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Editors

Prediction Methods for Blood Glucose Concentration

Design, Use and Evaluation

Springer

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Preface

Standard diabetes insulin therapy for type 1 diabetes and late stages of type 2 is based on the expected development of blood glucose (BG) both as a consequence of the metabolic glucose consumption as well as of meals and exogenous insulin intake. Traditionally, this is not done explicitly, but the insulin amount is chosen using factors that account for this expectation.

The increasing availability of more accurate continuous blood glucose measurement (CGM) systems is attracting much interest to the possibilities of explicit prediction of future BG values. Against this background, in 2014 a two-day workshop on the design, use and evaluation of prediction methods for blood glucose concentration was held at the Johannes Kepler University Linz, Austria. One intention of the workshop was to bring together experts working in various fields on the same topic, in order to shed light from different angles on the underlying problem of modeling the glucose insulin dynamics of type 1 diabetes patients. Among the international participants were continuous glucose monitoring developers, diabetologists, mathematicians and control engineers, both, from academia and industry. In total 18 talks were given followed by panel discussions which allowed to receive direct feedback from the point of view of different disciplines.

This book is based on the contributions of that workshop and is intended to convey an overview of the different aspects involved in the prediction. The individual chapters are based on the presentations given by the authors at the workshop but were written afterward which allowed to include the findings and conclusions of the various discussions and of course updates.

The chapter "Alternative Frameworks for Personalized Insulin–Glucose Models" by Harald Kirchsteiger et al. asks the question whether more and more detailed physiological descriptions of the glucose metabolism with an ever-increasing degree of sophistication and number of modeled phenomena are really what is needed for pushing the boundaries in glucose prediction for control. As an alternative, the chapter introduces two data-based approaches that focus not on the prediction of exact future blood glucose values, but rather on the prediction of changes in the patients' blood glucose range.

The chapter "Accuracy of BG Meters and CGM Systems: Possible Influence Factors for the Glucose Prediction Based on Tissue Glucose Concentrations" by Guido Freckmann et al. discusses performance metrics used to characterize the accuracy of continuous glucose measurement devices. This topic is highly relevant for prediction models since many of them rely on the data given by the continuous sensors which are previously calibrated with blood glucose meter measurements which are also subject to measurement errors. Inaccurate measurements will directly affect the performance of the corresponding predictions.

The chapter "CGM—How Good Is Good Enough?" by Michael Schoemaker and Christopher G. Parkin also tackles the problem of continuous glucose monitor performance evaluation. Several performance metrics used in different published studies are compared and their individual characteristics analyzed. The chapter reveals why the comparison of a sensor evaluated in two different clinical studies is not always straightforward.

The chapter "Can We Use Measurements to Classify Patients Suffering from Type 1 Diabetes into Subcategories and Does It Make Sense?" by Florian Reiterer et al. makes use of continuous time prediction models to describe the interaction between ingested carbohydrates, subcutaneously injected insulin, and continuously measured glucose concentration. The identified model parameters of 12 subjects were analyzed and statistically significant correlations between the parameters and patient characteristics such as weight and age could be found.

The chapter "Prevention of Severe Hypoglycemia by Continuous EEG Monitoring" by Claus Borg Juhl et al. shows how to use EEG signals to predict upcoming hypoglycemic situations in real-time by employing artificial neural networks. The results of a 30-day long clinical study with the implanted device and the developed algorithm are presented.

The chapter "Meta-Learning Based Blood Glucose Predictor for Diabetic Smartphone App" by Valeriya Naumova et al. demonstrates how a highly sophisticated glucose prediction model can be ported from a development language running on a PC to a format such that it can be used conveniently by the patients. A unique feature of the algorithm is its independence of any user input other than historic CGM data which is automatically transmitted from a CGM device. No parameter estimation nor prediction model individualization is required.

The chapter "Predicting Glycemia in Type 1 Diabetes Mellitus with Subspace-Based Linear Multistep Predictors" by Marzia Cescon et al. uses data-based methods to develop individualized prediction models. The model can be considered as a combination of physiological models to precompute the rate of appearance of injected insulin and ingested carbohydrates in the bloodstream and of data-based models to combine this information and compute predictions up to 120 min in the future. The results show the performance on data from 14 type 1 diabetes patients in a clinical trial.

The chapter "Empirical Representation of Blood Glucose Variability in a Compartmental Model" by Stephen D. Patek et al. shows a modeling technique designed to extract the information on the net effect of meals on the blood glucose concentration. By assuming that all major unexplained glycemic excursions can be

attributed to oral glucose ingestion, a meal vector is estimated which significantly improves the mathematical model. Results are shown on three patients during a clinical trial and on virtual patients where it is shown how the method can be used for adjustments of the basal insulin rate.

The chapter "Physiology-Based Interval Models: A Framework for Glucose Prediction Under Intra-patient Variability" by Jorge Bondia and Josep Vehi tries to cope with the large intrasubject variability by using the concept of interval predictions. Instead of predicting a single blood glucose value in the future, a whole solution envelope is determined. With the presented theory it can be guaranteed that the real value is always inside of the envelope and moreover the envelope is not conservative. The method is evaluated on a physiological diabetes model.

The chapter "Modeling and Prediction Using Stochastic Differential Equations" by Rune Juhl et al. considers uncertainty in the dynamics between different patients as well as within a patient by making use of stochastic differential equations. It is shown how the mixed effects modeling methodology can be applied such that the underlying information of several datasets from different patients is extracted to form the model.

