Safety Auxiliary Feedback Element for the Artificial Pancreas in Type 1 Diabetes

A. Revert, F. Garelli, J. Picó, H. De Battista, P. Rossetti, J. Vehi, and J. Bondia*

***Abstract*—The artificial pancreas aims at the automatic delivery of insulin for glycemic control in patients with type 1 diabetes, i.e., closed-loop glucose control. One of the challenges of the artificial pancreas is to avoid controller overreaction leading to hypoglycemia, especially in the late postprandial period. In this study, an original proposal based on sliding mode reference conditioning ideas is presented as a way to reduce hypoglycemia events induced by a closed-loop glucose controller. The method is inspired in the intuitive advantages of two-step constrained control algorithms. It acts on the glucose reference sent to the main controller shaping it so as to avoid violating given constraints on the insulin-on-board. Some distinctive features of the proposed strategy are that 1) it provides a safety layer which can be adjusted according to medical criteria; 2) it can be added to closed-loop controllers of any nature; 3) it is robust against sensor failures and overestimated prandial insulin doses; and 4) it can handle nonlinear models. The method is evaluated *in silico* with the ten adult patients available in the FDA-accepted UVA simulator.**

***Index Terms*—Artificial pancreas, glucose control, hypoglycemia, insulin-on-board, reference conditioning, safety, sliding mode (SM).**

I. Introduction

TYPE 1 diabetes mellitus (T1DM) is a chronic medical condition that affects millions of people all around the world. It is characterized by an irreversible lack of insulin production, with the consequence of high blood glucose levels.

Several studies, such as the diabetes care and complications trial (DCCT) [1] and the epidemiology of diabetes interventions and complications (EDIC) [2], have demonstrated that the achievement of a good metabolic control in diabetic patients reduces the chronic long-term micro- (DCCT) and macrovascular (EDIC) complications of T1DM.

Near-normoglycemia (safe blood glucose levels) can be achieved through intensive insulin treatment based either on multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) using insulin pumps. The latter has the advantage of fine tuning of insulin infusion according to the individual needs through real-time adjustments [3], [4]. Additionally, newest generations of insulin pumps have tools to aid diabetic subjects in the prandial bolus decision-making process: the bolus advisors [5], [6]. However, despite the availability of new insulin preparations [7] and smarter insulin pumps, achievement of good metabolic control in terms of HbA1c is still an elusive goal in more than 50% of patients with T1DM [1] due, among other things, to the patient's low compliance [8]–[10].

In the last 10–15 years, the development of sensors for continuous subcutaneous glucose monitoring (CGM) has fostered research in the artificial pancreas. Indeed, several experiments of CGM-based automated insulin infusion have been performed. Different controllers have been used in this task [11]–[15], but those with the best clinical evidence of efficacy are proportional-integral-derivative (PID) [16], [17] controllers and algorithms such as model predictive control (MPC) [18].

One of the barriers which is affecting the establishment of intensive insulin therapies is the demonstrated increase in hypoglycemia events (blood glucose below 70 mg/dL) [1], [19], [20]. Depending on the severity of these events, their consequences can be different including the patient's death.

In this way, the main challenge all closed-loop proposals have to face is the control of postprandial glycemia excursions avoiding overcorrection and subsequent hypoglycemia. Intrapatient variability, errors in the glucose sensor measurements, and, mainly, the delay in the control action are the difficulties that have to be overcome. This delay is inherent in subcutaneous infusion and can be higher than 60 min [21]. The use of intravenous or intraperitoneal pumps reduces this last difficulty, but their invasive nature entails additional drawbacks. Moreover, an aggressive tuning of the controller and changes in the patients' sensitivity to insulin are additional factors contributing to hypoglycemia.

In an attempt to improve the performance of the controllers, feedforward strategies with meal announcement have been added to the control schemes [17], [22]–[26]. Additionally, several safety strategies such as modular control to range [27]–[29], the addition of safety constraints in the residual insulin activity, the so-called insulin-on-board (IOB), or the addition of an

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insulin feedback [30]–[34] have demonstrated a reduction in the hypoglycemia events. Other proposals include bihormonal closed-loop control with the inclusion of glucagon as counter-regulatory control action [35], [36].

As far as the authors know, IOB constraints have been mainly addressed via MPC [30], [31]. In spite of the well-known advantages of this strategy, it implies solving an on-line open-loop optimization problem at each sample, which requires an accurate patient model [37]. Therefore, it seems important to propose and evaluate alternative methods to implement safety constraints on IOB. Indeed, two general approaches can be found in the control systems literature in order to deal with constraints [38], [39]:

1) one-step approaches, in which knowledge of constraints is explicitly exploited, and constraints accounted for, during the control law design. These are mostly MPC strategies;
2) two-step algorithms, originally inspired in reference governors schemes for industrial controllers.

The latter approach can be illustrated by the premise: "design the controller ignoring limitations, and then add a compensation to minimize adverse effects of limitations on closed-loop performance" [40]. This leads to some separation in the controller such that one part is devoted to achieving nominal performance and the other part is devoted to constraint handling. Thus, all the know-how on classical control and tuning techniques can be used for the main control loop design. In the case of glucose control, a two-step approach would permit exploiting clinical evidence and experience on other valuable control strategies which are not able to deal with IOB constraints by their own, such as ePID and ePID-IFB [33], [34], or even nonlinear control laws which take advantage of advanced physiological and pharmacokinetic dynamics knowledge. Despite the intuitive advantages attributed to two-step algorithms [41], they are usually criticized for being ad hoc methods without the background of a well-established theory.

In this study, sliding mode reference conditioning (SMRC) previously successfully used in different fields [42]–[46] is applied to the design of a safety algorithm to reduce hypoglycemia events in closed-loop glucose control. It follows the two-step approximation to constrained control with the advantage of providing a rigorous methodology design and robustness against sensor failures. In effect, differing from most two-step algorithms originally conceived as antiwindup methods for linear and biproper controllers, the proposed method can deal with both biproper/strictly proper controllers and linear/nonlinear controllers or IOB estimators, does not require the model of the controller and IOB estimator but only their relative degree (generally constant and known *a priori*), and provides insensitive IOB limits to matched disturbances and sensor errors.

