Control Engineering Practice 55 (2016) 80–90

Contents lists available at ScienceDirect

Control Engineering Practice

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

Estimation of insulin sensitivity in diabetic Göttingen Minipigs

Berno J.E. Misgeld [a,*], Philipp G. Tenbrock [a], Katrin Lunze [b], Johannes W. Dietrich [c], Steffen Leonhardt [a]

[a] Philips Chair for Medical Information Technology, RWTH Aachen University, Aachen, Germany
[b] Abiomed Europe GmbH, Aachen 52074, Germany
[c] Endocrine Research, Bergmannsheil University Hospitals, Ruhr University of Bochum, Bochum 44789, Germany

ARTICLE INFO

Article history:
Received 7 March 2016
Received in revised form
18 May 2016
Accepted 7 June 2016
Available online 18 July 2016

Keywords:
Type 1 diabetes mellitus
Extended Kalman filter
Nonlinear dynamics
State estimation
Göttingen Minipigs

ABSTRACT

In patients with type 1 diabetes mellitus, insulin sensitivity is a parameter which strongly affects insulin therapy. Due to its time-dependent variation, this parameter can improve the strategy for automatic closed-loop blood glucose control. The aim of this work is to estimate the insulin sensitivity of patients with type 1 diabetes mellitus based on measured blood glucose concentrations. For this, an Extended Kalman Filter is used, based on a simplified version of the well-known Sorensen model. The compartment model of Sorensen was adapted to the glucose metabolic behaviour in diabetic Göttingen Minipigs by means of experimental data and reduced by neglecting unobservable state variables. Here, the Extended Kalman Filter is designed for simultaneous state and parameter estimation of insulin sensitivity using the insulin infusion rate and the meal size as input signals, and measurements of blood glucose concentration as output signal. The performance of the Extended Kalman Filter was tested in *in silico* studies using the minipig model, and is analysed by comparing the output signal of the filter with measurement data from the animal trials.

1. Introduction

1.1. Diabetes mellitus

Diabetes mellitus is a widespread metabolic disease with increasing prevalence. It is characterised by unphysiologically high blood glucose concentration levels ≥126 mg/dl (7 mmol/l) in fasting state or ≥200 mg/dl (11.1 mmol/l) in oral glucose tolerance tests by an increased HbA1c fraction (> 6.5%) indicating increased blood glucose levels on a longer time scale. According to the World Health Organization about 347 million people suffer from diabetes mellitus. Moreover, according to the International Diabetes Federation, numbers are expected to increase up to 552 million by 2030 (Shaw, Sicree, & Zimmet, 2010). About 10% of patients suffer from type 1 diabetes (T1D) mellitus. In T1D patients, a deficiency of insulin producing pancreatic β-cells and a concomitantly high blood glucose levels can lead to secondary complications of diabetes, unless treated by adequate exogenous insulin therapy. Secondary diabetes complications may affect the heart, blood vessels and the peripheral nervous system, and may finally lead to, for example, cardiovascular disease or lower limb amputation.

An artificial pancreas (AP) has the potential to alleviate secondary diabetes complications by introducing a tight control of blood glucose levels. The basic concept is to automate (or semi-automate) the application of insulin in a system, consisting of three main components: a blood glucose sensor, a programmable insulin pump, and a control algorithm that calculates insulin infusion rates, based on the sensor data. Despite ongoing research over about 40 years, no fully automated AP is yet available. It is suggested that the main barriers to be overcome for a successful AP are of a technological nature (Heinemann, Benesch, & DeVries, 2011). For example, besides continuously monitoring blood glucose sensors and fail-safe insulin infusion pumps, the AP has to rely on robust feedback control algorithms that can handle intra- and interindividual variability in patient parameters, as well as time-varying and nonlinear effects, while also rejecting external disturbances of glucose metabolism. To avoid unnecessary controller over-conservatism, as seen in *e.g.* $\mathcal{H}_\infty$ – controller design procedures (Skogestad & Postlethwaite, 2007), the goal of an AP feedback control algorithm should be online controller adaptation based on physiological models of the pathological glucose metabolism. An important and time-varying metabolic parameter is the insulin sensitivity; this has been recently proposed as a suitable parameter for controller adaption (Hinshaw et al., 2013). A model applied in an AP scenario should be able to estimate internal states or parameters of the glucose metabolism with the required accuracy, while limiting model complexity.

