Unannounced meal analysis of the ARG algorithm

Emilia Fushimi[1], Patricio Colmegna[2,3], Hernán De Battista[1], Fabricio Garelli[1], Ricardo Sánchez-Peña[4]

Abstract— **One of the main challenges in automatic glycemic regulation in patients with type 1 diabetes (T1D) is to dispense with carbohydrate counting. In this context, we propose to equip a previously introduced switched Linear Quadratic Gaussian (LQG) controller—the so-called Automatic Regulation of Glucose (ARG) algorithm—with an automatic switching signal generator (SSG). The ARG algorithm not only regulates the basal insulin infusion rate but also generates feedback insulin spikes at meal times, i.e., no open-loop insulin boluses are needed to mitigate postprandial glucose excursions. However, in its former version, it was required to announce the meal time. In this work, the performance of the ARG algorithm combined with the proposed SSG is assessed *in silico* with unannounced meals. In addition, the response of the SSG is estimated using clinical data obtained with the ARG algorithm in the first-ever artificial pancreas (AP) trials carried out in Latin America.**

I. Introduction

The traditional treatment for type 1 diabetes (T1D) requires multiple daily injections (MDI) of exogenous insulin, together with constant glycemic monitoring using a glucometer and test strips. However, in recent years new technology to treat T1D has been developed. One that stands out is the so-called artificial pancreas (AP), which connects an insulin pump with a continuous glucose monitoring (CGM) sensor through a control algorithm. This algorithm calculates the adequate amount of insulin to be infused to maintain the patient's glucose concentration in a safe range [1]. Nevertheless, this is still an open problem, primarily due to the large delays introduced by the subcutaneous route [2]. It has been proven that the open-loop procedure is optimal under nominal conditions [3], [4]. However, as both disturbances and models are unknown in practice, a feedback solution is necessary.

In this context, several control strategies to automatically regulate the blood glucose (BG) level have been proposed by the scientific community, being most of them based on model predictive control (MPC) [5], [6], proportional-integral-derivative (PID) control [7], [8], and fuzzy logic (FL) [9]. Since high model uncertainty and large delays limit the autonomy of glucose controllers, the great majority of the proposed control strategies are hybrid, i.e., a combination of open-loop (manual) meal boluses and a closed-loop algorithm that modulates the basal infusion rate. Each meal bolus is calculated before the meal time from the estimated amount of carbohydrates (CHO). This is a significant burden for patients with T1D who, in addition, are exposed to the risk of postprandial hypo- or hyperglycemia in case of miscounting [10].

A few research groups have developed meal detection methods. In [11], a voting algorithm is proposed based on different detection methods applied to the CGM signal. The meal is detected when two out of three or three out of four methods detect the meal with an average delay in meal detection of around 30 min. In [12], the proposed detector uses a modified version of Bergman's minimal model with an unscented Kalman filter for state estimation, and the estimated rate of appearance is used for meal detection. In [13], a method for anticipating meals through the use of behavioral profiles is presented. There, a stochastic MPC strategy is used to anticipate the meal arrivals. In [14], the approach is to give reasonable amounts of insulin boluses based on a series of meal impulses, and not to estimate the amount of CHO accurately. The algorithm is based on continuous observations of the first and second derivatives of glucose to produce a series of meal impulses when a set of conditions are satisfied (detection delay of $\sim$30 min). The insulin boluses are then combined with a MPC algorithm. In [15], a probabilistic method for meal detection is developed. This algorithm compares the CGM signal to no-meal predictions made by a simple insulin–glucose model. Then, residuals are fit to potential meal shapes, and lastly, these fits are compared and combined to detect any meal. However, since these methods are based on CGM readings, there is always an unavoidable compromise between fast detection and false positives.

