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Linear Parameter-Varying Control to Minimize Risks in Type 1 Diabetes

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Abstract: This work provides a time-varying controller to improve the glycemic regulation in Type 1 Diabetes Mellitus (T1DM) patients. To this end, a Linear Parameter-Varying (LPV) control is designed in order to minimize the risk of hypoglycemia (glucose concentrations $<$ 60 mg/dl) and hyperglycemia (glucose concentrations $>$ 180 mg/dl). The controllers have been tested in the 10 *in silico* adults from the distribution version of the UVA/Padova metabolic simulator (30 patients). All Continuous Glucose Monitoring (CGM) and Continuous Subcutaneous Insulin Infusion (CSII) pump constraints are considered during the simulations. Different meal scenarios have been tested showing very promising results.

Keywords: Type 1 diabetes, LPV control, insulin on board.

1. INTRODUCTION

Type 1 diabetes is a disease characterized by the absolute deficiency of endogenous insulin secretion. Cases of T1DM have been increasing 3-4% per year in youths making diabetes one of the most common childhood diseases (Kaufman [2012]). Without insulin, the body is not able to preserve normal glucose metabolism resulting in prolonged hyperglycemia. As a consequence, some symptoms like polyuria and polydipsia emerge. In absence of an appropriate treatment, the patient can develop a state of ketoacidosis which generates coma and finally death. Therefore, patients with T1DM are usually subjected to multiple daily insulin injections or CSII (Peters and Laffel [2013]). On the other hand, the excess of insulin may produce hypoglycemia which can also result in diabetic coma or death. Consequently, it is very important to reduce hyperglycemic and hypoglycemic risks keeping the Blood Glucose (BG) concentration between safe values.

In order to describe the glucose-insulin dynamics some models and simulators have been developed (see Bondía et al. [2010], Wilinska and Hovorka [2008] and Colmegna and Sánchez Peña [2014] for a survey). One of them is the UVa/Padova T1DM simulator. This simulator has a cohort of 300 *in silico* patients, and it is accepted by the Food and Drug Administration (FDA) in lieu of animal trials in the development of an artificial pancreas (Kovatchev et al. [2009]). In this work, its distribution version, which has 30 *in silico* patients, has been selected to perform the simulations.

Model uncertainty (intra- and inter-patient variability), nonlinear phenomena, and sensor and actuator delays are issues that should be attended at the controller design stage. Although, the T1DM simulator does not include the intra-patient variability, it solves the inter-patient variability through a large cohort of *in silico* patients. In addition, it includes all other constraints related to the CGM and CSII pump.

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Based on the later, nonlinear and/or time-varying controllers seem to be a more suitable option than Linear Time Invariant (LTI) ones. Despite of that, simplified PID (Steil et al. [2006]) and Robust Control Theory (Ruiz-Velázquez et al. [2004], Parker et al. [2000] and Colmegna and Sánchez Peña [2012]) have been applied to this problem providing acceptable performance. As regards more sophisticated techniques, nonlinear control design methods have been implemented (Kovács et al. [2008]), but with no clear robustness guarantees. LPV solutions have also been tested, although in simplified models (Sánchez Peña and Ghersin [2010], Sánchez Peña et al. [2011] and Kovács et al. [2011]).

The objective of this work is to design an LPV controller to manage unannounced meals without excess insulin overdosing. Different scenarios are tested considering the 10 adults from the distribution version of the T1DM simulator to analyse the closed-loop performance.

The paper is organized as follows. A general model structure appropriate for control purposes is presented in Section 2. The controller design is performed in Section 3 and simulation results are depicted in Section 4. Final conclusions are introduced in Section 5.

2. MODEL IDENTIFICATION & PATIENT TUNING

From previous results in this area it is clear that the inter-patient uncertainty is large, even for a single class of patients, e.g. adults. This induces the use of an adaptive scheme and/or a patient model tuning, previous to the controller design (Colmegna and Sánchez Peña [2013]). To avoid a preliminary identification test on the patient in order to tune the model, a methodology similar to the one used in van Heusden et al. [2012] is applied. Therefore, a control-relevant model is adjusted without performing an identification, based solely on the *a priori* patient data. The procedure is described next.