The aim of this work is to present a new method for online

* Corresponding author.
E-mail address: misgeld@hia.rwth-aachen.de (B.J.E. Misgeld).

http://dx.doi.org/10.1016/j.conengprac.2016.06.004
0967-0661/

reconstruction of insulin sensitivity as an important metabolic parameter by means of an Extended Kalman Filter (EKF). As a basis, the well-known physiological model by Sorensen (1985) is used, which was adapted to the metabolic behaviour of diabetic Göttingen Minipigs in Lunze (2014) and Lunze et al. (2014). Compared to other metabolic models, such as the Bergman "minimal model" (Bergman, Phillips, & Cobelli, 1981) from 1981, or the more recent ones by Dalla Man, Raimondo, Rizza, and Cobelli (2007) and Hovorka et al. (2004), the Sorensen model showed very good dynamic behaviour with respect to blood glucose and blood insulin trajectories in an *in silico* study (Lunze, 2014). A possible reason is that the Sorensen model also takes the insulin-counteracting hormone, glucagon, into consideration. The nonlinear model consists of 13 compartments and 22 coupled differential equations and was intended to optimise the insulin therapy of T1D patients; this was the rationale to use the Sorensen model as a basis for our observer-based design.

1.2. State-of-the-art blood glucose estimation

Several model-based approaches for T1D estimation and therapy guidance have been published. One such approach is collectively known as the bolus calculator. In recent bolus calculators (for an overview see, *e.g.* Zisser et al., 2008), the size of an applicable insulin bolus is calculated based on an estimate of the meal size and the insulin-to-carbohydrates ratio. Further adjustments of the insulin bolus are proposed based on the measured blood glucose or the remaining nonactivated insulin in the body. Since patients are not always able to accurately estimate the size of a meal, it is preferable to employ estimates of postprandial glucose dynamics in the approaches for T1D estimation and therapy guidance (Boiroux et al., 2015). Therefore, a continuous estimation of internal states and selected parameters by use of input (insulin, meal size)–output (blood glucose) measurements is required. The recursive estimation of future glucose concentration based on low-order linear model is presented by Eren-Oruklu, Cinar, Quinn, and Smith (2009), whereas a stochastic modelling approach is presented by Compte et al. (2010). Schiavon, Dalla Man, Kudva, Basu, and Cobelli (2014) presented a new index of insulin sensitivity that is based on the solution of forward dynamics and is validated with respect to *in silico* trials. In an AP automation approach, state and parameter information are highly valuable. The states could be used for model-based or model predictive control, whereas the time-varying parameter information can be used for controller scheduling techniques.

Few reports on observer-based estimation of glucose metabolism are available. In Eberle and Ament (2012), the authors present an observability analysis for the simple Bergman model, followed by the design of an Unscented Kalman Filter (UKF) validated in simulations and with experimental data. In Szalay et al. (2014), the authors compare different UKF designs based on the Hovorka model (Hovorka et al., 2004), the performance of which has been validated in *in silico* studies only.

1.3. Structure of the paper

In contrast to previous approaches, our work focuses on the design of an EKF which is based on the detailed Sorensen model and reduced in model-order to obtain a suitable observable form:

- Section 2 describes the Sorensen model which has been adapted to the glucose metabolism in diabetic Göttingen Minipigs (see also Lunze, 2014; Lunze et al., 2014).
- The results of the observability study are presented in Section 3 including the application of model-order reduction which lead to the derivation of a novel nonlinear model suited for observer design.
- Section 4 describes the EKF design, its implementation and the *in silico* validation. The proposed estimator is extended to estimate the time-varying parameter of insulin sensitivity online.
- In Section 5, the filter performance is evaluated when applied to experimental *in vivo* measurement data with diabetic Göttingen Minipigs.
- Finally, the results are discussed in Section 6.