The chapter "Uncertainties and Modeling Errors of Type 1 Diabetes Models" by Levente Kovács and Péter Szalay analyzes the effect of prediction model uncertainties on the control system during a design procedure involving the steps model reduction by elimination of state variables, state estimation using extended Kalman Filters and Sigma Point filters and linear parameter-varying control synthesis.

The chapter "Recent Results on Glucose–Insulin Predictions by Means of a State Observer for Time-Delay Systems" by Pasquale Palumbo et al. introduces a prediction model which in real time predicts the insulin concentration in blood which in turn is used in a control system. The method is tested in simulation on a time-delay system representing the glucose–insulin system.

The chapter "Performance Assessment of Model-Based Artificial Pancreas Control Systems" by Jianyuan Feng et al. makes use of prediction models to compute treatment advices. The novelty of the proposed algorithm consists in explicitly considering (among others) the model prediction error and model error elimination speed. A retuning of the advisory system is done in case the prediction model does not perform well. Results on 30 virtual patients show the performance of the control system.

We would like to thank all people involved in the process of writing this book: All authors for their individual contributions, all reviewers of the book chapters, Daniela Hummer for the entire organization of the workshop, Boris Tasevski for helping with the typesetting, Florian Reiterer for his help editing the book, as well as Oliver Jackson and Karin de Bie for the good cooperation with Springer.

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Contents

Uncertainties and Modeling Errors of Type 1 Diabetes Models

Levente Kovács and Péter Szalay

Abstract Modeling and control are tightly connected if we want to guarantee safety and reliability. These are minimum requirements in the medical field. The more sophisticated methods usually require information beyond the available measurements, and one way or another incorporate all a priori knowledge. This can manifest in state estimation, model-based prediction, or robust design assuming the worst case, among others. The better the model the better the achievable control; however, all aspects of modeling are more difficult in the case of physiological systems compared to regular engineering applications. In the following, we will investigate how various errors resulting from modeling inaccuracies affect the prediction of the behavior in case of blood glucose prediction. Sigma-point filters are used to efficiently support Kalman filtering, while the error sources are introduced in a single uncertainty block.

1 Introduction

Diabetes mellitus is the dysfunction of the human glucose regulation that is currently incurable, but treatable. Normally, the concentration of plasma glucose is kept in a narrow range (3.9–7.8 mmol/L or 70–110 mg/dL) by a complex endocrine system, where insulin plays a key role in this process. Type 1 (insulin dependent), Type 2 (non-insulin dependent), gestational, and special types like genetic deflections are the types of diabetes. Classical therapy of type 1 diabetes mellitus (T1DM) consists of insulin injections administered by the patient. However, even the most cooperative patient can be subjected to the chronic complications, such as neuropathy, nephropathy, or retinopathy, among others [14]. Existing therapies could greatly benefit from an

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accurate prediction of the plasma glucose concentration, as well as optimized dosage of insulin based on these predictions.

Complete automation of the treatment is researched in the literature (for T1DM) under the artificial pancreas (AP) problem. AP consists on three components: a continuous glucose monitoring (CGM) sensor for the subcutaneous measurement of glucose concentrations, an insulin pump for the subcutaneous delivery of insulin, and a control algorithm that based on CGM measurements is able to determine the necessary insulin dosage to be injected by the insulin pumps [7, 8].

There are various control methods already developed: classical PID [25]; run-to-run control [39]; exact linearization-based nonlinear control [26]; $\mathscr{H}_\infty$ control [10, 13, 27, 29]; model predictive control (MPC) [16, 22, 24]; linear parameter varying (LPV)-based robust control [9, 21]. Soft computing-based methods, such as fuzzy logic control [28] and model-free soft computing-based control [36] are gaining popularity as well. Most of these techniques require signals beyond what is physically measurable; hence, accurate estimation of the state variables and precise modeling is needed.

In this chapter, various error sources related to modeling will be investigated using the widely used T1DM model of the literature [16]. Section 2 focuses on the general aspects of modeling the human metabolism, briefly presenting the used model for our investigations. Model reduction is examined in Sect. 3. State estimation in terms of novel versions of Kalman filtering is detailed in Sect. 4, while the modeling errors resulting from estimation is investigated in Sect. 5. Section 6 concludes the paper. Simulations have been performed using the in silico simulator of the University of Cambridge version 2.2 (SimEdu) [35].

2 Modeling Diabetes

Various models appeared in the literature to describe the normal or impaired human metabolism. One of the earliest and simplest can capture the dynamics using merely three state variables [4]. On the other hand, one of the most sophisticated models [31]—despite being potentially highly accurate—contains way too many states and parameters to be useful in the clinical practice. Furthermore, the representation of subcutaneous compartments is usually neglected in the early models. However, the ones presented in [24, 35] corrected these shortcomings by balancing complexity and manageable size and including the subcutaneous route for both sensor and actuator. Even if we consider ordinary differential equations only, the available models which are successfully used for various purposes are beyond count; but, they do share certain similarities: they contain some form of nonlinearity, most frequently the multiplication of two state variables, Michaelis–Menten functions, and saturation. In general, transfer rate between two states (representing compartments) are a function of other state variables. Most of the state variables cannot have negative value. There are inputs which cannot be measured and only vaguely represented, such as stress or

physical activity. Finally, the model parameters are assumed to be changing in time. In the followings, these models will be referred to as T1DM models.

