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The significance of LPV modeling of a widely used T1DM model

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Abstract— **The paper investigates the specificity of Linear Parameter Varying (LPV) modeling and robust controller design on a widely used Type 1 Diabetes Mellitus model. LPV systems can be seen as an extension of linear time invariant systems, which allows us to extend some powerful control methodologies to the highly nonlinear and uncertain models of the human metabolism. Different LPV models are proposed with their own advantages and disadvantages. The possible choices are separately analyzed for both controller and observer design perspective.**

I. Introduction

The blood glucose level is maintained through a complex endocrine system of the human body, which is responsible among others for energy transport. The normal blood glucose concentration varies in a narrow range (70-110 mg/dL). If the human body is unable to control the glucose-insulin interaction diabetes is diagnosed [2]. Due to its frightening increase the World Health Organization (WHO), warns that diabetes could be the "disease of the future" as diabetic population is predicted to be doubled from 2000 to 2030 [3]. From an engineering point of view, the treatment of diabetes mellitus can be represented as a control problem that aims to realize the "artificial pancreas" (AP), an automated system that can replace the partially or totally deficient blood glucose regulation. The system is researched for Type 1 Diabetes Mellitus (T1DM) as this diabetes type is characterized by a standard clinical picture, e.g. complete pancreatic β-cell insufficiency, and the treatment usually involves glucose concentration measurements, and subcutaneous insulin injections. An AP system should be composed from three parts [4-5]:

- Continuous Glucose Monitors (CGM) for the subcutaneous measurement of glucose concentration [6];
- insulin pumps for the subcutaneous delivery of insulin;
- control algorithm that based on CGM measurements, is able to determine the necessary insulin dosage to be injected by the insulin pumps.

The control methods proposed in the literature are mostly model-based; hence an adequate mathematical model of the human metabolism was needed. Numerous models appeared over the last decades, the most widely used being those introduced by [1], [7-8]. Although different control algorithms have been proposed in the literature [4-5], only four main control strategies have been used for AP prototype systems: Proportional Integral Derivative (PID) based controllers [9], Model Predictive Control (MPC) [10], run-to-run [11], and recently the fuzzy logic based [12]. The majority of the mentioned algorithms are able to achieve nocturnal glucose regulation. A recent overview can be found in [13].

Despite the effort put into adequately modeling the human metabolism, due to intra-patient variations, limited measurement and identification possibilities the estimated and measured blood glucose levels of the patient is expected to deviate even in the most ideal scenario. To address this uncertainty modern robust control methods represents an adequate choice to provide safety and stability under all reasonably expectable circumstances [14-15]. The applicability of this philosophy in the T1DM problem has been investigated in [16]. However, such a generally applicable method does not exist for nonlinear models, where even proving stability can be a difficult task, and the problem gets more complicated under parameter inaccuracies, uncertainties and neglected dynamics.

The current paper investigates the specificity of using Linear Parameter Varying (LPV) modeling and robust controller design on the widely used T1DM model of [1]. Although this concept has been investigated in the past for the AP problem, the models used for design were usually not the ones that are preferred in practical applications. The model cited in this paper appeared in the scope of robust controller development only recently [17].

II. The Investigated Model

The T1DM model of [1] is an 11th order model and was later updated in [18]. Let us introduce the following notations:

$$\begin{aligned} EGP(t) &= EGP_0 \ max\{1 - x_3(t), 0\} \\ R(t) &= R_{cl} \ max\{Q_1(t) - R_{th} V_G, 0\} \\ \tau(t) &= min\left\{ t_{max}, \frac{G_2(t)}{U_{G,ceil}} \right\} \end{aligned} \tag{1}$$

With this the model can be described as follows:

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$$
\begin{aligned}
\dot{C}(t) &= -k_{a,int}C(t) + \frac{k_{a,int}}{V_G}Q_1(t)\\
\dot{Q}_1(t) &= -\left(\frac{F_{01}}{Q_1(t)+V_G} + x_1(t)\right)Q_1(t) + k_{12}Q_2(t) + EGP(t) + \frac{1}{\tau(t)}G_2(t) - R(t) - Phy(t)\\
\dot{Q}_2(t) &= x_1(t)Q_1(t) - (k_{12} + x_2(t))Q_2(t)\\
\dot{x}_1(t) &= -k_{b1}x_1(t) + S_{IT}k_{b1}I(t)\\
\dot{x}_2(t) &= -k_{b2}x_2(t) + S_{ID}k_{b2}I(t)\\
\dot{x}_3(t) &= -k_{b3}x_3(t) + S_{IE}k_{b3}I(t)\\
\dot{I}(t) &= -k_e I(t) + \frac{k_a}{V_I}S_2(t)\\
\dot{S}_2(t) &= -k_a S_2(t) + k_a S_1(t)\\
\dot{S}_1(t) &= -k_a S_1(t) + u(t)\\
\dot{G}_2(t) &= -\frac{1}{\tau(t)}G_2(t) + \frac{1}{\tau(t)}G_1(t)\\
\dot{G}_1(t) &= -\frac{1}{\tau(t)}G_1(t) + d(t)
\end{aligned}
\tag{2}
$$

