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Overnight glucose control in people with type 1 diabetes☆

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ABSTRACT

This paper presents an individualized model predictive control (MPC) algorithm for overnight blood glucose stabilization in people with type 1 diabetes (T1D). The MPC formulation uses an asymmetric objective function that penalizes low glucose levels more heavily. We compute the model parameters in the MPC in a systematic way based on a priori available patient information. The model used by the MPC algorithm for filtering and prediction is an autoregressive integrated moving average with exogenous input (ARIMAX) model implemented as a linear state space model in innovation form. The control algorithm uses frequent glucose measurements from a continuous glucose monitor (CGM) and its decisions are implemented by a continuous subcutaneous insulin infusion (CSII) pump. We provide guidelines for tuning the control algorithm and computing the Kalman gain in the linear state space model in innovation form. We test the controller on a cohort of 100 randomly generated virtual patients with a representative inter-subject variability. We use the same control algorithm for a feasibility overnight study using 5 real patients. In this study, we compare the performance of this control algorithm with the patient's usual pump setting. We discuss the results of the numerical simulations and the in vivo clinical study from a control engineering perspective. The results demonstrate that the proposed control strategy increases the time spent in euglycemia.

1. Introduction

Patients with type 1 diabetes (T1D) need frequent exogenous insulin administration to tightly regulate their blood glucose. However, the dosage of insulin must be done carefully. An insulin overdose may lead to low blood glucose (hypoglycemia), which has immediate effects, such as severe discomfort, seizures, coma or even death. In contrast, prolonged periods of too high blood glucose (hyperglycemia) has long-term clinical complications, such as blindness, nerve diseases, kidney or cardiovascular diseases.

An increasing number of patients with T1D use an insulin therapy based on continuous glucose monitors (CGMs) and continuous subcutaneous insulin infusion (CSII) pumps instead of multiple daily insulin injections (MDI). CGMs provide more frequent subcutaneous (sc) glucose measurements than self-monitoring of blood glucose (SMBG). Insulin pumps can be adjusted to accommodate intraday variations in insulin needs. This sensor-augmented therapy combined with a CSII pump can reduce the risk of hypoglycemia and clinical complications [1–3], but yet only a minority of CGMs and CSII users can regulate their glucose tightly [4].

Closed-loop control of blood glucose, also known as the artificial pancreas (AP), has the potential to improve glucose regulation and to reduce the burden of deciding on the insulin amount to be infused. The AP uses the sc-sc route for glucose sensing and insulin administration and is a very active topic of research [5–8].

The fear of nocturnal hypoglycemia is one of the main concerns for people with T1D. As a consequence, most of the people with T1D do not meet the hemoglobin A1c (HbA1c) levels recommended by the American Diabetes Association [9]. Currently, insulin pumps with insulin suspension in case of predicted low blood glucose levels are being used to reduce the risk of hypoglycemia with promising results [10,11]. Moreover, A number of recent clinical studies have focused on overnight prevention of hypoglycemia and closed-loop control of blood glucose [12–18]. Improving overnight glucose regulation also has a positive impact on post-breakfast glu-

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cose regulation [19]. Some other clinical studies illustrated the use of an AP for day and night glucose regulation in T1D and demonstrated the feasibility of fully closed-loop AP algorithms [20–27]. A database of all the clinical trials is also available [28].

Nevertheless, the performance of current APs is limited by several factors. The main limiting factors are the intra- and inter-patient variability in the patient physiology and the lags and delays associated to the choice of the sc route for insulin administration [29,30,6,31]. The lag of current CGMs is not a major impediment when used is a closed-loop control system, and current CGMs are sufficiently accurate under normal calibration to correctly detect hypo- and hyperglycemia [32,33].

Model predictive control (MPC) is one of the most commonly used methods for the AP. One of the main advantages of MPC is the ability to handle constraints on input (the insulin infusion rate) and output (the CGM readings) variables in a systematic and straightforward way. Control algorithms based on nonlinear MPC (NMPC) have been tested [34–36]. These algorithms give an insight about the maximum achievable performance and usually result in a tighter glucose regulation than control algorithms based on linear MPC. The optimal control problems arising in NMPC-based algorithms can be solved in the range of micro- to milliseconds [37,38]. Nevertheless, NMPC-based algorithms may be challenging to tune and to personalize in a systematic way for glucose regulation in T1D [39,40]. Consequently, easy to tune control algorithms based on linear MPC are preferred. A convenient way to tune such a controller is to use patient information that are already accessible, such as the body weight, the total daily insulin dose, the basal insulin and the insulin sensitivity factor [41,42,13]. Adaptive tuning of linear MPC-based controllers has also been proposed [43].