Recently, an AP control law called Automatic Regulation of Glucose (ARG) was clinically evaluated in five patients with T1D at the Hospital Italiano de Buenos Aires (HIBA) [16], [17]. It consists of a switched Linear Quadratic Gaussian (SLQG) controller that works together with a sliding mode safety layer called Safety Auxiliary Feedback Element (SAFE) [18], [19]. In this work, an automatic switching signal generator (SSG) is proposed to be integrated into the ARG algorithm. The core element of this switching module is a Kalman filter that generates a filtered version of the amount of glucose in the stomach. The performance of the ARG algorithm combined with the SSG is evaluated using both (a) simulated data obtained from the UVA/Padova simulator [20], and (b) real data obtained during the clinical trial that was carried out at the HIBA.

The paper is organized as follows. Next section describes the ARG algorithm briefly. Section III introduces the proposed SSG module. *In silico* results are presented and analyzed in Section IV. Finally, in Section V, the performance of the SSG using clinical data from the clinical trial at the HIBA is discussed.

[1]GCA, Instituto LEICI, UNLP-CONICET, La Plata, Buenos Aires, Argentina emilia.fushimi@ing.unlp.edu.ar
[2]Center for Diabetes Technology, UVA, Charlottesville, USA
[3]Departamento de CyT, UNQ - CONICET, Buenos Aires, Argentina
[4]Instituto Tecnológico de Buenos Aires (ITBA) - CONICET, Argentina

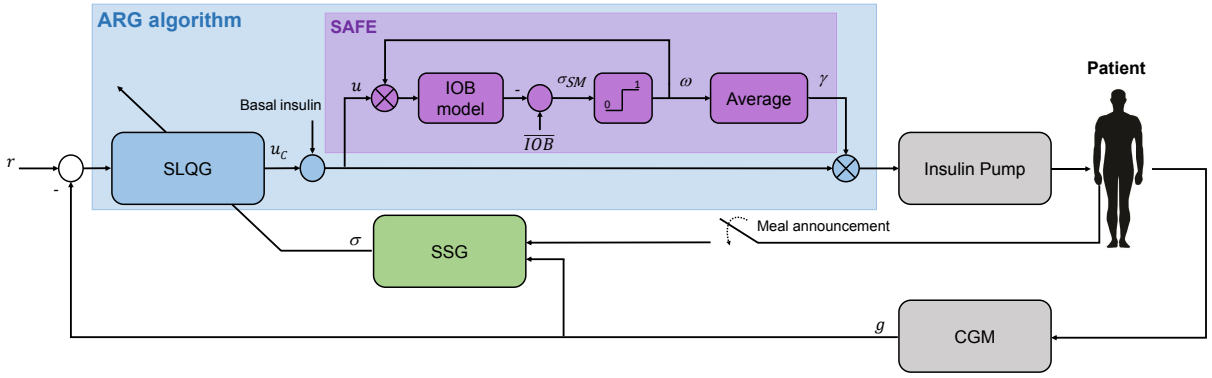

Fig. 1: Block diagram of the ARG algorithm.

II. The ARG Algorithm

The ARG algorithm regulates glycemia without requiring open-loop prandial boluses. Instead, it switches between two LQG controllers $\mathcal{K}_\sigma$: one aggressive ($\mathcal{K}_2$) that counteracts the effect of meals, and one conservative ($\mathcal{K}_1$) that takes over the insulin delivery at all other times. Figure 1 shows a block diagram of this AP algorithm. The SSG block commands the switching signal σ: $[0,\infty) \rightarrow \mathcal{I} = \{1,2\}$ that determines which LQG controller is active. Since the controller does not have integral action, the patient-specific basal rate is added to the insulin dose calculated by the SLQG controller (u_c), yielding u. Signal u is then modulated by the SAFE block through factor $\gamma \in [0,1]$ in order not to violate an imposed limit on the insulin-on-board (IOB). To this end, the SAFE mechanism defines a sliding function σ_{SM} as the difference between the predefined IOB threshold ($\overline{\text{IOB}}$) and the IOB estimate, and computes a switching logic ω. To avoid the chattering phenomenon in the control action γu, the modulation factor γ is defined as a low-pass filtered version of ω. In this way, the gain of the SLQG controller is smoothly attenuated when the given IOB limit is reached.

