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Artificial Pancreas: First Clinical Trials in Argentina ⋆

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Abstract: The first clinical trials using an Artificial Pancreas (AP) in Latin America have been defined in 2 stages. The first stage was carried out in November 2016 with the UVA controller (developed by the Center for Diabetes Technology and already clinically tested), and the second will be performed during the first semester of 2017 with the ARG (Automatic Regulation of Glucose) algorithm (developed by ITBA, UNQ, and UNLP in Argentina). Both tests are based on the DiAs (Diabetes Assistant) from the UVA, and are performed in the HIBA on 5 patients with Type 1 Diabetes Mellitus (T1DM), for 36 hours. For the first stage, Open-Loop (OL) insulin boluses were applied before meals and patient's physical activity was included. On the other hand, for the second stage, patients will not be involved in physical activity, but no OL insulin boluses will be injected before meals. In this work, experimental results from the first stage with the UVA controller, and preliminary results with the ARG control algorithm tested on the UVA/Padova simulator are presented. Due to the final paper deadline, the experimental results from the second stage are not included here, but will be presented at the IFAC World Congress.

Keywords: Artificial Pancreas, type 1 diabetes mellitus, switched control, LQG control, sliding mode control, clinical trial

1. INTRODUCTION

The Artificial Pancreas (AP) project has a longstanding evolution worlwide (Cobelli et al., 2011; Atlas et al., 2014; Doyle III et al., 2014). It consists of a Continuous Glucose Monitoring (CGM) and a Continuous Subcutaneous Insulin Infusion (CSII) pump connected through a control algorithm that regulates the patient's glucose concentration. Its development has been accelerated by the use of elaborated simulators, such as the UVA/Padova metabolic simulator which was accepted by the USA Food and Drug Administration (FDA) in lieu of animal trials (Kovatchev et al., 2008, 2009). Very recently, clinical trials were performed in different countries of the EU, USA, Israel and Australia (Hovorka et al., 2014; Gondhalekar et al., 2016; Phillip et al., 2013; de Bock et al., 2015).

Open-loop (OL) systems require an active participation of the patient to calculate the insulin dose, for example, based on the amount of carbohydrate (CHO) intake. However, this is a frequent source of error, because in practice the meal is sometimes over- or underestimated. On the other hand, ideally, closing the loop would not require the active participation of the patient, which is the foundation for the development of an AP. However, there are many difficulties in designing an adequate control algorithm for an AP: lag-times in glucose measurement and insulin action, model dynamic uncertainty, sensor errors, among others. Several control procedures based on the insulin-glucose dynamics have been used to minimize these issues (Cobelli et al., 2010; Sherr et al., 2013; Mauseth et al., 2013; Colmegna et al., 2016b). The current challenge is the validation of these algorithms in patients, during the night-time, along meals, and exercise. One purpose is to show that they can reduce the mean concentration of glucose without increasing the number of hypoglycemic events.

The first AP clinical trials in Argentina has been defined in two stages, using two different control algorithms, both programmed on the DiAs system. The UVA algorithm (Nov. 2016), which was previously clinically tested in the USA and in the EU (Kovatchev et al., 2014), automatically adjusts glycemia with meal announcement and physical activity. The second clinical stage (first semester 2017) will test the ARG (Automatic Regulation of Glucose) control algorithm designed in Argentina by ITBA, UNQ and UNLP, which was successfully tested *in-silico* on the UVA/Padova simulator. It automatically adjusts the

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glycemic levels without pre-meal insulin boluses. Both stages consider the same five T1DM patients, who have experience in the use of insulin pumps, and CGM sensors. It is worth mentioning that this study represents the first clinical experience with an AP in Latin America.

2. MEDICAL PROTOCOL

2.1 Description of the closed-loop (CL) system's components

The components of the CL system are described below.

