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Exercise-induced hypoglycemia in type 1 diabetes: in-silico comparison between announced and unannounced strategies in closed-loop control

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Abstract: It is recommended that those with Type 1 Diabetes Mellitus participate in physical activity. However, insulin management during and after exercise remains challenging for both patients and physicians. The artificial pancreas is a closed-loop system which aims to control blood glucose levels automatically however, with physical activity the system is unable achieve optimal glycemic control. In this work, two different strategies of announced and unannounced exercise are combined with a closed-loop algorithm to mitigate the risk of exercise-induced hypoglycemia caused by aerobic activity. In the announced strategy, patients must inform the system that they are planning to exercise, this allows the modification of various controller parameters and the suggestion of a controller calculated amount of carbohydrates before the onset of exercise. The unannounced strategy removes the need of exercise announcement and utilizes an algorithm to detect exercise and trigger a carbohydrate suggestion and changes to the controller parameters. Both strategies are evaluated in-silico using the UVa/Padova simulator, in a realistic scenario considering sessions of aerobic exercise with 60% of VO_{2max} for a duration of 50 minutes. Results show that both strategies are able to reduce the occurrence of hypoglycemia events, with the unannounced strategy achieving better outcomes.

Keywords: Artificial Pancreas, Biomedical systems, Exercise-induced hypoglycemia, PD Controllers, Type 1 Diabetes.

1. INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic condition which incidence is increasing worldwide. Pancreatic β-cell dysfunction results in critical deficiency in insulin secretion, which leads to elevated concentrations of blood glucose (BG) levels. Chronically elevated levels of BG may result in several complications, such as neuropathy, nephropathy, retinopathy, and cardiovascular disease (Jacobson et al., 2013). Therefore, individuals with T1DM must regulate BG levels through life-long exogenous administration of insulin .

Although it is recommended for subjects with T1DM (Colberg et al., 2016), physical activity is still a hurdle for many patients who may feel discouraged from engaging in exercise due to the fear of exercise-induced hypoglycemia (Brazeau et al., 2008). One obstacle of exercise management is the variability in BG response to different types of exercise. While aerobic exercise tends to decrease BG, anaerobic exercise leads to an increase in BG. A recent consensus statement (Riddell et al., 2017) highlights different approaches to deal with exercise for conventional insulin therapy, but it is dependent on various factors, such as intensity and duration of activity, initial BG concentrations, physical fitness, etc. Currently, the majority of people living with T1DM administer insulin via multiple daily insulin injections or continuous subcutaneous insulin infusion. However, both treatments require constant interventions by patients and are burdensome. The artificial pancreas is a closed-loop system which aims to reduce the burden caused by conventional therapies and at the same time improve safety to the patient. A traditional artificial pancreas integrates a continuous glucose monitoring (CGM) device, an insulin pump, and an embedded control algorithm. Physical activity is addressed differently by artificial pancreas researchers. The approaches to mitigate the risk of exercise-induced hypoglycemia include the use of dual-hormone systems (insulin and glucagon) to counteract the effects of exercise, the development of algorithms to suggest carbohydrate (CHO) consumption, and systems that require the announcement of exercise to

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modify an insulin controller to be less aggressive (Bertachi et al., 2018b).

The main objective of this work is to compare the performance of two strategies to control BG during physical activity. The first strategy consists of the announcement of exercise by the patient, allowing the re-configuration of the controller and also triggering feed-forward (FF) actions to deal with the expected disturbance in BG. The second strategy does not require the announcement of exercise and relies on an algorithm that includes an Unscented Kalman Filter to detect the occurrence of exercise, and then applies actions to mitigate the risk of exercise-induced hypoglycemia.