The model investigated in this paper is described by the following differential equations [35]:

$$
\begin{aligned}
\dot{C}(t) &= -k_{a,int}C(t) + \tfrac{k_{a,int}}{V_G}Q_1(t) \\
\dot{Q}_1(t) &= -\left(\tfrac{F_{01}}{Q_1(t)+V_G} + x_1(t)\right)Q_1(t) + k_{12}Q_2(t) \\
&\quad -R_{cl}max\{0, Q_1(t) - R_{thr}V_G\} - Phy(t) \\
&\quad +EGP_0max\{0, 1 - x_3(t)\} + min\left\{U_{G,ceil}, \tfrac{G_2(t)}{t_{max}}\right\} \\
\dot{Q}_2(t) &= x_1(t)Q_1(t) - \Big(k_{12} + x_2(t)\Big)Q_2(t) \\
\dot{x}_1(t) &= -k_{b1}x_1(t) + S_{IT}k_{b1}I(t) \\
\dot{x}_2(t) &= -k_{b2}x_2(t) + S_{ID}k_{b2}I(t) \\
\dot{x}_3(t) &= -k_{b3}x_3(t) + S_{IE}k_{b3}I(t) \\
\dot{I}(t) &= \tfrac{k_a}{V_I}S_2(t) - k_eI(t) \\
\dot{S}_2(t) &= -k_aS_2(t) + k_aS_1(t) \\
\dot{S}_1(t) &= -k_aS_1(t) + u(t) \\
\dot{G}_2(t) &= \tfrac{G_1(t)-G_2(t)}{max\left\{t_{max}, \frac{G_2(t)}{U_{G,ceil}}\right\}} \\
\dot{G}_1(t) &= -\tfrac{G_1(t)}{max\left\{t_{max}, \frac{G_2(t)}{U_{G,ceil}}\right\}} + D(t)
\end{aligned}
\tag{1}
$$

where the state variables are: $C(t)$ glucose concentration in the subcutaneous tissue [mmol/L], $Q_1(t)$ and $Q_2(t)$ the masses of glucose in accessible and nonaccessible compartments [mmol], $x_1(t)$, $x_2(t)$ and $x_3(t)$ remote effect of insulin on glucose distribution, disposal, and endogenous glucose production, respectively, [1/min], $I(t)$ insulin concentration in plasma [mU/L], $S_1(t)$, and $S_2(t)$ insulin masses in the accessible and nonaccessible compartments [mU], $G_1(t)$, and $G_2(t)$ glucose masses in the accessible and nonaccessible compartments [mmol]. $u(t)$-injected insulin flow of rapid-acting insulin [mU/min] is the input of the system, while $D(t)$ amount of ingested carbohydrates [mmol/min], and $Phy(t)$ effect of physical activity [mmol/min] are considered as disturbances.

The parameters of the model are $k_{a,int}$ transfer rate constant between the plasma and the subcutaneous compartment [1/min], V_G distribution volume of glucose in the accessible compartment [L], F_{01} parameter of the total non-insulin dependent glucose flux [mmol/min], k_{12} transfer rate constant from the nonaccessible to the accessible compartment [1/min], R_{cl} renal clearance constant [1/min], R_{thr} glucose threshold [mmol/L], EGP_0 endogenous glucose production extrapolated to the zero insulin concentration [mmol/min], t_{max} time-to-maximum appearance rate of glucose in the accessible compartment [min], $U_{G,ceil}$ maximum glucose flux from the gut [mmol/kg/min], k_{b1} and k_{b2} deactivation rate constants [$\frac{min^{-2}}{mU/L}$], k_{b3} deactivation rate constant for the insulin effect on endogenous glucose production [$\frac{min^{-1}}{mU/L}$], S_{IT},

S_{ID} and S_{IE} insulin sensitivities for transport, distribution, and endogenous glucose production $[\frac{min^{-1}}{mU/L}]$ and $[\frac{1}{mU/L}]$, k_a insulin absorption rate constant [1/min], V_I volume of distribution of rapid-acting insulin [L], k_e fractional elimination rate from plasma [1/min]. The following parameters are assumed to be time-varying with ± 5 % deviation: $k_{a,int}$, F_{01}, k_{12}, EGP_0, k_{b1}, k_{b2}, k_{b3}, S_{IT}, S_{ID}, S_{IE}, k_a, and k_e.

This can be extended with a continuous glucose monitor (CGM) model, with $C(t)$ as input and measured glucose concentration as output. There are various CGM models to choose from [5, 6, 12]. The sampling time associated with sensor is usually around 5 min.

2.1 Linear Parameter Varying Model

There are several ways to handle the nonlinearity of the model. The classical nonlinear methodology focuses on the differential geometric approach [17], while a more recent methodology is represented by linear parameter varying (LPV) systems [3, 23]. LPV is an acceptable compromise between the model's complexity and the developed control algorithm, as LPV systems can be seen as an extension of linear time invariant (LTI) systems, where the relations are considered to be linear, but model parameters are assumed to be functions of a time-varying signal.

Most T1DM models can be represented with a linear parameter varying (LPV) model [21, 32]. These models are essentially an extension of linear models, and have the following form:

$$\begin{aligned}
\dot{\mathrm{x}}(t) &= \mathbf{A}(\rho(t))\mathrm{x}(t) + \mathbf{B}(\rho(t))\mathrm{u}(t) \\
\mathrm{y}(t) &= \mathbf{C}(\rho(t))\mathrm{x}(t) + \mathbf{D}(\rho(t))\mathrm{u}(t) \\
\mathbf{A}(\rho(t)) &= \mathbf{A}_0 + \prod_{i=1}^{m} \rho_i(t)\mathbf{A}_i\mathbf{B}(\rho(t)) = \mathbf{B}_0 + \prod_{i=1}^{m} \rho_i(t)\mathbf{B}_i \\
\mathbf{C}(\rho(t)) &= \mathbf{C}_0 + \prod_{i=1}^{m} \rho_i(t)\mathbf{C}_i\mathbf{D}(\rho(t)) = \mathbf{D}_0 + \prod_{i=1}^{m} \rho_i(t)\mathbf{D}_i
\end{aligned} \tag{2}$$

where the scheduling variables ($\rho(t)$) are assumed to be bounded, as well as their first time derivatives. Although different configurations are possible [32], the following scheduling parameters have been chosen for model (1):

$$\rho(t) = \begin{pmatrix} \rho_1(t) \\ \rho_2(t) \\ \rho_3(t) \end{pmatrix} = \begin{pmatrix} Q_1(t) \\ F_{01}(Q_1(t) + V_G)^{-1} \\ Q_2(t) \end{pmatrix} \tag{3}$$