Some initial approaches based on conventional SM control have been reported both with [12] and without [47] meal announcement. In contrast, in this proposal SMs are not established within the main control loop but in an auxiliary software-based loop, which can operate at much faster sampling rates than the ones allowed by current glucose monitors. In this way, given a closed-loop controller (which can be of any nature), an outer control loop is added so as to impose constraints on the IOB. This loop, based on SMRC, is only active when the IOB amounts to undesirable values. It acts on the reference of the main controller shaping it so as to avoid the violation of the constraints. Both upper and lower constraints in IOB can be defined, reducing the hypoglycemia risk but also avoiding too high blood glucose values, mainly in the late postprandial period, acting as a second-layer control. The IOB is estimated through a subcutaneous insulin absorption model and different IOB limits can be imposed depending on the ingested meal and on the estimation of the insulin sensitivity for each patient. The main advantage of this scheme is that it does not affect the design of the inner controller, which could be designed previously and in an independent way.

This paper is organized as follows. Section II revises the theoretical concepts behind this proposal. Section III presents the method design and analysis showing its robustness properties and presenting some discussion about the definition of IOB bounds. In Section IV, some simulations are carried out to illustrate the robustness of the strategy against sensor failures and priming bolus overestimations. Moreover, the proposal is evaluated *in silico* using the ten adult patients available in the educational version of the the Food and Drug Administration-accepted University of Virginia Simulator (UVA Simulator) [48]. Finally, in Section V, a set of conclusions is provided.

II. General Framework And Methods

In order to address the glucose control problem with constrained IOB from a general framework, we revise in this section some important concepts on invariance control and sliding regimes. In particular, we study the necessary conditions to confine a nonlinear dynamical system to an invariant region of the state space, and we then compare these conditions with the equivalent continuous dynamics of a system operating in SM, i.e., when the system input consists of a high-frequency discontinuous signal.

A. Invariance Control

Let the system be

$$\begin{cases} \dfrac{dx(t)}{dt} = f(x,d) + g(x)w(t) \\ y(t) = h_1(x) \\ v(t) = h_2(x) \end{cases} \tag{1}$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $w(t) \in \mathbb{R}$ is a control input, and $d(t) \in \mathbb{R}^n$ an unmeasured perturbation which can represent either parametric uncertainties or external nonstructured disturbances. $f(x,d) : \mathbb{R}^n \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ and $g(x) : \mathbb{R}^n \longrightarrow \mathbb{R}^n$ are vector fields, and $h_1(x)$ and $h_2(x) : \mathbb{R}^n \longrightarrow \mathbb{R}$ scalar fields.

Variables $y(t)$ and $v(t)$ are both real-valued system outputs, $y(t)$ being the main controlled variable and $v(t)$ a variable to be bounded so as to belong to the set

$$\Sigma = \{x(t) \mid \sigma(t) = v(t) - v^*(t) \leq 0\} \tag{2}$$

with $v^*(t)$ the bound imposed to $v(t)$.

Thus, the goal is to find a control action $w(t)$ such that the region Σ becomes invariant (i.e., trajectories originating in Σ remain in Σ for all times t), while $y(t)$ is driven as close as

possible to its desired value r. To ensure the invariance of Σ, the control action $w(t)$ must guarantee that the right-hand side of the first equation in (1) points to the interior of Σ at all points on the border surface $\partial\Sigma = \{x(t)|\sigma(t) = 0\}$. Mathematically, this is verified if the implicit invariance condition [49], [50]

$$\inf_{w} \dot{\sigma}(t) \leqslant 0, \text{ with } x(t) \in \partial\Sigma \tag{3}$$

holds.

From (1), using Lie derivatives, we have

$$\begin{aligned} w(t) &= (L_g\sigma(t))^{-1}\left[\dot{\sigma}(t) - L_f\sigma(t) + \dot{v}^*(t)\right] \\ &= w^\sigma + (L_g\sigma(t))^{-1}\dot{\sigma}(t) \end{aligned} \tag{4}$$

with $w^\sigma = (L_g\sigma(t))^{-1}\left[-L_f\sigma(t) + \dot{v}^*(t)\right]$. Since $w(t)$ must be chosen so as to fit (3), it must verify $(w(t) - w^\sigma)L_g\sigma(t) \leqslant 0, \forall x(t) \in \partial\Sigma$.

Hence, the explicit invariance control for system (1) is obtained

$$\begin{aligned} &w(t) \in w \in \mathbb{R}|w < w^\sigma \text{ if } x(t) \in \partial\Sigma \wedge L_g\sigma(t) > 0 \\ &w(t) \in w \in \mathbb{R}|w > w^\sigma \text{ if } x(t) \in \partial\Sigma \wedge L_g\sigma(t) < 0 \\ &w(t) = 0 \text{ if } x(t) \in \Sigma \setminus \partial\Sigma \end{aligned} \tag{5}$$

with $L_f\sigma(t)$ assumed to be positive without loss of generality.

Note that the condition $L_g\sigma(t) = \frac{\delta\sigma(t)}{\delta x(t)}g(x) \neq 0$ must hold on $\partial\Sigma$ for w^σ to exist and invariance control be feasible. Observe also that once the surface $\partial\Sigma$ and the control field $g(x)$ are defined, only one of the two inequalities holds, i.e., $L_g\sigma(t)$ remains either positive or negative but never changes its sign.

B. Finite-Time Invariance Achievement Via Sliding Mode Reference Conditioning

The concept of reference conditioning to achieve a realizable reference arises in the context of constrained control systems. Specifically, Hanus and Walgama [51] and [52] applied this kind of solutions to solve the problem of actuator saturation (windup) in linear controllers. Based on these approaches and getting advance of the possibilities of SMs, Mantz and colleagues [43]–[45], [53] have used SMRC in several applications to robustly obtain realizable references under restrictions both in the actuators, in the outputs, or in any state or combination of states.

