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Research Paper

In silico validation of a customizable fully-autonomous artificial pancreas with coordinated insulin, glucagon and rescue carbohydrates

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ABSTRACT

Artificial pancreas systems should be designed considering different patient profiles, which is challenging from a control theory perspective. In this paper, a flexible-hybrid dual-hormone control algorithm for an artificial pancreas is proposed. The algorithm handles announced/unannounced meals by means of a non-interacting feedforward scheme that safely incorporates prandial boluses. Also, a coordination strategy is employed to distribute the counter-regulatory actions, which can be delivered as a continuous glucagon infusion via an automated pump, as an oral rescue carbohydrate recommendation, or as a rescue glucagon dose recommendation to be administrated through a glucagon pen. The different configurations of the proposed controller were evaluated in silico using a 14-day virtual scenario with random meal intakes and exercise sessions, achieving above 80% time-in-range and low time spent in hypoglycemia.

1. Introduction

People with type 1 diabetes (T1D) depend on exogenous insulin infusions to regulate their blood glucose levels. Artificial pancreas (AP) systems have emerged as a technological treatment for T1D, improving glycemic control over traditional therapies [1]. This improvement of the control quality envisages a reduction of the complications related to the conditions of persistent high glucose levels or hyperglycemia (e.g., retinopathy, neuropathy, cardiomyopathy or stroke [2]) and low glucose levels or hypoglycemia (e.g., palpitations, trembling, and, in severe cases, coma, or death [3]). However, diurnal control is still challenging because meal intake and exercise practice cause substantial fluctuations in glucose levels [4,5].

Current AP systems are referred to as hybrid systems because users must "announce meals" (inform the system about the meal carbohydrate content) which triggers an appropriately sized prandial bolus. Although relatively small meals (of about 20 g) may be handled without this user intervention [6–8], prandial boluses are needed to mitigate postprandial hyperglycemia in larger meals [1,9,10]. Carbohydrate counting is also prescribed for open-loop therapies. Hence, some users may feel that migrating to hybrid AP systems is not worth it unless these systems ultimately relieve them from this burdensome and prone-to-error task [11]. A whole meal-announcement-free system, however, may not fit all patients. Some of them, with extensive experience in carbohydrate estimation, may prefer to announce meals to enhance postprandial control. Thus, AP systems should perform well without meal announcements and, at the same time, safely incorporate prandial boluses in the event of announced meals. From a control perspective, meal announcements are seen as feedforward actions, which may interact with the feedback controller [12], leading to insulin overdelivery and, consequently, causing hypoglycemia [13].

Exercise is another major disturbance that challenges the performance of AP systems. Although highly intense exercise events may lead to hyperglycemia, mild-to-moderate aerobic exercise, the most habitual physical activity practiced by non-athletic people, drops glucose levels [5]. In current hybrid systems, users have to reduce insulin infusion hours before exercise onset, for instance, by temporarily increasing the glucose target, thus requiring planning the exercise [1,5]. When planning the exercise is not feasible, oral carbohydrate supplement recommendation is a handy strategy to avoid hypoglycemia. However,

Abbreviations: AP, Artificial pancreas; CGM, Continuous glucose monitor (reading); CV, Coefficient of variation; T1D, Type 1 diabetes; VO2, Oxygen consumption

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it requires user intervention. In addition, some patients aiming to lose weight by exercising may be reluctant to this extra caloric intake. Dual-hormone AP systems can overcome these drawbacks by automatically delivering glucagon, a non-caloric counter-regulatory action. Nevertheless, dual-hormone systems would require more complex and bulky hardware (two independent pumps or dual-chambers pumps). Therefore, people with a low risk of hypoglycemia may prefer to manually inject glucagon through pens or syringes, which has been proven to be effective in mitigating mild hypoglycemia [14]. Since some patients may not tolerate glucagon well (e.g., nausea or vomiting), AP systems should allow users to switch to carbohydrate suggestions when desired.

From the above discussion, the following three features are advisable in an AP system: (1) to compensate for meals without meal announcement, (2) to allow patients to announce meals if desired without compromising the performance of the feedback controller, and (3) to deliver a counter-regulatory control action to handle unannounced exercise events, allowing the user to select between carbohydrate recommendation, automatic glucagon infusion, or manual glucagon injection. Many methods have been proposed to remove meal announcements – see a review in [15] – but none count with mechanisms to reduce interactions with the feedback action in case the patient announces the meal. Regarding unplanned exercise compensation, most glucagon-insulin systems [16,17] lack carbohydrate suggestion modules, and vice-versa [18–20]. The algorithm proposed in [21] can utilize either glucagon or carbohydrate supplements to mitigate hypoglycemia but requires meal announcements. On the other hand, the solution adopted in [22] removes the need to announce meals and exercise; however, it does not offer flexibility to deliver prandial boluses.

This article aims to design a blood glucose control algorithm incorporating the all three features described above. For handling unannounced meals, the proposed system relies on a near-optimal feedback controller design [23]. The proposed method also implements a non-interacting feedforward control scheme [12] that incorporates prandial boluses by attenuating the feedback control action when a meal is announced. The system delivers regulatory and counter-regulatory control actions in a coordinated manner by exploiting a slightly modified version of the parallel structure in [21]. The proposed AP is validated with the ten-adult cohort of the academic version of the UVa/Padova simulator [24] extended with different sources of variability (more details in Section 4) under a challenging scenario with meals and exercise events.

The article is structured as follows: The building blocks of the proposed system are described in Section 2 while some practical considerations are addressed in Section 3. In silico validations are presented and discussed in Section 4. Finally, some conclusions and future work are drafted in Section 5.

2. Proposed control structure

The following subsections describe the patient model used for control design purposes and each of the building blocks of the system, whose overall structure is depicted in Fig. 1.