As previously stated, controllers $\mathcal{K}_1$ and $\mathcal{K}_2$ respond differently. While $\mathcal{K}_2$ generates large insulin spikes to reduce postprandial glucose excursions, $\mathcal{K}_1$ slightly modulates the basal insulin rate. For this reason, the weighting matrices used to design controller $\mathcal{K}_2$ were tailored to generate a faster and more aggressive response than controller $\mathcal{K}_1$ (see details in [16]). In its current state, the switching between $\mathcal{K}_2$ and $\mathcal{K}_1$ occurs automatically one hour after $\mathcal{K}_2$ is selected, although other techniques that involve the SAFE layer were explored [21]. On the other hand, the switching between $\mathcal{K}_1$ and $\mathcal{K}_2$ can be done with or without meal announcement. Although we had successfully evaluated closed-loop strategies with fully automatic SSG algorithms in simulation studies [22]–[24], meal announcement was required to enable the controller to switch from $\mathcal{K}_1$ to $\mathcal{K}_2$ in the first *in vivo* evaluation of the ARG algorithm. In this way, the compromise between fast detection and false positives was eliminated, focusing the trial on testing the feasibility of the control strategy.

It is important to emphasize that controller $\mathcal{K}_2$ is not immediately selected when a meal is announced, but instead a *listening* mode is triggered for 90 minutes. During that mode, the CGM trend is analyzed by a SSG module, and the SLQG switches to its aggressive mode only if an increasing trend is detected. In addition, the patient does not have to inform the exact amount of CHO. Instead, he/she has to classify the meal as small, medium or large to adapt the $\overline{\text{IOB}}$ proportionally to the informed meal size. A meaningful difference with treatments that require exact CHO calculation and even others that also use meal classification [25] is that the ARG does not deliver priming meal boluses. Another feature based on the SAFE mechanism that was added to the ARG algorithm is the possibility of decreasing the $\overline{\text{IOB}}$ when risk of hypoglycemia is detected. A more detailed description of how the $\overline{\text{IOB}}$ is defined can be found in [16], [17].

III. The SSG Module

The signal that commands which LQG controller is selected is σ. In order to eliminate the meal announcement input to the SSG module and take a step towards fully automatic control, an algorithm to automatically establish σ based on CGM readings is described in this section.

Figure 2 shows a block diagram of the proposed SSG module. The first block is a noise spike filter (NSF) that limits the maximum BG rate of change to 3 mg/dl/min [26]. The filtered signal g_f is the input to the second block, which is a Kalman filter. The Kalman filter is used to approximately estimate the amount of glucose in the first phase of the stomach $\hat{Q}_{sto1}$, which according to [27] can be modeled as:

$$\dot{Q}_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D\delta(t) \tag{1}$$

where k_{gri} [min ^{1}] is the rate of grinding, D [mg] is the amount of ingested glucose, and $\delta(t)$ is the Dirac delta

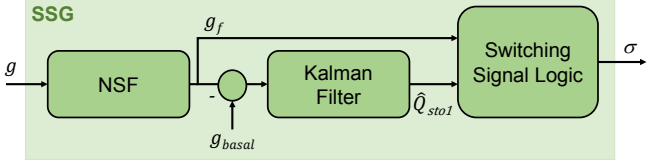

Fig. 2: Block diagram of the SSG module.

function. Thus, the problem of estimating Q_{sto1} can be associated with an initial condition problem, and therefore, Q_{sto1} can be estimated purely with CGM feedback. In the UVA/Padova simulator, a meal is represented by a rectangular signal in [mg/min] with a default duration of 15 minutes, which in any case, is considerably less than the time constant of the meal-glucose system.