In this paper, we present an AP using a CGM for glucose feedback, an insulin pump, and a control algorithm based on MPC. The AP described in this article is individualized using a priori available patient information. In the considered setup, the patient information required by the controller is: The basal insulin infusion rate, the insulin sensitivity factor (also called the correction factor), and the insulin action time. The controller is tested in silico on a cohort of 100 patients. These simulations mimic an overnight clinical trial and induce realistic variations in insulin needs. This paper discusses the implementation of our control algorithm [44] on real patients during an overnight clinical study [12].

This paper is organized as follows. In Section 2, we describe the model and the methods used to simulate a cohort of patients with T1D and noise-corrupted CGM measurements. In Section 3, we present the clinical protocol. Section 4 presents the procedure for computation of the personalized set of MPC model parameters using prior patient information. Section 5 states the optimal control problem solved at each time sample. An asymmetric cost function and other safety layers reduce the risk of hypoglycemia. In Section 6, we evaluate and discuss the controller performance using a cohort of 100 virtual patients. Section 7 presents the results of the controller applied to a clinical study. Conclusions are provided in Section 8.

2. Physiological models for people with T1D

Several physiological models have been developed to simulate virtual patients with T1D [34,45,46]. They describe subcutaneous insulin transport, intake of carbohydrates through meals, and include a model of glucose-insulin dynamics. Models simulating glucose transport from plasma to interstitial glucose and CGM noise have been developed [47–49]. Simulation environments for T1D have also been developed [50–52].

In this paper, we use the model developed by Hovorka et al. [34]. Based on the parameters and distributions provided in [29,51,53], we generate a cohort of 100 virtual patients. These parameters and their distribution are summarized in Table 1. We augment the model with the CGM model developed by Breton et al. [47]. Compared to an approach using an already available simulation environment, this method allows to generate an unlimited number of virtual patients following a normal distribution, and provides a full access to all the states and the parameters of the system.

Table 1
Parameters and distribution for the simulated cohort [51,53].

Parameter	Unit	Distribution
EGP_0	mmol/kg/min	$EGP_0 \sim N(0.0161, 0.0039^2)$
F_{01}	mmol/kg/min	$F_{01} \sim N(0.0097, 0.0022^2)$
k_{12}	min^{-1}	$k_{12} \sim N(0.0649, 0.0282^2)$
k_{a1}	min^{-1}	$k_{a1} \sim N(0.0055, 0.0056^2)$
k_{a2}	min^{-1}	$k_{a2} \sim N(0.0683, 0.0507^2)$
k_{a3}	min^{-1}	$k_{a3} \sim N(0.0304, 0.0235^2)$
S_{IT}^f	$\text{min}^{-1}/(\text{mU/L})$	$S_{IT}^f \sim N(51.2, 32.09^2)$
S_{ID}^f	$\text{min}^{-1}/(\text{mU/L})$	$S_{ID}^f \sim N(8.2, 7.84^2)$
S_{IE}^f	L/mU	$S_{IE}^f \sim N(520, 306.2^2)$
k_e	min^{-1}	$k_e \sim N(0.14, 0.035^2)$
V_I	L/kg	$V_I \sim N(0.12, 0.012^2)$
V_G	L/kg	$\ln(V_G) \sim N(\ln(0.15), 0.23^2)$
τ_I	min	$\frac{1}{\tau_I} \sim N(0.018, 0.0045^2)$
τ_G	min	$\ln\left(\frac{1}{\tau_G}\right) \sim N(-3.689, 0.25^2)$
A_g	Unitless	$A_g \sim U(0.7, 1.2)$
BW	kg	$BW \sim U(65, 95)$

Table 2
Parameters for the CGM model [47].

Parameter	Value	Unit
τ_{sub}	15	min
λ	15.96	mg/dL
ξ	−5.471	mg/dL
δ	1.6898	–
γ	−0.5444	–

2.1. CGM model

We use a CGM for glucose feedback in our controller setup. For the numerical simulations, we generate noisy CGM data based on the model and the parameters stated in [47]. This model consists of two parts. The first part describes the glucose transport from blood to interstitial tissues, which is

$$\frac{dG_{sub}}{dt} = \frac{1}{\tau_{sub}}\left(G(t) - G_{sub}(t)\right). \tag{1}$$

$G_{sub}(t)$ is the subcutaneous glucose and $G(t)$ is the blood glucose. τ_{sub} is the time constant associated to glucose transport from blood to subcutaneous tissues.

The second part models non-Gaussian sensor noise. It is given by

$$\begin{cases} e_1 &= v_1, \\ e_k &= 0.7(e_{k-1} + v_n), \end{cases} \tag{2a}$$

$$v_k \sim N_{iid}(0, 1), \tag{2b}$$

$$\eta_k = \xi + \lambda \sinh\left(\frac{e_k - \gamma}{\delta}\right). \tag{2c}$$

Consequently, the glucose value returned by the CGM is

$$G_{CGM}(t_k) = G_{sub}(t_k) + \eta_k. \tag{3}$$

Table 2 provides the numerical values used in our CGM model.