Hindawi Publishing Corporation
Journal of Electrical and Computer Engineering
Volume 2011, Article ID 697543, 10 pages
doi:10.1155/2011/697543

Research Article

Time-Varying Procedures for Insulin-Dependent Diabetes Mellitus Control

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Received 12 October 2010; Revised 28 January 2011; Accepted 26 March 2011

Academic Editor: Eldon D. Lehmann

This work considers the problem of automatically controlling the glucose level in insulin dependent diabetes mellitus (IDDM) patients. The objective is to include several important and practical issues in the design: model uncertainty, time variations, nonlinearities, measurement noise, actuator delay and saturation, and real time implementation. These are fundamental issues to be solved in a device implementing this control. Two time-varying control procedures have been proposed which take into consideration all of them: linear parameter varying (LPV) and unfalsified control (UC). The controllers are implemented with low-order dynamics that adapt continuously according to the glucose levels measured in real time in one case (LPV) and by controller switching based on the actual performance in the other case (UC). Both controllers have performed adequately under all these practical restrictions, and a discussion on pros and cons of each method is presented at the end.

1. Introduction

Under normal conditions, blood glucose concentration should be in the interval of 60, 120 mg/dL [1]. The body 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 insulin dependent diabetes mellitus (IDDM) and produces a higher glucose level in the blood (hyperglycaemia). The consequences of this fact can be atherosclerosis, retinopathy, and so forth. 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, respectively, to increase and decrease blood glucose levels. It is very important to maintain glucose levels between the previously mentioned bounds. Therefore, diabetic patients need external injections of insulin according to their actual conditions in order to regulate their glucose level. This is particularly painful in children with IDDM 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.

Glucose-insulin dynamics has been extensively studied. A few models based upon ordinary differential equations (ODE) can be used, for simulation or control system design purposes [2]. As controller design is concerned, solutions are frequently based upon either Bergman's 3rd. order model [2, 3], or Sorensen's 19th order model [4]. Both models are nonlinear and suitable for design purposes.

The control system design for this process has been approached in different ways using both models (see [5–7] for a survey). Solutions go from simplified PID control to heuristic fuzzy-logic procedures or parametric-programming [8]. The aforementioned models, present significant sources of uncertainty that are worth considering systematically. Recently [9, 10], robust control theory has been applied to this problem, accounting for uncertainty as linear time invariant (LTI). An LPV model has been derived in [11] based on

Sorensen's model and again an $\mathcal{H}_\infty$ LTI controller has been designed for it in [12, 13]. In addition, due to the nature of the dynamics in both standard models, nonlinear control design methods have also been applied [3, 12] but with no clear robustness guarantees. In previous work by the authors of this paper [14], an LPV controller design was presented for this problem. As a preliminary conclusion, based on the previous attempts to control this system, attention should be paid to the following issues:

(i) model uncertainty,

(ii) time-varying and/or nonlinear phenomena,

(iii) time delays, actuator saturation, measurement noise,

(iv) real time implementation.

There have been no previous attempts to consider all these restrictions in the controller design phase. This is particularly important if the final objective is to construct a device to control IDDM automatically. To this end, as mentioned in [6, 9], such a device needs the following items:

(i) an *in vivo* sensor for continuous blood glucose measurements; preferably noninvasive,

(ii) a control algorithm for computing the necessary insulin delivery concentration or the insulin delivery rate concentration,

(iii) a physical device, for example an electromechanical pump, to deliver the insulin calculated by the abovementioned algorithm.

The scientific community is already working towards accurate noninvasive glucose sensors (see [15–17]) and insulin pumps for this control system (see [18]). Noninvasive [16, 17] and semi-invasive methods, which work subcutaneously [19], are specially important. Therefore, both sensors and actuators are available and control algorithms may be implemented in real time applications.

The objective of this work is to test two time-varying algorithm design procedures to control glucose-insulin levels in IDDM, which contemplate all these practical issues: linear parameter varying (LPV) and unfalsified control (UC). This is a first step towards the construction of a *practical* device which may be applied effectively to patients.

This paper is organized as follows. Some brief background material on both techniques is presented in Section 2. Section 3 is devoted to transform the simplified Bergman's model into a *quasi*-LPV model in order to design both controllers. Structured model uncertainty considerations will also be taken into account in both design methods. Simulations illustrating the system's performance are presented in Section 4. Some technological issues which could complicate the implementation of such a controller are detailed at the end of that section. Final conclusions as well as future research ideas end this paper in Section 5.