To design the Kalman filter, a linearized model from the meal input to the glucose output was obtained for each virtual adult of the UVA/Padova simulator at the basal state. Due to high measurement noise and the fact that the system input (meal intake) is unknown, the estimation of Q_{sto1} will be rather slow and attenuated. However, the goal here is not to track Q_{sto1} perfectly, but to combine this signal with g_f to establish a switching policy that provides a good trade-off between fast detection of hyperglycemic conditions and false positives due to noisy CGM readings. In this regard, the meal-glucose model associated with the most sensitive *in silico* subject, adult #007, was selected at this stage where no model personalization was performed. Then, the selected model was discretized with a sampling time of 5 minutes:

$$\begin{aligned} x_m(k+1) &= A_m x_m(k) + B_m u_m(k) \\ y_m(k) &= C_m x_m(k) \end{aligned} \tag{2}$$

where u_m is the meal input and y_m is the glucose deviation output from the basal value. In order to estimate Q_{sto1}, the following Kalman filter was designed:

$$\begin{aligned} \hat{x}_m(k+1|k) &= A_m \hat{x}_m(k|k-1) \\ &\quad + L_m[y_m(k) - C_m \hat{x}_m(k|k-1)] \\ \hat{Q}_{sto1}(k) &= [1 \quad 0 \quad \dots \quad 0]\hat{x}_m(k) \end{aligned} \tag{3}$$

where L_m was obtained using the expected variances of the process (W) and measurement noise (V) as tuning parameters (W/V = 500).

The aim of the SSG module is to detect via g_f and $\hat{Q}_{sto1}$ hyperglycemic events that require the controller to switch to its aggressive mode, for example, to mitigate meal-related glucose excursions. To this end, the following conditions were defined to guarantee CGM noise immunity using the sensor model of the simulator in approximately 80% of the cases. If $\hat{Q}_{sto1}$ is greater than 1625 mg and increasing, and if g_f is greater than 140 mg/dl, the controller switches to its aggressive mode for an hour, as in the clinical trials at HIBA. To make the system more robust to false positives at night and during postprandial periods (multiple detections of a single meal), time-dependent thresholds for g_f and $\hat{Q}_{sto1}$ can be defined. In this work, the threshold for g_f is raised to 250 mg/dl in the time range from 11:30 PM to 6:30 AM, and the threshold for $\hat{Q}_{sto1}$ is increased to 3000 mg during the two hours after a hyperglycemic event is detected. It is worth remarking that in a real-life scenario, these thresholds can be personalized according to the system performance and subject's behavior.

As previously mentioned, the filter is not able to properly track the peak in Q_{sto1} after a meal, meaning that it cannot be directly used to adapt the IOB limit. Therefore, at this stage, it was decided as a trade-off to switch $\overline{\text{IOB}}$ from $\overline{\text{IOB}}_{\text{s}}$ (constraint defined for a small-sized meal) to $\overline{\text{IOB}}_{\text{m}}$ (constraint defined for a medium-sized meal) during the 90 minutes after hyperglycemia is detected. It is worth noting that the IOB limit implies only a constraint and not the exact amount of insulin to be delivered. Even so, as with the thresholds for g_f and $\hat{Q}_{sto1}$, the $\overline{\text{IOB}}$ can be tuned to a particular subject based on the hyper- and/or hypoglycemia frequency.

IV. ARG WITH UNANNOUNCED MEALS: IN SILICO TESTS

The performance of the ARG algorithm working together with the proposed SSG module was tested *in silico*, considering CGM as the sensor, unannounced meals and all 10 adults of the distribution version of the UVA/Padova simulator. To this end, the 36 h protocol defined for the clinical trial at HIBA is recreated in this section. Simulations start with subjects at their fasting state and involve 5 meals that are distributed as follows: two dinners of 55 grams of carbohydrates (gCHO) each, one breakfast (28 gCHO), one lunch (55 gCHO) and an afternoon snack (28 gCHO). Thus, a total of 50 meal tests are performed to: (a) verify the performance of the SSG module *per se*, and (b) evaluate

