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Artificial Pancreas: Evaluating the ARG Algorithm Without Meal Announcement

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Abstract

Background: Either under standard basal-bolus treatment or hybrid closed-loop control, subjects with type 1 diabetes are required to count carbohydrates (CHOs). However, CHO counting is not only burdensome but also prone to errors. Recently, an artificial pancreas algorithm that does not require premeal insulin boluses—the so-called automatic regulation of glucose (ARG)—was introduced. In its first pilot clinical study, although the exact CHO counting was not required, subjects still needed to announce the meal time and classify the meal size.

Method: An automatic switching signal generator (SSG) is proposed in this work to remove the manual mealtime announcement from the control strategy. The SSG is based on a Kalman filter and works with continuous glucose monitoring readings only.

Results: The ARG algorithm with unannounced meals (ARG_{um}) was tested *in silico* under the effect of different types of mixed meals and intrapatient variability, and contrasted with the ARG algorithm with announced meals (ARG_{am}). Simulations reveal that, for slow-absorbing meals, the time in the euglycemic range, [70-180] mg/dL, increases using the unannounced strategy (ARG_{am}: 78.1 [68.6-80.2]% (median [IQR]) and ARG_{um}: 87.8 [84.5-90.6]%), while similar results were found with fast-absorbing meals (ARG_{am}: 87.4 [86.0-88.9]% and ARG_{um}: 87.6 [86.1-88.8]%). On the other hand, when intrapatient variability is considered, time in euglycemia is also comparable (ARG_{am}: 81.4 [75.4-83.5]% and ARG_{um}: 80.9 [77.0-85.1]%).

Conclusion: *In silico* results indicate that it is feasible to perform an in vivo evaluation of the ARG algorithm with unannounced meals.

Keywords

artificial pancreas, carbohydrate counting, sliding mode control, switched control

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Introduction

Artificial pancreas (AP) systems usually consist of a subcutaneous insulin pump connected to a continuous glucose monitoring (CGM) sensor through a control algorithm that automatically calculates insulin doses according to CGM measurements.[1] Unfortunately, the subcutaneous route introduces considerable issues, including large delays in glucose measurements and insulin action.[2]

The vast majority of AP systems are based on model predictive control (MPC),[3-7] proportional-integral-derivative,[8,9] and fuzzy logic[10] (see Sánchez-Peña and Cherñavvsky[11] for a thorough description of the current situation). Since high model uncertainty and large delays limit the autonomy of the glucose controller, most of these control strategies are hybrid, ie, a combination of manual meal boluses and automatic basal modulations. However, carbohydrate (CHO) counting implies an important burden and risk for people with diabetes.[12] Therefore, a purely feedback solution is necessary.

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Recently, a control algorithm without premeal insulin boluses called automatic regulation of glucose (ARG) was proposed and clinically evaluated in five subjects with type 1 diabetes (T1D) at the Hospital Italiano of Buenos Aires (HIBA).[13,14] This algorithm consists of an inner switched linear quadratic Gaussian (SLQG) controller and an outer sliding mode safety layer called safety auxiliary feedback element (SAFE).[13,15] The inner controller switches between an aggressive LQG controller to compensate for the effect of meals and other large perturbations, and a conservative LQG controller to maintain normoglycemia at all other times (see also Colmegna et al[16]). During the clinical study at HIBA, participants were asked to announce the meals and classify them as small, medium, or large. When a meal was announced, a *listening* mode was triggered and the aggressive controller was selected only if rising glucose values were detected during the following 90 minutes. Information about the meal size was used by the safety layer to adjust the maximum allowable insulin on board (IOB) value for that particular meal. This approach reduced patients' burden associated with CHO counting. However, our goal here is to maximize patients' freedom to avoid complications such as those derived from diabetic burnout by eliminating the need for meal announcement, as long as closed-loop performance and patient safety are not compromised.

In recent years, several meal detection algorithms have been explored. In Dassau et al,[17] a voting algorithm is proposed based on different detection methods applied to the CGM signal, using a Kalman filter (KF) and estimations of the glucose rate of change. In Turksoy et al,[18] the proposed detector uses a modified version of Bergman's minimal model with an unscented KF for state estimation, and the estimated rate of appearance is used for meal detection. In Hughes et al,[19] a method using a stochastic MPC strategy is employed to detect meals through behavioral profiles. In Lee et al,[20] it is proposed to inject reasonable amounts of insulin boluses based on a series of meal impulses and not to estimate the grams of carbohydrates (gCHO) accurately. The algorithm is based on continuous observations of the first and second derivatives of the glucose level to produce a series of meal impulses when a set of conditions is satisfied. Insulin boluses are then combined with an MPC algorithm. In Cameron et al,[21] 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 finally, these fits are compared and combined to detect any meal. In Mahmoudi et al,[22] two CGMs and an adaptive unscented KF are employed to detect CGM faults and unannounced meals, distinguishing from one another. In Ramkissoon et al,[23] an unscented KF is used to estimate a disturbance term, which alongside CGM readings is utilized to detect meals.

