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Parallel control of an artificial pancreas with coordinated insulin, glucagon and rescue carbohydrate control actions

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Abbreviations: artificial pancreas (AP); type 1 diabetes (T1D); single-hormone artificial pancreas (SHAP); dual-hormone artificial pancreas (DHAP); multiple-input-single-output (MISO); single-input-single-output (SISO); Sliding Mode Reference Conditioning (SMRC); dual-hormone coordinated control (DH-CC); dual-hormone coordinated control with carbohydrates (DH-CC-CHO); insulin-on-board (IOB); mean blood glucose (MG); time in target range (TIR); daily average insulin (INS); daily average glucagon (GGON)

Keywords: artificial pancreas, carbohydrate suggestion, coordinated control, dual hormone, glucagon limitation, parallel control

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Abstract

Background: An artificial pancreas with insulin and glucagon delivery has the potential to reduce the risk of hypo- and hyperglycemia in people with type 1 diabetes. However, a maximum dose of glucagon of 1mg/day is recommended, potentially still requiring rescue carbohydrates in some situations. This work presents a parallel control structure with intrinsic insulin, glucagon and rescue carbohydrates coordination to overcome glucagon limitations when needed.

Methods: The coordinated controller that combines insulin, glucagon and rescue carbohydrate suggestions (DH-CCCHO) was compared with the insulin and glucagon delivery coordinated controller (DH-CC). The impact of carbohydrate quantization for practical delivery was also assessed. An in silico study using the UVA-Padova simulator, extended to include exercise and various sources of variability, was performed.

Results: DH-CC and DH-CC-CHO performed similarly with regard to mean glucose (126.25[123.43;130.73] vs 127.92[123.99;132.97] mg/dL, p=0.088), time in range (93.04[90.00;95.92] vs 92.91[90.05;95.75]%, p=0.508), time above 180 mg/dL (4.94[2.72;7.53] vs 4.99[2.93;7.24]%, p=0.966), time below 70mg/dL (0.61[0.09;1.75] vs 0.96[0.23;2.17]%, p=0.1364), insulin delivery (43.50[38.68;51.75] vs 42.86[38.58;51.36] U/day, p=0.383), and glucagon delivery (0.75[0.40;1.83] vs 0.76[0.43;0.99] mg/day, p=0.407). Time below 54mg/dL was different (0.00[0.00;0.05] vs 0.00[0.00;0.16]%, p=0.036), although non-clinically significant. This was due to the carbs quantization effect in a specific patient, since when carbs were not quantized, no statistical difference was found (0.00[0.00;0.05] vs 0.00[0.00;0.00]%, p=0.265).

Conclusions: The new strategy of automatic rescue carbohydrates suggestion in coordination with insulin and glucagon delivery to overcome constraints on daily glucagon delivery was successfully evaluated in an in silico proof of concept.

Introduction

An artificial pancreas (AP) is an automated insulin delivery system aiming at the improvement of glucose control in people with type 1 diabetes (T1D)[1]. A single-hormone AP (SHAP) consists in a continuous glucose monitor, an insulin pump and a control algorithm that modulates insulin infusion quasi-continuously. Dual-hormone AP systems (DHAP) also introduce glucagon infusion as control action to compensate the uni-directional effect of insulin on glucose. Recent developments on stable soluble glucagon formulations[2] are paving the way to such systems although no commercial formulation is yet available. However, long-term safety of glucagon delivery is unknown.

Since demonstration of feasibility of DHAP systems in humans[3], several studies have targeted head-to-head comparisons between SHAP and DHAP systems[4-10]. A recent review of results[11] concluded that: during nocturnal period SHAP was enough for a good glucose control while DHAP proved superior performance in reduction of hypoglycemia overall and during exercise; benefits in post-prandial control, reduction of severe hypoglycemia and mean glucose are unclear. In the 4-arm 4-day outpatient study with three moderate-intensity aerobic exercise sessions by Castle et al.[5], DHAP achieved lower time in hypoglycemia during exercise compared to SHAP and predictive-low-glucose-suspend, and similar to standard care where pre-exercise insulin adjustments were allowed. However, despite the use of glucagon and wearables to detect exercise, hypoglycemia was still present (1.3%(1.0) overall and 3.4%(4.5) during exercise; mean(SD)).