2.1. Control-oriented patient model

The linear model for control design purposes assumes the following simplified relation between the glucose variation y (mg/dL), the incremental insulin infusion rate u (pmol/kg/min), the glucagon infusion rate v (mg/kg/min), the rescue carbohydrates delivery rate w (g/kg/min), and the oral carbohydrate intake rate d (g/kg/min):

$$y(s) = G_u(s)u(s) + G_v(s)v(s) + G_w(s)w(s) + G_d(s)d(s) \tag{1}$$

The incremental glucose y is considered with respect to a basal glucose level G_b, which is achieved by a basal insulin infusion u_b. The oral carbohydrate intake rate is modeled by $d(s) = M/\mathrm{BW}$, where $M > 0$ is the actual carbohydrate content (g) and BW is the body weight (kg). The time-delay linear transfer functions $G_d(s)$, $G_u(s)$, $G_v(s)$, and $G_w(s)$ are described by:

$$G_i(s) = \tilde{G}_i(s)e^{-h_i s}, \quad i \in \{u, v, w, d\}$$
$$\tilde{G}_i(s) = \frac{k_i^j}{(\tau_{1i}s + 1)^2(\tau_{2i}s + 1)} \tag{2}$$

where the j-superindex denotes a patient-tailored gain. The control inputs are subject to the saturation constraints $u(t) > -u_b$ and $v(t), w(t) \geq 0$ for all t. The dynamics in (2) relies on three approximations to simplify the identification of the models and to mitigate identifiability issues: (1) two-compartment models represent the absorption of the inputs u, d, v and w [25]; (2) a first-order model represents the effect of these inputs on glucose variation; (3) the delays of the rescue carbohydrates and glucagon models cannot be larger than that of the insulin model, i.e., $h_v, h_w \leq h_u$. Similar gain-personalized models with the same number of poles are standard for diabetes control purposes [23,26–28]. The constraint regarding the delay size is needed to ensure that the controller is realizable. It should also be remarked that, although carbohydrates are assumed to be delivered continuously in the subsequent derivations, the controller will be modified to handle the more realistic situation in which they are delivered as quantized doses in Section 3.

2.2. Parameter identification

The model (1) was identified for the ten virtual adults of UVa/Padova distribution version [24], which was used to generate a data set for identification. The simulator was modified to incorporate the variability sources described below in Section 4. A conventional open-loop therapy was simulated for the virtual patients in the simulator, in a 14-day scenario generated with randomness in the meal size, intake time and carbohydrate counting errors. The postprandial responses were segmented from the continuous glucose monitor (CGM) data set. The meal and insulin models were identified following the same procedure described in [23]. The related parameters were fitted to match the median postprandial behavior by minimizing the root mean squared error. All delays h_i were set equal to 15 min in order to simplify the procedure and avoid potential identifiability issues [25]. For further details, the reader is referred to Section 4 in [23]. This procedure led to a set of parameters with population time constants and personalized gains. Moreover, a regression was fitted for the meal and insulin gains based on some of the open-loop basic parameters reported in the simulator, namely, the correction factor CF (mg/dL), the insulin-to-carb ratio CR (g/U), and the body mass BW (kg), leading to the following patient-tailored gains:

$$k_u^j = -125 \cdot \mathrm{CF}^j/\mathrm{BW}^j - 119 \qquad k_d^j = -6000 \cdot k_u^j/\mathrm{CR}^j \tag{3}$$

The rescue carbohydrates and glucagon models were identified by simulating a hyperinsulinic hypoglycemic clamp that takes each patient's glucose down to 60 mg/dL. When this glucose level is reached, a rescue of 15 g or a glucagon dose of 0.5 mg is delivered. The related model parameters are identified from the glucose variation after this event. It should be remarked that similar protocols are commonly used in the clinic to assess glucagon and rescue carbohydrates effectiveness [29]. A summary of the identified parameters is shown in Table 1.

2.3. Non-interacting feedforward scheme

As discussed in the Introduction, an AP system should be able to deal with unannounced meal events and yet allow the patient to deliver prandial boluses, if desired. However, doing so without having the feedback controller informed may result in an insulin overdose. To mitigate this issue, the master controller is informed about the patient actions through a non-interacting feedforward scheme [12]. Let us

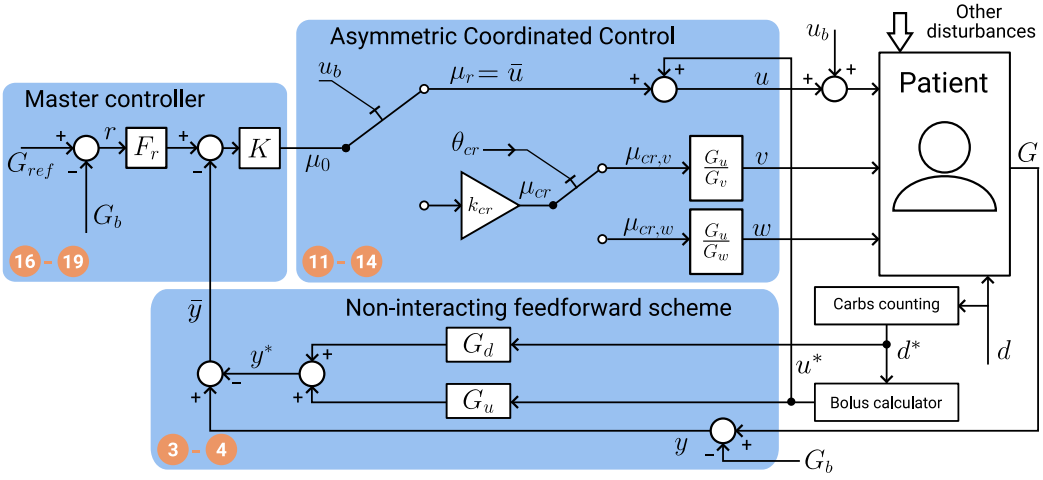

Fig. 1. Nominal control architecture blocks. Numbers inside orange circles correspond to the associated equations in the text.

Table 1
Control-oriented patient model parameters corresponding to the virtual adults in UVa/Padova simulator.

