

Model Identification using Continuous Glucose Monitoring Data for Type 1 Diabetes [★]

Dimitri Boiroux ^{*,**} Morten Hagdrup ^{*} Zeinab Mahmoudi ^{*,**}
Niels Kjølstad Poulsen ^{*} Henrik Madsen ^{*}
John Bagterp Jørgensen ^{*}

^{*} Department of Applied Mathematics and Computer Science,
Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

^{**} Danish Diabetes Academy, Odense University Hospital, DK-5000
Odense C, Denmark

Abstract: This paper addresses model identification of continuous-discrete nonlinear models for people with type 1 diabetes using sampled data from a continuous glucose monitor (CGM). We compare five identification techniques: least squares, weighted least squares, Huber regression, maximum likelihood with extended Kalman filter and maximum likelihood with unscented Kalman filter. We perform the identification on a 24-hour simulation of a stochastic differential equation (SDE) version of the Medtronic Virtual Patient (MVP) model including process and output noise. We compare the fits with the actual CGM signal, as well as the short- and long-term predictions for each identified model. The numerical results show that the maximum likelihood-based identification techniques offer the best performance in terms of fitting and prediction. Moreover, they have other advantages compared to ODE-based modeling, such as parameter tracking, population modeling and handling of outliers.

© 2016, IFAC (International Federation of Automatic Control) Hosting by Elsevier Ltd. All rights reserved.

Keywords: Type 1 diabetes, parameter identification, continuous glucose monitoring, least squares, Huber regression, maximum likelihood

1. INTRODUCTION

The artificial pancreas (AP), i.e. automated or semi-automated control of blood glucose, has the potential to improve the regulation of blood glucose levels in people with type 1 diabetes (T1D) compared to the current insulin therapy. According to Meece (2015), it is estimated to be commercially available within 5 to 7 years for the first versions. Although this estimate may be optimistic, it shows that the research on the AP is progressing rapidly and that the goal of having a commercially available AP is becoming closer. In its single-hormone version, current prototypes of the AP consist of a continuous glucose monitor (CGM) for glucose sensing, a control algorithm implemented on a smartphone and a continuous subcutaneous insulin infusion (CSII) pump. Fig. 1 illustrates the AP.

Meals represent a major challenge for the control algorithm due to the high nonlinearity of the insulin-glucose dynamics. For a normal or large meal size, algorithms based on linear model predictive control (MPC) are inadequate to handle meals, as they tend to underestimate the action of insulin on blood glucose, usually resulting in hypoglycemia, as shown in Boiroux et al. (2010c). To handle meals properly, some of the control algorithms based on MPC have attempted to separate the bolus calculator from the basal insulin administration, for instance Marchetti et al. (2008); Bátorá et al. (2015). Control algorithms

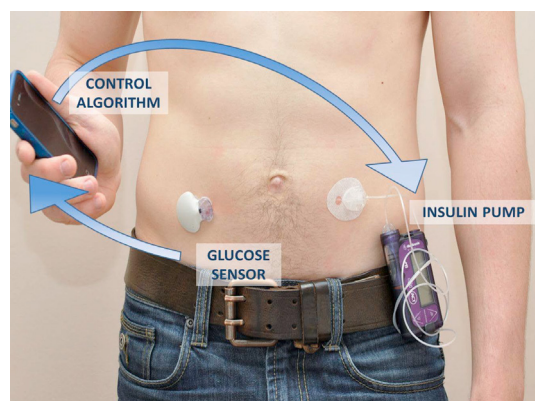


Fig. 1. The single-hormone artificial pancreas.

based on nonlinear MPC (NMPC) can be used to compute the optimal bolus delivery and to dose the basal and bolus insulin in a safe way, provided that they can be identified. Control algorithms based on NMPC have been tested on real patients (Hovorka et al. (2004); Schaller et al. (2006)) and on virtual patients (Magni et al. (2008); Boiroux et al. (2010b)).