2. Background

The LPV method applied in this work can be broadly considered within the area of *gain-scheduled* control. This technique is frequently applied to nonlinear problems. Knowledge of the plant's operating condition is used to adjust the gains of a linear controller, as the operating condition changes. This is typically used in aircraft control, where LTI controllers are switched for different operating points according to the real time measurement of altitude, angle of attack and speed. LPV controllers have improved characteristics with respect to previous *gain-scheduled* ones due to their time-varying dynamics, rather than LTI. They also provide theoretical guarantees of performance and stability, through the smooth real time adaptation of the controller to the operating condition.

Instead, UC does not fall into the category of *gain-scheduled* control because it does not use a scheduling parameter. Nevertheless there is also a change between controllers through switching, which indicates its time-varying nature. These switching events depend on the falsification of controllers by means of the real time measurement of the input-output signals of the system, which are contrasted using a performance figure. The controller is falsified whenever the performance objective cannot be met. The fact that there is no need to measure a system parameter in real time has a clear advantage over LPV control. In a sense, the operating point is here directly determined from the input/output data of the system.

2.1. LPV Controllers. Linear parameter varying control methods received considerable attention since the mid 90s. The work in [20–22] set up a basis of methods for the analysis of LPV systems and the synthesis of LPV controllers. More recently, full block multiplier (FBM) methods allowed a wider application of this methodology [23]. 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 $\mathcal{P} \subset \mathbb{R}^p$

$$\begin{aligned} \dot{x}(t) &= A[\rho(t)]x(t) + B[\rho(t)]u(t), \\ y(t) &= C[\rho(t)]x(t) + D[\rho(t)]u(t). \end{aligned} \tag{1}$$

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

(i) A large number of practical (nonlinear) systems can be cast properly in the LPV framework [24]. 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.

(ii) An LPV controller is a very convenient way of representing a systematic gain-scheduling control scheme.

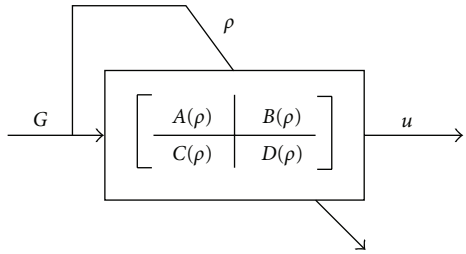

Figure 1: LPV controller implementation, where G is the plasma-glucose concentration above the basal value G_b, input u is the insulin infusion rate and ρ is the time-varying measurable parameter, in this case $\rho = G$.

The matrices of the linear state space representation of the controller change according to a time-varying parameter $\rho(t)$ which can be measured in real time, that is, $K[\rho(t)]$ (see Figure 1). The complexity of this controller is equivalent to the augmented model by which it has been designed, that is, 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. This is faster than *classical* adaptive control which is dominated by its identification phase.

(iii) These results come originally from robust control theory [25–27]. 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.

(iv) Stability and performance analysis and controller synthesis for these systems can be formulated as linear matrix inequalities (LMIs), see [28, 29]. LMIs pose convex problems and can be efficiently solved by numerical software packages [30–32].

Therefore, this is an analysis and controller design procedure that can cope with nonlinear and uncertain dynamical problems and that may be solved offline by efficient convex optimization algorithms. In addition controllers can be efficiently implemented in real time. Recent work has been carried out based on these models, oriented towards fault detection [33] and modelling [11]. In [12, 13] an $\mathcal{H}_\infty$ controller was designed based on a transformation of the Sorensen model into an affine-LPV model [11]. Finally, a previous work by the authors produced an LPV controller for this problem in [14], based on Bergman's model.

2.2. Unfalsified Controllers. The Unfalsified Control (UC) concept [34–36] is based on Popper's [37] theory of the knowable: "*The Scientist ... can never know for certain whether his theory is true, although he may sometimes establish ... a theory is false.*" Therefore, the concept of discovery in science as a process of elimination of hypotheses which are falsified by experimental evidence may be applied to the development of a theory for implementing good controllers from experimental data without reliance on prejudicial assumptions about the plant, sensors, uncertainties, or noises [35]. Since the initial concept was presented, the following applications can be mentioned among others: PID [38], Fault-Tolerant control [39], and robotics [40].