Subject j	k_d^j $\left(\frac{\text{mg/dL}}{\text{g/kg/min}}\right)$	k_u^j $\left(\frac{\text{mg/dL}}{\text{pmol/kg/min}}\right)$	k_v^j $\left(\frac{\text{mg/dL}}{\text{mg/kg/min}}\right)$	k_w^j $\left(\frac{\text{mg/dL}}{\text{g/kg/min}}\right)$
1	$4.95 \cdot 10^4$	−157.99	$8.13 \cdot 10^6$	$8.73 \cdot 10^4$
2	$4.04 \cdot 10^4$	−151.50	$1.60 \cdot 10^7$	$7.71 \cdot 10^4$
3	$5.95 \cdot 10^4$	−144.38	$5.58 \cdot 10^7$	$7.27 \cdot 10^4$
4	$6.66 \cdot 10^4$	−218.67	$4.80 \cdot 10^6$	$6.06 \cdot 10^4$
5	$8.92 \cdot 10^4$	−200.17	$8.35 \cdot 10^6$	$6.46 \cdot 10^4$
6	$7.23 \cdot 10^4$	−108.45	$3.49 \cdot 10^6$	$8.02 \cdot 10^4$
7	$8.38 \cdot 10^4$	−253.36	$2.11 \cdot 10^6$	$6.55 \cdot 10^4$
8	$7.77 \cdot 10^4$	−103.80	$3.90 \cdot 10^6$	$1.03 \cdot 10^5$
9	$6.64 \cdot 10^4$	−218.69	$1.41 \cdot 10^7$	$5.51 \cdot 10^4$
10	$6.21 \cdot 10^4$	−142.59	$1.01 \cdot 10^7$	$7.59 \cdot 10^4$

τ_{1d} (min)	τ_{1u} (min)	τ_{1v} (min)	τ_{1w} (min)	τ_{2d}, τ_{2u} (min)	τ_{2v}, τ_{2w} (min)
25	50	30	20	350	250

define the expected output variation after a meal event with prandial bolus as

$$y^*(s) = G_d(s)d^*(s) + G_u(s)u^*(s) \tag{4}$$

which is based on the meal size d^* informed by the patient and the corresponding prandial insulin bolus u^*. Without loss of generality, the latter is computed by

$$u^* = v \cdot \frac{M^*}{\text{CR}} \cdot \frac{1}{6000 \cdot \text{BW}}$$

where CR and BW have been already defined, M^* is the announced meal carbohydrate content (g), $v \in [0, 1]$ is an attenuation factor, and the remaining factor converts the insulin units from U to pmol/kg. Subtracting (1) and (4) leads to

$$\bar{y}(s) = G_u(s)\bar{u}(s) + G_v(s)v(s) + G_w(s)w(s) + G_d(s)\bar{d}(s) \tag{5}$$

where $\bar{y}(s) = y(s) - y^*(s)$, $\bar{u}(s) = u(s) - u^*(s)$, and $\bar{d}(s) = d(s) - d^*(s)$ have been defined. After this transformation, $\bar{u}$ and $\bar{y}$ replace u and y as manipulated input and regulated output, respectively. Also, the external disturbance is now $\bar{d}$, which represents the mismatch between the actual meal size and the estimation given by the patient.

2.4. Asymmetric coordinated control

Having more manipulated inputs than regulated outputs, as is the case of the multiple-input single-output model (5), can be exploited to improve performance at different operating conditions and to handle input saturation. However, it also poses difficulties in the design procedure. In order to simplify this task and attending to the nature of the different control actions, the model (5) is conveniently rewritten as follows, inspired by the coordination mechanism proposed by [30]:

$$\bar{y}(s) = G_u(s)\mu(s) + G_d(s)\bar{d}(s) \tag{6}$$

where

$$\mu(s) \triangleq \mu_r(s) + \mu_{cr}(s) \tag{7}$$

is regarded as a virtual control action that comprises both the regulatory and counter-regulatory actions, defined by

$$\mu_r(s) \triangleq \bar{u}(s) \tag{8}$$

$$\mu_{cr}(s) \triangleq \mu_{cr,v}(s) + \mu_{cr,w}(s) \tag{9}$$

the latter including two terms, which represent the counter-regulatory effect implemented via glucagon infusion (v) or carboyhydrate delivery (w), given by

$$\mu_{cr,v}(s) \triangleq \frac{G_v(s)}{G_u(s)}v(s) \tag{10}$$

$$\mu_{cr,w}(s) \triangleq \frac{G_w(s)}{G_u(s)}w(s) \tag{11}$$

The counter-regulatory mode should be more aggressive in order to compensate for any drop in the glucose level that may have severe consequences for the patient. Let μ_0 be a suitable control action for (6), to be designed in Section 2.5. An asymmetric closed-loop control action is defined by

$$\mu(t) = \begin{cases} \mu_0(t) & \text{if} \quad \mu_0(t) \geq -u_b \\ k_{cr} \cdot \mu_0(t) & \text{if} \quad \mu_0(t) < -u_b \end{cases} \tag{12}$$

with a controller gain increased by $k_{cr} \geq 1$ in the counter-regulatory mode. The following distribution scheme is proposed between regulatory and counter-regulatory actions

$$\begin{aligned} \mu_r(t) &= \begin{cases} \mu_0(t) & \text{if} \quad \mu_0(t) \geq -u_b \\ -u_b & \text{if} \quad \mu_0(t) < -u_b \end{cases} \\ \mu_{cr}(t) &= \begin{cases} 0 & \text{if} \quad \mu_0(t) \geq -u_b \\ k_{cr} \cdot \mu_0(t) + u_b & \text{if} \quad \mu_0(t) < -u_b \end{cases} \end{aligned} \tag{13}$$

where the latter are further distributed by

$$\mu_{cr,v}(s) = (1 - \theta_{cr})\mu_{cr}(s), \quad \mu_{cr,w}(s) = \theta_{cr}\mu_{cr}(s) \tag{14}$$

with a parameter $\theta_{cr} \in \{0, 1\}$ that can be adjusted to choose between glucagon or rescue carbohydrates. It is readily verified that (12), (13) and (14) are consistent with (7) and (9), respectively. Finally, having $\mu_r(s)$, $\mu_{cr,v}(s)$, and $\mu_{cr,w}(s)$ as defined above, the control signals that

guarantee the closed-loop coordination can be computed from (8) and (10)–(11) as

$$\begin{aligned} \bar{u}(s) &= \mu_r(s) \\ v(s) &= \frac{G_u(s)}{G_v(s)}\mu_{cr,v}(s) \\ w(s) &= \frac{G_u(s)}{G_w(s)}\mu_{cr,w}(s) \end{aligned} \tag{15}$$

