Reducing Risks in Type 1 Diabetes Using $\mathcal{H}_\infty$ Control

P. Colmegna[1], R. S. Sánchez Peña[1,2], *Senior Member, IEEE*, R. Gondhalekar[3,4], *Senior Member, IEEE*, E. Dassau[3,4], *Senior Member, IEEE*, and F. J. Doyle III[3,4], *Fellow, IEEE*

[1]Centro de Sistemas y Control, Instituto Tecnológico de Buenos Aires (ITBA), Buenos Aires, C1106ACD, Argentina
[2] CONICET, Argentina
[3]Department of Chemical Engineering, University of California, Santa Barbara, CA 93106, USA
[4]Sansum Diabetes Research Institute, Santa Barbara, CA 93105, USA

A control scheme was designed in order to reduce the risks of hyperglycemia and hypoglycemia in Type 1 Diabetes Mellitus (T1DM). This structure is composed of three main components: an $\mathcal{H}_\infty$ robust controller, an Insulin Feedback Loop (IFL) and a Safety Mechanism (SM). A control-relevant model that is employed to design the robust controller is identified. The identification procedure is based on the distribution version of the UVA/Padova metabolic simulator using the simulation adult cohort. The SM prevents dangerous scenarios by acting upon a prediction of future glucose levels, and the IFL modifies the loop gain in order to reduce postprandial hypoglycemia risks. The procedure is tested on the complete *in silico* adult cohort of the UVA/Padova metabolic simulator, which has been accepted by the Food and Drug Administration (FDA) in lieu of animal trials.

***Index Terms*—Type 1 diabetes, hypoglycemia, hyperglycemia, $\mathcal{H}_\infty$ control**

I. Introduction

T1DM is an autoimmune disease which is characterized by the destruction of the pancreatic β-cells and consequently, insulin deficiency. This pathology has been increasing 3-4$\%$ per year in youths, making diabetes one of the most common childhood diseases [1]. In order to avoid being exposed to prolonged hyperglycemia and ketoacidosis, a T1DM patient is dependent on insulin injections and self-monitoring of blood glucose throughout his/her life. Therefore, the self-management of this disease is extremely demanding and does not reliably lead to effective glycemic control. Consequently, the problem of automatically controlling the blood glucose level in T1DM patients is a long standing problem [2]–[8].

An artificial pancreas consist of a Continuous Subcutaneous Insulin Infusion (CSII) pump, a Continuous Glucose Monitoring (CGM) and a control algorithm which closes the loop. A variety of Model Predictive Control (MPC) strategies and Proportional Integral Derivative (PID) controllers have been extensively tested both *in silico* and also in clinical trials [9]–[15]. Furthermore, other control techniques like adaptive control [16], Linear Parameter-Varying (LPV) control [17], $\mathcal{H}_\infty$ control [18]–[20] and even fuzzy logic theory [21], [22] have also been considered. However, both LPV and also $\mathcal{H}_\infty$ control have not been tested in clinical trials yet. In addition, the feasibility of safe blood glucose control with subcutaneous delivery of both insulin and glucagon has been demostrated in several works [23]–[25].

In any artificial pancreas scheme based on subcutaneous insulin delivery and/or glucose measurement, there is great difficulty in dealing with the long actuation/sensing delays, and also the large inter- and intra-patient variability. Due to the fact that the system is highly uncertain and time-varying, it is clear that some tuning to patient-specific characteristics is necessary to achieve high closed-loop performance [26]. One way to tune or adapt to a particular patient would be to perform an in-depth *a priori* identification procedure [27], although the complexity of such a procedure, and the time required to perform it, are likely to render such individualization infeasible in practice. Nevertheless, a general model structure could be adapted to a particular patient by using certain *a priori* clinical information that is easily obtainable, e.g., the patient's Total Daily Insulin (TDI) amount. Here, only adult patients are considered to present the first results of this algorithm, because a lack of efficacy in adults could lead to dismissal of possible therapies that could benefit children, the highest-risk population [28]. In this work a control model is synthesized by performing system identification on the ten adult *in-silico* subjects of the UVA/Padova simulator. A third order model was chosen, and the model gain is personalized by means of the subjects' TDI. That personalized model, whose parameters lack physiological meaning because so-called black-box procedures were used to identify the model, is employed to synthesize an $\mathcal{H}_\infty$ controller by solving a mixed-sensitivity problem. The $\mathcal{H}_\infty$ control, which to our knowledge has never before been tested on the complete adult cohort of the UVA/Padova metabolic simulator, represents an alternative approach to other well known control algorithms. This technique provides a good balance between insulin dosing and glucose tracking, by a practical, low order controller.

In order to achieve safe hypoglycemia control, an IFL has been added to adequately regulate an estimate of the patient's Insulin on Board (IOB). In addition, a SM is used to perform better control based on a prediction, over a 20 minute horizon, of future glucose levels. Auxiliary modules that modify insulin dosing when safety alarms are detected have been applied in several papers, demonstrating their importance in achieving safe blood glocuse control [29]–[33].

