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Artificial Pancreas System with Unannounced Meals based on a Disturbance Observer and Feedforward Compensation

Ricardo Sanz, Pedro García, José-Luis Díez and Jorge Bondia

Abstract—This paper is focused on closed-loop control of postprandial glucose levels of patients with type 1 diabetes mellitus after unannounced meals, still a major challenge towards a fully autonomous artificial pancreas. The main limitations are the delays introduced by the subcutaneous insulin pharmacokinetics and the glucose sensor, which typically lead to insulin over-delivery. Current solutions reported in the literature typically resort to meal announcement, which requires the patient intervention. In this paper, a disturbance observer is used to estimate the effect of unannounced meals and the insulin pharmacokinetics is taken into account by means of a feedforward compensator. The proposed strategy is validated in silico with the UVa/Padova metabolic simulator. It is demonstrated how the disturbance observer successfully estimates and counteracts not only the effect of meals but also sudden drops in the glucose levels that may lead to hypoglycemia. For unannounced meals, results show a median time-in-range of 80% in a 30-day scenario with high carbohydrate content and large intra-subject variability. Optionally, users may decide to announce meals. In this case, considering severe bolus mismatch due to carbohydrate counting errors, the median time-in-range is increased up to 88%. In every case, hypoglycemia is avoided.

Index Terms—Artificial pancreas, disturbance observer, feedforward compensation, type 1 diabetes

I. INTRODUCTION

TYPE 1 diabetes Mellitus (T1DM) is an auto-immune disorder that destroys the pancreatic β cells, which results in the incapability of secreting insulin, a hormone that plays a crucial role in glucose homeostasis as it is responsible of lowering plasma glucose concentration. Therefore, people with T1DM generally fail to maintain appropriate glucose levels and they tend to suffer chronic hyperglycemia, which leads to severe health problems in the long term, e.g., cardiovascular diseases, nephropathy, retinopathy and neuropathy [1]. This is the reason why exogenous insulin delivery is needed. Open-loop (manual) control by individuals with T1DM is highly demanding as it requires carbohydrate counting and a great number of insulin dosing decisions per day. It is not surprising then that closed-loop (automatized) insulin delivery has been an active research field since the 1970s [2], [3], [4]. The device that performs such task is widely known today as an artificial pancreas (AP).

In an AP, the insulin dose is computed by a control algorithm based on glucose measurements coming from a continuous glucose monitoring (CGM) device and automatically delivered through an insulin pump [5]. There is a substantial delay between the subcutaneous insulin delivery, its appearance in the blood stream and, ultimately, its effect in lowering blood glucose levels. Such long delay typically causes a feedback controller to over-deliver insulin, resulting in hypoglycemia, which is the main risk of closed-loop glucose control [6]. Nevertheless, the improvement of an AP in glucose regulation compared to open-loop therapy is widely acknowledged [7], [8], [9], [10]. A wide variety of control strategies have been applied to tackle this problem. Controllers based on model predictive control (MPC) [11], [12], [13], [14], proportional-integral-derivative (PID) control [15], [16], fuzzy logic [17], [18] or linear parameter varying (LPV) models [19], [20] have been tested in human trials. However, mitigation by the AP of hyperglycemia due to large meals is still challenging because of the limitations discussed above. Quite often, current APs deal with this problem by delivering an insulin bolus at meal time. However, this requires the patient intervention, who has to announce the meal and provide an estimate of its carbohydrate (CHO) content. Misestimation of CHO content and/or skipping meal announcements is indeed a risk and thus the controller should be able to handle these situations. In order to face unannounced meals, heuristic meal detection and carbohydrate counting algorithms based on CGM readings have been investigated, which are often used to deliver meal boluses accordingly [21], [22], [23], [24], [25]. In [19], a meal detection algorithm is used to trigger a switching controller. Within the framework of MPC, a switching cost-function based on the blood glucose rate of change has been employed in [26].

In the context of control theory, maintaining blood glucose near the target level can be seen as a standard regulation problem, in which disturbance rejection is the central issue.

R. Sanz is with the Instituto Universitario de Automática e Informática Industrial, Universitat Politècnica de València, 46022, València, Spain (e-mail: risanda@upv.es)

P. García is with the Instituto Universitario de Automática e Informática Industrial, Universitat Politècnica de València, 46022, València, Spain (e-mail: pggil@isa.upv.es)

J. L. Díez is with the Instituto Universitario de Automática e Informática Industrial, Universitat Politècnica de València, 46022, València, Spain, and also with the Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), 28029, Madrid, Spain (e-mail: jldiez@isa.upv.es)

J. Bondia is with the Instituto Universitario de Automática e Informática Industrial, Universitat Politècnica de València, 46022, València, Spain, and also with the Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), 28029, Madrid, Spain (e-mail: jbondia@isa.upv.es)

When disturbances are known, their effect can be mitigated by means of feedforward compensators [27]. However, quite often, disturbances cannot be directly measured (for example, meals in the application here considered). Disturbance observers (DOBs) emerged as a powerful tool to estimate unknown disturbances from other measurable input/output signals. Then, the estimated disturbance can be used to take appropriate actions, leading to the so-called DOB-based control. The reader is referred to [28] for an overview of available methods. DOB-based controllers have demonstrated simpler tuning and improved performance over equivalent PID-based strategies even in high-demanding real-time applications [29]. Furthermore, DOBs to estimate the rate of glucose appearance have been already designed and successfully validated through simulations in [30], [31].