Another requirement for control algorithms based on MPC is to determine a suitable and adaptive control-relevant prediction model, as in Jørgensen and Jørgensen (2007b); Boiroux et al. (2015). For patients with T1D, numerous physiological models exist. These models describe the subcutaneous insulin absorption, the glucose-insulin dynamics

[★] This work has been funded by the Danish Diabetes Academy supported by the Novo Nordisk Foundation.

and the carbohydrates (CHO) absorption. They usually consist either of a system of ordinary differential equations (ODEs) (e.g. the models developed by Hovorka et al. (2004); Kanderian et al. (2009); Dalla Man et al. (2014)), or a system of stochastic differential equations (SDEs) (Duun-Henriksen et al. (2013)). The former uses in most cases least squares fitting, while the latter uses maximum likelihood for parameter identification. In both cases, the identification requires to have access to parameters that are inaccessible in everyday life, for example plasma glucose and plasma insulin data. In practice, patients with T1D must only rely on data from a CGM to obtain frequent (usually, every 5 minutes) glucose measurements usable for model identification and glucose regulation.

The key contribution of the present paper is to evaluate and discuss model identification procedures based on CGM data that can be used for simulation and/or NMPC. To our knowledge, this problem has not been addressed so far. Here, we compare least squares, Huber regression and maximum likelihood fitting using continuous-discrete filtering for state estimation. We design these identification techniques in such a way that they could be part of a closed-loop control algorithm. We generate a 24-hour simulated dataset including bolused meals and simulate a virtual patient using a modified version of the Medtronic Virtual Patient (MVP) model, such that we can compare the identified parameter values with the actual ones. This version of the MVP model simulates random metabolic variations and comprises a noise-corrupted CGM model. We also discuss the potential and the challenges of these identification techniques regarding their applicability to nonlinear control.

This paper is structured as follows. Section 2 gives a stochastic formulation of a physiological model for patients with T1D. Section 3 shows the methods used for parameter estimation. Section 4 shows the performance of the model identification techniques and discusses the potential application to closed-loop control. Section 5 summarizes the main contributions of this paper.

2. PHYSIOLOGICAL MODEL

In this paper, we use model similar to the Medtronic Virtual Patient (MVP) model presented in Kanderian et al. (2009). The initial MVP model consists of a set of nonlinear ODEs. It has been designed to be easier to identify.

We augment this model with the CGM noise model developed by Facchinetti et al. (2014), and we reformulate this model as a stochastic differential equation-grey box (SDE-GB) model as in Duun-Henriksen et al. (2013). A SDE-GB model is a model in the form

$$dx(t) = f(t, x(t), u(t), \theta)dt + \sigma d\omega(t) \quad (1a)$$

$$y_k = h(t_k, x(t_k)) + v_k \quad (1b)$$

in which $x(t)$ is the state vector. $u(t)$ is the input vector. Here, we assume a zero-order hold parametrization, i.e. $u(t) = u_k$ for $t_k \leq t < t_{k+1}$. θ represents the model parameters we want to identify. $\{d\omega(t), t \geq 0\}$ is a standard Wiener process with covariance Idt . $\sigma d\omega(t)$ models the unknown disturbances to the system, e.g. changes in the metabolism, cyclic hormone variations etc. For simplicity,

we assume in this paper that the matrix σ is diagonal and time-invariant. The measurement noise v_k is normally distributed, $v_k \sim N_{iid}(0, R)$.

The following subsections state the SDE-GB model used for simulation and parameter identification. The numerical values of the model parameters are summarized in Table 1.

2.1 Insulin Absorption Subsystem

The insulin absorption subsystem is given by the following two-compartment model

$$dI_{SC} = \left(\frac{u(t)}{C_I \tau_1} - \frac{I_{SC}(t)}{\tau_1} \right) dt + \sigma_1 d\omega_1 \quad (2a)$$

$$dI_P = \left(\frac{I_{SC}(t) - I_P(t)}{\tau_2} \right) dt + \sigma_2 d\omega_2 \quad (2b)$$

where $I_{SC}(t)$ [mU/L/min] is the subcutaneous insulin concentration, and $I_P(t)$ [mU/L] is the plasma insulin concentration. $u(t)$ [mU/min] is the insulin infusion rate, C_I [L/min] is the clearance rate. τ_1 and τ_2 [min] are the insulin absorption time constants. It must be pointed out that these time constants are interchangeable.