This work is organized as follows. The model identification

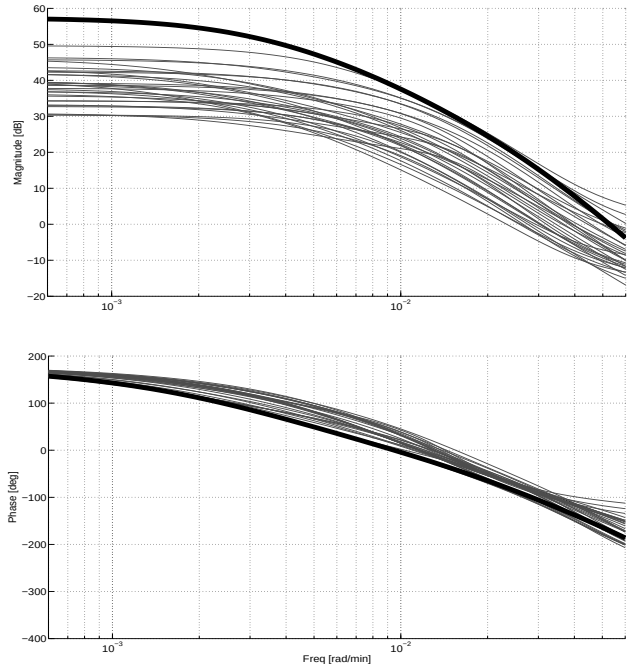

Figure 1. Bode diagram of all 10 virtual adult patients at three different glucose levels (thin lines) and $G_0(z)$.

is performed in Section II. An explanation about how the controller is designed, and how it works, is presented in Section III. Results of numerical simulations are provided in Section IV, and conclusions are presented in Section V.

II. Model Identification & patient tuning

Several models that describe the glucose-insulin dynamics have been developed [15], [34], [35]. However, the model parameters typically have physiological significance and cannot easily be estimated in real patients. In addition, for control synthesis a simple, low order-model is frequently more desirable than a complex, sophisticated model [36]. Therefore, a low-order control-relevant model is identified using a black-box approach, and subsequently adjusted based solely on *a priori* patient data, as in [37]. The procedure is described next.

For each *in-silico* adult of the distribution version of the T1DM simulator, a linear model of the transfer characteristics from the insulin delivery (pmol/min/kg) to the deviation from a particular glucose concentration (mg/dl) is identified. Three different interstitial glucose concentrations[1] are considered here: 90, 120 and 150 mg/dl to capture the frequency response at different operating points. 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) that produces the particular glucose concentration at steady state is obtained. Then, I_b is added to a sinusoidal insulin sweep. Over 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.

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

Third-order models were obtained in all 30 cases using subspace identification algorithms [38], [39]. Considering these models, the following discrete-time transfer function is defined:

$$G_0(z) = -\frac{c_0 z^{-3}}{(1-z^{-1}p_1)(1-z^{-1}p_2)(1-z^{-1}p_3)} \tag{1}$$

where $c_0 = 0.132$ and the poles are: $p_1 = 0.965$, $p_2 = 0.95$ and $p_3 = 0.93$. Figure 1 depicts the Bode diagrams of $G_0(z)$ and all identified models. The gain of $G_0(z)$ is intentionally overestimated, and its phase is purposefully chosen lower than the phase of all identified models, in order to obtain robust controllers as in [37]. From previous experience, a controller based on this *nominal* model could be too conservative and consequently may lead to poor performance. In order to limit this conservatism, an individualized transfer function $G_{0,\mathrm{j}}(z)$ is defined:

$$G_{0,\mathrm{j}}(z) \quad = \quad -\frac{cr_{\mathrm{j}} z^{-3}}{(1-z^{-1}p_1)(1-z^{-1}p_2)(1-z^{-1}p_3)}. \tag{2}$$

Here, as in [37], $r_{\mathrm{j}} = 1800/\mathrm{TDI_j}$ is based on the *1800 rule* (see [40]) and represents the gain, which adapts to the patient's TDI, where the TDI of the patient with index j is denoted by $\mathrm{TDI_j}$, and

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

is a constant that scales units. Therefore, cr_{j} is adapted to each patient instead of using the constant value c_0.

III. Controller Design

The glucose controller consists of 3 parts:

1) an $\mathcal{H}_\infty$ controller;
2) a SM;
3) an IFL.

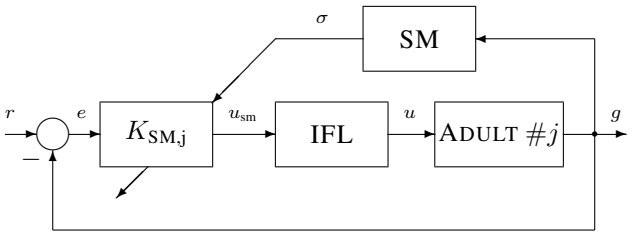

Figure 2. Block diagram of the closed loop.

A schematic of the closed-loop system, considering one adult from the simulator database, is depicted in Fig. 2, in which $K_{\mathrm{SM,j}}$ is the $\mathcal{H}_\infty$ controller modified by the SM, g is the measured glucose concentration, u_{sm} is the control signal proposed by $K_{\mathrm{SM,j}}$, u is the insulin input that is finally commanded to the CSII pump, r and e are, respectively, the reference and error signals, and σ is a switching signal, which is defined in Section III-B.

A. $\mathcal{H}_\infty$ Controller

$\mathcal{H}_\infty$ has proven to be a practical controller synthesis approach when using LTI plant models. The low order robust controller characterized by $\mathcal{H}_\infty$ naturally performs an effective tradeoff between the strength of control action and the tracking error. This compromise is known as the *mixed-sensitivity* problem and the optimal solution in terms of the lowest gain between the input disturbance and the output errors is achieved by this optimal control procedure.

