix} \mathrm{x}(t) + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{pmatrix} u(t) \quad (13)$$
$$y(t) = \begin{pmatrix} 1\,0\,0\,0\,0 \\ 0\,1\,0\,0\,0 \\ 0\,0\,1\,0\,0 \end{pmatrix} \mathrm{x}(t)$$

The M_c controllability and M_o observability matrix of the subsystem has full rank as long as the following expressions (14) do not equal zero:

$$\begin{aligned} |M_c| &= -\frac{S_{IT}S_{ID}k_a^7 k_{b1}k_{b2}(k_{b1}-k_{b2})}{V_I^3} \\ |M_{o,(1,2,3,6,9)}| &= \frac{k_a^3}{V_I^2} \end{aligned} \quad (14)$$

Let us investigate the P_{core} subsystem, that captures glucose dynamics and insulin effect. It is a third order nonlinear system with the outputs of the P_{ins} insulin subsystem as input $(u_1(t), u_2(t), u_3(t))$, and $x_2(t)$ as output (15).

$$\begin{aligned} &\dot{x}_2(t) = -\frac{F_{01}^s}{x_2(t)+V_G}x_2(t) + k_{12}x_3(t) - x_2(t)u_1(t) - \\ &-R_{cl}(x_2(t) - R_{thr}V_G)\cdot \\ &\cdot\left(0.5 + \frac{1}{\pi}atan\Big(M(x_2(t) - R_{thr}V_G)\Big)\right) + \\ &+EGP_0(1-x_6(t))\left(0.5 + \frac{1}{\pi}atan\Big(M(1-x_6(t))\Big)\right) \\ &\dot{x}_3(t) = -k_{12}x_3(t) + x_2(t)u_1(t) - x_3(t)u_2(t) \\ &\dot{x}_6(t) = -k_{b3}x_6(t) + S_{IE}k_{b3}u_3(t) \end{aligned} \quad (15)$$

This system is definitely controllable, since the three inputs directly effect each and every state variables separately. The inputs however are not independent, since $x_4(t)$ and $x_5(t)$ are merely the filtered signals of $x_7(t)$. To take this into consideration, we can approximate (15) with the following nonlinear SISO system:

$$\begin{aligned} &\dot{x}_2(t) = -\frac{F_{01}^s}{x_2(t)+V_G}x_2(t) + k_{12}x_3(t) - x_2(t)S_{IT}\tilde{u}(t) - \\ &-R_{cl}(x_2(t) - R_{thr}V_G)\cdot \\ &\cdot\left(0.5 + \frac{1}{\pi}atan\Big(M(x_2(t) - R_{thr}V_G)\Big)\right) + \\ &+EGP_0(1-x_6(t))\left(0.5 + \frac{1}{\pi}atan\Big(M(1-x_6(t))\Big)\right) \\ &\dot{x}_3(t) = -k_{12}x_3(t) + x_2(t)S_{IT}\tilde{u}(t) - x_3(t)S_{ID}\tilde{u}(t) \\ &\dot{x}_6(t) = -k_{b3}x_6(t) + S_{IE}k_{b3}\tilde{u}(t) \\ &y(t) = x_2(t) \end{aligned} \quad (16)$$

Let us introduce the following notation:

$$\begin{aligned} &f_2 = -\frac{F_{01}^s}{x_2(t)+V_G}x_2(t) + k_{12}x_3(t) - \\ &-R_{cl}(x_2(t) - R_{thr}V_G)\cdot \\ &\cdot\left(0.5 + \frac{1}{\pi}atan\Big(M(x_2(t) - R_{thr}V_G)\Big)\right) + \\ &+EGP_0(1-x_6(t))\left(0.5 + \frac{1}{\pi}atan\Big(M(1-x_6(t))\Big)\right) \end{aligned} \quad (17)$$