2.5. Master feedback controller

In this section, the master controller is designed for a postprandial scenario, which is the main challenge of automated glucose regulation. From (6) and (12), the postprandial behavior is governed by

$$\bar{y}(s) = G_u(s)\mu_0(s) + G_d(s)\bar{d}(s) \tag{16}$$

provided that, ideally, the counter-regulatory action should not be used to this end. A standard two-degree-of-freedom structure is adopted

$$\mu_0(s) = K(s)(F_r r(s) - \bar{y}(s)) \tag{17}$$

where $K(s)$ is designed for feedback stability and disturbance rejection performance while the prefilter $F_r(s)$ is designed to achieve the desired tracking performance of the reference signal $r(s)$. It is already known that a positive insulin pulse, that is, an insulin bolus, is the optimal insulin infusion to minimize the postprandial peak while keeping the subsequent glucose undershoot below a prescribed threshold [23, 31]. Applying the methodology in [23] to model (16), the following expression for the feedback controller is obtained

$$K(s) = -\frac{\kappa^j F(s)\tilde{G}_d^{-1}(s)}{1 + \kappa^j F(s)\tilde{G}_d^{-1}(s)G_u(s)} \tag{18}$$

where $\kappa^j > 0$ is a patient-tailored gain and $F(s)$ is a strictly-proper filter with time constant $\alpha > 0$

$$F(s) = \frac{1}{(\alpha s + 1)^3} \tag{19}$$

that makes the inverse operations in (18) realizable. Then, the set-point filter is simply selected as

$$F_r(s) = \frac{T^{-1}(0)}{(\alpha_r s + 1)^3} \tag{20}$$

where $\alpha_r > 0$ is the filter time constant and $T(s)$ is the transfer function of the closed-loop system from $r(s)$ to $\bar{y}(s)$, given by $T(s) = K(s)G_u(s)/(1 + K(s)G_u(s))$.

3. Practical considerations

This section describes some practical considerations to implement and tune the controller described in Section 2.

3.1. Optimization of counter-regulatory actions

The use of glucagon should be minimized as it may have side effects such as nausea or vomiting. Limiting caloric intake due to carbohydrate suggestions is also convenient to avoid weight gain. Some strategies adopted to pursue these goals are discussed in this section.

3.1.1. Coordinated control

The coordinated control, when implemented as described in Section 2.4, may lead to undesired switches between the regulatory and counter-regulatory modes. In order to reduce the number of switches, the distribution (13) is slightly modified for implementation as follows

$$\begin{aligned} \mu_r(t) &= \begin{cases} \max(-u_b, \mu_0(t)), & \mu_0^f(t) \geq -\gamma u_b \\ -u_b, & \mu_0^f(t) < -\gamma u_b \end{cases} \\ \mu_{cr}(t) &= \begin{cases} 0, & \mu_0^f(t) \geq -\gamma u_b \\ \min(0, k_{cr}\cdot\mu_0(t) + u_b), & \mu_0^f(t) < -\gamma u_b \end{cases} \end{aligned} \tag{21}$$

which incorporates two mechanisms to minimize the counter-regulatory action consumption. On the one hand, the switching is performed upon a filtered signal μ_0^f, resulting from applying a moving-average filter with a three-sample window to the signal μ_0. This filter is added to avoid undesired activation of the counter-regulatory mode due to noise contained in the control action. On the other hand, the threshold for the activation of the counter-regulatory mode is slightly shifted by an adjustable factor γ, further explained in Section 3.3 below. This modification implies that there is a small dead-zone $-\gamma u_b < \mu_0^f < -u_b$ in which the insulin pump is shutdown but counter-regulatory actions are not delivered. The min and max functions are employed only to guarantee the feasibility of the resulting control actions.

3.1.2. Non-interacting feedforward

The non-interacting feedforward scheme may also contribute to an inefficient use of counter-regulatory actions in some scenarios. To see this, let us use $\bar{y}(s) = y(s) - y^*(s)$ to rewrite (17) as

$$\mu_0(s) = \underbrace{K(s)(F_r r(s) - y(s))}_{\mu_{0,e}} + \underbrace{K(s)y^*(s)}_{\mu_{0,y^*}} \tag{22}$$

where $\mu_{0,e}$ is the contribution of the tracking error and μ_{0,y^*} is the contribution of the non-interacting feedforward strategy. The latter will always be negative in the nominal case by the properties of $K(s)$. If, for some reason, it happens that $y^* \gg y$, the term μ_{0,y^*} may trigger the use of counter-regulatory actions, which is not desired. This would happen, for example, if the patient has an abnormally high insulin sensitivity. In this case, it would not make sense to steer the glucose up by using counter-regulatory actions to match the expected trajectory y^*. In order to prevent this situation, the master control signal (17) is slightly modified as

$$\mu_0(t) = \begin{cases} \max(-\gamma u_b, \mu_{0,e}(t) + \mu_{0,y^*}(t)), & \mu_{0,e}(t) \geq -\gamma u_b \\ \mu_{0_e}(t), & \mu_{0,e}(t) < -\gamma u_b \end{cases} \tag{23}$$

After this modification, in regulation mode, the contribution of the term μ_{0,y^*} can inhibit insulin infusion to the point of shutting down the insulin pump. However, it cannot trigger the use of counter-regulatory actions.

3.2. Quantized counter-regulatory actions

Given the nature of the computations involved in this section, all equations are derived in the discrete-time domain, denoting the sampling period by τ_s and the sampling instants with the variable $k \in \mathbb{Z}_{\geq 0}$. Also, the common notations $\wedge, \vee, \neg$ for the logic operators AND, OR, and NOT, respectively, are employed. A logic flag indicating the risk of hypoglycemia is denoted by $\mathcal{B}_{hypo}(k)$, which is computed by $\mathcal{B}_{hypo}(k) = (\hat{G}_{1h}(k) < 60) \vee (G(k) < 54)$ where $G(k)$ is the current continuous glucose monitor (CGM) reading and $\hat{G}_{1h}(k)$ is the 1-h ahead glucose prediction. The latter is computed by a first-order Taylor expansion using a numerical derivative low-passed through a filter with unit gain and 15-min time constant.