- **CGM** sensor: This device allows the continuous measuring of the glucose levels in the interstitial fluid. It is composed of a sensor that is fixed to a smooth surface in the abdomen or in the upper gluteus of the patient, and a transmitter that is attached to the sensor once it is placed. This study uses Dexcom G4 Share® devices.
- **Smartphone**: The measurements taken by the sensor are sent in real time to a Google Nexus 5®, which is used exclusively for this study. It works as the data processing platform by means of a program created by UVA, the DiAs, where the control algorithm is deployed. This platform allows a wireless communication between the controller, the sensor and the insulin pump, allowing free movement of the patient in the hospital (the active participation of the patient will be required when the system detects hypo or hyperglycemic events). In addition, it accounts for the sensor's calibrations, and in the UVA algorithm case, the standard insulin bolus calculator according to the amount of CHO and the level of capillary glycemia before the meals. It also includes alarms for hypoglycemic (< 70 mg/dl) or hyperglycemic (> 180 mg/dl) episodes, and a predictive alarm in case it detects a potential hypo or hyperglycemic event.
- **CSII** pump: Roche's Accu-Check Combo® insulin pumps have been selected for this study. The pump receives wirelessly the Insulin Infusion Rate (IIR), according to the control algorithm output.

2.2 Goals

The purpose of this study is to test the performance of the UVA and ARG algorithms in automatically controlling the glucose concentration in T1DM patients.

Main goals

(a) To test UVA control algorithm with meal announcement for 36 hours under short and mild exercise situations.
(b) To test the ability of the ARG control algorithm without insulin boluses before meals to maintain the patient's glucose concentration in a safe region for 36 hours.

In both cases the adequate operation of the system will be considered verified, if the system works properly at least 80% of the total connection time. The glycemic target range is identical for both algorithms.

Secondary goals

(a) Estimation of the technical failure rate of the system's components.
(b) Percentage of total time within the desirable range of glycemia (70-180 mg/dl).
(c) Percentage of total time within the acceptable range of glycemia (70-250 mg/dl).
(d) Percentage of total time in hypoglycemia (< 70 mg/dl).
(e) Percentage of total time in hyperglycemia (> 180 mg/dl).
(f) Symptomatic, asymptomatic hypoglycemic episodes.
(g) Comparison of the glycemic registries obtained during the trial with the registries one week before hospitalization.
(h) Assessment of the nutritional content of the meals and their impact in the effectiveness of the glycemia correction.

2.3 Study and outcome variables

The outcome variables are the percentage of time satisfying an active connection between the system's components, and items (b)-(e) of the secondary goals. Also, the percentage of total time in significant hyperglycemia: Trial's total time in which the glucose remained over 250 mg/dl.

2.4 Sample size and justification

Although the UVA algorithm has been extensively tested abroad, this is a pilot study for the ARG algorithm, that has prior successful *in-silico* tests on the UVA/Padova simulator. For this reason, the sample size calculation prioritizes the least number of subjects to be exposed. The FDA guidance for human studies proposes around 12 subjects (FDA, 2013) to validate the analytical methodology and variability. As a consequence, five patients were simultaneously enrolled in the study.

2.5 Study schedule

Day -7: Pre-selected patients received information about the study and signed the *Informed Consent* at HIBA. Inclusion/exclusion criteria was revised and participants were confirmed. Blood samples were taken to the screening lab and a supervised routine glycemic control was performed. Patients received the CSII pump and the CGM sensor, and were trained to use both devices, highlighting the main differences between them and the ones they already use (Medtronic devices, Paradigma 754, VEO). They received the glycemic control sheets in order to complete the measured levels of glycemia during the 7 days previous to the study.

First stage: UVA algorithm

Day -1: Inclusion/exclusion criteria was revised and hospitalization time scheduled.
Day 0: Patients arrived at 1600-1630 h, without previous alimentary restrictions and after having lunch, to re-evaluate their understanding of the study, the selection criteria and to provide a blood sample. Next the CL components were connected. First capillary glycemia control was made, and it was acceptable (70

to 180mg/dl). After 2000 h the system was closed, with a previous verification.

