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Optimal online selection of type 1 diabetes-glucose metabolism models

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ABSTRACT

We address an optimal experimental design (OED) procedure for the online selection of type-1-diabetes (T1D) mellitus glucose metabolistic models. A fully observable reduced-order nonlinear dynamic model is presented and subsequently parameterised for Göttingen Minipigs and patients, that were both subject to an automatic insulin delivery. A bank of continuous–discrete unscented Kalman filters (CDUKF) is designed and parameterised for Göttingen Minipigs and patients. Based on this filter bank of CDUKF, a novel online OED design procedure is developed, that is used to identify the correct parameter set out of several available sets for measured blood glucose concentrations. The procedure utilises forward model simulations to calculate optimal system inputs. This leads to the identification of the correct parameter set under arbitrary conditions. Results are presented for both subgroups.

1. Introduction

The regulation of blood glucose (BG) concentration is an critical control loop of the human body. In the case of diabetes mellitus, the body internal regulation of BG concentration is not functioning properly anymore leading to an often increased blood glucose concentration (hyperglycaemia). Diabetes mellitus is characterised by high BG levels beyond 126 mg/dl (7 mmol/l) in fasting state or beyond 200 mg/dl (11.1 mmol/l) in oral glucose tolerance test by increased HbA1c fraction (> 6.5 %). Diabetes mellitus is a metabolic disease with a worldwide increasing prevalence; global estimates predict a number of 592 million people with diabetes mellitus by the year 2035, while 382 million people were accounted with diabetes mellitus in 2013 (International Diabetes Federation (IDF), Shaw, Sicree, & Zimmet, 2010).

In this contribution we concentrate on type-1-diabetes mellitus (T1D), which makes up for about 10% of all diabetes mellitus patients. T1D is characterised by a deficiency of insulin producing β-cells and associated with hyperglycaemia that may, in turn, lead to severe secondary complications, if not properly treated (Libby, et al., 2005). Manual insulin therapy is currently conducted by T1D patients and consists of (1) glucose concentration measurements and (2) the computation of suitable insulin dose, that is (3) subcutaneously injected by the patient. The manual therapy is suboptimal for a number of reasons: Manual insulin therapy typically consists of a number of time-discrete and occasional measurements (3–5 measurements/day), such that a sufficiently fast reaction to changes in BG concentration cannot be guaranteed in general. As a result, episodes of hyper- or hypoglycaemia occur relatively often in manual insulin therapy. Moreover, uncertainties associated with subcutaneous insulin application (Binder, Lauritzen, Faber, & Pramming, 1984) and time-varying parameters of the metabolic system (Hirsch, Farkas-Hirsch, & Skyler, 1990) make the manual therapy difficult even for experienced adult patients. Although continuous glucose monitors (CGM), continuous subcutaneous insulin infusion (CSII), and sensor-augmented pumps (SAP) have been introduced in recent years, the use requires significant patient input and the compliance of the patients (Giani, Scaramuzza, & Zuccotti, 2015).

The artifical pancreas (AP) has been proposed in the former century and has been well researched over the last decades (Chee & Fernando, 2007; Lunze, Singh, Walter, Brendel, & Leonhardt, 2013; Parker, Doyle, Ward, & Peppas, 2000). Three main components are needed for a realisation of the AP: (I) a feedback controller, (II) measured BG concentration or CGM values, and (III) insulin pump infusion rates. Although there exist first studies of an AP validated in clinical closed-loop studies (for example Dassau, et al., 2013) and an FDA approved device that can automatically adjust an insulin basal rate (670G, Medtronic plc, Dublin Ireland) there is still no fully automated AP available as a product. The main reasons for this are twofold: There exist technical

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difficulties associated with minimising overall process time-delay by the use of continuously measuring blood glucose sensors and fail-safe insulin infusion pumps (Heinemann, Benesch, DeVries, et al., 2011). Moreover, the glucose metabolism is an uncertain, nonlinear dynamic system, undergoing exogenous disturbances, like meal uptake or activity. Uncertainties in the glucose metabolism consist, for example, of time-varying insulin sensitivity (the insulin sensitivity $k_{IS}(t)$ is a time-varying parameter that describes the amount of glucose that is transported from the blood to the muscle cells at a constant insulin concentration in blood) and intra-individual and inter-individual parameter uncertainty. From the literature (Skogestad & Postlethwaite, 2007), it is well known that the incorporation of, for example, large parametric uncertainty into a robust controller design procedure might lead to controller over-conservatism. However, controller over-conservatism with respect to robust performance is not acceptable, as it tends to lead to large overshoots (hyperglycaemia) in disturbance rejection. To alleviate the disadvantages associated with controller over-conservatism, adaptive or model-based controller design techniques can be employed (Misgeld, Tenbrock, Lunze, & Leonhardt, 2016b). Towards this end, we present a new method for the online selection of glucose metabolism models.

An optimal experimental design (OED) might have different goals, such as the optimal identification of parameters or the discrimination of a mathematical model that best fits with experimentally measured data. Here, we will concentrate on the latter approach, of which one can think as to derive a mathematical model S for each of the R hypothesis: $S_1, S_1, \dots, S_R$ (Burnham, Anderson, & Huyvaert, 2011). A general overview on OED is given by Franceschini and Macchietto (2008) and Pronzato (2008). The idea of competing hypotheses of possibly structurally different models can be found in many application areas, for example, systems biology (Schenkendorf, Kremling, & Mangold, 2009). Various methods are available in the literature, which are based on statistics/information theory. These methods typically rely on batch processing of measurements data $\boldsymbol{y}(t_k)$, where t_k denotes discrete time. Moreover, uncertainties are often not explicitly considered (Kremling et al., 2004; Ludden, Beal, & Sheiner, 1994). To overcome these shortfalls, we present an online OED that is able to employ an online adjustment in the feedback control-loop in order to optimise model discrimination. We furthermore develop a bank of filters with already existing parameter sets $\boldsymbol{\theta}(S_i)$ that represent characteristic animals or patients from the population. To our knowledge, this is the first OED approach for model discrimination with respect to glucose metabolism models.