3.2.1. Carbohydrates quantization

The rescue carbohydrate delivery rate must be recommended to the patient as quantized doses of pre-defined size. Therefore, a quantization scheme is implemented, in which the recommended carbohydrate intake is given by

$$\tilde{w}(k) = \begin{cases} \left\lfloor \frac{z_w(k)}{q_w} \right\rceil \cdot q_w, & \mathcal{B}_w \wedge \mathcal{B}_{hypo} \\ 0, & \text{otherwise} \end{cases} \tag{24}$$

where $\lfloor\cdot\rceil$ denotes the nearest integer operator, $q_w > 0$ is the pre-defined dose size and $\mathcal{B}_w(k) = z_w(k) > \underline{z}_w$ is a logic condition that is triggered

whenever a cumulative variable z_w reaches the prescribed threshold $\underline{z}_w < q_w$. The cumulative variable is computed by

$$z_w(k+1) = \begin{cases} 0, & \mathcal{B}_w \wedge \neg\mathcal{B}_{hypo} \\ \left(1 - \frac{\tau_s}{\tau_{cl}}\right) z_w(k) + \Delta_w(k), & \text{otherwise} \end{cases} \tag{25}$$

where $\Delta_w(k) = \tau_s \cdot \mathrm{BW} \cdot w(k) - \tilde{w}(k)$ and $\tau_{cl} > 0$ is a clearing time constant. The first term in $\Delta_w(k)$ acts as an integrator of the continuous carbohydrate delivery rate $w(k)$. The quantization scheme will trigger a carbohydrate recommendation, multiple of q_w, whenever the cumulative variable $z_w(k)$ reaches $\underline{q}_w$. The second term in $\Delta_w(k)$ subtracts such recommendation from the cumulative variable to compensate for the excess. Also, a fading memory mechanism is implemented so that the cumulative variable clears over time with a decaying rate $\tau_{cl} > 0$. Finally, when the threshold is reached, but no risk of hypoglycemia exists ($\mathcal{B}_w$ becomes true while $\mathcal{B}_{hypo}$ is false), then the cumulative variable is reset to zero.

3.2.2. Glucagon quantization

Unlike the rescue carbohydrate intake, the glucagon infusion rate can be automatically administrated through a pump. However, this would require either having two independent pumps, which is very inconvenient, or a dual-chamber pump, which is still under development [22,32]. Therefore, in the short-term, glucagon is more likely to be injected manually as quantized doses via glucagon pens rather than pumps, which has already been proved useful to treat mild hypoglycemia [14]. In order to allow this possibility, a glucagon quantization strategy implements the equivalent equations to (24)–(25) of the carbohydrate quantization scheme in which z_w, $\tilde{w}$, $\mathcal{B}_w$, q_w, w, and $\underline{q}_w$ are replaced by z_v, $\tilde{v}$, $\mathbb{B}_v$, q_v, v, and $\underline{q}_v$, respectively.

3.2.3. Accommodation of quantized control actions

The quantized control actions are impulse signals that have a rapid and significant impact on glucose variation. In order to prevent the master controller from counteracting their effect, they are treated as if they were feedforward control actions, which are accommodated using the non-interacting feedforward scheme by slightly modifying the expected output variation in (4) as follows

$$\begin{aligned} y^*(s) = {} & G_u(s)u^*(s) + G_d(s)d^*(s) + \\ & + G_v(s)\tilde{v}(s)\eta_v + G_w(s)\tilde{w}(s)\eta_w \end{aligned} \tag{26}$$

where η_v and η_w are adjustable parameters that are selected so that the quantized implementation matches the performance of its continuous counterpart.

3.3. Parameter tuning

The gain κ^j of the master controller was individualized per subject according to

$$\kappa^j = 6000 \cdot \frac{\eta}{\mathrm{CR}} \tag{27}$$

where the safety attenuation factor $\eta = 0.7$ was selected as suggested in [23]. Simulations showed that a value of $\alpha = 8\ \mathrm{min}^{-1}$ leads to good disturbance rejection performance without introducing too much noise into the control signal. The reference prefilter is tuned with $\alpha_r = 30\ \mathrm{min}^{-1}$, which provides a fast enough tracking performance. The set-point, $G_{ref}(t)$, may be time-varying but is fixed to 110 mg/dL for simplicity. This set-point value can be found in most commercial systems [33]. Regarding the quantization schemes, carbohydrate supplements are typically available as 15 g snacks; thus, $q_w = 15$ g was selected. For the glucagon recommendations, a value of $q_v = 0.08$ mg was chosen based on [29]. The thresholds that trigger recommendations are selected as one-third of the corresponding quantized doses, that is, $\underline{q}_w = 5$ g, and $\underline{q}_v = 0.03$ mg, while the clearing time constant was set to $\tau_{cl} = 30$ min. The remaining parameters, namely, the increased gain factor in counter-regulation mode k_{cr}, the coordinated control switching threshold factor γ, and the prandial bolus attenuation factor ν were optimized in simulations for each patient, and finally adjusted to their mean values, leading to the population values $k_{cr} = 3.9$, $\gamma = 1.33$, and $\nu = 0.8$.

Table 2
Prescribed morning exercise (ME) and evening exercise (EE) daily routines for the validation scenario. Onset time is relative to a main meal: before breakfast (BB), after breakfast (AB) or before dinner (BD).

