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Adaptive tuning of basal and bolus insulin to reduce postprandial hypoglycemia in a hybrid artificial pancreas

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ABSTRACT

Objective: We introduce an adaptive learning algorithm to better adjust postprandial basal and pre-meal bolus insulin for reducing postprandial hypoglycemia in a hybrid artificial pancreas (AP). An AP uses a control algorithm and sensed glucose to automate the delivery of insulin to people with type 1 diabetes (T1D). A hybrid AP requires the person to dose insulin in advance of a meal. Insulin sensitivity is dynamic in people with T1D, making it challenging for an AP to maintain euglycemia. Adaptive approaches to meal dosing can help prevent postprandial hypoglycemia.
Methods: An adaptive learning postprandial hypoglycemia-prevention algorithm (ALPHA) is introduced. One implementation of ALPHA adjusts the rate of postprandial insulin (ALPHA-BR) proportionally in response to prior postprandial episodes. This is achieved by an adaptive aggressiveness factor applied to postprandial basal insulin. The second implementation adaptively updates the pre-meal bolus insulin by changing the insulin-to-carbohydrate ratio (ALPHA-ICR), also proportionally in response to prior postprandial hypoglycemia. Both implementations were evaluated within an AP on an in-silico T1D virtual population of 99 subjects with circadian insulin sensitivity variations and 30% errors on meal estimations. Twenty real-world 4-day meal scenarios were given and glycemic outcomes were compared with an AP with no adaptation.
Results: Out of the 99 in-silico subjects, 23 of them experienced postprandial hypoglycemia leading to greater than 1% overall time in hypoglycemia. Of these 23 subjects, we evaluated the benefit of using ALPHA-BR and ALPHA-ICR to prevent postprandial hypoglycemia. ALPHA-BR yielded substantially fewer percent time in hypoglycemia compared to AP (0.54% vs 1.92%, $p < 0.001$) and fewer rescue carbs per day (0.36 vs. 1.29, $p < 0.001$). For the control algorithm evaluated, it yielded an average aggressiveness factor of 0.72 for reducing postprandial basal insulin. ALPHA-ICR slightly reduced time in hypoglycemia compared to AP (1.77% vs. 1.92%, $p = 0.09$).
Conclusion: Incorporating adaptive meal dosing into an AP can help reduce postprandial hypoglycemia, and the reduction is primarily due to changes in postprandial insulin delivery rather than pre-meal bolus.
Significance: Adapting postprandial insulin can lead to substantial reduction in postprandial hypoglycemia and the adaptive algorithm presented can be used both to tune an algorithm prior to a study and to adapt to individuals during real-time usage.

1. Introduction

People with type 1 diabetes produce little or no insulin and therefore require insulin for survival. Different insulin therapy methods are used by people with T1D to control glucose levels. Multiple daily injection (MDI) is where long-acting basal insulin is administered once or twice per day, and rapid-acting insulin is administered for meals. Continuous subcutaneous insulin infusion (CSII) therapy is another type of open-loop therapy where rapid-acting insulin is delivered via an insulin pump. MDI and CSII therapies require multiple adjustments by the user throughout the

Abbreviations: AP, artificial pancreas; ALPHA, adaptive learning postprandial hypoglycemia-prevention algorithm; BR, basal rate; ICR, insulin to carbohydrate ratio; T1D, type 1 diabetes; MDI, multiple daily injection; CSII, continuous subcutaneous insulin infusion; CGM, continuous glucose monitor; IIR, insulin infusion rate; CHO, carbohydrate; FMPD, fading memory proportional derivative; LBGI, low blood glucose index; HBGI, high blood glucose index.

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day. Closed-loop therapies have been developed to reduce patient burden by automating delivery of insulin and optionally glucagon to enable better glucose control with less patient interaction. The artificial pancreas (AP) is a closed-loop therapy where the delivery rate of rapid-acting insulin is calculated based on continuous glucose measurements (CGM) and delivered by an insulin pump.

Many AP systems are hybrid, meaning that patients are still required to announce meals and in certain systems estimate the amount of carbohydrates consumed so that a pre-meal bolus can be delivered. Dosing of insulin for meals is a challenging aspect of T1D glucose management. Pre-meal insulin boluses help to reduce postprandial excursions, though the delayed pharmacokinetics of subcutaneously delivered insulin limits this effect resulting in some hyperglycemia. Over-estimation of the amount of pre-meal insulin, on the other hand, leads to postprandial hypoglycemia, a common and dangerous situation. Severe hypoglycemia (< 54 mg/dl) if left untreated can lead to coma and can be life threatening. In a recent hybrid insulin-only AP study by our group [1], we observed that some of the participants experienced postprandial hypoglycemia. A number of factors can lead to postprandial hypoglycemia in hybrid AP systems. First, there is variability in insulin kinetics of people with T1D making it challenging for a single control algorithm to work well for all patients. Second, insulin sensitivity tends to vary throughout the day making the estimation of the optimal dose of insulin a challenge. Third, people commonly misestimate the amount of carbohydrates consumed for a given meal, which can lead to over or under-delivery of pre-meal insulin. An adaptive system would be helpful to respond to meal-based insulin deliveries within a hybrid AP system. An adaptive system can modify the insulin-to-carbohydrate (ICR) or the post-prandial basal insulin in response to postprandial hypoglycemia.