Day 1: At 2100 h a meal of 40-80g carbohydrates was given, and the CL system's response is evaluated. During all the night, the system was remotely monitored by the team. Patients were allowed to drink water freely and even eat when it was necessary according to the glucose controls. Four meals were administered during the day, with insulin infusion determined by UVA algorithm. Before each meal, the patient calculated the insulin bolus according to the amount of CHO and the capillary glycemia. One and three hours after meals, capillary glycemic controls were carried out. Two 30-minutes walks were scheduled in the morning and in the afternoon.

Day 2: After 8 hours of fasting night-time control with the CL system, the loop was opened, concluding the trial. A capillary glycemic control was performed at the end of the evaluation period and afterwards, the patient was authorized to have breakfast. The insulin infusion mechanism used previously by the patient was re-established and appropriate controls were carried out. After verifying the results, the patient was discharged.

Day 7 ($\pm$1) The patient was called to talk about any doubts he/she might have, get clinical controls, and check the appropriate operation of his/her insulin pump.

Second stage: ARG algorithm

The following *a priori* clinical information is needed for the tuning of the ARG algorithm:

- the Total Daily Insulin (TDI) [U];
- the Carbohydrate/Insulin Ratio (CR) [gCHO/U];
- the insulin action curve, or the Duration of Insulin Action (DIA) [h];
- the body weight [kg];
- Correction Factor (CF) [mg/dl/U].

The test will be carried out in a similar fashion from days -7 to +7, except for two events:

- No insulin boluses will be delivered at the time of meal ingestion, hence the meal quantity is unannounced.
- Physical activity will not be included during the trial.
- If the night CL performance is adequate, according to the team's evaluation, it will continue in CL. Otherwise the control loop will be opened during the daytime.

3. UVA DIAS SYSTEM

The UVA DiAs is a modular architecture with the following main components: The Unified Safety System (USS Virginia), the Artificial Pancreas Controller (APC) and a meal bolus calculator (usual CSII calculator), all described in the following sections (see Patek et al. (2012) for more detailed information).

3.1 Artificial Pancreas Controller

The artificial pancreas system module is designed for control to range, known as the Range Correction Module (RCM). The main responsibility of the RCM is to appropriately adjust a patient's basal and bolus insulin delivery to maximize the time in euglycemia. The overall strategy employed by the RCM is to use an unconstrained linear Model Predictive Control (MPC) superimposed onto conventional therapy (see section IV-A in Patek et al. (2012)), deferring safety decisions to the safety module (USS).

3.2 Unified Safety System

Provides multiple data and decision filtering services, including: 1) data coordination and state estimation (particularly of the blood glucose and Insulin on Board (IOB)); 2) safety supervision algorithm which classifies insulin requests generated by the APC and applies corrective measures; 3) implementation of safety measures and adjustments such as a "Power Brakes" algorithm and the enforcement of IOB contraints; 4) response to anomalies in CGM readings; and 5) triggers safety alerts and information (red/yellow/green lights) for both hypo and hyperglycemia.

3.3 Meal Activity

This system uses the standard meal interface of DiAs, with Self Monitoring Blood Glucose (SMBG) and CHO information entered by the user, and IOB accounted for (the user can choose to ignore IOB, default is IOB on). Meal boluses are calculated using current user's CSII settings (insulin sensitivity factor and carb ratio).