The system (16) is reachable, as long as the following expression does not equals zero:

$$\begin{aligned} &S_{ID}^2\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2} + k_{12} + k_{b3}\right)k_{12}k_{b3}x_3^2 + S_{ID}S_{IT}\cdot \\ &\cdot\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2}\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2}k_{b3}x_2 + f_2(2k_{12}-k_{b3}) + \right.\right. \\ &\left.+(k_{12}-k_{b3})^2x_2\right)x_3 - x_6\frac{\partial f_2(\mathrm{x})}{\partial x_6}(k_{12}+k_{b3})k_{b3}x_3 + \\ &+f_2\left(4k_{12}^2 - (k_{12}-k_{b3})^2 - \frac{\partial^2 f_2(\mathrm{x})}{\partial x_2^2}k_{b3}x_2\right)x_3 + \\ &\left.+2k_{12}(k_{12}^2 - k_{b3}^2)x_2x_3 - k_{12}^2(k_{12}+k_{b3})x_3^2\right) - S_{IE}\cdot \\ &\cdot S_{ID}\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2}\frac{\partial f_2(\mathrm{x})}{\partial x_6} + \frac{\partial^2 f_2(\mathrm{x})}{\partial x_6^2}x_6k_{b3}\right)k_{b3}^2x_3 + \\ &+S_{IT}^2\left(\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2}\right)^2\Big(2f_2 + (k_{12}-k_{b3})x_2\Big)x_2 + \right. \\ &+\frac{\partial f_2(\mathrm{x})}{\partial x_2}\left(x_2\left(k_{b3}\left(2f_2 - x_6\frac{\partial f_2(\mathrm{x})}{\partial x_6}\right) - k_{12}^2x_3\right) - \right. \\ &\left.-2f_2^2 - f_2k_{12}x_2\right) - \frac{\partial^2 f_2(\mathrm{x})}{\partial x_2^2}f_2^2x_2 + (k_{12}-k_{b3})\cdot \\ &\cdot\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2}k_{b3} - \frac{\partial^2 f_2(\mathrm{x})}{\partial x_2^2}f_2\right)x_2^2\Big) + S_{IT}S_{IE}\cdot \\ &\cdot\left(\frac{\partial f_2(\mathrm{x})}{\partial x_6}\left(\frac{\partial f_2(\mathrm{x})}{\partial x_2}\Big(x_2(k_{b3}-k_{12}) - 2f_2\Big) + \frac{\partial f_2(\mathrm{x})}{\partial x_6}\cdot\right.\right. \\ &\left.\cdot x_6k_{b3} + f_2(k_{b3}-2k_{12}) + k_{12}^2(x_3-x_2) + k_{12}k_{b3}x_2\right)\cdot \\ &\left.\cdot k_{b3} + \frac{\partial f_2(\mathrm{x})}{\partial x_6}\Big(x_2(k_{b3}-k_{12}) - f_2\Big)x_6k_{b3}^2\right) \end{aligned} \quad (18)$$

The most important conclusion that can be drawn from (18) is that the core subsystem is controllable as long as the state variables belonging to insulin effect (x_4, x_5 and x_6) do not equal zero. This always occurs when insulin is given to the patient. Apart from this only distinct singular points can be found, and certain relationship between parameters must be avoided.

When investigating the observability of the system, the following cases must be considered:

(1) $x_2(t) \geq R_{thr}VG,\ x_6(t) \leq 1,\ \frac{x_{10}}{t_{max}} \leq U_G$
(2) $x_2(t) < R_{thr}VG,\ x_6(t) \leq 1,\ \frac{x_{10}}{t_{max}} \leq U_G$
(3) $x_2(t) \geq R_{thr}VG,\ x_6(t) > 1,\ \frac{x_{10}}{t_{max}} \leq U_G$
(4) $x_2(t) < R_{thr}VG,\ x_6(t) > 1,\ \frac{x_{10}}{t_{max}} \leq U_G$
(5) $x_2(t) \geq R_{thr}VG,\ x_6(t) \leq 1,\ \frac{x_{10}}{t_{max}} > U_G$
(6) $x_2(t) < R_{thr}VG,\ x_6(t) \leq 1,\ \frac{x_{10}}{t_{max}} > U_G$
(7) $x_2(t) \geq R_{thr}VG,\ x_6(t) > 1,\ \frac{x_{10}}{t_{max}} > U_G$
(8) $x_2(t) < R_{thr}VG,\ x_6(t) > 1,\ \frac{x_{10}}{t_{max}} > U_G$