	Intensity (% VO2 max)	Duration (min)	Onset (min)	Probability (–)
ME1	No Exercise			0.5
ME2	66–80	15–45	60–90 (BB)	0.25
ME3	50–65	45–90	15–45 (AB)	0.25
ME1	No Exercise			0.75
ME2	66–80	15–45	60–90 (BB)	0.25

The training scenario consisted of three daily meals, randomized in size and time following normal distributions. Meals were 45 g, 75 g and 65 g on average, with a coefficient of variation of 10%, delivered at 7 h, 14 h and 21 h on average with a standard deviation of 20 min. Also, one exercise session per day was prescribed at 15 h on average with a large standard deviation of 120 min. The exercise intensity and duration were also randomized with an average of 50% maximal oxygen consumption (VO2 max) and 60 min, respectively, and a coefficient of variation of 10% in both cases. It should be remarked that the validation scenario, described in the following section, is more realistic and significantly different from this training scenario.

4. In silico validation

The robustness of the proposed controller under a challenging scenario with meals and exercise is assessed in this section. The controller can be configured as a hybrid (with meal announcement) or fully-autonomous (without meal announcement) system. Furthermore, it allows the patients to select the way hypoglycemia is counteracted (rescue carbohydrates or glucagon), possibly having one preferred option and letting the other one as a backup. In addition, glucagon can be delivered in quantized doses or continuously, which is more of a technical aspect depending on the availability of a glucagon pump than on the user's preference.

4.1. Simulation environment

The six configurations of the controller described above were simulated for the ten virtual adults of the UVa/Padova simulator [24], which was extended to include the following sources of variability: the nominal values of the parameters meal absorption rate and carbohydrate bioavailability of the meal absorption model in [24] were varied per meal with a uniform distribution of ±30% and ±10% respectively; the nominal values of the parameters describing the insulin pharmacokinetics in [24] were modified according to a uniform distribution of ±30% for each meal; the circadian variation in insulin sensitivity was represented with a 24-h period sinusoidal change with random amplitude following a uniform ±30% and random phase; and a misestimation of meal carbohydrate content was implemented following the model in [34]. The built-in noisy sensor model *dexcom25* was employed. The exercise effect on glucose was implemented by increasing insulin sensitivity [35], which affects the insulin-dependent glucose uptake.

To assess the robustness of the proposed controller against meals and exercise events, a new validation scenario, different from the one utilized for training purposes, was configured. The meal events were generated to match the distributions reported in [36], which are based on real data gathered in free-living conditions. Each day consists of three main meals, which are complemented with snacks random in

Table 3
Performance metrics for the three configurations of the proposed controller with meal announcement.

	Carbs recommendation	Glucagon continuous infusion	Glucagon recommendation
Mean CGM (mg/dL)	128.6 [123.6, 132.5]	135.7 [133.3, 140.6]	129.2 [125.4, 132.2]
CV CGM (%)	23.6 [22.8, 25.7]	23.9 [23.0, 26.1]	23.2 [22.6, 25.7]
<54 mg/dL (% time)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
<70 mg/dL (% time)	0.6 [0.4, 0.7]	0.1 [0.0, 0.5]	0.3 [0.1, 0.6]
[70, 180] mg/dL (% time)	92.8 [91.4, 94.5]	90.7 [87.1, 91.4]	93.2 [90.9, 94.7]
>180 mg/dL (% time)	6.6 [5.0, 8.1]	9.3 [8.3, 12.5]	6.7 [5.1, 8.3]
>250 mg/dL (% time)	0.4 [0.0, 1.2]	0.9 [0.2, 1.7]	0.5 [0.1, 1.2]
Insulin (U/day)	39.2 [34.5, 44.8]	41.9 [37.1, 47.2]	39.3 [34.6, 44.9]
Carbs/Glucagon (g/day or mg/day)	9.6 [4.6, 12.9]	0.7 [0.5, 0.7]	0.1 [0.1, 0.1]
Ex. activations[a]	23.3 [15.0, 38.3]	90.0 [86.7, 93.3]	43.3 [26.7, 65.0]
Carbs/Glucagon[b] (g or mg)	15.0 [15.0, 19.3]	0.1 [0.1, 0.2]	0.2 [0.1, 0.2]
Meal Activations[a] (% events)	4.6 [3.5, 6.2]	99.2 [96.2, 100.0]	3.1 [3.1, 6.2]
Carbs/Glucagon[b] (g or mg)	15.0 [15.0, 18.8]	0.1 [0.1, 0.1]	0.1 [0.1, 0.2]

Metrics are presented in the form of median [25th percentile, 75th percentile].
[a] Percentage of exercise/meal events requiring counter-regulatory actions within 3 h after the event.
[b] Amount of counter-regulatory actions delivered within 3 h after the event.

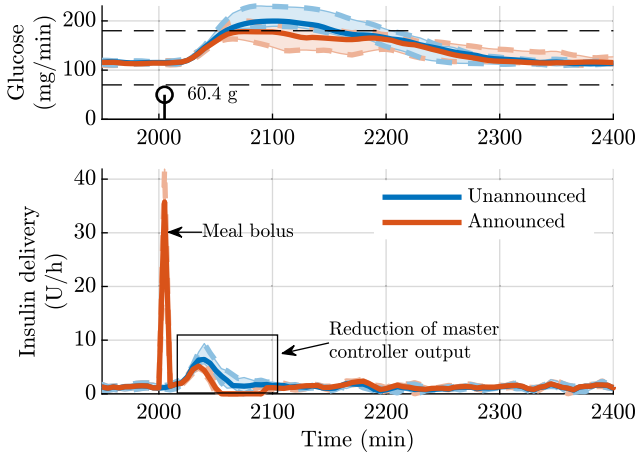

Fig. 2. Population plot illustrating the non-interacting scheme. Glucose concentration and meal size (represented by a circle) are shown at the top and insulin infusion at the bottom. Thick lines correspond to median values of the ten virtual adults and shaded areas represent the 25th and 75th percentiles.

