Control-Oriented Linear Parameter-Varying Model for Glucose Control in Type 1 Diabetes

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***Abstract*— The contribution of this paper is a controller-design oriented model of insulin-glucose dynamics in Type 1 Diabetes Mellitus (T1DM). The novelty of the proposed model is to more effectively include the time-varying nature, and also the inter-patient variability, associated with the glucose-control problem. Importantly, this is achieved in a manner that straightforwardly facilitates well-known and standard controller synthesis procedures. In that way, an average Linear Parameter-Varying (LPV) model that captures the dynamics from the insulin delivery input to the subcutaneous-glucose concentration output is constructed based on the Universities of Virginia (UVA)/Padova metabolic simulator. In addition, a system-oriented reinterpretation of the classical ad-hoc 1800 rule is applied to adapt the model's gain.**

In order to quantify the effectiveness of this approach, the ν-gap between this new modeling strategy and the UVA/Padova model is computed at different glucose levels, together with the Root Mean Square Error (RMSE) between the glucose deviation predicted by both models. For comparison purposes, both open-(RMSE) and closed-loop (ν-gap metric) metrics are also determined for other control-oriented models previously presented.

From the results, it could be concluded that the proposed model is more suitable for controller design than the other control-relevant models, due to the fact that it provides a better fit and a smaller distance to the UVA/Padova model in a closed-loop setting. Furthermore, it would allow one to obtain a LPV controller for both postprandial and overnight control in a straightforward way, considering its affine dependence on the glucose level, which is measured in real-time.

***Index Terms*— Artificial pancreas, insulin-glucose dynamics, control-oriented model, ν-gap metric.**

I. Introduction

An Artificial Pancreas (AP) is a system that automatically controls glycemia in Type 1 Diabetes Mellitus (T1DM) patients by infusing an adequate amount of insulin, according to the measured glucose level. The decision of how much insulin to infuse is made by a control algorithm. In general, this algorithm is based on a mathematical model that is required to suitably describe the insulin-glucose dynamics. Thus, the model constitutes a key element in the development of a reliable AP.

Several simulation models have been proposed since the late 1970s [1]–[4]. They have been used to perform a vast amount of *in-silico* studies, giving an affordable and safe means of testing glucose controllers. Thus, the use of computer simulation has accelerated the development of AP [5].

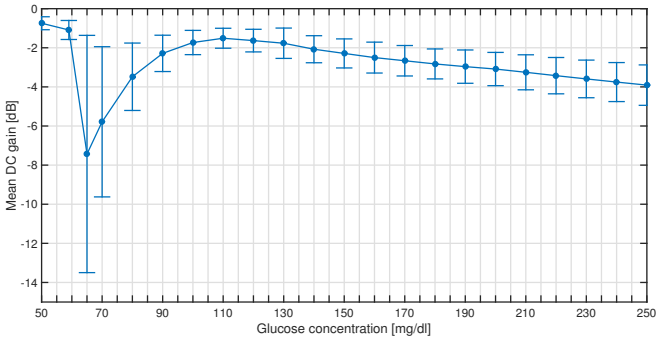

Fig. 1. Mean DC gain for the adult patients of the distribution version of the UVA/Padova simulator, linearized at different glucose concentrations. The mean $\pm$ 1 STD values are represented by vertical bars.

The main goal of simulation models is to provide a blood glucose prediction as close as possible to a real situation. However, this class of models is not generally used for controller synthesis, due to its mathematical complexity. Therefore, simplifications of these models are generally considered at the controller design phase, because most of the well established theory of control law design accommodates only simpler models that are normally referred to as control-oriented models. Thus, although control-oriented models have to represent the underlying dynamics, they are mainly obtained for synthesis purposes and have a much simpler mathematical formulation.

Another aspect that is worth considering in designing glucose controllers is that most metabolic parameters related to the insulin-glucose system are not easily identifiable in practice. Therefore, some tuning based on only a small number of easily obtainable patient-specific characteristics is recommended for a safe and effective AP [6]. Consequently, a few works have been focused on such personalization [7]–[11].

