LPV control of glucose for Diabetes type I

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***Abstract*— This paper considers the problem of automatically controlling the glucose level in a Diabetes type I patient. Three issues have been considered: model uncertainty, time-varying/nonlinear phenomena and controller implementation. To that end, the dynamical model of the insulin/glucose relation is framed as a Linear Parameter Varying system and a controller is designed based on it. In addition, this framework allows not only a better performance than other classical methods, but also provides stability and performance guarantees. Design computations are based on convex Linear Matrix Inequality (LMI) optimization. Implementation is based on a low order controller whose dynamics adapts according to the glucose levels measured in real-time.**

I. INTRODUCTION

The blood glucose concentration should be in the interval of $[60, 120]$ mg/dL [1]. The body in normal conditions regulates this concentration by means of *glucagon* and *insulin*, both pancreatic endocrine hormones secreted from α and β cells respectively. The absence of insulin released by the pancreas is called Type I diabetes mellitus and produces a higher glucose level in the blood (hyperglycaemia). The consequences of this fact can be atherosclerosis, retinopathy, etc. The excess of insulin on the other hand, may produce a lower value of glucose (hypoglycaemia) which may produce diabetic coma or even death. Meals and exercise tend to increase and decrease respectively the glucose levels in the blood. It is very important to maintain the glucose levels between the previously mentioned bounds. Therefore, diabetic patients need external injections of insulin according to their actual conditions in order to regulate the glucose level. This is particularly painful in children with diabetes type I which may need several insulin shots a day, plus regular glucose measurements which may involve finger picks. Instead, type II diabetes is generally produced in the long term and has to do with patient's aging, which may not even need external insulin provision.

The dynamics of the glucose-insulin have been studied extensively. Several models can be used, depending if the purpose is to simulate this phenomena or to design a regulatory system to control it (see [2]). For the latter, two dynamical models based on Ordinary differential equations (ODE) have been produced: Bergman's simplified model [2], [3] and Sorensen's high order dynamics [4]. Both are nonlinear models that may be useful for controller design.

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The control of this process has been attempted in several ways (see [5] for a survey), by using both models. From the simplified PID control, to the heuristic fuzzy-logic procedures or parametric-programming [6]. In any case controller design models, even Sorensen's high order one, have a great deal of uncertainty. To this end, robust controllers have been applied to this problem recently [7], [8], but from a Linear Time Invariant (LTI) perspective. In addition, due to the nature of the dynamics in both standard models, nonlinear control design methods have also been applied [3], [9], although with no clear robustness guarantees. As a preliminary conclusion, based on the previous attempts in controlling this system, there are three issues which should be payed special attention:

- Model uncertainty.
- Time-varying and/or nonlinear phenomena.
- Real-time implementation

As a consequence, in this work we have adopted Linear Parameter Varying (LPV) models for design purposes, which accommodates all three issues and provides a performance which is similar to previous approaches.

LPV control methods received considerable attention since the mid 90s. The works in [10]–[12] set up a basis of methods for the analysis of LPV systems and the synthesis of LPV controllers. More recently, the Full block Multiplier (FBM) method allowed a wider application of this methodology [13]. These models represent a large class of dynamical systems with a special structure, allowing for a systematic approach for controller design. In addition, but at the cost of conservatism the approach can be applied to an even wider range of systems known as *quasi*-LPV systems. An LPV system is essentially a family of linear time-varying systems which are described by the standard state space equations, but where the matrices (A, B, C, D) are functions of a time varying parameter vector $\rho(t)$, measured in real time and contained within a compact set $\mathcal{P} \in \mathbb{R}^p$:

$$\dot{x}(t) = A\left[\rho(t)\right] x(t) + B\left[\rho(t)\right] u(t) \quad (1)$$

$$y(t) = C\left[\rho(t)\right] x(t) + D\left[\rho(t)\right] u(t) \quad (2)$$

A number of qualities make LPV methods appealing from the practical viewpoint.

- A large number of practical (nonlinear) systems can be cast properly in the LPV framework [14]. An LPV model can be interpreted as a linear *tangent* model that

moves along the nonlinear system according to its working point. If this working point can be measured in real time by means of a certain parameter, a very practical representation of a nonlinear system is obtained.