Adaptive AP systems have been presented by a number of research groups. Palerm et al. [2,3] presented a run-to-run control algorithm to adjust pre-meal bolus insulin each day based on glucose readings of the previous day with similar meal amounts. They showed higher rates for both time in range and hypoglycemia. Dassau et al. [4,5] tested a 12-week adaptive artificial pancreas where the ICR and the basal delivery were adapted every 4 weeks and one week, respectively. They demonstrated a decrease in time in hypoglycemia (from 2% to 1.9%) and time in range (76.7% to 72.6%) after the 12th week. Toffanin et al. [6] proposed an adaptive run-to-run approach in which the basal rate was adjusted based on the patient's clinical performance during the last 24 h. If time in hypoglycemia was observed, their algorithm reduced the basal rate. If time in hyperglycemia was observed, their algorithm increased basal rate accordingly. They tested their algorithm on 100 virtual patients using the UVA/Padova simulator. They showed that time in hypoglycemia was reduced from 8.3% to 1.5% after 8 days. Their algorithm treated non-meal and meal hypo/hyper events equivalently. In a recent paper by the same group, Toffanin et al. [7] adapted basal rates based on performance during non-meal/ overnight periods and they adjusted pre-meal boluses using the same run-to-run structure. While time in range improved, there was not a change in hypoglycemia based on this approach to adaptation. Ruiz et al. [8] integrated an insulin feedback method in a proportional-integral-derivative controller, preventing possible hypoglycemic events induced by the delay between the infused insulin and glucose level. They found no postprandial hypoglycemia across four participants. Turksoy et al. [9] developed a hypoglycemia early alert system, embedded in an AP, enabling the prediction of hypoglycemia 25 min in the future. For each hypoglycemia alert, a 15-gram carbohydrate (CHO) was delivered. They tested their algorithm across three AP experiments with random meal size and found 13 hypoglycemic events occurred. Time in hypoglycemia reduced to zero and time in hyperglycemia increased to 47% from 38% when the hypoglycemia alert system was not enabled. In a different study, Galati et al. [10] developed a hierarchical diagram to diagnose and prevent postprandial hypoglycemia. Their method required measuring C-peptide, insulin, β-hydroxybutyrate, insulin antibodies and sulfonylurea screen to prevent hypoglycemia. Herrero et al. [11] described an adaptive algorithm to modify ICR for a meal bolus calculator in a hybrid AP. This algorithm improved time in range and did not change postprandial hypoglycemia. Like Toffanin et al. [7], they did not focus on adapting postprandial basal insulin, which may be necessary for avoiding hypoglycemia as we show in the current paper.

The current paper presents two approaches to postprandial hypoglycemia prevention using a new Adaptive Learning Postprandial Hypoglycemia-prevention Algorithm (ALPHA), designed to be used in hybrid AP insulin therapy. In one implementation, ALPHA modifies the aggressiveness of the basal rate of postprandial insulin (ALPHA-BR) and in the second implementation, ALPHA adjusts the aggressiveness of the pre-meal bolus insulin by modifying the ICR which is a similar approach to Toffanin et al. [7] and Herrero et al. [11]. The objective of the comparison was to determine whether adapting pre-meal vs. postprandial basal insulin was optimal in preventing postprandial hypoglycemia. In addition, we demonstrate how the ALPHA algorithm can be used to tune the post-prandial insulin delivery aggressiveness factor for any AP control algorithm using an in-silico virtual patient population.

ALPHA-BR and ALPHA-ICR were evaluated by a series of in-silico simulations conducted under closed loop control across four days on 99 virtual patients that are further described below. Each virtual patient was given 20 real-world meal scenarios acquired during real-world AP studies. Performance of ALPHA-BR and ALPHA-ICR was compared while using the current version of the OHSU Fading Memory Proportional Derivative controller (FMPD), described further in [12,13], which does not have postprandial meal adaptation. We also evaluated the ALPHA algorithm using a model predictive control (MPC) algorithm [14,15] to demonstrate that ALPHA is algorithm agnostic and can work on various types of AP control methodologies.

The primary contributions of the paper are as follows. First, we introduce a method for adapting aggressiveness of insulin dosing after meals. Second, we introduce a method for adapting aggressiveness of carbohydrate ratios for dosing insulin prior to meals. Third, we show that adapting postprandial insulin is significantly more effective than adapting carbohydrate ratios when it is necessary to address problems of postprandial hypoglycemia in patients.

2. Materials and methods

A virtual T1D patient population was generated based on a glucoregulatory model consisting of insulin kinetics and dynamics models and a glucose kinetics model [16]. The parameters of insulin dynamics model were statistically sampled to build a virtual population with different insulin sensitivities as described further in the Supplementary Material and in [16].

2.1. ALPHA-BR description

ALPHA-BR is an algorithm that adapts postprandial insulin delivery to achieve a certain target range. In other words, it adjusts postprandial basal insulin delivery if postprandial glucose following prior meals is outside of a target range. If post-prandial hypoglycemia occurs, ALPHA-BR will reduce postprandial insulin for the next meal. The factor by which postprandial insulin is decreased is determined by an aggressiveness factor (A_f). The initial postprandial insulin infusion rate calculated by the AP is called IIR_{orig} (i.e. before aggressiveness factor is applied). Smooth adaptation was realized by averaging A_f values from prior meals to give

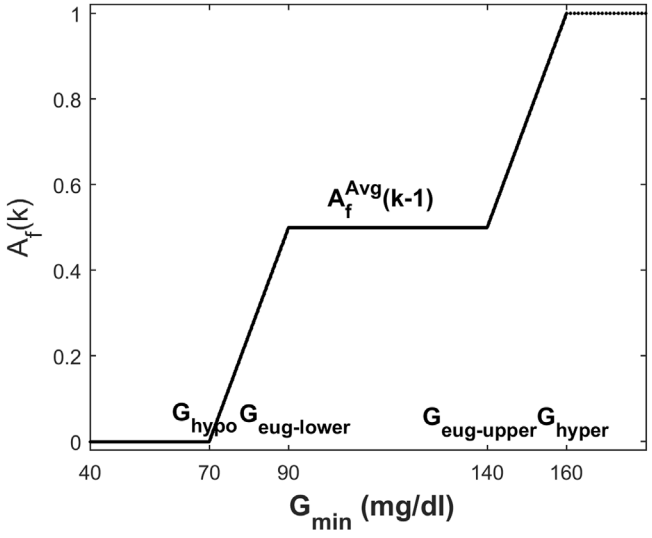

Fig. 1. $A_f(k)$ as a function of minimum postprandial glucose excursion. The graph is re-scaled after each meal based on the A_f^{Avg}. Notice that, the A_f^{Avg} is not necessarily at 0.5 by default and is changing after each meal. The $A_f^{Avg}(k\text{-}1) = 0.5$ is only shown as an example.

