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Postprandial response improvement via safety layer in closed-loop blood glucose controllers

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ABSTRACT

Traditional type 1 diabetes therapies are prone to show poor glucose regulation especially in the postprandial period owing to both physiological and technological limitations. Although a closed-loop controller for glucose regulation has to be tuned to minimize the postprandial excursion and avoid late hypoglycemia, the intrinsic limitations of the problem lead to a trade-off between postprandial peak and late hypoglycemia risk. This paper reveals through an intensive in-silico study with multiple controller tuning combinations that a novel safety layer for glucose controllers, the so-called SAFE loop (Revert et al., 2013), not only reduces the hypoglycemia events but also allows reducing the postprandial glucose excursion, thus breaking the implicit trade-off present in single controllers. The SAFE outer loop monitors the estimated amount of insulin on board, and modifies the control action if it is close to a unique constraint which can be adjusted with clinical criteria. A very challenging test scenario is here implemented including the rate of blood glucose appearance from intakes of mixed meals, diurnal and day-to-day time-varying metabolic changes, inherent drawbacks in sensor and actuator, and other realistic conditions. The results show a significant reduction of hypoglycemia events when SAFE is added, regardless the closed-loop glucose controller, together with a potential postprandial response improvement.

1. Introduction

Treatments with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) have been widely used by type 1 diabetes patients to keep their glucose near normoglycemia. Insulin pumps used for CSII therapy have shown more advantages over MDI allowing a more comfortable lifestyle. Modern insulin pumps incorporate bolus advisors that help patients to calculate prandial boluses, a customizable basal insulin flow to daily sensitivity changes, preventive alarms, etc. [3,4]. Similarly, the increasingly reliable continuous glucose monitoring (CGM) systems has enabled the development of more corrective actions improving the performance of these open-loop treatments. Even so, imprecise estimation of the amount of carbohydrates ingested, metabolic changes in the glucose-insulin system, stress, physical activity, etc., are prone to cause hypoglycemia [2,6,7].

The concept of artificial pancreas (AP) arises to overcome drawbacks from conventional therapies. This consists of a CGM system connected to an automatic closed-loop controller responsible for continuously calculating an appropriate dose to infuse through an insulin pump. However, current CGM systems are not reliable enough to ensure an accurate glucose measurement due to large drift, lags and bias errors. Moreover, the subcutaneous route used by the insulin pumps involves a serious lag in the insulin action.

Main concern in scientific community has focused on developing safe and robust closed-loop glucose controllers. To this end, a wide range of control approaches have been proposed, including model predictive control (MPC) [8–10], $\mathcal{H}_\infty$ [11,12], or sliding mode control [13,14] Another main research line is based on PID control techniques widely used in industry, well-established, reliable, having few parameters and intuitive tuning [15–17]. Readers are referred to [18,19] for a comprehensive state of the art of the topic. On the other hand, only few of these approaches, mainly MPC and PID techniques, have been assessed in clinical trials, particularly to perform glucose control in

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conditions as overnight, postprandial, ambulatory, and including consumption of alcohol or exercise among others [8,20]. Regarding the postprandial response, a single control loop for the AP has to be tuned to: (1) minimize the postprandial excursion and (2) avoid late hypoglycemia. Meal compensation through semi-closed control schemes allows for better performance than fully automatic ones. Limitations related to the subcutaneous route and the large disturbance caused by the meal encourage the use of a feed-forward action combined with the feed-back controller [16,21,22].

Regardless the scheme used, the trade-off between postprandial peak and late hypoglycemia risk is one of the distinctive challenges of blood glucose control for closed-loop systems. The more aggressive the controller, the lower the postprandial peak but the higher the hypoglycemia risk and vice versa.

Several proposals mainly focused on PID and MPC control approaches have been designed in order to improve postprandial performance. For example, pole placement techniques are used to compensate for delays in the subcutaneous route implementing a negative feedback of the estimated plasma insulin in the so-called ePID-IFB algorithm [23,24]. In [17], the PID controller is switched off just before the ingestion with a restarting time calculated as function of the current blood glucose concentration and its corresponding rate of change. In MPC approaches, risk management strategies, auto-tuning nonlinear strategies, model individualization or meal compensation have been proposed [26,25]. In the same way, constraints based on insulin-on-board (IOB) have been incorporated to the optimization algorithm of an MPC, which needs to be shaped as function of the meal size and the current glucose measurements [27,28].

Recently, a novel safety scheme based on sliding mode reference conditioning technology has provided a new approach to prevent hypoglycemia events, both for fully closed-loop control (the so-called Safety Auxiliary Feedback Element, SAFE [1]) and for hybrid configurations (the hybrid adaptive PD controller [29]). This safety layer employs an IOB estimation along with a flexible constraint which can be set based on individual parameters. According to its mathematical basis, the variable structure systems and the sliding mode control [30], the SAFE algorithm can be applied to any practical closed loop controller and used to improve their response in a safe way.