Consider Adult #j from the simulator database and let $G_{0,\mathrm{j}}(z)$ be its nominal model. A discrete $\mathcal{H}_\infty$ controller K_j is synthesized solving a mixed-sensitivity problem with a performance objective defined as:

$$\min\left\{\gamma \text{ such that } \left\|\begin{bmatrix} W_\mathrm{p}(z)S_{0,\mathrm{j}}(z) \\ W_{\Delta,\mathrm{j}}(z)K_\mathrm{j}(z)S_{0,\mathrm{j}}(z) \end{bmatrix}\right\|_\infty < \gamma\right\}. \quad (4)$$

Here, $S_{0,\mathrm{j}}(z) = (1 + G_{0,\mathrm{j}}(z)K_\mathrm{j}(z))^{-1}$ is the sensitivity function, $W_\mathrm{p}(z)$ and $W_{\Delta,\mathrm{j}}(z)$ are the performance and control weights, respectively, and the sample-period is 10 min.

To reduce the risk of hypoglycemia, $W_{\Delta,\mathrm{j}}(z)$ resembles a derivative in order to penalize fast changes in the insulin delivery. Regarding $W_\mathrm{p}(z)$, it is chosen to be close to an integrator, i.e., large at low frequencies, to induce fast tracking of the safe blood glucose levels.

In all cases, $W_\mathrm{p}(z)$ and $W_{\Delta,\mathrm{j}}(z)$ are as follows:

$$W_\mathrm{p}(z) = \frac{0.01434z - 0.01365}{z - 0.9993} \quad (5)$$

$$W_{\Delta,\mathrm{j}}(z) = \mathrm{IS_j} \times \frac{0.001992(z-1)}{z - 0.992} \quad (6)$$

where $\mathrm{IS_j}$ is the individualized gain based on the subject's sensitivity to insulin, which is related to the following *a priori* clinical information:

- the average TDI regimen, in units of insulin;
- the Correction Factor (CF), which is the maximum drop in mg/dl per unit of insulin;
- the Carbohydrate Ratio (CR), which is used to compute the meal bolus as a function of the meal size.

IS values greater than unity are desired for patients with high insulin sensitivity, in order to increase the weighting on the control signal, and thereby reduce the amount of insulin infused. In general:

$$\downarrow \text{TDI and} \uparrow \{\text{CF, CR}\} \Rightarrow \uparrow \text{insulin sensitivity} \Rightarrow \text{IS} > 1$$

and vice versa. It means that low TDI and high CF and CR are likely related to patients with high insulin sensitivity and therefore, IS should be defined greater than unity, and vice versa. In order to quantify the effect of CR and CF, we define $C_\mathrm{av} = \alpha\mathrm{CR} + \beta\mathrm{CF}$, with $\alpha \geq 0$, $\beta \geq 0$, and $\alpha + \beta = 1$. Units of α and β are [U/g] and [UdL/mg], respectively. Here, the solution is obtained choosing $\alpha = 0.5$ U/g, and $\beta = 0.5$ UdL/mg. However, if one coefficient (CR or CF) needs to be emphasized because it is more important or accurate than the other, then α and β can be selected with different weightings.

The TDI and the C_av of an adult from the simulator database, should be selected as the reference values: $\mathrm{TDI_r}$, $\mathrm{C_{avr}}$ and $\mathrm{IS_r} = 1$. Due to the fact that both the patient's model and also its design weight $W_{\Delta,\mathrm{j}}(z)$ both depend on its *a priori* $\mathrm{TDI_j}$, any adult from the database can be selected as the reference. Without loss of generality, patient #9 has been considered as a starting point. Finally, for Adult #j the $\mathrm{IS_j}$ is calculated as follows:

$$\mathrm{IS_j} = \frac{\mathrm{TDI_r}}{\mathrm{TDI_j}}\frac{\mathrm{C_{avj}}}{\mathrm{C_{avr}}}. \quad (7)$$

Therefore, if Adult #j is likely to be more sensitive to insulin than Adult # 9, $\mathrm{IS_j}$ will be greater than unity, otherwise it will be less than unity.

B. Safety Mechanism

In order to reduce the risk of hypoglycemia and hyperglycemia, a SM is included to modify the $\mathcal{H}_\infty$ controller output (u_K). As shown in Fig. 3, the SM is composed of a Decision Algorithm (DA) and 2 prediction strategies:

- Linear Extrapolation (E) to predict future glucose levels considering the last 3 glucose measurements;
- Kalman Filtering (F) to predict the levels, rates of change, and acceleration, of future glucose concentrations.

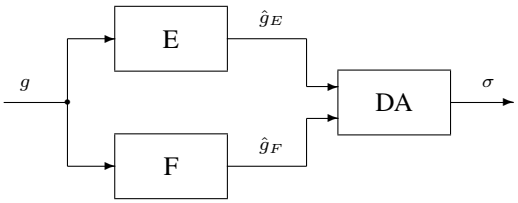

Figure 3. Block diagram of the SM including the decision (DA) and prediction (E and F) algorithms.

Any one prediction strategy has disadvantages compared to others, and a safety module based on only one single strategy would suffer from these weaknesses as a consequence. In this work the use of parallel prediction strategies E and F, in conjunction with a DA, allows us to exploit the strengths of the individual algorithms, to better predict dangerous future glucose scenarios and thereby to create a more robust system [41].

Both E and F have a sample-period of 10 min and a forecasting horizon of 20 min. In [41] a similar approach is presented, but considering a greater number of prediction algorithms and a different DA. Here, the SM process can be described as follows.

