Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 58-24 (2024) 315–320

Online Estimation of Insulin Sensitivity in Diabetes Type 1 Patients during Menstrual Cycles using Extended Kalman Filtering

Jörg Kunkelmoor * **Ann-Kathrin Klinger** ** **Paolo Mercorelli** * **Benedikt Haus** *

* *Leuphana University of Lüneburg, Institute for Production Technology and Systems, Lüneburg, Germany (emails: joerg.kunkelmoor@phd-research.com, paolo.mercorelli@leuphana.com, haus@leuphana.de)*

** *Europa-Universität Flensburg, Wirtschaftswissenschaften, Flensburg, Germany (email: ann-kathrin.klinger@phd-research.com)*

Abstract: Diabetes mellitus, a chronic condition affecting millions of people worldwide, is characterised by the body's inability to regulate blood glucose levels independently. The prevalent forms include type 1, type 2, and gestational diabetes, each necessitating distinct management strategies. This article focuses on type 1 diabetes, particularly the challenges faced by female patients due to menstrual cycle-induced variations in insulin sensitivity. An extended Kalman filter, applied within the Bergman Minimal Model framework, is proposed for estimating unmeasured state variables crucial for effective diabetes management. The study underscores the impact of menstrual cycle phases on insulin sensitivity, highlighting the need for tailored insulin administration strategies to maintain optimal glucose levels. Through simulation studies based on a two-compartment model for insulin and glucose dynamics, the potential of Kalman filtering to enhance the knowledge about the influence of the insulin sensitivity for female type 1 diabetes patients is demonstrated.

Copyright © 2024 The Authors. This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/)

Keywords: Bergman's Minimal Model, Diabetes Mellitus Type 1, Extended Kalman Filter, Menstrual Cycle

1. INTRODUCTION

Diabetes mellitus is a chronic disability which affects millions of people worldwide. The body is no longer able to regulate the blood glucose level by itself. There are many forms of diabetes mellitus, but the most common forms are diabetes mellitus type 1, diabetes mellitus type 2 and gestational diabetes. (Kharroubi, 2015) Type 1 is characterized by an autoimmune condition where the body destroys the insulin producing cells in the pancreas. (Kharroubi, 2015) People with diabetes type 1 have to inject insulin by themselves to regulate the blood glucose levels. Type 2 is more linked to lifestyle factors, such as bad nutrition, sedentary behavior and obesity. These factors can cause the cells to become more resistant to insulin. (Kharroubi, 2015) Gestational diabetes can occur during pregnancy. Hormonal changes during pregnancy can lead to insulin resistance. (Choudhury and Rajeswari, 2021) A good diabetes management is needed to prevent secondary diseases. Type 1 requires an insulin therapy with injections or an insulin pump to regulate the blood glucose level. This is not always necessary for type 2. Furthermore patients with diabetes have to control their nutrition, doing regular exercises, track their blood glucose level and have regular meetings with health care specialists to reduce the risk of complications. (Aloke et al., 2022) (Freckmann et al., 2021) People with diabetes type 1 must maintain strict control of their glucose levels. Recently, *Continuous Glucose Measurement Systems* (CGM) are often used, also in combination with an insulin pump (Freckmann, 2020). The CGM measures the blood glucose levels continuously with a sample rate between 1 minute to 15 minutes. To achieve a stable glucose level throughout the day, in fasting periods and during exercises, there is the basal rate, which continuously delivers a pre-programmed rate of insulin (Laimer et al., 2016). In addition, a bolus or a correction for high blood glucose values must be calculated and injected individually for meals (Freckmann, 2020), which is often very difficult (Laimer et al., 2016). Especially for women during the menstrual cycle it can be hard to calculate those boluses, because female hormones can influence the insulin sensitivity (Toor et al., 2023). Those influences and inappropriate insulin dose administrations are a few impact factors and can lead to hypoglycemia. (Toor et al., 2023; Agrawal et al., 2022) The length of the menstrual cycle is approx. 28 days on average and can be divided into three phases. The Follicular Phase, Ovulation and Luteal Phase. In each phase, hormones change significantly. In a study involving 26 women with diabetes mellitus type 1, for two thirds of the patients there were changes of glucose levels and insulin sensitivity throughout the menstrual cycle. Also, an observation of 257 women without diabetes mellitus type 1 showed changes in insulin sensitivity and glucose levels. However, other studies did not exhibit such

2405-8963 Copyright © 2024 The Authors. This is an open access article under the CC BY-NC-ND license.
Peer review under responsibility of International Federation of Automatic Control.
10.1016/j.ifacol.2024.11.056

differences in insulin sensitivity and glucose levels in the different phases. (Toor et al., 2023) In any case, it can help female diabetes type 1 patients to obtain a deeper knowledge of their insulin sensitivity. This paper focuses on diabetes mellitus type 1. A possible approach is an extended Kalman filter (EKF) to suboptimally estimate the desired state variables, so that deeper knowledge of unmeasured quantities can be provided. The EKF is a nonlinear filter for estimation problems and is used in many practical cases, but first it has to be adapted to the specific application. Other state estimation algorithms like the Unscented Kalman Filter (UKF) were already used to observe unmeasured states of the Bergman minimal model to detect unannounced meals (Turksoy et al., 2016). The EKF and UKF are both nonlinear state observers. The difference between them is, that for the EKF one point is used for approximation and calculation of the jacobian and for the UKF we choose a set of sigma points representative of the distribution (Turksoy et al., 2016). The idea behind the set of sigma points is to approximately fit a Gaussian distribution. As shown in (Eigner et al., 2018) and (DK, 2022), the Bergman minimal model is already used with an EKF for control purposes. In the following, an EKF is developed for the widely employes Bergman minimal model that is extended using compartmental models of insulin infusion and meal intake dynymics. The simulation studies are implemented in MATLAB/Simulink and are based on an extended model as in (Eigner et al., 2018) and (DK, 2022) to take delay of the meals and insulin into account.