In this paper, the SAFE algorithm is revisited and extensively evaluated against a number of control schemes currently used by researchers in the Artificial Pancreas field. Unlike the precedent study [1], in this work we used a single IOB limit to reduce the risk of late postprandial hypoglycemia. This limit is related to the upper IOB constraint and its value is considered constant here. This assumption greatly simplifies the process of tuning the algorithm, which can be changed intuitively with medical criteria. A procedure based on common clinical practices to determine the IOB limit is used here. Additionally, in this work a more realistic simulation scenario including different types of uncertainties and disturbances is implemented. It includes estimated profiles of blood glucose rate of appearance from mixed meals data, diurnal and day-to-day variations in insulin sensitivity and insulin absorption, controller mistuning, discrete measurement and actuation, and sensor errors. Therefore the results obtained here provide increased impact than those of preliminary investigations, and allow observing the performance potential that has the method in realistic circumstances. The results obtained in this paper present the SAFE approach not merely as a safety net against hypoglycemia but also as a useful tool for re-tuning the inner controller in a safe way towards an overall improvement of the postprandial response. It is shown that the method not only reduces the hypoglycemia events but also allows reducing the postprandial glucose excursion.

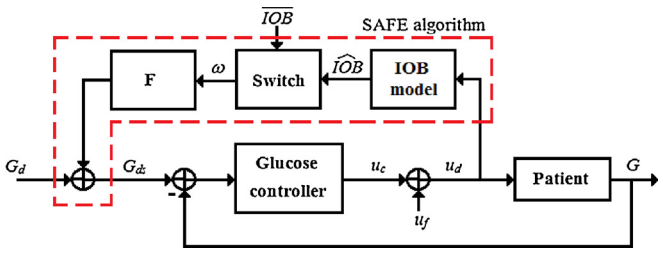

Fig. 1. Basic scheme of a glucose control loop with the SAFE algorithm.

2. The SAFE method

In this section, we briefly present the method to be refined.[1]

Fig. 1 presents a block diagram of a general glucose control loop to which the SAFE layer has been added. In the main control loop, the control action u_c is the pump's insulin infusion rate, whereas u_f represents the feed-forward action of priming bolus in meal announcement schemes. The glucose controller can be of any type, even nonlinear. For simplicity, the controller is assumed biproper (i.e., with a direct path from the error to the control action), which is of practical significance.

The SAFE algorithm implements an outer safety loop for glucose control with the main objective of reducing the number and severity of postprandial hypoglycaemic events. The algorithm automatically adjusts the desired glucose reference G_d to a safety reference G_{d_S} when the residual insulin in the subcutaneous tissue, the *IOB*, exceeds a given upper limit $\overline{IOB}$. That is, the outer control loop is only active when the *IOB* changes to undesirable values beyond the imposed constraints.

As the *IOB* is inaccessible, it must be estimated. From the estimated $\widehat{IOB}$, a switching law is defined to generate the correct signal for the glucose reference G_d, which prevents surpassing $\overline{IOB}$. The main advantage of this approach is that it is applicable to any main control loop controller and thus provides a generalised method to address the over-reaction problem. The following paragraphs describe how the switching function of the SAFE layer is implemented in this study.

2.1. Insulin on board estimation

As already mentioned, the amount of administered insulin that is still active in the body is also known as the insulin on board. IOB estimation is used by smart pumps to prevent from excessive insulin stacking, particularly when boluses are given close together [5]. An individualization of IOB estimation is usually characterized by the duration of insulin action (DIA), a parameter that clinicians are used to tune when setting up insulin pumps [4].

Here, the IOB estimation is represented by a two-compartment dynamical model [31], although any of the published insulin absorption models (see for instance [32,33]) could have also been used:

$$\begin{aligned} \frac{dC_1}{dt}(t) &= u_d(t) - K_{DIA}C_1(t) \\ \frac{dC_2}{dt}(t) &= K_{DIA}(C_1(t) - C_2(t)) \\ IOB(t) &= C_1(t) + C_2(t) \end{aligned} \tag{1}$$

where C_1 and C_2 are the two compartments and $u(t)$ is the insulin dose. The constant K_{DIA} is tuned for each patient so as model (1) replicates its corresponding DIA. Table 1 shows the corresponding values of K_{DIA} for several DIA values.

[1] The reader is referred to [1] for further details.

Table 1
IOB model parameter K_{DIA} (min^{-1}) for different durations of insulin action.

DIA (h)	2	3	4	5	6	7	8
$K_{DIA} \times 10^{-3}$	39	26	19.5	16.3	13	11.3	9.9

2.2. Switching law

Only an upper constraint $\overline{IOB}$ for *IOB* is considered as the main objective to mitigate the problem of postprandial hypoglycaemic incidence. To fulfil this constraint, the following switching law is proposed.

$$w(t) = \begin{cases} w^+ & \text{if } \sigma(t) > 0 \\ 0 & \text{otherwise,} \end{cases} \tag{2}$$

with

$$\sigma(t) = IOB - \overline{IOB} + \tau(\dot{IOB} - \dot{\overline{IOB}}) \tag{3}$$

where τ can advance the reference conditioning as a function of the rate of change of *IOB*; for τ small the comparison is performed with the $\overline{IOB}$, for τ large the comparison is performed in advance.