A_f^{Avg}. The value of A_f^{Avg} is between 0 and 1 and is re-calculated after each meal.

$$A_f^{Avg}(k) = \frac{A_f(k) + A_f^{Avg}(k-1) + A_f^{Avg}(k-2)}{3} \tag{1}$$

where, the variable k denotes the meal event. The new postprandial insulin infusion rate (IIR_{adapt}) is calculated according to Eq. (2). The aggressiveness factor is applied from the time that the meal starts (t_{meal}) through a window of time ($t_{agg\text{-}win}$).

$$IIR_{adapt}(t)|_{t_{meal}}^{t_{meal}+t_{agg-win}} = A_f^{Avg}(k) \times IIR_{orig}(t)|_{t_{meal}}^{t_{meal}+t_{agg-win}} \tag{2}$$

$A_f(k)$ is adjusted using a piece-wise linear adjustment that is a function of the minimum glucose measured within an observation time-window after the last meal ($Gmin$) whereby the window begins at t_{start} and ends at t_{stop} relative to t_{meal}(k-1). Fig. 1 and Eq. (3) show how A_f(k) is modified based on $Gmin$ and A_f^{Avg}.

$$A_f(k) = \begin{cases} 0, \ 0 \le G_{min} \le G_{hypo} \\ \dfrac{G_{min} - G_{hypo}}{G_{eug-lower} - G_{hypo}} \times A_f^{Avg}(k-1), \ G_{hypo} \le G_{min} \\ \quad \le G_{eug-lower} \\ A_f^{Avg}(k-1), \ G_{eug-lower} \le G_{min} \le G_{eug-upper} \\ \dfrac{G_{min} - G_{hyper}}{G_{hyper} - G_{eug-upper}} \times \left(1 - A_f^{Avg}(k-1)\right) \\ \quad +1, \ G_{eug-upper} \le G_{min} \le G_{hyper} \\ 1, \ G_{hyper} \le G_{min} \end{cases} \tag{3}$$

If $Gmin$ is within a euglycemic range of $G_{eug\text{-}lower}$ = 90 to $G_{eug\text{-}upper}$ = 140 mg/dl, then the aggressiveness factor does not change and $A_f = A_f^{Avg}$. However, if $Gmin$ drops below $G_{eug\text{-}lower}$, the aggressiveness factor, A_f, is reduced proportionally down to a hypoglycemic threshold of G_{hypo} (70 mg/dl in Fig. 1). Below the hypo threshold (G_{hypo}), $A_f = 0$ meaning that insulin being delivered during $t_{agg\text{-}win}$ for the next meal is the least aggressive since A_f is zero in Eq. (1). The aggressiveness factor is likewise increased if $Gmin$ is above the upper limit of euglycemia ($G_{eug\text{-}upper}$). Again, the aggressiveness factor is increased proportionally with respect to $Gmin$ until $Gmin$ exceeds the hyperglycemic threshold (G_{hyper}). Above G_{hyper}, the value of IIR_{adapt} is closer to the original AP-calculated postprandial basal rate insulin (IIR_{orig}) since A_f is set to one in Eq. (1).

Fig. 2 shows graphically every example from the piecewise linear function to demonstrate how A_f adapts with respect to prior postprandial glycemic responses. Prior to adaptation, $A_f(1)$ is 1 for the first meal. For the second meal, $A_f(2)$ was reduced since glucose dropped below $G_{eug\text{-}lower}$ after the first meal. For the third meal, $A_f(3)$=$A_f(2)$ as the glucose fell within the euglycemic range after the second meal. After the third meal, glucose never dropped into/below the euglycemic range, so $A_f(4)$ was increased. After the fourth meal, hypoglycemia occurred so $A_f(5) = 0$. After the fifth meal, glucose never fell below the hyperglycemic limit, and so $A_f(6) = 1$.

A special exception to the above rules is if a subsequent meal, snack or exercise event occurs during the postprandial observation time window (i.e. between t_{start} and ends at t_{stop}). If this occurs, the observation end time (t_{stop}), is the time of the subsequent meal, snack, or exercise event. Adaptation of A_f proceeds as described above using the shorter observation window, but A_f is only changed if it is determined that hypoglycemia has occurred and A_f needs to be decreased. This is to avoid adaptively increasing A_f in response to observation periods that are too soon after a meal has occurred when postprandial hyperglycemia is still likely and acceptable.

2.2. ALPHA-ICR

ALPHA-ICR, like ALPHA-BR, is also an adaptive algorithm that adapts to a target range. However, rather than adjusting the postprandial basal insulin, ALPHA-ICR adjusts the ICR if postprandial glucose from a prior meal is outside of a target range. The pre-meal bolus prior to adaptation is a function of CHO, ICR, and the percentage of the insulin bolus given prior to the meal (I_p). The ICR is defined as $ICR = \frac{1}{3} \times \frac{1700}{TDIR}$ [17].

$$Bolus(k) = I_p^{Avg}(k) \times \frac{CHO}{ICR} \tag{4}$$

$$I_p^{Avg}(k) = \frac{I_p(k) + I_p^{Avg}(k-1) + I_p^{Avg}(k-2)}{3} \tag{5}$$

The ALPHA-ICR works similarly to ALPHA-BR except that it is the I_p which adapts based on postprandial hypoglycemia rather than the postprandial A_f. I_P is computed according to a similar piecewise linear equation given in Eq. (6). The same relationship can be shown as is given in Fig. 1 except that the y-axis is for I_P, which has an upper and lower range of pre-meal insulin (I_P) on the y-axis set to 40%–100%.

$$I_P(k) = \begin{cases} 0.4, \ 0 \le G_{min} \le G_{hypo} \\ \dfrac{G_{min} - G_{hypo}}{G_{eug-lower} - G_{hypo}} \times I_P^{Avg}(k-1), \ G_{hypo} \\ \quad \le G_{min} \le G_{eug-lower} \\ I_P^{Avg}(k-1), \ G_{eug-lower} \le G_{min} \le G_{eug-upper} \\ \dfrac{G_{min} - G_{hyper}}{G_{hyper} - G_{eug-upper}} \times \left(1 - I_P^{Avg}(k-1)\right) \\ \quad +1, \ G_{eug-upper} \le G_{min} \le G_{hyper} \\ 1, \ G_{hyper} \le G_{min} \end{cases} \tag{6}$$