In this paper, a DOB-based control strategy is proposed to deal with unannounced meals. The observer estimates any unexpected variation in the glucose level by using information of the CGM, the insulin infusion rate and a control-oriented nonlinear model of the patient adapted from [12], [32], [33]. The estimation provided by the observer is then combined with a feedforward strategy to compensate for the delay of the subcutaneous insulin pharmacokinetics. On the other hand, in order to handle the constraint of positive control action and to avoid insulin over-delivery, the insulin feedback strategy reported in [6] is employed.

II. METHODS

A. Control-oriented patient model

A subject-dependent model is employed for control purposes, adapted from [12], [32]. For each subject j, the following switched nonlinear personalized model is considered

$$
\begin{aligned}
\dot{G}(t) &= -(S_G(G) + r(G)X(t))G(t) + S_G(G)G_b + R_a(t), \\
\dot{X}(t) &= -p_2 X(t) + p_2 S_I c_j I(t), \\
\dot{I}(t) &= -k_I I(t) + (1/(t_{max_I} V_I))S_2(t), \\
\dot{S}_2(t) &= -(1/t_{max_I})S_2(t) + (1/t_{max_I})S_1(t), \\
\dot{S}_1(t) &= -(1/t_{max_I})S_1(t) + \bar{u}_j(t),
\end{aligned}
\tag{1}
$$

where G (mg/dL) is the plasma glucose concentration, R_a (mg/dL/min) is the rate of glucose appearance, X (1/min) is the remote insulin action, I (μU/mL) is the deviation in plasma insulin concentration, S_2, S_1 (μU/kg) are the deviations in insulin amount at each compartment of the absorption model and $\bar{u}_j$ (μU/kg/min) is the incremental infusion rate with respect to the basal insulin infusion u_{b_j}, needed to maintain the fasting glucose value G_b. The functions $r, S_G : \mathbb{R}^+ \to \mathbb{R}^+$ are defined by $r(G) = \{\bar{r}$ if $G \geq G_b$; $\underline{r}$ if $G < G_b\}$ and $S_G(G) = \{\overline{S}_G$ if $G \geq G_b$; $\underline{S}_G$ if $G < G_b\}$, which are intended to account for the increase of the insulin action when glucose decreases under a given threshold towards hypoglycemia (this is a simplification of the risk function reported in [33]). The individualized parameter c_j is used to adapt the model gain as

$$
c_j = \max \left\{ 0.7, \min \left\{ CR_j/\overline{CR}, CF_j/\overline{CF} \right\} \right\},
\tag{2}
$$

where CR_j, CF_j are, respectively, the individual insulin-to-carbohydrate ratio, given by the simulator, and the correction factor, computed upon the total daily insulin (TDI) as $CF_j = 1800/TDI$ (this is referred to as the 1800-rule, often used in conventional diabetes therapy [34]); and $\overline{CR} = 15.9$ g/U, $\overline{CF} = 40.8$ mg/dL/U are the mean population values based on the ten adult virtual subjects of the distribution version of the UVa/Padova simulator. The factor c_j is lower bounded by 0.7 for safety to avoid too aggressive controllers. It should be stressed that the use of compact models for controller design purposes is well celebrated in the field [35], [36]. More specifically, gain-personalized models have been previously used in the literature as a useful tool to account for the variability of total daily insulin requirement among patients [37], [14], [38]. Moreover, CF_j and CR_j are clinical parameters that are known for every patient and thus the proposed tuning rule would be feasible in a clinical trial.

B. Model identification

A data set for identification was generated using the UVa/Padova simulator. This data set is based on an open-loop therapy and it includes meals of different size, bolusing and changes in the basal rate adjustment, including sinusoidal variations. Each of the ten adult virtual patients was identified using the genetic algorithm provided by Matlab® and population values were obtained by averaging them. The value $\bar{r} = 1$ was set manually to avoid identification problems because, otherwise, the effect of the insulin sensitivity S_I and the free parameters $\underline{r}, \bar{r}$ would be indistinguishable. The following mean values were obtained: $t_{max_I} = 48.8$ min, $k_I = 0.58$ min^{-1}, $V_I = 28.4$ mL/Kg, $S_I = 6 \cdot 10^{-4}$ mL/μU/min, $p_2 = 0.027$ min^{-1}, $\overline{S}_G = 0.017$ min^{-1}, $\underline{S}_G = 0.007$ min^{-1} and $\underline{r} = 1.41$. It should be remarked that G_b is a control parameter defining the operating coditions in the absence of disturbances, which was set to $G_b = 100$ mg/dL, and the corresponding basal insulin infusions for each patient, u_{b_j}, are obtained from the equilibrium equations of the simulator model [33].