When the upper bound is violated (or about to be violated), the w switches to $w^+ \neq 0$ to increase the safety reference G_{d_S} and reduce the control action u_c, with the aim of preventing hypoglycaemia due to excess insulin.

The resulting discontinuous signal w during the *IOB* limitation is smoothed out by the first-order filter represented in the block F before being added to G_d to produce G_{d_S}.[2]. The reference returns to G_d once the *IOB* is under the safety level (as the auxiliary signal equals zero in such a case, i.e. $w = 0$).

2.3. Determination of insulin-on-board limit

For the sake of this study, the determination of the $\overline{IOB}$ is based on open-loop postprandial tests [29]. A complete description of this procedure is beyond the scope of the present paper [34]. We applied the following postprandial open-loop clinical test:

1 Achieve an initial condition of preprandial blood glucose concentration between 80 and 120 mg/dL without insulin bolus administration during the previous 5 h.
2 Administer a meal with 40–100 g of carbohydrates together with an insulin bolus.
3 Observe blood glucose evolution during the following 10 h,
- If minimum glucose is outside the set (70,90), then repeat step 2 adjusting the bolus. Alternatively the correction factor, for a retrospective calculation of bolus, can be used.
- Else, use as $\overline{IOB}$ the IOB value obtained at time: $\frac{CHO+80\,g}{60\,g/h}$, where *CHO* (g) is the amount of carbohydrate intake. This time can take values between 2 and 3 h according to amounts of *CHO* between 40 and 100 g.

The open loop tests performed to obtain this method showed a low dependency of the $\overline{IOB}$ with the meal size used. In tests using a 40 g meal, the best $\overline{IOB}$ was found 2 h after, while in tests using a 100 g meal, the best $\overline{IOB}$ was found 3 h after. Both $\overline{IOB}$ were found to be almost the same value [34]. Note that unlike the approach presented in [1], the $\overline{IOB}$ derived in this way is almost independent of the meal size used. This encourages implementing a constant value of $\overline{IOB}$ in order to evaluate the robustness using a single upper limit,

[2] Note that the filter F has been replaced with respect to [1] as we assume G_d is constant.

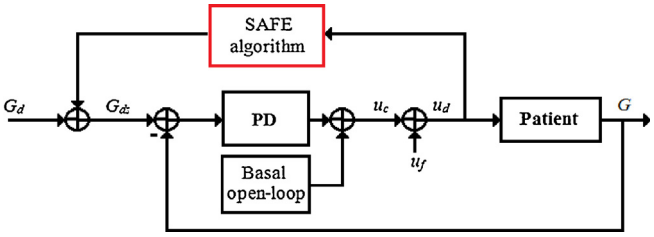

Fig. 2. PDBasal hybrid scheme implementing the SAFE method.

which simplifies the tuning procedure. However, the possibility to compute a time-varying $\overline{IOB}$ could be investigated.

It is also worthy noting that the bound $\overline{IOB}$, calculated as suggested before or in any other way, can be intuitively adjusted with medical criteria according to the closed-loop response exhibited by the patient. For instance, the physician should decrease $\overline{IOB}$ in the case of frequent hypoglycemia, or increase it if the controller action is too conservative or the restriction is active during too long time.

3. Control schemes and testing scenario

The evaluation about the significance of the SAFE layer in the control performance includes the main glucose controllers implemented for artificial pancreas in clinical trials. Two PID-like glucose controllers and a basic MPC controller with and without the SAFE method are addressed in this study.

3.1. Semiautomated PID hybrid control

The first controller is the classical PID algorithm, in which the integral term is replaced by the basal insulin from the open-loop therapy, and a prandial bolus defined by the patient's insulin-to-carbohydrate (*I:CHO*) ratio and the corresponding meal size is implemented. This scheme is referred to as the PDBasal hybrid controller, as shown in Fig. 2.

3.2. PID with insulin feedback

The second controller is the well established fully closed-loop PID with insulin feedback (PID-IFB) algorithm presented in [24], see Fig. 3. The control law is as follows:

$$\begin{aligned} u_d(t) &= u_c(t) - \gamma I_p(t) \\ u_c(t) &= k_p \left[e(t) + \frac{1}{\tau_I} \int e(t)dt + \tau_D \frac{de(t)}{dt} \right] \end{aligned} \tag{4}$$

where γI_p is the feedback component. The estimated plasma insulin I_p is a two-compartment model assumed for the pharmacokinetics of insulin, with a bi-exponential impulse response given by:

$$I_p(t) = \frac{I_B}{K_{cl}(\tau_2 - \tau_1)}(e^{-t/\tau_2} - e^{-t/\tau_1}) \tag{5}$$

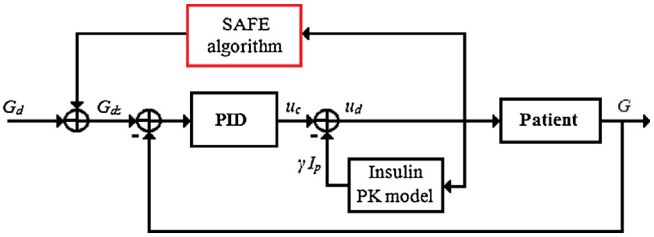

Fig. 3. PID-IFB scheme implementing the SAFE method. The prandial bolus insulin was not used in this realization.

where τ_1 and τ_2 are time constants (in minutes) associated to the subcutaneous absorption of insulin, K_{cl} is the insulin clearance, and I_B is the magnitude of the impulse (bolus) of insulin delivered at time $t = 0$.