- At every sampling time k, the glucose is measured (g) and the prediction algorithms estimate the future glucose level ($\hat{g}$). According to the following 4 regions:
  - Region λ_1: $\hat{g} < 90$ mg/dl
  - Region λ_2: $90 \leq \hat{g} \leq 110$ mg/dl
  - Region λ_3: $110 < \hat{g} \leq 220$ mg/dl
  - Region λ_4: $\hat{g} > 220$ mg/dl

  the DA defines the variables

  $$n_{i,p,k} = \begin{cases} 1 & \text{if } \hat{g}_{p,k} \,\epsilon \text{ Region } \lambda_i \\ 0 & \text{otherwise} \end{cases}$$

  $\forall\ i\ \epsilon\ \{1, ..., 4\}$ and $p\ \epsilon\ \{E, F\}$. The variable $\hat{g}_{p,k}$ represents the estimated glucose value at step $k + 2$

	Breakfast 1		Lunch 1		Dinner 1		Breakfast 2		Lunch 2		Dinner 2		Breakfast 3		Lunch 3		Dinner 3	
	Time	Size	Time	Size	Time	Size	Time	Size	Time	Size	Time	Size	Time	Size	Time	Size	Time	Size
#1	7 AM	50 g	2 PM	60 g	8 PM	50 g	6 AM	50 g	1 PM	70 g	7 PM	50 g	7 AM	50 g	1 PM	65 g	9 PM	55 g
#2	7 AM	50 g	-	-	8 PM	60 g	-	-	12 PM	55 g	9 PM	50 g	7 AM	50 g	2 PM	55 g	8 PM	50 g

Table I
PROTOCOL #1 AND #2.

(twenty minutes later) by the prediction algorithm p as predicted at actual step k.

- Finally, the switching signal σ is defined in the following Matlab-like code.

```
if n_{1,F} ≥ 1 && n_{1,E} ≥ 1 || g < 90 mg/dl
    σ = 1;
elseif  n_2 ≥ n_3 && n_2 > 0
    σ = 2;
elseif  n_3 ≥ n_4 && n_3 > 0
    σ = 3;
else
    σ = 4;
end
u_sm = ρ_σ u_K;
```

where $n_i = \sum_{p,m} n_{i,p,m}$, $n_{i,p} = \sum_m n_{i,p,m}$, $\rho_1 = 0$, $\rho_2 = 0.5$, $\rho_3 = 1$, $\rho_4 = 1.25$ and $m = \{k-2, k-1, k\}$.

Therefore, if low glucose values are predicted, the insulin delivery is either suspended or attenuated. On the other hand, if high glucose values are predicted, the insulin delivery proposed by the $\mathcal{H}_\infty$ controller is increased.

C. Insulin Feedback Loop

The main risks of insulin therapy are an overdose of insulin and a high level of IOB in the body. An estimate of IOB is made and employed to prevent insulin stacking due to frequent insulin boluses. Therefore, an IFL as shown in Fig. 4 is included at the $K_{\text{SM,j}}$ output to inhibit the insulin infusion when the plasma insulin concentration is estimated to be excessive [32], [33]. The SIM block is the Subcutaneous Insulin Model presented in Appendix A and employs the mean population values for all its parameters. The model is discretized with a sample-period of 10 min and it is used to estimate the plasma insulin relative to the basal conditions. The parameter μ is a tuning gain, fixed to 7.5 for all subjects according to the magnitude of the signals involved and the desired closed-loop performance. Its selection depends on the compromise between having a slow (high μ) or a more aggressive and fast (low μ) response, after verifying the closed-loop stability. Consequently, if the estimated insulin concentration is higher than its nominal value the control signal is reduced by an amount proportional to that difference.

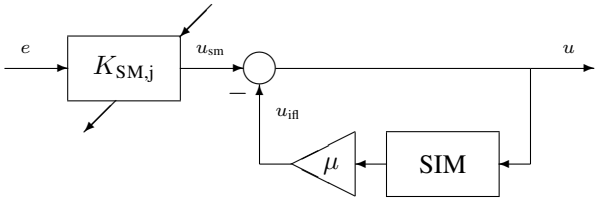

Figure 4. Block diagram of $K_{\text{SM,j}}$ and the IFL.

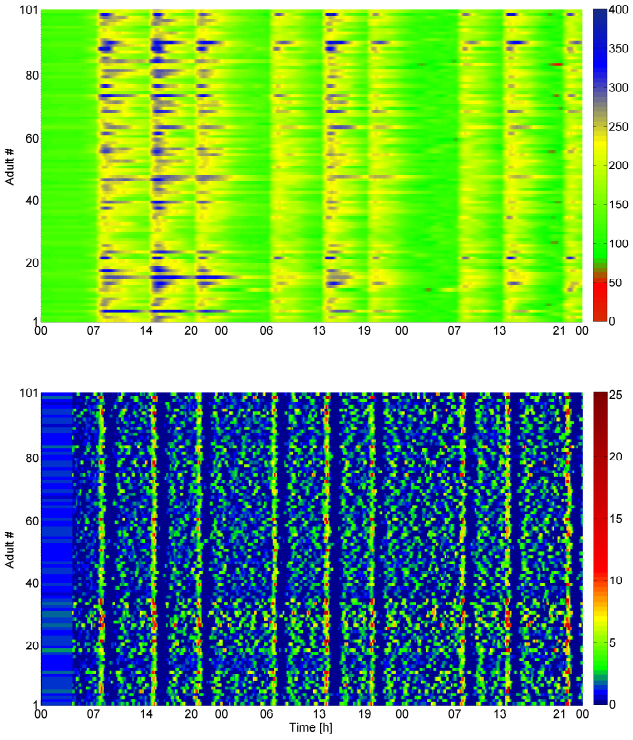

Figure 5. Closed-loop responses for the 101 *in silico* adults to protocol #1. Above: blood glucose [mg/dl]. Below: insulin [U/h].