	Dinner 1		**Breakfast**		**Lunch**		**Snack**		**Dinner 2**	
Adult #	Δt_1	Δt_2	Δt_1	Δt_2	Δt_1	Δt_2	Δt_1	Δt_2	Δt_1	Δt_2
001	0	20	0	25	-5	15	0	30	5	20
002	0	15	5	30	-10	10	0	20	0	15
003	0	25	-5	30	0	20	-5	35	10	30
004	0	15	-10	25	5	20	-5	30	5	15
005	0	15	0	25	0	15	0	30	5	15
006	0	15	0	25	0	30	0	40	10	20
007	0	15	5	25	-10	5	-5	25	5	15
008	0	15	-5	25	0	20	0	25	5	15
009	-5	15	5	30	-5	25	-5	25	5	20
010	5	25	-5	25	0	20	0	40	5	20
Mean (STD)	0 (2.4)	17.5 (4.2)	-1 (5.2)	26.5 (2.4)	-2.5 (4.9)	18.0 (7.1)	-2 (5.6)	30.0 (6.7)	5.5 (2.8)	18.5 (4.7)
Median [IQR]	0 [0–0]	15 [15–20]	0 [-5–5]	25 [25–30]	0 [-5–0]	20 [15–20]	0 [-5–0]	30 [25–35]	5 [5–5]	17.5 [15–20]

TABLE I: Time difference in meal detection (in minutes) between the ARG$_{md}$ and the SSG module with open-loop insulin infusion (Δt_1), and between the ARG$_{md}$ and the ARG$_{ma}$ (Δt_2).

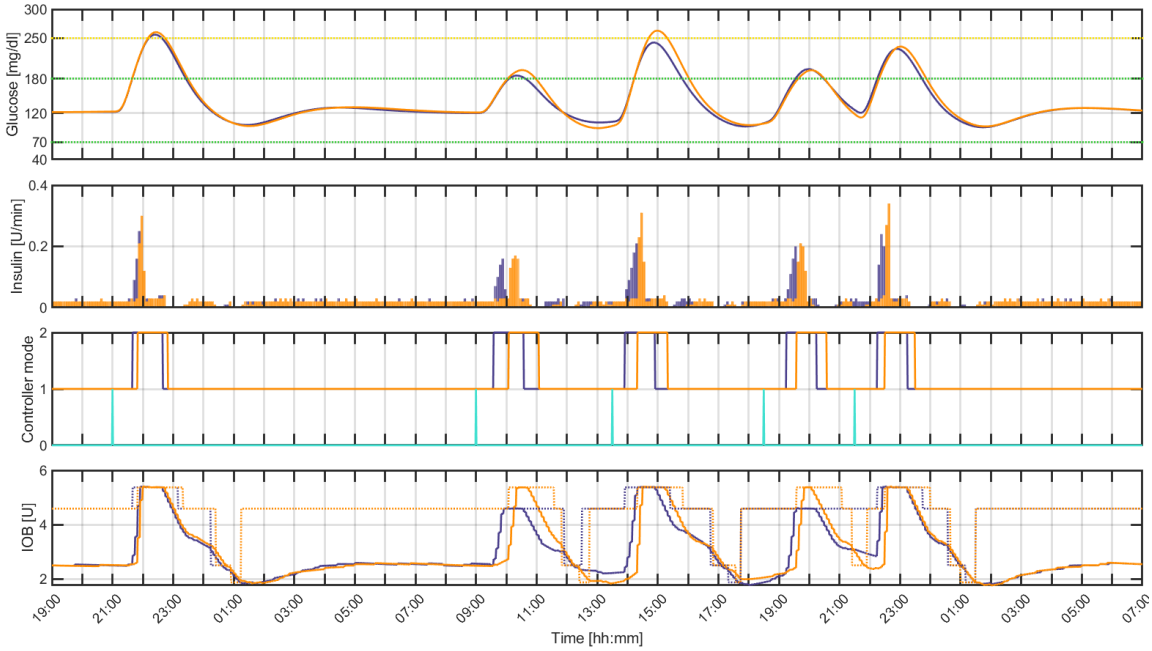

Fig. 3: Closed-loop response for adult #001 obtained with the ARG$_{ma}$ (purple) and the ARG$_{md}$ (orange). The light-blue line plotted in the controller-mode figure indicates the meal time, and the dotted lines in the IOB figure represent the IOB limits.

the performance of the ARG algorithm when its switching behavior is commanded by the SSG module, ARG$_{md}$. These results are compared to the ones obtained with the ARG algorithm with meal announcement, ARG$_{ma}$.