This insulin pharmacokinetic model is represented by the following equations:

$$\frac{dL(t)}{dt} = u_d(t) - a_2 L(t)$$
$$\frac{dI_p(t)}{dt} = \frac{a_1 a_2}{K_{cl}} L(t) - a_1 I_p(t) \quad (6)$$

where u_d is the input insulin, L is an intermediate compartment, $a_1 = 1/\tau_1$ and $a_2 = 1/\tau_2$. The values for the model time constants are $\tau_1 = 55$ min and $\tau_2 = 70$ min, and for insulin clearance $K_{cl} = 1$ L/min. According to [24], the PID algorithm with insulin feedback must deliver the same insulin-infusion rate to the subject as in the case without insulin feedback (i.e., when $\gamma = 0$). Therefore, for a given controller gain selected for the case without insulin feedback, such as the nominal value given in [24], it can be adjusted by multiplying it by the factor:

$$f = \left(1 + \frac{\gamma}{K_{cl}}\right) \quad (7)$$

3.3. Linear model predictive control

A basic constrained MPC controller is based on a linear model representing the glucose-insulin system for prediction. The model in state-space is represented as follows

$$x(k+1) = Ax(k) + Bu(k)$$
$$y(k) = Cx(k) \quad (8)$$

where $x(k)$, $u(k)$, and $y(k)$ are the future states of the system, the input insulin, and the blood glucose concentration at the kth sampling instant respectively. The basic formulation of the MPC cost function in this study is defined as

$$\min_{u \in R} \left(y_s^T y_s \cdot w^y + u_s^T u_s \cdot w^u + \Delta u^T \Delta u \cdot w^{\Delta u}\right) \quad (9)$$

subject to

$$u_{\min} \le u_s(k) \le u_{\max}$$
$$\Delta u_{\min} \le \Delta u(k) \le \Delta u_{\max} \quad (10)$$

where y_s are blood glucose concentrations after subtraction of the set point, and u_s is the future insulin moves after the subtraction of the basal insulin. u_{min}, u_{max}, Δu_{min}, and $\triangle u_{max}$ denote lower and upper bounds on the insulin input and insulin increments respectively; and w^y, w^u, and $w^{\triangle u}$ are optimizations weights for the glucose concentrations, future insulin moves, and insulin increments, respectively. The size of y_s and u_s defines the prediction and control horizon implemented in the cost function respectively.

3.4. Testing scenario

A realistic and very challenging simulated scenario is created to evaluate the robustness performance of each control strategy with and without the SAFE layer. Concerns about the control algorithm as hypoglycemic protection and its consequence on patient safety are especially observed with this scenario design.

A cohort of 10 virtual patients from Dalla Man et al model [35] is subjected to individualized circadian variations in insulin sensitivity, see Fig. 4. In addition, sinusoidal day-to-day variations of 20% amplitude with 19 and 29 h period in the insulin sensitivity and in the insulin absorption respectively, were implemented. Moreover,

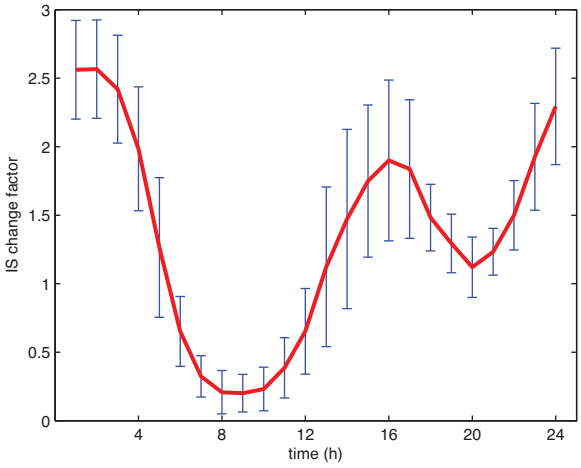

Fig. 4. Mean and standard deviation of individualized circadian variations of insulin sensitivity applied to the virtual patients cohort.

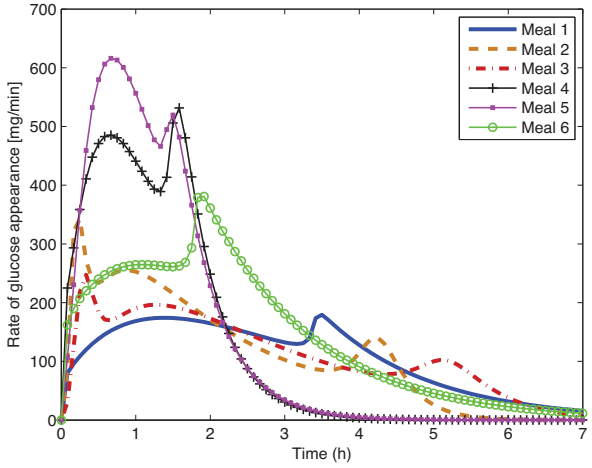

Fig. 5. Rate of blood glucose appearance of mixed meals used in simulations.

rate of blood glucose appearance profiles corresponding to six different meals from [36] were implemented in a 18-meals simulation trial per patient, for a total of 180 meal tests. The corresponding profile of the rate of blood glucose appearance for each meal used is shown in Fig. 5.