The sliding control loop appears in SMRC schemes as an additional loop that makes the reference realizable under certain constraints, instead of representing the main control loop. In that way, in contrast with conventional variable structure controllers and SMs, the sliding regime is intended as a transitional mode of operation.

Fig. 1 shows a generic implementation of an SMRC loop. It basically consists of two elements: a switching logic driving the search so as to fulfill the constraints and force the system to remain in the invariance set, and a filter F which purpose is to smooth out the conditioned signal $r_f(t)$. Note that the block Θ in the figure may represent a control loop, in which case r is the set-point while in (1), $x(t)$ is the extended state vector comprising the process, controller, and filter states.

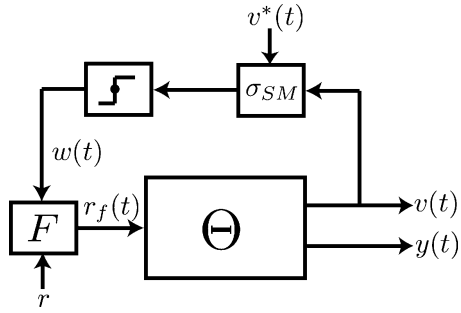

Fig. 1. SMRC general scheme.

The switching logic is implemented as

$$w(t) = \begin{cases} w^+ & \text{if } \sigma_{SM}(t) > 0 \\ 0 & \text{if } \sigma_{SM}(t) \leqslant 0 \end{cases} \tag{6}$$

where

$$\sigma_{SM}(t) = v(t) - v^*(t) + \sum_{i=1}^{l-1} \tau_i \left(v(t)^{(i)} - v^*(t)^{(i)}\right) \tag{7}$$

with l being the relative degree between the output $v(t)$ and the input $w(t)$. $v(t)^{(i)}$ and $v^*(t)^{(i)}$ are the ith derivative of $v(t)$ and $v^*(t)$ respectively. τ_i are constant gains and w^+ is the $w(t)$ upper value. The filter F is implemented as the first-order filter $\dot{r}_f(t) = -\alpha\left(r_f(t) + w(t) - r\right)$ with α a design parameter.

According to the definition of the switching function in (7), it always has relative degree unitary with respect to $w(t)$ (its first derivative explicitly depends on $w(t)$), which is a necessary condition for SM establishment known as the transversality condition [54]. Indeed, it is interesting to observe that for a general system as the one described in (1), this condition coincides with the existence condition of invariant control, $L_g\sigma(t) \neq 0$ [see (4)]. Then, as long as $w^+ \geqslant w^\sigma$—recall (5)—the SMRC loop leads to a sliding regime on $\sigma_{\mathrm{SM}}(t) = 0$ whenever the variable $v(t)$ is about to violate its constraint $v^*(t)$, robustly ensuring the invariance of Σ.

Note that if the initial condition is beyond the frontier defined by $\sigma_{\mathrm{SM}}(t) = 0$, the switching logic (6) sets a control action w^+ which drives the system to the invariant region in finite time. The same would happen if an abrupt (and not sufficiently bounded) disturbance led the system to transiently leave the allowed region.

III. Safety Auxiliary Feedback Element (SAFE) in Diabetes Control

In this section, the theoretical framework presented in Section II is applied to develop a safety algorithm for glucose control loops with the aim of reducing the number and severity of hypoglycemia events and to avoid late postprandial glucose rebounds. The main approach here is to limit the concentration of residual insulin in the subcutaneous tissue, the so-called IOB, whose excess is the main cause of late hypoglycemia due to delayed absorption and action.

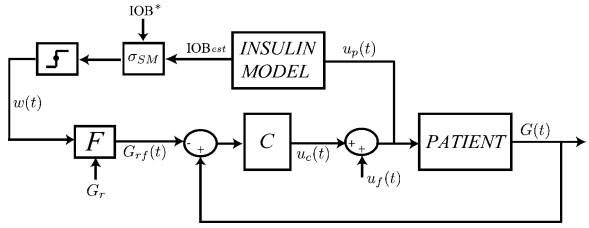

Fig. 2. SMRC implementation for diabetes application.

A. Basics of the Algorithm

Assume now that the block Θ in Fig. 1 stands for a glucose control loop, in which the main controlled variable $y(t)$ is the glucose concentration $(G(t))$ and the constrained variable $v(t)$ is the IOB(t) (from here on IOB).

A representation of the proposed closed-loop scheme is shown in Fig. 2. C represents a controller. The control action is the pump's insulin infusion rate $(u_c(t))$, while $u_f(t)$ represents a priming bolus in meal announcement schemes. For the subsequent analysis, the inner controller C is assumed to be a realizable PID controller. However, it is worth remarking that it could be any other controller, even nonlinear and strictly proper ones.

Hence,

$$u_c(t)=k_P e(t)+k_D \dot{G} + k_I \int_0^t e(t)\,\mathrm{d}t \tag{8}$$

where $e(t) = G(t) - G_{rf}(t)$ with $G_{rf}(t)$ the conditioned reference further defined in (11) and k_P, k_D, and k_I the constants of the proportional, derivative, and integral parts of the PID respectively. Notice that when $u_c(t)$ (insulin injected) increases, the glucose concentration $G(t)$ decreases. This fact explains the error sign.

Since the IOB is inaccessible, it must be estimated. Again, the proposed methodology does not restrict the way in which IOB is estimated, which can be performed by means of any of the published insulin absorption models [22], [55]–[64], or even employing static pharmacokinetic curves as currently done in commercially available insulin pumps. Here, the insulin absorption model developed by Cobelli's group [22] is used for the method description. Its equations for the subcutaneous insulin absorption take the form

$$\begin{aligned}\dot{S}_1(t) &= -(k_{a1}+k_d)S_1(t) + u_p(t)\\ \dot{S}_2(t) &= k_d S_1(t) - k_{a2} S_2(t)\end{aligned} \tag{9}$$

where $S_1(t)$ and $S_2(t)$ are subcutaneous tissue compartments (insulin mass), $u_p(t)$ represents the administration of insulin, k_{a1}, k_{a2} are rate constants of insulin absorption, and k_d is the intercompartment transport rate.