Table I indicates the time delay in selecting the aggressive mode between the ARG$_{md}$ and the SSG module with open-loop basal insulin infusion (Δt_1), and between the ARG$_{md}$ and the ARG$_{ma}$ (Δt_2). Results evidence that the performance of the SSG module is scarcely affected by the ARG algorithm, and that the delay in triggering controller $\mathcal{K}_2$ without meal announcement is on average less than 30 min. The reason for such delay is that the meal announcement informs the ARG$_{ma}$ that an increasing CGM trend during the *listening* mode is likely related to a meal intake. On the other hand, the ARG$_{md}$ must verify additional conditions to avoid false positives that might lead to insulin overdose. Overall, the delay between the meal is ingested and the ARG$_{md}$ switches to controller $\mathcal{K}_2$ is on average 50 min for the 55 gCHO meals and 60 min for the 25 and 28 gCHO meals. Another interesting observation of Table I is that the larger the meal, the less the delay. This is particularly important since large meals are the ones that might lead to more pronounced hyperglycemia, and a fast detection is desired.

Figure 3 shows the outcome of the closed-loop simulation for adult #001. As shown in that figure, both ARG$_{ma}$ and ARG$_{md}$ result in similar glucose control in terms of hyperglycemia (% time $>$ 180 mg/dl: 17.5 with ARG$_{ma}$; 19.4 with ARG$_{md}$) and hypoglycemia (% time $<$ 70 mg/dl: 0.0 with ARG$_{ma}$; 0.0 with ARG$_{md}$). The slight tendency towards postprandial hyperglycemia observed in both versions is due

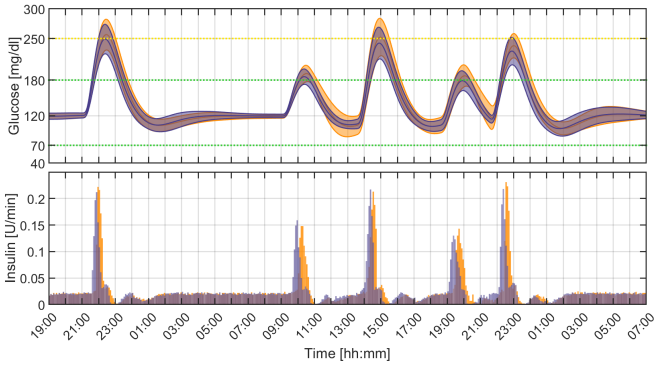

Fig. 4: Closed-loop responses for all *in silico* adults obtained with the ARG$_{ma}$ (purple) and the ARG$_{md}$ (orange). The thick lines are the mean glucose values, and the boundaries of the filled areas are the mean $\pm$ 1 STD values. The yellow and green dashed lines represent the 70-180 mg/dl and 70-250 mg/dl ranges, respectively.

to the absence of feedforward meal boluses. In addition, note that the insulin delivery experiences larger spikes with the ARG$_{md}$ than with the ARG$_{ma}$ for the 55 gCHO intakes but not for the smaller ones. This confirms the fact that $\overline{\text{IOB}}$ represents only a limit and not the exact amount of insulin to be infused. Lastly, as expected, Figure 3 shows that insulin response with the ARG$_{md}$ is shifted in time compared to the response obtained with the ARG$_{ma}$ due to the delay introduced by the SSG module.