Each meal test covers a day starting at 12:00 with a preprandial glycemia near to 90 mg/dL. However the focus of the analysis is on the 8 h postprandial period. Each meal is administered three times during the simulation of the virtual patient, but under different intra-patient variability conditions (the diurnal and day-to-day variations). The simulation sampling period is 1 min. However, the control action performed to the patient is updated every 10 min. The sensor error considered is non-white, non-Gaussian proposed by [37], where an autoregressive-moving-average (ARMA) model is used along with a Johnson transformation of a unbounded system. Constrained performance of the insulin pump is included.

4. Results

4.1. Evaluation of nominal-tuning controllers performance

In order to evaluate the control performance when the SAFE layer is added, the PDBasal Hybrid and the PID-IFB controller were tuned based on default parameters values. In both cases the gain

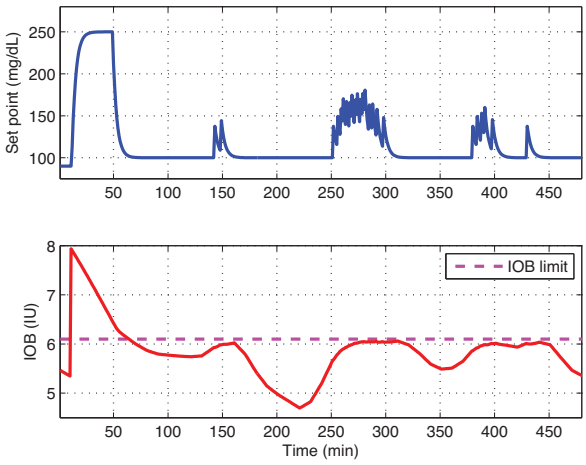

Fig. 6. Dynamic behaviour of the set point for a meal when the SAFE layer is included in the PDBasal controller. IOB estimation is also included here to show its relationship with the set point variations.

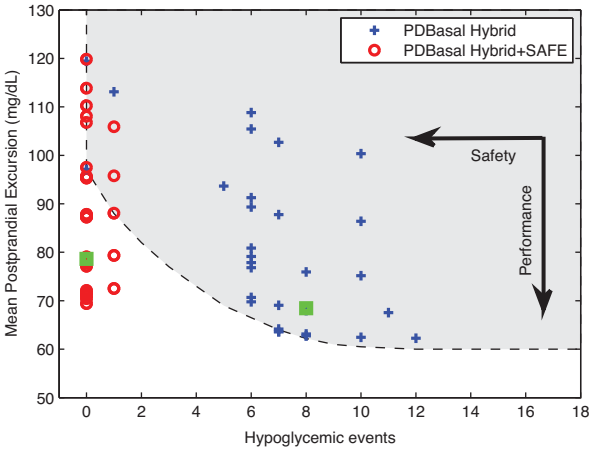

Fig. 7. Performance results on a single patient for the PDBasal Hybrid with (circle) and without (cross) the SAFE layer using several combinations of the control gain and the prandial Bolus size. The nominal performance with and without the SAFE layer are highlighted with green squares. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was tuned in proportion to the total daily dose of insulin (I_{TDD}) [15,23]:

$$K_p = \frac{60}{T_d}\frac{I_{TDD}}{1500} \tag{11}$$

where I_{TDD} was obtained using a protocol of 200 g CHO distributed in 40, 80 and 80 g at 08:00, 13:00 and 19:00 respectively.

The K_{DIA} parameter of the *IOB* estimator was derived from the *DIA* value, which was calculated following the trial described in [4]. The filter cut-off frequency of the SAFE algorithm was set to 0.25 min^{-1}. The w^+ value was set to 150 mg/dl, and τ was set to 10 min. Finally, the $\overline{IOB}$ limit was determined following the procedure described in Section 2 instead of the provisional method suggested by [1]. All relevant parameters used in the controller are listed in Table 2. Information about insulin sensitivity profile, glucose measurement errors, calorie content or the rate of glucose appearance, are not used in the controllers.

The derivative gain was set to $T_d = 90$ min for all patients in both controllers. The basal insulin profile from the open-loop control designed to counteract the variation in insulin sensitivity was used in the PDBasal Hybrid controller whereas the integral gain was set to $T_i = 450$ min and the feedback term γ was set to 5/6 in the PID-IFB algorithm.

The performance results for nominal tuning are presented in Table 3 with special focus on the number of hypoglycemia events, the mean blood glucose excursion and the mean blood glucose.

Note the high number of hypoglycaemic events found with the nominal tuning of the controllers, which reveals that these suggested tunings are not sufficient for a proper glucose control under the demanding conditions imposed by the testing scenario. The addition of the SAFE layer results in enhanced performance of hypoglycaemic events despite a moderate increment in the mean blood glucose excursion and the mean blood glucose in both controllers.