A few AP systems that do not require exact CHO counting have been developed.[24,25] However, in these works, meal announcement is used to deliver a meal priming bolus based on a meal size classification. On the other hand, AP systems that do not require any kind of meal announcement involving both single-hormone[26,27] and dual-hormone[28] therapy have been proposed as well. Despite achieving good results, there is still an unavoidable compromise between prandial hyperglycemia and postprandial hypoglycemia, mainly due to the slow pharmacokinetics and pharmacodynamics of the current insulin analogs. In Turksoy et al,[26] this compromise was reduced since meals were compensated with an additional module that delivered insulin boluses when an intake was detected. Also, clinical studies involving closed-loop control in patients with noncritical care have been carried out.[29]

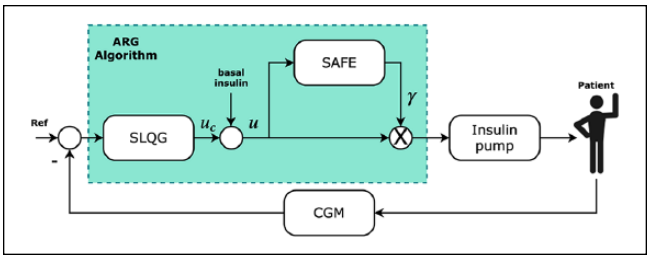

Figure 1. Block diagram of the automatic regulation of glucose algorithm.

In this work, the ARG algorithm is combined with a switching signal generator (SSG) to eliminate the need for manual mealtime announcement by automatically commanding the switching between the conservative and aggressive modes. The switching to the aggressive controller is based on the most recent CGM readings and an auxiliary signal generated by a KF. On the other hand, the switching to the conservative controller is made when a decreasing glucose trend is inferred from the CGM signal. The main difference between this AP system and others without meal announcement is that this SSG module is not meant to deliver meal-priming boluses but only to command the activation of the aggressive mode. This mode is selected when a triggering event that can be associated with an increase in the glucose rate of appearance, like a meal ingestion, is detected.

The performance of the proposed algorithm is evaluated *in silico* using the UVA/Padova simulator[30] with intraday variability and several mixed meals, comparing the performance of the ARG with and without meal announcement (ARG_{am} and ARG_{um}, respectively).

Methods

The ARG Algorithm

The ARG algorithm regulates glycemia without delivering open-loop prandial boluses. Instead, it switches between an aggressive controller K_2 that counteracts the effect of meals and other large perturbations and a conservative controller K_1 that regulates insulin infusion at all other times.

Figure 1 shows a block diagram of the ARG algorithm. The SLQG controller calculates an insulin infusion rate u_c

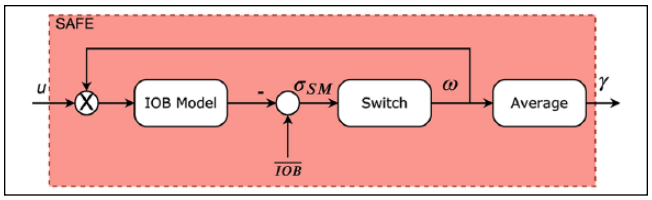

Figure 2. Block diagram of the safety auxiliary feedback element algorithm.

according to the CGM readings. Since the controller does not have integral action, the open-loop basal insulin is added to u_c, yielding u. Signal u is then modulated by the SAFE layer through $\gamma \in [0,1]$ in order to avoid violating an imposed restriction on the IOB. Thus, the insulin pump is commanded by $\gamma \cdot u$.

The SAFE layer. Figure 2 shows a block diagram of the SAFE layer. The first block estimates the IOB. The IOB model used here is a two-compartment dynamical system (although any other model or estimator could be used for this purpose) with the following set of equations:

$$\begin{aligned} \dot{C}_1(t) &= u(t) - K_{\mathrm{DIA}} C_1(t) \\ \dot{C}_2(t) &= K_{\mathrm{DIA}}[C_1(t) - C_2(t)] \\ \mathrm{IOB} &= C_1(t) + C_2(t) \end{aligned} \tag{1}$$

where C_1 and C_2 are the two compartments, $u(t)$ is the insulin infusion rate, and K_{DIA} is a rate constant that represents the duration of insulin action (DIA). The estimated IOB is compared to a pre-established constraint ($\overline{\mathrm{IOB}}$), yielding the sliding function $\sigma_{\mathrm{SM}}(t) = \overline{\mathrm{IOB}} - \mathrm{IOB}$. Then, the switching signal ω is determined as follows according to the sign of σ_{SM} :

$$\omega(t) = \begin{cases} 0 & \text{if } \sigma_{\mathrm{SM}} < 0 \\ 1 & \text{if } \sigma_{\mathrm{SM}} \geq 0 \end{cases} \tag{2}$$