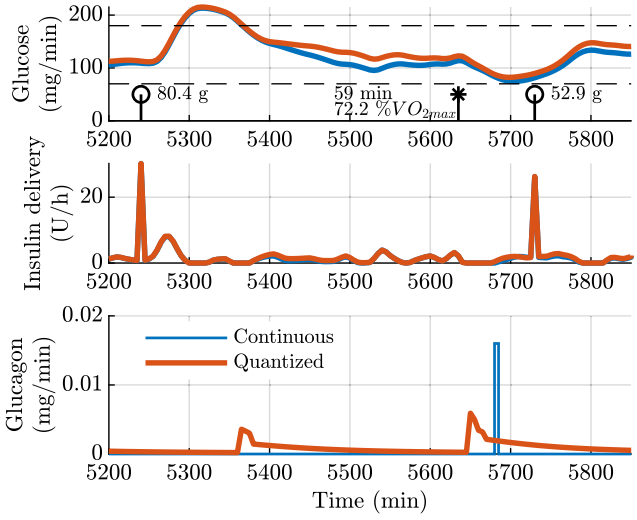

Fig. 3. Illustration of continuous vs quantized glucagon delivery. Glucose concentration, meal size (circles), and exercise (asterisk) descriptors – duration, start time, and intensity – are shown at the top; insulin infusion rate in the middle; and glucagon infusion rate at the bottom.

number, size and time, according to the statistical distributions reported therein. Regarding exercise, in order to challenge the controller, the exercise routines reported in Table 2 were designed, including three morning exercise (ME) and two evening exercise (EE) sessions. Both mid-low (50%–65% VO2 max) and mid-high (66%–80% VO2 max) intensity sessions were considered. For each day, a morning session and an evening session was randomly chosen according to the probabilities reported in Table 2. The probability of choosing "No exercise" was larger to avoid having many days with two exercise sessions, which is unrealistic. The exact exercise onset time, duration and intensity were assigned randomly as a uniform distribution within the bounds reported in Table 2.

Using the procedure described above, a challenging scenario has been generated with daily consumption of 194.8 [122.8, 231.5] g/day, up to six meals per day, up to two exercise sessions per day, some of which are close to the nocturnal fasting periods. Nevertheless, some limitations should be noted. Regarding the exercise simulation, there is room for improvement by including insulin-independent effects on glucose consumption or implementing other exercise typologies such as resistance or high-intense interval exercise. Also, the distribution of the snacks could be improved by considering other variables such as the fasting period or the amount of carbohydrates consumed in the previous meal [37].

4.2. Overall performance

The performance of the controller configurations was evaluated through the CGM mean and coefficient of variation (CV), percentage of time in, below, or above range, and daily consumption of insulin, glucagon, and carbohydrates. In addition, to gain more insight into the postprandial and postexercise periods, the following metrics were calculated: the percentage of meals and exercise requiring a counter-regulatory control action within the three first hours after the meal or exercise onset, and the glucagon, or carbohydrate consumption in that period.

As shown in Tables 3 and 4, all controller configurations can handle meals and unannounced exercise events, leading to population metrics within the recommended targets defined by [38]. The individual metrics are also within the recommended targets except for subject 7 in the meal-announcement-free configurations, since its time in range is 5% points below the recommended target. Hypoglycemia episodes are sparse in all the configurations. Regarding counter-regulatory control actions usage, in the configuration with glucagon, the mean daily dose is lower than 1 mg, a threshold above which subjects are likely to

Table 4
Performance metrics for the configurations of the proposed controller without meal announcement.

	Carbs recommendation	Glucagon continuous infusion	Glucagon recommendation
Mean CGM (mg/dL)	141.3 [134.6, 146.0]	143.1 [138.3, 148.6]	141.3 [135.1, 146.3]
CV CGM (%)	27.3 [26.2, 30.7]	27.0 [26.1, 30.6]	27.2 [26.1, 30.6]
<54 mg/dL (% time)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
<70 mg/dL (% time)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
[70, 180] mg/dL (% time)	84.3 [80.7, 88.9]	83.0 [79.2, 87.5]	84.3 [80.8, 88.6]
>180 mg/dL (% time)	15.7 [10.9, 19.3]	17.0 [12.5, 20.8]	15.7 [11.4, 19.2]
>250 mg/dL (% time)	1.9 [1.4, 3.3]	2.0 [1.5, 3.9]	1.9 [1.3, 3.5]
Insulin (U/day)	36.8 [32.3, 41.0]	38.2 [33.0, 42.4]	36.8 [32.4, 41.0]
Carbs/Glucagon (g/day or mg/day)	3.2 [1.1, 5.6]	0.2 [0.1, 0.4]	0.1 [0.0, 0.1]
Ex. activations[a]	13.3 [1.7, 20.0]	90.0 [86.7, 93.3]	30.0 [8.3, 43.3]
Carbs/Glucagon[b] (g or mg)	15.0 [15.0, 15.0]	0.1 [0.1, 0.1]	0.1 [0.1, 0.2]
Meal Activations[a] (% events)	0.0 [0.0, 2.7]	97.7 [86.2, 100.0]	1.5 [0.0, 3.1]
Carbs/Glucagon[b] (g or mg)	18.8 [15.0, 22.5]	0.0 [0.0, 0.1]	0.1 [0.1, 0.2]

Metrics are presented in the form of median [25th percentile, 75th percentile].
[a] Percentage of exercise/meal requiring counter-regulatory actions within 3 h after the event.
[b] Amount of counter-regulatory actions delivered within 3 h after the event.

experience nausea. The mean daily dose in the carbohydrate configuration is similar to that of other controllers in the literature evaluated under equivalent in silico scenarios [19–21]. Furthermore, the counter-regulatory control actions are delivered when the hypoglycemia risk is high, as supported by the fact that more than 10%, in median, of exercise events are followed by a glucagon or carbohydrate suggestion (Tables 3 and 4). In contrast, less than 1.6% of meals require a counter-regulatory recommendation. Remark that, in the case of continuous glucagon administration, glucagon was delivered after most meal events. However, the total amount administered in the postexercise period is usually higher than in the postprandial period, especially for the unannounced configurations.

4.3. Differences among configurations

The purpose of the following analysis is threefold: (1) to quantify the performance gain achieved by the hybrid configuration over the announcement-free configuration, (2) to evaluate the effect of the glucagon administration mode (continuous vs. quantized), and (3) to compare the two types of quantized counter-regulation (carbohydrate vs. glucagon). To this end, first, a multilevel model was fit for each metric using the virtual subject identifier as a random intercept. Gaussian family models were fitted with the `lme4` [39] package in R (version 3.4.1, [40]), while beta and zero-inflated beta regressions were conducted with `glmmTMB` [41]. Then, estimated average contrasts, i.e., the difference in means estimated by the statistical models, were derived from the model predictions using the package `marginaleffects` [42].