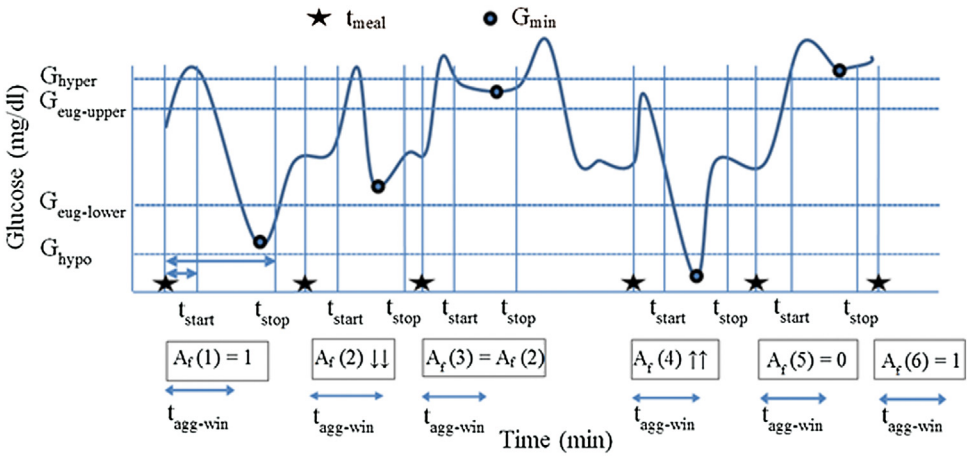

Fig. 2. Changes of $A_f(k)$ with respect to G_{min} values over meal events for the ALPHA-BR. Changes of Ip(k) is similar to $A_f(k)$ for the ALPHA-ICR. This figure is a cartoon example to better demonstrate how ALPHA-BR works under different scenarios. The glucose and meal scenarios in this figure do not represent actual clinical or in-silico data.

2.3. Tuning parameters

ALPHA-BR has seven parameters to be determined. These parameters are G_{hypo}, $G_{eug\text{-}lower}$, $G_{eug\text{-}upper}$, G_{hyper}, t_{start}, t_{stop} and $t_{agg\text{-}win}$. ALPHA-ICR has the same parameters as ALPHA-BR except $t_{agg\text{-}win}$ is unnecessary since only the pre-meal bolus is adjusted and there is no window of postprandial adjustment. Changing G_{hypo} affects how gradually the adaptation occurs when postprandial hypoglycemia is observed. Changing $G_{eug\text{-}lower}$ affects the euglycemic range over which adaptation does not occur. Likewise, changing the G_{hyper} parameter will affect how rapidly adaptation occurs when postprandial hyperglycemia is observed and $G_{eug\text{-}upper}$ affects the upper range of euglycemia when no adaptation occurs.

We determined ad-hoc that three parameters were most sensitive for preventing hypoglycemia and optimizing time in euglycemia: G_{hypo}, $G_{eug\text{-}upper}$ and $t_{agg\text{-}win}$. Other parameters were fixed based on ad-hoc experimentation. The beginning of the postprandial observation window, t_{start} was fixed at 60 min to provide adequate time for glucose to peak following a meal [2]. The end of the postprandial observation window, t_{stop}, was fixed at 240 min. $G_{eug\text{-}lower}$, was fixed at 90 mg/dl and G_{hyper} was fixed to 160 mg/dl. To tune the parameters we compared performance outcome metrics (percent time less than 70 mg/dl, percent time between 70 and 180 mg/dl, and percent time greater than 180 mg/dl) as we varied the parameters. We varied G_{hypo} between 40 and 80 mg/dl, $t_{agg\text{-}win}$ between 0.5 h to 3 h, and $G_{eug\text{-}upper}$ between 110 and 140 mg/dl. Under the results section, we show how performance varied with respect to the different combinations of these tuned parameters.

2.4. Testing under real-world meal scenarios

2.4.1. Background on FMPD control algorithm used in testing

For the evaluation of the ALPHA algorithm, we used a control algorithm on which we have previously reported. The OHSU FMPD controller is a classical fading memory proportional derivative controller that considers both the proportional error (i.e. distance from a glucose target) as well as the derivative error (i.e. how rapidly the glucose is changing with respect to time). The glucose target was set to 130 mg/dL and the derivative error was calculated using the slope of the glucose curve measured over the prior 15 min in time. The fading memory aspect of the controller is implemented by including exponentially weighted prior proportional and derivative error components in the control estimation of insulin. In addition to utilizing the proportional error and derivative error, there is a steady-state basal insulin delivered to the patient that is calculated using the patient's total daily insulin requirement. We have published extensively on the FMPD algorithm both on in-silico evaluations and in human clinical trials [12,13,18].

2.4.2. Background on MPC control algorithm used in testing

While ALPHA was tuned and evaluated primarily on the FMPD control algorithm, we did additional preliminary analysis of the ALPHA algorithm using the OHSU model predictive control algorithm (MPC) described under [14]. The OHSU MPC uses a physical model of the glucoregulatory system including a model of insulin kinetics, insulin dynamics, carbohydrate absorption kinetics, and a model for exercise to predict future glucose trajectories across a prediction horizon and selects an optimal dosing schedule for insulin [15]. It then delivers the current insulin dose. The optimization is carried out every 5 min when new CGM data arrives at the controller. The analysis on the MPC algorithm was not as extensive as the analysis and tuning done on the FMPD algorithm. The purpose of doing additional analysis on the MPC algorithm was do demonstrate that ALPHA can be used on different control algorithms.

2.4.3. Evaluation of ALPHA using FMPD and real-world meal scenarios

Twenty real-world meal scenarios were acquired from a 4-day outpatient AP study [1]. Each virtual patient was given each of the 20 meal scenarios while the patients' glucose was controlled using (1) the OHSU FMPD controller [12,13,18] (called AP), (2) the OHSU FMPD + ALPHA-BR (called ALPHA-BR), and (3) the OHSU FMPD + ALPHA-ICR (called ALPHA- ICR). The system was further challenged by introducing a randomly selected -30% to 30% meal uncertainty that was applied to each carbohydrate intake in each meal scenario as has been done in other in-silico trials of postprandial meal adaptation [11]. Circadian variability of insulin sensitivity was introduced to the insulin parameter S_{f1}, S_{f2} and S_{f3} by varying these parameters with respect to time of day using Eq. (7) [11]:

$$S_{fi}(t) = S^{*}_{fi} \times \left(1 + 0.3\sin\left(\frac{2\pi}{24 \times 60/Ts} \times t + 2\pi \times RND\right)\right), \quad i = 1, 2, 3 \tag{7}$$

where, RND is a random variable generated from a uniform distribution between 0 and 1; Ts is the sampling interval (5 min). S_{fi}^{*} in Eq. (7) denotes the nominal value of each of the insulin sensitivity factors. Notice that, in this paper, we have not changed ICR throughout a day. The AP system is designed to compensate for the intra-day variability of the ICR value. Our AP delivers 80% of the meal insulin at the time of the meal and then allows the controller