If the feedback controller tries to increase the IOB above $\overline{\mathrm{IOB}}$, a high frequency switching in ω will occur, called the sliding mode. To avoid the chattering phenomenon in the control action $\gamma \cdot u$, 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.

Hypo- and hyperglycemia protection. The ARG algorithm, besides the SLQG controller and the safety layer described above, has two additional auxiliary modules to reduce risks of hypo- and hyperglycemia. Hypoglycemia is further prevented by reducing the IOB constraint when low glycemia levels are detected. On the other hand, if the controller is not aggressive enough to compensate for sustained high glucose concentrations during relatively long periods of time, automatic correction boluses (ACBs) will be delivered by the hyper-related module. For a more detailed explanation of the ARG algorithm and its auxiliary modules, refer to Colmegna et al.[13]

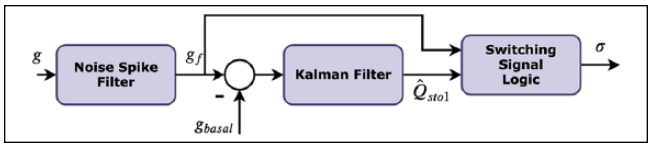

Figure 3. Block diagram of the proposed automatic switching signal generator.

Meal announcement in the clinical trials at HIBA. As mentioned, the ARG algorithm does not require neither exact CHO information nor feedforward insulin boluses to cope with meal ingestions. However, a manual mealtime announcement was still used during the clinical trial at HIBA to command the switching between K_1 and K_2. When a meal was announced, a *listening* mode was activated in which the algorithm waited to detect an increasing trend in CGM measurements to switch to the aggressive mode. The aggressive controller remained active for a full hour and then switched back to K_1 automatically. When a meal was announced, the participants were asked to classify the meal size in one of the following three categories: small, medium, or large. This information was used to tune the $\overline{\mathrm{IOB}}$ at meal times, allowing higher $\overline{\mathrm{IOB}}$ for larger meals. After 90 minutes, it was set to its default value that was defined as the IOB limit associated with a small-sized meal ($\overline{\mathrm{IOB}}_{\mathrm{s}}$).

Switching Signal Generator

The signal σ commands the modes of the SLQG controller. Here, an automatic SSG algorithm to establish σ based on CGM readings is proposed to eliminate the need for meal announcement and take a step further toward a fully automatic AP controller.

Figure 3 shows the block diagram of the proposed SSG. The first block is a noise spike filter that limits the maximum blood glucose rate of change to 3 mg dL^{-1} min^{-1}.[31] The filtered signal g_{f} is the input to the second block, which is a KF. The KF is used to generate an auxiliary signal in order to establish the SSG switching law. This signal is the estimation of the amount of glucose in the first phase of the stomach $\hat{Q}_{\mathrm{sto1}}$, which is part of the gastrointestinal subsystem presented in the following equation[32]:

$$\begin{aligned} Q_{\mathrm{sto}}(t) &= Q_{\mathrm{sto1}}(t) + Q_{\mathrm{sto2}}(t) \\ \dot{Q}_{\mathrm{sto1}}(t) &= -k_{\mathrm{gri}} \cdot Q_{\mathrm{sto1}}(t) + D\delta(t) \\ \dot{Q}_{\mathrm{sto2}}(t) &= -k_{\mathrm{empt}}(Q_{\mathrm{sto}}) \cdot Q_{\mathrm{sto2}}(t) + k_{\mathrm{gri}} \cdot Q_{\mathrm{sto1}}(t) \\ \dot{Q}_{\mathrm{gut}}(t) &= -k_{\mathrm{abs}} \cdot Q_{\mathrm{gut}}(t) + k_{\mathrm{empt}}(Q_{\mathrm{sto}}) \cdot Q_{\mathrm{sto2}}(t) \\ R_{\mathrm{a}}(t) &= \frac{f \cdot k_{\mathrm{abs}} \cdot Q_{\mathrm{gut}}(t)}{\mathrm{BW}} \end{aligned} \tag{3}$$