2. MATERIAL AND METHODS

To evaluate the proposed strategies, the FDA-accepted UVa/Padova simulator is considered (Dalla Man et al., 2014). Both strategies were developed to complement a closed-loop system that maintains BG levels in normoglycemia. The system is composed by an insulin-only controller with a CHO recommender loop. Both loops are interconnected and operate in a coordinated way. In addition, the system is classified as a hybrid closed-loop system, because it requires the announcement of meals to deliver insulin boluses. In Figure 1 both control-loops are depicted and in the following sections, the system is detailed.

2.1 Insulin Controller

The insulin control-loop is composed by a clinically tested PD controller (Rossetti et al., 2017) with Insulin Feedback (IFB) (Sala-Mira et al., 2017) and by a safety layer with Sliding Mode Reference Conditioning (SMRC), the so-called SAFE layer (Revert et al., 2013). The PD+IFB controller aims to compute the required insulin to follow the desired reference. The outer loop works as a safety layer that aims to limit the concentration of insulin on board (IOB), i.e., the residual amount of insulin still active in the subcutaneous tissue ($\widehat{IOB}$). The SAFE layer is composed by two elements: a switching logic that regulates IOB within a specific range and by a first-order filter that smooths the discontinuous signal applied by the switching logic, ensuring a smoothed signal in the PD computation. In other words, the SAFE layer creates a virtual glucose reference in the case of a violation of the IOB boundaries. In this work, solely the upper IOB limit (IOB_{max}) is considered, therefore, if $\widehat{IOB}$ violates IOB_{max}, the SAFE layer will increase the reference signal $G_{ds,INS}$ avoiding controller overactuation. For further details regarding the insulin controller, readers should refer to Rossetti et al. (2017).

2.2 Carbohydrate Controller

The CHO controller is a second feedback controller based on a predictive PD and is designed to mitigate any disturbance that lowers BG levels and poses a threat of hypoglycemia. The controller suggests that the patient consume rescue CHO to increase BG levels in order to minimize the risk of hypoglycemia. The PD_{CHO} controller computes control actions equivalent to negative signals of the insulin PD control action. This means that the control action performed by this controller must have the opposite effect of insulin, i.e., increase BG. In addition to the PD_{CHO} controller, a fourth order auto-regressive model is used to compute predictions of BG up to 20 minutes in the future, and these predictions are considered in the the final control action computation. Finally, the output of this controller is quantified, and if it surpasses a determined threshold, 15 grams of fast-acting CHO are recommended. For further details regarding the CHO controller, readers should refer to previous publications (Beneyto and Vehi, 2017; Beneyto et al., 2018).

2.3 Announced strategy

This strategy is intended to make use of the announcement of physical activity by the patients to perform several FF actions to anticipate the expected effects of aerobic exercise on BG control. Such actions were previously designed to be applied in an insulin-only controller (without the CHO controller) configuration and has been presented in Bertachi et al. (2018a). In the current work, these strategies were slightly modified in order to consider the inclusion of the CHO controller in the control-loop. The FF actions are: a suggestion of CHO consumption at the announcement of exercise, modification of insulin controller's parameters in order to deliver less insulin than usual, and a reduction of the next meal bolus after an exercise session.

The amount of CHO that is suggested in the moment of the announcement (20 minutes before the start of the exercise) follows the consensus statement published by Riddell et al. (2017) and is computed according to (1)–(3).

$$CHO_G = \begin{cases} 20 & if \quad G(t) \leq 90 \\ 10 & if \quad 90 < G(t) \leq 124 \\ 0 & otherwise \end{cases} \tag{1}$$

$$CHO_{IOB} = \left(\widehat{IOB}(t) - IOB_{basal}(t) \cdot 0.7\right) \cdot CR \tag{2}$$

$$CHO_{FF} = 5\lfloor CHO_G + CHO_{IOB} - COB_{PDCHO} \rceil, \quad s.t.\ CHO_{FF} \leq \left(\overline{G_{ex}} - G(t)\right) \cdot K_{FF} \tag{3}$$

