Journal of Process Control 24 (2014) 171–181

Contents lists available at ScienceDirect

Journal of Process Control

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

Experimental blood glucose interval identification of patients with type 1 diabetes☆

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ARTICLE INFO

Article history:
Received 5 March 2013
Received in revised form
20 September 2013
Accepted 20 September 2013
Available online 21 December 2013

Keywords:
Interval model
Identification
Type 1 diabetes
Variability

ABSTRACT

Many problems are confronted when characterizing a type 1 diabetic patient such as model mismatches, noisy inputs, measurement errors and huge variability in the glucose profiles. In this work we introduce a new identification method based on interval analysis where variability and model imprecisions are represented by an interval model as parametric uncertainty.

The minimization of a composite cost index comprising: (1) the glucose envelope width predicted by the interval model, and (2) a Hausdorff-distance-based prediction error with respect to the envelope, is proposed. The method is evaluated with clinical data consisting in insulin and blood glucose reference measurements from 12 patients for four different lunchtime postprandial periods each.

Following a "leave-one-day-out" cross-validation study, model prediction capabilities for validation days were encouraging (medians of: relative error = 5.45%, samples predicted = 57%, prediction width = 79.1 mg/dL). The consideration of the days with maximum patient variability represented as identification days, resulted in improved prediction capabilities for the identified model (medians of: relative error = 0.03%, samples predicted = 96.8%, prediction width = 101.3 mg/dL). Feasibility of interval models identification in the context of type 1 diabetes was demonstrated.

1. Introduction

The term diabetes mellitus describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin. Type 1 diabetes mellitus (T1DM), one of the most common chronic diseases in childhood, is caused by absolute insulin deficiency following destruction of the insulin-producing pancreatic beta cells. It most commonly presents in childhood, but one-fourth of cases are diagnosed in adults. Hyperglycemia, if not treated, can result either in acute (ketoacidosis) or chronic complications (microangiopathy leading to blindness and renal failure). The standard treatment consists in insulin replacement by means of insulin pens (multiple daily injections – MDI) or insulin pumps (continuous subcutaneous insulin infusion – CSII), based on self-monitoring of capillary blood glucose concentration (SMBG). However, insulin dosing is an empirical process and frequently results in under- or over-insulinization, causing respectively hyper- and hypoglycemia. Hypoglycemia may have severe short-term complications such as confusion, falls, seizures, coma or even death.

Recent advances in continuous glucose monitoring (CGM) devices allow for the estimation of plasma glucose concentration every 1–5 min, providing much more information than the traditional sparse capillary measurements of SMBG. Although CGM devices are only approved as adjunctive to SMBG due to their suboptimal accuracy, especially in hypoglycemia [1], they have fostered research on closed loop glucose control (the so-called artificial pancreas, AP) [2]. Several prototypes of an AP have been proven successful in the nocturnal period [3,4], but an efficient control for the postprandial period remains a challenge, due to the big disturbance introduced by the meal and limitations inherent to the administration of insulin into the subcutaneous tissue [5].

Effectiveness of an AP implementing model-based controllers depends on the accuracy of the individual model obtained for each patient. However, model individualization has been proven difficult for data-based models [6–8] or physiology-based models [9]. Several strategies have been proposed for improving the quality of the data acquired for model identification using optimal experiment design [10,11], but very few of these experiments have actually

Abbreviations: CGM, continuous glucose monitoring; AP, artificial pancreas; CHO, carbohydrates; CSII, continuous subcutaneous insulin infusion; MARD, mean absolute relative deviation; SMGB, self-monitored blood glucose.

☆ The research leading to these results has received funding from the Spanish Ministry of Science and Innovation under grant DPI2010-20764-C02-01, the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement FP7-PEOPLE-2009-IEF, Ref 252085 and the GeneralitatValenciana through Grant GV/2012/085.

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http://dx.doi.org/10.1016/j.jprocont.2013.09.015

come to execution due to its complexity. Furthermore, suitability of classical metrics such as mean square error for model evaluation has recently been questioned in the context of diabetes [12] where clinical implications of prediction errors must be considered.

There are two main barriers to individual patient's model identification: error/noise sources in the measurement devices (especially with the use of CGM devices for ambulatory data acquisition), and uncertainty/variability in the patient's behavior because of circadian rhythms and other non-modeled dynamics, such as alterations in the endocrine system, changes in daily life, stress and illness. Despite the high variability observed in the clinical practice [13], parametric uncertainty has not generally been included into the identification process, leading to average models with poor predictive capabilities. Exceptionally, in [14] the identification of input–output models with uncertain parameters is considered. An interval model is built based on standard optimization techniques penalizing the variance of the identified values for a collection of model instances. However, this ad hoc solution lacks the inclusion properties and mathematical guarantee expected for an interval model, which is granted by the well-established area of interval analysis [15,16] and error-bounded identification [17]. In [18] a guaranteed method is presented, and evaluated with in silico data.

