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Artificial pancreas clinical trials: Moving towards closed-loop control using insulin-on-board constraints

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ABSTRACT

Artificial pancreas (AP) systems for people with type 1 diabetes (T1DM) combine the use of a smart insulin pump with a Continuous Glucose Monitor (CGM) and a control algorithm to improve the regulation of glycaemia. Based on the extensive clinical evidence provided by the main research groups in the area, a hybrid control algorithm combining insulin meal boluses and glucose feedback action has been recently approved. However, this sort of algorithms should be refined especially during the postprandial period. In turn, fully closed-loop control strategies have to be further developed. In either case, intensive *in vivo* validation is necessary to ensure the viability of the proposed strategy as an effective method to treat T1DM patients. In this paper, a safety layer called SAFE loop [1] is reformulated to be employed during clinical trials in two different ways: the time enable mode to gradually activate the closed-loop control after an insulin meal bolus in hybrid configurations; and the amplitude enable mode to activate the full closed-loop control as long as the insulin infusion does not exceed the conventional therapy to a given extent. The SAFE module decides the activation of the controller as a function of a constraint on the insulin on board (IOB). In the case of the Time Enable, this results in the use of a constant restriction on the IOB, whereas in the amplitude enable it results in the use of a time-varying IOB constraint. Both operation modes are evaluated *in silico* using broadly accepted high-order models and the results contrasted with the ones obtained without the SAFE protection.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease that consists in an autoimmune destruction of the pancreatic beta cells, which are responsible for the excretion of insulin. Insulin is an anabolic hormone that stimulates the absorption of glucose and the synthesis of glycogen. Therefore, people with type 1 diabetes tend to have high levels of glycaemia (presence of glucose in the blood – BG) which can cause micro and macro vascular complications.

Nowadays, the treatments that help T1DM patients stay within the limits of normoglycemia (BG $\in$ [70–180 mg/dl]) are multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) using an insulin pump. This latter one allows the addition of control algorithms to regulate the insulin delivery by the pump with the aid of continuous glucose monitors (CGM). The algorithms must be validated *in silico* and then tested in humans in a clinical trial.

The subcutaneous route introduces several restrictions on the achievable performance of an artificial pancreas system. This includes:

- The patients response to insulin is slower than to meal intake.
- Large perturbations (the meals).
- No negative action (insulin can be delivered but not drawn out).
- Variation in significant parameters of the patient (such as insulin sensitivity).

These restrictions together with technological limitations do not allow successfull fully automatic gycaemic control yet. For these reasons, nowadays the great majority of the clinical trials evaluate hybrid control strategies, i.e. a combination of an insulin bolus (which is calculated from the information of the meal to be ingested) and a control algorithm that delivers insulin during the late postprandial period [2–5]. Nonetheless, achieving full closed-loop control remains as the main goal. Completely automatic algorithms have been evaluated in randomized trials as well, but mainly in the nocturnal period, when no perturbations are present [6,7]. Only a few closed-loop trials during both day and

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night have taken place [8,9]. Therefore, it is important to develop measures to test *in vivo* both hybrid and automatic control therapies in a safe environment.

Different control strategies are being developed and tested by the scientific community, mainly based on PID [10–12], Model Predictive Control (MPC) [13–15] and Fuzzy Logic (FL) [16–18]. Hypoglycemia is usually a result of an overestimation of the insulin dose by the controller (the delay in the systems response incites insulin stacking). The use of constraints on the amount of insulin active in the body (insulin on board – IOB) to prevent this insulin-induced hypoglycemia has proven to improve glycaemic control both *in silico* [19,20] and *in vivo* [21]. These constraints can be addressed by an MPC control strategy [21]. With MPC controllers the constraint is taken into account explicitly during the controller's design. In contrast, there are other techniques that allow the main controller to be designed separately without including IOB limitations and to then add the safety layer that accounts for the desired constraint (two-step design) [1]. This way, potentially simpler controllers that would not be able to handle IOB constraints can incorporate them as a safety mechanism.

Recently, a new method using sliding mode control was introduced called the SAFE (safety auxiliary feedback element) algorithm [1], which was inspired on the sliding mode reference conditioning (SMRC) technique originally proposed by some of the authors of this work [22]. This algorithm works as a safety layer adding an IOB constraint around any main controller (including MPC) and has shown to reduce the number and severity of hypoglycemic events (BG < 70 mg/dl) [23]. This strategy has been successfully validated in clinical trials as part of the controller [24,5].