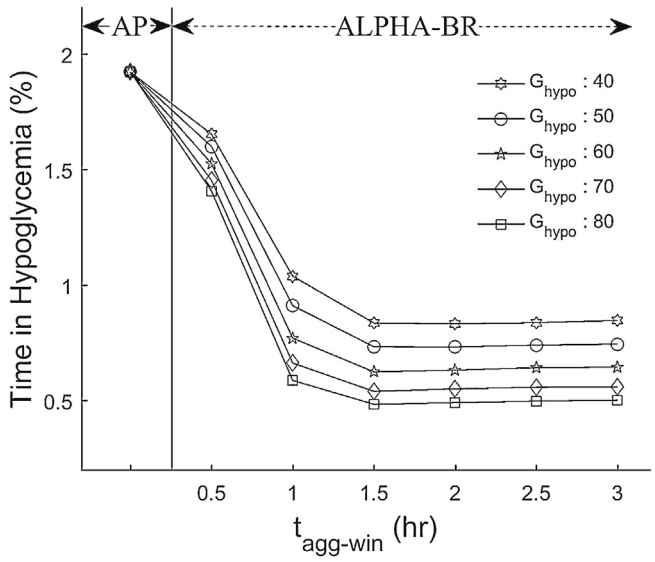

Fig. 3. Percent time in hypoglycemia across different $t_{agg\text{-}win}$ and G_{hypo}, for $G_{eug\text{-}upper}$ fixed at 140 mg/dl. Time in hypoglycemia is lowest when $t_{agg\text{-}win}$ is 1.5 h and G_{hypo} is 80 mg/dl.

to deliver the additional meal insulin during the hours following the meal. This approach has also been implemented and described in [11]. Notice also that the AP algorithms used in this work and the in-silico virtual patient population models are designed to work with rapid-acting insulin; the AP systems presented in this paper are not designed to be used with long-acting insulin.

2.5. Evaluation metrics and statistical analysis

We evaluated the performance of ALPHA-BR and ALPHA-ICR on the 23 patients from the in-silico population who experienced greater than 1% time in hypoglycemia. The primary outcome measure for the experiment was percent time in hypoglycemia (<70 mg/dl). Secondary outcome measures were percent time in hyperglycemia (>180 mg/dl), percent time in range (70–180 mg/dl), number of times rescue carbs were required, low blood glucose index (LBGI) and high blood glucose index (HBGI). The Wilcoxon rank-sum test was used to test statistical difference between AP, AP + ALPHA-BR and AP + ALPHA-ICR with significance level set to 0.05. In addition to showing adaption results on the 23 patients who experienced greater than 1% time in hypoglycemia (Table 2), we also show results on all 99 of the virtual patients (Table 3).

3. Results

3.1. Determining $G_{min\text{-}lower}$ and $t_{agg\text{-}win}$

Figs. 3 and 4 show the performance comparisons between AP and ALPHA-BR across different parameters that were tuned for the subjects with greater than 1% time in hypoglycemia. Fig. 3 shows a substantial reduction in percent time in hypoglycemia when comparing AP with the ALPHA-BR and the improvement is greater for larger $t_{agg\text{-}win}$ sizes. This makes sense since if $t_{agg\text{-}win}$ is larger, it means that the postprandial insulin dosing is changed over a longer period of time. The optimal time for applying the aggressiveness factor is for $t_{agg\text{-}win}$ = 1.5 h, after which there is not a significant improvement. There is also a reduction in percent time in hypoglycemia by increasing G_{hypo} with minimal hypoglycemia observed when G_{hypo} = 80 mg/dl. Fig. 4 shows how adjusting $t_{agg\text{-}win}$ and G_{hypo} affected percent time in hyperglycemia and time in range for $G_{eug\text{-}upper}$ fixed to 140 mg/dl. We selected a G_{hypo} of 70 mg/dl based

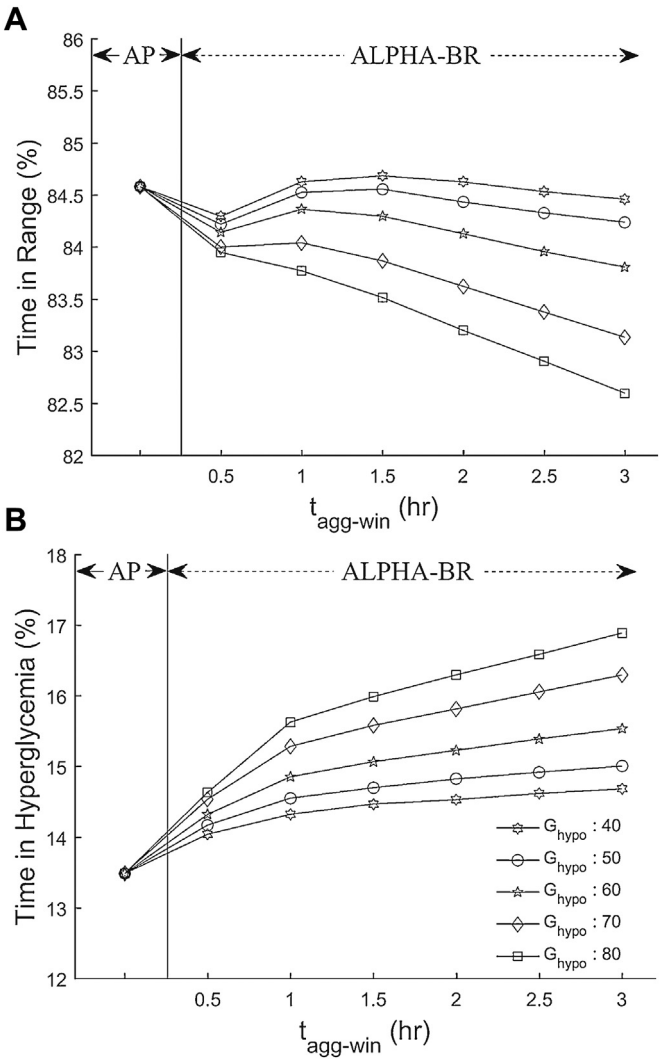

Fig. 4. Percent time in hyperglycemia (top) and euglycemia (bottom) across different parameter settings.