The theory is based on the following sets:

$$\begin{aligned}
&\text{(Signals) } \mathcal{S} = \mathcal{R} \times \mathcal{U} \times \mathcal{Y},\\
&\text{(Systems) } P = \{(r,u,y) \in \mathcal{S} \mid y = Pu\},\\
&\text{(Data) } M_{\text{data}} = \{(u,y) \in \mathcal{U} \times \mathcal{Y}\} \text{ embedded in}\\
&\qquad P_{\text{data}} = \{(r,u,y) \in \mathcal{S} \mid (u,y) \in M_{\text{data}}\} \subset P,\\
&\text{(Specifications) } T_{\text{spec}} \subset \mathcal{S},\\
&\text{(Controllers) } K = \left\{(r,u,y) \in \mathcal{S} \mid u = K\begin{bmatrix} r \\ y \end{bmatrix}\right\}.
\end{aligned} \tag{2}$$

Here, (u, y) are the input and output of the plant and r is the closed loop reference signal.

The main technical definition involving these sets is as follows.

Definition 1. The controller $K \in \mathcal{K}$ is *falsified* by the experimental information if this is sufficient to deduce that $(r,u,y) \in T_{\text{spec}}$ for all $r \in \mathcal{R}$ would be invalidated when K is in the loop. Otherwise, K is *unfalsified*.

Therefore, several LTI controllers may be designed by any procedure available, not even having to be based on a particular model. This is the main advantage of UC, a model-free procedure which is purely based on real time input-output information and a falsification test with no prejudice concerning its mathematical model. Nevertheless from a practical viewpoint, as a starting point the set of controllers may be focused on different operating points of the nonlinear model. The falsifier selects *online* which is the most adequate one to use, according to the best performance at disposal. Therefore, this reduces to a performance-scheduled switched controller methodology.

The implementation of these controllers is based on the following result.

Theorem 1. *Controller $K \in \mathcal{K}$ is unfalsified by experimental data P_{data} if and only if for each triad $(r_0, u_0, y_0) \in K \cap P_{data}$ there exists at least a pair (u_1, y_1) such that $(r_0, u_1, y_1) \in K \cap P_{data} \cap T_{spec}$, for example, $r_0 = y_0 + K^{-1}u_0 = y_1 + K^{-1}u_1 = \cdots$.*

According to this result, controller $K \in \mathcal{K}$ is unfalsified by the experiments if and only if $K \cap P_{\text{data}} \in T_{\text{spec}}$ (complete information case). The control scheme is depicted in Figure 2.

It is important to highlight several outstanding characteristics of this method.

(i) No linearity, time-invariance or finite dimension is assumed on the plant model, and neither on the noise or perturbations. All conclusions are based solely on the actual real time information with no *a priori* assumptions.

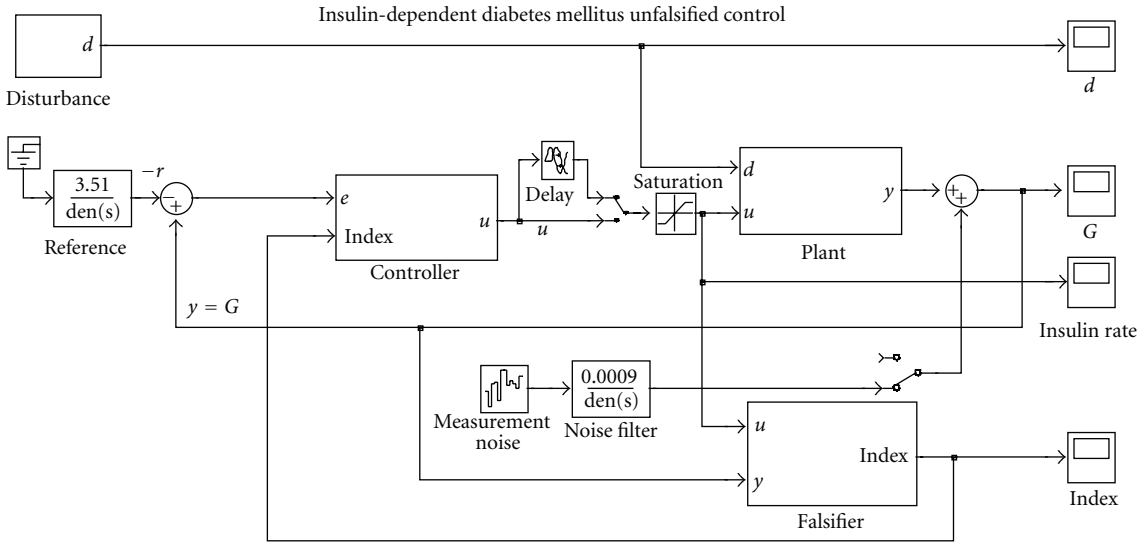

Figure 2: Unfalsified controller implementation. The reference signal is in (8), the disturbance and band-limited measurement noise are described in Section 4, a 30 min. delay and actuator saturation (100 mU/min) have also been added. G and u have been defined in Figure 1 and the *index* ($i = 1, \ldots, 5$) indicates the controller to be used.