4. ARG CONTROL ALGORITHM

The purpose of this control strategy is to regulate the blood glucose level in T1DM patients with a practical approach that consists in a switched Linear Quadratic Gaussian (LQG) controller that works together with the Safety Auxiliary Feedback Element (SAFE) procedure presented in Revert et al. (2013) and León-Vargas et al. (2013, 2015). The idea behind the switched LQG controller is similar to the proposal presented in Gondhalekar et al. (2014) and Colmegna et al. (2016c). In this case, there are two LQG controllers: one conservative, which is selected most of the time, and one aggressive, which is designed in order to cope with large hyperglycemic excursions. The trigger into the "aggressive" mode can be performed by means of a supervision system as in Colmegna et al. (2016c), or by user notification as in Colmegna et al. (2016b). Simulations are performed using the distribution version of the UVA/Padova metabolic simulator (Dalla-Man et al., 2014; Kovatchev et al., 2009).

4.1 Switched LQG Synthesis

Patient Design Model In Colmegna et al. (2016a), an average third-order Linear Parameter-Varying (LPV) model from the subcutaneous-insulin delivery input (pmol/min) to subcutaneous-glucose concentration deviation (mg/dl) is obtained based on the adult cohort of the distribution version of the UVA/Padova simulator. Since the interpatient variability should be considered (Patek et al., 2009), the model is then tuned by means of the 1800 rule, obtaining a personalized gain k denoted by k_j.

In order to design a LQG controller, here, we consider the Linear Time Invariant (LTI) model resulting by holding the glucose-varying parameter $p_1(g)$ fixed at $p_{1,j} =$

$p_1(g_{b,j})$, with $g_{b,j}$ being the corresponding basal glucose concentration. We establish that operating point, due to the fact that the control action is added to the basal IIR $i_{b,j}$ during the implementation phase. Thus, each Adult $\#j$ is associated with the following control-oriented LTI model:

$$\mathcal{G}_j(s) = k_j \frac{s+z}{(s+p_{1,j})(s+p_2)(s+p_3)} \mathrm{e}^{-15s} \qquad (1)$$

with $z = 0.1501$, $p_2 = 0.0138$, and $p_3 = 0.0143$. Because the desired control system operates in discrete-time, the continuous-time plant model $\mathcal{G}_j(s)$ is converted to the discrete-time plant model $\mathcal{G}_j(z)$ at the design stage.

Controller Design As stated before, two LQG controllers are designed for each *in-silico* Adult $\#j$ of the distribution version of the UVA/Padova simulator: $\mathcal{K}_{i,j}(z)$ with $i \in \{1,2\}$. Controller $\mathcal{K}_{1,j}(z)$ is designed to be conservative, while $\mathcal{K}_{2,j}(z)$ is designed to generate an insulin infusion signal akin to an insulin bolus.

In order to design both LQG controllers, we consider the aforementioned Single Input Single Output (SISO) system $\mathcal{G}_{r,j}(z)$:

$$\begin{aligned} x(k+1) &= A_{r,j}x(k) + B_{r,j}u_\Delta(k) \\ y_\Delta(k) &= C_{r,j}x(k) \end{aligned} \qquad (2)$$

with $u_\Delta(k) = u(k) - i_{b,j}$, and $y_\Delta(k) = y(k) - g_{b,j}$ being, respectively, the difference between the insulin delivery input $u(k)$ and the glucose deviation output $y(k)$ from the operating point $\{i_{b,j}, g_{b,j}\}$. Then, a state-feedback control

$$u_\Delta(k) = -K_{i,j}x(k) \qquad (3)$$

that minimizes the following quadratic cost function:

$$J_i(u_\Delta, y_\Delta) = \sum_0^\infty \left(R_i u_\Delta^2 + Q y_\Delta^2\right) \qquad (4)$$

with $R_1 = 1$, $R_2 = 0.5$, and $Q = 5 \times 10^3$ is designed. Parameter R_2 is purposefully defined smaller than R_1 to make $\mathcal{K}_{2,j}(z)$ be more aggressive than $\mathcal{K}_{1,j}(z)$. In addition, states are estimated by a Kalman filter of the form:

$$\begin{aligned} \hat{x}(k+1|k) = A_{r,j}\hat{x}(k|k-1) + B_{r,j}u_\Delta(k) + \dots \\ \cdots + L_{i,j}[y_\Delta(k) - C_{r,j}\hat{x}(k|k-1)] \end{aligned} \qquad (5)$$