IV. RESULTS

The complete UVA/Padova T1DM simulator, which is accepted by the FDA in lieu of animal trials in the development of an artificial pancreas [42], is used to test the closed-loop performance. Simulations are performed for all 101 *in silico* adults (one is an average patient), considering unannounced meals, a CSII pump, CGM as sensor, and two different protocols, which are presented in Table I. Protocol #1 includes three meals per day, while protocol #2 is used to evaluate the safety of the algorithm when long fasting periods appear.

In addition, in both protocols the simulation starts in the fasting state of each subject, and the basal insulin is infused during the first 4 hours. Then, the glucose controller takes over the insulin delivery considering a constant setpoint. A postprandial period (PP) is defined as the 5 hour time interval following the start of a meal, and night (N) is defined as the period from 00:00 to 7:00 AM.

The glucose responses to protocol #1 are depicted in Fig. 5, employing differing colors to differentiate between risky and safe situations. Note that the glucose graph is mainly green and the insulin graph blue, which means that glucose levels are mostly near the safe values, and that the insulin injection is generally low.

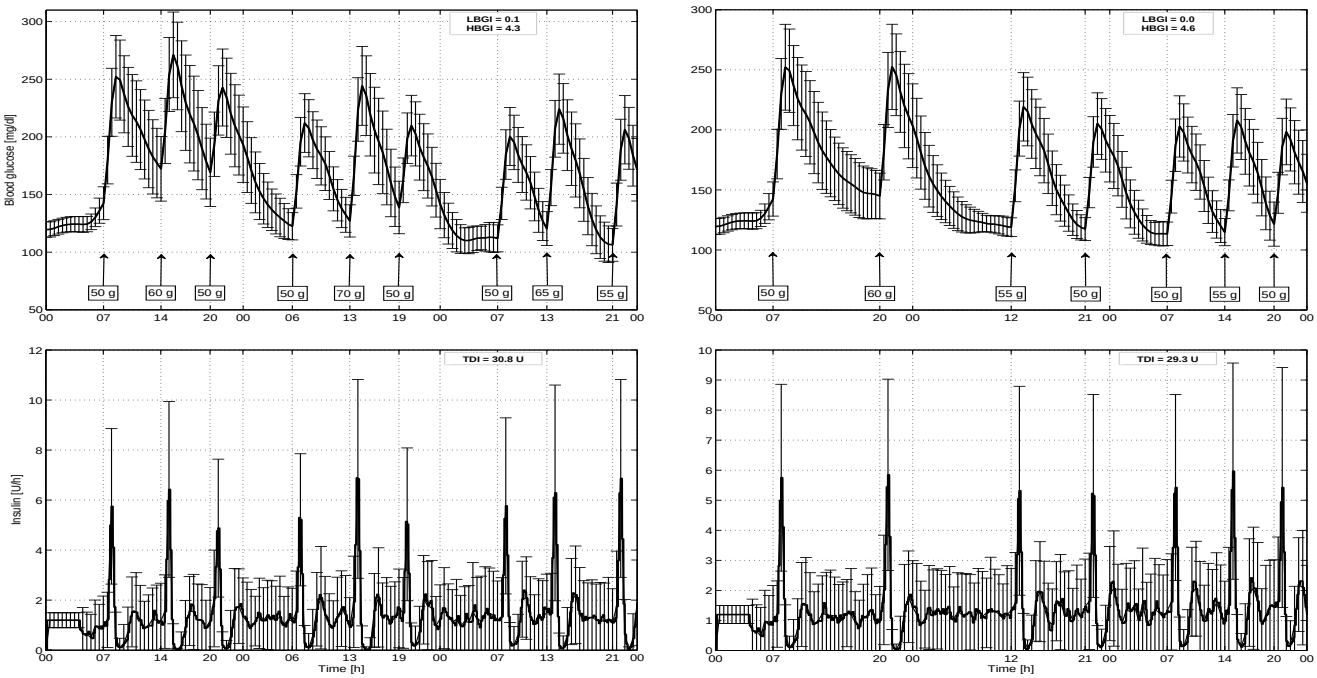

Figure 6. Average closed-loop responses for the 101 *in silico* adults to protocol #1 (left) and to protocol #2 (right). The mean ±1 STD values are represented by vertical bars, every 30 minutes.

	Mean BG			**Max BG**			**Min BG**			**% in [70 180]**			**% > 300**			**% > 180**			**% < 70**		
	O	**PP**	**N**	**O**	**PP**	**N**	**O**	**PP**	**N**	**O**	**PP**	**N**	**O**	**PP**	**N**	**O**	**PP**	**N**	**O**	**PP**	**N**
#1	148	176	116	226	229	142	96	108	100	75.9	54.2	99.5	0.1	0.3	0.0	24.0	45.8	0.4	0.1	0.0	0.0
#2	154	177	135	220	224	183	108	114	107	75.5	54.4	91.4	0.0	0.1	0.0	24.5	45.6	8.6	0.0	0.0	0.0

Table II
AVERAGE RESULTS FOR THE 101 ADULTS TO PROTOCOL #1 AND #2.