where the state variables are: $C(t)$ glucose concentration in the subcutaneous tissue [mmol/L], $Q_1(t)$ and $Q_2(t)$ the masses of glucose in accessible and non-accessible compartments [mmol], $x_1(t)$, $x_2(t)$ and $x_3(t)$ remote effect of insulin on glucose distribution, disposal and endogenous glucose production respectively [1/min], $I(t)$ insulin concentration in plasma [mU/L], $S_1(t)$ and $S_2(t)$ insulin masses in the accessible and non-accessible compartments [mU], $G_1(t)$ and $G_2(t)$ [mmol] are related to intestinal glucose absorption.

The $u(t)$ injected insulin flow of rapid-acting insulin [mU/min] is the input of the system, while amount of ingested glucose $d(t)$ [mmol/min], and the $Phy(t)$ effect of physical activity [mmol/min] are considered as disturbances. Detailed description of the parameters of the model can be found in [1] and [18] and will not be presented here due to lack of space. Some of the parameters are assumed to be time-varying: $k_{a,int}$, F_{01}, k_{12}, EGP_0, k_{b1}, k_{b2}, k_{b3}, S_{IT}, S_{ID}, S_{IE}, k_a and k_e. This is represented in the in-silico simulator of [18] by sinusoidal oscillations superimposed on nominal values with 3 hour period and a randomly generated phase. The parameter values of 6 virtual patients were available for experiments.

Due to the *max{.}* and *min{.}* functions, switching must be introduced when designing a robust controller for [1]. The transfer related to glucose ingestion can be characterized as a bounded disturbance, which is convenient in case of robust controller design, and can be handled differently.

However, for the renal clearance $R(t)$ and endogenous glucose production $EGP(t)$ four different cases should be separated:

- There is endogenous glucose production, but no renal clearance: $x_3(t) < 1$, $Q_{1,min} \le Q_1(t) < R_{th}V_G$;
- No endogenous glucose production, but no renal clearance: $x_3(t) \ge 1$, $Q_{1,min} \le Q_1(t) < R_{th}V_G$;
- Renal clearance is acive, and there is endogenous glucose production: $x_3(t) < 1$, $Q_1(t) \ge R_{th}V_G$;
- Renal clearance is acive, but no endogenous glucose production: $x_3(t) \ge 1$, $Q_1(t) \ge R_{th}V_G$.

Moreover, in accordance with [19] further regions can be added based on $Q_1(t)$ or $C(t)$. For example the controller should be different when blood glucose levels are closer to hypoglycaemia.

III. LPV SYSTEM INVESTIGATION FOR CONTROLLER DESIGN

LPV methodology [20] represents a useful modeling tecnique for certain types of nonlinear systems. 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 vector of time-varying signals $\rho(t) = (\rho_1(t) \quad \cdots \quad \rho_m(t))^T$:

$$
\begin{aligned}
\dot{x}(t) &= A(\rho(t))x(t) + B(\rho(t))u(t)\\
y(t) &= C(\rho(t))x(t) + D(\rho(t))u(t)\\
A(\rho(t)) &= A_0 + \sum_{i=1}^{m} A_i\rho_i(t) \quad B(\rho(t)) = B_0 + \sum_{i=1}^{m} B_i\rho_i(t)\\
C(\rho(t)) &= C_0 + \sum_{i=1}^{m} C_i\rho_i(t) \quad D(\rho(t)) = D_0 + \sum_{i=1}^{m} D_i\rho_i(t)
\end{aligned}
\tag{3}
$$

If the elements of this vector are bounded $\rho_i(t) \in [\rho_{i,min}, \rho_{i,max}]$, $i = 1,\dots,m$, and their derivatives as well $\dot{\rho}_i(t) \in [\lambda_{i,min}, \lambda_{i,max}]$, $i = 1,\dots,m$, then stabilizing controller can be designed [16], [21-22]. However, in order to use an LPV controller the parameter $\rho(t)$ must be measured. If $\rho(t)$ is not available from measurements accurate estimation is needed, and the estimation error must be considered when designing the controller.