On the other hand, an example of the relationship between the dynamic behaviour of the set point with the IOB estimation, when the SAFE layer is added, is shown in Fig. 6. In this example, a progressive change in the set point from 100 to 250 mg/dL is observed at the beginning of the meal test. This occurs because the prandial bolus used with the PDBasal controller, causes the limit $\overline{IOB}$ of this virtual patient is exceeded. However, once the IOB estimation returns to safety values, the set point variation, which is produced by the SAFE method and is the minimum needed, prevents this limit is exceeded again. The set point does not change if the limits on IOB estimation are met according to the switching law (2) and (3).

Fig. 6 also shows a rebound effect on the variation of set point, which appears at different times of the postprandial response. This is because the rate of blood glucose absorption of the mixed meal has a growing profile of double peak, see Fig. 5. This behaviour results in a change of the set point, through the SAFE method, when necessary.

The change made by the SAFE method to the set point can be softened using a smaller simulation sampling period, there is no limit to this as the whole computation is performed by software.

4.2. Performance evaluation with several tuning controller combinations

Extensive controller tunings were evaluated for the PDBasal Hybrid and the PID-IFB to look for the best achievable performance with and without the SAFE layer in terms of hypoglycemia reduction in the first place and minimum postprandial excursion in the second place. We will refer to the resulting tuning as the "safest" tuning. Based on the preceding nominal-tuning, the PDBasal Hybrid controller gain K_p was changed to −100%, −75%, −50%, −25%, 0%, +25%, +50%; whereas the *I:CHO* was changed to 0%, 35%, 70%, 100%, 125% of the full pre-bolus. Moreover, the PID-IFB controller gain K_p was changed to −60%, −40%, −20%, 0%, +20%, +40%, +60%; whereas the γ term was changed to −60%, −30%, 0%, +30%, +60%. Therefore, 35 different tuning combinations were evaluated in each case with and without the SAFE layer.

Figs. 7 and 8 illustrate the resulting number of hypoglycaemic events vs. the mean excursion obtained for each tuning combination with and without the SAFE layer in a single FDA-accepted patient. These illustrative cases graphically show how the SAFE algorithm can be used to improve both safety and postprandial performance (in the direction indicated by the arrows), allowing to break the inherent trade-off between these requirements. Indeed, based on the results obtained for all the virtual patients, we assumed that the red circles below the shaded area are not reachable using the same controller without SAFE. The edge of the shaded area is a logic assumption that represents the estimated achievable performance for the controllers without SAFE.

Table 4 displays the safest performances for each patient for the PDBasal Hybrid and the PID-IFB controller. The mean blood glucose excursion and the mean blood glucose are listed for each case. The corresponding number of hypoglycaemic events is omitted as it is zero in all cases. Note that in the case of PDBasal Hybrid controller,

Table 2
Controller and other relevant parameters.

Patient	1	2	3	4	5	6	7	8	9	10
I_{TDD} (IU)	51.2	56.4	57.7	33.2	68.9	54.6	42.2	43.4	59.7	63.2
K_p (IU/h per mg/dL)	0.0227	0.0250	0.0256	0.0147	0.0306	0.0242	0.0187	0.0193	0.0265	0.0281
K_{DIA} (min^{-1})	0.0122	0.0315	0.0147	0.0113	0.0122	0.0122	0.0147	0.0122	0.0099	0.0113
I:CHO (IU/g)	0.0833	0.0833	0.0750	0.0333	0.1166	0.0500	0.0250	0.0550	0.1166	0.1250
$\overline{IOB}$ (IU)	6.1	1.9	5.7	3.9	7.8	6.1	3.8	5.3	8.9	8.1

Table 3
Performance result of PDBasal Hybrid and PID-IFB with and without the SAFE layer using the nominal-tuning. Excursion and mean values are in mg/dL.

Patient	PDBasal Hybrid						PID-IFB					
	With SAFE			Without SAFE			With SAFE			Without SAFE		
	Hypos	Excursion	Mean	Hypos	Excursion	Mean	Hypos	Excursion	Mean	Hypos	Excursion	Mean
1	1	64.6	120.1	10	60.2	102.3	0	74.2	129.1	7	72.4	117.0
2	0	52.0	118.6	6	39.7	99.8	0	87.2	141.2	3	72.0	115.4
3	0	68.7	115.6	9	54.7	94.4	3	107.8	136.4	8	93.9	109.1
4	0	67.0	121.7	8	46.4	98.1	3	102.5	141.2	12	87.6	107.9
5	0	63.1	111.3	6	51.1	94.5	1	90.6	125.4	6	86.7	111.2
6	0	69.6	123.1	8	46.2	92.7	3	111.8	149.6	10	96.3	103.6
7	0	63.5	123.4	8	41.2	95.8	1	96.5	147.5	9	74.8	108.5
8	0	62.1	113.5	12	54.2	94.4	0	75.1	122.2	6	72.7	109.8
9	1	121.7	144.2	18	108.6	111.5	0	134.9	151.5	10	129.3	124.3
10	0	78.6	120.0	8	68.4	100.0	1	108.1	133.1	7	103.1	114.4
Mean	0.2	71.1	121.1	9.3	57.1	98.4	1.2	98.8	137.7	7.8	88.8	112.1

open-loop combinations (K_p changed to −100%) are included in the results and they lead to the lowest excursions for some patients when SAFE is not included. Therefore, the postprandial excursion improvement due to SAFE addition is even greater to the one of Table 4 when only hybrid combinations (including a closed-loop gain different from zero) are compared.