One interesting approach to obtain a personalized control-oriented model is to adapt a low-order model structure based on *a priori* patient information. For example, given the patient's Total Daily Insulin (TDI), an insulin sensitivity factor can be obtained using the 1800 rule (1800/TDI) [12]. From the medical point of view, the 1800 rule indicates the maximum drop in glucose concentration, measured in mg/dl, after a 1 U injection of rapid-acting insulin. Since the work in [13], that rule has been used in several studies, both clinical and *in-silico*, to tune the gain of a Linear

P. Colmegna and R. S. Sánchez-Peña were supported by CONICET and by Nuria (Argentina) and Cellex (Spain) Foundations.

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Time Invariant (LTI) model to a particular patient [14]–[18]. Nevertheless, the 1800 rule is an empirical rule, and it is not indicated at which glucose concentration it works best, or is most appropriate. This is important because, as illustrated in Fig. 1, a patient's insulin sensitivity depends, amongst other factors (see [19], [20]), on the glucose concentration, meaning that a LTI representation of the insulin-glucose system is not enough to totally describe it.

Multiple Linear Parameter-Varying (LPV) models have been proposed in the past [21]–[26]. In [21] and [22], the Bergman minimal model [1] was considered and transformed into a quasi-LPV model by an appropriate choice of parameters. In [23]–[25], the Sorensen compartmental model [2] was linearized at different points, which were defined as the vertexes of an affine-LPV model that covers the original nonlinear one. This model was used as an uncertainty LTI model set, and an $\mathcal{H}_\infty$ controller was designed to control it, hence, the time-varying characteristics were not exploited. Finally, in [26], an LPV approach using the Cambridge model [4] was developed.

In this work, the discussion presented in [27] is considered and adapted to the AP application. There, it is explained that the use of complex models for synthesis is not necessarily related to better closed-loop performance. In that sense, a simple third-order LPV model from the insulin delivery input to the deviation from the glucose concentration output is proposed here, and personalized by a system-oriented reinterpretation of the 1800 rule. Thus, a combination of the model personalization using *a priori* patient-specific characteristics with the time-varying description of the dynamics by means of a LPV system representation, is achieved. Due to the fact that this modeling strategy is intended for controller design, the ν-gap metric δ_ν (see [28], [29]) is employed to quantify the quality of achievable closed-loop performance afforded by the control-oriented model. Model identification and tuning are performed using the distribution version of the UVA/Padova metabolic simulator [30], [31].

The paper is organized as follows. In Section II, we describe the procedure to obtain the personalized LPV model. In Section III, we present open- and closed-loop indexes to quantify the effectiveness of this approach, including comparisons with other control-oriented models presented in previous works. Finally, conclusions are drawn in Section IV.

II. Methods

In order to quantitatively estimate subjects' insulin sensitivity, a 1 U insulin bolus was applied to each *in-silico* adult of the distribution version of the UVA/Padova simulator at a large number of different steady-state glucose concentrations (operation conditions), and the maximum glucose decrease was captured in each case. The distribution version of the simulator has 11 adults (one, Adult #11, is an average patient). Because Adult #007 from the database has an insulin sensitivity that is not coherent with its TDI, it has been excluded, leaving 10 subjects for the following analysis. In Fig. 2, the glucose drop for each patient, and the mean values excluding Adult #007, are plotted along with the

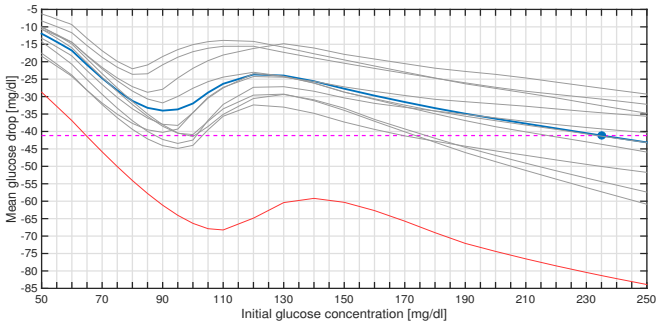

Fig. 2. Glucose drop for each *in-silico* adult (gray lines: Study patients, red line: Adult #007) and the mean values excluding Adult #007 (blue line) at different operation conditions after a 1 U insulin bolus. The magenta dashed line indicates the average value of the 1800 rule.

average value of the 1800 rule. As shown in that figure, Adult #007 is the patient most sensitive to insulin, despite having a TDI of 43 U, which is close to the mean TDI dose of around 46 U. It is worth mentioning that the Correction Factor (CF) implemented in the simulator follows the 1800 rule, even though it is stated (seemingly erroneously) in [31] that the simulator's CF is characterized according to 1700/TDI.