In case of model [1] the parameter vector $\rho(t)$ could be:

$$
\rho(t) = \begin{pmatrix} Q_1(t) \ or \ x_1(t) \\ \dfrac{F_{01}}{Q_1(t)+V_G} \\ Q_2(t) \ or \ x_2(t) \end{pmatrix}
\tag{4}
$$

There are two candidates for each of two parameter signals. Choosing each of them has its advantages and disadvantages in either case. The choice defines the dynamics of the model from control perspective. For example by regarding $Q_1(t)$ as part of $\rho(t)$ we extend our original model to one which can depend from any bounded $\rho(t)$, and $Q_1(t) = \rho(t)$ is only a special case. Considering that we can only estimate $\rho(t)$ this extension is necessary.

Let us focus on the state variables $Q_1(t)$ and $Q_2(t)$. [1] is basically a compartment model, relationship of these two compartments with each other and their environment is presented in Fig. 1.

In the first case (Fig. 1.1) when $x_1(t)$ and $x_2(t)$ are chosen as LPV parameters, the system is uncontrollable. Endogenous glucose production can only raise the blood glucose levels and every other process is not under our influence. On the other hand $x_1(t)$ and $x_2(t)$ can be estimated rather accurately, considering that no unknown disturbance is affecting the state variables of insulin transfer (if we assume that we can detect errors of the insulin pump); therefore only the inaccuracies of k_{b1}, k_{b2}, k_{b3}, S_{IT}, S_{ID}, S_{IE}, k_a and k_e must be considered. The same does not apply for the other two candidates, especially for $Q_2(t)$. Hence, this configuration can be effectively used for observer design.

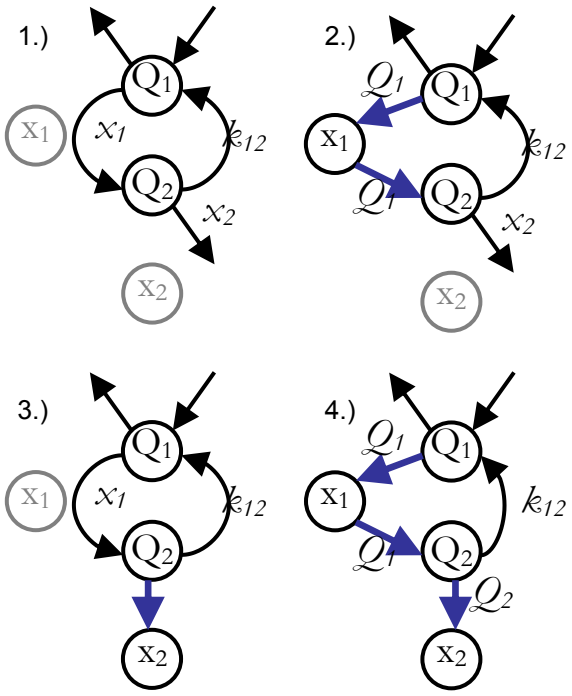

Figure 1. Relationship between $Q_1(t)$ and $Q_2(t)$ and their environment in case of model [1].

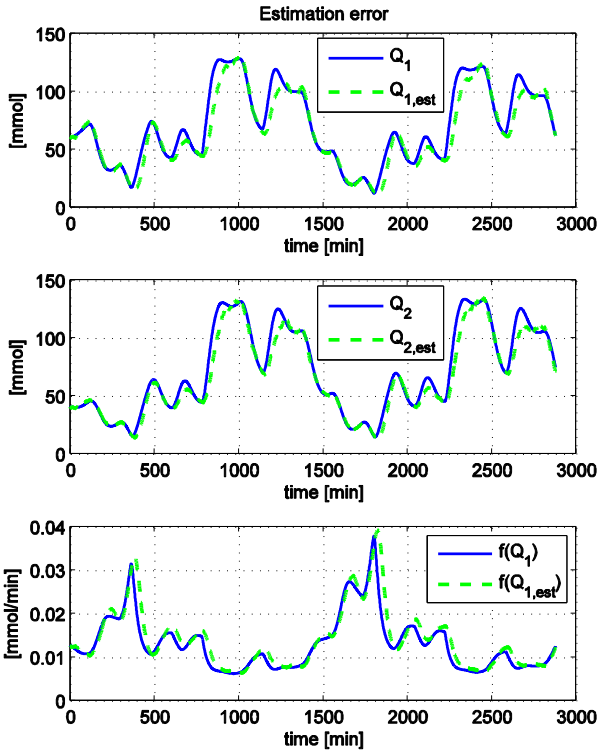

Figure 2. Switching LPV Kalman filter design for optimal estimation of LPV parameter candidates of model [1].