2.2 Insulin-Glucose Dynamics

The effect of insulin on blood glucose is described by the following SDEs

$$dI_{EFF} = (-p_2 I_{EFF}(t) + p_2 S_I I_P(t)) dt + \sigma_3 d\omega_3 \quad (2c)$$

$$dG = -(I_{EFF}(t) + GEZI)G(t) + EGP + R_A(t) dt + \sigma_4 d\omega_4 \quad (2d)$$

$I_{EFF}(t)$ [min⁻¹] is the effect of insulin. p_2 [min⁻¹] is a parameter and S_I [mL/mU] reflects the insulin sensitivity. The glucose concentration $G(t)$ [mg/dL] is also affected by the glucose elimination at zero insulin rate ($GEZI$) [min⁻¹], the endogenous glucose production (EGP) [mg/dL/min] and the glucose rate of appearance $R_A(t)$ [mg/dL/min].

The insulin effect and the glucose dynamics (2c)-(2d) are similar to the one developed by Bergman et al. (1981). This formulation allows for an easier parameter identification compared to other physiological models.

2.3 CHO Absorption Model

We use the two-compartment model introduced by Hovorka et al. (2004) to describe the CHO absorption and conversion to glucose. The model describes the effect of orally ingested carbohydrates on the rate of appearance of glucose $R_A(t)$ [mg/dL/min] in the blood stream. The model is

$$dD_1 = \left(d(t) - \frac{D_1(t)}{\tau_G} \right) dt + \sigma_5 d\omega_5 \quad (2e)$$

$$dD_2 = \left(\frac{D_1(t) - D_2(t)}{\tau_G} \right) dt + \sigma_6 d\omega_6 \quad (2f)$$

$$R_A(t) = \frac{D_2(t)}{\tau_G V_G} \quad (2g)$$

$d(t)$ [mg/min] is the meal intake. τ_G [min] is the meal absorption time constant and V_G [dL⁻¹] is the glucose distribution volume.

2.4 CGM Model

We use here the CGM model from Facchinetti et al. (2014). This model represents the glucose transport from plasma to interstitial tissues and the sensor noise. The glucose transport is given as

$$dG_{SC} = \frac{1}{\tau_{G,SC}} (G(t) - G_{SC}(t)) dt + \sigma_7 d\omega_7 \quad (2h)$$

where the time constant $\tau_{G,SC}$ is 6.7 min. The sensor noise is represented by the sum of the two following autoregressive processes

$$cc_k = 1.23cc_{k-1} - 0.3995cc_{k-2} + w_{cc,k} \quad (3a)$$

$$\hat{v}_k = 1.013\hat{v}_{k-1} - 0.2135\hat{v}_{k-2} + w_k \quad (3b)$$

in which $w_{cc,k} \sim N(0, 11.3 \text{ mg}^2/\text{dL}^2)$ and $w_k \sim N(0, 14.45 \text{ mg}^2/\text{dL}^2)$. Thus, the discrete noise-corrupted value returned by the glucose sensor and used in (1b) at the time t_k is

$$y_k = G_{SC}(t_k) + cc_k + \hat{v}_k \quad (4)$$

3. PARAMETER ESTIMATION

In this section, we introduce the model identification techniques used in this paper. In total, we implemented five different techniques: the least squares, the weighted least squares, the Huber regression, the maximum likelihood using an extended Kalman filter and the maximum likelihood using an unscented Kalman filter. All the optimization computations have been performed in MATLAB R2014a (Mathworks, Natick, Massachusetts).

3.1 Least Squares Estimation

In the least squares estimation, the aim is to find the set of parameters $\hat{\theta}$ minimizing the unweighted squares of the residuals, i.e.

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \sum_{i=1}^N \|y_i(\theta) - \bar{y}_i\|_2^2 \quad (5)$$

in which $y_i(\theta)$ is the estimated output (here, the BG level) and \bar{y}_i is the measured output. A more general formulation is the weighted least squares given by

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \sum_{i=1}^N \|y_i(\theta) - \bar{y}_i\|_{W_i}^2 \quad (6)$$

A popular choice of weight is $W_i = \operatorname{diag}(1/\bar{y}_i)^2$. This choice gives more weight to smaller observations (here, to low BG levels), and ensures that the term in the objective function is unitless.