3 Model Reduction

As model (1) is an 11th order model, it is rather difficult to handle for anything beyond simulations. A decreased number of state variables would be more practical for tasks with memory and computation power requirements rising exponentially with the model order. Based on the parameter bounds presented in [16, 35] the speed of transfer between certain compartments is comparable to the sampling time of the CGM. Hence, the states associated with them can be eliminated. The resulting reduced model is as follows:

$$\begin{aligned}
\dot{Q}_1(t) &= -\left(\tfrac{F_{01}}{Q_1(t)+V_G} + x_1(t)\right) Q_1(t) + k_{12} Q_2(t) \\
&\quad -R_{cl} max\{0,\, Q_1(t) - R_{thr} V_G\} - Phy(t) \\
&\quad +EGP_0 max\left\{0,\, 1 - \tfrac{k_a S_{IE}}{V_I k_e} S_2(t)\right\} + min\left\{U_{G,ceil},\, \tfrac{G_2(t)}{t_{max}}\right\} \\
\dot{Q}_2(t) &= x_1(t) Q_1(t) - \left(k_{12} + \tfrac{k_a S_{ID}}{V_I k_e} S_2(t)\right) Q_2(t) \\
\dot{x}_1(t) &= k_{b1}\left(\tfrac{k_a S_{IT}}{V_I k_e} S_2(t) - x_1(t)\right) \\
\dot{S}_2(t) &= -k_a S_2(t) + k_a S_1(t) \\
\dot{S}_1(t) &= -k_a S_1(t) + u(t) \\
\dot{G}_2(t) &= \tfrac{G_1(t) - G_2(t)}{max\left\{t_{max},\, \frac{G_2(t)}{U_{G,ceil}}\right\}} \\
\dot{G}_1(t) &= -\tfrac{G_1(t)}{max\left\{t_{max},\, \frac{G_2(t)}{U_{G,ceil}}\right\}} + D(t)
\end{aligned} \tag{4}$$

where the output is $C(t) \approx Q_1(t)/V_G$.

The equations for state variables $S_1(t)$, $S_2(t)$ and $x_1(t)$ can be regarded as a third-order linear system with injected insulin $u(t)$ as the only input and three outputs: $x_1(t)$, $x_2(t) \approx (k_a S_{ID} S_2(t))/(V_I k_e)$ and $x_3(t) \approx (k_a S_{IE} S_2(t))/(V_I k_e)$. Graphical representation of state elimination is presented in Fig. 1.

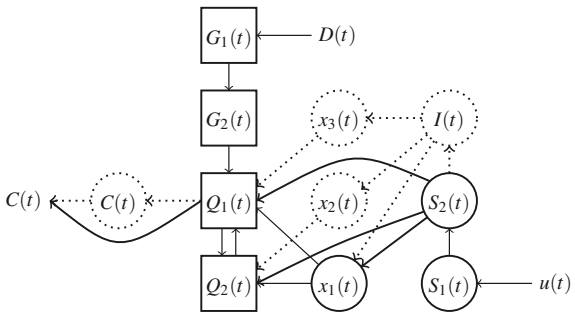

Fig. 1 Eliminating state variables. *Circle* nodes represent linear, *square* nodes represent nonlinear equations. Disturbance input $Phy(t)$ is not displayed

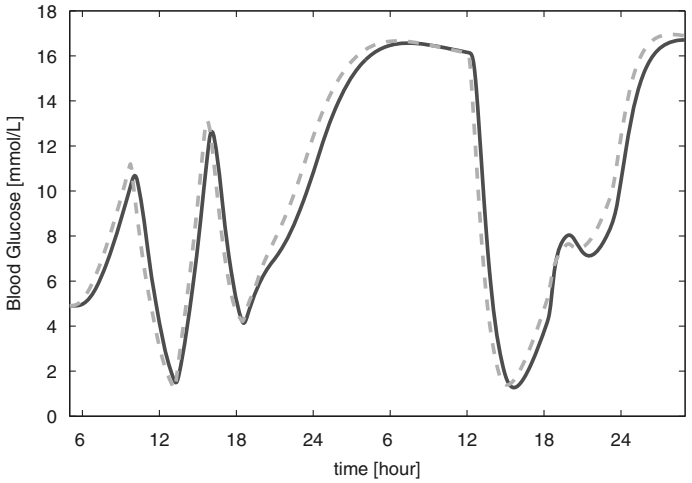

Fig. 2 Output of the original (*solid line*) and reduced system (*dashed line*)