In this paper, the IOB constraint imposed by the SAFE algorithm is designed for its use in clinical trials, giving rise to a safe mechanism for testing both hybrid and fully closed-loop controllers *in vivo*. To this end, two different modes of operation are proposed. One is designed to work with hybrid controllers and the other one is designed to be used with fully automatic controllers. The first one, called Time Enable, is to be used with hybrid configurations. This mode is the classical SAFE loop previously proposed [1,23] where a constant IOB constraint is used. In this work however, it is reinterpreted to be used in clinical trials. It provides a criterion to establish the required IOB constraint and to, from that point on, safely decrease the open-loop action to make way to the closed-loop controller. It also works as a safety mechanism against mistuned controllers, reducing the severity and duration of potential hypoglycemic events. The second one, called Amplitude Enable, is focused on fully closed-loop clinical trials. This operation mode is designed to ensure that the controller action will not exceed to a given extent the traditional therapy's insulin infusion. In this case, the constraint on the IOB is based on the time-varying IOB profile that would result from an open-loop treatment for the same meals. Both algorithms are intensively evaluated *in silico* using the FDA (Food and Drug Administration) approved UVa/Padova simulator [25,26] under inter- and intra-patient variability. The intake of meals of mixed composition is also considered [27].

2. The SAFE algorithm

Fig. 1 shows a block diagram of a generic glucose control loop with the SAFE algorithm added. The main control loop may have any type of glucose controller, even non-linear. For hybrid configurations, the signal 'OL Bolus' represents the insulin bolus that is administered when the patient announces a meal (feedforward action). For a fully closed-loop therapy, 'OL Bolus' is zero.

The SAFE algorithm is aimed at reducing the risk of hypoglycemia. To achieve this, it decreases the gain of the glucose

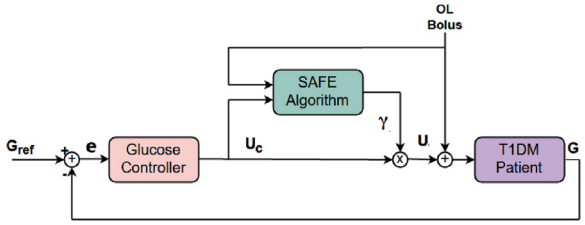

Fig. 1. Block diagram of a glucose control loop with the SAFE algorithm.

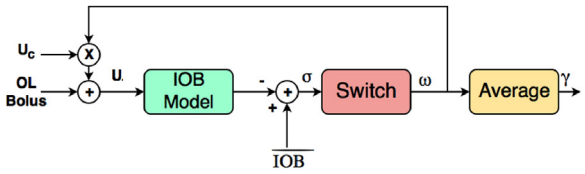

Fig. 2. Block diagram of the SAFE algorithm.

controller if a given upper constraint on the IOB ($I\bar{O}B$) is violated. Fig. 2 shows a detailed block diagram of the SAFE algorithm.

Due to its software-based nature, the SAFE block has a much smaller sampling period (T_{Ssafe}) than the rest of the controller (T_S). Within each T_S, the SAFE algorithm predicts the evolution of the IOB. This is used to calculate the adaptive gain γ that should multiply the controller output in the next sampling period T_S (for greater details see [23]).

The first block that constitutes the SAFE estimates the IOB from an IOB model and the insulin being delivered. The IOB model used here is a two-compartment dynamical system (although any other dynamical model or estimator could be used for this purpose). The set of equations describing it are the following:

$$\begin{cases} \dfrac{dC_1}{dt}(t) = u(t) - K_{DIA}C_1(t) \\ \dfrac{dC_2}{dt}(t) = K_{DIA}(C_1(t) - C_2(t)) \\ IOB(t) \;\; = C_1(t) + C_2(t) \end{cases} \tag{1}$$

where C_1 and C_2 are the two compartments, $u(t)$ is the total insulin that is administered to the patient, and K_{DIA} is a constant that represents each person DIA (duration of insulin action). The output of this block is the estimated IOB.

A switching law is then defined from the IOB in order to modify the main controller gain so that the limit $I\bar{O}B$ cannot be violated by anything other than an insulin bolus. Its goal is to avoid surpassing the IOB limit due to the feedback action. The switching law proposed in this paper is simply:

$$\omega(t) = \begin{cases} 0 & if \quad \sigma < 0 \\ 1 & if \quad \sigma \geq 0 \end{cases} \tag{2}$$

where

$$\sigma(t) = IOB - I\bar{O}B \tag{3}$$

While the feedback controller tries to increase the IOB above $I\bar{O}B$, a high frequency switching in ω will occur, called sliding mode. The signal ω is then averaged, yielding γ which is the factor (between 0 and 1) that will scale the controller output until the feedback action stops pushing the IOB upwards. Note that, in this configuration, the 'OL Bolus' is outside the SAFE loop and therefore not affected by the scaling factor γ regardless if it violates the IOB constraint or not.

Two different modes of operation are proposed for the SAFE algorithm to test both hybrid (with meal announcement) and fully closed-loop (without meal announcement) controllers in clinical trials with humans.