- An LPV controller is a very convenient way of representing a systematic gain-scheduling control scheme. The dynamics of the controller changes according to a time-varying parameter $\rho(t)$ which can be measured in real-time, i.e. $K[\rho(t)]$. The complexity of this controller is equivalent to the augmented model by which it has been designed, i.e. order of the model plus performance and robustness weights. It is implemented in real-time as a controller which is updated by real-time measurements, which is faster than *classical* adaptive control which is dominated by its identification phase.
- These results come originally from Robust Control Theory [15]–[17]. Hence, model uncertainty may fit naturally in the framework and in fact, the application of LPV techniques to practical problems can be seen as an extension of $\mathcal{H}_\infty$ control for a class of time-varying systems.
- Stability and performance analysis and controller synthesis for these systems can be formulated as linear matrix inequalities (LMIs), see [18], [19]. LMIs pose convex problems and can be efficiently solved by numerical software packages [20]–[22].

Therefore we have an analysis and controller design procedure that can cope with nonlinear and uncertain dynamical problems and may be solved by efficient convex optimization algorithms off-line, and at the same time produces a fast real-time implementation algorithm. Recent work have been carried out based on these models, oriented towards Fault Detection [23] and modelling [24]. In [9], and LPV controller was designed based on a transformation of the Sorensen model into an affine-LPV model [24]. Here it is not clear if the affine-LPV model should mimic the actual phenomena. This is due to the fact that taking several linearizations of a system and combining them as if they where vertices of a convex set of models does not clearly reproduce the original system. Interpolation of vertex models into an LPV format is not a trivial task, not to mention if also closed-loop stability and performance need to be considered [25].

Instead, an LPV model could be attempted by taking the original model into consideration and broadening the parameter dependence from the mere affine combination. This could be done by using a more general Linear Fractional Transformation (LFT) parameter dependency, as may be considered using the FBM LPV methodology [13] which may still be solved by a finite number of LMI computations.

As mentioned in [7], an automatic glucose regulation procedure needs the following items:

- An *in vivo* sensor for blood glucose continuous measurements; preferably noninvasive.
- A control algorithm for computing the necessary insulin delivery concentration or the insulin delivery rate concentration.

P_1	P_2	P_3	V_1	G_b	I_b	n
0	0.025	0.000013	12	81	15	0.09

TABLE I
MODEL PARAMETERS.

- A physical device, for example, an electromechanical pump, to deliver the insulin calculated by the above-mentioned algorithm.

The scientific community is already working towards accurate noninvasive glucose sensors (see [26]) and insulin pumps for this control system (see [27]). Non-invasive methods are specially important, which work subcutaneously [28]. Therefore both, sensors and actuators are available and control algorithms may be implemented in real time applications.

The objective of this work is to illustrate the current research at the *Centro de Sistemas y Control* to automatically control the glucose-insulin levels in Diabetes Mellitus type I, based on an LPV framework. To this end, we will use the simplified Bergman's model and transform it directly into a *quasi*-LPV model in order to design an LPV controller, in section II. Model uncertainty considerations will be also taken into account in the design procedure. Simulation illustrating the system's performance are presented in section III. Final conclusions and future research end this paper in section IV.

II. MAIN RESULTS

Bergman's model will be used here to illustrate the LPV methodology as a way to control the insulin-glucose dynamics taking into account both the nonlinear and time-varying nature of the problem as well as the inherent model uncertainty. This model is as follows:

$$\dot{G}(t) = -P_1 G(t) - X(t)\left[G(t) + G_b\right] + d(t) \quad (3)$$

$$\dot{X}(t) = -P_2 X(t) + P_3 I(t) \quad (4)$$

$$\dot{I}(t) = -n\left[I(t) + I_b\right] + \frac{1}{V_1} u(t) \quad (5)$$

where G is the plasma-glucose concentration above the basal value G_b in mg/dL, I is the plasma-insulin concentration above the basal value I_b in mU/L, and X is proportional to the plasma-insulin concentration in the remote compartment (1/min). The disturbance $d = \frac{F_G}{V_G}$ is the meal glucose perturbation in mg/mL/min, where F_G is the rate of exogenously infused glucose in mg/min, and V_G is the glucose distribution space in dL. V_1 is the insulin distribution volume in L, and n is the fractional disappearance rate of insulin (1/min). The parameters considered here are shown in Table I.