C. Control strategy

The system (1) can be seen as the interconnection between a nonlinear subsystem, that is, the glucose metabolism, and a linear subsystem, namely, the insulin pharmacokinetics. According to this decomposition and defining

$$
x(t) = [X(t), I(t), S_2(t), S_1(t)]^T,
$$

the model (1) can be expressed as

$$
\begin{aligned}
\dot{G}(t) &= f(G(t), x_1(t), R_a(t)), \\
\dot{x}(t) &= Ax(t) + B\bar{u}_j(t), \\
y(t) &= x_1(t) = X(t),
\end{aligned}
\tag{3}
$$

where the function f and the matrices A, B are easily obtained from (1). For the sake of clarity, let us assume for the moment that both the state x, and the rate of glucose appearance $R_a(t)$, are known.

The proposed controller has a cascade structure. First, by looking at the nonlinear subsystem, the following exponentially stable target system[1] given by $\dot{G}(t) = -S_G(G)G(t) + S_G(G)G_{ref}(t)$, is proposed, which can be achieved by choosing a target trajectory $x_1^*(t)$ as follows

$$x_1^*(t) = \frac{1}{G(t)r(G)}\left(R_a(t) + S_G(G)\big(G_b - G_{ref}(t)\big)\right), \quad (4)$$

being $G_{ref}(t)$ a piecewise constant function representing the desired glucose concentration. Second, a tracking controller is designed so that the error $e(t) = x_1(t) - x_1^*(t)$ approaches to zero exponentially. To that end, let us consider the transformation $z(t) = Tx(t)$ so that the system in z-coordinates, given by $\dot{z}(t) = A_z z(t) + B_z \bar{u}_j(t)$, is in controllable canonical form, i.e.,

$$A_z = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ -a_1 & -a_2 & -a_3 & -a_4 \end{bmatrix}, \quad B_z = \begin{bmatrix} 0 \\ 0 \\ 0 \\ b \end{bmatrix}, \quad (5)$$

and $y(t) = z_1(t) = x_1(t) = X(t)$. It is well known that the transformation matrix is given by $T = \mathcal{C}(A_z, B_z)\mathcal{C}(A, B)^{-1}$, where $\mathcal{C}$ denotes the controllability matrix [40]. Once in controllable canonical form, it is easy to design the following tracking controller

$$\begin{aligned} \bar{u}_j(t) = {} & \frac{1}{b}\left(a_4 z_4(t) + a_3 z_3(t) + a_2 z_2(t) + a_1 z_1\right) \\ & + \frac{1}{b}\left(x_1^{*(4)}(t) - \sum_{j=1}^{4} k_j\big(z_j(t) - x_1^{*(j-1)}(t)\big)\right), \end{aligned} \quad (6)$$

that leads to the exponentially stable tracking error system

$$e^{(4)}(t) + k_4 e^{(3)}(t) + k_3 e^{(2)}(t) + k_2 e^{(1)}(t) + k_1 e(t) = 0, \quad (7)$$

for any set of gains $k_j > 0$. The overall stability of the $(\tilde{G}, e)$-system, being $\tilde{G}(t) = G(t) - G_{ref}(t)$, has a rather common cascade structure where the exponentially stable e-subsystem drives the $\tilde{G}$-subsystem. The latter can be cast into a switched system with vanishing perturbations whose stability is proved by means of a common Lyapunov function [41], [42].

D. Extended state observer

The controller strategy described above relies on the knowledge of the whole state x and the disturbance R_a. Since these variables are not measurable in practice, an extended state observer is adopted to estimate them [28], [30]. Using the notation introduced in (3), the proposed observer is given by

$$\begin{bmatrix} \dot{\hat{G}}(t) \\ \dot{\hat{x}}(t) \\ \dot{\hat{R}}_a(t) \end{bmatrix} = \begin{bmatrix} f(\hat{G}, \hat{x}_1, \hat{R}_a) \\ A\hat{x}(t) + B\bar{u}_j(t) \\ 0 \end{bmatrix} + L(G)(y(t) - \hat{G}(t)) \quad (8)$$

where $\hat{G}, \hat{x}, \hat{R}_a$ are the observer estimates and $L: \mathbb{R} \rightarrow \mathbb{R}^6$ is the matrix gain to be designed. The proposed observer (8) is composed of a nonlinear model with a switched linear gain,

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[1]This is a scalar switched system with two exponentially stable modes whose exponential stability under arbitrary switching is easily proved [39].