where $Q_{sto2}(t)$ (mg) is the amount of glucose in the second phase of the stomach, k_{gri} (min^{-1}) is the rate of grinding, D (mg) is the amount of ingested CHO, $\delta(t)$ is the Dirac delta function, k_{empt} (min^{-1}) is the rate constant of gastric emptying, Q_{gut} (mg) is the glucose mass in the intestine, k_{abs} (min^{-1}) is the rate constant of intestinal absorption, R_a (mg kg^{-1} min^{-1}) is the appearance rate of glucose in plasma, f is the fraction of intestinal absorption which actually appears in plasma, and BW (kg) is the body weight. Note that 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, the meal input is represented by a pulse-wise 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 KF, a linearized model from the meal input to the glucose output was obtained for every virtual adult of the distribution version of the UVA/Padova simulator at the basal state. In this first approach where no model personalization is considered, the meal-glucose model associated with the most sensitive *in silico* subject, adult #007, was selected. Then, the selected single-input single-output model was discretized with a sampling time of five minutes:

$$\begin{aligned} x_m(k+1) &= A_m x_m(k) + B_m u_m(k) \\ y_m(k) &= C_m x_m(k) \end{aligned} \tag{4}$$

where the input $u_m \in \mathbb{R}$ is the meal signal, the output $y_m \in \mathbb{R}$ is the glucose deviation from the basal value, $x_m \in \mathbb{R}^{18\times 1}$ represents the model's states,[33] and Q_{sto1} is the first element of x_m. Therefore, the dimensions of the model's matrices are $A_m \in \mathbb{R}^{18\times 18}$, $B_m \in \mathbb{R}^{18\times 1}$, and $C_m \in \mathbb{R}^{1\times 18}$. Since the matrix $\begin{pmatrix} \lambda I - A_m \\ C_m \end{pmatrix}$ has rank 18 for the eigenvalue λ associated with Q_{sto1}, this mode belongs to the observable subspace according to the Popov-Belovich-Hautus test. In order to estimate Q_{sto1}, the following KF was designed:

$$\begin{aligned} \hat{x}_m(k+1|k) &= A_m \hat{x}_m(k|k-1) \\ &\quad + L_m\left[y_m(k) - C_m \hat{x}_m(k|k-1)\right] \\ \widehat{Q}_{sto1}(k) &= \begin{bmatrix} 1 & 0 & \dots & 0 \end{bmatrix} \hat{x}_m(k) \end{aligned} \tag{5}$$

where L_m was obtained using the expected variances of the process (W) and measurement (V) noises as tuning parameters (W/V=1000).

The SSG determines if the controller should switch to its aggressive mode or not, using g_f and $\widehat{Q}_{sto1}$. In order to guarantee noise immunity, the following logic was defined. If $\widehat{Q}_{sto1}$ is greater than $\overline{Q}_{sto1} = 1425\,mg$ and increasing, and if g_f is greater than $\overline{g}_f = 140$ mg/dL, the controller switches to its aggressive mode. 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 $\widehat{Q}_{sto1}$ 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 $\widehat{Q}_{sto1}$ 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. For example, if frequent false positives unnecessarily triggered the aggressive mode and that generated controller-induced hypoglycemia, then thresholds for $\widehat{Q}_{sto1}$ and g_f could be raised to mitigate this situation. Also, the time range from 11:30 PM to 6:30 AM can be adjusted according to behavioral patterns.

It is worth mentioning that the estimation of Q_{sto1} is rather slow and attenuated due to measurement noise. Therefore, a low threshold of Q_{sto1} is used in order to switch to the aggressive controller. If the peak of Q_{sto1} could be perfectly followed, then the exact amount of CHO ingested by the subject could be estimated. Nonetheless, our goal is not to perfectly track Q_{sto1}, but to use this signal along with g_f to establish a switching signal policy that addresses the tradeoff between fast detection of a hyperglycemia situation and false positives due to noisy CGM readings.

At this stage, $\overline{IOB}$ switches from $\overline{IOB}_s$ (constraint defined when the conservative controller is active) to $\overline{IOB}_m$ (constraint defined for a medium-sized meal) during the time the aggressive controller is active plus 30 minutes afterward. 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 $\widehat{Q}_{sto1}$, the $\overline{IOB}$ can be tuned to a particular subject based on the hyper- and/or hypoglycemia frequency. For example, if a subject is experiencing frequent postprandial hypoglycemia, then $\overline{IOB}$ should be lowered in order to restrict the aggressive controller response. An *in silico* demonstration regarding the tuning of the $\overline{IOB}$ can be found in Colmegna et al.[13] In addition, here, the aggressive mode remains active until a decreasing trend in the CGM measurements is detected. Then, the conservative mode is automatically selected. This allows the aggressive mode to be active as long as needed, instead of being deactivated automatically after one hour, as it was described in "Meal announcement in the clinical trials at HIBA" section.