This can be considered as a *quasi*-LPV model by defining variable $\rho(t) = G(t)$ in equation (3) as a real-time measured parameter, due to the fact that it is also the output of the system. In addition, the input has been re-defined as $v(t) =$

$\frac{1}{V_1}u(t) - nI_b$ for simplicity. Therefore, the system is:

$$\dot{x}(t) = \begin{bmatrix} -P_1 & -(\rho + G_b) & 0 \\ 0 & -P_2 & P_3 \\ 0 & 0 & -n \end{bmatrix} x(t) + \begin{bmatrix} d(t) \\ 0 \\ v(t) \end{bmatrix} \quad (6)$$

$$y(t) = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} x(t) \quad (7)$$

where the state vector is $x(t) = \begin{bmatrix} G & X & I \end{bmatrix}^T$. The last vector of the state equation can be interpreted as a disturbance in the first element and the control variable in the last component. The state-space structure appears as a sort of canonical representation. Note that this model has the same LPV structure as in equations (1)-(2), where the parameter $\rho(t)$ is the plasma-glucose (time-varying) level which may be measured in real-time.

In order to evaluate robustness against model uncertainty, the three parameters (P_2, P_3, n) have been considered, according to the inter-patient and intra-patient variations mentioned in [6]. These parameters appear in the first stage of this model which is LTI, and therefore can be evaluated by robustness margins as the structured singular value [15]–[17]. By transforming the transfer function between $v(t) \rightarrow X(t)$ using the Laplace transform and introducing parametric uncertainty variables $(\delta_n, \delta_2, \delta_3)$ and the weights (w_n, w_2, w_3), we obtain:

$$X = \frac{1}{(s+n)} \cdot \frac{P_3}{(s+P_2)} v \quad (8)$$

$$= \frac{1}{(s+n_o)\left(1 + \frac{w_n \delta_n}{s+n_o}\right)} \frac{(P_{3o} + w_3\delta_3)}{(s+P_{2o})\left(1 + \frac{w_2\delta_2}{s+P_{2o}}\right)} v$$

where the nominal values have index o and all uncertainties are in the unitary interval $\delta_i \in [-1, 1]$. This uncertainty structure will be evaluated to test both the stability and performance robustness of the design.

III. SIMULATIONS

The controller has been designed based on a Single Quadratic Lyapunov function (SQLF) with pole placement constraints [29]. The latter has been used to avoid the *fast pole* phenomena which is typical of these type of controllers.

The uncertainty in all three model parameters (P_2, P_3, n) is in the order of 40% according to the inter-patient and intra-patient figures mentioned in [6]. This has been defined in the previous section and corresponds to the intervals $\delta_i \in [-1, 1],\ i = n, 2, 3$.

The meal perturbations can take very different values and dynamics, but in this framework it has been modelled as a set of (normalized) disturbances $\|d\|_2 \leq 1$, where $\|\cdot\|_2$ stands for the signal energy.

The final objective is to achieve the smallest variation in the glucose levels (around the basal value G_b) for a set of meal disturbances and under all possible model uncertainties considered. Therefore Robust performance can be defined as follows:

$$\min \|G\|_2 \qquad \forall \|d\|_2 \leq 1, \text{ and } \forall \delta_i \in [-1, 1],\ i = n, 2, 3$$

Robust performance analysis is carried out using the structured singular value (SSV) under parametric uncertainty [16], [17]. The resulting measure was taken for the glucose levels $(40, 60, 80, 100, 120)$ mg/dL, showing the designed controller meets robustness requirements, against the usual uncertainty considered for this problem [6] (note in Fig. 1 that all the SSV are below unity). This means that the controller achieves the lowest possible value of G (measured in terms of its energy) for all possible energy bounded disturbances, for the worst case model uncertainty combination, and the worst case *scenario*. This is a very strong result, particularly because it has theoretical guarantees in terms of performance and robustness.

In order to simulate the system's response, the following disturbance, taken from [3] has been considered: $d(t) = 10e^{-t/100}$ (see plot in [3]), which corresponds to a meal peak of 0.5 mmoles/L. The result is presented in Fig. 2 and shows how the basal level of glucose is reached. In the same figure, it can be noted that the injected insulin levels are specifically bounded by 100 mU/min. This is in order to meet practical saturation constraints imposed by commercial pumps [6].

The controller implementation needs a measurement of the glucose level, which is considered simultaneously as the output $y(t)$ and as a time-varying parameter $\rho(t)$ of the system. The dynamics of the controller therefore changes in real-time according to this parameter $\rho(t)$, i.e. $u(t) = K[\rho(t)] \star G(t)$ where $\star$ is the convolution operator. The output of the controller provides the necessary instantaneous insulin level for the patient. The complexity of this controller is very reasonable (order 5), and according to the system dynamics, it can be implemented with commercially available hardware.