The average time responses to both protocols are depicted in Fig. 6. As shown in that figure, large insulin spikes appear after meals. Then, the insulin infused is reduced and thereafter, a constant amount of insulin is administered on average.

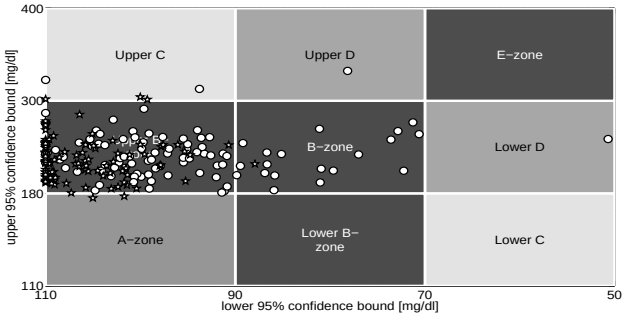

Figure 7. CVGA of all the 101 closed-loop responses to protocol #1 (circles) and protocol #2 (stars).

Although meals are unannounced and there is not any particular adjustment for any patient, besides the automatic one at the controller design stage, a minimal High BG Index (HBGI $<$ 5.0) and a minimal Low BG Index (LBGI $<$ 1.1) were achieved in both protocols as shown in Fig. 6. As shown in Table II, for both protocols the proposed controller achieves meal glucose values that are less than, or equal to, 154 mg/dl, which is in accordance with recommendations made by the American Diabetes Association (ADA) [43]. Therefore, due to the fact that hypoglycemia occurs only for one subject, we conclude that safe hyperglycemic control has been achieved.

The Control Variability Grid Analysis (CVGA) and the average results for both protocols are presented in Fig. 7 and Table II, respectively. In Table II the overall (O), PP and N time intervals are analyzed separately. Because of the high measurement noise[2], a reduced closed-loop bandwidth has been proposed. Therefore, higher blood glucose peaks appear during the first day of trial. Consequently, and furthermore because each day of the protocol has similarly sized meals, both the CVGA plot, as well as the average results, related to protocol #1 are computed based on the results of the third day. On the other hand, the CVGA plot and the average results related to protocol #2 are obtained considering the data from the second day, to include its long fasting period. In order to reflect how the IFL helps to avoid postprandial hypoglycemia, the IFL signal obtained considering the last day of protocol #1 is depicted in Fig. 8. As was mentioned above, a large insulin spike appears after a meal. Consequently, as u_{ifl} starts to increase the insulin infused $u = u_{\text{sm}} - u_{\text{ifl}}$ starts to be reduced. This process avoids insulin overdosing, and therefore mitigates postprandial hypoglycemia. The usefulness of the SM is also reflected in Fig. 8. For protocol #1, the mean minus one STD value obtained every 30 minutes for all 101 adults, both with

[2]In [42] it is anticipated that the real sensor errors would tend to be smaller during controlled inpatient clinical trials.

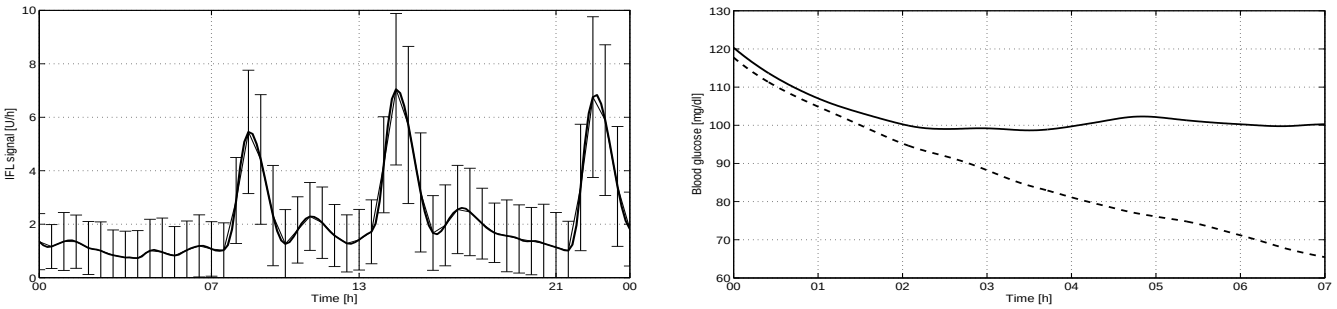

Figure 8. Left: Average IFL signal for the 101 *in silico* adults to the third day of protocol #1. The mean ± 1 STD bar is plotted every 30 minutes. Right: The mean minus one STD value of the 101 closed-loop night response to protocol #1 with (continuous line) and without (dashed line) the SM.

and without the SM, are compared. As illustrated, the SM assists the algorithm in preventing low glucose outcomes.

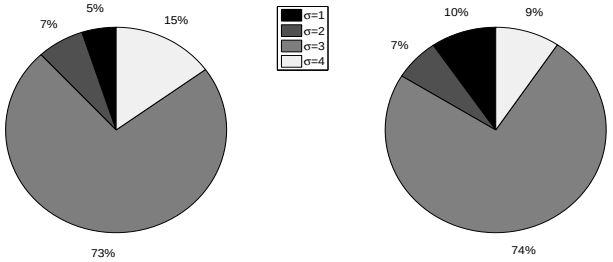

Figure 9. Percentage of time each value of σ is selected. Left: protocol #1. Right: protocol #2.