3.2 Huber Regression

An alternative to the least square fitting is the Huber regression (Finan et al. (2010); Huber (2011)). The underlying idea behind the Huber regression is to decrease the influence of outliers on the identification by decreasing the penalty for high residual values. In the case of model identification based on CGM data, outliers may occur, if for instance the patient lies on the sensor. The objective function is to find the set of parameters $\hat{\theta}$ satisfying

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \sum_{i=1}^N \rho(e_i) \quad (7)$$

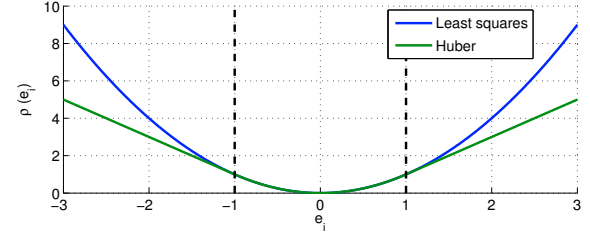


Fig. 2. Penalty function for the least squares and the Huber norm regression for $\gamma = 1$.

in which the cost $\rho(e_i)$ is defined as

$$\rho(e_i) = \begin{cases} e_i^2 & |e_i| \leq \gamma \\ 2\gamma|e_i| - e_i^2 & |e_i| > \gamma \end{cases} \quad (8)$$

where $e_i = y_i(\theta) - \bar{y}_i$ is the residual. It must also be pointed out that the function ρ is continuously differentiable. Fig. 2 depicts the penalty function for the least squares and the Huber norm regression.

3.3 Maximum Likelihood

For a Gaussian distribution and a set of observations given a set of model parameters $Y_N|\theta$, the -log-likelihood function is

$$L(\theta) = -\ln(p(Y_N|\theta)) \quad (9)$$

$$= \frac{(N+1)n_y}{2} \ln(2\pi) + \frac{1}{2} \sum_{k=0}^N \ln[\det(R_{e,k})] + e_k' [R_{e,k}]^{-1} e_k \quad (10)$$

where $R_{e,k}$ is the output covariance of the one step ahead prediction. $e_k = \hat{y}_{k|k-1} - \bar{y}_k$ is the innovation. n_y is the number of data points. The model parameters estimate $\hat{\theta}$ is the minimizer of (10), i.e.

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} (L(\theta)) \quad (11)$$

Here, we compare the extended Kalman filter (EKF) with the unscented Kalman filter (UKF) for the estimation of e_k and $R_{e,k}$. The EKF has been designed for state estimation of nonlinear systems. It is based on a first-order linearization, see for instance Ljung (1979); Boiroux et al. (2010a) for an implementation of the EKF.

The UKF has been developed by Julier et al. (1995, 2000). It propagates the state and covariance estimates for a set of wisely chosen points (also called sigma points) such that the nonlinearities are more accurately propagated than for the EKF. The UKF has been applied to plasma insulin estimation based on glucose measurements, see Eberle and Ament (2011). In many applications, the UKF shows better performance than the EKF. Sarkka (2007) presents a continuous-time and continuous-discrete unscented Kalman filter (CDUKF).

Since only CGM glucose measurements are available, it is quite likely that identifying all diffusion terms simultaneously will be difficult. In this paper, we applied the following iterative procedure to determine which diffusion terms can be identified, as shown in Kristensen et al. (2004b); Duun-Henriksen et al. (2013)

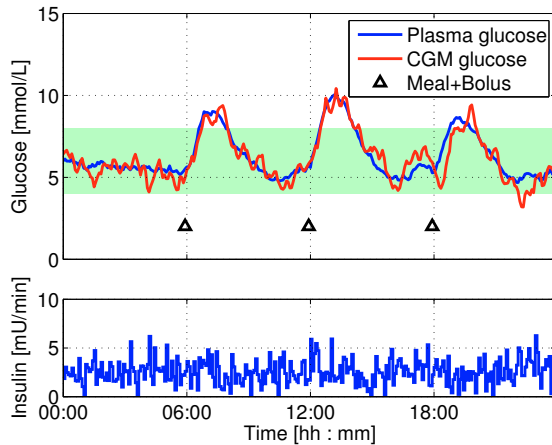


Fig. 3. Plasma and CGM glucose traces (top), and insulin trace (bottom) for the considered virtual patient.