where $L_{i,j}$ is obtained assuming that process $w(k)$ and measurement $v(k)$ noises are uncorrelated white processes that satisfy:

$$E[w(k)w(k)^T] = W_i, \quad E[v(k)v(k)^T] = V_i \qquad (6)$$

with $W_1 = V_1 = W_2 = 3$, and $V_2 = 45 \times 10^{-4}$. Note that V_2 is intentionally smaller than V_1 in order to make $\mathcal{K}_{2,j}(z)$ be much faster than $\mathcal{K}_{1,j}(z)$.

The stability analysis of this switched system can be performed following Hespanha and Morse (2002).

4.2 IOB Constraints

The SAFE structure is added to the switched LQG control scheme in order to reduce hypoglycemic events that could be induced. In Fig. 1, the switched LQG controller connected with the SAFE mechanism is depicted. This safety mechanism is based on sliding mode concepts, and adapts the controller's gain by means of the parameter γ to avoid violating a given constraint on the IOB denoted by $\overline{\text{IOB}}$ (see Revert et al. (2013) and León-Vargas et al. (2013, 2015) for details). The IOB constraint is initially defined as the maximum IOB estimated when an insulin bolus calculated using the patient's Carbohydrate Ratio (CR) for a 50 g meal is applied. That definition is a starting point that later can be adjusted according to medical criteria. In this way, the SAFE provides a safety layer that is robust against sensor failures and over-estimated prandial insulin doses.

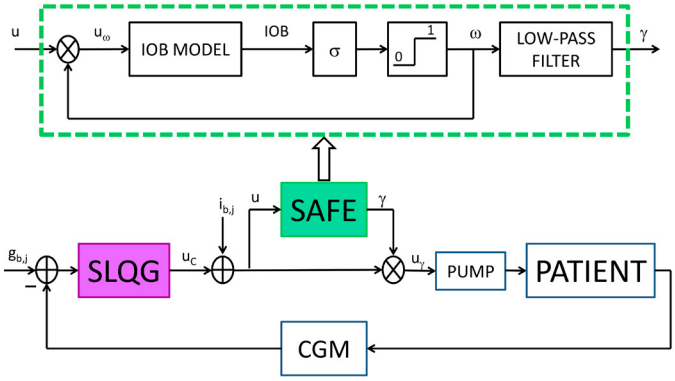

Fig. 1. Block diagram of the switched LQG controller connected with the SAFE mechanism.

5. CLINICAL RESULTS WITH UVA ALGORITHM

The test was performed at the HIBA during 36 hours on Nov. 18-20, 2016 [1]. In Fig. 2, a comparison between OL and CL was performed during the night with promising results. Note that the CL average remains inside the green dashed lines zone (70-180 mg/dl) almost all the time, with no hypoglycemic events. In addition, the same comparison but for a one-day period is presented in Fig. 3. In this case differences between OL and CL results are not so evident, but results with the UVA algorithm can still be considered positive. Note in Table 1 that, in average, the meals in CL were more demanding (larger) than the OL meals, which could partially explain this result.

This trial was useful as a hardware/software test previous to the pilot study with the ARG algorithm, which will be presented at the IFAC World Congress.

[1] Registered in Clinicaltrials.gov as NCT02994277.

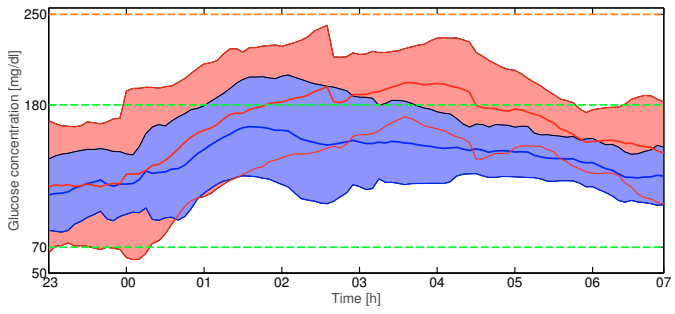

Fig. 2. Average value of Dexcom G4 in OL (red) and CL (blue) during the night. The filled areas represent ±1 STD. Dashed lines (green and orange) indicate glucose concentration limits (70-180 and 70-250 mg/dl).