A. Average Model

As shown in Fig. 2, the 1800 rule is only rendered correct at 235 mg/dl. Hence, for each adult of the T1DM simulator, a linearized model from the insulin delivery (pmol/min) to the subcutaneous-glucose concentration deviation (mg/dl) is calculated at this operation condition. Subsequently one LTI model, based on the mean of the frequency responses of each subject's frequency response, is identified. In order to obtain a simple low-order system, a grey-box identification method was performed with the following model structure:

$$G(s) = k\frac{s+z}{(s+p_1)(s+p_2)(s+p_3)}\mathrm{e}^{-15s}. \tag{1}$$

The identified parameters are $k = -1.6788 \times 10^{-5}$, $z = 0.1501$, $p_1 = 0.0035$, $p_2 = 0.0138$, and $p_3 = 0.0143$, achieving a 98.58% fitting. Note that the structure for model (1) is similar to the structure of previous control-oriented models [13], [14], [17]. The reason is that a more effective model for controller design is sought, but without increasing its order. In Fig. 3, the Nyquist plots of both the average frequency response and the identified model are depicted.

The bandwidth (BW) of a system is commonly defined as the first frequency satisfying -3dB from DC gain. Here, we use that definition to represent the insulin sensitivity variation detected in Figs. 1 and 2, by making the BW of the proposed model (1) vary with subcutaneous-glucose concentration g [mg/dl] appropriately. In this way, the average BW variation of the linearized models at different glucose values was obtained, and fitted with a 88.08% accuracy by the following continuous, piecewise polynomial function:

$$\overline{\mathrm{BW}}(g) = a_i g^3 + b_i g^2 + c_i g + d_i \tag{2}$$

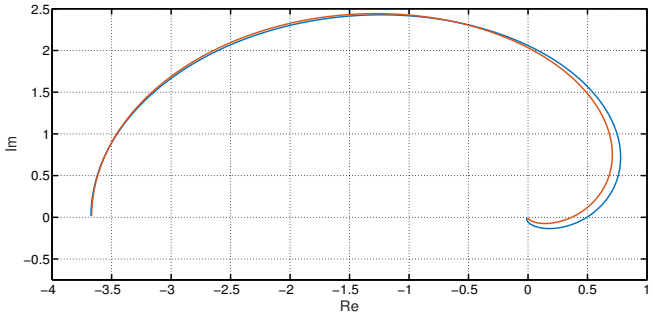

Fig. 3. Nyquist plots of the mean frequency response of the linearized models (light-blue) and the identified LTI model (orange).

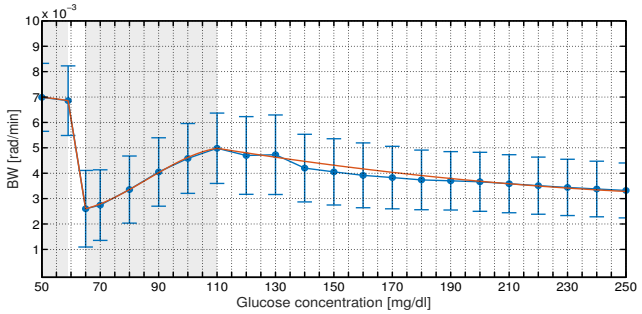

Fig. 4. Piecewise polynomial function $\overline{\text{BW}}(g)$ (orange line), and average variation of the BW for the *in-silico* adults linearized at different glucose values (light-blue line). Vertical lines represent the average BW $\pm$ 1 STD.

where:

$$i = \begin{cases} 1 & \text{if } 110 \text{ mg/dl} \leq g \\ 2 & \text{if } 65 \text{ mg/dl} \leq g < 110 \text{ mg/dl} \\ 3 & \text{if } 59 \text{ mg/dl} \leq g < 65 \text{ mg/dl} \\ 4 & \text{if } g < 59 \text{ mg/dl.} \end{cases} \tag{3}$$

In this way, data is adjusted with good accuracy without the use of a high-order function. Results are illustrated in Fig. 4, and parameter values are given in Table I.

According to Fig. 4, the average BW has a similar shape to the average DC gain depicted in Fig. 1. For example, in the region where the absolute value of the gain is larger (between 65 and 80 mg/dl), the BW is lower. Observe that, as shown in Figs. 1 and 4, there is an abrupt change at 60 mg/dl. The explanation for that can be found in [31], where the increase in insulin action when the glucose decreases below a certain value is modeled by including a blood glucose risk function in the insulin-dependent utilization description. The risk function is defined so as to increase when glucose concentration decreases below its basal value (around 120 mg/dl), and to saturate at a hypoglycemic threshold $G_{\text{th}} = 60$ mg/dl.