- (1) Estimate the parameters of the deterministic version of the model, i.e. set all the diffusion terms σ_i , $i = 1, 2, \dots, 7$ to zero and only estimate the parameters related to the deterministic part in (2a)-(2h). Compute the likelihood function value L_0 .
- (2) Estimate the model (2a)-(2h) augmented with one diffusion term. For each possible state (seven in total), compute the statistic

$$D = 2(L - L_0) \quad (12)$$

where L is the likelihood of the augmented model, and L_0 is the initial likelihood. D follows a χ^2 distribution with one degree of freedom.

- (3) If a statistically significant improvement can be obtained, i.e. if the p -value of (12) is below 0.05: take the diffusion term that gave the lowest log-likelihood value, and augment again the system with another diffusion term to be estimated. Compute the new D statistic for the augmented system compared to the previous one.
- (4) Iterate step 3 until no further improvement can be obtained.

In our case, only the diffusion related to $G(t)$ in (2d) can be identified.

4. NUMERICAL RESULTS AND DISCUSSION

We use the parameters in Table 1 (second column) to simulate a 24-hour scenario. The meals given in the considered scenario are: 70g CHO at 6AM, 70g CHO at 12PM and 75g CHO at 6PM. A bolus of appropriate size has been administered at mealtime for every meal. We assume that the inputs (insulin infusion rate and meal size) are perfectly known, and that the output is given by the CGM measurements. For each state, we set $\sigma_i = 0.01x_{ss,i}$, where $x_{ss,i}$ is the steady state value for the i -th state in (2a)-(2h), $i = 1, 2, \dots, 7$. We use a random insulin administration sequence $u_k = u_{ss} + \eta_k$, where u_{ss} is the steady state insulin administration and $\eta_k \sim N(0, 0.5u_{ss})$, such that we can identify the time constants of the model. We use the Euler-Maruyama method Kloeden and Platen (1992) with a constant stepsize to solve numerically the SDEs (2a)-(2h). Fig. 3 shows the simulated plasma glucose, CGM glucose and insulin traces for the considered patient.

4.1 Results

Using the algorithm presented in section 3.3 on the glucose data reveals that only the diffusion term corresponding to plasma glucose $G(t)$ can be identified.

Table 1 shows the estimated parameter value and their relative errors. It can be noticed that the errors can be quite large, in particular for *GEZI* and *EGP*. It shows that using data from a single patient makes the identification of the MVP model quite difficult. The methods based on maximum likelihood perform better at identifying the parameters related to meal absorption (V_G and τ_M) as well as the insulin sensitivity S_I , which are the key parameters for the design of a bolus calculator and the adjustment of basal insulin.

Fig. 4 depicts the fits of each identification method for the plasma glucose. Except for the weighted least squares method, all the other methods show similar performance. The unweighted least squares, Huber regression and maximum likelihood are able to capture the variations in glucose level quite accurately. All the fittings show correlated residuals since they approximate the SDE-GB model (2a)-(2h) with a system of ODEs.

Table 2 illustrates the prediction results for the MVP model. We investigated three prediction horizons: 1 step (5 minutes), 6 steps (30 minutes) and 12 steps (60 minutes). The ability to make accurate prediction of the glucose level is important in particular for model-based control applications. We used the relative mean square error (RMSE) to quantify the performance of the different models. The RMSE is computed as

$$RMSE = \sqrt{\frac{\sum_{k=1}^N (\bar{y}_i - \hat{y}_i)^2}{N}} \quad (13)$$

in which \hat{y}_i is the estimated output from the model and \bar{y}_i is the actual output value. Table 2 shows that the unweighted least squares and the maximum likelihood performs similarly. Interestingly, no improvement has been noticed by using the unscented Kalman filter instead of the extended Kalman filter for maximum likelihood estimation. The weighted least squares performs the worst. The Huber regression performs as well as the other methods for short-term predictions, but its performance degrades for long-term predictions (6- and 12-steps ahead).

4.2 Discussion

Unlike ODE models, SDE-GB model provide information about the process noise distribution along with the parameter values. Therefore, it can be used to design a robust predictive controller, as in Mahmood and Mhaskar (2012).