Current DHAP systems are based on an insulin controller and a glucagon controller which is activated in certain circumstances in order to initiate the counterregulatory action. These independent control loops may create unwanted interactions among

hormones delivery reducing effectiveness. Besides, an excess of plasma insulin has been found to reduce effectiveness of glucagon microboluses by El Youssef et al.[12], which does not support the design of DHAP systems with aggressive insulin infusion considering the availability of glucagon to compensate the increased risk of hypoglycemia. Indeed, physiologically there is a coordination between insulin and glucagon secretion[13]. On the one hand, an increment in plasma insulin levels produces a suppression of glucagon secretion in T1D patients; and a decrement in insulin levels together with low plasma glucose concentration stimulates glucagon secretion[14]. On the other hand, alpha cells anticipate the possible hyperglycemic rebounds due to the glucagon secretion by means of beta cell sensitization[15].

Motivated by this paracrine communication, control algorithms incorporating coordinated insulin and glucagon delivery have been investigated. In Herrero et al.[16], potentiation of insulin by glucagon was incorporated in the Imperial College AP system, reporting in silico a reduction in hyperglycemia without increased hypoglycemia. In Bondia et al.[17,18] a control algorithm with intrinsic coordination based on a collaborative parallel control formulation was first introduced. Thorough in silico evaluation showed the benefit of coordination with lower glucagon delivery, although room for improvement under exercise was identified[19]. Further refinements incorporating Sliding Mode Reference Conditioning (SMRC) techniques for insulin-on-board limitation were carried out in Moscardó[20] (see Section 7.6). When compared to the original algorithm[19], the refined controller showed improvements in percentage of time in target (92.98%(3.24) vs. 91.56%(3.42)) and time in hypoglycemia (1.45%(2.01) vs. 3.40%(2.92)) in a two-week scenario with daily 60-min exercise sessions. Nevertheless, some few patients required glucagon delivery higher than 1 mg/day (0.75 mg/day [0.40;1.83]; median[25-75 percentiles]).

In this work, parallel control structure (DH-CC) is further exploited to compensate such excess of glucagon need in some patients with the integration of rescue carbohydrate as an alternative control route (DH-CC-CHO). Parallel control computes a virtual

control action (control effort) that later is distributed into the different control actions to get a combined effect equal to the needed control effort. This gives rise to a flexible control structure where different configurations combining insulin, automatic rescue carbs suggestions and glucagon can be designed by reconfiguring the distribution logics. DH-CC and DH-CC-CHO are compared to analyze the benefits of this new proposal during the challenging exercise scenario in Moscardó et al. [19,20].

Methods

Coordinated parallel control DHAP including rescue carbohydrates

Coordinated control techniques for multiple-input-single-output systems have been developed in different ways in literature[21]. Of interest is the concept of habituating control[22,23], where control actions are classified as “slow and cheap” (primary) and “fast and expensive” (secondary). In a DHAP, the “fast and expensive” control action can be associated to glucagon, with a faster subcutaneous PK/PD, although its delivery must be restricted to 1mg/day due to the possible side effects such as nausea, vomiting and headache[24]; instead, the “slow and cheap” action is associated to insulin. Additional inputs can also overcome saturation problems of the primary action contributing with the additional control effort not able to be provided by the latter.

These concepts can be casted into a parallel control structure where a main controller computes the needed control effort (virtual control action), which is later distributed by a divisor among the available control actions, giving rise to intrinsic coordination[25]. This technique was applied to derive a DHAP coordinating insulin and glucagon delivery[19,20] (see diagram in black in Figure 1). In this controller, the divisor was designed so that glucagon acts as a secondary control action when insulin delivery is below a given threshold (set in this case to 75% of basal insulin infusion) for hypoglycemia mitigation.