For every adult from the reduced T1DM simulator, a linear model from the insulin delivery (pmol/min) to the deviation

from a particular glucose concentration (mg/dl) is identified. Three different interstitial glucose concentrations [3] are considered here: 90, 120 and 150 mg/dl, hence three linear models are obtained for each patient.

The identification process for a particular glucose concentration is as follows. First, the basal insulin (I_b) which produces the particular glucose concentration at steady state is obtained. Then, I_b is added to a sinusoidal insulin sweep. During 12 h and with a sampling time of $T_s = 10$ min, this signal is infused through a CSII pump, and the glucose deviation is captured.

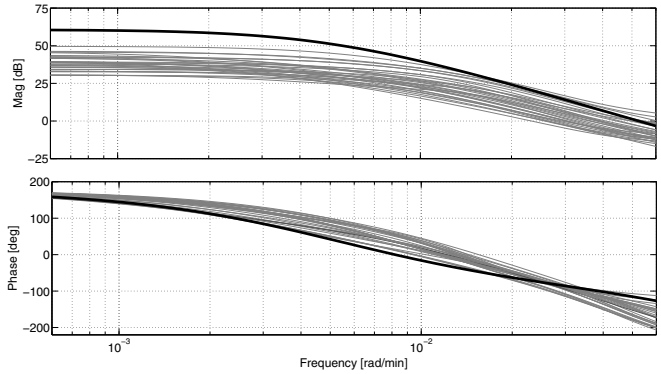

Fig. 1. Bode diagram of $G_0(z)$ and the 10 virtual adult patients at three different glucose levels (thin lines).

Third-order models have been obtained in all 30 cases using subspace identification algorithms (Overschee and Moor [1994], Cescon et al. [2009]). Considering these models, the following discrete transfer function is defined:

$$G_0(z) = -\frac{132 \times 10^{-3} z^{-3}}{(1 - z^{-1}p_1)(1 - z^{-1}p_2)(1 - z^{-1}p_3)} \tag{1}$$

where the poles are: $p_1 = 0.965$, $p_2 = 0.95$ and $p_3 = 0.93$. The Bode diagrams of $G_0(z)$ and all identified models are depicted in Fig. 1. As can be seen from this figure, $G_0(z)$ is conservative in gain and phase to cover all possible cases. In order to limit this conservatism, $G_{0p}(z)$ is defined:

$$G_{0p}(z) = -\frac{cK_i z^{-3}}{(1 - z^{-1}p_1)(1 - z^{-1}p_2)(1 - z^{-1}p_3)}. \tag{2}$$

Here as in van Heusden et al. [2012], $K_i = 1800/\text{TDI}$ is based on the *1800 rule* (see Walsh and Roberts [2006]) and represents the gain which adapts to the patient's Total Daily Insulin (TDI), and

$$c = \frac{1}{100}(1 - p_3)(1 - p_2)(1 - p_1)60T_s \tag{3}$$

is a constant which scales units.

3. CONTROLLER DESIGN

$G_{0p}(z)$ is converted to $G_{0p}(s)$ using a Zero Order Hold (ZOH), because the design is performed in continuous time. Figure 2 depicts the augmented model for controller design, where:

$$P(s) = \begin{bmatrix} 0 & 1 \\ 1 & -G_{0p}(s) \\ 1 & -G_{0p}(s) \end{bmatrix} \tag{4}$$

[3] The simulator has access to that particular variable without the CGM measurement noise.