In addition, SDE-GB model identification can be used for parameter tracking (Duun-Henriksen et al. (2013)). It can identify intra-patient variability in physiology such as changes in insulin sensitivity or changes in the postprandial meal dynamics, for instance if the fat content differs. Parameter tracking is a more systematic way to estimate time-varying parameters or different meal absorption dynamics than defining different time windows. Automatic parameter tracking is one of the major challenges in modeling of glucose-insulin dynamics (Steil et al. (2010)).

Table 1. Summary of the model identification results for the least squares (LS), weighted least square (LS-W), maximum likelihood using an extended Kalman filter (ML-EKF) and maximum likelihood using an unscented Kalman filter (ML-UKF), and their relative error (RE) compared to the actual value.

Parameter	Actual	LS	RE(%)	LS-W	RE(%)	Huber	RE(%)	ML-EKF	RE(%)	ML-UKF	RE(%)
τ_1 (min)	49	65	31.8	71	44.2	62.8	21.9	69.0	40.8	71.2	45.3
τ_2 (min)	47	65	37.5	71	50.5	60.7	22.6	69.0	46.8	70.9	50.8
C_I (L/min)	2.01	2.6	27.3	3.1	52.3	3.5	43.2	2.7	32.7	2.6	29.5
p_2 (10^{-2} min $^{-1}$)	1.06	1.3	21.4	0.79	25.5	0.95	11.6	1.4	36.1	1.5	39.4
S_I (10^{-3} dL/mU)	8.11	9.8	20.5	13.0	60.1	14.5	44.0	9.2	12.9	9.4	15.9
$GEZI$ (10^{-3} min $^{-1}$)	2.2	10	360.7	5.8	165.3	3.2	32.2	11.2	435.5	12.3	458.1
EGP (mg/dL/min)	1.3	2.0	50.0	1.8	32.7	1.55	14.6	2.1	55.3	2.1	61.4
V_G (dL)	253	228	10.1	376	48.5	309.2	18.2	239.9	5.2	226	10.5
τ_M (min)	47	45.3	3.6	68.9	46.5	43.7	7.5	44.6	5.4	45.7	2.8
σ_G	-	-	-	-	-	-	-	2.4	-	2.84	-

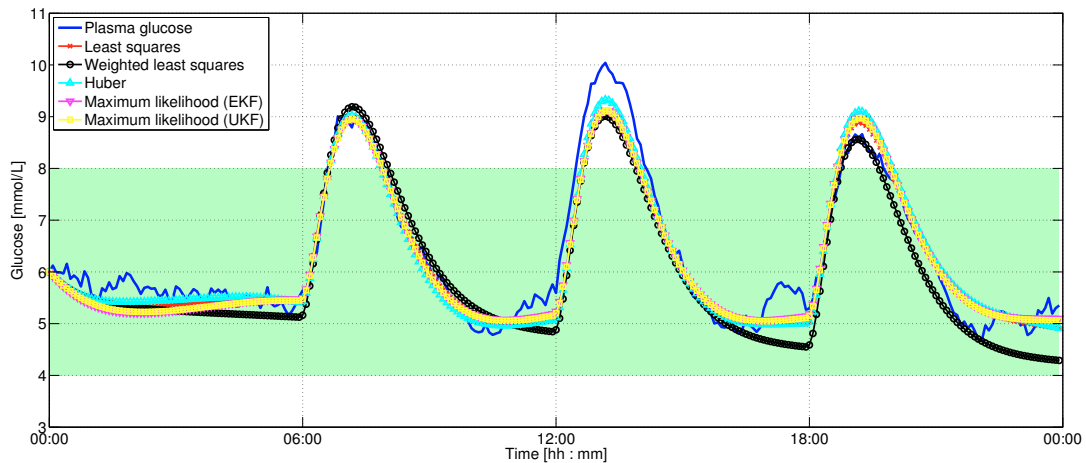


Fig. 4. Fits of the CGM data for the least squares (LS), weighted least square (LS-W), maximum likelihood using an extended Kalman filter (ML-EKF) and maximum likelihood using an unscented Kalman filter (ML-UKF).