In a first stage, this controller could be used as part of a glucose monitor which provides an indication for the patient as to how much insulin he needs at any given time. In a further development stage, it could be used to close the loop between a glucose monitor and a insulin pump.

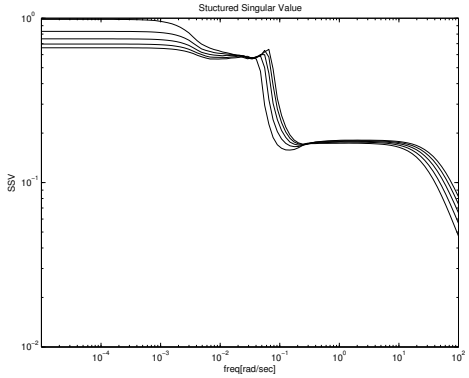

Fig. 1. Robustness analysis: structured singular value for parametric uncertainties and glucose levels $(40, 60, 80, 100, 120)$ mg/dL.

IV. CONCLUSIONS AND FUTURE RESEARCH

This work has considered several important and practical issues in the automatic control of glucose levels in blood:

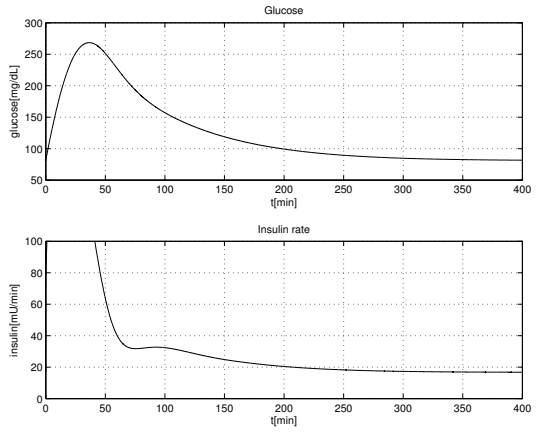

Fig. 2. Time response of the closed loop system subject to a meal disturbance.

model uncertainty, time variations, nonlinearities and real-time implementation. All of them can be handled in an LPV framework, which guarantees stability and performance and can be solved (off-line) by convex optimization methods and implemented (on-line) in a very simple way.

Future research needs to be done with more accurate models, as the 19th. order one due to Sorensen [4]. In that case, an LPV model could be attempted by taking the original model into consideration with an LFT parameter dependency by using the FBM LPV methodology [13] which may still be solved by a finite number of LMI computations. Also, an important issue to be considered are the time delays in insulin injection and glucose measurement due to subcutaneous application.

In addition, identification and model invalidation experiments [30] also need to be performed in order to obtain a more precise description of this complicated phenomena. To this end, a first stage will be attempted based on a High-Fidelity simulator (*in silico* experiments). This may allow to complete a series of identification, invalidation and control experiments before turning into *in vivo* experimentation.

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REFERENCES

[1] The diabetes control and complications trial research group (DCCT), "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus," *N. Engl. J. Med.*, vol. 329, p. 977986, 1993.

[2] A. Makroglou, J. Li, and Y. Kuang, "Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview," *Applied Numerical Mathematics*, vol. 56, pp. 559–573, 2006.

[3] G. Cocha, V. Constanza, and C. D'Atellis, "Control nolineal de la diabetes mellitus Tipo I," in *Actas de la RPIC*, Rosario, Argentina, 2009, pp. 240–245.

[4] J. Sorensen, "A physiologic model of glucose metabolism in man and its use to design and asses improved insulin therapies for diabetes," Ph.D. dissertation, Massachusetts Institute of Technology, Cambridge, MA, USA, 1985.

[5] L. Kovács, B. Benyó, Z. Benyó, and A. Kovács, "Past and present of automatic glucose-insulin control research at BME," in *10th International Symposium of Hungarian Researchers*, 2009, pp. 245–252.

[6] P. Dua, F. Doyle III, and E. N. Pistikopoulos, "Model-based blood glucose control for type 1 diabetes via parametric programming," *IEEE Transactions on Biomedical Engineering*, vol. 53, no. 8, pp. 1478–91, 2006.

[7] E. Ruiz-Velázquez, R. Femat, and D. Campos-Delgado, "Blood glucose control for type i diabetes mellitus: A robust tracking $\mathcal{H}_\infty$ problem," *Control Engineering Practice*, vol. 12, pp. 1179–1195, 2004.