However, in some occasions the delivery of glucagon is not enough to prevent hypoglycemia, as revealed by the need of rescue carbohydrates in DHAP clinical studies, or an overdelivery of glucagon beyond the limit of 1mg/day may result. In these

cases, integration of automatic suggestion of rescue carbohydrates into a DHAP can overcome these limitations. To this end, a third control action can be incorporated into the above-described parallel control strategy (branch highlighted in red in Figure 1), considering ideal administration of rescue carbohydrate, with a posteriori quantization for practical dosing by the patient. In this work, constraint on the maximum delivery of glucagon per day is addressed through the replacement of glucagon as a secondary action by rescue carbohydrate when the accumulated glucagon in a given 24-h time window is greater than the total daily dose restriction imposed.

In the following the proposed controller is described. Consider the system linearization

$$\Delta G(s) = \alpha H_1(s)\Delta u(s) + \beta H_2(s)\Delta\omega(s) + \varepsilon H_3(s)\Delta r(s) + d(s), \quad (1)$$

where $\Delta G(s)$ is the deviation of plasma glucose concentration from the equilibrium value G^*; $\Delta u(s)$ is the deviation of insulin infusion from its equilibrium value u^*; $\Delta\omega(s)$ is the deviation of glucagon infusion from the equilibrium value ω^*, which is null; $\Delta r(s)$ is the fast-acting rescue carbohydrate intake and d(s) a disturbance (e.g., glycemic effect of meal and exercise). Transfer functions $H_1(s)$, $H_2(s)$, and $H_3(s)$ are the linearized plants representing the glycemic effect of insulin, glucagon and rescue carbohydrate respectively, with $H_1(0) = H_2(0) = H_3(0) = 1$. Thus, gains α, β and ε correspond to sensitivities to insulin, glucagon and rescue carbohydrate, respectively, which will be patient-dependent. Remark that $H_1(s)$ and $H_3(s)$ will have a slower dynamics than $H_2(s)$ because of faster glucagon PK/PD.

In the absence of disturbance, the plant with faster dynamics, i.e., $H_2(s)$, is factorized as follows:

$$\Delta G(s) = H_2(s)\left(\alpha\frac{H_1(s)}{H_2(s)}\Delta u(s) + \beta\Delta\omega(s) + \varepsilon\frac{H_3(s)}{H_2(s)}\Delta r(s)\right), \quad (2)$$

leading to the following definition of the control effort $\Delta\mu$ (new virtual control action) and its primary/secondary actions, Δv_1, Δv_2, and Δv_3:

$$\Delta\mu(s) \coloneqq \Delta v_1(s) + \Delta v_2(s) + \Delta v_3(s), \quad (3)$$

$$\Delta v_1(s) \coloneqq \alpha \frac{H_1(s)}{H_2(s)} \Delta u(s), \quad (4)$$

$$\Delta v_2(s) \coloneqq \beta \Delta \omega(s), \quad (5)$$

$$\Delta v_3(s) \coloneqq \varepsilon \frac{H_3(s)}{H_2(s)} \Delta r(s). \quad (6)$$

Remark that now equation (2) can be expressed as a single-input-single-output (SISO) system in terms of the new virtual control action:

$$\Delta G(s) = H_2(s) \Delta \mu(s), \quad (7)$$

where no saturation constraints apply to $\Delta \mu(s)$, as compared to insulin, glucagon and rescue carbohydrate control actions, which must be non-negative. A controller $C(s)$ (see Figure 1) can then be designed for the system (7) to get a given closed-loop dynamics

$$H_{cl}(s) = \frac{C(s)H_2(s)}{1+C(s)H_2(s)}. \quad (8)$$

The controller $C(s)$ will be denoted as “master controller” in the parallel control structure. Here, a PD controller is considered