In this way, IOB is defined as

$$\text{IOB} = S_1(t) + S_2(t). \tag{10}$$

As mentioned in the previous section, the outer SMRC loop consists of two main elements. A switching logic responsible for constraining IOB inside the desired bounds, and a first-order filter F whose purpose is to smooth out the conditioned reference.

The first-order filter takes the form

$$\dot{G}_{rf}(t) = -\alpha\left(G_{rf}(t) + w(t) - G_r\right) \tag{11}$$

where G_r (usually constant) is the desired reference when IOB does not reach the defined bounds, $G_{rf}(t)$ is the conditioned reference, $w(t)$ is the injected discontinuous signal, and α determines the filter cutoff frequency.

Two constraints for the IOB can be defined: one upper constraint ($\overline{\text{IOB}(t)}$) (from here on $\overline{\text{IOB}}$) to mitigate, as explained before, the problem of hypoglycemia incidence, and an additional lower constraint ($\underline{\text{IOB}(t)}$) (from here on $\underline{\text{IOB}}$) to avoid undesirable glucose rebounds and maintain a minimum quantity of IOB. To design the corresponding sliding functions, it is necessary to know the relative degree l between IOB and $w(t)$. Defining IOB as $S_1(t) + S_2(t)$, this relative degree is $l = 2$. Hence, according to (7), the sliding functions are defined as[1]

$$\begin{aligned}\sigma_1(t) &= \text{IOB} - \overline{\text{IOB}} + \tau(\dot{\text{IOB}} - \dot{\overline{\text{IOB}}})\\ &= (1-\tau k_{a1})\,S_1(t) + (1-\tau k_{a2})\,S_2(t)\\ &\quad + \tau u_p(t) - \overline{\text{IOB}} - \tau\dot{\overline{\text{IOB}}}\\ \sigma_2(t) &= \text{IOB} - \underline{\text{IOB}} + \tau(\dot{\text{IOB}} - \dot{\underline{\text{IOB}}})\\ &= (1-\tau k_{a1})\,S_1(t) + (1-\tau k_{a2})\,S_2(t)\\ &\quad + \tau u_p(t) - \underline{\text{IOB}} - \tau\dot{\underline{\text{IOB}}}\end{aligned} \tag{12}$$

and the associated switching logic is

$$w(t) = \begin{cases} w^+ & \text{if } \sigma_1(t) > 0\\ w^- & \text{if } \sigma_2(t) < 0\\ 0 & \text{otherwise.}\end{cases} \tag{13}$$

Note that, because of the way the system is defined, w^+ is negative and w^- positive. That is, when the upper bound is violated, the reference value is increased so as to reduce the control action, and vice versa for the lower constraint. In other words, when $\sigma_1(t) > 0$, IOB is higher than $\overline{\text{IOB}}$. In order to decrease IOB, the insulin injected $(u_c(t))$ must decrease. This effect is achieved increasing $G_{rf}(t)$, avoiding hypoglycemia due to an excess of insulin. In the same way, when $\sigma_2(t) < 0$, IOB is lower than $\underline{\text{IOB}}$ and $G_{rf}(t)$ must decrease in order to force an increase in $u_c(t)$ and inject more insulin. This procedure avoids undesirable later glucose rebounds once the effect of the meal has already been counteracted.

As the algorithm is thought to be added to any closed-loop controller in order to provide an additional safety layer, we will from now on refer to it as the safety auxiliary feedback element (SAFE).

Remark: It is well known that the main drawback of SM control is the chattering phenomena, but in the proposed SAFE algorithm this problem is not present. On the one hand, the

[1]Note that the compensation design is exactly the same independently of the controller and estimator provided their relative degree is the same, which is the case in practice as otherwise additional lag would be unnecessarily introduced to the control loop.

discontinuous action is not a physical signal due to the software-based nature of the algorithm. On the other hand, it is filtered previous to being used to modify the reference. Therefore, all signals in the main control loop are smooth.

B. Robustness and Fault-Tolerance Properties

One of the most relevant features of SMs is their robustness against an important sort of uncertainties and disturbances, the so-called matched perturbations. Indeed, the matching condition of sliding regimes [54] states that the dynamics during SM is insensitive (which is more than robustness) to any bounded disturbance being collinear with the discontinuous action.

For the SAFE algorithm, combining the expressions related to IOB of the insulin system (9), the controller (8) and the filter (11), the open-loop dynamics of the whole conditioning system can be rewritten in the general form of (1) as

$$\begin{aligned}\begin{pmatrix}\dot{S}_1(t)\\ \dot{S}_2(t)\\ \dot{u}_p(t)\end{pmatrix} &= \begin{pmatrix}(-\mathrm{k_{a1}}-\mathrm{k_d})\,S_1(t)+u_p(t)\\ k_d S_1(t)-k_{a2}S_2(t)\\ -u_p(t)\end{pmatrix}\\ &\quad+\begin{pmatrix}0\\0\\ \psi\end{pmatrix}+\begin{pmatrix}0\\0\\ k_P\alpha\end{pmatrix}w(t)\\ \psi &= -k_P\alpha G_r-(k_I-k_P\alpha+k_P)G_{rf}(t)\\ &\quad+(k_P+k_I)G(t)\\ &\quad+(k_P+k_D)\dot{G}(t)+k_D\ddot{G}(t)+k_I\int_0^t G(t)\,\mathrm{d}t\\ &\quad-k_I\int_0^t G_{rf}(t)\,\mathrm{d}t+u_f(t)+\dot{u}_f(t)\end{aligned}\tag{14}$$

where following the general notation of (1)

$$x(t)=\begin{pmatrix}S_1(t)\\ S_2(t)\\ u_p(t)\end{pmatrix},\ g(x)=\begin{pmatrix}0\\0\\ k_P\alpha\end{pmatrix}\tag{15}$$

and $f(x,d)$ is composed of the first two terms on the right-hand side of (14).