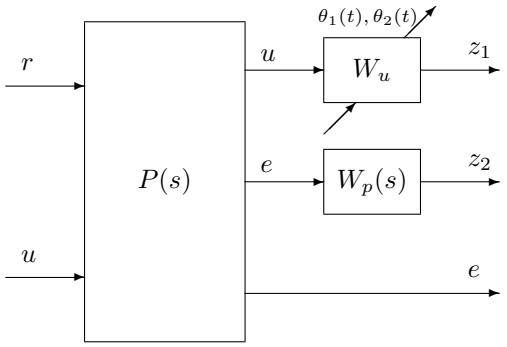

Fig. 2. Augmented model for controller design.

and the performance and actuator weights in order to design the LPV controller are:

$$W_p(s) = \frac{sT_1 + 1}{sT_2 + A}, \tag{5}$$

$$W_u \equiv \left[\begin{array}{c|c} -\frac{1}{R_2} & \frac{\sqrt{2R_1}}{2R_2} \\ \hline -\frac{\sqrt{2R_1}}{2R_2}\left[\theta_1(t) + \theta_2(t)\right] & \frac{R_1}{2R_2}\left[\theta_1(t) + \theta_2(t)\right] \end{array}\right] \triangleq \left[\begin{array}{c|c} A_u & B_u \\ \hline C_u(t) & D_u(t) \end{array}\right] \tag{6}$$

with $T_1 = 10^3/6$, $T_2 = 10^5/7$, $R_1 = 2$, and $R_2 = 10^4/9$ in all cases.

Two real-time measurable (and estimated) parameters have been included in the augmented model in order to adapt the controller during closed-loop implementation. Note that due to this LPV nature, the weight W_u is presented in a state-space fashion. The time varying parameters are $\theta_1 = 110/G_s$ and $\theta_2 = 1.5I_{pe}/I_{pb}$. The first one depends on the glucose level G_s measured by the CGM. The second parameter depends on (I_{pe}, l_{pb}), which are the estimated current and basal plasma insulin levels, respectively. The estimation is performed through the model proposed in Man et al. [2007] considering its mean population values. In the case of I_{pe}, the input to the model is the current injected insulin, and in the case of I_{pb}, the basal insulin dosage. The latter is performed off-line, before the simulation.

The parameters (θ_1, θ_2) may move in the rectangular set $[0.2, 5] \times [0, 8]$ according to the expected values of G_s and I_{pe}. The time-varying model is used to replace the hypoglycemia Safety Mechanism (SM) and the Insulin on Board (IOB) feedback loop, which appear for example in Herrero et al. [2012]. In particular an increase in θ_1 due to a low glucose level will reduce the insulin injection thus minimizing the risk of hypoglycemia. In addition, an increase in θ_2 due to a high level of IOB also reduces the controller action in a way similar to the IOB feedback loop.

Therefore, there are two important aspects of this augmented model:

- The LTI part of the model $G_{0p}(z)$, can be tuned *off-line* to a particular patient using *a priori* history data based on his clinical history. This takes care of the inter-patient variability and replaces an initial patient-model tuning.
- The LPV part can be tuned *on-line* by direct measurement and estimation of two parameters $[\theta_1(t), \theta_2(t)]$ in order

to replace the hypoglycemia safety mechanism and the Insulin On Board (IOB) feedback loop.

Finally, to solve numerical issues in the implementation and/or simulation, the following Linear Matrix Inequality (LMI) region is adopted so that the (continuous time) poles are constrained to a particular zone of the complex plane:

$$\mathcal{D} = \{p \,\epsilon\, \mathbb{C} : \quad f_{\mathcal{D}}(p) < 0\} \tag{7}$$

with

$$f_{\mathcal{D}}(p) = \begin{bmatrix} 0 & 0 \\ 0 & -\dfrac{2\pi}{100} \end{bmatrix} + p \begin{bmatrix} 1 & 0 \\ 0 & -1 \end{bmatrix} + \overline{p} \begin{bmatrix} 1 & 0 \\ 0 & -1 \end{bmatrix}. \tag{8}$$

This corresponds to the closed loop poles located in the complex region $-2\pi/100 < p < 0$, i.e. ten times slower than the sampling time T_s. Before implementation, the vertex controllers are discretized and transformed to an LPV affine model structure.

