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A Bolus Calculator Based on Continuous-Discrete Unscented Kalman Filtering for Type 1 Diabetics ⋆

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Abstract: In patients with type 1 diabetes, the effects of meals intake on blood glucose level are usually mitigated by administering a large amount of insulin (bolus) at mealtime or even slightly before. This strategy assumes, among other things, a prior knowledge of the meal size and the postprandial glucose dynamics. On the other hand, administering the meal bolus during or after mealtime could benefit from the information provided by the postprandial meal dynamics at the expense of a delayed meal bolus. The present paper investigates different bolus administration strategies (at mealtime, 15 minutes after or 30 minutes after the beginning of the meal). We implement a continuous-discrete unscented Kalman filter to estimate the states and insulin sensitivity. These estimates are used in a bolus calculator. The numerical results demonstrate that administering the meal bolus 15 minutes after mealtime both reduces the risk of hypoglycemia in case of an overestimated meal and the time spent in hyperglycemia if the meal size is underestimated. Faster insulin and the use of glucagon will have the potential to encourage postprandial meal bolus administration and hence will not require to accurately estimate the meal size.

Keywords: Type 1 diabetes, Kalman filter, state estimation, parameter identification

1. INTRODUCTION

It is essential for patients with type 1 diabetes (T1D) to regulate their blood glucose tightly using frequent insulin injections, ideally in the range 4-8 mmol/L. Prolonged high blood glucose levels (hyperglycemia) may lead to long-term clinical complications, while low blood glucose levels have immediate effects.

An increasing number of patients use continuous glucose monitors (CGMs) and continuous subcutaneous infusion of insulin (CSII) pumps instead of multiple daily injections (MDI). This sensor- and pump- augmented therapy has proven to improve glycemic regulation compared to the conventional insulin therapy (Haidar et al. (2015)). Nevertheless, yet only a minority of patients using a CGM and CSII pump can manage to control their blood glucose level correctly according to the study by Nørgaard et al. (2013).

Automated or semi-automated control of blood glucose, also called the artificial pancreas (AP), has the potential to improve glycemic control and assist patients with T1D in their therapy. Current prototypes of the AP consist of a CGM, a control algorithm residing on a mobile platform (e.g. a smartphone) and a CSII pump. Fig. 1 illustrates the AP. Clinical studies demonstrated that the use of an AP during the night reduces the risk of nocturnal hypo- or hyperglycemia (Hovorka et al. (2010); Schmidt et al. (2013)). More recently, outpatient clinical studies were performed (Kovatchev et al. (2014)). However, tight glucose regulation during daytime is more difficult to achieve than during night time because of various disturbances that can affect the glucose level.

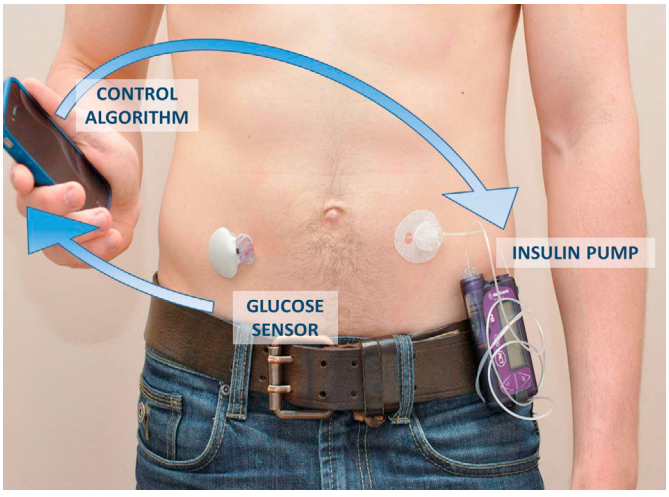

Fig. 1. The artificial pancreas.

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As a matter of fact, meals represent a major challenge both for the patient and the control algorithm due to the high nonlinearity of the insulin-glucose dynamics, the difficulty to accurately estimate the carbohydrates (CHO) content and the slower action of insulin compared to the meal intake. Brazeau et al. (2013) show the difficulty for patients with T1D to correctly estimate the CHO content of a given meal. An example illustrating the nonlinearity of glucose-insulin dynamics and the effects of the delayed insulin action on the postprandial glucose excursion can be found in Boiroux et al. (2010).