For how long each value of σ is selected is represented in Fig. 9. According to this figure, the algorithm settles on $\sigma = 3$, the unscaled $\mathcal{H}_\infty$ controller, more than 70% of the time in both protocols. The last situation is also reflected in Table II in which the percentages of time in the range [70, 180] mg/dl are presented. This is a desirable situation, because the selection of this control implies that the glucose values tend to remain in a safe region. Hence, according to the results obtained, it could be concluded that a safe hyper- and hypoglycemia blood glucose control has been achieved. Because the UVA/Padova metabolic simulator does not include intra-patient variations, that scenario could not be tested. However, the Proposed Approach (PA) has proved robust to large inter-patient variations. In addition, parameter IS_j could also be modified to a controller that is either more, or less, aggressive, depending on whether the subject's sensitivity to insulin changed drastically over time.

Finally, results for the standard open-loop basal-bolus treatment, with boluses delivered at the time of meal ingestion, are presented in Table III for comparison. As expected, because the PA considers unannounced meals, better performance is obtained with an Optimal Bolus Treatment (OBT). However, in practice the meal is sometimes wrongly estimated, and as a result the bolus size is not appropriate. In order to illustrate the risk of that situation, the CVGA obtained with the PA and with a 30% overestimated OBT is presented in Fig. 10.

Control Strategy		PA	70% of OB	OBT	130% of OB
Mean BG [mg/dl]	**O**	148	144	127	110
	PP	176	165	143	125
	N	116	119	109	99
Max BG [mg/dl]	**O**	226	199	175	162
	PP	229	202	178	164
	N	142	129	117	115
Min BG [mg/dl]	**O**	96	115	99	73
	PP	108	119	105	80
	N	100	115	101	76
% time in [70 180] mg/dl	**O**	75.9	86.5	95.9	92.2
	PP	54.2	73.6	91.8	94.6
	N	99.5	100	100	91.2
% time > 300 mg/dl	**O**	0.1	0.0	0.0	0.0
	PP	0.3	0.0	0.0	0.0
	N	0.0	0.0	0.0	0.0
% time > 180 mg/dl	**O**	24.0	13.5	4.1	1.9
	PP	45.8	26.5	8.2	3.7
	N	0.4	0.0	0.0	0.0
% time < 70 mg/dl	**O**	0.1	0.0	0.0	5.9
	PP	0.0	0.0	0.0	1.7
	N	0.0	0.0	0.0	8.8

Table III
COMPARISON BETWEEN THE AVERAGE RESULTS FOR THE 101 ADULTS TO PROTOCOL #1 OBTAINED WITH THE PA, WITH AN OBT, WITH A 30% UNDERESTIMATED OBT, AND WITH A 30% OVERESTIMATED OBT.

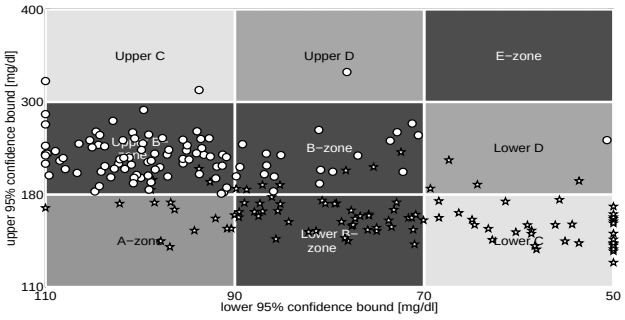

Figure 10. CVGA of all the 101 closed-loop responses to protocol #1. (Circles) PA. (Stars) OBT overestimating the bolus sizes by 30%.

V. CONCLUSION

A controller structure is designed focused on hyper– and hypoglycemia protection. The system identification is based on the 10 subject cohort, in order to mimic a reduced spectrum of information present for controller design, and to design a controller that is suitably safe. The robust $\mathcal{H}_\infty$ controller is synthesized via a mixed-sensitivity problem with weights focused on maintaining the glucose level near to the reference value while being cautious with the insulin injection. The IFL is intended as a postprandial hypoglycemia risk reduction based on the IOB estimation. Finally, the SM considers an

estimation of future glucose levels in order to maintain the patient's glucose concentration in a safe region. The method is practical because it only uses *a priori* patient information that is easily obtainable, and works for both different patients and unannounced meals. For validation purposes, the full cohort of the 101 subject simulator was employed to rigorously test the proposed control strategy, showing good performance and minimal hyper– and hypoglycemia risks.

APPENDIX A
SUBCUTANEOUS INSULIN MODEL

The insulin model employed in the IFL is presented in [35] and the subcutaneous insulin kinetics, which complete the model equations, are introduced in [44].

$$\begin{aligned} \dot{I}_{sc1} &= -(k_d + k_{a1})I_{sc1}(t) + IIR(t) \\ \dot{I}_{sc2} &= k_d I_{sc1}(t) - k_{a2} I_{sc2}(t) \\ \dot{I}_l &= -(m_1 + m_3)I_l(t) + m_2 I_p \\ \dot{I}_p &= -(m_2 + m_4)I_p + m_1 I_l + k_{a1} I_{sc1} + k_{a2} I_{sc2} \\ I &= I_p / V_I \end{aligned} \tag{8}$$

Variables	
I_{sc1} :	Amount of nonmonomeric insulin in the subcutaneous space [pmol/l].
I_{sc2} :	Amount of monomeric insulin in the subcutaneous space [pmol/l].
I_p :	Insulin mass in plasma [pmol/l].
I_l :	Insulin mass in liver [pmol/l].
I :	Plasma insulin concentration [pmol/l].
IIR :	Exogenous insulin infusion rate [pmol/kg/min].
Parameters	
k_d :	Rate constant of insulin dissociation [min^{-1}].
k_{a1} :	Rate constant of nonmonomeric insulin absorption [min^{-1}].
k_{a2} :	Rate constant of monomeric insulin absorption [min^{-1}].
m_i :	Rate parameters [min^{-1}], i=1,...,4.
V_I :	Distribution volume of insulin [l/kg].