where $G(k)$ is BG measurements in mg/dl, $\widehat{IOB}$ is the IOB estimation, IOB_{basal} is the IOB estimation considering basal conditions, CR is a individualized insulin-to-CHO ratio, COB_{PDCHO} is the carbohydrates on board in case of any CHO suggested by the PD_{CHO} controller, $\overline{G_{ex}}$ is the maximum desired BG level due to CHO_{FF} (set to 250 mg/dl), K_{FF} is a gain related with the increase on BG caused by CHO_{FF} (set to 0.37) and has been tuned from an open-loop experiment. t stands for the current sampling time. The notation $5\lfloor\ \rceil$ denotes that CHO_{FF} is rounded to the nearest 5.

The aforementioned modifications in the insulin controller are triggered by patients' announcement, and happens in two different stages, as illustrated in Figure 2.

- Exercise configuration – mode 1: this mode starts when the patient announces exercise. This should be done 20 minutes before the beginning of exercise. From the moment of the announcement several parameters of the insulin controller are modified (as described in Bertachi et al. (2018a)), and lasts for up to 30 minutes after the ending of exercise or if any

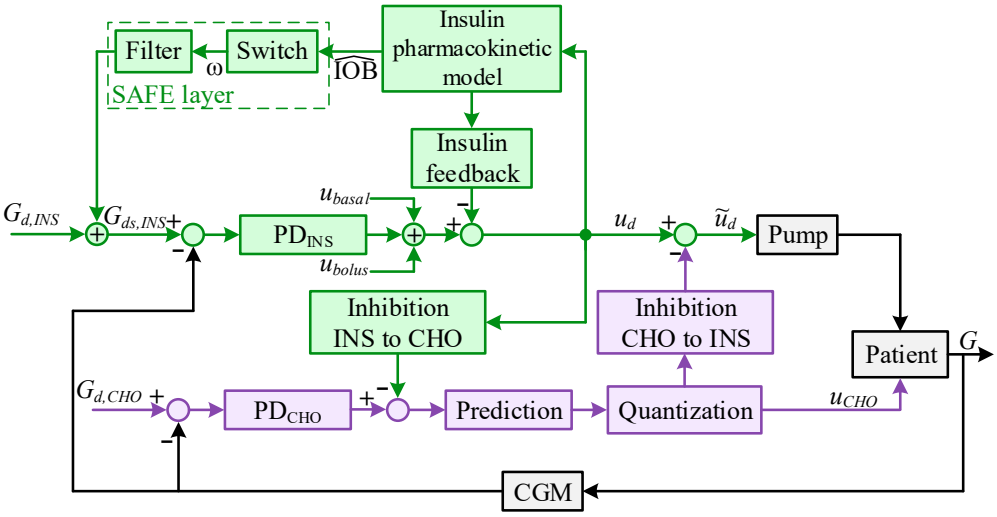

Fig. 1. Closed-loop scheme. The insulin control loop is represented by green lines. CHO control loop is represented by purple lines.

of the following conditions ("escape conditions") are observed after the ending of exercise:

i) $G(k) > 140 \wedge \dot{G}(k) > 0, \forall k \in (t-2, ..., t)$

ii) $\dot{G}(k) > 1 \wedge \tilde{u}_d(k) = 0, \forall k \in (t-2, ..., t)$

iii) $\dot{G}(j) > 1.5 \wedge \tilde{u}_d(j) = 0, \forall j \in (t-1, t)$

where $\dot{G}$ is the derivative of G in mg/dl/min and $\tilde{u}_d$ is the insulin delivered, in units/hour . It is important to mention here that the variable t stands for the time instant related with the sampling period of the system. The variables k and j represents different time intervals related with t. Taking the first condition as example, it is necessary that $G(t-2)$, $G(t-1)$ and $G(t)$ must be greater than 140 and also $\dot{G}(t-2)$, $\dot{G}(t-1)$ and $\dot{G}(t)$ must be greater than 0, since k is defined as the samples at instants $t-2$, $t-1$ and t.