Results

In this section, the performance of the ARG_{um}, ie, the ARG combined with the SSG module, is assessed through diverse *in silico* tests performed on the UVA/Padova simulator, considering the ten *in silico* adult cohort and a Dexcom CGM model as the sensor.

In Silico *Evaluation Considering Mixed Meals*

As mentioned in "Switching Signal Generator" section, the SSG was tuned using the regular meal model of the

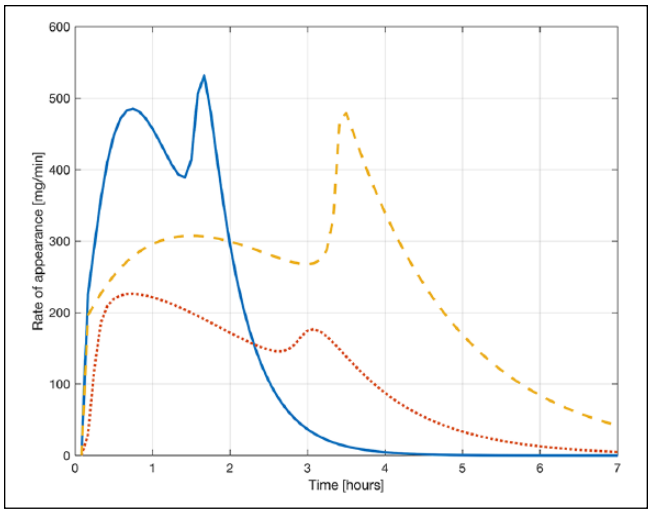

Figure 4. Rate of appearance of the mixed meals used in "*In silico* Evaluation Considering Mixed Meals" section. The solid blue line corresponds to a fast-absorbing meal, the dotted red line to a slow-absorbing meal, and the dashed yellow line to a double-peak meal.

Table 1. Mixed Meals Used in the First Set of Simulations.

Mixed meal	Absorption	CHO (g)
Milk, white rice, pear, bran-cookies, low-fat cheese, and oil	Double peak	110
High fat meal	Slow	27
Oatmeal, meal, bread, and margarine	Rapid	62

Abbreviation: CHO, carbohydrate.

UVA/Padova simulator.[32,33] Therefore, in order to test the robustness of the proposed ARG_{um}, here, it is subject to a battery of tests that include mixed meals with different nutritional composition and absorption rates.[34] Specifically, three sets of 16-hour simulations were designed, each one including a particular mixed meal from the library introduced in León-Vargas.[35] Figure 4 depicts the corresponding absorption rates and Table 1 summarizes their composition. Results are then compared to the ones obtained with announced meals, ie, using the ARG_{am} as described in "Meal announcement in the clinical trials at HIBA" section.

Slow-absorbing meal. Postprandial glucose excursions related to slow-absorbing meals are difficult to mitigate for closed-loop algorithms like the ARG that does not use feedforward insulin boluses and lack integral action to avoid insulin stacking. In this case, the decay of glucose to normoglycemia may be slow, since the insulin signal is mainly sensitive to the glucose rate of change, which tends to be slow for this type of meals. Here, both the ARG_{am} and the ARG_{um} are subject to a high-fat low-CHO meal. Results are presented in the first row of Figure 5 and the first column of Table 2. As shown, the percentage of time within the target range of 70 to 180 mg/dL is higher with the ARG_{um} than with the ARG_{am}. The reason is that the ARG_{um} does not switch back to the conservative mode until the CGM readings start to decrease, while the ARG_{am} switches back to the conservative mode automatically one hour after the aggressive mode is triggered. In the latter case, it can be observed that although the ACBs play a key role in lowering the glucose values after the conservative mode is resumed, its action is not as effective as the one generated by the ARG_{um}. While time in range is similar between the ARG_{am} with and without ACBs, the first row of Figure 5 shows that the use of ACBs results in a faster return to the euglycemic range.

Fast-absorbing meal. The second row of Figure 5 and the second column of Table 2 summarize the results for a fast-absorbing mixed meal. As expected, similar responses are achieved under ARG_{am} and ARG_{um}, due to the fact that the meal is rapidly absorbed. In addition, given that no ACBs are administrated, the results with and without activating the hyper-related module are almost identical (slight variations are related to measurement noise).