4. RESULTS

Two different protocols have been proposed to analyse the closed loop performance.

Protocol #1:

- **1st day:** 50 g of CHO is given at 7 AM and 50 g at 8 PM.
- **2nd day:** 60 g of CHO is given at 2 PM and 40 g at 9 PM.
- **3rd day:** 40 g of CHO is given at 7 AM, 50 g at 2 PM and 50 g at 8 PM.

Protocol #2:

- **1st day:** 50 g of CHO is given at 7 AM, 70 g at 2 PM and 60 g at 8 PM.
- **2nd day:** 50 g of CHO is given at 6 AM, 60 g at 1 PM and 65 g at 7 PM.
- **3rd day:** 40 g of CHO is given at 7 AM, 70 g at 1 PM and 50 g at 9 PM.

Both protocols consider

- an initial glucose concentration of 90 mg/dl;
- unannounced meals of 15 minute duration;
- a setpoint of 110 mg/dl;
- all CSII pump and CGM constraints;
- the 10 adults of the reduced T1DM simulator.

In addition, each protocol is run three times for each subject in order to test the repeatability of the results.

Protocol #1 is used to evaluate the safety of the algorithm when long fasting periods appear. The closed loop response for adult #2 is presented in Fig. 3, and average, minimum and maximum responses for the 10 adults to protocol #1, in Fig. 4. As shown in Fig. 4, insulin peaks occur at meal times such as in an optimal bolus treatment. The Control Variability Grid Analysis (CVGA), which is presented in Magni et al. [2008] and depicted in Fig. 5, shows the 95% confidence bounds of the maximal and minimal blood glucose values for the 30 closed loop responses. Average results are presented in Table 1. Due to the limited closed loop bandwidth and the initial absence of insulin, larger glucose peaks appear during the first day. Therefore, both CVGA and average results are performed considering the data from the 2nd day.

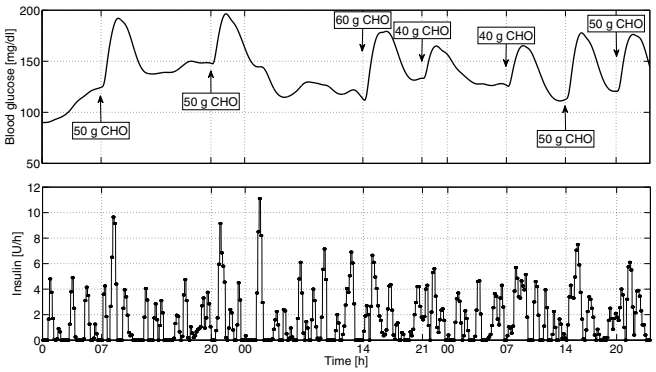

Fig. 3. Closed loop response for adult #002 to protocol #1.

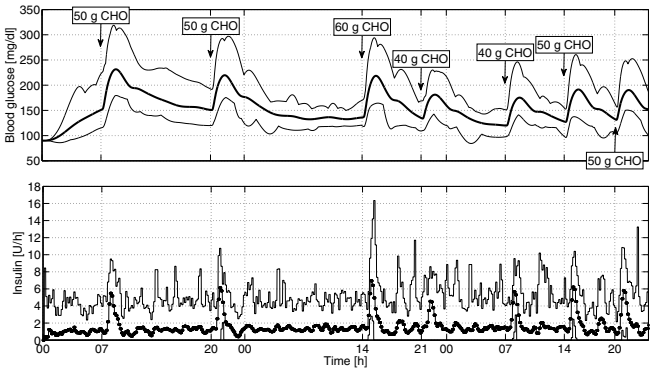

Fig. 4. Average closed loop response for the 10 *in silico* adults to protocol #1. The minimum and maximum values at each time are represented by the thin lines.