This article is organised as follows. After briefly introducing the reduced-order model in Section 2, the design of the continuous–discrete unscented Kalman filters (CDUKF) and the approach to online OED design for model discrimination is presented in Section 3. Section 4 introduces the experimental studies from which the parameter sets are obtained. The OED model discrimination method is implemented in an *in-silico* study in Section 5. Finally, Section 6 concludes with a summary of the results and a discussion.

2. Reduced-order glucose metabolism model

The basis for the CDUKF bank is a fully observable reduced-order version of the Göttingen Minipig model (Lunze, et al., 2014) that was presented by Misgeld, Tenbrock, Lunze, Dietrich, and Leonhardt (2016a). In the following, for convenience, the reduced-order model is presented in a compact form. An overview of the reduced-order model is shown in Fig. 1 and consists of three main subsystems. These subsystems are the interstitium, the gastro-intestinal tract and the blood circulation. Interstitium and gastro-intestinal tract model account for the delay dynamics of subcutaneously applied insulin and orally uptaken carbohydrates (CHO), respectively. The blood circulation is described by a reduced-order dynamics and consists of insulin, glucose and glucagon compartments. Interstitial and gastro-intestinal models are connected to the blood circulation model via the subcutaneous insulin appearance rate $r_{ISC}(t)$ and the intravenous glucose appearance rate $r_{GGA}(t)$, respectively. Moreover, the model has a number of external inputs: $U_{sc}(t)$ is a subcutaneous infusion rate and $U_{iv}(t)$ is an intravenous insulin infusion rate. The pancreatic glucagon infusion rate $S_\Gamma(t) = r^N_{P\Gamma P}(t) r^B_{P\Gamma P} = r_{P\Gamma P}(t)$ is given by the pancreatic glucagon production $r^N_{P\Gamma P}(t)$, normalised to the basal rate by $r^B_{P\Gamma P}$. Externally applied glucose rates are the orally applied glucose rate $D_{oral}(t)$ and intravenously applied glucose rate $D_{iv}(t)$; the model output is the plasma glucose $G_P(t)$. Note that not all of the external inputs are used in the proposed filter and model discrimination procedure described below.

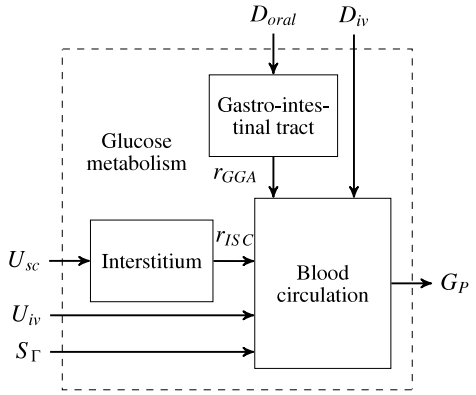

Fig. 1. Block diagram overview of the order-reduced glucose metabolism model showing external inputs and outputs.

2.1. Interstitium model

To model delay-dynamics (absorption kinetics) of subcutaneously administered insulin to appearance rate of insulin in the blood, a linear second-order ordinary differential equation (ODE) model is adopted from Wilinska, et al. (2005):

$$\begin{aligned} \frac{d\dot{M}^I_{sc,1}(t)}{dt} &= \frac{1}{T_{sc,1}}\left((1-x_U)U_{sc}(t) - \dot{M}^I_{sc,1}(t)\right) \\ \frac{d\dot{M}^I_{sc,2}(t)}{dt} &= \frac{1}{T_{sc,2}}\left(\dot{M}^I_{sc,1}(t) + x_U U_{sc}(t) - \dot{M}^I_{sc,2}(t)\right) \\ r_{ISC}(t) &= \dot{M}^I_{sc,2}(t). \end{aligned} \tag{1}$$

In Eq. (1), the states $\dot{M}^I_{sc,1}(t)$ and $\dot{M}^I_{sc,2}(t)$ denote nonmonomeric (inactive) insulin and monomeric (active) insulin, respectively. Moreover, x_U is a fractional parameter used to describe the partially activated insulin. Time constants are denoted as $T_{sc,1}$ and $T_{sc,2}$.

2.2. Gastro-intestinal tract model

Time-delay of orally uptaken glucose is described by two coupled first-order ODEs

$$\begin{aligned} \frac{d\dot{M}^G_{ing,1}(t)}{dt} &= \frac{1}{T_{ing,1}}\left(D_{oral}(t) - \dot{M}^G_{ing,1}(t)\right) \\ \frac{d\dot{M}^G_{ing,2}(t)}{dt} &= \frac{1}{T_{ing,2}}\left(\dot{M}^G_{ing,1}(t) - \dot{M}^G_{ing,2}(t)\right) \\ r_{GGA}(t) &= f_G\,\dot{M}^G_{ing,2}(t), \end{aligned} \tag{2}$$

adopted from Hovorka, et al. (2004). The states $\dot{M}^G_{ing,1}(t)$ and $\dot{M}^G_{ing,2}(t)$ in Eq. (2) represent solid phase glucose mass flow in the stomach and liquid phase mass flow in the intestine, respectively. Moreover, f_G is the bioavailability of glucose, that is employed to calculate the glucose appearance rate in the blood $r_{GGA}(t)$. $T_{ing,1}$ and $T_{ing,2}$ denote time-constants.