Another advantage of maximum likelihood modeling is the possibility to refine the identification with data from a large population. Population modeling and maximum a posteriori estimation can improve the quality of the PK/PD modeling Kristensen et al. (2004a); Jørgensen and Jørgensen (2007a) and contribute to identify the parameters of the MVP model more easily and accurately.

The main drawback of maximum likelihood estimation remains the computation time needed to determine the maximum of the log-likelihood function (10). This can be overcome, as the model identification does not need to be performed frequently (e.g. once a day or even less frequently) and, if necessary, can be made remotely. Also, efficient and robust implementation of the optimization algorithm as well as faster mobile device can solve this issue.

The Huber regression is an alternative if a lower computational cost is needed. It has the advantage of handling outliers better than the classical least squares identification without compromising the quality of the predictions. However, the identification will have to be performed on several time windows as in Kanderian et al. (2009) to handle the intra-patient variability and the differences in meal absorption dynamics.

Table 2. Model predictions Relative Mean Square Error (RMSE, in mg/dL) for the five different identification techniques.

ID Tech	1-step RMSE	6-step RMSE	12-step RMSE
LS	9.8	12.9	13.7
LS-W	12.0	17.8	21.1
Huber	9.6	13.1	14.1
ML-EKF	9.9	12.9	13.6
ML-UKF	9.9	12.9	13.6

5. CONCLUSION

This paper compared different methods for model identification in people with T1D using CGM data for a single patient with a possible application to NMPC. From the numerical results and the subsequent discussion, we can conclude that identification based on maximum likelihood is the most suitable method for model identification in people with T1D. It gives better results and offers more flexibility, for instance for parameter tracking or to use information from a large population. It also gives information about the uncertainties that can be used in robust control. Also, the use of a continuous-discrete unscented Kalman filter does not bring any significant improvement compared to the extended Kalman filter in that particular case. Therefore, the use of an extended Kalman filter will

reduce the computational cost compared to the unscented Kalman filter for a similar performance. Further statistical validation of the results will be conducted.