For a fixed value of p_1, the DC gain of model (1) is $\frac{kz}{p_1 p_2 p_3}$. Therefore, if we assume the simplification that all parameters from the model are invariant, except for parameter p_1, a decrease in the model's BW is associated with a decrease in the value of p_1, and as a consequence, an increase in the absolute value of the model's static gain.

The next step is to characterize the dependence of parameter p_1 on glucose g in order to make the BW of model (1) coincide with the piecewise function $\overline{\text{BW}}(g)$ for any given value of g. To this end, for a glucose concentration g^*, a desired BW w^* is defined as $\overline{\text{BW}}(g^*)$. Then, parameter

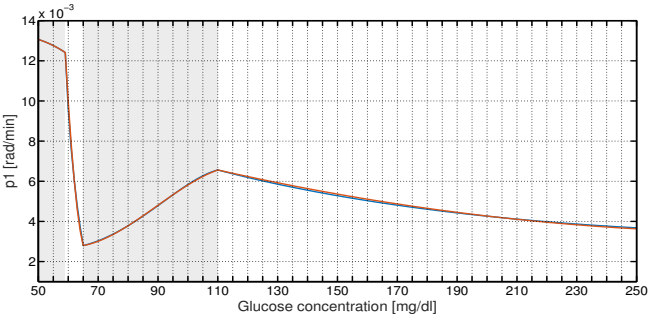

Fig. 5. Parameter p_1 computed at different values of glucose concentration g (light-blue), and piecewise polynomial function $p_1(g)$ (orange).

p_1 is computed so that:

$$\frac{\left|\frac{jw^*}{z}+1\right|}{\left|\frac{jw^*}{p_1}+1\right|\left|\frac{jw^*}{p_2}+1\right|\left|\frac{jw^*}{p_3}+1\right|} = 10^{-3/20}. \tag{4}$$

Note that $10^{-3/20}$ is equivalent to -3 dB expressed in magnitude units. Parameter p_1 was calculated by repeating this procedure for multiple values of g, and then fitting with a 97.24% accuracy by the following function:

$$p_1(g) = q_i g^3 + r_i g^2 + s_i g + t_i \tag{5}$$

with i defined as in (3). Results are illustrated in Fig. 5, and parameter values are given in Table II.

Finally, an average LPV model with the following state-space representation can be obtained by including the glucose-varying parameter $p_1(g)$ into the model structure (1):

$$\begin{aligned} \dot{x}(t) &= A(p_1)x(t) + Bu_\Delta(t) \\ y_\Delta(t) &= Cx(t) \end{aligned} \tag{6}$$

TABLE I

PARAMETER VALUES OF $\overline{\text{BW}}(g)$ OF (2).

i	a_i	b_i	c_i	d_i
1	0	4.5505×10^{-8}	-2.8536×10^{-5}	7.5712×10^{-3}
2	-2.8294×10^{-8}	7.3020×10^{-6}	-5.6072×10^{-4}	1.5967×10^{-2}
3	0	0	-7.0925×10^{-4}	4.8702×10^{-2}
4	0	-6.4804×10^{-7}	5.6075×10^{-5}	5.8039×10^{-3}

TABLE II

PARAMETER VALUES OF $p_1(g)$ OF (5).

i	q_i	r_i	s_i	t_i
1	0	9.0580×10^{-8}	-5.3562×10^{-5}	1.1357×10^{-2}
2	-4.2382×10^{-8}	1.1402×10^{-5}	-9.1676×10^{-4}	2.5849×10^{-2}
3	0	1.7321×10^{-4}	-2.3080×10^{-2}	7.7121×10^{-1}
4	0	-2.9126×10^{-6}	2.4514×10^{-4}	8.0865×10^{-3}

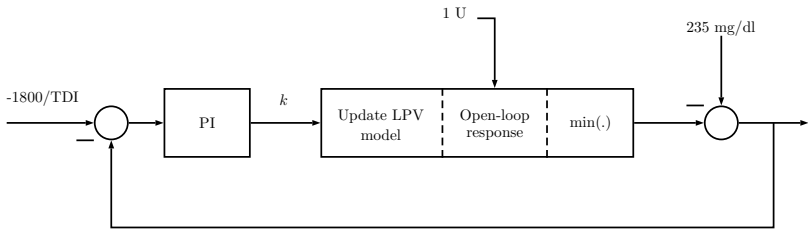

Fig. 6. Control loop to update gain k.