Indeed, interval models are a natural way to express intra-patient variability and have been used in the past for model-based insulin therapy design [19,20], risk analysis [21] and fault-detection [22]. However, the identification of such interval models from clinical data has not been sufficiently addressed. In this work, the feasibility of interval model identification for the characterization of intra-patient variability is investigated in clinical data. The minimization of a composite cost index comprising: (1) the glucose envelope width predicted by the interval model, and (2) a Hausdorff-distance-based prediction error with respect to the envelope, is proposed. A cross-validation study is performed for the evaluation of the method using clinical data from 12 patients with type 1 diabetes who underwent four in-clinic mixed meal tests with standardized initial conditions.

2. Methods

2.1. Data sets

Twelve subjects with type 1 diabetes under CSII (male/female 3/9, age 41.8 ± 7.3 years, diabetes duration 20 ± 10 years, HbA1c 8.0 ± 0.6%, [mean ± SD]) were monitored in their postprandial state on four occasions. On two occasions the patients received a mixed meal containing 40 g of CHO. On the other two occasions they ate a meal with the same relative macronutrients composition but with greater CHO content (100 g). For each meal, either a standard bolus or a computer-generated bolus–basal combination was administered following randomization [13]. Pre-prandial plasma glucose was set around 100 mg/dL by means of a manual feedback intravenous insulin infusion. Hypoglycemia was avoided by using intravenous glucose infusion in case the patient's glucose levels were decreasing rapidly toward hypoglycemic levels. Plasma glucose was measured for 5 h after the meal, every 5 min the first 2 h after the meal and every 10 min afterwards, using a reference method (YSI 2300 STAT Plus Glucose analyzer, Yellow Springs Instruments, Ohio, USA). Plasma insulin was also measured periodically (every 15 min the first 2 h, and every 30 min afterwards) along all the duration of the experiment. To remove antibody-bound insulin, plasma was mixed with an equal volume of 30% polyethylene glycol immediately after blood collection [23]. The local Ethical Committee approved the study and the patients gave the written consent.

Due to the different sampling periods of the measurements, cubic spline interpolation was applied in order to get sample-per-minute data on all variables. Due to the high accuracy of YSI measurements [24] uncertainty modeling effort can be focused only in model inaccuracies and within-patient variability.

2.2. Interval models

Interval models represent model uncertainty as interval-valued parameters and have been successfully applied to robust analysis and control in diverse domains [16]. Identification of interval models has been traditionally addressed under the framework of bounded-error identification [17], i.e., the set of parameter values consistent with a given acceptable bound on the prediction error is computed:

$$\mathbb{P} = \left\{ p \in \mathbb{R}^{n_p} | y(t_i; p) - y^*(t_i)| \leq e_i \right\} \tag{1}$$

where p is the parameter vector of dimension n_p, $y^*(t_i)$ and $y(t_i; \boldsymbol{p})$ are the measurement and model prediction, respectively, at sample i and e_i is the acceptable prediction error bound. However, when large intra-patient variability is present no consistent parameter values will generally be found. If for the same meal and insulin dose the patient behaves very differently, no intersection between the acceptable output intervals will exist yielding an empty set for $\mathbb{P}$.

However, robust predictions for therapeutical decisions can be achieved if the interval model is able to *bound* the patient's response, i.e., the experimental measurements should be included in the output envelope predicted by the model at each time instant i

$$y^*(t_i) \in y(t_i; \mathbb{P}), \quad \forall i \in I \tag{2}$$

where $y(t_i; \mathbb{P}) = [\underline{y}(t_i; \mathbb{P}), \bar{y}(t_i; \mathbb{P})]$ stands for the *interval* prediction at time instant i for the to-be-identified parameter set $\mathbb{P}$ and $I = \{1, \ldots, n\}$ is the index set of the available measurements. In practice, a relaxation of the above problem may be needed, allowing for small errors with respect to the inclusion envelope due to noise in the measurements and compensation for non-modeled dynamics.

2.3. Model identification

2.3.1. Model

The glucoregulatory model published by Hovorka et al. [25] was used in this work. The model has been extensively used in the context of glucose control, and was recently included in a simulation platform for in silico evaluation of controllers [26]. The model equations are included in the following for self-containment of the manuscript:

$$U_g(t) = \frac{D_g \cdot A_g \cdot t \cdot \mathrm{e}^{-t/t_{\max G}}}{t_{\max G}^2} \tag{3}$$

$$\dot{x}_1(t) = -k_{a1} \cdot x_1(t) + k_{a1} \cdot S_{IT} \cdot I(t) \qquad x_1(0) = 0 \tag{4}$$

$$\dot{x}_2(t) = -k_{a2} \cdot x_2(t) + k_{a2} \cdot S_{ID} \cdot I(t) \qquad x_2(0) = 0 \tag{5}$$

$$\dot{x}_3(t) = -k_{a3} \cdot x_3(t) + k_{a3} \cdot S_{IE} \cdot I(t) \qquad x_3(0) = 0 \tag{6}$$

$$\mathrm{EGP}(t) = \max(0, \mathrm{EGP}_0 \cdot [1 + x_3(t)]) \tag{7}$$

$$F_{01}^c(t) = \frac{F_{01} \cdot G(t)}{0.85 \cdot (G(t) + 1)} \tag{8}$$

$$F_R(t) \begin{cases} R\_cl \cdot [G(t) - R\_thr] & \text{if } G(t) \geq R\_thr \\ 0 & \text{otherwise} \end{cases} \tag{9}$$