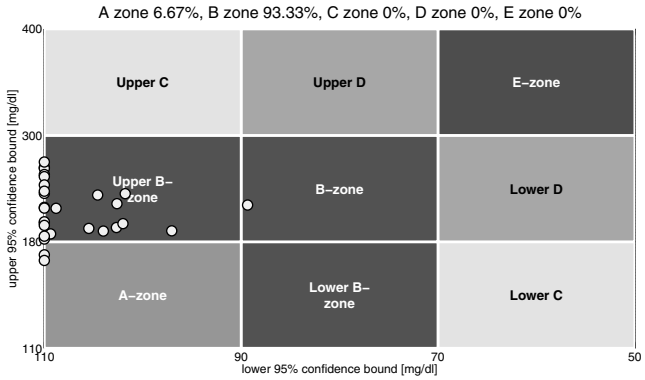

Fig. 5. CVGA of the 30 closed loop responses to protocol #1.

The closed loop response for adult #2 to protocol #2 is depicted in Fig. 6. Average, minimum and maximum responses for the 10 adults to protocol #2, and the corresponding CVGA are presented in Fig. 7 and 8, respectively.

The time variation of (θ_1, θ_2) is illustrated in Fig. 9. Note that these parameters evolve in regions that avoid dangerous scenarios. For example, situations where (θ_1, θ_2) are both low or both high do not occur. This means that when the BG level decreases or increases, so does the plasma insulin level. As a consequence, unsafe conditions like low BG and high plasma insulin levels or *vice versa* are avoided with this approach. Also it should be mentioned that for the design stage, both parameters are included in a rectangular region, which according to this figure is not fully covered by the actual time-varying

Mean BG [mg/dl]	Max BG [mg/dl]	Min BG [mg/dl]
151.92 ± 21.79	223.47 ± 32.23	109.0 ± 10.14
% **of time in [80 140]**	% **of time in [70 180]**	$\#$ **< 70**
40.15 ± 12.92	84.62 ± 10.59	0
TDI [U]	**LBGI**	**HBGI**
26.97 ± 4.26	~ 0	3.95 ± 1.61

Table 1. Average results for the 10 adults to protocol #1. Standard deviations are given in parentheses.

parameters. Nevertheless, this conservative choice is necessary in order to have stability and performance guarantees if this is not the case.

Despite protocol #2 contains larger meals than protocol #1, the results presented in Table 2 are similar to the ones given in Table 1. In both protocols, no hypoglycemia occurs for any patient, and a low hyperglycemic risk is obtained (see Clarke and Kovatchev [2009] for a survey about tools to analyse glucose data). Results are comparable to the ones obtained in Colmegna and Sánchez Peña [2013], where a protocol similar to protocol #2 is applied with an $\mathcal{H}_\infty$ controller closing the loop. However, here the controller design is the same for every patient, while in Colmegna and Sánchez Peña [2013] it is adapted for each one. In order to compare with other control techniques, it is worth mentioning that in van Heusden et al. [2012] a Model Predictive Control (MPC) is applied with similar results, but considering the complete version of the T1DM simulator that contains 100 adults.

The authors and members of the Doyle's group at the University of California, Santa Barbara (UCSB) have also some ongoing research using $\mathcal{H}_\infty$ control combined with an IOB feedback loop and a hypoglycemia SM, which in turn has been compared with an Optimal Bolus Treatment (OBT). The LPV controller presented here provides similar results, with the advantage of a simpler design procedure.

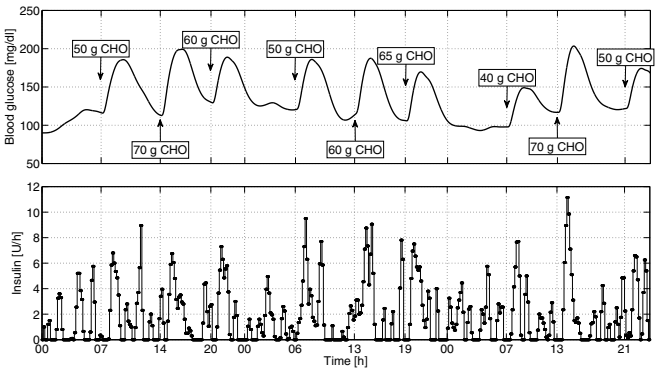

Fig. 6. Closed loop response for adult #002 to protocol #2.