Figure 4 shows the mean $\pm$ 1 STD glucose values obtained

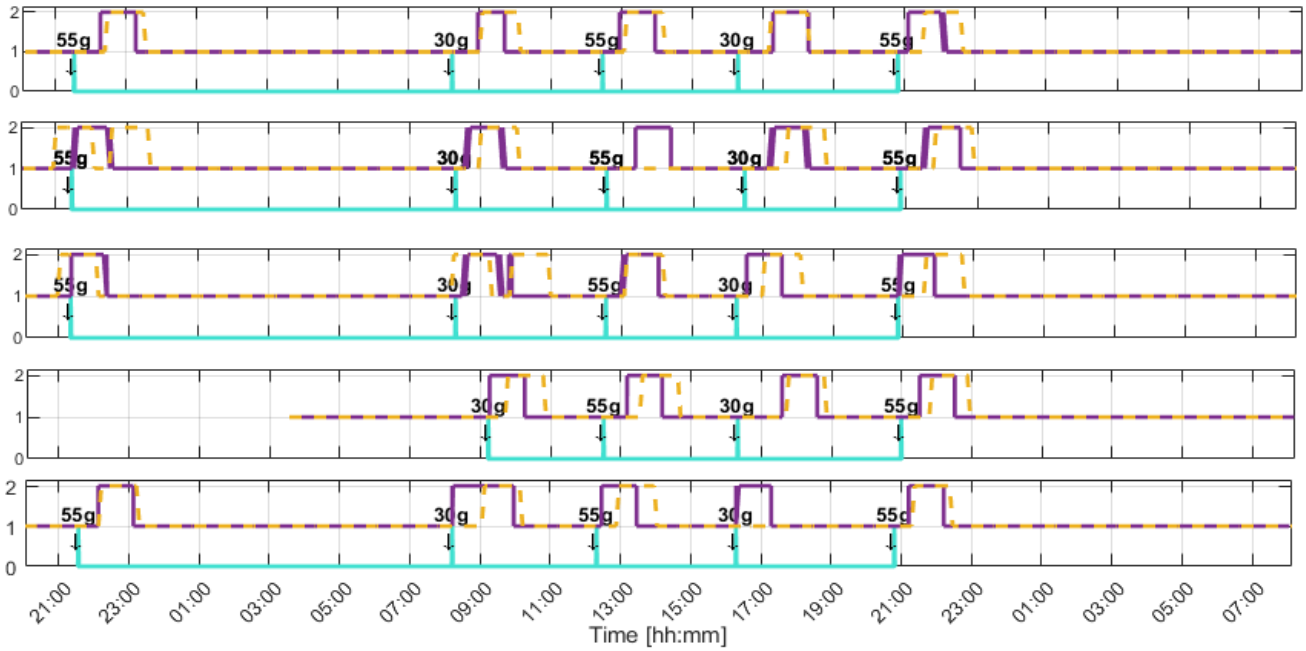

Fig. 5: Controller mode (1 - conservative, 2 - aggressive) selected by the ARG$_{ma}$ (purple) and the ARG$_{md}$ (dashed orange), and the meal announcement (light-blue line) using data from the clinical trial performed at HIBA.

Participant #	**Dinner 1**	**Breakfast**	**Lunch**	**Snack**	**Dinner 2**
54112	12	7	12	0	28
54113	-26 | FP	29	FN	34	24
54114	-18	-13 | FP	11	31	48
54115	-	31	26	11	21
54116	5	55	30	FN	10
Mean (STD)	-6.8 (18.1)	21.8 (25.8)	19.8 (9.7)	19 (16.3)	26.2 (13.9)
Median (IQR)	-6.5 [-22–8.5]	29 [2–37]	19 [11.5–28]	21 [5.5–32.5]	24 [18.3–33]

TABLE II: Time difference in the switching to the aggressive controller (in minutes) between the ARG$_{md}$ and the ARG$_{ma}$ using data from the clinical trial at HIBA. (FN: false negative, FP: false positive).