"Double-peak" meal. The third row of Figure 5 shows the mean glucose and mean insulin ± one standard deviation (SD) obtained with both the ARG_{um} and the ARG_{am} for a mixed meal that presents "double peak," which is difficult to control with an algorithm that depends on a meal announcement. The third column of Table 2 summarizes the results for this meal. As expected, the first peak is better compensated by the ARG_{am}, since a meal announcement was used and the switching to the aggressive controller was made earlier than with the ARG_{um}. However, since the ARG_{um} switches to the aggressive mode when a hyperglycemia episode might occur, it can compensate the second peak more efficiently than the ARG_{am}, which highly depends on ACBs to reduce substantial glucose excursions. The advantage of using the ARG_{um} to compensate this type of meals is better illustrated when the hyper-related auxiliary module is not activated. Note that the ARG_{um} mitigates faster the delayed glucose peak than the ARG_{am} without ACBs (the right-hand side of Figure 5).

In Silico *Evaluation Considering Intrapatient Variability*

A second set of simulations was performed in order to evaluate the performance of the ARG_{um} under intrapatient variability. To this end, intraday variability of insulin sensitivity (S_I) was considered, following the work of Visentin et al.[36] There, S_I was characterized by two parameters: V_{mx} that governs the insulin-dependent glucose utilization and k_{p3} that governs the insulin action on the liver. Seven S_I daily patterns were defined based on the level of S_I at breakfast (V_{mx}^{b}, k_{p3}^{b}), lunch (V_{mx}^{l}, k_{p3}^{l}), and dinner (V_{mx}^{d}, k_{p3}^{d}), and each *in silico* subject was randomly associated with one of them. Thus, to