As shown in Table 5, the most considerable differences in performance occur between the hybrid and meal-announcement-free configurations. The price to pay for removing the burden of meal announcement is a statistically significant increase in the glucose mean (+11.63 mg/dL), the CGM coefficient of variation (+3.92 %), the percentage of time above 180 mg/dL (+8.48 %) and the percentage of time above 250 mg/dL (+2.18 %) as well as a decrease in the time-in-range (−8.10 %). On the other hand, the hybrid configuration increases insulin consumption (+3.08 U/day) compared to the meal-announcement-free operation. Although this additional insulin delivery is related to a statistically significant increase in the percentage of time below 70 mg/dL compared to the unannounced configuration, the estimated increase is 0.33%; thus, it will have a relatively small clinical impact. The non-interacting scheme played a role in this result since it mitigates insulin over-delivery by reducing the master controller output when a bolus is administrated, as illustrated in Fig. 2. Lastly, a statistical significant increase in glucagon and carbohydrate consumption is also observed for the hybrid case, which may indicate that the announced configuration compensates an insulin overdelivery with the counter-regulatory actions. Note, however, that the increase in the counter-regulation consumption is small.

Regarding the glucagon administration method, delivering it as recommendations leads to a statistically significant reduction in glucagon consumption (−0.32 mg/day), the mean CGM (−5.40 mg/dL), and the percentage time above 180 mg/dL (−2.37%), compared to its delivery as a continuous infusion. However, the reduction in the amount of glucagon delivered is not associated with a statistically significant increase in the percentage of time below 70 mg/dL, which motivates the use of this administration method not only for manual injections with a pen but also for automatic delivery with a pump. An illustration of the quantization effect is illustrated in Fig. 3. It can be observed that the configuration using continuous infusions of glucagon (orange line) administers glucagon within the postprandial of the first meal when the risk of hypoglycemia is low. Conversely, the configuration that quantizes glucagon only applies this control action when the hypoglycemic risk is higher, that is, after the exercise that occurs at 5635 min.

Finally, regarding the differences between glucagon and carbohydrate recommendations, most of the estimated average contrasts are not statistically significant, as observed in Table 5. Therefore, both counter-regulation suggestions perform similarly.

5. Conclusions

A flexible-structure dual-hormone control algorithm for artificial pancreas systems was presented in this work. The results of the in silico study indicate that all configurations can handle meals, announced or not, and unannounced exercise, yielding metrics compliant with recommended targets in clinical guidelines. When meals are announced, the percentage of time in hyperglycemia is reduced with only a slight increase in the percentage of time below 70 mg/dL, negligible from a clinical perspective. Moreover, no relevant differences were found between using glucagon or carbohydrates as counter-regulatory action when administrated in quantized doses, which allows the patients to select the way hypoglycemia is counteracted (rescue carbohydrates or glucagon), possibly having one preferred option and letting the other one as a backup.

Future work should develop techniques for adapting the free-tuning controller parameters to handle other sources of disturbances not considered in this work, such as the effect of macronutrients other than

Table 5
Average marginal contrasts for the validation.

	Unannounced vs Announced	Glucagon infusion vs Glucagon recommendations	Carbs recommendations vs Glucagon recommendations
Mean CGM (mg/dL)	11.3 (9.93, 13.3)*	5.4 (3.3, 7.5)*	−0.55 (−2.64, 1.54)
CV (%)	3.92 (3.59, 4.25)*	0.13 (−0.27, 0.53)	0.10 (−0.30, 0.50)
<70 mg/dL (% time)	−0.33 (−0.41, −0.25)*	−0.07 (−0.17, 0.03)	0.10 (−0.03, 0.22)
[70, 180] mg/dL (% time)	−8.10 (−8.93, −7.27)*	−2.31 (−3.38, −1.24)*	0.14 (−0.88, 1.16)
>180 mg/dL (% time)	8.48 (7.64, 9.32)*	2.37 (1.29, 3.46)*	−0.22 (−1.26, 0.81)
>250 mg/dL (% time)	2.18 (1.91, 2.46)*	0.23 (−0.16, 0.62)	0.03 (−0.36, 0.42)
Insulin (U/day)	−3.08 (−3.55, −2.62)*	1.52 (0.96, 2.09)*	−0.06 (−0.63, 0.51)
Carbs (g/day)	−5.5 (−8.3, −2.6)*	–	–
Glucagon (mg/day)	−0.18 (−0.27, −0.08)*	0.32 (0.21, 0.42)*	–
Ex. activations[a] (% events)	−0.12 (−0.19, −0.06)*	0.50 (0.42, 0.56)*	−0.15 (−0.24, −0.07)*
Carbs[b] (g)	−2.3 (−4.5, −0.15)*	–	–
Glucagon[b] (mg)	−0.07 (−0.13, −0.02)*	−0.04 (−0.09, 0.02)	–

Estimated difference in means and 95% confidence interval are shown.

* Statistical significance of the difference (p-value <0.05).

[a] Percentage of exercise events that triggered the use of counter-regulatory actions within 3 h after the event.

[b] Amount of counter-regulatory actions delivered within 3 h after the event.

carbohydrates, anaerobic or high-intense interval exercise, or hormonal changes. Despite the limitations in the simulation environment, the control algorithm presented in this work has been evaluated under challenging conditions (e.g., up to six meals or up to two exercise sessions in a day, exercise sessions closed to meals, and exercise sessions near nights). The acceptable results obtained under these conditions motivate future validations of the controller in clinical trials.

CRediT authorship contribution statement

Ricardo Sanz: Conceptualization, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Iván Sala-Mira:** Conceptualization, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Clara Furió-Novejarque:** Writing – original draft, Writing – review & editing. **Pedro García:** Conceptualization, Methodology, Supervision. **José-Luis Díez:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision. **Jorge Bondia:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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