(ii) The real time data can be taken from open or closed loop. No extra system parameter needs to be measured in real time, as in the case of LPV control.

(iii) The only objective to seek is the best possible performance, which is measured by the cost function T_{spec}.

(iv) A controller can be tested (falsified) even if it is not physically inserted in the loop, as a way not to perturb the closed loop system.

As an example we may consider the following (invertible) controller $u = K \star (r - y)$, that is, proper and minimum phase, where $\star$ is the convolution operator. The specification function is defined as $T_{\text{spec}} = \|w_1 \star (r - y)\|_{2T} + \|w_2 \star u\|_{2T} - \|r\|_{2T} \leq 0$ (usually the 2-norm $\|\cdot\|_2$ stands for the signal energy, integrated in $[0, \infty)$, but here $\|\cdot\|_{2T}$ is integrated in the interval $[0, T]$ to allow a real time test.), with impulse response (w_1, w_2) which weight the tracking error and control signal, respectively. The plant input/output experimental data is $M_{\text{data}} = (u_0, y_0) \subset P_{\text{data}} \subset P$. The *fictitious* reference signal $\tilde{r} = K^{-1} \star u_0 + y_0$ is computed in real time, which should be in the loop when controller K is in place, hence K can be tested without actually inserting it in the closed loop system. If $T_{\text{spec}} = \|w_1 \star (\tilde{r} - y_0)\|_{2T} + \|w_2 \star u_0\|_{2T} - \|\tilde{r}\|_{2T} > 0$ this controller is falsified.

3. Uncertain Mathematical Model

Bergman's model will be used here to illustrate both methodologies 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:

$$\dot{G}(t) = -P_1 G(t) - X(t)[G(t) + G_b] + d(t), \tag{3}$$

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

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

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 $d = F_G/V_G$ 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 1.

Table 1: Model parameters.

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

This can be considered as a *quasi*-LPV model by defining variable $\rho(t) = G(t)$ in (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 redefined as $v(t) = (1/V_1)u(t) - nI_b$ for simplicity. Therefore, the system is:

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

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

where the state vector is $x(t) = [G \quad X \quad I]^T$. 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 (1), 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, 40% simultaneous variations in all three parameters (P_2, P_3, n) have been considered, according to the inter-patient and intra-patient variations mentioned in [8]. 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 [25–27]. 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:

$$\begin{aligned} X &= \frac{1}{(s+n)} \cdot \frac{P_3}{(s+P_2)} v \\ &= \frac{1}{(s+n_o)(1 + w_n \delta_n/(s+n_o))} \\ &\quad \times \frac{(P_{3o} + w_3 \delta_3)}{(s+P_{2o})(1 + w_2 \delta_2/(s+P_{2o}))} v, \end{aligned} \quad (7)$$

where the nominal values have index o and all uncertainties are in the unitary intervals $\delta_i \in [-1, 1]$, $i = n, 2, 3$. This uncertainty structure will be evaluated to test both the stability and performance robustness of the design.

4. Designs and Simulations

The example which tests both controllers has been taken from [9]. There, a normal response is averaged over a group of patients that have been subject to a disturbance of 100 g of glucose at time $t = 0$. Therefore, the following is taken as a reference model which needs to be followed by the closed-loop control system.

$$P_{\text{ref}} = \frac{K\omega_n^2}{s^2 + 2\omega_n \xi s + \omega_n^2} \quad (8)$$

with $K = 3900$, $\omega_n = 0.03$ and $\xi = 0.7$. The stability and performance objectives need to be satisfied under all possible model uncertainties described in the previous section. In addition, the insulin pump is limited to values of 100 mU/min in order to meet practical saturation constraints imposed by commercial pumps [8].

Furthermore, two important practical issues have been considered here: measurement noise in the glucose monitors and delay between subcutaneous and intravenous insulin levels, assuming semi-invasive pump technology is used.

4.1. LPV Design. The controller has been designed based on a Single Quadratic Lyapunov Function (SQLF) with pole placement constraints [41]. The latter has been used to avoid the *fast pole* phenomena which is typical of this type of controllers.

The meal perturbations can take very different values and dynamics, but in this framework they have been modelled as a set of (normalized) disturbances $\|d\|_2 \leq 1$.