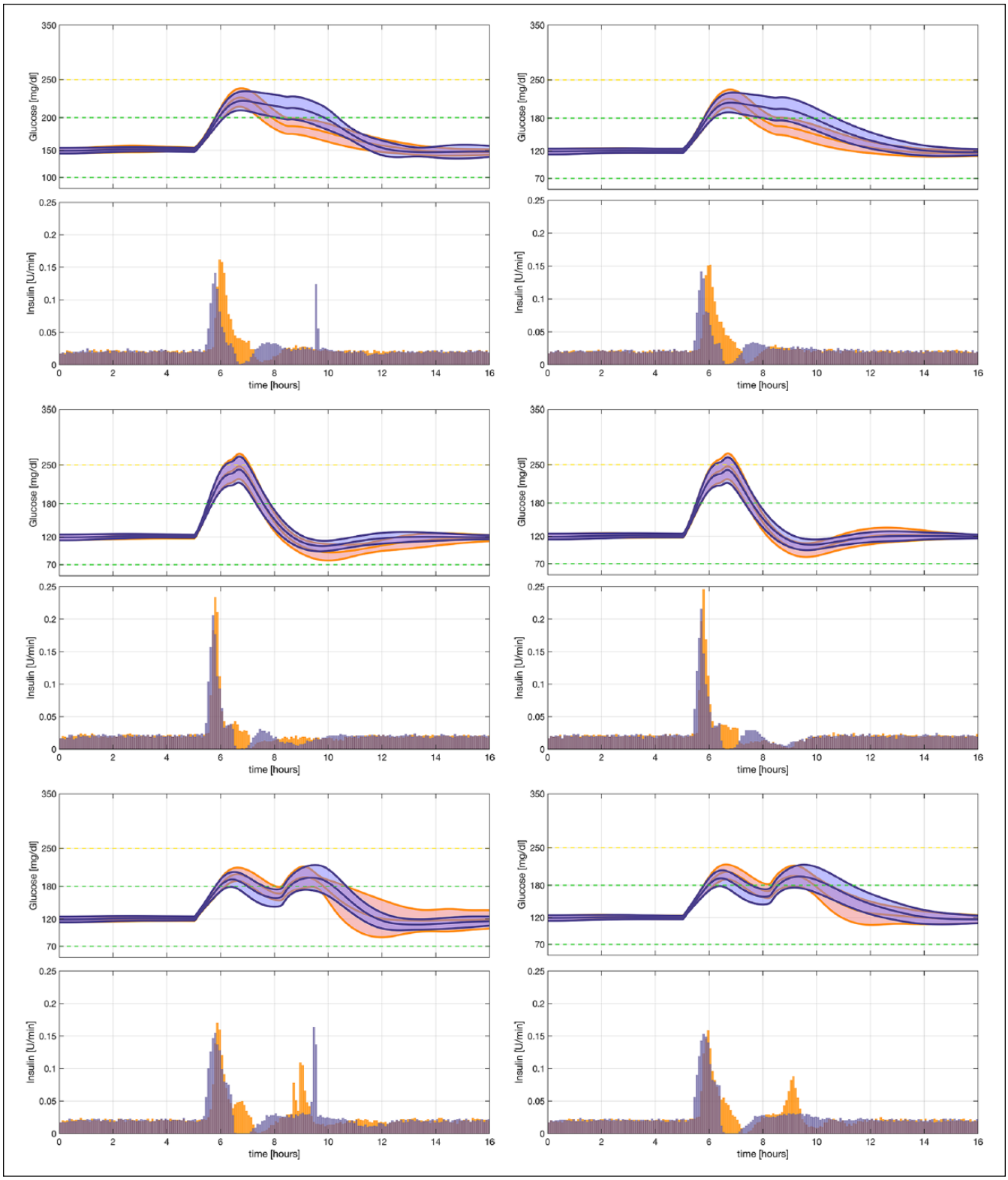

Figure 5. Mean glucose and insulin ± one standard deviation for the mixed meal simulations. The first column displays the results with the hyperglycemia protection layer and the second column shows the results without the use of automatic correction boluses. The first row corresponds to the slow-absorbing meal, the second row to the fast-absorbing meal, and the third row to the double-peak meal. The purple lines correspond to the automatic regulation of glucose algorithm with announced meals and the orange lines to the automatic regulation of glucose algorithm with unannounced meals. The dashed green lines show the desired range, and the dashed yellow line shows the acceptable range.

Table 2. Results (Median [0.25-0.75 Quantile]) for Three Kinds of Mixed Meals Using the Automatic Regulation of Glucose Algorithm With Unannounced Meals and the Automatic Regulation of Glucose Algorithm With Announced Meals With and Without the Hyperglycemia Protection Layer.

	Control method	Slow absorption		Rapid absorption		Double peak	
		ACB	No ACB	ACB	No ACB	ACB	No ACB
% Time <70 mg/dL	ARG_{am}	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]
	ARG_{um}	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]
% Time [70-180] mg/dL	ARG_{am}	77.5 [71.6-79.5]	78.1 [68.6-80.2]	84.8 [77.6-96.7]	84. 6 [74.0-93.9]	87.6 [86.0-89.0]	87.4 [86.0-88.9]
	ARG_{um}	87.5 [84.7-89.8]	87.8 [84.5-90.6]	80.2 [72.2-87.8]	79.8 [74.8-87.6]	87.4 [86.0-88.3]	87.6 [86.1-88.8]
% Time [70-250] mg/dL	ARG_{am}	100.0 [100.0-100.0]	100.0 [100.0-100.0]	100.0 [100.0-100.0]	100.0 [100.0-100.0]	100.0 [96.3-100.0]	100.0 [96.5-100.0]
	ARG_{um}	100.0 [100.0-100.0]	100.0 [100.0-100.0]	100.0 [100.0-100.0]	100.0 [100.0-100.0]	99.6 [94.3-100.0]	100.0 [94.4-100.0]
% Time >180 mg/dL	ARG_{am}	22.5 [20.5-28.4]	21.9 [19.8-31.4]	15.2[3.3-22.4]	15.4 [6.1-26.0]	12.4 [11.0 -14.0]	12.6 [11.1-14.0]
	ARG_{um}	12.5 [10.2-15.3]	12.2 [9.4-15.5]	19.8 [12.2-26.4]	20.2 [12.4-25.2]	12.3 [11.7-13.7]	12.1 [11.2-13.3]
% Time >250 mg/dL	ARG_{am}	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 [0.0-3.7]	0.0 [0.0-3.5]
	ARG_{um}	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.4 [0.0-3.0]	0.0 [0.0-3.9]

Abbreviations: ACB, automatic correction bolus; ARG_{am}, automatic regulation of glucose algorithm with announced meals; ARG_{um}, automatic regulation of glucose algorithm with unannounced meals.