The current bolus calculators mainly rely on the patient ability to correctly estimate the meal size and the insulin-to-carbohydrates ratio. The computed bolus may then possibly be adjusted depending on the current glucose level and the estimated insulin on board

$$u_B = \frac{CHO}{ICR} + CF(G - \bar{G}) - IOB \tag{1}$$

in which u_B [U] is the insulin bolus, CHO [g] is the estimated meal content, ICR [g/U] is the insulin-to-CHO ratio (the amount of CHO), CF [U/(mmol/L)] is the correction factor (the amount of insulin needed to decrease the blood glucose level by 1 mmol/L), G [mmol/L] is the current glucose level, $\bar{G}$ [mmol/L] is the target glucose level and IOB [U] is the estimated insulin on board (see e.g. Zisser et al. (2008) for a review of bolus calculators). In the case where the meal size and time are perfectly known, it is usually optimal to administer the meal bolus either at mealtime, or even before, excepted for meals with high-fat content (Srinivasan et al. (2014)). On the other hand, if the patient cannot estimate the meal size accurately, it may be preferable to estimate the bolus size based on the postprandial glucose dynamics.

In this paper, we want to investigate whether it is preferable to administer the meal bolus at mealtime and rely solely on the meal announcement provided by the patient, or to use the information provided by the postprandial dynamics - here, we consider waiting for 15 or 30 minutes. Waiting will provide a more accurate information about the CHO contents of the meals at the expense of a delayed bolus administration.

This paper proposes an approach based on a continuous-discrete unscented Kalman filter (CDUKF) to estimate the current states and parameters of the system. This estimate is used to compute the optimal prandial bolus in patient with T1D. The CDUKF has already been tested on the Bergman minimal model (Eberle and Ament (2012)) and on the Hovorka model (Szalay et al. (2014)). It is structured as following. Section 2 presents the physiological model of the patient used for simulation. Section 3 describes the continuous-discrete filter algorithm and its implementation. Section 4 introduces the bolus calculator. Section 5 discusses the simulation results for a population of 10 patients with T1D. Finally, section 6 summarizes the main findings of this paper.

2. PHYSIOLOGICAL MODEL

Several models describing the insulin-glucose dynamics and the CHO absorption have been developed, see e.g. Hovorka et al. (2004) or Cobelli et al. (2009). More recent models also include a description of the glucagon-glucose dynamics, see Herrero et al. (2013) or Dalla Man et al. (2014). In this paper, we use the Medtronic Virtual Patient (MVP) model presented in Kanderian et al. (2009). This model has the main advantage to be easier to identify compared to the others, and therefore more suitable for the design of state and parameter estimators. It has been identified for 10 patients. The parameters for these 10 patients are used for the numerical simulations.

2.1 Insulin absorption subsystem

The insulin absorption subsystem is given by the following two-compartment model

$$\frac{dI_{SC}}{dt}(t) = \frac{u(t)}{C_I \tau_1} - \frac{I_{SC}(t)}{\tau_1} \tag{2a}$$

$$\frac{dI_P}{dt}(t) = \frac{I_{SC}(t) - I_P(t)}{\tau_2} \tag{2b}$$

where $I_{SC}(t)$ [mU/L/min] is the subcutaneous insulin concentration, and $I_P(t)$ [mU/L] is the plasma insulin concentration. $u(t)$ [mU/min] in the insulin infusion rate, C_I [L/min] is the clearance rate. τ_1 and τ_2 [min] are the insulin absorption time constants. It must be pointed out that these time constants are interchangeable.

2.2 Insulin-glucose dynamics

In the MVP model, the effect of insulin on blood glucose is described by the following ODEs

$$\frac{dI_{EFF}}{dt}(t) = -p_2 I_{EFF}(t) + p_2 S_I I_P(t) \tag{3a}$$

$$\frac{dG}{dt}(t) = -(I_{EFF} + GEZI)G(t) + EGP + R_A(t) \tag{3b}$$

$I_{EFF}(t)$ [min^{-}1] is the effect of insulin. p_2 [min^{-}1] is a parameter and S_I [mL/mU] reflects the insulin sensitivity. The glucose concentration $G(t)$ [mg/dL] is also affected by the glucose elimination at zero insulin rate ($GEZI$) [min^{-}1], the endogenous glucose production (EGP) [mg/dL/min] and the glucose rate of appearance $R_A(t)$ [mg/dL/min].

The insulin effect and the glucose dynamics (3) are similar to the one developed by Bergman et al. (1981). This formulation allows for an easier parameter identification compared to other physiological models.

2.3 Meal absorption subsystem

We consider here the two-compartment model used in Hovorka et al. (2004) to describe the CHO absorption and conversion to glucose. The model describes the effect of orally ingested carbohydrates on the rate of appearance of glucose $R_A(t)$ [mg/dL/min] in the blood stream. The model is

$$\frac{dD_1}{dt}(t) = d(t) - \frac{D_1(t)}{\tau_G} \tag{4a}$$

$$\frac{dD_2}{dt}(t) = \frac{D_1(t) - D_2(t)}{\tau_G} \tag{4b}$$

$$R_A(t) = \frac{D_2(t)}{\tau_G V_G} \tag{4c}$$