$L(G) = \{\overline{L}$ if $G \geq G_b$; $\underline{L}$ if $G < G_b\}$. Each of the gains is designed by pole placement using the corresponding linearized model around $G_b \pm \epsilon$ with $\epsilon \rightarrow 0$. The closed-loop poles of the observer are selected according to [30], in order to avoid overshoot in the estimation.

E. Tracking differentiator

One can see from (6) that the time-derivatives of the target signal $x_1^*(t)$ are also needed. Instead of computing those numerically, they are rather obtained by means of a simple linear tracking differentiator [43], given by

$$\dot{\xi}(t) = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ -\omega^4 & -4\omega^3 & -6\omega^2 & -4\omega \end{bmatrix} \xi(t) + \begin{bmatrix} 0 \\ 0 \\ 0 \\ \omega^4 \end{bmatrix} x_1^*(t).$$

It is readily verified that $\lim_{t\to\infty} \big(\xi_j(t) - x_1^{*(j)}(t)\big) = 0$ with $j \in \{1, 2, 3, 4\}$ for any $\omega > 0$, which determines the bandwidth and hence the speed of convergence.

F. Insulin limitation

The proposed control strategy does not take into account the control input constraint, that is, $0 \leq u(t) \leq u_{max}$, where u is the absolute insulin infusion rate. Therefore, an aggressive tuning of the controller will result in insulin overdose, which is a known issue in the field of diabetes control [44]. One of the solutions to mitigate this problem is the insulin feedback technique, which consists on the inhibition of the insulin infusion by high values of plasma insulin concentration [6], [45]. It was pointed out in [45] and validated in clinical trials in [46], that the insulin located at the subcutaneous compartments (yet to appear in plasma) could be also included as an inhibition. Following these ideas, the absolute insulin rate delivered by the proposed controller is computed by

$$\begin{aligned} u_j(t) = {} & \bar{u}_j(t) + u_{b_j} - \gamma_3 \max\big(0, I(t) - \hat{I}_{ss}\big) \\ & - \gamma_2 \max\big(0, \hat{S}_2(t) - S_{2,ss}\big) \\ & - \gamma_1 \max\big(0, \hat{S}_1(t) - S_{1,ss}\big), \end{aligned} \quad (9)$$

where $\gamma_1, \gamma_2, \gamma_3 > 0$ are tuning parameters and $I_{ss} = x_{1,ss}/(c_j S_I)$, $S_{2,ss} = t_{max_I} k_I V_I I_{ss}$, $S_{1,ss} = S_{2,ss}$ with $x_{1,ss} = S_G(G_{ref})\big(G_b - G_{ref}\big)/G_{ref}/r(G_{ref})$, are the steady-state values corresponding to G_{ref}, which are computed from (1) and (4) assuming $R_a(t) = 0$.

On the other hand, an upper limit on the maximum insulin infusion rate is imposed in order to avoid insulin over-delivery due to very large meals. In practice, this limit is imposed by the pump capability to deliver insulin and, in any case, it serves as a safety mechanism. A patient-dependent saturation of the control action is proposed so that $u(t) \in [0, (c_j/0.7)u_{max}]$. Recall that c_j is the non-dimensional factor used to personalize insulin sensitivity in the patient model (1). The individualized bound allows the patient with lowest c_j to exploit the maximum insulin infusion rate u_{max}, and constraints the other patients proportionally. For this application, the value $u_{max} = 16$ U/h is chosen, which corresponds to maximum insulin infusion rate of the Dana Diabecare R® insulin pump (Sooil, Seoul, Korea).

TABLE I

MEAL TIMES AND CARBOHYDRATE CONTENT FOR SCENARIOS 1 AND 2

	Day 1			Day 2			Day 3		
Scenario 1	7h (50g)	14h (60g)	20h (50g)	6h (50g)	13h (70g)	19h (50g)	7h (50g)	13h (65g)	21h (55g)
Scenario 2	7h (50g)	14h (80g)	20h (40g)	6h (50g)	19h (40g)	21h (70g)	7h (50g)	13h (100g)	21h (40g)