The above equation shows that the second term, which can be seen as the perturbation vector $d(t)$, is collinear with the control vector $g(x)$ which determines the direction of the discontinuous action, i.e., they satisfy the matching condition. Thus, once SM is established on surfaces $\sigma_1(t)=0$ or $\sigma_2(t)=0$, the resulting SM dynamics is insensitive to changes in G_r, $G(t)$, and $u_f(t)$. This means that the limits imposed to IOB are robust against set-point changes, measurement noise, and overestimated priming bolus doses, and avoid also high concentrations of residual insulin due to sensor failures. Note that this robustness is referred to the IOB limits and does not imply a delay in the inner controller reaction to those changes.

Observe that although $\dot{G}(t)$, $\ddot{G}(t)$, and $\dot{u}_f(t)$ appear in $d(t)$, they do not affect the robustness of the algorithm as they could only be unbounded during given time instants (e.g., at glucose monitor samplings or start of bolus doses), after which the commanded signal to the pump will be consistent with the IOB constraints. Recall that the software-based SAFE algorithm can operate at the much faster rates than the main control loop, which guarantees that, in case IOB is going to violate the constraints in the period between sensor measurements, the algorithm detects this violation. In this way, the algorithm continuously calculates the insulin needed for keeping the IOB under the constraint between samples and, at the next sampling rate of the insulin pump it can inject, for example, the mean value of all the calculations. Moreover, $\ddot{G}(t)$ does only appear if we consider a controller with a pure differentiator, something improbable in practice, and $\dot{u}_f(t)$ can always be bounded by means of a fast filtering (imperceptible for the slow open-loop system dynamics) of the feedforward action.

C. SM Establishment on Safety IOB Constraints

From Section II, the necessary condition that must be fulfilled so as the SM to exist is the transversality condition, that is $L_g\sigma(t)=\frac{\partial\sigma(t)}{\partial x(t)}g(x)\neq 0$. As $L_g\sigma_1(t)=L_g\sigma_2(t)$, calculations are carried out in the following for $\sigma_1(t)$ being the procedure for $\sigma_2(t)$ analogous

$$\begin{aligned}L_g\sigma_1(t)&=\frac{\partial\sigma_1(t)}{\partial x}(t)g(x)\\ &=(1-\tau k_{a1}\quad 1-\tau k_{a2}\quad \tau)\begin{pmatrix}0\\0\\ k_P\alpha\end{pmatrix}=\tau k_P\alpha\end{aligned}\tag{16}$$

where k_P, τ, and α are design parameters, always different from 0 and positive. Therefore, the transversality condition holds.

Since the objective here is to shape the reference signal $G_{rf}(t)$, as a rule of thumb it is reasonable to take w^+ of the order of the glucose set-point G_r. Nevertheless, the exact minimum amplitude to guarantee SM can be explicitly computed from the invariance condition stated in Section II

$$(w^+-w^{\sigma_1})L_g\sigma_1(t)\leqslant 0,\quad \forall x(t)\in\partial\Sigma.\tag{17}$$

According to (5), since in this case $L_g\sigma_1(t)>0$, w^+ must be chosen to fit the equation

$$w^+\leqslant w^{\sigma_1}=-(L_g\sigma_1(t))^{-1}[L_f\sigma_1(t)+\dot{\overline{\mathrm{IOB}}}]=\xi(x,\tau,\alpha)<0\tag{18}$$

with $\xi(x,\tau,\alpha)$, derivable from (14) and (18), defining the minimum amplitude for the negative value w^+ so as to guarantee SM.

D. IOB Constraints Definition

One of the critical points to guarantee the reduction of the hypoglycemia events using SAFE is the selection of the proper IOB constraints. This decision can be based on different criteria and it differs from one individual to another. Indeed, the most suitable IOB constraints depend on the insulin sensitivity of each patient, together with the meal amount and composition ingested.

Different parameters can be used as insulin sensitivity estimation. Demographic (age) and anthropometric parameters such as the body mass index (relation between height and weight), the body fat (fat percentage of body weight), and the waist circumference [65], [66] together with metabolic parameters as TDD

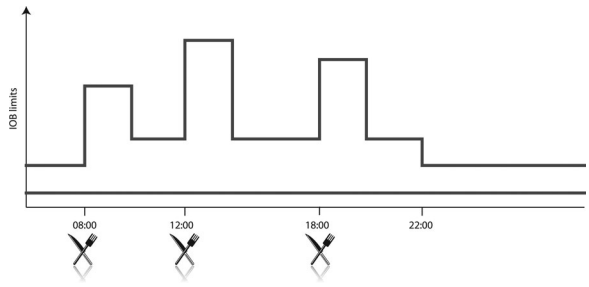

Fig. 3. Daily IOB constraint function.

of insulin, the insulin-to-carbohydrate ratio, correction factor, and basal rate prescribed by the physician (insulin pump tuning), can be combined to perform the estimation. Remark also the time-varying nature of insulin sensitivity due, among others, to the circadian rhythms [67] that can be taken into account in the definition of the IOB constraints, making them time-variable along the day. In order to avoid the uncertainty caused by the inaccurate estimation of the carbohydrate content of a meal by the patients, meal size could be estimated using the measured glucose slope, but the high variability observed in glucose absorption advises against this approach. Finally, the physician's knowledge and experience always play an important role in the selection of the proper IOB constraints for each patient. Note also that the bounds $\overline{\text{IOB}}$ and $\underline{\text{IOB}}$ can initially be chosen in a conservative way so as to compensate for uncertainty in the insulin absorption model (9), and then they could be easily adjusted by the physicians to each patient.

One approach to define $\overline{\text{IOB}}$ limit is to adjust it to a piecewise function as illustrated in Fig. 3. It consists of a security constraint during the night period, a higher constraint (meal dependent) for the postprandial period and a more restrictive constraint for the late postprandial period specially useful in meals with high fat content. Depending on the scenario, other option could be to fix just one daily (conservative) and one nightly security constraint in order to obtain a non-meal dependent outer loop to be used in fully automated control loops. An additional lower constraint can be added to avoid glucose rebounds. A good way to define this lower constraint is to build it proportional to the usual basal rate of the patient, that could be time-variable in case of pump therapies.

