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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.

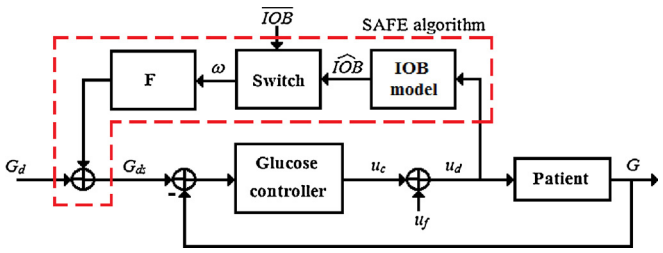

Fig. 1. Basic scheme of a glucose control loop with the SAFE algorithm.

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.