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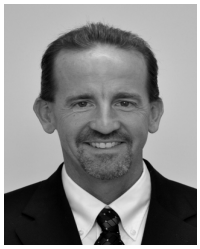
Patricio Colmegna received the B.S. degree in Automation and Control Engineering from the Universidad Nacional de Quilmes (UNQ), Buenos Aires, Argentina in 2010. He is currently pursuing the Ph.D. degree in Automatic Control at the Instituto Tecnológico de Buenos Aires (ITBA), being supported by a research scholarship from the Agencia Nacional de Promoción Científica y Tecnológica, Ministerio de Ciencia y Tecnología e Innovación Productiva, Argentina. He is also working as a teaching assistant at control systems courses at UNQ. His research interests include modeling, identification and robust control for type 1 diabetes mellitus and mechatronics systems.

Ricardo S. Sánchez-Peña (StM'86-M'88-SM'00) received the Electronic Engineer degree from the University of Buenos Aires (UBA, 1978), and the M.Sc. and Ph.D. from the California Institute of Technology (1986, 1988), both in Electrical Engineering. In Argentina he worked in CITEFA, CNEA and the space agencies CNIE and CONAE. He collaborated with NASA in aeronautical and satellite projects and with the German (DLR) and Brazilian (CTA/INPE) space agencies. He was Full Professor at UBA (1989-2004), ICREA Senior Researcher at the Universitat Politècnica de Catalunya (2005-2009, Barcelona) and visiting Prof./Researcher at several Universities in the USA and the EU. He has consulted for ZonaTech (USA), STI and VENG (Argentina) in aerospace applications and with Alstom-Ecotecnia (Spain) in wind turbines applications. He is recipient of the *Premio Consagración* in Engineering by the National Academy of Exact, Physical and Natural Sciences (ANCEFN, Argentina) and the Group Achievement Award fom NASA as a Review Board member for the Aquarius/SAC-D satellite. Since 2009 he is Director of the PhD Department in Engineering at the Buenos Aires Institute of Technology (ITBA) and a CONICET Principal Investigator. He has applied Identification and Control techniques to acoustical, mechanical and aero & astronautical engineering and also to type 1 diabetes.

Ravi Gondhalekar (M'10-SM'13) is a Project Scientist at the University of California Santa Barbara (UCSB), USA. His research interests include model predictive control, constrained control and optimization. At UCSB he is applying constrained model predictive control techniques to an artificial pancreas that performs automated delivery of insulin to people with type 1 diabetes. Ravi received a PhD degree in informatics in 2008 from the Tokyo Institute of Technology, Japan, and MEng and BA degrees in engineering in 2002 from the University of Cambridge, UK. From 2008 to 2012 Ravi was an Assistant Professor at Osaka University, Japan. Prior to that he held short-term positions at the Massachusetts Institute of Technology, USA, the University of Cambridge, UK, Princeton University, USA, Pi Technology, UK, the Rutherford Appleton Laboratory, UK, and the United Kingdom Atomic Energy Authority, UK.

Eyal Dassau (M'08-SM'12) received the B.Sc., M.Sc., and Ph.D. degrees in chemical engineering, in 1999, 2002, and 2006, respectively, all from Technion Israel Institute of Technology. He is currently a Senior Investigator and Diabetes Research Manager with the University of California, Santa Barbara. He is also Adjunct Senior Investigator with the Sansum Diabetes Research Institute, Santa Barbara, CA. His current research interests include modeling, design and control of an artificial pancreas for type 1 diabetes mellitus. Process and product design with emphasis on medical and biomedical applications. Dr. Dassau is a Senior Member of the American Institute of Chemical Engineering and a member of the American Diabetes Association.



Frank J. Doyle III (M'02-SM'04-F'08) received the B.S.E. degree from Princeton University, Princeton, NJ, in 1985, the C.P.G.S. degree from the University of Cambridge, Cambridge, U.K., in 1986, and the Ph.D. degree from the California Institute of Technology, Pasadena, CA, in 1991, all in chemical engineering.

He holds the Duncan and Suzanne Mellichamp Chair in process control in the Department of Chemical Engineering, University of California, Santa Barbara, as well as appointments in the Electrical Engineering Department and the Biomolecular Science and Engineering Program. He is also a Guest Investigator with the Sansum Diabetes Research Institute, Santa Barbara. His research interests include systems biology, network science, modeling and analysis of circadian rhythms, drug delivery for diabetes, model-based control, and control of particulate processes.

Dr. Doyle is a Fellow of a number of societies including the International Federation of Automatic Control, the American Institute of Medical and Biological Engineering, and the American Association for the Advancement of Science. In 2005, he was awarded the Computing in Chemical Engineering Award from the American Institute of Chemical Engineers for his innovative research in systems biology.