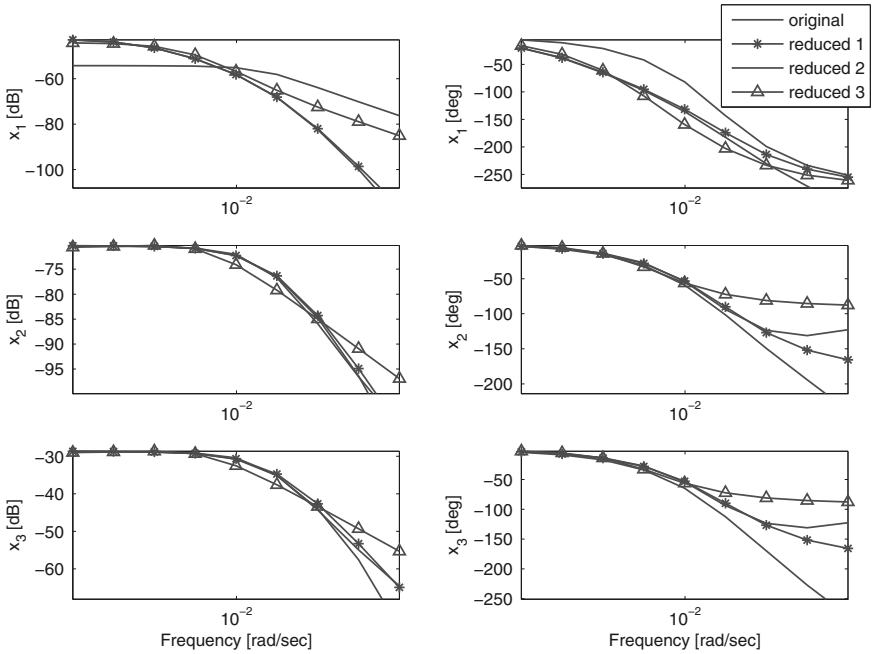

Fig. 3 Bode diagram for different types of reduction. *Reduced 1* represents the effect of state elimination only (4). *Reduced 2* displays the Bode diagram in case the subsystem is reduced to a 2nd-order one, but no weighting is used, unlike in case of *reduced 3* where weighting has been also applied

Further reduction of this third-order system is possible using frequency-weighted balanced reduction presented in [11] or [37]. If weighting is needed, one might use the nonlinear subsystem of the model—described by the equations belonging to states $Q_1(t)$ and $Q_2(t)$—linearized at a chosen working point. However, when the system is used in other working points, this may not be the most effective choice. In Fig. 2, the outputs of the original 11th-order model (1) is compared with the reduced 7th-order model (4), where four state variables were neglected. The insulin, meal, and physical activity inputs are randomly generated [32], assuming time-invariant parameters.

Figure 3 presents the Bode diagrams of the above-mentioned third-order subsystem for all three outputs in the case of different types of reduction.

The parameters changing in time can alter the dynamics of the model quite significantly, which can lead to errors in prediction as well as instability in closed-loop control. The ± 5 % deviation can be considered a rather optimistic assumption. Figure 4 shows the comparison of the output of the time-invariant model with an example in the case of time-varying parameters, as well as the envelope for the maximum deviation from the nominal behavior during simulation. Note, that not even these figures represent the theoretically possible highest deviation, for randomized simulations cannot guarantee a deterministic worst case scenario [33].

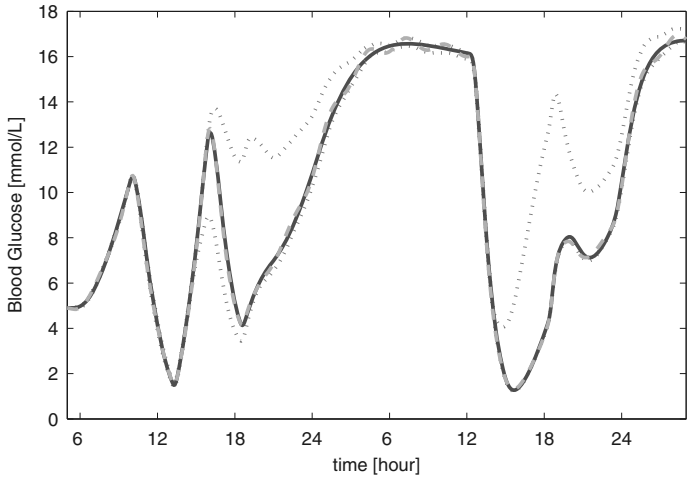

Fig. 4 Time-varying parameters. The *solid line* is the output of the nominal model, the *dashed line* is an example output in case of changing parameters, while the bounds marked with *dotted lines* are the results of numerous simulations with randomized settings

4 State Estimation

Prediction usually needs information about all state variables of the system, as well as some of the more advanced control techniques. Hence, since they are not available for measurement, reliable estimation is needed. Kalman filter is a popular choice for such tasks. They are especially useful in the case of prediction, since Kalman filters provide not only the estimated values of the states, but the variance of the estimation error as well. When the CGM has significant drift, this information can be used for recalibration. Let us approximate the combination of T1DM and sensor models with the following discrete-time nonlinear system:

$$\begin{aligned} \mathrm{x}_{k+1} &= \mathrm{f}(\mathrm{x}_k, \mathrm{u}_k, \mathrm{w}_k) \\ y_k &= h(\mathrm{x}_k) + n_k \end{aligned} \tag{5}$$

where $\mathrm{x}_k \in \mathbb{R}^{n_x}$ is the vector of state variables, $y_k \in \mathbb{R}$ denotes the measured output disturbed with $n_k \sim \mathcal{N}(0, R_k)$ additive white noise. $\mathrm{u}_k \in \mathbb{R}^{n_u}$ is the vector of known deterministic inputs, while $\mathrm{w}_k \sim \mathcal{N}(0, \mathbf{Q}_k)$ is the vector of disturbances affecting the states, with assumingly zero mean Gaussian distribution and $n_w \times n_w$ real positive semidefinite covariance matrix $\mathbf{Q}_k$. $\mathrm{f} : \mathbb{R}^{n_x} \times \mathbb{R}^{n_u} \times \mathbb{R}^{n_w} \to \mathbb{R}^{n_x}$ and $h : \mathbb{R}^{n_x} \to \mathbb{R}$ are piecewise continuous nonlinear mappings. The errors resulting from the assumptions made about the disturbances and measurement noise are not investigated in this paper.