An improved performance is achieved in general not only for hypoglycaemic events but also for the mean blood glucose excursion and the mean blood glucose when the SAFE layer is added to the controllers. This is observed in the mean values of Table 4.

A particular case is found for the patient two under the PID-IFB controller, where the SAFE layer leads to a greater glucose excursion. This is related to the extremely low value of $\overline{IOB}$ set for this patient via the procedure suggested in Section 2, which is neither unique nor infallible but it is just a starting point for further adjustments based on medical criteria. Indeed, the glucose excursion can be easily reduced for this patient by gradually increasing $\overline{IOB}$ without producing hypoglycaemic events.

Results suggest that the SAFE layer can improve the performance of control algorithms obtained in Section 4.1 using a different tuning from default. The method to get this new tuning in a systematic way could be investigated later.

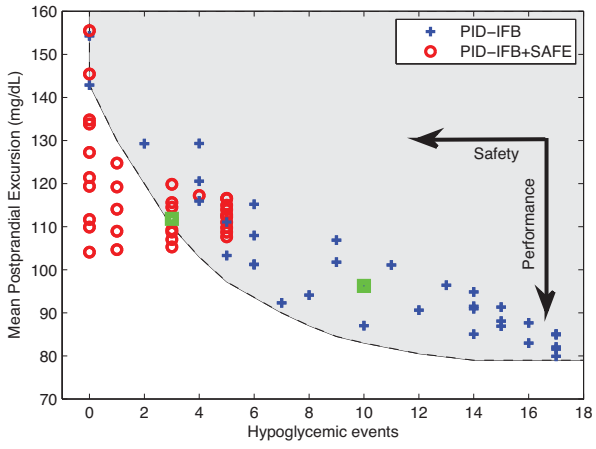

Fig. 8. Performance results on a single patient for the PID-IFB algorithm with (circle) and without (cross) the SAFE layer using several combinations of the control gain and the insulin feedback term γ. The nominal performance with and without the SAFE layer are highlighted with green squares. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.3. SAFE in other control schemes (MPC)

One way to illustrate the adaptability of the SAFE layer to control schemes other than those based on PID controllers is to evaluate its effect on predictive controllers. In this case, model predictive control (MPC) is used. One class of MPC is the constrained type, in which constraints are explicitly included in the objective function. However, this test is implemented illustratively to demonstrate attractive SAFE features on a linear MPC scheme. As the MPC is a model-based controller, a model representing glucose-insulin dynamics based on ARX models is employed [10,27]. The ARX model identification implemented in this proof uses the meal glucose and the variation in insulin delivered with respect to basal rate as inputs and the variation in blood glucose concentration with respect to basal as an output.

To obtain a good representability of the glucose-insulin dynamics, 1-day open-loop experiment including conditions of hypoglycemia, normoglycemia and hyperglycemia was performed. The identification protocol includes a first breakfast (breakfast1), lunch, dinner, and a second breakfast (breakfast2) at 08:00, 13:00, 21:00, and 08:00 respectively. In particular, insulin is not administered during breakfast1 (hyperglycemia condition), meal intake is not administered during lunch but insulin is given (hypoglycemia condition), meal intake and standard bolus insulin are given during dinner (normoglycemia condition), and the insulin delivered during breakfast2 is four times higher than a typical dosage (severe hypoglycemia condition). The prediction performance was enhanced by transforming the inputs with a first-order transfer function [38] and by the "recursively estimate ARX model" function included in the LabVIEW system identification toolkit.

The validation data were obtained from several variations of an open-loop experiment, including three meals during which the

Table 4
Performance results per patient of the PDBasal Hybrid and the PID-IFB controller with and without the SAFE layer regarding to the minimum glucose excursion (mg/dL) using the safest-tuning (zero hypoglycemia events). Corresponding mean glucose values (mg/dL) are also included.

Patient	PDBasal Hybrid				PID-IFB			
	Excursion (mg/dL)		Mean (mg/dL)		Excursion (mg/dL)		Mean (mg/dL)	
	With SAFE	Without SAFE	With SAFE	Without SAFE	With SAFE	Without SAFE	With SAFE	Without SAFE
1	62.7	68.8	123.8	135.0	71.3	77.4	124.5	128.6
2	36.8	36.8	105.3	105.3	83.8	72.9	142.9	119.2
3	54.1	62.9	111.1	119.7	104.1	114.5	131.9	141.4
4	55.1	63.1	120.5	129.0	97.4	128.0	136.5	157.3
5	52.4	64.5	110.4	120.9	89.5	94.6	123.4	127.6
6	63.0	72.7	123.1	139.2	104.1	142.9	145.9	166.9
7	51.6	79.8	122.3	145.1	86.5	106.7	142.0	148.6
8	58.1	62.3	115.7	114.3	73.3	75.3	118.7	120.3
9	116.8	120.8	145.1	152.6	134.1	140.2	151.6	156.4
10	69.4	83.8	119.3	131.6	109.9	115.5	134.9	140.1
Mean	62.0	71.5	119.7	129.3	95.4	106.8	135.2	140.6

insulin delivered to each patient was modified using different pre-meal and post-meal bolus sizes [39].

