Journal of Process Control 68 (2018) 105–117

Contents lists available at ScienceDirect

Journal of Process Control

journal homepage: www.elsevier.com/locate/jprocont

Adaptive model predictive control for a dual-hormone artificial pancreas

Dimitri Boiroux[a,b], Vladimír Bátora[c], Morten Hagdrup[a], Sabrina Lyngbye Wendt[a,d], Niels Kjølstad Poulsen[a], Henrik Madsen[a], John Bagterp Jørgensen[a,*]

[a] Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark
[b] Danish Diabetes Academy, Odense University Hospital, DK-5000 Odense C, Denmark
[c] Faculty of Electrical Engineering and Information Technology, Slovak University of Technology, SK-81243 Bratislava, Slovakia
[d] Department of Bioanalysis & Pharmacokinetics, Zealand Pharma A/S, DK-2600 Glostrup, Denmark

ARTICLE INFO

Article history:
Received 27 March 2017
Received in revised form 2 May 2018
Accepted 7 May 2018

Keywords:
Type 1 diabetes
Artificial pancreas
Insulin and glucagon
Model predictive control
Adaptive control

ABSTRACT

We report the closed-loop performance of adaptive model predictive control (MPC) algorithms for a dual-hormone artificial pancreas (AP) intended for patients with type 1 diabetes. The dual-hormone AP measures the interstitial glucose concentration using a subcutaneous continuous glucose monitor (CGM) and administers glucagon and rapid-acting insulin subcutaneously. The discrete-time transfer function models used in the insulin and glucagon MPCs comprise a deterministic part and a stochastic part. The deterministic part of the MPC model is individualized using patient-specific information and describes the glucose-insulin and glucose-glucagon dynamics. The stochastic part of the MPC model describes the uncertainties that are not included in the deterministic part of the MPC model. Using closed-loop simulation of the MPCs, we evaluate the performance obtained using the different deterministic and stochastic models for the MPC on three virtual patients. We simulate a scenario including meals and daily variations in the model parameters for two settings. In the first setting, we try five different models for the deterministic part of the MPC model and use a fixed model for the stochastic part of the MPC model. In the second setting, we use a second-order model for the deterministic part of the MPC model and estimate the stochastic part of the MPC model adaptively. The results show that the controller is robust to daily variations in the model parameters. The numerical results also suggest that the deterministic part of the MPC model does not play a major role in the closed-loop performance of MPC. This is ascribed to the availability of feedback and the poor prediction capability of the model, i.e. the large disturbances and model-patient mismatch. Moreover, a second order adaptive model for the stochastic part of the MPC model offers a marginally better performance in closed-loop, in particular if the model-patient mismatch is large.

1. Introduction

Diabetes is a metabolic disease affecting around 9% of the worldwide adult population in 2014 and its prevalence is increasing [1]. When untreated, it is characterized by elevated blood glucose levels, i.e. hyperglycemia. Type 1 diabetes (T1D) accounts for 5–10% of the patients suffering from diabetes. T1D develops when the immune system destroys the insulin-producing β-cells in the islets of Langerhans in the pancreas. This condition leads to a deficiency in endogenous insulin production. To keep the glucose level under control and avoid the long-term complications associated with hyperglycemia, patients with T1D have to administer insulin exogenously. Nowadays, an increasing number of patients with T1D use a continuous subcutaneous (sc) insulin infusion (CSII) pump combined with an sc continuous glucose monitor (CGM). This sensor-augmented pump therapy has improved glucose regulation compared to multiple daily insulin injections (MDI) using a pen combined with fingerprick glucose measurements [2–4]. Nevertheless, the current insulin therapies are usually titrated empirically by the patient and their physician, and still a majority of patients with T1D do not meet treatment goals due to difficulties to control their blood glucose [5].

For more than 50 years, scientists have been trying to replace the patient decisions with an automated closed-loop insulin deliv-

* Corresponding author.
E-mail address: jbjo@dtu.dk (J.B. Jørgensen).

https://doi.org/10.1016/j.jprocont.2018.05.003
0959-1524/

Nomenclature

A_G [–] Carbohydrate bioavailability
$D_1(t), D_2(t)$ [mg/kg] Glucose in the first and the second compartment per body weight
$D_G(t)$ [mg/kg/min] Carbohydrate intake per body weight
$G(t)$ [mg/dL] Blood glucose concentration
G_b [mg/dL] Basal blood glucose concentration
$G_{sub}(t)$ [mg/dL] Interstitial glucose concentration
$I(t)$ [μU/dL] Plasma insulin concentration
I_b [μU/dL] Basal plasma insulin concentration
k_e [min^{-1}] Insulin clearance rate
k_N [min^{-1}] Glucagon clearance rate
$N(t)$ [pg/dL] Plasma glucagon concentration
N_b [pg/dL] Basal plasma glucagon concentration
p_2 [min^{-1}] Inverse of a time constant describing insulin action
p_3 [min^{-1}] Inverse of a time constant describing glucagon action
$R_a(t)$ [mg/min/kg] Glucose rate of appearance per body weight
$S_1(t), S_2(t)$ [μU/kg] Two-compartment absorption model of subcutaneously administered insulin
S_G [min^{-1}] Fractional glucose effectiveness
S_I [min^{-1}/(μU/dL)] Insulin sensitivity
S_N [min^{-1}/(pg/dL)] Glucagon sensitivity
t_I [min] Insulin absorption time constant
t_N [min] Glucagon absorption time constant
t_{sub} [min] Time constant associated to glucose transport from blood to interstitial tissues
$u_1(t)$ [μU/kg/min] Subcutaneous insulin infusion rate per body weight
$u_2(t)$ [pg/kg/min] Subcutaneous glucagon infusion rate per body weight
V [dL/kg] Glucose distribution volume
V_I [mL/kg] Distribution volume of plasma insulin
$X(t)$ [min^{-1}] Insulin action
$Y(t)$ [min^{-1}] Glucagon action
$Z_1(t), Z_2(t)$ [pg/kg] Two-compartment absorption of subcutaneously administered glucagon