To determine the observability of the system, the rank of the matrix (6) must be computed. Instead of using the transformed model (3), the observability will only be investigated for the eight cases mentioned earlier, and the switching of the system will be neglected. Due to lack of space, neither the Lie-derivatives, nor the respective matrices and determinants will be presented here. General remarks will be given instead:

(1) State variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ are observable,

(2) $x_9(t)$, $x_8(t)$ and $x_7(t)$ are observable if at least one of $x_4(t)$, $x_5(t)$ or $x_6(t)$ is observable.
(3) $x_4(t)$ is observable if $x_4(t) \neq 0$, which always apply as long as there is injected insulin flow.
(4) $x_5(t)$ is observable if $x_5(t) \neq 0$ and $x_3(t)$ is observable, which always apply as long as there is injected insulin flow.
(5) $x_6(t)$ is observable if $x_6(t) \leq 1$.
(6) x_{10} and x_{11} are observable if $\frac{x_{10}}{t_{max}} < U_{G,ceil}BW$

Apart from these, there are several points of the state-space and certain parameter configurations, where the system is locally not observable. The most important constraints however, that need to be taken into consideration when constructing a state estimator for the model, is the above mentioned six.

Finally the relative degree of the system is investigated from both inputs (insulin and meal). Let us consider the model without the subcutaneous glucose dynamics, described by the mapping $\tilde{\mathrm{f}}(\mathrm{x}) = (\, f_2(\mathrm{x}) \,\cdots\, f_{13}(\mathrm{x}) \,)$ with $\tilde{h(\mathrm{x})} = x_2(t)$ as output. The relative degree for both input and disturbance is 5 on this reduced system, therefore it is 6 on (3).

$$\mathcal{L}_g \mathcal{L}_{\tilde{\mathrm{f}}}^3 \tilde{h}(\mathrm{x}) = \mathcal{L}_{h_d} \mathcal{L}_{\tilde{\mathrm{f}}}^3 \tilde{h}(\mathrm{x}) = 0 \tag{19}$$

$$\mathcal{L}_g \mathcal{L}_{\tilde{\mathrm{f}}}^4 \tilde{h}(\mathrm{x}) = \frac{k_a^2}{V_I} \left(S_{IE} k_{b3} \frac{\partial f_2(\mathrm{x})}{\partial x_6} - S_{IT} k_{b1} x_2 \right) \tag{20}$$

$$\mathcal{L}_{h_d} \mathcal{L}_{\tilde{\mathrm{f}}}^4 \tilde{h}(\mathrm{x}) = Bio \cdot p_r^2 \frac{\partial f_2(\mathrm{x})}{\partial x_{10}} \frac{\partial f_{10}(\mathrm{x})}{\partial x_{11}} \tag{21}$$

3.3 Discussion

Previously, for both models, after dividing them into subsystems, the controllability and observability has been investigated for several components. P_{ins}, P_{core} and P_{sc} are controllable/reachable through their inputs, as long as $|M_c|$ in (8), (9), (14) and (18) do not equal zero. It is easy to recognize, that the series of these subsystems are also controllable/reachable, and that agrees with physiological facts. The observability of these subsystems separately also apply, as long as $|M_o|$ (8) and (14) do not equal zero.

Local observability of both models were also investigated, although due to lack of space the complete analysis were not presented. The specific cases were investigated separately, and conclusions were drawn, which can be used when creating state observer for the models, especially in case of the Hovorka model. There at least two observer is needed, one for all state variables and one that excludes the states linked to meal ingestion when the glucose flux from the gut saturates.

Finally the relative degree of the models allows exact linearization, asymptotic output tracking and partial disturbance rejection as long as adequate state observer is present and the zero dynamics of the systems are asymptotically stable in Ljapunov sense.

Due to lack of space, numerical values are not presented as parameters differ from patient to patient and are also time-varying. Hence, the paper was structured to give a general view of the presented approach.

4. CONCLUSION

The controllability, observability and relative degree properties of two frequently used and complex T1DM models have been investigated. The findings can be used as a stepping stone to implement controllers using nonlinear methodologies. As long as an adequate state estimator is present, exact linearization and asymptotic output tracking (Isidori (1995)) can be performed on the systems. Since these methods are sensitive to parameter and modeling inaccuracies, robustness must be investigated.

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