Fig. 1. Closed-loop responses without meal announcement under Scenario 1. Thick lines are median values while shaded areas embrace the 15% and 85% percentiles.
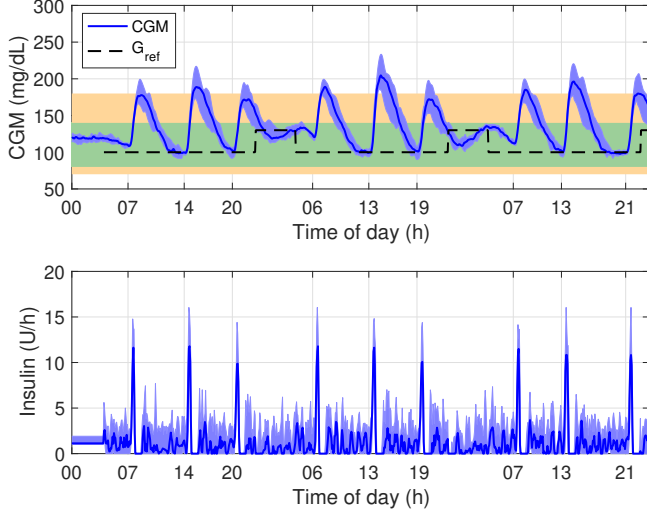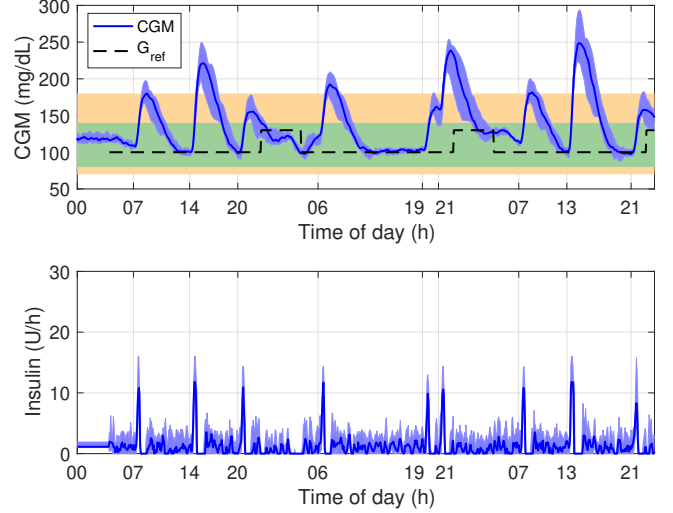

Fig. 2. Closed-loop responses without meal announcement under Scenario 2. Thick lines are median values while shaded areas embrace the 15% and 85% percentiles.

G. Glucose target

The use of different glucose targets during nocturnal and diurnal periods was reported in [14]. This is a safety measure to reduce the risk of nocturnal hypoglycemia. In this work, a glucose target of $G_{ref} = 130$ mg/dL is set for the nocturnal period (between 23 h and 4 h), whereas $G_{ref} = 100$ mg/dL is set during the rest of the day. Notice that the mean values of the noctural and diurnal target zones reported in [14] are similar to the target values chosen here.

H. Tuning

The controller gains k_j (which determine the closed-loop bandwidth) are tuned in relation to the tracking differentiator bandwidth, ω, so that they are the same. A simple way to achieve this is to select the gains as $k_1 = \omega^4$, $k_2 = 4\omega^3$, $k_3 = 6\omega^2$ and $k_4 = 4\omega$. Recall that the CGM readings are available every 5 min, that is, at rate of $1/5$ min^{-1}, which already imposes a limitation on the achievable bandwidth. Based on this limitation, a closed-loop bandwidth of $\omega = 1/10$ min^{-1} is selected. Regarding $\gamma_1, \gamma_2, \gamma_3$, those are selected by trial and error to avoid insulin overdose without loosing too much performance. Recall that the factor γ_1 inhibits the control action based on the insulin amount at the first compartment and hence is the fastest inhibition of all three. Therefore, high values of γ_1 have a large impact on performance in the early postprandial period. Keeping that in mind, the value of γ_1 is chosen as small as possible. On the other hand, larger values of γ_3 can be set without affecting performance significantly because its effect takes place after the postprandial peak. The

tuning is performed through simulations with the entire cohort of patients, in which a meal with a carbohydrate content of 70 g is given. The population values are finally selected as $\gamma_1 = 0.05$, $\gamma_2 = 0.2$ and $\gamma_3 = 100$, in order to avoid undershoot in the glucose response (respect to the fasting value). This tuning is conservative as it ensures safe operating conditions for every subject of the cohort.

I. Optional hybrid mode

Without meal announcement, the proposed control system estimates disturbances and delivers insulin accordingly, based solely on CGM measurements. However, if desired, an AP system should allow the patient the possibility to announce meals. In that case, the control law (9) is modified by adding up the term $u_{bolus}(t) = \text{CHO}/\text{CR} \cdot \delta(t - t_{meal})$, where CHO is the patient's carbohydrate content estimation, $\delta(\cdot)$ is the Dirac delta function and t_{meal} is the time when the meal is announced. Notice that the bolus is computed using only the meal size and there is no correction term due to neither the deviation between the glucose target and the current one nor insulin-on-board. The injection of an insulin bolus causes a rapid increase in the estimated compartmental and plasma insulin, leading to a fast inhibition. This mechanism plays the same role as the insulin on board limitation reported in other strategies [6], [14].