A switching LPV Kalman filter has been created to give an optimal estimation of all LPV parameter candidates for this case (Fig. 2). Note that no information regarding meal intake is considered to be available. In Fig. 1.1 the $f(Q_1(t))$ function stands for $F_{01}(Q_1(t)+V_G)^{-1}$. No parameter inaccuracy or unmodelled dynamics were considered, and as for LPV parameters the filter uses its own estimates. It can be observed that there is a lot of room for imporvement. The performance of the filter will be detailed later.

In the second case (Fig. 1.2) $Q_1(t)$ takes the role of LPV parameter instead of $x_1(t)$. The system can be controlled now, but technically speaking we can only adjust the transfer rate from $Q_1(t)$ to $Q_2(t)$. Hence, this situation is not yet applicable for control.

The third case (Fig. 1.3) however is more favorable. $Q_2(t)$ can be directly affected, however the transfer from $Q_1(t)$ to $Q_2(t)$ is not. If the estimation of $x_1(t)$ is more accurate than $Q_1(t)$ this choice can be more effective for controller design than the fourth situation (Fig. 1.4) in which we have the highest level of influence, but also the highest inaccuracy.

Once the LPV model has been chosen the effect of merely estimating the parameters must be investigated. Even with the most effective observers, the estimation error in the percentage of the signal can grow large when the values are small and rapidly changing (Fig. 3). To grasp the range of estimation errors 200 simulations were conducted for all virtual patients. These simulations covered 48 hours with meal intakes, physical activity and insulin shots of randomised timing and quantity. Table 1 summarizes the parameters.

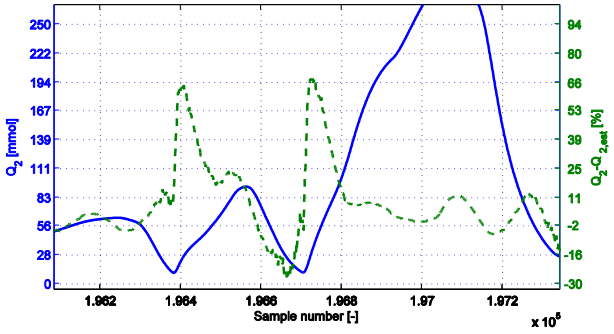

Figure 3. Estimation error and estimation error percentage.

TABLE I. SIMULATION PARAMETERS

Input type	Table Column Head		
	Chance of occurence	*Amount*	*Time*
Breakfast	100 %	50-90 g	6:00-10:00
Snack 1	50 %	10-50 g	8:00-11:00
Lunch	100 %	60-120 g	11:00-15:00
Snack 2	50 %	10-30 g	15:00-18:00
Dinner	100 %	35-95 g	18:00-22:00
Snack 3	50 %	10-20 g	22:00-24:00
Insulin	100% 3-9 / day	1-9 U	0:00-24:00

Furthermore there is 50% chance of physical activity starting between 9:00-12:00 for 1-4 hours. Uniform distribution was used in all cases. The insulin and meal inputs are independent so that hypo- and hyperglycamemic episodes would also appear.

Based on the results considering the deviation from the actual LPV parameters as purely additive or purely multiplicative error was proved to leave too much of a burden on the controller. For this reason, the following method was used:

- The real and estimated values of the LPV parameters were recorded and collected from the simulations;
- The mean of the absolute value of estimation error percentage was computed for all virtual patients. Upper bound of these values were chosen as multiplicative uncertainty;
- The remaining error outside these bounds were considered as additive disturbance. Once again, the upper bound was chosen of all available virtual patients;
- The multiplicative uncertainty values have been increased with 25% for further robustness.

Once the LPV model has been chosen we can move on to controller design. Since there are significant inaccuracies of both parameters and the estimated LPV parameter vector, robust control methodologies are favorable. Contollers based on the L_1, H_2 and H_∞ norm gained popularity over the last decade [14-17], [20-24]. Moreover, hybrid methods are also available [21].

IV. CONCLUSIONS

The LPV modeling of the widely used T1DM model [1] has been investigated from control design perspective. Different LPV models have been proposed with particular advantages and disadvantages for both controller and observer design. Previously, various controller structures (integral, two-degree of freedom) for linear H_∞ robust controller design have been investigated [17]. However, the linearity of the controller resulted in poor performance. A robust LPV controller could overcome those limitations. Furthermore, using Linear Matrix Inequalities (LMI) techniques, different norms (L_1, H_2, H_∞ and their combination) and additional constrains can be applied, such as defining stability regions for the closed loop system. Consequently, further research directions will be focused on implementing and comparing these controllers.

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