$$C(s) = k_p(1 + T_d s), \quad (9)$$

where k_p is the proportional gain and T_d is the derivative time. The control action $\Delta \mu(s)$ computed by (9) can be distributed in terms of Δv_1, Δv_2, and Δv_3 with consideration of the constraint imposed by (3). Then, by inverting equations (4)-(6), the final insulin, glucagon and (ideal) rescue carbohydrate actions can be obtained:

$$\Delta u(s) = \frac{1}{\alpha} \left(\frac{H_1(s)}{H_2(s)} \right)^{-1} \Delta v_1(s), \quad (10)$$

$$\Delta \omega(s) = \frac{1}{\beta} \Delta v_2(s), \quad (11)$$

$$\Delta r(s) = \frac{1}{\varepsilon} \left(\frac{H_3(s)}{H_2(s)} \right)^{-1} \Delta v_3(s), \quad (12)$$

$$u(s) = \Delta u(s) + u^*, \quad (13)$$

$$\omega(s) = \Delta \omega(s), \quad (14)$$

$$r(s) = \Delta r(s). \quad (15)$$

A key element is the design of the divisor that distributes the virtual control action $\Delta \mu(s)$ fulfilling (3). The following distribution is considered here:

$$\Delta v_1(s) = (1 - \gamma_1) \Delta \mu(s), \quad (16)$$

$$\Delta v_2(s) = \gamma_1\gamma_2\Delta\mu(s), \quad (17)$$

$$\Delta v_3(s) = \gamma_1(1-\gamma_2)\Delta\mu(s). \quad (18)$$

where $\gamma_1 \epsilon [0,1]$ is the design parameter to fix the relative weight of the control actions Δv_1 and counterregulatory actions ($\Delta v_2, \Delta v_3$); and $\gamma_2 \epsilon [0,1]$ is the design parameter to fix the relative weight of the control actions Δv_2 and Δv_3 determining the degree of collaboration between them.

Counterregulatory actions are designed to be delivered only when insulin infusion is below a certain threshold, u_{th}. Regarding glucagon and rescue carbohydrates, the latter will be triggered when the accumulated glucagon from the start of the considered 24-h time window is higher than 1mg. Thus, the following divisors are defined as:

$$\gamma_1 = \begin{cases} 1 & \tilde{u}(t) \leq u_{th} \\ 0 & \tilde{u}(t) > u_{th} \end{cases} \quad (19)$$

$$\gamma_2 = \begin{cases} 1 & \int_{t-t_0}^{t} \omega(\tau)d\tau \leq 1\, mg \\ 0 & otherwise \end{cases} \quad (20)$$

where $\tilde{u}(t)$ is the would-be insulin infusion if directing the total control effort through the insulin input channel, i.e., $\Delta v_1(s) = \Delta\mu(s)$. This means that if the control effort can be supplied by insulin, relative to the defined threshold u_{th}, then no counterregulatory action is triggered. Notice that the time that define the start of each 24-h time window (t_0) is customizable.

The switching due to equations (19)-(20) does not affect the closed-loop transfer function. Therefore, the closed-loop transfer function remains unaltered and it will be stable by design conditions on $C(s)$.

An SMRC loop[26,27] is also considered for the limitation of insulin-on-board (IOB). Remark that this does not modify the stability of the closed-loop system since it acts on the glucose reference. Here, IOB is represented by subcutaneous insulin

compartments in Hovorka model[28], $S_1(t)$ and $S_2(t)$, giving rise to the following definition

$$IOB(t) \coloneqq S_1(t) + S_2(t) \tag{21}$$

Given the system in Figure 1 and an upper limit of IOB, $IOB_{max}(t)$, the set $\sum \coloneqq \{x(t)|IOB(T) \leq IOB_{max}(t)\}$, where $x(t)$ denotes the system state, is invariant for the discontinuous signal ω:

$$\omega(t) = \begin{cases} \omega^+ & if\ \sigma_{SM}(t) > 0 \\ 0 & otherwise, \end{cases} \tag{22}$$

$$\sigma_{SM}(t) \coloneqq IOB(t) - IOB_{max}(t) + \sum_{i=1}^{l-1} \tau_i \left(IOB^{(i)}(t) - IOB_{max}^{(i)}\right), \tag{23}$$

where $\omega^+ > 0$ is large enough and l is the relative degree between the output $IOB(t)$ and the input $\omega(t)$, (i) is the i-th derivative, and τ_i are gains to fit. Signal $\omega(t)$ will discontinuously increase the glucose target, which is smoothed by the first-order filter

$$\frac{dG_{ref}^F(t)}{dt} = \lambda G_{ref}^F(t) + \lambda(G_{ref}(t) + \omega(t)), \tag{24}$$

where G_{ref} is the original glucose reference (constant here), G_{ref}^F is the conditioned reference, and defines the cut-off frequency of the filter. Relative degree l in (23) will be 2, as determined by the relative degree of the filter (24) and the relative degree of the IOB predictor (21), since the same structure is obtained for $H_1(s)$ and $H_2(s)$ describing insulin and glucagon PK/PD.

Rescue carbohydrate quantization

Rescue carbohydrate control action is quantized in rescue events of 15g for practical administration by the patient. The event will be triggered only when an accumulated rescue carbohydrate action over half this dose is required, and will not be triggered again unless the dose administered in excess was required, repeating the strategy.

The quantized rescue carbohydrate control action, $u_{CHO}(t)$, is then given by

$$u_{CHO}(t) = \begin{cases} 15 & f(t) \geq 7.5 \\ 0 & f(t) < 7.5, \end{cases} \tag{25}$$

where

$$f(t) = \int_0^t (r(\tau) + g(\tau))d\tau, \quad (26)$$

$$g(t) = \begin{cases} -15 & f(t) \geq 7.5 \\ 0 & f(t) < 7.5, \end{cases} \quad (27)$$

A value of 7.5g in (25) was used similarly to Beneyto et al.[29], although other values could be considered.

Controllers tuning

Table 1 shows the parameters values for the DHAP without and with rescue carbohydrates. As said before, the DHCC-CHO is an improvement of the DH-CC structure by means of the addition of a third loop. Thus, both structures share the tuning of the master controller parameters, which was manually tuned to achieve the best possible glycemic outcomes (i.e. percentage of time in range [70,180] mg/dL and percentage of time below target).

For all the evaluated subjects, parameters were fixed to the same value except parameters $\alpha, \beta, \varepsilon$ and IOB_{max}. Parameters α, β and ε were individualized for each patient following an identification procedure based on the impulse response for a set of bolus doses. Parameter IOB_{max} was time invariant and defined as 30% above basal IOB for each patient, IOB^*. Lastly, the effect of the parameter u_{th} on the controller performance was evaluated in Moscardó[20] (see Appendix C therein) in order to determine the optimal switch condition for CC. Threshold values 0, $0.25u^*$, $0.5u^*$, and $0.75u^*$ were considered and outcome metrics assessed in three different scenarios (with meal, snack and exercise disturbances) for the average patient. Results are summarized in Figure 2. The best result was obtained for $u_{th} = 0.75u^*$ with lower time in hypoglycemia without compromising time in range and without glucagon over-delivery. To ease tuning, this value will be considered populational for the whole cohort.

In silico evaluations

The educational version of the UVA/Padova simulator[30] with the addition of the exercise model in Schiavon et al.[31] and intra-day and intra-subject variability was used to assess and compare the above control structures.

Intra-day variability was incorporated to the simulator by modifying some of the parameters: meal variability was emulated by introducing meal-size variability (CV=10%), meal-time variability (STD=20) and uncertainty in the carbohydrate estimation (uniform distribution between -30% and +40%). Variability of meal absorption rate (k_{abs}) and carbohydrate bioavailability (f) were considered to be ±30% and ±10% respectively. For intra-day meal variability, the 11 meal model parameters from the cohort were randomly assigned at each meal intake.

