Journal of Process Control 64 (2018) 27–36

Contents lists available at ScienceDirect

Journal of Process Control

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

Glucose-insulin model identified in free-living conditions for hypoglycaemia prevention

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ARTICLE INFO

Article history:
Received 20 December 2017
Received in revised form 5 February 2018
Accepted 6 February 2018

Keywords:
Identification
Validation
Artificial pancreas
Clinical trial
Type 1 diabetes
MPC

ABSTRACT

Hypoglycaemia avoidance is one of the main barriers to the optimal management of Type 1 Diabetes (T1D). In order to attenuate the effect of hypoglycaemia, alarm systems support T1D subjects equipped with Continuous Glucose Monitoring (CGM) devices. The development of predictive detection tools for hypoglycaemia and CGM have been accelerated by Artificial Pancreas (AP), a closed-loop systems for automatic blood glucose control in T1D subjects. The methods to generate hypoglycaemia alarms can be divided in two categories: low-threshold detection and prediction. The first notifies the crossing of a critical blood glucose level, while the second predicts this risk in advance and it is typically based on a patient model. Considering the significant inter-patient variability characterizing T1D subjects, patient-tailored models are required. In this regard, different individualization techniques have been proposed showing significant improvements compared to "average" models. This paper proposes an alarm system based on patient-tailored models obtained through an identification technique that exploits impulse response data collected in silico and that is extended here to be used on free-living data. In particular, the data used in this work derive from a 1 month AP trial performed in free-living conditions. Individualized models obtained with different identification parameters are compared. Independently of the selected parameters, the patient-tailored models show superior predictive performance with respect to the "average" model used in the Model Predictive Control (MPC) algorithm used in the trial. The best model is used to design an alarm system which shows significant improvements in hypoglycaemia detection in comparison with the safety system used in the trial: true positive are increased by 31% with a decrease of the false positive by 57%. The promising prediction capabilities of the proposed patient-tailored models can be a key ingredient for a new generation of individualised MPC for AP.

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1. Introduction

Type 1 Diabetes (T1D) is a pathology characterized by high Blood Glucose (BG) level, known as hyperglycemia (BG > 180 mg/dl), caused by the dysfunction of pancreatic β-cells responsible for the production of insulin. Subjects with T1D need exogenous insulin administration to maintain the BG level in the acceptable range [70–180 mg/dl]; the goal is to minimize diabetes complications related to hyperglycemia and simultaneously avoid hypoglycaemia (BG < 70 mg/dl), a condition that could be caused by excessive insulin administration. Hypoglycaemia avoidance is one of the main barriers to optimal management of diabetes.

In order to ensure the patient safety, alarm systems were designed to detect hypoglycaemia risks and eventually prevent them [1]. These alarms are already present on some commercial CGM devices and they have a key role in a successful insulin treatment. The development of detection systems for hypoglycaemia has been accelerated by Artificial Pancreas (AP), a closed-loop system for automatic blood glucose control in T1D subjects [2–4]. In fact, in order to perform long trial in free-living conditions, the AP has to be equipped with a safety system to prevent hypoglycaemia. In the last two years a number of clinical studies have shown the efficacy of AP prototypes used from 1 to 6 months [5–9].

The methods designed to generate the alarms can be divided in two categories: low-threshold detection or prediction. Hypoglycaemia alarms based on low-threshold detection notify the crossing of a critical BG level [10], while alarms based on prediction try to forsee this risk in advance to give the user the opportunity to act

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https://doi.org/10.1016/j.jprocont.2018.02.003
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ahead of time in order to avoid the event [11–14]. The latter typically requires the use of patient models to perform glucose trend predictions.

Glucose-insulin minimal models were the first to be accepted both as a clinical tool and an approach to understand the composite effects of insulin secretion and insulin sensitivity on glucose tolerance [15,16]. However, since a significant inter-patient variability characterizes T1D population, the need for more detailed models equipped with a virtual population was absolutely clear in order to accelerate the development of an AP. A rich population model could in fact substitute the animal trials with the in silico ones. The first example was the UVA/Padova simulator [17,18] that offers a compartmental model equipped with 100 vectors of model parameters, the so called "virtual patients". The average parameters vector of these patients describes the so called "average patient" that represents a patient with the average dynamics of the population. A third class of models typically identified from real-life data consists in black-box linear models. Recently, new identification techniques have been investigated [19–26]. For a comprehensive literature review and some interesting related papers we refer the interested reader to [27–31].

Promising results have been obtained on this topic also by our group [32–34]. These algorithms have been successfully tested in silico, i.e. using the UVA/Padova simulator [17,18] and some of them have been compared to "average" virtual model in [34]. In silico data were obtained through closed-loop simulations of realistic clinical protocols designed to produce a sufficient input-output excitation without compromising the patient safety.