The final objective is to achieve the smallest tracking error in the glucose levels for meal disturbances, under all possible model uncertainties considered and for the reference profile mentioned previously. Therefore, robust performance can be defined as follows:

$$\min \|G\|_2 \quad \forall \|d\|_2 \leq 1, \ \forall \delta_i \in [-1, 1], \ i = n, 2, 3. \quad (9)$$

Robust performance analysis is carried out using the structured singular value (SSV) under parametric uncertainty [26, 27]. The resulting measure was taken at glucose levels (40, 60, 80, 100, and 120) mg/dL, showing the designed controller meets robustness requirements against the usual uncertainty considered for this problem [8] (note in Figure 3(a) that all the SSV are below unity). This means that the controller achieves the lowest tracking error (measured in terms of its energy) for all possible energy bounded disturbances, for the worst case model uncertainty combination, and the worst case *scenario* (in terms of glucose levels). This is a very strong result, particularly because it has theoretical guarantees in terms of performance and robustness.

The result is presented in Figure 4 and shows how the tracking error is reduced. Note in the same figure that the injected insulin levels are specifically bounded by 100 mU/min. The first saturation in this signal produces a 176 mg/dL peak in the glucose levels, which rapidly follows the normal (reference) curve.

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 $\rho(t)$, that is, $u(t) = K[\rho(t)] \star G(t)$ (see Figure 1).

The output of the controller provides the necessary instantaneous insulin rate for the patient. Its complexity is reasonable (5th order) and in accordance with the model's dynamics. It can be implemented with commercially available hardware.

In addition, a 30-minute delay combined with a 5 mg/dL band-limited random error in the glucose measurement are applied to this system as indicated in Figure 2. Figure 5 shows that performance is degraded when these practical issues are accounted for in the simulation. In spite of the fact that the peak now increases to 200 mg/dL, proper tracking of the reference profile is achieved. This illustrates the design's robustness.

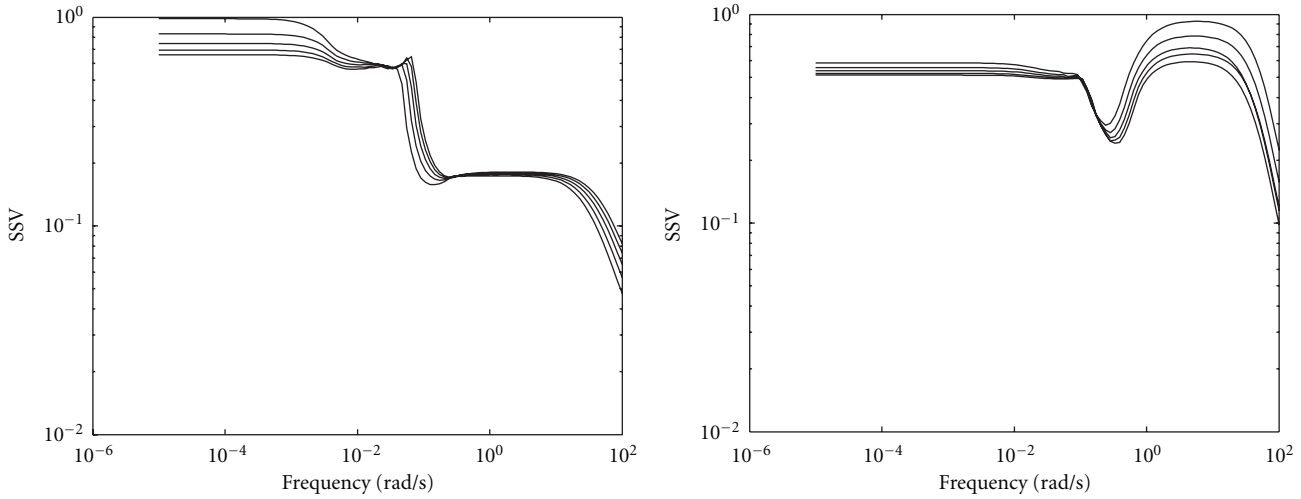

Figure 3: Structured singular value for parametric uncertainties and glucose levels (40, 60, 80, 100, and 120) mg/dL for (a) LPV, (b) UC.