- Exercise configuration – mode 2: this mode starts as soon as the mode 1 is concluded. During this mode, the controller begins to linearly return to its default configuration, i.e., all the parameters that had been altered during mode 1 return to their original values in a linear fashion during the following 60 minutes.

And the final action considered is the reduction of the next meal bolus by 50% after an exercise session.

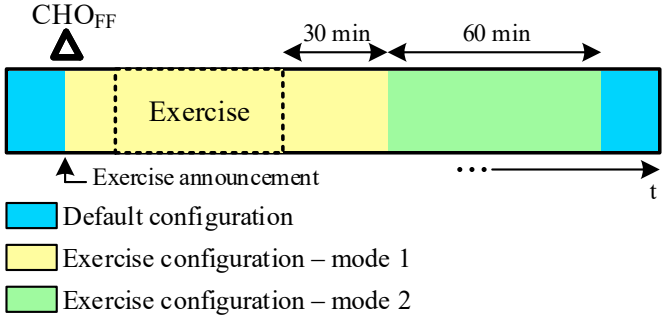

Fig. 2. Summary of the feed-forward actions applied in the case of announcement of exercise.

2.4 Unannounced strategy

The unannounced strategy includes an exercise detection algorithm that triggers disturbance rejection actions that aim to reduce the risk of exercise-induced hypoglycemia. The algorithm collects glucose and insulin infusion rate values and computes a disturbance parameter, $D(t)$ from an augmented minimal model using an Unscented Kalman Filter (UKF) (Ramkissoon et al., 2018) and detects exercise if a patient specific threshold, k_{TH} is crossed and more than 60 min have elapsed since the last exercise detection. k_{TH} was determined using the minimum $D(t)$ value found in an in silico 15-day well-controlled closed-loop scenario without exercise. The principal idea behind the tuning of the exercise detection algorithm was that glucose uptake during aerobic exercise produces a more profound effect on D than the effect of insulin-promoted glycogenesis; therefore, D values during exercise should be lower than those experienced in the absence of exercise.

Three actions adapted from Bertachi et al. (2018a) are applied when exercise is detected:

(1) Reduction in basal insulin (u_{basal}) and reduction in the controller parameter IOB_{max}.
(2) A specified amount of CHO is suggested to the patient.
(3) The following meal insulin bolus (u_{bolus}) is reduced by 30%.

After the detection of exercise, action (1) is applied for 60 min and then these values are linearly returned to their nominal values over a period of 120 min. However, if at any point any of the escape conditions are met, all parameters modified are immediately returned to their nominal state. The escape conditions are:

i) $G(k) > 120 \wedge \dot{G}(k) > 0, \forall k \in (t-2, ..., t)$

ii) $(G(k) > 90 \wedge \dot{G}(k) > 1), \forall k \in (t-2, ..., t)$

iii) $(\dot{G}(k) > 0 \wedge \tilde{u}_d(k) > 0), \forall k \in (t-2, ..., t)$

iv) $(\dot{G}(j) > 1.5 \wedge \tilde{u}_d(j) > 0), \forall j \in (t-1, t)$

The reason why the former escape conditions differ from the announced case is because in the unannounced strategy the system may detect an exercise session erroneously, i.e., a false positive. In this situation, the escape conditions are more relaxed to avoid severe hyperglycemia, since a false positive detection triggers CHO delivery and also insulin infusion reduction. The CHO suggestion is computed in the same way as in the announced strategy, Equations (1)–(3), but CHO_{FF} is also limited to the maximum of 30 grams of CHO for each detection.