with

$$A(p_1) = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & -p_2p_3 & -(p_2+p_3) \end{bmatrix} + p_1 \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ -p_2p_3 & -(p_2+p_3) & -1 \end{bmatrix} \quad (7)$$

$$B = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}^T, \quad C = k \begin{bmatrix} z & 1 & 0 \end{bmatrix},$$

and with $u_\Delta(t) = u(t) - u_{\text{op}}$, and $y_\Delta(t) = y(t) - y_{\text{op}}$ being, respectively, the difference between the insulin delivery input $u(t)$ and the glucose deviation output $y(t)$ from the operation point $\{u_{\text{op}}, y_{\text{op}}\}$. Note that model (6) is affine in the parameter $p_1(g)$, and that a delay of 15 min should be added to the output (see (1)). In addition, it is worth mentioning that if $p_1(g)$ is evaluated at $g = 235$ mg/dl, it produces a result (0.0038) that is slightly different from the value previously obtained with the grey-box identification method (0.0035). Thus, in order to maintain coherence with the static gain of the LTI model previously identified, the static gain of the LTI model resulting from holding parameter p_1 fixed at 0.0038 is consistently adjusted by modifying the value of parameter k from -1.6788×10^{-5} to -1.8244×10^{-5}.

B. Model Tuning

As mentioned before, the interpatient variability should be considered in modeling the insulin-glucose dynamics, and in consequence, the model should be tuned to each patient. To this end, the following procedure is carried out. For each *in-silico* Adult #j, its TDI is selected from the UVA/Padova simulator database, and defined as TDI$_j$. Then, the 1800 rule, i.e., 1800/TDI$_j$, indicates the maximum glucose drop to be reached by the personalized LPV model when it is excited with a 1 U insulin bolus, starting from a glucose concentration g of 235 mg/dl. Finally, the tuning

TABLE III

PERSONALIZED GAIN k FOR EACH IN-SILICO ADULT.

Adult #j	$k \times 10^5$	Adult #j	$k \times 10^5$
001	-1.7888	006	-1.0343
002	-1.7451	008	-1.4379
003	-1.4343	009	-2.2024
004	-2.1396	010	-1.5919
005	-1.8650	011	-1.8864

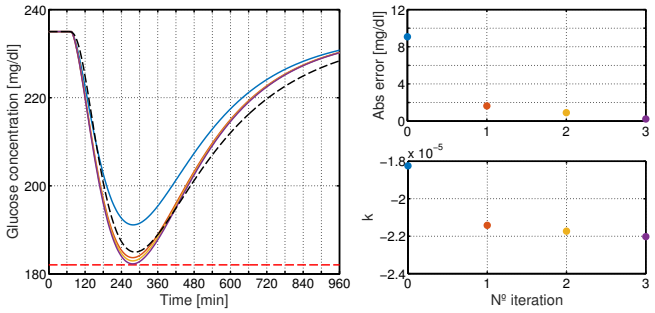

Fig. 7. Tuning procedure of parameter k for Adult #009. Left: Average model (light-blue line); nonlinear model (black dashed line); set-point based on the 1800 rule (red dashed line). Right-top: Absolute error between desired and actual glucose. Right-bottom: Evolution of parameter k.

method consists in computing a suitable gain k that makes the model achieve that condition.

An intuitive and simple way to approach this problem is by means of a control loop, like the one depicted in Fig. 6, where a discrete Proportional-Integral (PI) controller with transfer-function $3.5 \times 10^{-7}\left(1 + \frac{1}{z-1}\right)$ is used to adjust the value of k. An analytical procedure could also be used for this same purpose, but has not been explored here. In summary, the average LPV model at 235 mg/dl is excited with a 1 U insulin bolus and the minimum of its response is computed. Then, the operation point $g = 235$ mg/dl is subtracted from that value, and the result is compared with the glucose drop indicated by the 1800 rule for that particular patient. The PI controller increments (less sensitive model) or decrements (more sensitive model) the value of parameter k until the relative error between the set-point (1800/TDI$_j$) and the closed-loop output (glucose drop) is within the predefined threshold of 5×10^{-3}. As an example, the process to obtain k for Adult #009 is illustrated in Fig. 7. Finally, the personalized values of gain k for all *in-silico* adults are presented in Table III.