The following equation shows the ARX model structure

$$A(z)y(k) = B(z)u(k-n) + e(k) \quad (12)$$

where $u(k)$ is the system input, $y(k)$ is the system output, n is the system delay, and $e(k)$ is the system disturbance. The model order used in this implementation was $A[B1\,B2][n1\,n2]$, where $A = 15$, $B1 = B2 = 15$, $n1 = 10$ and $n2 = 0$. The sampling period was 1 min.

Constant MPC tuning parameters were maintained during the simulation based on similar implementations [27,40]. A meal announcement is assumed available, i.e. the disturbance signal (the meal) is known in advance. The prediction horizon and the control horizon were set to 250 time steps (250 min) and 50 time steps (50 min), respectively. The weight for the glucose set point tracking and the future insulin moves were set to 1. The set point was set to 140 mg/dl for the first four postprandial hours and was set to 100 mg/dl for the remaining time. Fig. 9 graphically illustrates the blood glucose response, the delivered insulin, and the *IOB* estimation obtained for a single FDA-accepted patient with and without the SAFE layer added to the MPC.

Table 5 displays the resulting MPC control performance per meal with focus on the minimum glucose and the excursion obtained. Note that six meals (in bold) are prone to present hypoglycaemic events without the SAFE layer. In addition, the blood glucose excursion is not significantly affected when the SAFE layer is added.

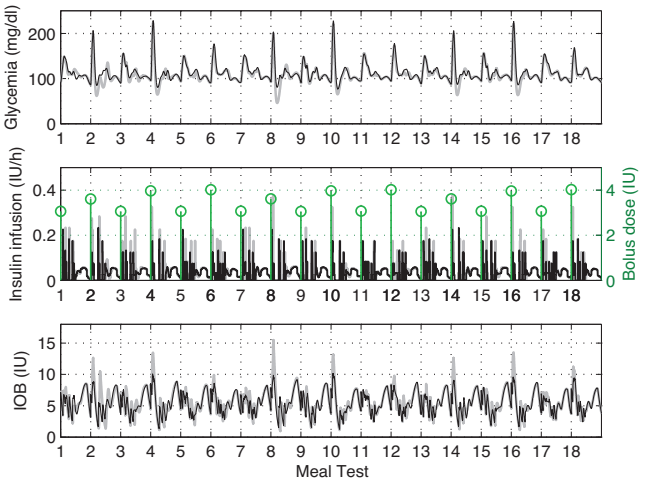

Fig. 9. Blood glucose, insulin infusion, and IOB calculation corresponding to the MPC (gray) and the MPC-SAFE (black) on a single patient. The bolus doses are shown in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Performance results on a single patient of the basic MPC with and without the SAFE layer regarding to the minimum glucose (mg/dL) and glucose excursion (mg/dL) per meal.

Meal	With SAFE		Without SAFE	
	$Glucose_{min}$	Excursion	$Glucose_{min}$	Excursion
1	91.0	58.6	91.9	56.2
2	**84.8**	**120.2**	**61.5**	**113.1**
3	89.6	66.7	91.3	63.0
4	**80.3**	**132.5**	**64.3**	**128.8**
5	93.5	56.2	93.1	58.3
6	91.0	85.8	90.6	80.6
7	91.6	60.6	92.2	57.4
8	**80.5**	**110.5**	**45.8**	**107.5**
9	90.7	58.0	88.2	57.6
10	**77.0**	**136.7**	**65.1**	**130.1**
11	95.0	59.9	94.7	61.4
12	94.2	82.8	94.4	77.4
13	88.0	62.5	88.9	60.9
14	**87.1**	**118.4**	**63.3**	**112.7**
15	94.3	62.0	92.4	62.6
16	**86.0**	**131.0**	**63.3**	**126.1**
17	90.9	63.9	91.5	61.2
18	92.1	76.5	92.1	69.1

5. Conclusion

Extensive trials under a strongly demanding scenario including mixed meals, intra- and inter-patient variability, sensor and actuator drawbacks and other realistic conditions have been performed to assert the postprandial performance of different closed-loop glucose controllers with and without the novel SAFE layer. A safest tuning criterion in which hypoglycemia avoidance is the first priority and postprandial excursion reduction the second priority has been adopted. In this sense, the extensive in silico study presented herein has shown the flexibility and effectiveness of the SAFE method to enhance the postprandial glucose performance of several closed-loop control schemes. Indeed, the study reveals that the SAFE layer is not only a safety net against hypoglycaemic events, but that it also allows a safe re-tuning of the inner controller so that postprandial response can be improved by intuitively adjusting a single parameter (the IOB limit $\overline{IOB}$) with medical criteria.

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