on the consideration that there was not a significant difference in time in hypoglycemia between 70 and 80 mg/dl (p = .46), but there was less time in hyperglycemia when G_{hypo} was set to 70 mg/dl as shown in Fig. 4. When we varied $G_{eug\text{-}upper}$ between 90 and 140 mg/dl with G_{hypo} = 70 mg/dl and $t_{agg\text{-}win}$ = 1.5 h, we observed marginally increased time in range for smaller values of $G_{eug\text{-}upper}$. However, to maintain a stable target glycemic range during which the system did not adapt (see Fig. 1), we set $G_{eug\text{-}upper}$ to 140 mg/dl. Time in hypoglycemia was lowest (0.54%) with the ALPHA-BR for the optimized $t_{agg\text{-}win}$ = 1.5 h and G_{hypo} = 70 mg/dl, compared to AP (1.92%). However, time in hyperglycemia increased slightly from 13.5% to 15.6%.

The ALPHA parameters were also tuned for ALPHA-ICR. The ALPHA-ICR implementation was far less sensitive to the parameters than ALPHA-BR. For example, when we varied G_{hypo} from 40 to 80 mg/dl with $G_{eug\text{-}upper}$ = 140 mg/dl, it only changed the percent time in hypoglycemia from 1.92% to 1.77% and the difference was not significant (p = .72). Similarly, when we varied the $G_{eug\text{-}upper}$ from 90 to 140 mg/dl with G_{hypo} = 80 mg/dl, we saw no change in percent time in range and hypoglycemia (p = .73). Therefore, we used the same $G_{eug\text{-}upper}$ and G_{hypo} parameters in the ALPHA-ICR implementation that we used in the ALPHA-BR implementation. Table 1 shows the final values of the ALPHA-BR and ALPHA-ICR parameters. Table 2 shows improvement in glycemic control for

Table 1
the optimal parameters of alpha-br and alpha-icr.

G_{hypo} [mg/dl]	$G_{eug\text{-}lower}$ [mg/dl]	$G_{eug\text{-}upper}$ [mg/dl]	G_{hyper} [mg/dl]	t_{start} [min]	t_{stop} [min]	$t_{agg\text{-}win}$ [hr]
70	90	140	160	60	240	1.5

Table 2
Comparison between ap, alpha-br, alpha-icr across the meal scenarios for subjects with hypoglycemia greater than 1%.

$\mu \pm \sigma$	AP	ALPHA-BR	ALPHA-ICR
Time in Hypoglycemia [%]	1.92 ± 0.74	$0.54 \pm 0.3^{*}$	1.77 ± 0.8
rescue carbs [event/day/patient]	1.29 ± 0.47	$0.36 \pm 0.19^{*}$	1.19 ± 0.52
Time in Euglycemia [%]	84.6 ± 4.4	83.9 ± 4.6	83 ± 4.4
Time in Hyperglycemia [%]	13.5 ± 4.2	15.6 ± 4.4	15.3 ± 4.1
Average glucose [mg/dl]	142.1 ± 5.2	$147.3 \pm 5.47^{*}$	$144.6 \pm 5.2^{*}$
HBGI	4.6 ± 0.9	4.8 ± 1.1	5 ± 1
LBGI	2.73 ± 0.44	$1.74 \pm 0.28^{*}$	2.7 ± 0.5

* shows significance compared to AP. (p-value < 0.05).

Table 3
Comparison between ap, alpha-br, alpha-icr across the meal scenarios for all virtual subjects.

$\mu \pm \sigma$	AP	ALPHA-BR	ALPHA-ICR
Time in Hypoglycemia [%]	0.57 ± 0.86	$0.17 \pm 0.27^{*}$	0.53 ± 0.83
rescue carbs [event/day/patient]	0.38 ± 0.57	$0.11 \pm 0.18^{*}$	0.35 ± 0.55
Time in Euglycemia [%]	80.9 ± 6.9	80.1 ± 6.9	80.3 ± 6.7
Time in Hyperglycemia [%]	18.5 ± 7.2	19.7 ± 6.9	19.2 ± 6.8
Average glucose [mg/dl]	150.9 ± 11	$153.5 \pm 11^{*}$	151.8 ± 10.7
HBGI	5.3 ± 1.9	5.5 ± 1.9	5.4 ± 1.9
LBGI	1.46 ± 0.94	$1.09 \pm 0.56^{*}$	1.45 ± 0.93

* shows significance compared to AP. (p-value < 0.05).

subjects who experienced high hypoglycemia under the AP condition (>1%). Comparable glycemic outcomes were observed across all the in-silico subjects as shown in Table 3.

3.2. Comparison of adaptive AP vs. non-adaptive AP

Overall, the ALPHA-BR implementation was successful in reducing post-prandial hypoglycemia while ALPHA-ICR reduced hypoglycemia, but not as significantly. The comparison between the performance of ALPHA-BR, ALPHA-ICR and AP across all meal scenarios for subjects with higher hypoglycemia (>1%) is shown in Table 2. ALPHA-BR significantly reduced time in hypoglycemia compared with AP (0.54% vs. 1.92%, $p < 0.001$) whereas ALPHA-ICR reduced time in hypoglycemia slightly and the difference was not significant (1.77%, $p = .41$). ALPHA-BR also reduced average rescue carbs per day (0.36 vs. 1.29, $p < 0.001$). However, ALPHA-BR resulted in modest increase in time in hyperglycemia (15.6% vs. 13.5%, $p = .06$) and an increased average glucose level (147.3 vs. 142.1 mg/dl, $p < 0.001$) compared with AP.

Table 3 shows the outcome measures for all virtual subjects. Time in hypoglycemia was significantly reduced with ALPHA-BR compared to AP whereas this reduction was not significant with ALPHA-ICR. ALPHA-BR resulted in increased time in hyperglycemia and HBGI compared with AP, but these differences were not significant. ALPHA-BR did result in a small increase in average glucose compared to AP (153.5 vs. 150.9 mg/dl, $p = 0.04$).