2.5 Testing scenario and outcomes

To asses the performance of the aforementioned strategies to mitigate the risks of exercise-induced hypoglycemia, the adult cohort from the modified UVa/Padova simulator is tested in a challenging and realistic scenario, including intra-patient variability. The exercise model presented by Dalla Man et al. (2009) has been modified to cause a similar drop on BG as observed in real patients performing aerobic exercise in a clinical study (Bertachi et al., 2018a). In a 20-day scenario with meals at 7:00 (50g) , 13:00 (70g) and 20:00 (70g), the virtual cohort has been challenged with 10 exercise sessions on alternate days. Exercise sessions were scheduled to mimic regular daily activities in real patients, either before or after meals. The sessions were intended to replicate the effect of aerobic exercise during 50 minutes, with an intensity of 60% of VO_{2max}, that represents the maximum rate of oxygen consumption during exercise.

3. RESULTS

Results are presented in Table 1 and are based on CGM measurements. Individual metrics are computed and then the results are presented as the median (25th,75th percentile) among the all the patients, except in relation to the total number of hypoglycemic events, which is presented as the total amount of events among the entire cohort. The results are divided into three different periods: the the overall outcomes for the 20-day simulation, the first 2 hours after the beginning of exercise, and from 2-h after the start of exercise to 6-h after the start of exercise. Hypoglycemia is defined following the consensus report (Agiostratidou et al., 2017): Level 1 is defined as BG $<$ 70 mg/dl and BG $\geq$ 54 mg/dl, and Level 2 as BG $<$ 54 mg/dl. Hypothesis testing is performed by Wilcoxon two-sided signed-rank test, considering a significance level of 0.05. Figure 3 is intended to show the difference caused by each strategy during exercise periods regarding: (a) glycemic control, (b) insulin delivery, (c) suggestions of CHO due to the FF actions and, (d) CHO suggestions by the PD_{CHO} controller. This Figure is the aggregation of all exercise sessions of all patients, and ranges from 1-h before the onset of exercise to 6-h after the start of exercise.

4. DISCUSSION

Results obtained for the 20-day period show that both strategies achieve similar outcomes in almost all the metrics analyzed. Exercise sessions were performed during different hours of the day. Thereby, we could evaluate the