III. Results

A. Open-loop comparison

For each of the 10 virtual adult patients of the distribution version of the UVA/Padova simulator (see Section II), a 1 U insulin bolus was applied at different operation conditions to test (i) the personalized LPV model. A comparison with, (ii) the average LTI model in (1), and (iii) the model presented in [13], as well as (iv) and (v), the extensions described in [14] and [17], respectively, are considered. As an example, in

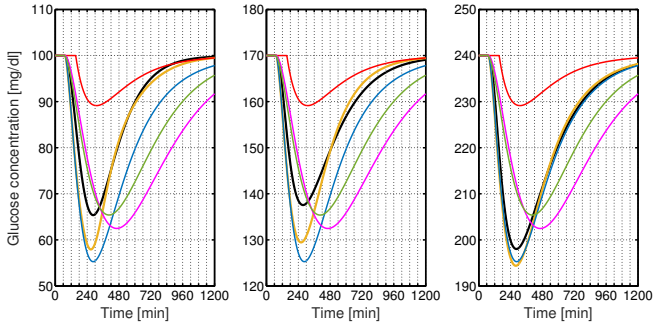

Fig. 8. Response to a 1 U insulin bolus starting from 100, 170 and 240 mg/dl for Adult #011, considering models (i) (orange), (ii) (light-blue), (iii) (green), (iv) (red), (v) (magenta), and the UVA/Padova nonlinear model (black line).

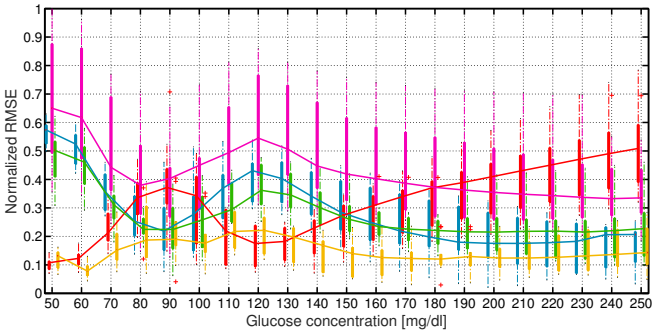

Fig. 9. Normalized RMSE between the time-response of the control-oriented models (i) (orange), (ii) (light-blue), (iii) (green), (iv) (red), and (v) (magenta), and the nonlinear UVA/Padova description to a 1 U insulin bolus at different operation conditions. The continuous lines indicate the medians, and the red crosses the outliers. The vertical bars are limited by the 25th and 75th percentiles.

Fig. 8, the response of all those models starting at 100, 170 and 240 mg/dl for Adult #011 (average patient) are depicted. It can be observed that with 240 mg/dl as an operating point, the average LTI and the proposed personalized LPV have similar behavior. Nevertheless, the BW adjustment in the LPV model provides a much better fit to the original nonlinear model, when the concentration moves away from that condition. In Fig. 9, the normalized Root Mean Square Error (RMSE) between the time-response of each control-oriented model (i)-(v) and the nonlinear dynamics is compared, considering as the unit the highest norm. As shown in that figure, the median value of the normalized RMSE and its dispersion for all 10 patients at different operation conditions are illustrated. It is worth noting that the LPV model has the best fit for most of the glucose concentration values that were considered. The model in [14] also presents good performance in regions where, according to Fig. 2, g does not tend to drop significantly. This is because that model is less sensitive to insulin than the others, and, as a consequence, is compensated by an Insulin Feedback Loop (IFL) when controlled. Instead, the average LTI model reaches its best performance at large values of g, due to the fact that it was identified at a high glucose level.

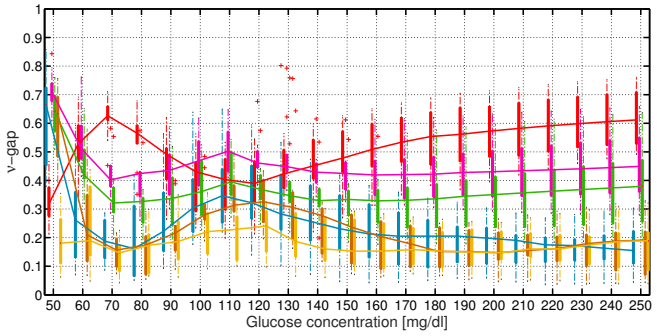

Fig. 10. ν-gap δ_ν between the UVA/Padova model linearized at different glucose concentrations and models (i) (orange), (ii) (light-blue), (iii) (green), (iv) (red), (v) (magenta), and (vi) (brown). The continuous lines indicate the medians, and the red crosses the outliers. The vertical bars are limited by the 25th and 75th percentiles.