To emulate intra-subject variability, insulin absorption model parameters (k_d, k_{a1}, k_{a2}) were varied ±30%. Insulin sensitivity parameters (V_{mx}, k_{p3}) were assumed to change along the day following a sinusoidal pattern, Finally, the variability into exercise was added by modifying the starting time (STD= 20 min), the exercise intensity (CV=10), and the duration (CV= 10).

The scenario considered meal and exercise. The selected daily pattern of carbohydrate doses was 7am (50g), 1pm (80g), 8pm (60g), and the daily exercise started at 3pm with a duration of 60 minutes and an intensity of 50%.

A two-week scenario duration was used to compare the DH-CC with DH-CC-CHO configurations in 100 adults. The subjects are based on the 10 adults that are available in the educational version of the UVA/Padova simulator, with 10 repetitions each getting different instances of variability. Moreover, the chosen basal insulin infusion rates, u^*, were the ones provided by the simulator for each subject.

Data analysis

In order to carry out the comparison between both proposed control structures, the standard glycemic control metrics[32] were used: mean blood glucose (MG); percentage time in target range [70,180] mg/dL (TIR); percentage time below target (<70mg/dL and <54mg/dL); percentage time above target (>180 mg/dL); daily average of insulin delivered in units of insulin (INS); and daily average of glucagon delivered in mg (GGON). Statistical differences were assessed by the Non-Parametric Wilcoxon signed-rank test due to non-normality of the data. Significant p-value was 0.05.

Results and discussion

Table 2 shows the results corresponding to the cohort analyzed for both control structures, DH-CC (column 1) and DH-CC-CHO (column 2). For a better analysis, configurations of DH-CC-CHO with no quantization of rescue carbohydrate (column 3) and DH-CC with limitation of glucagon to 1mg/day without additional carbs (column 4) are also presented.

Performance of DH-CC and DH-CC-CHO was similar in terms of mean glucose (p=0.088), time in range (p=0.508), time above 180 mg/dL (p=0.966), time below 70mg/dL (p=0.1364), insulin delivery (p=0.383), and glucagon delivery (p=0.407). For DH-CC, glucagon doses higher than 1mg/day were only required by 30 adults (derived from the same 3 patients in the original 10-adult cohort) who seem to be more glucagon resistant. Statistically significant difference in time below 54 mg/dL was found (p=0.036), although median time was 0% and 75-percentile 0.16% with low clinical significance. All events were mainly related to the same patient. This difference was not found in case of DH-CC-CHO (non-quantized) (p=0.265), where ideal continuous administration of carbs is considered, which indicates that rescue carbohydrate quantization might be the responsible for the above difference, especially for that patient. However, no statistical difference was found in any metrics between DH-CC-CHO and DH-CC-CHO (non-quantized) concluding no major impact of the quantization process in the system performance. Limitation of glucagon delivery to 1mg/day without

additional carb intake to complete the required control effort (column 4 in Table 2) yielded higher time below 70mg/dL and 54mg/dL, with statistical significance with all the other three configurations analyzed. If studies where delivered glucagon was greater than 1mg/day for DH-CC are analyzed (n=30), the addition of rescue CHO (DH-CC-CHO) implied a glucagon delivery lower than 1mg/day (0.997 [0.997;0.998] mg/day) and the need of 2.04 [1.71; 2.5] CHO rescues (1 rescue=15g).

Figure 3 illustrates the controllers performance of two patients where the glucagon limitation was needed, as compared to glucagon limitation without rescue carb intake. Two days instead of all 14 days are represented in order to depict better the behavior described by the considered approaches. It can be observed that in these patients limitation of glucagon delivery to 1mg/day would have provoked hypoglycemia during the afternoon (green dashed line), which was successfully avoided by the DH-CC-CHO controller (solid blue line) with the automatic suggestion of rescue carbs contributing with the same control effort than the needed glucagon, achieving a similar performance than DH-CC (dashed purple line).