Note that although IOB limits can be time-variant (see $v^*(t)$ in Section II-A), their variation must be slower than the bandwidth of SAFE. Thus, the case of IOB limits piecewise constant should be addressed in practice with ramp-like changes instead of steps. In any case, the dynamics of the changes could still be much faster than patient dynamics (e.g., 5 min ramps) but slow enough for SAFE.

In this study, the size of the meal together with the TDD of insulin as an estimator of the insulin sensitivity are used for the definition of the postprandial IOB limits in the *in silico* evaluation of the methodology (see Section IV-B). The time-varying nature of the insulin sensitivity has not been taken into account in this step in order not to complicate the tuning of the IOB limits definition. The lower IOB constrained has been defined proportional to the basal rate (in this case the same during the whole day) of each patient. However, any other approximation to define IOB limits could be used.

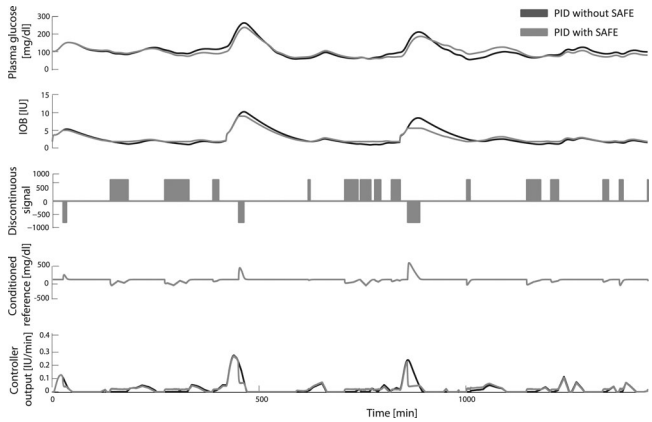

Fig. 4. Comparison of the performance of the controller in one virtual patient (patient 4) with a conventional PID and with a PID plus the additional SAFE loop during one day. The glucose profile, together with the IOB profile, and the discontinuous signal with the realizable reference derived from it are presented. Additionally, the actual response of the controller with and without SAFE is also shown.

IV. Simulations And Results

The evaluation of the above explained methodology has been carried out through an *in silico* study using the UVA simulator [48]. Previously, some simulations are presented to illustrate the robustness of the methodology, demonstrated theoretically in Section III-B.

A. SAFE Algorithm Simulations Illustrating Robustness

As an illustration of the SAFE principle, a one-day simulation (40–80–70 g) is shown in Fig. 4 comparing performance of a PID with and without SAFE. A discontinuous signal $(w(t))$ driving the PID set-point (after filtering) is generated when the IOB is in the upper (lower) limit imposed by the constraints. When IOB remains inside the allowed region, the discontinuous signal is zero. For this simulation and the followings, the initial set-point of the inner controller [G_r in (11)] is fixed to 100 mg/dL. Note that, in this particular example, the lower IOB limit allows a reduction in the glucose peaks, whereas the upper limit reduces hypoglycemia risk. It is worth mentioning that the lower IOB bound does not prevent the controller from suggesting insulin delivery to zero, although the time the insulin delivery is zero is reduced. The objective of this constraint is to avoid a situation of total absence of insulin $(\text{IOB} = 0)$.

In Fig. 5, the robust behavior of the proposed algorithm is demonstrated through three simulations that represent typical failures of CGMs. The solid lines represent the sensor measurements with their corresponding failures and dotted lines the actual glucose profile. The black and gray lines correspond to the performance with and without SAFE against the same sensor failures. Case 1 represents a sensor drift where the upper deviation from the actual glucose value is forced to be abrupt to illustrate the worst case scenario. The calibration point at $time = 200$ min makes the sensor return to the correct value.

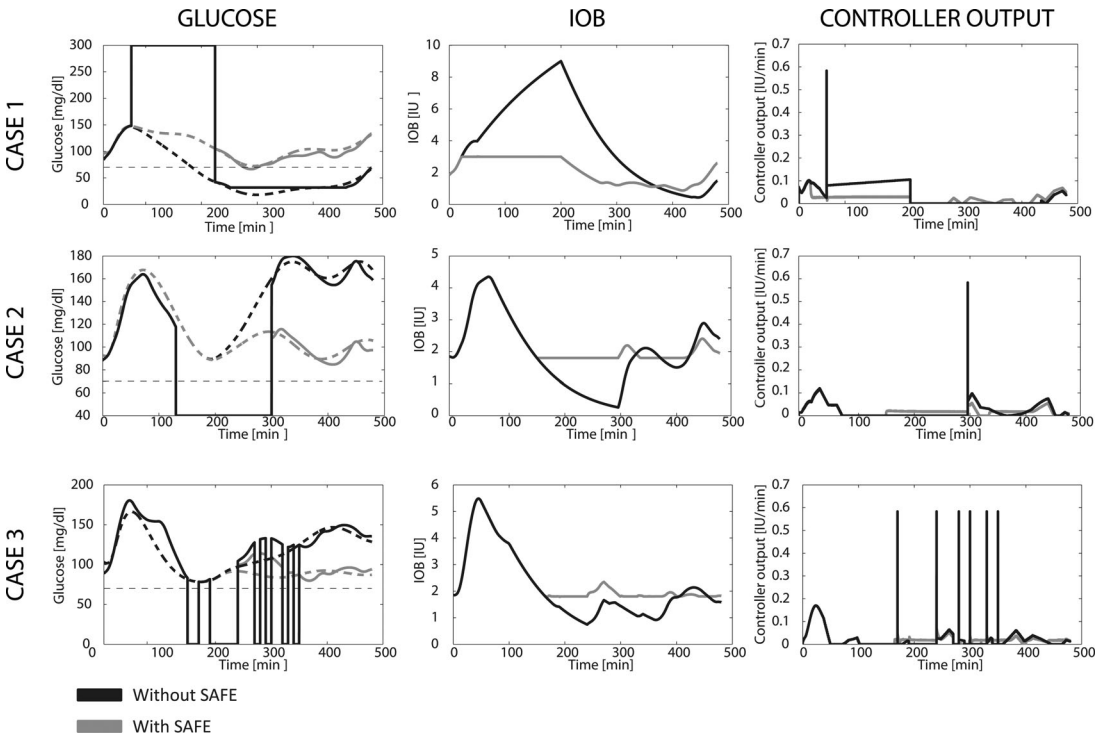

Fig. 5. Glucose response, IOB profile and controller response (no priming bolus is considered here) in the presence of sensor failures. The dark lines represent the response without the SAFE loop, whereas the light lines correspond to the response using SAFE. In the glucose profiles, the solid lines are the sensor signal and the dotted lines the actual glucose profile.