Once the new model (5) is available, it is possible to use Kalman filter for state estimation or prediction. Extended Kalman filter is the usual choice in the case of nonlinear systems. However, the precision of this filter is only satisfactory in case of mild nonlinearity and disturbances, since it is based on first-order linearization [15].

A more effective alternative are the use of sigma-point filters. They use a number of deterministic samples, called sigma points, to represent the probability distribution of the system state needed in the Kalman filter algorithm [19]. There are several versions which differ mainly on how these sigma points are selected. Cubature Kalman filter (CKF) is based on the cubature rule [1] and is one of the most straightforward approaches. Unscented Kalman Filter (UKF) relies on the unscented transformation with parameters that can be tuned for each filtering problem in order to achieve better performance [19]. Gauss–Hermite quadrature filter (GHQF) can be used if Gaussian distribution is guaranteed offering the highest accuracy [2]. However, it also requires a large amount of sigma points and hence increased computational power which can be undesirable in certain practical applications. As a result, our choice went on sparse-grid quadrature filtering method (SGQF) developed in order to overcome the dimensionality problem of GHQF [18]. Moreover, CKF and UKF can be considered as a special form of SGQF.

4.1 Sigma-Point Selection

Let us introduce the notation χ for a set of sigma points. This set contains N sigma points denoted as $\xi_i, i = 1, \ldots, N$. The sigma points represent the stochastic variable μ with $\hat{\mu}$ mean and $\boldsymbol{\Sigma}$ covariance matrix, and can be written in the following form:

$$\xi_i = \boldsymbol{\Sigma}^{\frac{1}{2}} \varphi_i + \hat{\mu} \tag{6}$$

$\Sigma^{\frac{1}{2}}$ is the factor of $\boldsymbol{\Sigma}$ so that $\boldsymbol{\Sigma} = \boldsymbol{\Sigma}^{\frac{1}{2}} (\Sigma^{\frac{1}{2}})^T$, and since $\boldsymbol{\Sigma}$ is positive definite, Cholesky decomposition is commonly used. In case $\boldsymbol{\Sigma}$ is close to being singular, or nondefinite due to sigma-point collapse [34], singular value decomposition can be used as well [18]. μ is not limited to state variables only, it contains the disturbances and measurement noises as well [30], so that:

$$\hat{\mu} = \begin{pmatrix} \hat{\mathrm{x}} \\ 0 \\ 0 \end{pmatrix} \quad \boldsymbol{\Sigma} = \begin{bmatrix} \Sigma & 0 & 0 \\ 0 & \mathbf{Q} & 0 \\ 0 & 0 & \mathbf{R} \end{bmatrix} \tag{7}$$

where $\mathbf{Q}$ and $\mathbf{R}$ denote covariance matrices of the disturbances and measurement noise, just like earlier. Using these sigma points, one can estimate the mean and covariance of the distribution of $f(\chi)$ as a weighted sum, where $f(.)$ is a nonlinear function:

$$\begin{aligned} \mathrm{E}\{f(\mu)\} = \bar{\mathrm{f}}_\mu &\approx \textstyle\sum_{i=1}^{N} \omega_i^{(m)} f(\xi_i) \\ cov\{f(\mu)\} &\approx \textstyle\sum_{i=1}^{N} \omega_i^{(c)} \left((f(\xi_i) - \bar{\mathrm{f}}_\mu)(f(\xi_i) - \bar{\mathrm{f}}_\mu)^T \right) \end{aligned} \tag{8}$$

There are various strategies to choose φ_i and the weights $\omega_i^{(m)}$ and $\omega_i^{(c)}$. In case of CKF, there are $2L$ sigma points, where L is the dimension of μ. The weights and basis functions $\omega^{(m)}$, $\omega^{(c)}$, and φ in the case of a CKF are:

$$\begin{aligned} \varphi_i &= \begin{cases} \mathrm{e}_i \sqrt{L} & i = 1, \ldots, L \\ -\mathrm{e}_i \sqrt{L} & i = L+1, \ldots, 2L \end{cases} \\ \omega_i^{(m)} &= \omega_i^{(c)} = \frac{1}{\sqrt{L}} \end{aligned} \tag{9}$$

where e_i denotes the unit vector in $\mathbb{R}^L$ with the $(i-1)$th element being 1. Note that CKF does not have any adjustable parameter, opposed to UKF which has three: κ, α, and β. The weights and basis functions ω and ϕ in the case of a CKF are:

$$
\begin{aligned}
\varphi_i &= \begin{cases} 0 & i = 1 \\ \mathrm{e}_i\sqrt{L+\lambda} & i = 2,\ldots,L+1 \\ -\mathrm{e}_i\sqrt{L+\lambda} & i = L+2,\ldots,2L+1 \end{cases} \\
\omega_i^{(m)} &= \begin{cases} \frac{\lambda}{n+\lambda} & i = 1 \\ \omega_i^{(m)} = \frac{1}{2(n+\lambda)} & i = 2,\ldots,2L+1 \end{cases} \\
\omega_1^{(c)} &= \begin{cases} \frac{\lambda}{n+\lambda} + 1 - \alpha^2 + \beta & i = 1 \\ \omega_i^{(c)} = \frac{1}{2(n+\lambda)} & i = 2,\ldots,2L+1 \end{cases}
\end{aligned} \tag{10}
$$

where $\lambda = \alpha^2(L+\kappa) - L$ is a scaling parameter [15]. The constant α determines the spread of sigma points around μ, and is usually set to a small positive value (e.g., $1 \geq \alpha \geq 10^{-4}$). The constant κ is a second scaling parameter usually set to $3 - L$ so that the kurtosis of the sigma points agrees with that of the Gaussian distribution [20]. β is used to incorporate prior knowledge of the distribution of μ and usually set to 2 for Gaussian distribution. In case $\alpha = 1$ and $\beta = 0$, both CKF and UKF can be seen as a special case of level-2 SGQF.