Meal	CHO in OL [g]	CHO in CL [g]
Breakfast	21	35
Lunch	56	65
Tea	4	39
Dinner	52	47

Table 1. Average amount of CHO in each meal in OL and CL.

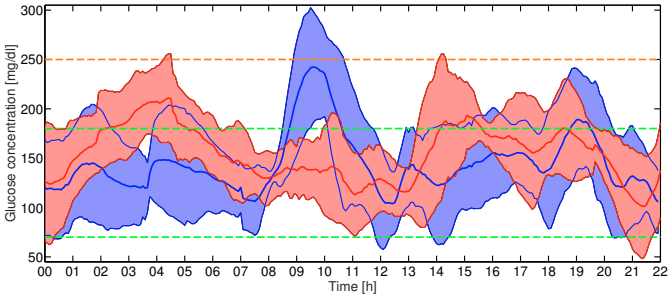

Fig. 3. Same as Fig. 2 but for 1 day (00-22 hs).

6. *IN-SILICO* RESULTS WITH ARG ALGORITHM

All eleven *in-silico* adults of the distribution version of the UVA/Padova metabolic simulator (one is an average patient) are taken into account for simulations, using CGM as the sensor, a generic CSII pump, and announcing the meal time.The controller returns to the conservative mode automatically 60 minutes after the commutation to the "aggressive" mode. A protocol that contains one meal is employed for controller performance analysis, considering the following:

(1) The protocol starts at 1500 h, assuming the fasting state of each subject.
(2) The switched LQG controller with IOB constraints and a sample-period $T_s = 5$ min, takes over the insulin delivery until the end of the simulation, with a constant setpoint of 120 mg/dl.
(3) A meal of 50 g CHO is ingested at 2000 h, and the meal time is announced.
(4) The CL system is opened at 0700 h, and the protocol finishes.
(5) A postprandial period (PP) and night (N) are defined as the 5 hour time interval following the start of the meal, and the period from 2300 h to 0700 h, respectively.

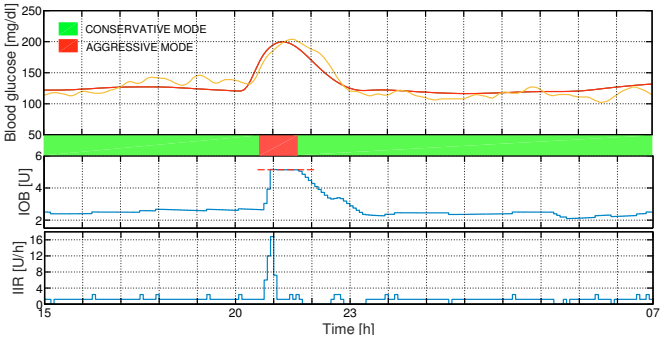

Fig. 4. CL response for Adult #1 of the distribution version of the UVA/Padova simulator. **Above:** Blood glucose concentration (red), and CGM signal (orange). **Middle**: IOB estimation. The red dashed line indicates the IOB limit $\overline{\text{IOB}}$. **Below:** IIR.