III. RESULTS

In this section, the proposed strategy is validated in silico under three different scenarios. Scenarios 1 and 2 are evaluated

Fig. 3. CVGA plot of comparing the closed-loop responses under Scenario 1 with (blue squares) and without (black circles) meal announcement. Each of the points at the graph is computed upon 24 h of CGM readings.
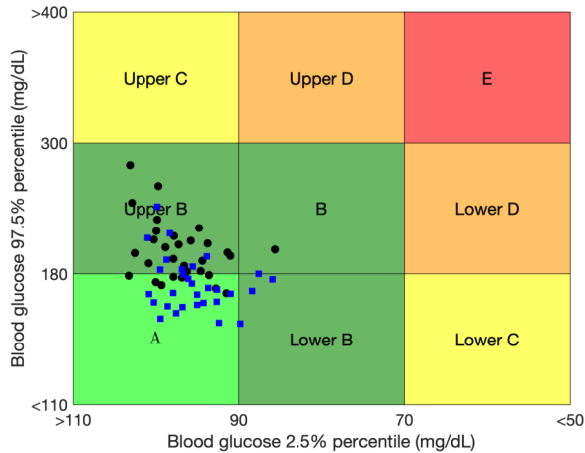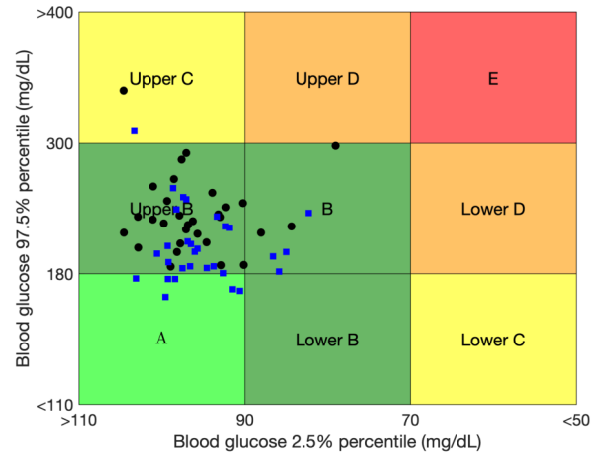

Fig. 4. CVGA plot of comparing the closed-loop responses under Scenario 2 with (blue squares) and without (black circles) meal announcement. Each of the points at the graph is computed upon 24 h of CGM readings.

using the distribution version of the UVa/Padova simulator [33]. In order to assess robustness to intra-patient variablity, a modified version (described below in Section III.C) of the simulator was used to evaluate Scenario 3. In all three scenarios, closed-loop control with and without meal announcement was considered. In the case of announced meals, CHO misestimation has been simulated according to the study carried out in [47] (see the curve fitted by regression analysis in Fig. 3 therein), which basically reports a tendency to overestimate small meals and underestimate the large ones. In every simulation, open-loop control with basal insulin rate is applied during the first 4 h, after which the controller takes over the insulin delivery [19]. The fasting state of each subject is taken to start the simulation.

A. Scenario 1

Scenario 1, taken from [19], contains medium-size meals with a CHO content up to 65 g (see Table I). Breakfast, lunch and dinner are considered during three consecutive days. The closed-loop responses (median and 15%-85% percentiles) without meal announcement for all in silico subjects of the distribution version of the UVa/Padova simulator under Scenario 1 are shown in Fig. 1. One can see that the proposed controller has good performance but it still avoids drops near the hypoglycemic range. Detailed performance indices of the 3-day period can be found in Table II. The overall performance in this scenario with medium-size meals is very good, scoring a median time-in-range of 90% and avoiding hypoglycemia. An average time-in-range of 83% was reported in [19] for the same scenario, although the size of the virtual cohort was substantially larger. Another simulation is performed considering the same scenario with meal announcement. The comparison is illustrated by means of a Control-Variability Grid Analysis (CVGA) plot in Fig. 3. Each of the points depicted in the CVGA plot corresponds to the 2.5% and 97.5% distribution of CGM data over a 24 h period [48]. One can see how the points in the CVGA are shifted downwards when

meals are announced in spite of the CHO mismatch, leading also to an outstanding median time-in-range of 99%.