REFERENCES

- Bátora, V., Tárník, M., Murgaš, J., Schmidt, S., Nørgaard, K., Poulsen, N.K., Madsen, H., Boiroux, D., and Jørgensen, J.B. (2015). The contribution of glucagon in an artificial pancreas for people with type 1 diabetes. In *American Control Conference (ACC), 2015*, 5097–5102.
- Bergman, R.N., Phillips, L.S., and Cobelli, C. (1981). Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *Journal of Clinical Investigation*, 68(6), 1456 – 1467.
- Boiroux, D., Finan, D.A., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2010a). Meal estimation in nonlinear model predictive control for type 1 diabetes. In *Symposium on Nonlinear Control Systems 2010 (NOLCOS 2010)*.
- Boiroux, D., Finan, D.A., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2010b). Nonlinear model predictive control for an artificial β -cell. In *Recent Advances in Optimization and its Applications in Engineering*, 299 – 308. Springer.
- Boiroux, D., Finan, D.A., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2010c). Optimal insulin administration for people with type 1 diabetes. In *Proceedings of the 9th International Symposium on Dynamics and Control of Process Systems (DYCOPS 2010)*, 234 – 239.
- Boiroux, D., Bátora, V., Hagdrup, M., Tárník, M., Murgaš, J., Schmidt, S., Nørgaard, K., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2015). Comparison of prediction models for a dual-hormone artificial pancreas. In *9th IFAC Symposium on Biological and Medical Systems (BMS2015)*, 7 – 12.
- Dalla Man, C., Micheletto, F., Lv, D., Breton, M., Kovatchev, B., and Cobelli, C. (2014). The UVA/PADOVA type 1 diabetes simulator new features. *Journal of diabetes science and technology*, 8(1), 26–34.
- Duun-Henriksen, A.K., Schmidt, S., Røge, R.M., Møller, J.B., Nørgaard, K., Jørgensen, J.B., and Madsen, H. (2013). Model identification using stochastic differential equation grey-box models in diabetes. *Journal of diabetes science and technology*, 7(2), 431–440.
- Eberle, C. and Ament, C. (2011). The unscented Kalman filter estimates the plasma insulin from glucose measurement. *Biosystems*, 103(1), 67–72.
- Facchinetti, A., Del Favero, S., Sparacino, G., Castle, J.R., Ward, W.K., and Cobelli, C. (2014). Modeling the glucose sensor error. *IEEE Transactions on Biomedical Engineering*, 61(3), 620 – 629.
- Finan, D.A., Jørgensen, J.B., Poulsen, N.K., and Madsen, H. (2010). Robust model identification applied to type 1 diabetes. In *American Control Conference (ACC), 2010*, 2021–2026.
- Hovorka, R., Canonico, V., Chassin, L.J., Haueter, U., Massi-Benedetti, M., Federici, M.O., Pieber, T.R., Schaller, H.C., Schaupp, L., Vering, T., and Wilinska, M.E. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological Measurement*, 25, 905–920.
- Huber, P.J. (2011). *Robust statistics*. Springer.
- Jørgensen, J.B. and Jørgensen, S.B. (2007a). Comparison of prediction-error-modelling criteria. In *American Control Conference, 2007. ACC'07*, 140–146. IEEE.
- Jørgensen, J.B. and Jørgensen, S.B. (2007b). MPC-relevant prediction-error identification. In *American Control Conference, 2007. ACC'07*, 128–133. IEEE.
- Julier, S.J., Uhlmann, J.K., and Durrant-Whyte, H.F. (2000). A new method for the nonlinear transformation of means and covariances in filters and estimators. *IEEE Transactions on Automatic Control*, 45(3), 477–482.
- Julier, S.J., Uhlmann, J.K., and Durrant-Whyte, H.F. (1995). A new approach for filtering nonlinear systems. In *Proceedings of the 1995 American Control Conference*, volume 3, 1628–1632.
- Kanderian, S.S., Weinzimer, S., Voskanyan, G., and Steil, G.M. (2009). Identification of intraday metabolic profiles during closed-loop glucose control in individuals with type 1 diabetes. *Journal of Diabetes Science and Technology*, 3(5), 1047 – 1057.
- Kloeden, P.E. and Platen, E. (1992). *Numerical solution of stochastic differential equations*, volume 23. Springer Science & Business Media.
- Kristensen, N.R., Madsen, H., and Jørgensen, S.B. (2004a). Parameter estimation in stochastic grey-box models. *Automatica*, 40, 225 – 237.
- Kristensen, N.R., Madsen, H., and Jørgensen, S.B. (2004b). A method for systematic improvement of stochastic grey-box models. *Computers and chemical engineering*, 28(8), 1431–1449.
- Ljung, L. (1979). Asymptotic behavior of the extended Kalman filter as a parameter estimator for linear systems. *Automatic Control, IEEE Transactions on*, 24(1), 36–50.
- Magni, L., Raimondo, D., Man, C.D., Breton, M., Patek, S., Nicolao, G.D., Cobelli, C., and Kovatchev, B. (2008). Evaluating the efficacy of closed-loop glucose regulation via control-variability grid analysis. *Journal of Diabetes Science and Technology*, 2(4), 630 – 635.
- Mahmood, M. and Mhaskar, P. (2012). Lyapunov-based model predictive control of stochastic nonlinear systems. *Automatica*, 48(9), 2271–2276.
- Marchetti, G., Barolo, M., Jovanović, L., Zisser, H., and Seborg, D.E. (2008). A feedforward-feedback glucose control strategy for type 1 diabetes mellitus. *Journal of Process Control*, 18(2), 149–162.
- Meece, J. (2015). The artificial pancreas: where we are, where we re going. *AADE in Practice*, 3(2), 42–44.
- Sarkka, S. (2007). On unscented Kalman filtering for state estimation of continuous-time nonlinear systems. *IEEE Transactions on Automatic Control*, 52(9), 1631–1641.
- Schaller, H., Schaupp, L., Bodenlenz, M., Wilinska, M., Chassin, L., Wach, P., Vering, T., Hovorka, R., and Pieber, T. (2006). On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: evaluation under fasting conditions in patients with type 1 diabetes. *Diabetic medicine*, 23(1), 90–93.
- Steil, G.M., Hipszler, B., and Reifman, J. (2010). Update on mathematical modeling research to support the development of automated insulin delivery systems. *Journal of diabetes science and technology*, 4(3), 759–769.