This proof-of-concept study demonstrates (in silico) the flexibility of the parallel control strategy, where different divisor strategies can be devised attending to scenario particularities and user preferences, besides overcoming constraints on glucagon delivery. For instance, glucagon has shown to be more effective in exercise scenarios than postprandial periods, where rescue carbohydrate can be a better option for hypoglycemia mitigation. Additionally, other quantization strategies for practical carb intake by the patient could be derived. Clinical validation supporting the in silico results is needed since simulations might suffer from TIR overestimation, given current clinical results where TIRs of 75-80% are achieved in closed-loop settings at the best.

Conclusions

A new control strategy for a dual hormone artificial pancreas system incorporating automatic suggestion of rescue carbohydrates in coordination with insulin and glucagon delivery was presented. The method allows to select among glucagon or rescue carbohydrate counterregulatory action, providing the same equivalent required control effort as computed by a master controller, following a parallel control structure. Application of this strategy to overcome constraints on daily glucagon delivery was successfully evaluated in a proof-of-concept in silico study.

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Disclosures

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Table 1. Controller parameters. The symbol † indicates a patient-dependent parameter.

Parameters	Controller configuration	
	DH-CC	DH-CC-CHO
k_p	$3.1350 \cdot 10^{-4}$	$3.1350 \cdot 10^{-4}$
T_d(min)	90	90
G_{ref}(mg/dL)	100	100
t_0	-	8:00pm
α	(†)	(†)
β	(†)	(†)
ε	(†)	(†)
u_{th}	0.75·u* (†)	0.75·u* (†)
τ (min)	10	10
ω^+(mg/dL)	200	200
IOB_{max} (U)	1.3·IOB* (†)	1.3·IOB* (†)

Table 2. Evaluation results. Notation ^{*i,j} indicates statistically significant difference with respect to systems i and j (p-value <0.05). For simplicity explicit p-values are not shown. Data are median[25-75 percentiles].

	DH-CC[1]	**DH-CC-CHO[2]**	**DH-CC –CHO[3] (non-quantized)**	**DH-CC[4] (Glucagon ≤ 1mg/day)**
MG (mg/dL)	126.25 [123.43;130.73]	127.92 [123.99;132.97]	127.93 [123.13;133.01]	127.92 [119.97;132.17]
TIR (%)	93.04 [90.00;95.92]	92.91 [90.05; 95.75]	92.86 [90.09;95.75]	92.45 [88.33;95.73]
>180 (%)	4.94 [2.72;7.53]	4.99 [2.93;7.24]	5.00 [2.91;7.30]	4.79 [2.84,7.06]
<70 (%)	0.61*[4] [0.09;1.75]	0.96*[4] [0.23;2.17]	0.97*[4] [0.16;2.13]	1.71*[1,2,3] [0.24;5.15]
<54 (%)	0.00*[2,4] [0.00;0.05]	0.00*[1,4] [0.00; 0.16]	0.00*[4] [0.00;0.00]	0.00*[1,2,3] [0.00;2.21]
INS (U/day)	43.50 [38.68;51.75]	42.86 [38.58;51.36]	42.83 [38.58;51.36]	42.38 [38.58;51.36]
GGON (mg/day)	0.75 [0.40;1.83]	0.76 [0.43;0.99]	0.76 [0.43;0.99]	0.76 [0.44;0.99]
CHO rescue events (15g)	-	0.00*[1,4] [0.00; 2.07]	0.00*[1,4] [0.00;1.84]	-

Figure 1. Block diagram of the proposed coordinated parallel control DHAP including rescue carbohydrates. An external SMRC loop is also considered for insulin-on-board limitation which modulates glucose target.