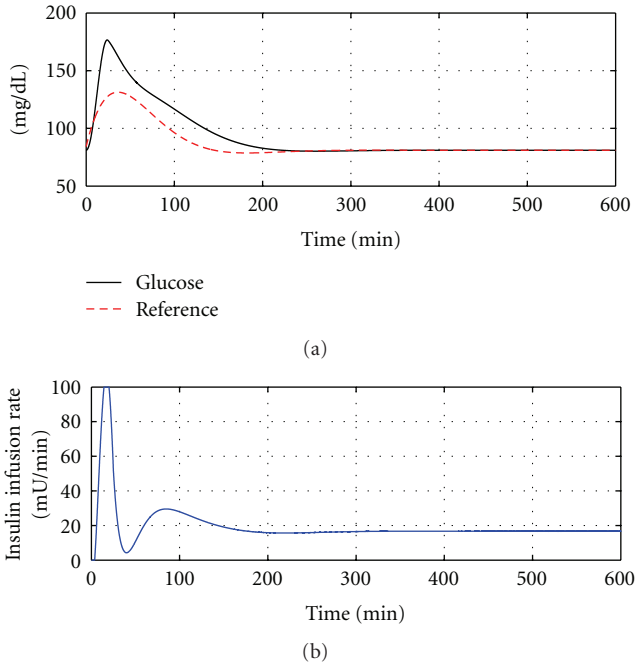

Figure 4: LPV control: glucose monitoring and insulin control.

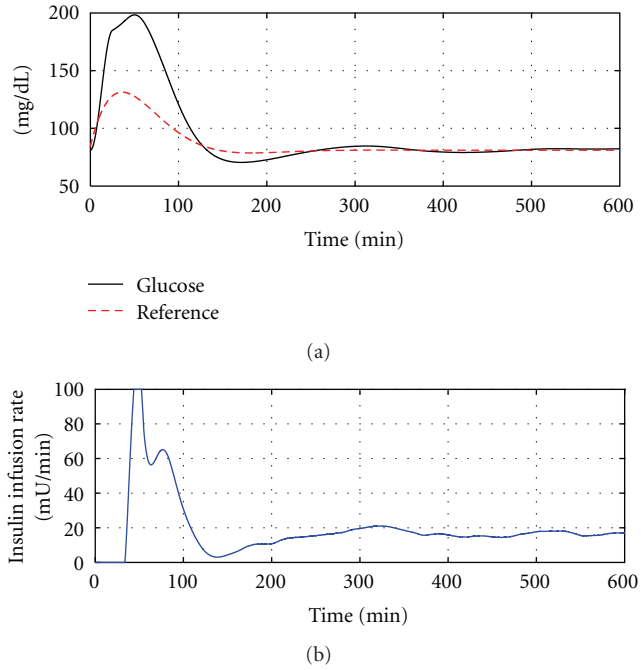

Figure 5: LPV control: glucose monitoring and insulin control under actuator delay and measurement noise.

4.2. UC Design. Here, 5 candidate controllers have been designed according to the previous specifications at different glucose levels (linearization points): (40, 60, 80, 100, and 120) mg/dL, denoted K_1 to K_5, respectively. The designs have been performed using the $\mathcal{H}_\infty$ optimal control methodology.

In all cases the performance objective has been defined as a combination of the tracking error and control action, weighted by W_y and W_u, respectively, as follows

$$\min\left\{\gamma \text{ such that } \left\|\begin{bmatrix} W_y(s)S(s) \\ W_u(s)K(s)S(s) \end{bmatrix}\right\|_\infty < \gamma\right\}, \quad (10)$$

where $S(s)$ is the sensitivity function of the closed loop. Therefore, the falsifier cost function reflects this objective and has been constructed as $T_{\text{spec}} = \|W_y(r-y)\|_{2T} + \|W_u u\|_{2T} - \gamma\|r\|_{2T} \leq 0$.

As in the previous design, the robust performance test has been performed via the structured singular values for all 5 controllers and is illustrated in Figure 3(b). All values are below unity, therefore the desired performance is achieved at all linearization points and for all possible combinations of the uncertain parameters.