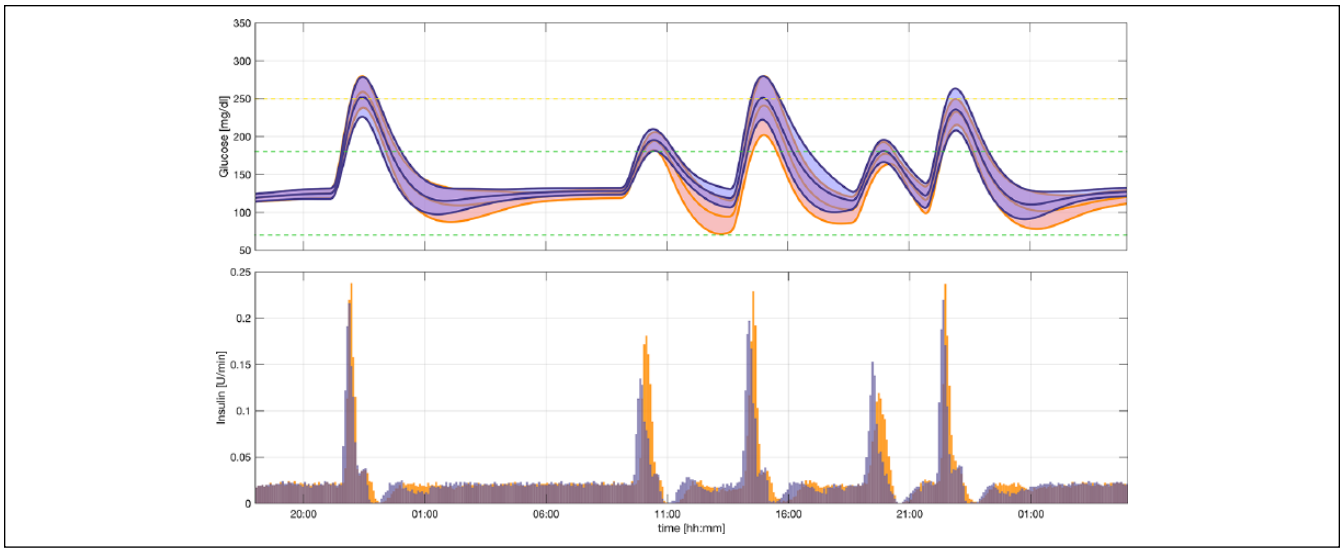

Figure 6. Mean glucose and insulin ± one standard deviation for the simulations with intrapatient variability. The purple lines correspond to the automatic regulation of glucose algorithm with announced meals and the orange lines to the automatic regulation of glucose algorithm with unannounced meals. The dashed green lines show the desired range and the dashed yellow line shows the acceptable range.

represent intraday variability, V_{mx} and k_{p3} were transformed to time-varying parameters. To this end, they were defined as step-wise signals that vary three times a day and then smoothed using a low pass filter. Deviations from the nominal values were allowed by modulating the nominal pattern with a multiplicative noise normally distributed with mean 1 and SD 0.2. The simulation scenario was designed to replicate the clinical trial at HIBA, which had a duration of 36 hours (start time 6 PM) and five meals: two dinners (55 gCHO each), one breakfast (28 gCHO), one lunch (55 gCHO), and an afternoon snack (28 gCHO).

The time responses to this protocol are depicted in Figure 6. Time spent in the euglycemic range was similar under both controllers (ARG_{am}: 81.4 [75.4, 83.5]% and ARG_{um}: 80.9 [77.0, 85.1]%). Although the ARG_{um} may remain in the aggressive mode longer and the default IOB is set to IOB_m even with small meals, time in hypoglycemia was negligible in both cases (ARG_{am}: 0.0 [0.0, 0.0]% and ARG_{um}: 0.0 [0.0, 0.0]%). This confirms the fact that IOB represents only a limit and not the exact amount of insulin to be infused.

Discussion

Although promising results were obtained with the ARG algorithm with meal announcement in the clinical trial at HIBA, the end goal is to eliminate the need for meal announcement and design an appropriate method to switch

between the two LQG controllers (K_1 and K_2). In this work, an automatic SSG is proposed to command both transitions: from K_1 to K_2, by using a KF and flexible glucose thresholds, and from K_2 to K_1, by detecting a decreasing trend in CGM measurements. Results from *in silico* tests under several challenging conditions indicate that the ARG combined with the SSG shows similar or, in some cases, even better performance than the ARG_{am}, while reducing patient intervention.

Despite this, the ARG_{um} presents also some disadvantages due to the lack of meal announcement. The first one is a potentially higher glucose peak after meals, as a result of the increased delay in the switching from K_1 to K_2. The other one is the current inability to establish an appropriate IOB for every meal size or type. It should be noted that the long-term objective of our team is to minimize as much as possible the patient's burden. It is clear that with extra information, as in a hybrid procedure, a better performance can be achieved, but at the cost of a greater and persistent involvement of the patient.

It is worth highlighting that the mealtime announcement does not directly trigger the ARG_{am} into the aggressive mode. Instead, the ARG_{am} has a simple "meal detection" algorithm to confirm that a meal is present. Therefore, it must be kept in mind that, in this work, the ARG_{um} was contrasted with a strategy that already has a delay in meal compensation and not with a perfect meal-bolus therapy. Finally, note that faster insulin analogs could mitigate the impact of this inherent delay on glucose control by helping to align the insulin and meal rates of appearance.

Conclusion

In this work, an algorithm to automatically command the switching between the conservative and the aggressive mode of the clinically tested ARG AP controller was designed and evaluated *in silico*. Promising preliminary results were obtained, indicating that the proposed strategy is robust with respect to different meals and intraday variability in S_I. Therefore, it can be concluded that a clinical trial with the ARG_{um} is feasible.

Declaration of Conflicting Interests

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