$$
\varphi_i = \begin{cases}
0 & i = 1 \\
\mathrm{e}_i p_1 & i = 2,\ldots,L+1 \\
-\mathrm{e}_i p_1 & i = L+2,\ldots,2L+1 \\
\mathrm{e}_i p_2 & i = 2L+2,\ldots,3L+1 \\
-\mathrm{e}_i p_2 & i = 3L+2,\ldots,4L+1 \\
\mathrm{e}_i p_3 & i = 4L+2,\ldots,5L+1 \\
-\mathrm{e}_i p_3 & i = 5L+2,\ldots,6L+1 \\
\mathrm{e}_i p_1 + \mathrm{e}_j p_1, & i = 6L+2,\ldots,6L+1+C \quad j \neq i \\
-\mathrm{e}_i p_1 + \mathrm{e}_j p_1, & i = 6L+2+C,\ldots,6L+1+2C \quad j \neq i \\
\mathrm{e}_i p_1 - \mathrm{e}_j p_1, & i = 6L+2+2C,\ldots,6L+1+3C \quad j \neq i \\
-\mathrm{e}_i p_1 - \mathrm{e}_j p_1, & i = 6L+2+3C,\ldots,6L+1+4C \quad j \neq i
\end{cases} \tag{11}
$$

$$
\omega_i = \begin{cases}
\left(\frac{(L-2+L\hat{\omega}_1^2)}{2} - L\hat{\omega}_1\right)(L-1) + L\hat{\omega}_3 & i = 1 \\
(L-1)\hat{\omega}_2(\hat{\omega}_1 - 1) & i = 2,\ldots,2L+1 \\
\hat{\omega}_4 & i = 2L+2,\ldots,4L+1 \\
\hat{\omega}_5 & i = 4L+2,\ldots,6L+1 \\
\hat{\omega}_2^2 & i = 6L+2,\ldots,6L+1+4C
\end{cases}
$$

The level-3 SGQF requires $2L^2 + 4L + 1$ or less sigma points. The exact number depends on how the three free parameters—p_1, p_2, and p_3—are chosen. Similarly to the GHKF, these parameters are selected from the perspective of an univariate estimation, where the points $\mu + \{-p_1, 0, p_1\}$ and $\mu + \{-p_3, -p_2, 0, p_2, p_3\}$ are used to estimate certain moments of an univariate Gaussian distribution transformed by a nonlinear function. If all parameters are different, the sigma points used in the level-3 SGQF are shown in Eq. (11), where $C = L(L-1)/2$, while $\hat{\omega}_1, \ldots, \hat{\omega}_5$ are

defined from the parameters p_1, p_2, p_3 using moment matching method. Furthermore, $\omega_i^{(c)} = \omega_i^{(m)}$ and $j \neq i$.

5 Model Uncertainty

Control methods using state feedback, like the popular MPC [24, 35] or exact linearization-based control [26], require all state variables. LPV modeling (and control) is less strict requiring only that the scheduling parameters should be available for measurement. However, since these signals cannot be measured directly, the estimation error must be taken into consideration. Consequently, it can be regarded as additional parameter inaccuracy or a virtual disturbance. For model (1), a combination of the two approaches have been chosen. For the scheduling variable $\rho_i(t)$, we can assume that the estimated $\hat{\rho}_i(t)$ is the correct value, but additive $\Delta\rho_{i,0}$ and multiplicative $\Delta\rho_{i,1}$ error is present, as well as a disturbance $d_{\rho,i}(t)$ with Gaussian distribution and zero mean. Hence:

$$\rho_i(t) \approx \hat{\rho}_i(t)(1 + \Delta\rho_{i,1}) + \Delta\rho_{i,0} + d_{\rho,i}(t) \tag{12}$$

The values of $\Delta\rho_{i,0}$ and $\Delta\rho_{i,1}$ can be defined using least squares (LS) or weighted least squares (WLS) method based on a series of simulations with carefully chosen randomized inputs, initial conditions, and measurement noises. Once these two parameters are set, the worst case value of the variance of $d_{\rho,i}(t)$ can be defined (Fig. 5). Figure 6 displays how the additive and multiplicative error of the scheduling parameters can change the behavior of the nominal model in worst case scenario.

5.1 Error Weighting Function

Due to the high number of error sources and inaccuracies, estimating the worst case behavior of the system can be demanding for computations. However, it is possible to capture them in a single weighting function $W(s)$ [38] in an offline way (Fig. 7). Once this function is available, the online tasks of prediction and control can consider worst case deviation from the nominal model easier. An example is displayed in Fig. 8 obtained by simulations on the in silico simulator of the University of Cambridge version 2.2 (SimEdu) [35]. $W(s)$ incorporates parameters changing in time, reduction using state elimination and scheduling variable estimation error.