2. Glucose metabolism model

As mentioned, the design of the EKF was based on the Sorensen model adapted to the glucose metabolic behaviour of diabetic Göttingen Minipigs (Lunze et al., 2014). The basis of the Sorensen model is the blood circulation model depicted in Fig. 1. The model consists of three subsystems describing the blood circulation, the interstitium and the gastro-intestinal tract (shown in Fig. 2). Here, we use a blood circulation model that consists of 12 ordinary differential equations (ODEs). The blood circulation model consists of three main compartments. These interconnected compartments are insulin, glucose and the hormone glucagon, appearing in plasma (heart, brain, lung, kidneys, gut), liver and muscle/adipose tissue. As indicated in Fig. 2, interstitium and gastro-intestinal tract models are connected to the blood circulation model by means of the subcutaneous insulin appearance rate $r_{\mathrm{ISC}}(t)$ and intravenous glucose appearance rate $r_{\mathrm{GGA}}(t)$, respectively. External inputs to the model are subcutaneous $U_{\mathrm{sc}}(t)$ or intravenous $U_{\mathrm{iv}}(t)$ insulin infusion rates. Moreover, $S_{\Gamma}(t) = r^{\mathrm{N}}_{P\Gamma\mathrm{P}}(t) r^{\mathrm{B}}_{P\Gamma\mathrm{P}} = r_{P\Gamma\mathrm{P}}(t)$ is the pancreatic glucagon infusion rate, which is given by the pancreatic glucagon production $r^{\mathrm{N}}_{P\Gamma\mathrm{P}}(t)$, normalised to the basal rate by $r^{\mathrm{B}}_{P\Gamma\mathrm{P}}$. Further external inputs are the orally and intravenously applied glucose rates, denoted by $D_{\mathrm{oral}}(t)$ and $D_{\mathrm{iv}}(t)$, respectively.

2.1. Blood circulation model

The basis for the blood circulation model is a compartmental approach. The general compartment is divided into a vascular (blood) and an interstitial (bloodless) volume space denoted by indices V and I, respectively. By assuming a homogeneous mass distribution over the whole compartment and denoting $X(t)$ as the mass distribution of a substance (glucose G, insulin I or glucagon Γ) in the compartment i, we obtain the general equations

$$\begin{aligned} \underbrace{V^X_{iV}\cdot\frac{dX_{iV}(t)}{dt}}_{\text{mass change}} &= \underbrace{Q_i^X\cdot\left(X_{in}(t)-X_{iV}(t)\right)}_{\text{convection}} - \underbrace{\frac{V^X_{iI}}{T^X_i}\cdot\left(X_{iV}(t)-X_{iI}(t)\right)}_{\text{diffusion}} \\ \underbrace{V^X_{iI}\cdot\frac{dX_{iI}(t)}{dt}}_{\text{mass change}} &= \underbrace{\frac{V^X_{iI}}{T^X_i}\cdot\left(X_{iV}(t)-X_{iI}(t)\right)}_{\text{diffusion}} + \underbrace{\left(r_{in}(t)-r_{out}(t)\right)}_{\text{mass in- and outflow}}, \end{aligned} \tag{1}$$

(shown in the interaction diagram in Fig. 3). A dashed line is used to divide the ith compartment into an interstitial and a vascular volume space. Fig. 1 gives an overview of modelled compartments and interstitial and vascular volume spaces. In Eqs. (1), a change in mass over time is due to convection by the blood stream Q_i^X (assumed to be constant) and diffusion over the vascular wall. Associated with the diffusion is the time constant T_i^X. In the interstitial fluid space, there is an additional mass inflow and outflow $r_{in}(t)$ and $r_{out}(t)$, respectively and no convection. Additional variables in Eqs. (1) are the mass concentration in the inflowing blood stream $X_{in}(t)$ and the mass concentration in the outflowing blood stream X_{iV}. For convenience, the equations of the reduced-order model are given in Appendix A. As an example for the model