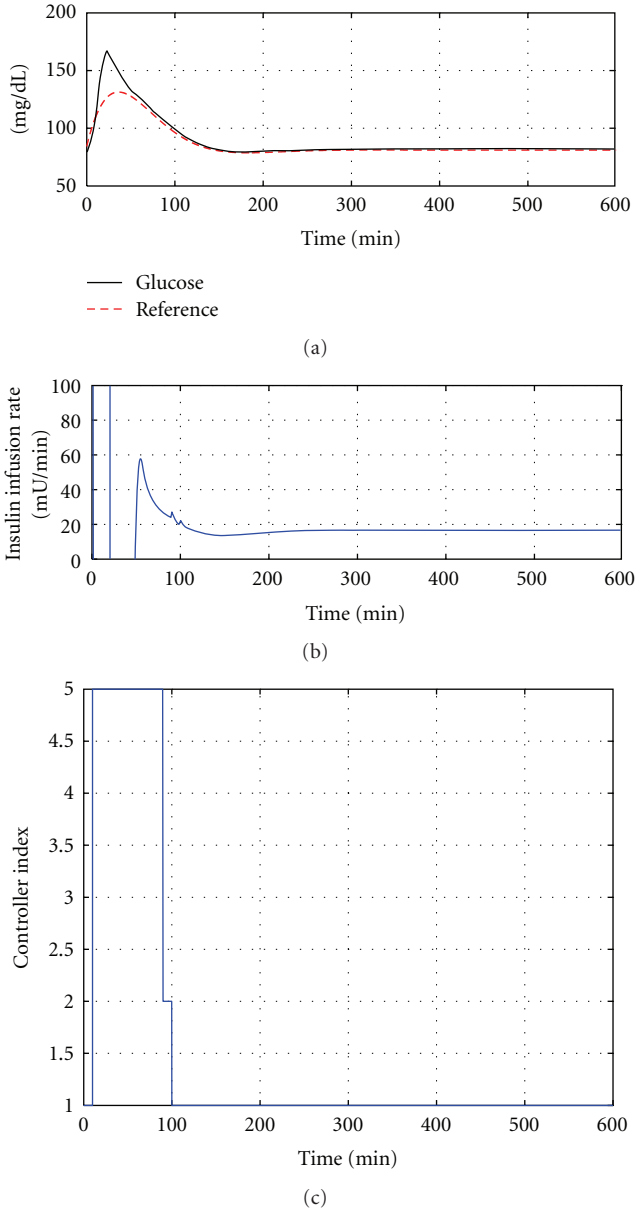

Figure 6: Unfalsified control: glucose monitoring, insulin control and controller switching.

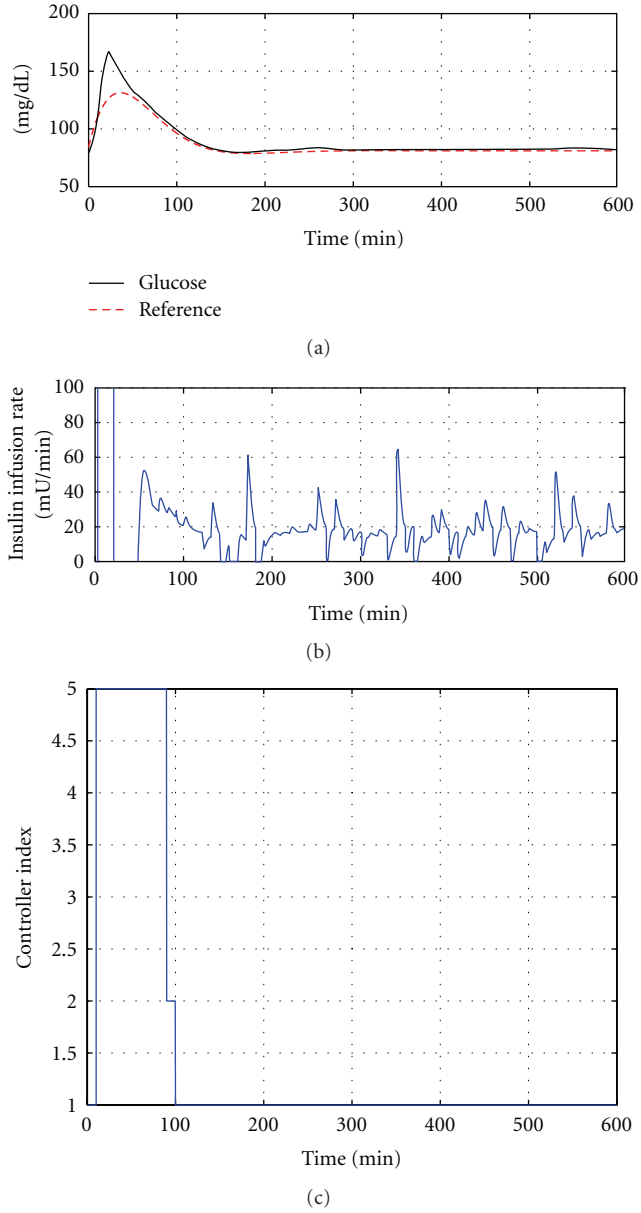

Figure 7: Unfalsified control: glucose monitoring, insulin control and controller switching under measurement noise.