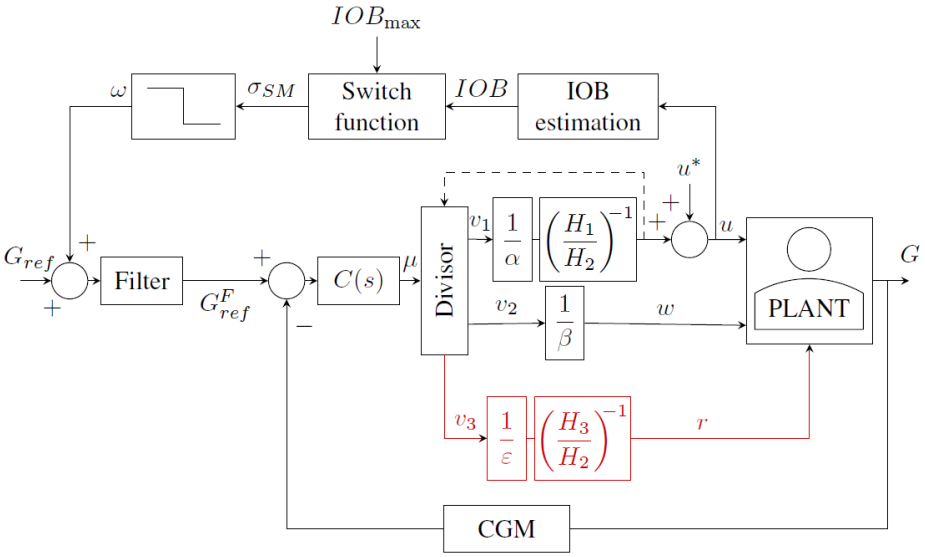

Figure 2. Effect of the threshold value u_{th} on percent time in range (70-180mg/dL), time in hypoglycemia (<70mg/dL), daily insulin delivery and daily glucagon delivery for the average patient in three scenarios comprising meals, snack and exercise[20].

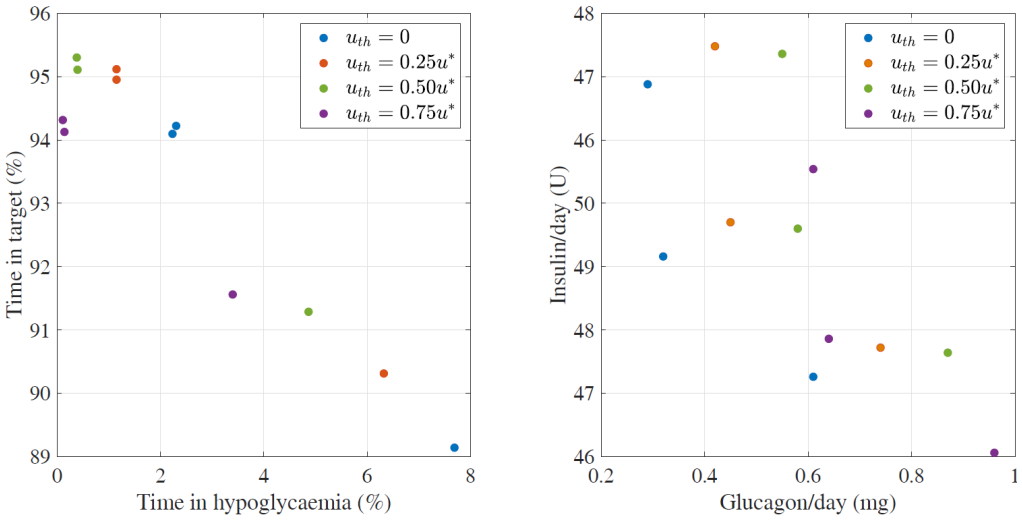

Figure 3. Comparison between different controller approaches: DH-CC (dashed purple line), DH-CC-CHO (solid blue line) and DH-CC (glucagon ≤ 1mg/day) (dashed green line). Meals and exercise events are marked with triangles and stars respectively.