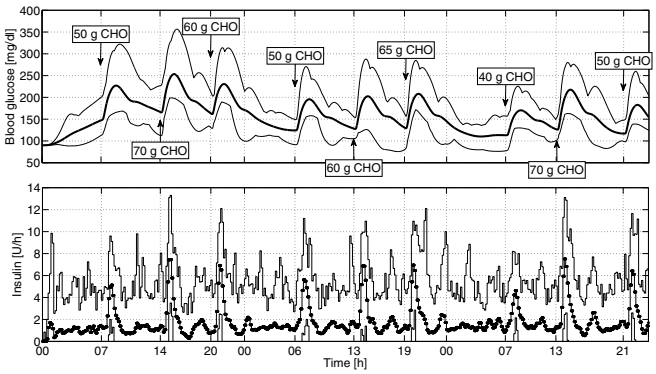

Fig. 7. Average closed loop response for the 10 *in silico* adults to protocol #2. The minimum and maximum values at each time are represented by the thin lines.

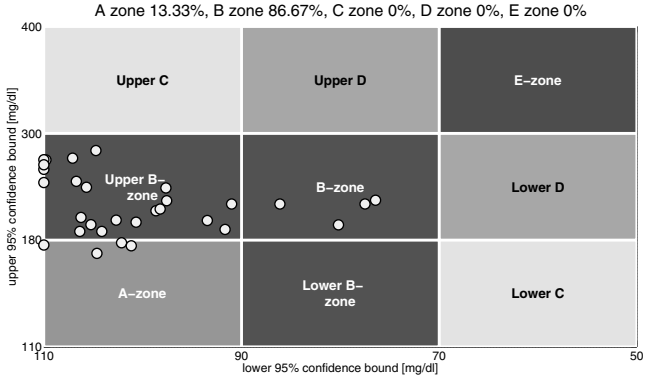

Fig. 8. CVGA of the 30 closed loop responses to protocol #2.

Mean BG [mg/dl]	Max BG [mg/dl]	Min BG [mg/dl]
151.31 ± 27.28	225.12 ± 34.02	98.48 ± 10.92
% **of time in [80 140]**	% **of time in [70 180]**	$\#$ **< 70**
42.70 ± 10.56	80.74 ± 12.02	0
TDI [U]	**LBGI**	**HBGI**
29.61 ± 4.94	~ 0	4.30 ± 1.66

Table 2. Average results for the 10 adults to protocol #2. Standard deviations are given in parentheses.

5. CONCLUSIONS

Here, an LPV control procedure has been applied to the BG regulation in T1DM *in silico* adult patients. The advantage of this controller is that it has proven stability and robustness guarantees based on Lyapunov theory. It has an *on-line* tuning which takes care of inter-patient variability, and hypoglycemic and hyperglycemic situations, thus resulting in an elegant and efficient way of minimizing patient's risks.

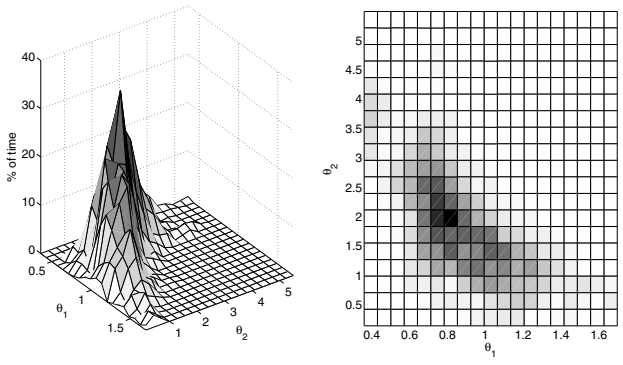

Fig. 9. Variation of parameters to protocol #2.

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