Time simulations with the UC in the loop can be observed in Figure 6. Glucose levels follow the normal (reference) response after the meal disturbance with a better performance than the LPV case. Insulin injection is limited to 100 mU/min at the beginning which does not destabilize the closed loop system, although it leaves a 167 mg/dL peak due to this saturation. Controller switching is depicted in Figure 6, which changes between controllers K_1 and K_5 at the beginning, with a short change to controller K_2 before the first 100 minutes. From there on, controller K_1 follows the reference very tightly up to the end of the 10-hour period. No transient behavior due to controller switching can be noticed.

As in the previous subsection, a 5 mg/dL band-limited random error in the glucose measurement is applied to this system and its performance is indicated in Figure 7. Here, glucose level profiles are almost the same, with changes in the insulin injection profiles. Instead, when a 30-minute delay is applied in the actuator, UC does not respond as well and decreases to levels near to hypoglycaemia.

4.3. Final Comments. From a certain perspective, the falsifier selects the most adequate controller as if it *estimated* the scheduling parameter ρ, which the LPV needs to measure in real time. In general, this is an advantage of UC over LPV because there is no need to measure a parameter, which

Table 2: Noninvasive glucose-meters.

Name	Description	Status
Cybiocare (Photonic Medical Devices)	Infrared technology	Clinical testing
SCOUT DS (VeraLight)	Fluorescence spectroscopy	Restricted to investigational use only
GlucoTrack (Integrity Applications)	Ultrasound, conductivity and heat capacity (ear clip)	EU approval, waiting for FDA
LighTouch Medical, Inc.	Spectroscopy	Not submitted to FDA
OrSense Ltd	Proprietary occlusion spectroscopy	FDA approval for NBM 200-G
Sentek	Patented crystalline colloidal array (CCA)	Licensed University of Pittsburgh
Symphony (Sontra Medical)	Ultrasonically permeated skin	
Visual Pathways Inc.	Fluid measurement (anterior chamber of eye)	Federal Grant

in many cases could be unavailable or suffer from large measurement errors. Another advantage is that theoretically, the controller at the operating point could be designed in a less conservative way, thus offering better performance. This is the case here, illustrated by Figures 4 and 6, where UC has a tighter tracking of the reference. The disadvantage of UC is that practical controller selection could be more difficult in many cases.

In the LPV case, the design is carried out for all operating conditions simultaneously, which guarantees stability and a smooth transition between operating points. This, in general, produces lower performance. A consequence possibly due to guaranteed stability and smooth controller scheduling, is that the LPV controller has better robustness characteristics against actuator delays, as indicated at the end of Section 4.2.

In a first stage, both controllers 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, they could be used to close the loop between a glucose monitor and a insulin pump. In order to do this, some technological issues need to be mentioned.

To build a device which could implement any of these algorithms, a semi-invasive or noninvasive glucose monitor would be necessary. Similarly, at least a semi-invasive insulin delivery system would be desirable. In the case of noninvasive sensors, there are great efforts to develop a commercially available product, but there is still work to be done until such a product exists (see Table 2).

Two other important issues that should also be considered, based on previous sensor and actuator technologies, are glucose measurement errors and time delay, both in insulin delivery and glucose monitoring. As presented previously, time delay can significantly influence controller performance in the UC case.

5. Conclusions and Future Research

This work has considered several important and practical issues in the automatic control of glucose levels in blood: model uncertainty, time variations, nonlinearities, measurement noise, actuator delay and saturation, and real time implementation. All of them can be handled in an LPV and UC framework, which are time-varying controller methodologies. In the first case with a smooth transition among controllers, and in the second via switching. Both are implemented online in a very simple way.

Future research which approaches the controller design problem based upon more accurate models, as the 19th order one due to Sorensen [4], needs to be done. The existing LPV model [11] linearizes at different operating points and combines those models as vertices of a convex set, but it is not clear if this affine-LPV model would mimic the actual phenomena. 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 [42]. Instead, an LPV model could be attempted by taking the original nonlinear one 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. The controller design based on such a model could use the FBM LPV methodology [23], which may still be solved through a finite number of LMI computations.

As mentioned along this work, time delays in insulin injection and glucose measurement due to subcutaneous application are important issues to continue exploring when designing controllers for this application.

Finally, identification and model invalidation experiments [43] also need to be performed in order to obtain a more precise description of this complicated phenomena. To this end, a first stage could be attempted based on a High-Fidelity simulator (*in silico* experiments), which may include better sensor and actuator models. This may allow to complete a series of identification, invalidation and control tests before turning into *in vivo* experimentation.

Acknowledgments

The first author gratefully acknowledges the PRH Program of the Ministry of Science and Technology of Argentina and also the motivating mails and talks with Sofía Perazzo and her son Benjamín, which inspired this research.

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