Fig. 5 compares the performance of AP and ALPHA-BR with the optimized ALPHA-BR parameters for the 5th meal scenario. The adaptation of the A_f^{Avg} over the meal events is shown in the lower subplot. The aggressiveness factor started at a value of 1 and then converged over time to a final value. ALPHA-BR gradually began reducing hypoglycemia after the first day. We defined convergence of A_f to be the meal number when A_f changed less than 5% from the median of the next three A_f values. Notice that for this example scenario in Fig. 5, A_f converged after 8 meals. Table 4 shows the convergence number for each of the meal scenarios across the subjects with hypoglycemia greater than 1%.

Table 4
Convergence at each meal scenario in alpha-br.

Meal Scenario	Mean carbs and std	Total meals	# meals to converge	*Final* A_f^{Avg}
1	40.2 ± 9.9	20	2	0.77 ± 0.08
2	72.8 ± 36.6	13	5	0.65 ± 0.09
3	45.1 ± 8.7	11	7	0.6 ± 0.09
4	42.6 ± 30.1	16	2	0.74 ± 0.11
5	42.8 ± 28.7	15	8	0.67 ± 0.05
6	47.4 ± 21.9	17	1	0.79 ± 0.13
7	46.4 ± 15.5	16	2	0.73 ± 0.11
8	32.6 ± 18.9	25	2	0.79 ± 0.11
9	40.2 ± 34.7	19	3	0.75 ± 0.09
10	38.9 ± 20	17	2	0.75 ± 0.1
11	45.1 ± 25.4	12	3	0.67 ± 0.12
12	31.6 ± 16.9	14	2	0.75 ± 0.1
13	40.4 ± 30.4	14	5	0.63 ± 0.07
14	55.8 ± 35.2	21	2	0.79 ± 0.1
15	57.2 ± 15.9	12	7	0.62 ± 0.09
16	33.9 ± 21.6	14	2	0.75 ± 0.09
17	48.4 ± 24.8	11	2	0.74 ± 0.11
18	32.2 ± 11.1	14	2	0.75 ± 0.08
19	40.9 ± 21.7	15	5	0.65 ± 0.12
20	38.9 ± 2.6	12	2	0.71 ± 0.1
Average	43.7 ± 9.7	15.4 ± 3.5	3.3 ± 2.1	0.72 ± 0.06

A natural alternative to the ALPHA algorithm could be to simply increase the glucose target of the control algorithm. The performance of ALPHA-BR was compared with the FMPD algorithm when the target for the FMPD algorithm was increased from 115 mg/dl to 130 mg/dl. By increasing the target value to 130 mg/dl, time in hypoglycemia was reduced; however, this reduction was not as significant compared to ALPHA-BR, which used a target of 115 mg/dL. In addition, by increasing the target value, the time in hyperglycemia increased more than ALPHA-BR. And the time in hyperglycemia significantly increased with the higher target value. Table 5 summarizes these results. From this analysis, we concluded that using ALPHA was more effective at reducing postprandial hypoglycemia than simply raising the glucose target of the control algorithm.

4. Discussion and conclusion

We describe here an adaptive AP algorithm to reduce postprandial hypoglycemia by adjusting either postprandial basal insulin (ALPHA-BR) or pre-meal bolus insulin (ALPHA-ICR). Both implementations reduced time in hypoglycemia; however, ALPHA-BR reduced hypoglycemia further and was selected as the better implementation. For the 23 subjects with hypoglycemia greater than 1%, ALPHA-BR was able to significantly reduce time in hypoglycemia from 1.92% to 0.54% while ALPHA-ICR only reduced hypoglycemia to 1.77% (Table 2).

To demonstrate whether ALPHA-BR is effective on an algorithm different than the OHSU-FMPD algorithm, we evaluated ALPHA-BR on the OHSU single-hormone MPC algorithm described in section 2.3b and in [14]. ALPHA-BR significantly reduced percent time in hypoglycemia compared with MPC from 0.55% to 0.19% ($p < 0.001$) in the same virtual patient population and same meal scenarios. ALPHA-BR also significantly reduced average rescue carbohydrates

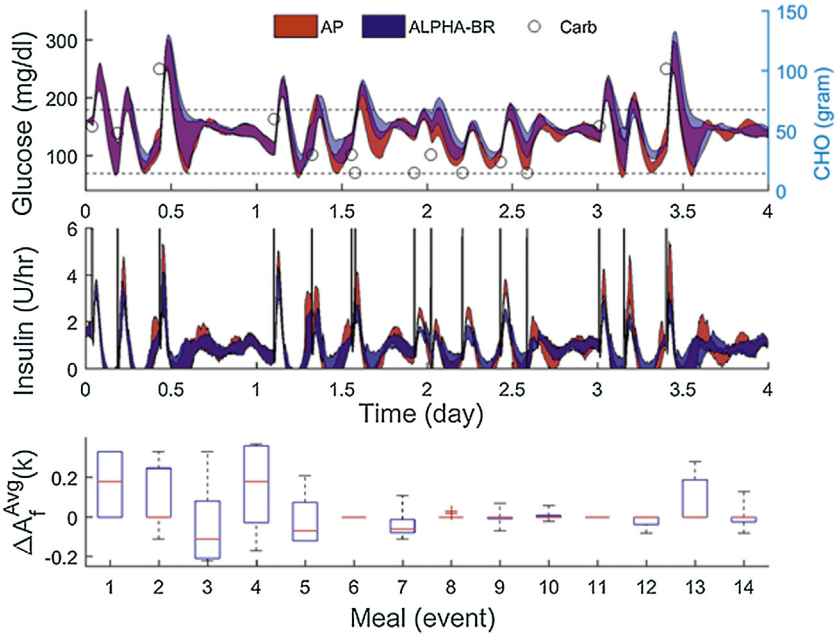

Fig. 5. Interquartile range of the glucose profile and the box-plot of the changes of the A_f^{Avg} over the meal events across the virtual patients for the 5th meal scenario. 'o' denotes the amount of CHO. Dashed lines denote the hypoglycemia threshold (70 mg/dl) and hyperglycemia threshold (180 mg/dl). Note that, the insulin y-axis is capped at 6 unit/hr for better visualization of the ALPHA-BR effect.

Table 5
Comparison between ap with higher target value and alpha-br across the meal scenarios for all virtual subjects.