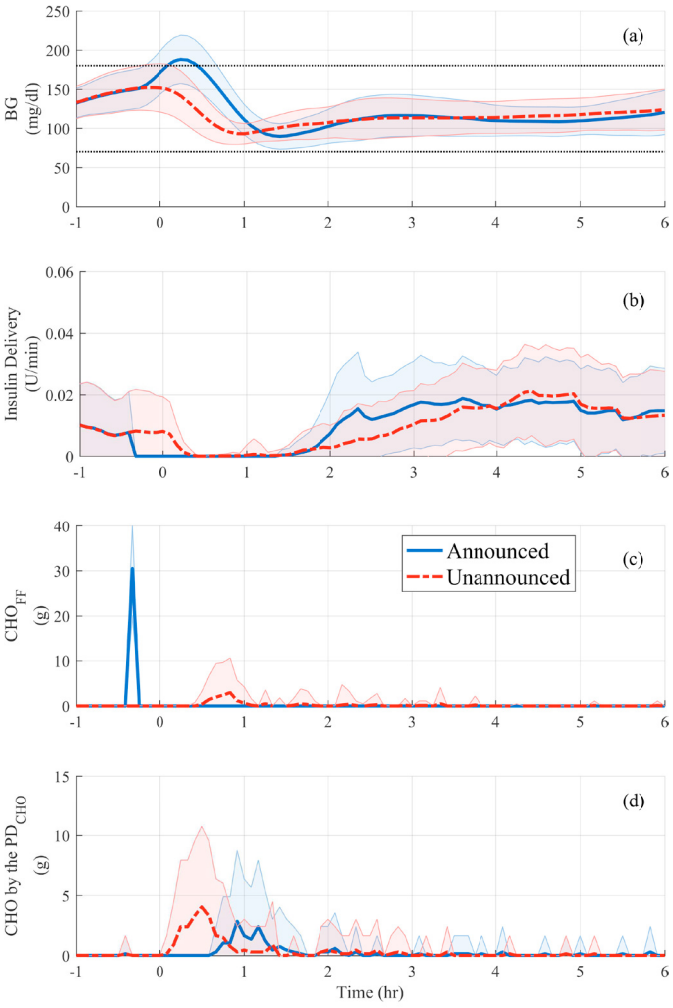

Fig. 3. Population graphs for all the exercise sessions for the entire cohort. Blue lines are mean ± SD for the announced case and red lines are mean ± SD for the unannounced case. Each exercise sessions lasted for 50 minutes and the commencement of all sessions are aligned at hour 0. Hypoglycemia threshold of 70 mg/dl and hyperglycemia threshold of 180 mg/dl are the dotted lines in black. (a) BG readings; (b) Insulin delivery; (c) CHO delivery either by the announced strategy or unannounced strategy; (d) CHO delivery by the PD_{CHO} controller.

performance of the mitigation strategies under different conditions. In the overall outcomes the only metric observed with a statistically significant difference was the percentage of time spent below 70 mg/dl (0.1% vs. 0.0%). In addition, the unannounced strategy achieved superior results in the total amount of Level 1 hypoglycemic events. In both arms no Level 2 hypoglycemic events occurred, indicating the robustness of the PD_{CHO} controller to minimize the severity of hypoglycemic events. Regarding the exercise-related outcomes, it can be observed that the unannounced strategy is able to mitigate almost all the exercise-induced hypoglycemia, in only 3 exercise sessions

Table 1. Comparison of outcomes between announced and unannounced strategy.

	Announced	Unannounced	p-value
Overall outcomes – 20 days			
Mean Glucose (mg/dl)	131.5 (127.7, 138.1)	132.6 (129.8, 136.1)	0.28
% of time spent between 70-180 mg/dl	94.2 (89.3, 94.9)	94.1 (91.2, 95.3)	0.63
% of time spent above 180 mg/dl	5.3 (4.6, 10.6)	5.8 (4.7, 8.8)	0.92
% of time spent below 70 mg/dl	0.1 (0.0, 0.5)	0.0 (0.0, 0.0)	<0.05
% of time spent below 54 mg/dl	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1
Total Level 1 hypoglycemic events	17	3	–
Total Level 2 hypoglycemic events	0	0	–
Exercise related outcomes			
BG at exercise start (mg/dl)	171.1 (164.4, 178.5)	152.8 (141.3, 161.5)	<0.05
CHO_{FF} announced (grams/session)	31.0 (27.5, 35.0)	0.0 (0.0, 0.0)	<0.05
From exercise start + 2 hours			
Glucose drop (mg/dl)	86.3 (77.9, 93.0)	68.5 (57.5, 73.7)	<0.05
Mean Glucose (mg/dl)	127.3 (122.8, 136.1)	109.7 (105.7, 117.8)	<0.05
CHO_{FF} unannounced (grams/session)	0.0 (0.0, 0.0)	13.0 (9.0, 15.0)	<0.05
CHO (grams/session)	15.0 (10.5, 15.0)	23.3 (21.0, 25.5)	<0.05
% of time spent between 70-180 mg/dl	78.0 (69.6, 84.0)	95.2 (94.0, 100.0)	<0.05
% of time spent above 180 mg/dl	15.6 (14.0, 19.2)	3.4 (0.0, 4.8)	<0.05
% of time spent below 70 mg/dl	1.2 (0.0, 8.0)	0.0 (0.0, 0.8)	<0.05
% of time spent below 54 mg/dl	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1
Total Level 1 hypoglycemic events	14	3	–
Level 1 hypoglycemic events per session	0.1 (0.0, 0.3)	0.0 (0.0, 0.0)	0.063
Total Level 2 hypoglycemic events	0	0	–
Level 2 hypoglycemic events per session	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1
From 2 hours after exercise start + 4 hours			
Mean Glucose (mg/dl)	111.5 (105.1, 118.2)	114.2 (113.0, 119.3)	0.23
CHO_{FF} (grams/session)	0.0 (0.0, 0.0)	0.5 (0.0, 6.5)	0.08
CHO (grams/session)	3.0 (1.5, 6.0)	3.0 (1.5, 4.5)	0.84
% of time spent between 70-180 mg/dl	98.3 (97.6, 99.6)	98.9 (97.6, 100.0)	0.69
% of time spent above 180 mg/dl	0.8 (0.0, 2.0)	1.1 (0.0, 2.4)	0.97
% of time spent below 70 mg/dl	0.0 (0.0, 1.2)	0.0 (0.0, 0.0)	0.13
% of time spent below 54 mg/dl	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1
Total Level 1 hypoglycemic events	2	0	–
Level 1 hypoglycemic events per session	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.5
Total Level 2 hypoglycemic events	0	0	–
Level 2 hypoglycemic events per session	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1