The big challenge of this paper is to use one of the proposed algorithms to identify individualized models from free-living data [5] and to develop a personalized hypoglycaemia alarm system validated on a rather long period (1 month). Along this line, an intermediate step was successfully addressed in [33] where real data were used even if not collected in free-living conditions, but during a short and controlled trial on hospitalized patients (less than 24h). In that case the non-parametric technique described in [34] was tested. The identification of reliable models on real data is more difficult than on simulated ones. Moreover, free-living conditions are much more challenging than the highly controlled experimental conditions of in hospital studies, due to the many confounding factors affecting blood glucose in real-life, such as physical exercise and differences in daily activities. Technical issues affecting the AP prototype, adopted during the trials, and human errors in patient-provided information further complicate this set-up. All these aspects require adaptations of the identification techniques, originally developed for in silico data, to deal with all these issues.

The identification technique adopted in this paper is the extension of the Impulse-Response (IR) technique described in [32] to cope with free-living data proposed in [35]. This technique is rather simple and obtained very promising in silico results. In order to evaluate the quality of the proposed individualized model, two different comparisons have been performed: the first with the "average" model used to design an MPC and the second with a safety system. Both the considered MPC and the safety system were used in several recent clinical trials and in particular in the one considered in this paper [5]. The performance achieved on the real-life data by the proposed individualized model with different identification parameters are compared with the one achieved by the model used to design the MPC algorithm which was derived via linearization from the "average" model of the adult population of the UVA/Padova simulator. This "average" model showed good performance when used in the MPC algorithm tested during several trials and in particular in the one which achieved a significant reduction of the HbA1c [36]. The patient-tailored model with the parameters that obtained the best performance is used to create a system to detect in advance hypoglycaemia phenomena. The performance of the proposed system is compared to the one achieved by the algorithm for hypoglycaemia prevention [12] used in several clinical trials, see e.g. [5,36]. The new alarm system shows significant improvements in hypoglycaemia detection in terms of both true and false positive. The core of the AP adopted in [5,7,37–41] is constituted by the MPC algorithm described in [42]. The improvement of the prediction capability of the individualized model with respect to "average" model used to synthetize this MPC algorithm paves the way for a new generation of individualized MPC for AP.

The paper is structured as follows. In Section 2 we describe the model identification method. In Section 3 we describe the type of data employed in this paper: trials description, data preprocessing, training and test sets. Section 4 introduces the metrics used to evaluate the model identification technique. Section 5 presents and discusses the identification results. In Section 6 the individualized alarm system is proposed. In Section 7 the metrics used to evaluate the alarm system are introduced. The results obtained with the new alarm system are proposed in Section 8. Conclusions are drawn in Section 9.

2. Model identification

The measurable inputs of the patient model are the injected insulin in pmol/min/kg, $i(k)$, and the carbohydrates content in mg, $m(k)$. The model output is the glucose concentration measured by the CGM sensor, $CGM(k)$. All these signals are collected every T_s minutes, with $T_s = 5$ [min]. Denoting with $I(z)$, $M(z)$ and $CGM(z)$ the Z-transforms of inputs and output, the model has the following structure:

$$CGM(z) = G_i(z)I(z) + G_m(z)M(z) + E(z) \tag{1}$$

where $G_i(z)$ and $G_m(z)$ are transfer functions to be estimated from the data and $E(z)$ is the Z-transform of the residual error $e(k)$. Besides insulin and meal, a number of other unmeasurable factors affect blood glucose concentration, first and foremost physical exercise, but also stress, illness, menstrual cycle, etc. The effect of these unmeasured factors and other unmodeled dynamics are partially accounted for by assuming $e(k)$ to be a coloured noise, i.e. assuming that $e(k)$ is correlated with the past errors $e(k-1)$, $e(k-2)$, ... Also the spectral characterization of the error has to be estimated from the data.

2.1. Continuous-time impulse response model

In order to successfully identify a black-box model, it is necessary to have sufficiently exciting input data and to properly define the order of the system. Impulse signals are the most exciting inputs and are naturally used in continuous time. Hence, following the procedure described in [32], we first identify a continuous-time model to describe the deterministic part of the system:

$$CGM(s) = G_i(s)I(s) + G_m(s)M(s)$$

where $G_i(s)$ and $G_m(s)$ are transfer functions to be estimated from the data, $I(s)$, $M(s)$ and $CGM(s)$ are the Laplace transforms of inputs, $i(t)$ and $m(t)$, and output, $CGM(t)$. Due to the impossibility of performing extensive and potentially dangerous experiments on human subjects, the identification technique is divided in two steps: the first one is entirely developed on the "average" in silico patient (Av) of the UVA/Padova simulator [18] with highly exciting input data that could not be applied on human subjects. For example, it is important to have insulin boluses (impulse-like amount) without meal intake as well as uncontrolled meals (meals without insulin boluses). The outputs of this first step are the two transfer functions $G_i(s)$ and $G_m(s)$ that describe the dynamics of the "average" patient. Starting from the Av model obtained in step 1, the

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