[8] R. Parker, F. Doyle III, J. Ward, and N. Peppas, "Robust $\mathcal{H}_\infty$ glucose control in diabetes using a physiological model," *A.I.Ch.E. Journal*, vol. 46, no. 12, p. 25372549, 2000.

[9] L. Kovács, B. Kulcsár, J. Bokor, and Z. Benyó, "Model-based nonlinear optimal blood glucose control of Type I diabetes patients," in *30th Annual International IEEE EMBS Conference*, Vancouver, Canada, 2008, pp. 1607–1610.

[10] P. Gahinet and P. Apkarian, "An LMI approach to $\mathcal{H}_\infty$ control," *International Journal of Robust and Nonlinear control*, vol. 4, no. 8, pp. 421–448, 1994.

[11] G. S. Becker and A. Packard, "Robust performance of LPV systems using parametrically-dependent linear feedback," *Systems and Control Letters*, vol. 23, pp. 205–215, 1994.

[12] A. Packard, "Gain scheduling via LFTs," *Systems and Control Letters*, vol. 22, pp. 79–92, 1993.

[13] C. W. Scherer, "LPV control and full block multipliers," *Automatica*, vol. 37, no. 3, pp. 361–375, 2001.

[14] J. Shamma and M. Athans, "Gain scheduling: Potential hazards and possible remedies," *IEEE Control Systems Magazine*, vol. 12, no. 3, pp. 101–107, 1992.

[15] G. E. Dullerud and F. Paganini, *A Course in Robust Control Theory: A Convex Approach*, ser. Texts in Applied Mathematics. Springer-Verlag, 2000, no. 36.

[16] R. S. Sánchez Peña and M. Sznaier, *Robust Systems Theory and Applications*. John Wiley & Sons, Inc., 1998.

[17] K. Zhou, J. C. Doyle, and K. Glover, *Robust and Optimal Control*. Prentice–Hall, 1996.

[18] S. Boyd, L. Ghaoui, E. Feron, and V. Balakrishnan, *Linear Matrix Inequalities in System and Control Theory*. Philadelphia: SIAM Studies in Applied Mathematics, 1994, vol. 15.

[19] C. Scherer and S. Weiland, *Linear Matrix Inequalities in Control*. Dutch Institute of Systems and Control, 2005.

[20] P. Gahinet, A. Nemirovski, A. J. Laub, and M. Chilali, *LMI Control Toolbox*, The Mathworks, Inc., 1995.

[21] J. F. Sturm, "Using SeDuMi 1.02, a MATLAB toolbox for optimization over symmetric cones," *Optimization Methods and Software*, vol. 11–12, pp. 625–653, 1999, version 1.1R3 available from `http://sedumi.mcmaster.ca`.

[22] K. C. Toh, R. H. Tütüncü, and M. J. Todd, "SDPT^3 - a MATLAB software package for semidefinite-quadratic-linear programming," `http://www.math.cmu.edu/řeha/sdpt3.html`, 2007.

[23] L. Kovács, B. Kulcsár, J. Bokor, and Z. Benyó, "LPV fault detection of glucose-insulin system," in *Proc. 14th Mediterranean Conference on Control and Automation*, Ancone, Italy, 2006.

[24] L. Kovács and B. Kulcsár, "LPV modeling of type i diabetes mellitus," in *8th International Symposium of Hungarian Researchers*, 2007, pp. 163–173.

[25] F. Bianchi and R. S. Sánchez Peña, "Interpolation for gain scheduled control with guarantees," july 2009, submitted to Automatica.

[26] http://www.childrenwithdiabetes.com/continuous.htm, 2010.

[27] http://www.diabetesnet.com/diabetes_technology/insulin_pump_models.php, 2010.

[28] D. Campos-Delgado and A. Gordillo-Moscoso, "Regulación de glucosa en pacientes diabéticos a través de infusiones subcutáneas: Retos y perspectivas," in *Proc. Congreso Nacional de la AMCA*, Mexico D.F., Mexico, 2004.

[29] A. S. Ghersin and R. S. Sánchez Peña, "LPV control of a 6 DOF vehicle," *IEEE Transactions on Control Systems Technology*, 2002.

[30] F. Bianchi and R. S. Sánchez Peña, "Robust identification/invalidation in an LPV framework,," *International Journal of Robust and Nonlinear Control*, vol. 20, no. 3, pp. 301–312, 2010.