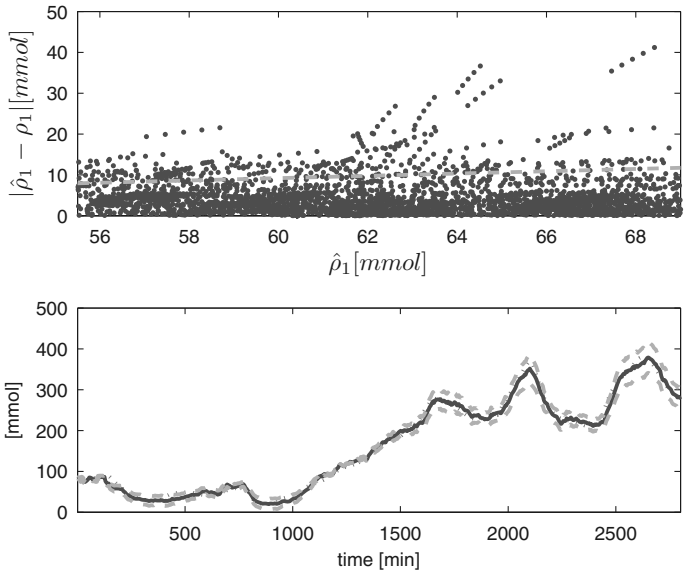

Fig. 5 Defining parameter uncertainty parameters for $\rho_1(t)$. In the *upper* subplot, the absolute difference between the estimated ($\hat{\rho}_1$) and the real (ρ_1) value of a scheduling variable is displayed as a function of the estimated value. The *dashed line* represents the chosen additive and multiplicative uncertainty. Everything that is not covered by the uncertainty is considered disturbance. The *lower* subplot shows the time function of a scheduling variable (*dotted line*), the estimation (*solid line*), and the uncertainty bounds (*dashed line*)

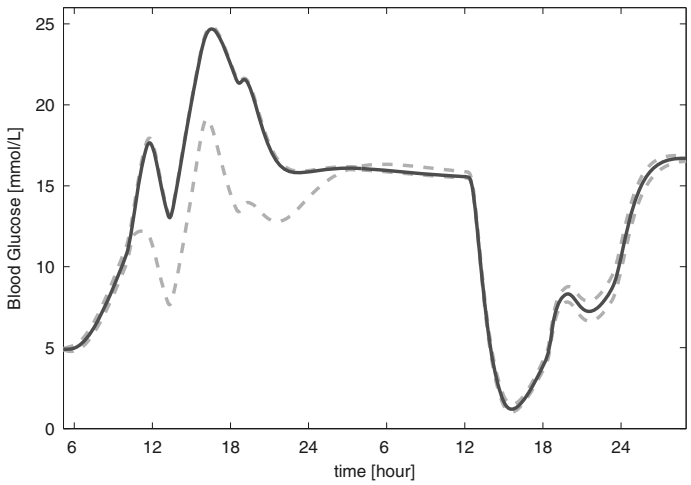

Fig. 6 Effects of scheduling variable estimation error. The *solid line* is the output of the nominal model; the *dashed lines* are the bounds for how much the response of the actual system can deviate

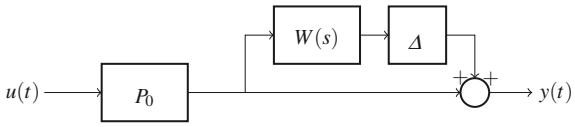

Fig. 7 Output multiplicative uncertainty. Δ represents an unstructured uncertainty block, which is an unknown linear system assumed to have $\mathscr{H}_\infty$ norm smaller than 1, stable and minimal phase

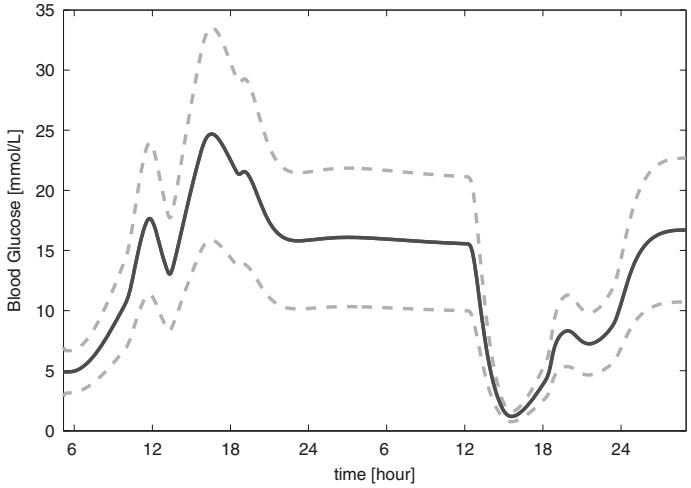

Fig. 8 Uncertainties and errors represented with a single weighting function. The *solid line* is the output of the nominal model, the *dashed lines* are the bounds for how much the response of the actual system can deviate

6 Conclusion

In this chapter, the effects of changing parameters, model reduction, and state estimation errors were examined on the widely used T1DM model of [16] to show the challenges they impose on model-based prediction and control. Sigma-point filters have been used as an extension of the nonlinear Extended Kalman Filtering technique, offering higher accuracy in this particular problem.

Further work will focus on parameter sensitivity of each sigma-point method, but a more sophisticated sensor model could be used as well. Filters requiring less sigma points should be included also in the comparison. The question of robustness has to be investigated as well, since it is safe to assume that the used T1DM model is inaccurate. Finally, additional safety measures must be taken in case the patient would be less cooperative, and occasionally neglect the requested sensor calibration or be simply late with the measurement.

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