The controller reaction to a high increase in glucose concentration is to apply more insulin, overreacting with the subsequent hypoglycemia risk. Constraints in IOB reduce this overreaction avoiding risk situations. Case 2 shows a similar situation where the sensor drifts until saturation at the lower limit of a typical CGMs (40mg/dL). In this case, SAFE prevents the hyperglycemia after the sensor drift. Case 3 represents a common situation of signal loss, that also can cause later hyperglycemia events.

These sensor failures can produce undesired responses of the controller leading to late hypo or hyperglycemia events. By adding the SAFE loop with the upper and lower constraints for IOB, this effect is avoided, showing the robustness of the algorithm against sensor failures as it was mathematically demonstrated in Section III-B. In the same way, the SAFE algorithm is also robust against other type of perturbations, as for example an overestimation of the priming bolus usually used to compensate for meals. This effect is shown in Fig. 6 where for a 50 g meal, a $4IU$ bolus (30% higher than the usual patient's therapy) is administered as feedforward bolus. The SMRC loop detects too high IOB values and it is capable of keeping IOB below its constraint, provided that the amplitude of w^+ designed in (18) is high enough. If that was not the case, the IOB limit could be temporally violated but SAFE would contribute to enter again in the allowed region with $w(t) = w^+$ (see Section II-B). In both cases, the insulin given by the inner controller is reduced, and therefore hypoglycemia is avoided. This simulation has been repeated for all the ten available in UVA simulator and the area under the curve (AUC) of plasma glucose (PG) below 70 mg/dL with and without SAFE has been represented in Fig. 7. It shows

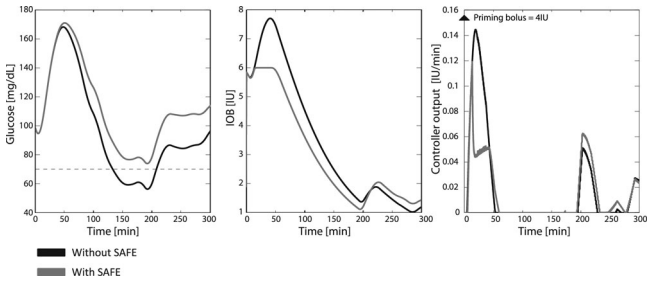

Fig. 6. Plot that illustrates the SAFE reaction against overestimated priming bolus. In this case, a 4IU bolus is added to the control output for a small meal (50 g). The third figure represents the controller output $u_c(t)$ in Fig. 2. The actual insulin delivery is $u_p(t) = u_c(t) + u_f(t)$ with $u_f(t)$ being the priming bolus.

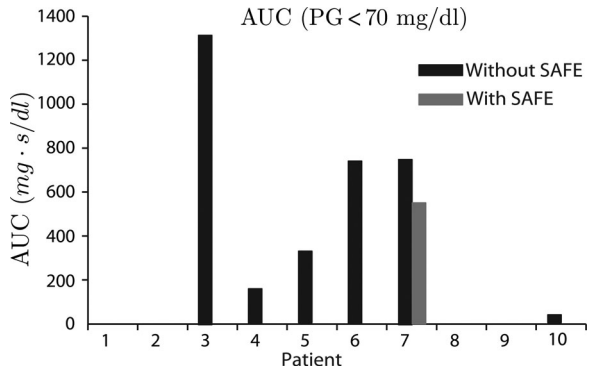

Fig. 7. Plot that shows the AUC of $PG < 70$ mg/dL for the ten available virtual patients for a 50 g meal and a feedforward bolus 30% higher than the usual.

TABLE I
PID TUNING FOR EACH OF THE PATIENTS

PID constants \ Patient	1	2	3	4	5	6	7	8	9	10
k_P $(IU/h*dl/mg)$	0.063	0.077	0.056	0.023	0.085	0.033	0.038	0.058	0.041	0.058
k_D $(IU*dl/mg)$	7.603	9.216	6.735	2.816	10.240	3.980	4.608	6.912	4.896	6.912
k_I $(IU/h^2*dl/mg)$	0.14e-3	0.17e-3	0.12e-3	0.05e-3	0.19e-3	0.07e-3	0.08e-3	0.13e-3	0.91e-4	0.13e-3

TABLE II
UPPER POSTPRANDIAL $\overline{\text{IOB}}$ LIMITS

CHO (gr) \ $TDD(IU)$	$TDD <= 60$	$60 < TDD < 75$	$75 < TDD < 85$	$TDD > 85$
$CHO < 40gr$	3	3	3	3
$40gr < CHO < 70gr$	5	7	9	10
$70gr < CHO < 100gr$	7	9	11	13
$CHO > 100gr$	9	10	13	15

that the AUC with SAFE is always lower than without it, being the time spent below 70mg/dL zero in most cases.

B. In Silico Evaluation Using UVA Simulator

Finally, an *in silico* study using a cohort of ten adult virtual patients available in the educational version of the UVA simulator [48] is presented below. This simulator has been accepted by the FDA as a substitute of animal trials prior to clinical evaluation.