B. Closed-Loop Comparison

The comparison of different model representations of a physical system for simulation purposes is well established, and has been explored in the previous subsection. Nevertheless, when the model is intended for controller design, the comparison is not so obvious. A good model, i.e., one that fits adequately a set of experimental data (in this case a Hi-Fi simulator as the UVA/Padova one), does not necessarily provide a good model for control design [27]. For this reason, we have used a measure that indicates whether a particular model is capable of providing a good closed-loop performance. This measure is the ν-gap metric δ_ν [28], [29] that considers the distance between two models according to their achievable closed-loop performance. The latter is measured in the sense of an $\mathcal{H}_\infty$ loop-shaping index as will be briefly reviewed next. It is worth mentioning that this is the only distance that measures the closed-loop performance before a controller is designed, making it particularly adequate when comparing control-oriented models.

For LTI models, given a controller K and a model P_0, a performance measure/stability margin for the (stable) closed-loop system (P_0, K) is defined in [28] and [29] as:

$$b_{P_0,K} = \left\| \begin{bmatrix} P_0 \\ I \end{bmatrix} (I - KP_0)^{-1} \begin{bmatrix} -K & I \end{bmatrix} \right\|_\infty^{-1}. \tag{8}$$

A larger $b_{P_0,K}$ corresponds to a better performance/stability margin, with $b_{opt} = \sup_K b_{P_0,K}$ its optimal value. An interesting property of the ν-gap is that any controller K stabilizing P_0 with $b_{P_0,K} > \beta$, also stabilizes the model set $\{P : \delta_\nu(P, P_0) \leq \beta\}$. In addition, the difference in the closed-loop performance of a nominal model P_0 and a perturbed model P for the same controller K can be quantified in terms of $\delta_\nu(P, P_0)$, i.e., the smaller $\delta_\nu(P, P_0)$, the closer their performances (see details in [28], [29]). Here, due to the fact that the UVA/Padova simulator has been linearized at different glucose concentrations g, the δ_ν distance between each linearized model and the personalized LPV description has been computed as a function of g. For comparison purposes, the distance between the simulator and models (i)-(vi), where (vi) is the average LTI model (1) personalized

TABLE IV

MODEL COMPARISON IN TERMS OF THE δ_ν.

Model	Average δ_ν	Improvement (%)
(i)	0.1803	38.3
(vi)	0.2261	10.3
(ii)	0.2493	0
(iii)	0.3739	-33.3
(v)	0.4619	-46.0
(iv)	0.5087	-51.0

by its gain k using the 1800 rule, is also calculated. This is illustrated in Fig. 10 where the median value of the ν-gap and its dispersion for all 10 patients is depicted in each case. Note that this figure indicates an important improvement in (i), (ii) and (vi) with respect to the other three models. In addition, among models (i), (ii) and (vi), the improvement goes from (ii)$\rightarrow$(vi)$\rightarrow$(i), being therefore, the tuned LPV model, the one with the lowest δ_ν. The main differences between them lie in the glucose region $[90, 180]$ mg/dl and at 50 mg/dl. The average values, and the relative improvement with respect to model (ii), are indicated in Table IV.

Finally, note that although model (iv) presents less RMSE than the other LTI models in several situations according to Fig. 9, this does not imply that it is better for designing glucose controllers, as reflected in Table IV.

IV. CONCLUSION

A control-oriented LPV model was formulated. Importantly, the LPV is affine in the parameter p_1. This parameter is itself a more general function of the glucose level. The model was compared to previous control-oriented models in an *open-loop* fashion, by measuring the RMSE with the UVA/Padova distribution version simulator. Also a *closed-loop* comparison quantified by the ν-gap was made. In both cases, the personalized LPV model achieved smaller errors, possibly due to the fact that time-varying dynamics and a detailed interpretation of the well-known 1800 rule are considered. This anticipates a better means of designing LPV controllers to achieve a higher performance in the T1DM control problem. The authors are aware that improvements in the ν-gap are incidental, because the proposed modeling approach does not explicitly optimize the ν-gap metric. The rigorous ν-gap optimization may be the object of future research.

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