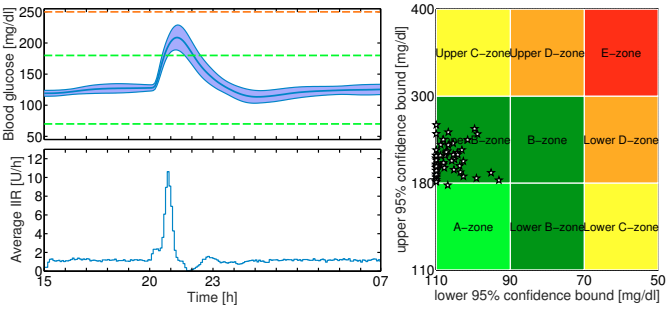

Fig. 5. CL responses for all *in-silico* adults (left) and the CVGA plot (right), considering a different CGM noise for each simulation. **Upper-left:** The thick lines are the mean blood glucose values, and the boundaries of the filled areas are the mean ±1 STD values. Dashed lines (green and orange) indicate glucose concentration limits (70-180 and 70-250 mg/dl). **Bottom-left:** Average IIR.

Mean BG [mg/dl]	**O**	131 (5)
	PP	154 (8)
	N	121 (6)
Max BG [mg/dl]	**O**	207 (18)
	PP	210 (19)
	N	141 (11)
Min BG [mg/dl]	**O**	109 (7)
	PP	112 (8)
	N	109 (7)
% time in [80 140] mg/dl	**O**	82.7 (5.5)
	PP	44.6 (10.2)
	N	95.9 (6.2)
% time in [70 180] mg/dl	**O**	93.8 (2.7)
	PP	74.4 (8.8)
	N	100.0 (0.0)
% time > 250 mg/dl	**O**	0.0 (0.0)
	PP	0.3 (1.5)
	N	0.0 (0.0)
% time > 180 mg/dl	**O**	6.2 (2.7)
	PP	25.6 (8.8)
	N	0.0 (0.0)
% time < 70 mg/dl	**O**	0.0 (0.0)
	PP	0.0 (0.0)
	N	0.0 (0.0)
Mean IIR [U/h]		1.1 (0.2)

Table 2. Average results for all the adults of the distribution version of the UVA/Padova simulator with the ARG algorithm. The overall (O), and the PP and N time intervals defined previously are analyzed separately, and standard deviations are given in parenthesis. Low (High) Blood Glucose Index = 0.0 (1.5) (Kovatchev et al. (2000)).

In addition, in order to test the robustness of the proposed approach against the measurement noise, for each *in-silico* patient, the protocol is run five times, each one considering a different CGM noise.

An individual response to the protocol is depicted in Fig. 4 to illustrate how the control strategy works. As shown in that figure, when $\mathcal{K}_{2,j}$ is selected ($\sigma = 2$), insulin delivery experiences a spike, reducing postprandial glucose levels. Immediately after the IOB reaches its limits, a fast switching sequence occurs on the constraint $\sigma_{\text{SM}} = \overline{\text{IOB}} - \text{IOB} = 0$, establishing a transitory sliding regime. Finally, the filtered signal γ is used to modulate the control signal

proposed by the switched LQG controller in order to command the CSII pump.

The CL responses and the Control Variability Grid Analysis (CVGA) plot (Magni et al., 2008) for all simulations are illustrated in Fig. 5. In addition, the average results are presented in Table 2, considering a 95% confidence interval. It is noteworthy that low hypo- and hyperglycemic risks are obtained. This means that the controller reduces the high glucose values after the meal, avoiding an overdose of insulin. An algorithm that automatically detects the meal time is an ongoing work by the authors.

7. CONCLUSIONS AND FUTURE RESEARCH

The clinical results using the UVA control procedure are in accordance with previous results performed with this algorithm in the USA and the EU, using the DiAs hardware. The ARG algorithm has been previously tested *in-silico* on the distribution (Section 6) and complete versions of the UVA/Padova simulator, in both cases with promising results. These previous, clinical and *in-silico*, tests were the basis to proceed to a clinical test with the ARG over the same five patients under the same protocol and glycemic target range as in the first stage. Due to the deadline for paper final submission, the clinical results with the ARG algorithm will be presented at the IFAC World Congress on July 2017.

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