A 16-h clinical protocol corresponding to active daily hours (from 8 to 24 h) of three meals (8:00 am, noon, and 6:00 pm) of 40, 80, and 70 g during ten days was considered. In order to test the robustness of the methodology with respect to intrapatient variability, sinusoidal oscilations of 5% amplitude (except for insulin sensitivity which was 10%) and 3 h period have been superimposed on nominal values of the model parameters in a similar way as in [68]. A PID controller tuned individually for each patient was used as a main controller. A subcutaneous glucose sensor model was also included to account for noisy measurements. Performance of the controller with and without SAFE was compared.

The specific PID parameters used for each patient are shown in Table I. They have been determined, taking advanced of the *in silico* nature of the evaluation, through simulations using plasma glucose measures. In real practice, the parameters of the controller could be determined using the information of the usual pump therapy of the patient in a similar way as in [16]. Due to its proved superiority against fully closed-loop systems, a feedforward meal announcement was added to the control scheme. In this case, a fixed 2IU bolus was infused at mealtime as in [34].

In order to deal with interpatient variability, different postprandial upper limits for IOB were defined depending on an estimation of the insulin sensitivity of each patient. This estimation was carried out computing TDD using the basal insulin rate of each patient, i.e., basal infusion normalizing PG around 100 mg/dL (TDD=basal[IU/h]*24*2). The IOB limit depended also on the meal size, allowing higher IOB values for big meals and being more restrictive with small meals. Table II shows the specific limits that have been used for this evaluation.

Additionally, these limits were reduced if they were caused by the second peak of the meal absorption (later postprandial period) or if the patients initial condition was moderate hypoglycemia (10% decrease). Moreover, initial conditions of hyperglycemia allowed higher values of IOB (10% increase). In order to maintain always a minimum of IOB to keep a good basal glucose concentration and avoid glucose rebounds, a fixed lower IOB bound for each patient (proportional to their basal rate) was established for all the situations.

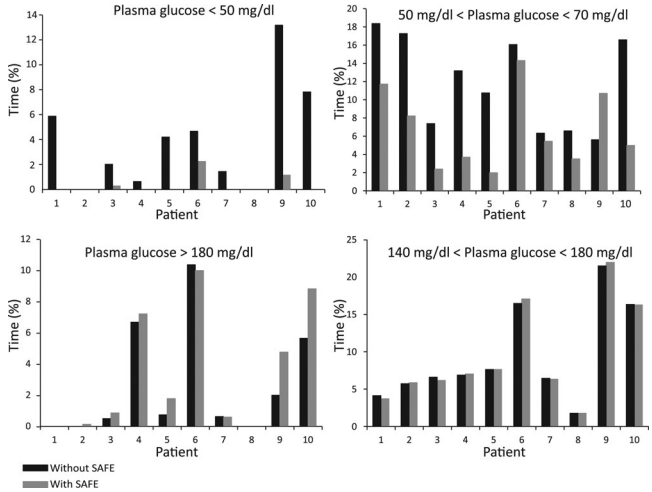

Fig. 8. Percentage of time in hypo- and hyperglycemia of each patient with and without the SAFE loop.

In Table III, a set of indicators are provided comparing the performance of a controller with and without SAFE. The number of potentially severe (PG $<$ 50 mg/dL) and moderate hypoglycemia (50 mg/dL $<$ PG $<$ 70 mg/dL) events together with the percentage of time in these values are provided. Additionally, the percentage of time above 180 mg/dL and between 140 and 180 mg/dL is also provided. Normoglycemia is here defined as 70 mg/dL $<$ PG $<$ 140 mg/dL. All data were subjected to repeated-measures analysis of variance with Huynh–Feldt adjustment for nonsphericity (the p-value of each comparison is also included in Table III) [69]. Note that the parameters used in (9) to estimate IOB are population parameters, so the results presented here demonstrate also robustness with respect to discrepancies between the estimated IOB and the real one.

Potentially severe hypoglycemia events (PG $<$ 50 mg/dL) were almost avoided using SAFE (44 versus 9, $p = 0.002$) reducing the percentage of time in hypoglycemia (PG $<$ 70 mg/dL) more than 50% ($p < 0.001$). Reduction of hypoglycemic exposure was not associated with an increase in the risk of hyperglycemia. Indeed, hyperglycemic exposure (time spent above 180 mg/dL) was not different (2.84% of time versus 3.39%, $p = 0.389$).

Fig. 8 shows graphically the detailed indicators for each of the ten patients. In most of the patients, the reduction in the time in hypoglycemia does not imply a corresponding increase in hyperglycemia. In fact, in some cases, the time above 180 mg/dL is reduced with SAFE. Note that the cases where this increase exists correspond to the cases with highest reduction in potentially severe hypoglycemia, mainly due to the initial conditions of the last meal.

TABLE III
DIFFERENT INDICATORS FOR THE EVALUATION OF SAFE

	$PG < 50(\%)$	$50 < PG < 70(\%)$	$PG > 180(\%)$	$140 < PG < 180(\%)$	$Normo(\%)$	Severe hypo events	Moderate hypo events
Without SAFE	3.96	11.79	2.64	9.25	72.34	44	97
With SAFE	0.35	6.64	3.39	12.52	77.08	9	72
p value	*0.018*	*0.01*	*0.389*	*0.006*	*0.011*	*0.002*	*0.003*

V. CONCLUSION

In this contribution, a new approach for reducing the risk of hypoglycemia, especially in the postprandial period, that slows down the development of an efficient artificial pancreas has been presented. The algorithm, called SAFE, is shown as a security loop to be added to the main control loop that is only active when IOB is about to violate any previously defined constraint. Otherwise, the SAFE loop is inactive and the original control system is not altered at all. In this way, the approach exploits the attributes of the sliding regime as a transitional mode of operation.

The theoretical basis of the algorithm are detailed, demonstrating its robustness against perturbations. Moreover, an *in silico* evaluation with a sample of the adults' cohort of the UVA Simulator is presented. The results obtained are promising, reducing the number and the duration of hypoglycemia events, in spite of considering intrapatient variability and population parameters for the IOB estimation.

In conclusion, despite the limitations of every *in silico* evaluation, this is a proof of concept study that may prelude the development of clinical studies to validate the SAFE algorithm.

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