ery system, known as the artificial pancreas (AP) [6,7]. A major concern for an AP is safety and in particular its ability to avoid insulin-induced hypoglycemia (low blood glucose). One way to prevent hypoglycemia or to reduce the duration of hypoglycemic events is to include glucagon in the AP. While insulin decreases the blood glucose concentration, glucagon increases the blood glucose concentration. An AP able to administer insulin and glucagon is referred to in this paper as a dual-hormone AP while it in other works also is referred to as a bihormonal AP or a (bihormonal) bionic pancreas [8–16]. Current versions of the dual-hormone AP consist of a CGM, a control algorithm, and two pumps for insulin and glucagon administration. Regular glucagon is not stable in an aqueous liquid formulation under standard conditions and has to be dissolved immediately before use. Therefore, its use has been limited to hypoglycemia rescue kits. Stable liquid formulations of glucagon or glucagon analogues have the potential to be used in pumps [17–19]. Results from simulations and clinical studies show that a dual-hormone AP has the potential to increase the safety of the glucose control and provide tighter regulation than a single-hormone AP without increasing the risk of hypoglycemia [10,11,14,15,20–22]. However, the conditions at which glucagon is efficient as well as the long-term benefits and risks of exogenously administered glucagon still remain to be investigated [23–25].

Various control strategies for the AP have been investigated and tested [26–32]. The comparison between these control strategies is beyond the scope of this paper. Yet, a popular approach with promising results is Model Predictive Control (MPC) [33–41]. At every time sample, an optimal control problem (OCP) is solved to optimize the insulin or glucagon dosage based on (i) the glucose levels, the insulin and the glucagon history, (ii) an individualized filtering and prediction model describing the effects of sc delivered insulin and glucagon on the interstitial glucose concentration measured by an sc CGM, (iii) a desired glucose trajectory, and (iv) feedforward information (e.g. meal announcement). The insulin or glucagon input corresponding to the first sample period is administered to the patient and this procedure is repeated at the next time sample (for instance when a new CGM measurement becomes available). The main advantage of MPC is the ability to take into account the constraints on inputs and outputs in a straightforward and proactive way.

One component of the MPC is the model used to make predictions. Several linear models used for modeling and/or control have been tested: Gondhalekar et al. used a second order transfer function with a delay [42]; Kirchsteiger et al. used a third order transfer function with an integrator [43]; Heusden et al. used a third order discrete transfer function model [44]; Percival et al. applied a first order transfer function with a time delay and an integrator [45]. Soru et al. and Messori et al. used higher order linear models with 13 states [46,47]. In our previous work, we established that the choice of the transfer function model describing the glucose-insulin dynamics does not significantly affect the performance of the closed-loop controller [48] and we used a second order transfer function model [22,49,50].

Disturbances, such as meal intake, physical exercise, stress, illness and metabolic changes affect the insulin needs throughout the day. These disturbances have to be distinguished from CGM noise. The effects of these disturbances are difficult to estimate, and therefore are usually represented as a disturbance model [51]. The tuning of this disturbance model can play a significant role in the performance of the closed-loop controller [52–55], but its importance in the design of an AP has not been investigated in detail. An adaptive control algorithm can contribute to the tuning of the disturbance model [37,56,57].

The purpose of the present paper is to discuss the importance of the model used by the MPC in an AP for its closed-loop performance. We investigate the effect of the deterministic part of the MPC model as well as the effect of the stochastic part of the MPC model. We do this by studying the resulting simulated closed-loop performance obtained by the MPC for different filtering and prediction models using a nonlinear simulation model, which is different from the filtering and prediction models used by the MPC. We use a control strategy that allows administration of insulin and glucagon. We state and compare MPCs based on five different low order models for the deterministic part of the MPC model, and two different lower order models for the stochastic part of the MPC model, such that these models can easily be identified in a clinical study. Also, an advantage of our approach is that the controller design only requires patient-specific information and does not use any prior clinical data. The closed-loop simulations are conducted for three virtual patients using a scenario consisting of 30 h with everyday meal events and parameter variations reflecting the circadian rhythm.

Fig. 1 shows a diagram of the AP setup used in this paper. A model simulates the glucose-insulin-glucagon dynamics for three virtual patients. This *simulation* model is summarized in Section 2. Section 3 introduces individualized control-relevant deterministic transfer function models of insulin-glucose and glucagon-glucose dynamics that are used in the MPC. Section 4 describes the stochastic model structure considered in the paper, the recursive extended