B. Scenario 2

Scenario 2 is based on the previous one and it includes the following challenging features: i.) large-size meals with CHO content up to 100 g are included (see Table I); ii.) a fasting period is considered on the second day in which lunch is skipped; iii.) a fairly large snack is given shortly before dinner on the second day ; and iv.) a nocturnal hypoglycemic episode is simulated by introducing an undetected insulin bolus of 2 U the first night at 2 AM. The closed-loop responses under Scenario 2 are shown in Fig. 2. At first glance, the overall performance is also good in spite of the simulated nocturnal hypoglycemic episode. The postprandial excursions get further into the hypoglycemic range due to the large-size
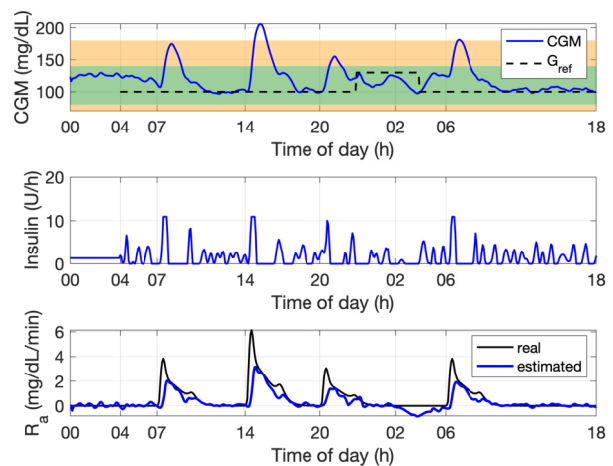

Fig. 5. Detail of the first 42 h of the closed-loop response under Scenario 2 (3-day simulation with large-size meals and nocturnal hypoglycemia), for the virtual subject #2 of the distribution version of the UVa/Padova simulator.

TABLE II
OVERALL PERFORMANCE INDICES (MEDIAN VALUES WITH 15% AND 85% PERCENTILES) FOR THE IN SILICO EVALUATION

	Scenario 1		Scenario 2		Scenario 3	
	Announced	Unannouced	Announced	Unannouced	Announced	Unannouced
Mean BG	128 (123, 130)	136 (125, 140)	130 (123, 132)	138 (126, 142)	135 (128, 144)	144 (131, 153)
$\% \in [70, 180]$	99 (97, 100)	90 (83, 98)	93 (90, 98)	85 (83, 95)	88 (80, 94)	80 (74, 88)
$\% \in [80, 140]$	71 (69, 84)	65 (59, 76)	72 (71, 79)	65 (59, 74)	66 (58, 71)	57 (50, 68)
$\% < 70$	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)
$\% < 60$	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
$\% < 50$	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
$\% > 250$	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.5)	0.4 (0.0, 1.7)	0.2 (0.0, 2.0)	1.3 (0.1, 4.2)
$\% > 300$	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.0 (0.0, 0.6)
HBGI	1.3 (0.8, 1.6)	2.5 (1.2, 2.8)	1.9 (1.1, 2.1)	3.2 (1.5, 3.8)	2.6 (1.8, 4.0)	3.8 (2.4, 5.0)
LBGI	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)	0.1 (0.0, 0.2)

meals. However, the performance indices (see Table II) are still fairly good, scoring a median time-in-range of 86% and avoiding hypoglycemia. The comparison with the announced scenario is again illustrated by means of a CVGA plot in Fig. 4, where improvement is also observed, achieving 93% of median time-in-range.

In order to provide a better insight in how the observer works, a detailed view of the individual closed-loop response of patient #2 for the first 42 h is shown in Fig. 5. The meal glucose rate of appearance (black) and its estimation (blue) are depicted at the bottom plot. The estimated value aggregates any unexpected change in the glucose level. That includes the effect of meals but also model uncertainties and other disturbances such as induced nocturnal hypoglycemia. One can see how the estimation drops below zero shortly after 2AM (when the 2U insulin bolus is delivered) leading to a pump suspension that mitigates that glucose drop. On the other hand, one can also appreciate in this plot the delay between the real meal glucose rate and its estimation, which is due to the sensing delay and observer dynamics. At this point, it should be remarked that this observer would also estimate a glucose drop due to exercise, which could be compensated using specific strategies proposed in the literature [49].

C. Scenario 3

Finally, a third scenario is considered to evaluate the robustness of the proposed strategy. Scenario 3 has a duration of 30 days, with three randomized meals per day of 65 g, 70 g, 65 g with a CV = 10% delivered at 7 h, 14 h and 21 h with STD = 60 min, respectively. The scenario also takes into account large intra-subject variability by varying insulin absorption model parameters up to ±30% from one meal intake to another, and insulin sensitivity parameters up to ±30% with a sinusoidal pattern along the day [50]. For intra-subject meal variability, the ten sets of meal model parameters of the cohort were randomly assigned to each other at each meal intake. This is a very challenging scenario in which 35 out of 90 meals have a CHO content over 70 g, being the average 66.5 g per meal. The results of this simulation are displayed by means of a CVGA plot in Fig. 6. Without meal announcement, a few number of samples lay on the out of the A+B zones, of which approximately 77% correspond to patient #7 (as pointed out in [38], this patient has an insulin sensitivity that is not coherent with its TDI). Nevertheless, the
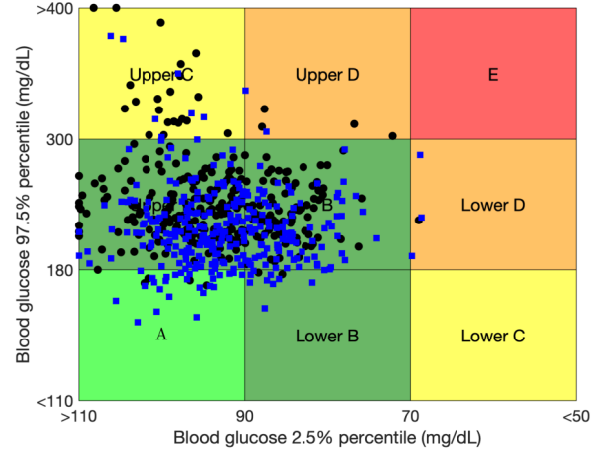