(out of a total of 100) a Level 1 hypoglycemic event occurred. In the announced arm, a total of 16 Level 1 hypoglycemic events has been observed, with 14 in the first two hours after the beginning of exercise. These results can also be observed in the percentage of time spent below 70 mg/dl. The announced strategy spent more time below 70 mg/dl than the unannounced strategy (1.2% vs. 0.0%) in the 2-h period after the onset of exercise. Both strategies performed similarly in the late postexercise period. No statistical significance is observed in Table 1 and the glycemic responses (Figure 3 (a)) are very similar during this period as well. The difference observed in the results may be explained by the different manner in which CHO are suggested by each strategy. The announced strategy is based on IOB estimation and on BG readings in the moment when exercise is announced. This is a drawback of this strategy, because whether the effects caused by the exercise is far from the expected, CHO_{FF} may be insufficient leading to hypoglycemia or may be exaggerated, leading to hyperglycemia. Figure 3 (a) indicates that such a strategy is able to avoid hypoglycemia especially during the first hour after the beginning of exercise, but the delayed effects of exercise still resulted in some Level 1 hypoglycemic events, even with the action of the PD_{CHO} controller (Figure 3 (c)) after the cessation of exercise. The unannounced strategy suggests CHO if exercise is detected, i.e. if an unexpected glucose uptake is observed. This allows the suggestion of CHO only when there is a pronounced effect on BG due to exercise. On one hand this can be a problem, because there is a delay between exercise onset and exercise detection. However, on the other hand the PD_{CHO} controller can reduce the risk of hypoglycemia while exercise is not detected. Note that in Figure 3 (d) the PD_{CHO} controller starts to suggest CHO earlier for the unannounced arm, and then when exercise is detected, the suggestion of CHO is due to the unannounced strategy instead of the PD_{CHO} action. The detection algorithm achieved 84.0 $\pm$ 16.5 % of sensitivity, with a detection time of 49.5 $\pm$ 18.6 minutes. As with all in-silico studies, our work has several limitations. The simulator includes a modified-model which is intended to cause a similar drop to glucose due to aerobic physical activity. The strategies presented in this work were adjusted based on this model. Therefore, such strategies may not be useful during physical activities that result in a different response than those of the model used.

5. CONCLUSION

This work presented the comparison of two different approaches to deal with aerobic exercise in the artificial pancreas. Results showed that both strategies are able to reduce the risk of exercise-induced hypoglycemia. Never-

theless, the unannounced strategy achieved better results, indicating that such method may be feasible in future generations of the artificial pancreas that aim to be a fully-automated system. Unlike systems that rely on glucagon to increase BG during exercise, insulin-only hybrid closed-loop systems are already available allowing easy implementation of the proposed systems However, it is necessary to validate such an approach with real patients, firstly in a well-controlled clinical environment and then in free-living conditions.

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