$\mu \pm \sigma$	AP (TGT = 115 mg/dl)	AP (TGT = 130 mg/dl)	ALPHA-BR
Time in Hypoglycemia [%]	0.57 ± 0.86	0.38 ± 0.67	$0.17 \pm 0.27^{*}$
rescue carbs [event/day/patient]	0.38 ± 0.57	0.26 ± 0.45	$0.11 \pm 0.18^{*}$
Time in Euglycemia [%]	80.9 ± 6.9	$78.1 \pm 7.2^{*}$	80.1 ± 6.9
Time in Hyperglycemia [%]	18.5 ± 7.2	$21.5 \pm 7.4^{*}$	19.7 ± 6.9
Average glucose [mg/dl]	150.9 ± 11	$156.4 \pm 11.4^{*}$	$153.5 \pm 11^{*}$
HBGI	5.3 ± 1.9	$5.9 \pm 2^{*}$	5.5 ± 1.9
LBGI	1.46 ± 0.94	1.31 ± 0.95	$1.09 \pm 0.56^{*}$

* shows significance compared to AP. (p-value < 0.05).

needed per day from 0.42 [S.D. 0.41] to 0.16 [S.D. 0.21] ($p < 0.001$). For the MPC algorithm without ALPHA-BR, the percent time in range (70–180 mg/dL) was 84.39% while time in range was lower at 81.27% with MPC plus ALPHA-BR ($p < 0.001$). The percent time in hyperglycemia for MPC was 15.08% while the MPC plus ALPHA-BR had time in hyperglycemia of 18.54% ($p < 0.001$). These results are summarized in a Supplemental Table 1 in the supplementary section.

To further evaluate across alternative in-silico simulators, we tested the ALPHA-BR across 10 virtual adults of the single hormone UVa/Padova simulator [19] using the OHSU-FMPD controller. However, we did not observe any postprandial hypoglycemia using this simulator with the non-adaptive OHSU-FMPD algorithm. Therefore, we were unable to evaluate the ALPHA-BR and ALPHA-ICR algorithms using this simulator.

A major finding and contribution of this paper is that adapting post-prandial basal insulin is more effective at influencing postprandial hypoglycemia than adaptively changing pre-meal insulin. In addition, ALPHA-BR demonstrates that the average aggressiveness factor should be reduced after each meal for 1.5 h to gain substantial reduction in time in hypoglycemia. The ALPHA-BR algorithm can be used to initialize the postprandial insulin dosing based on in-silico testing. For example, for the FMPD algorithm evaluated here, we determined that the postprandial insulin should be reduced by 28 percent from the typical insulin dosing (i.e. not after a meal). ALPHA-BR can also be used to adapt to each individual during usage as that patient's insulin sensitivity, diet and behavior change with time.

The ALPHA-BR adaptation converged on average after approximately 3 meals (Table 4), showing the feasibility of the ALPHA-BR in real-time applications. Other papers have also presented adaptive algorithms to improve glycemic control in people with T1D and these algorithms typically require about a week to converge. Toffanin et al. [7] developed a run-to-run algorithm for use within an AP study with fixed amount of meals at specific times (40, 80 and 60 g for breakfast, lunch and dinner, respectively). They adjusted nighttime basal insulin and daytime bolus insulin adaptively to reduce time in hypoglycemia and increase time in range. The algorithm was tested in two different scenarios across 100 virtual patients of the UVA/Padova simulator using a model predictive control algorithm. In one scenario, a random ±30% variation was added to the nominal insulin sensitivity for 8 weeks and in the other, the random variation was added gradually from ±10% to ±30% during 4 weeks. In the 1st scenario, time in range improved from 86% after week 1 to 90.86% and 91.35% after week 4 and 8. Time in hypoglycemia was reported as 0.66%, 0.17%, 0.91% for week 1, 4 and 8 respectively. In the 2nd scenario, time in hypoglycemia was reported as 0.52% and 0.65% after week 1 and 4, respectively. The convergence rate of their algorithm exceeded one week. In another run-to-run study by Herrero et al. [11], only meal bolus insulin was adaptively changed to improve glycemic controls. Herrero et al. used fixed pattern of carbs dose intake (60, 100 and 80 g for break-

fast, lunch, dinner, respectively) and incorporated inter-day and intra-day insulin sensitivity and meal variabilities to their simulations. They evaluated their algorithm across 11 adolescences and 11 adults within the UVA/Padova simulator using their developed controller, Imperial College Artificial Pancreas. After a 3-month simulation, time in range was improved from 82% to 89.5% whereas time in hypoglycemia did not change (0.21%) among 11 adults. A major difference between these studies and the current study is that the meal scenarios presented to our virtual patients were taken from real-world meals consumed by patients in an AP study. The meal times and amounts were sporadic both in times and amounts. ALPHA can robustly manage this variability and convergence still occurred rapidly across all 20 real-world meal scenarios.

A limitation of the ALPHA algorithm is that it treats all meals equivalently, which may not be appropriate if insulin sensitivities change throughout the day. We considered using a case-based-reasoning approach similar to Herrero et al.'s approach [11], to handle difference in meal times. However, we found that even with insulin sensitivity varying +/−30% throughout the day and incorporating real-world sporadic meals into our simulations, convergence of the adaptation was rapid without the need for separately accounting for time-of-day or case-based meals. Another limitation of this study is that it was only done on an in-silico virtual patient population. While real-world meals were used from real-world AP studies, the results are still based on a glucoregulatory model. In the future, we plan to evaluate ALPHA-BR within a clinical hybrid AP study. The preliminary analyses of ALPHA-BR across study participants demonstrated that the initial aggressiveness factor of 0.7 (also shown in Table 4) could reduce time in hypoglycemia substantially. For our new clinical studies, we start all subjects with an aggressiveness factor of 0.7, and then allow the aggressiveness factor to range from 0 to 1. In this way, the ALPHA algorithm can be used to increase or decrease the postprandial insulin from a starting value.

5. Conclusions

This paper has shown that adaptation is important within an AP as the physiology differences amongst people with T1D can be challenging for an AP to handle. If post-prandial hypoglycemia is observed, the best way to handle this is through post-prandial basal adjustments. Adjustments of pre-meal bolus on postprandial hypoglycemia had minimal benefit.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jprocont.2019.05.018.

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