Fig. 6. CVGA plot of comparing the closed-loop responses under Scenario 3 with (blue squares) and without (black circles) meal announcement. Each of the points at the graph is computed upon 24 h of CGM readings.

overall counting indicates that 91% of the samples lay within the A+B zones in the unannounced case, which is not far from the 95% scored in the announced case. It should be pointed out that the tendency to hyperglycemia in spite of meal boluses is due to the fact that the simulated uncertainty in CHO counting severely under-estimates large meals. As indicated in Table II, the unannounced strategy leads to a median time-in-range of 80%, which is increased up to 88% when meals are announced.

IV. CONCLUSIONS

A novel control algorithm for artificial pancreas system has been proposed in this work, based on a disturbance observer and feedforward compensation. It has been shown how the disturbance observer is capable of estimating disturbances that cause unexpected variations in glucose levels. That includes the effect of meals but also model uncertainties or sudden drops that could result in hypoglycemia. The tuning of the proposed controller is feasible as it is based on a priori information of each subject. For unannounced meals, the results are promising, showing a median time-in-range of 80% in a challenging 30-day scenario with high carbohydrate content and large intra-subject variability. Results show this performance is further improved by +10% in the same scenario when meals are announced in spite of severe CHO misestimation.

While successful postprandial control with meal announcement has been reported, exercise was not discussed in this work, which is a another major challenge towards a fully automated artificial pancreas. Future research will be directed to exploit the information provided by the disturbance observer in order to mitigate hypoglycemia induced by exercise.

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Pedro García received the Ph.D. degree in Control Systems and Industrial Computing from the Universitat Politècnica de València, València, Spain, in 2007, where he is currently an Associate Professor within the Department of Systems Engineering and Control. He has been a visiting researcher at the Lund Institute of Technology, Sweden, the Université de Technologie de Compiègne, France, the University of Florianopolis, Brazil, the University of Sheffield, UK, and the University of Zhejiang, Hangzhou, China. He has coauthored one book, and more than 80 refereed journal and conference papers. His current research interests include control of time-delay systems, disturbance observers and control in type 1 diabetes.

José Luis Díez received the M.Sc degree in Industrial Engineering in 1995 and the Ph.D. degree in Control Engineering in 2003, both from the Universitat Politècnica de València (UPV), València, Spain. He is currently an Associate Professor and he has been lecturing since 1995 with the Department of Systems Engineering and Control of the UPV. He has been a visiting researcher at the Politecnico di Milano, Italy, and the Illinois Institute of Technology, Chicago, IL, USA. He is Deputy Director of the Iberoamerican Journal of Control and Industrial Informatics (RIAI) and he has coauthored more than 100 refereed journal and conference papers. His research interests include complex systems modeling and identification, data mining and intelligent control in type 1 diabetes.

Jorge Bondia received the Ph.D. degree in Computer Science from the Universitat Politècnica de València (UPV), València, Spain, in 2002. In 1995, he started lecturing with the Department of Systems Engineering and Control at the UPV, where he is Full Professor since 2017. He is Principal Investigator at the Diabetes and Associated Metabolic Diseases Networking Biomedical Research Centre (CIBER-DEM), Madrid, Spain, since 2018, and coordinator of the Spanish Consortium on Artificial Pancreas and Diabetes Technology. He has authored more than 60 journal articles and more than 120 conference contributions in the area of diabetes technology. His research interests include modeling and control in type 1 diabetes, biomedical applications, systems medicine, uncertain dynamical systems, monotone systems and robust control.

Ricardo Sanz received his M.Sc. degree in Aerospace from the Universitat Politècnica de Valtència (UPV), Spain, in 2013. He has been exchange student at the Royal Institute of Technology, Stockholm, Sweden and at the Georgia Institute of Technology, Atlanta, GA, USA. He received his M.Sc. degree in Robotics and Automation in 2014 and his Ph.D. in Automatic Control in 2018, both from the School of Industrial Engineering at the UPV. He has been a visiting researcher at the Université de Technologie de Compiègne, France, the University of Zhejiang, Hangzhou, China and the University of California San Diego, CA, USA. His current research interests include control of time-delay systems, predictive control, disturbance observers and biomedical applications.