with both methods. It can be observed that although post-prandial glucose peaks are slightly higher with the ARG$_{md}$ due to the larger delay in switching to $\mathcal{K}_2$ (% time > 250 mg/dl: 0.4 [0.0-2.7] with ARG$_{ma}$; 2.1 [0.0-3.6] with ARG$_{md}$), no hypoglycemic event was detected under both controllers (% time <70 mg/dl: 0.0 [0.0-0.0] with ARG$_{ma}$; 0.0 [0.0-0.0] with ARG$_{md}$). It is important to highlight that the time spent in the acceptable range was nearly not affected (% time in $[70, 250]$ mg/dl: 99.6 [97.3-100.0] with ARG$_{ma}$; 97.9 [96.4-100.0] with ARG$_{md}$). Thus, the main advantage of using the ARG$_{md}$ resides in the increased freedom provided to the patient.

V. Tests using clinical data

The ARG$_{ma}$ was clinically evaluated at the HIBA in 2017 in 5 subjects with T1D [17]. Here, the CGM readings obtained from that clinical trial are used to evaluate the performance of the SSG module.

In the previous section, it was shown through simulations that the increased delay in selecting controller $\mathcal{K}_2$ when the ARG is used without meal announcement does not produce a significant impact on the overall glucose control. Figure 5 shows the controller mode (1- conservative, 2- aggressive) during the clinical trial using the ARG$_{ma}$, and the controller mode that would have been selected by the ARG$_{md}$. Readings for participant #54115 were discarded during the first dinner (Dinner 1) due to pump occlusion. As shown, the SSG module triggered the aggressive mode ($\sigma = 2$) twice when there was no meal, and did not trigger the aggressive mode twice when there was a meal. Therefore, in terms of meal detection, it had an efficiency of 83.3%: 2 false positives (8.3%) and 2 false negatives (8.3%) out of the 24 meals. Table II shows the time difference in selecting the aggressive mode between the ARG$_{md}$ and the ARG$_{ma}$. As indicated, although results related to Dinner 1 are affected by the initial transient of the controller, results for the other meals are in agreement with what was previously detected in simulation (see Table II). Note that in three cases the time difference was negative, meaning that controller $\mathcal{K}_2$ would have been triggered before using the ARG$_{md}$. In two of

them, the detection by the ARG$_{md}$ happened even before the meal was announced (participants #54113 and #54114 - Dinner 1). The reason is the initial insulin infusion was not sufficient to maintain those participants at normoglycemia, and sustained glucose increases were observed. In the case of participant #54114, the switching of the ARG$_{md}$ to the aggressive mode during breakfast coincides with the announcement of the meal. The two false positives that took place (patient #54113 - Dinner 1 and patient #54114 - Breakfast) were both consecutive to a faster detection by the ARG$_{md}$. It is reasonable to suppose that the early detection of the meal by the ARG$_{md}$ would have reduced the postprandial glucose excursion and, therefore, avoided the second detection. Lastly, the two false negatives took place because the ARG$_{ma}$ significantly limited the glycemic excursions associated with those meal ingestions.

It is worth remarking that the CGM readings used in this analysis are affected by the performance achieved by the ARG$_{ma}$, and conclusions should be made taking that into account. In addition, it should be considered that either a false negative, because glucose excursion was not enough to be detected, or a false positive, due to insulin underdosing, could be a desired behavior in terms of glycemic control.

VI. Conclusions

In this work, an automatic SSG module was proposed to be integrated into the ARG algorithm. Its performance was evaluated *in silico* and using clinical data. Although both tests evidenced a larger delay in selecting the aggressive mode after a meal when the ARG$_{md}$ is used instead of the ARG$_{ma}$, simulations indicated that this does not significantly increase neither hypo- nor hyperglycemia. In terms of meal detection, results from clinical data indicated that false positives and false negatives were scarce (16.67 % of the meals), and that it should be taken into account that, in certain situations, their occurrence could be desired from the control view point. In addition, the performance using both *in silico* and clinical data was similar, although at this point it has no statistical relevance. Despite limitations, these preliminary results indicate that an automatic SSG implemented into the ARG algorithm is feasible.

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