2. MODEL DESIGN

2.1 Two Compartment Minimal Model

The Bergman's minimal model is based on an Intravenous Glucose Tolerances Test (IGTT). This model can be used for people who are not affected by diabetes. In the IGTT the patients received a glucose injection of 0.3g/kg. Then their insulin level was measured over three hours to track the response. Afterwards, the parameters were fitted to the dynamics. The resulting model provides a simplified representation of glucose and insulin dynamics, focusing on the interplay between insulin action, glucose uptake and production. The ordinary differential equations from (Andersen and Højbjerre, 2003) are used. Their parameters p_{1-3} can be translated as

$$S_I = \frac{p_3}{p_2}, \quad S_G = p_1. \tag{1}$$

Where S_1 is the insulin sensitivity and S_G the glucose effectiveness. (Andersen and Højbjerre, 2003)

$$\dot{G}(t) = -S_G(G(t) - G_b) - X(t)G(t), \tag{2}$$
$$\dot{X}(t) = p_2[-X(t) + S_I(I(t) - I_b)], \tag{3}$$
$$\dot{I}(t) = -n(I(t) - I_b) + \gamma(G(t) - h)^+. \tag{4}$$

In Table 1 the used symbols are summarized. Since the pancreas releases the insulin above a certain threshold, following condition is used (Kartono et al., 2020):

$$\gamma(G(t) - h)^+ = \begin{cases} \gamma(G(t) - h) & \text{if } h < G(t), \\ 0 & \text{else.} \end{cases} \tag{5}$$

Table 1. Parameters of the Bergman minimal model (Andersen and Højbjerre, 2003)

Symbol	Description	Unit
$\dot{G}(t)$	Glucose concentration in plasma	[mg/dl]
$\dot{X}(t)$	Insulin effect on the net glucose disappearance	$[\text{min}^{-1}]$
$\dot{I}(t)$	Insulin concentration in plasma	[μU/ml]
G_b	Basal preinjection level of glucose	[mg/dl]
I_b	Basal preinjection level of insulin	[μU/ml]
p_1	Rate of glucose uptake in muscles	$[\text{min}^{-1}]$
p_2	Rate for decrease in tissue glucose uptake ability	$[\text{min}^{-1}]$
p_3	insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration	$[\text{min}^{-2}\left(\mu\frac{\text{U}}{\text{ml}}\right)^{-1}]$
n	The first order rate decay for insulin in plasma	$[\text{min}^{-1}]$
h	Threshold value above the pancreatic β-cells release insulin	[mg/dl]
γ	the rate of the pancreatic β-cells release of insulin after glucose injection and with glucose concentration above h	$[\mu\frac{\text{U}}{\text{ml}}\text{min}^{-2}\,[\text{mg/dl}]^{-1}]$

Since patients with diabetes type 1 often have an insulin pump, the equation (4) can be changed to (Mandal and Sutradhar, 2023):

$$\dot{I}(t) = \gamma(G(t) - h)^+ - n(I(t) - I_b) + u(t). \tag{6}$$

With $u(t)$ which is the external insulin infusion rate in [U/h] (Mandal and Sutradhar, 2023). The positive term $u(t)$ can be seen as the bolus which is calculated for the patient for meals to correct the glucose levels. For patients with diabetes mellitus, the parameter $S_G = 0$ and $\gamma = 0$. (Sylvester et al., 2017) For the simulation study, the model of the glucose dynamic $\dot{G}(t)$ is changed to take the input of meals into account. So the equation (2) will be extended with $D(t)$, which can be any kind of positive dynamic to take the glucose peaks of meals into account.

$$\dot{G}(t) = -S_G(G(t) - G_b) - X(t)G(t) + D(t). \tag{7}$$

However, the two inputs, $u(t)$ and $D(t)$ do not directly influence the actual G and I levels. When ingesting glucose and injecting insulin, there obviously is a lag behavior before their respective concentrations increase. In the previously described model equations, the dynamics are influenced directly by the input. To take these delays into account, a two compartment model is used to extend the Bergman minimal model. (Deichmann and Kaltenbach, 2021) In the treatment of diabetes type 1, the insulin pump therapy is nowadays often proposed, where an insulin bolus $u(t)$ is injected for every meal and and a basal rate $u_b(t)$ is injected as a small rate throughout the day. (Laimer et al., 2016) This can be compared to the model from (Shimoda et al., 1997) which is reviewed by (Gianluca Nucci, 2000). The model for the insulin absorption is as follows

$$\dot{S}_1(t) = \frac{-S_1(t)}{t_{1\max}} + u(t) + u_b(t), \tag{8}$$

$$\dot{S}_2(t) = \frac{S_1(t) - S_2(t)}{t_{1\max}}, \tag{9}$$

where $t_{1\max}[min]$ is the rate constant, S_1 is the insulin infusion, and S_2 is the mass which is transfered to the plasma. The model in (Gianluca Nucci, 2000) proposed two different rate constants for the insulin infusion and transfer to the insulin plasma, the model in (8-9) is simplified. Futhermore $\dot{I}(t)$ and $\dot{X}(t)$ are changed to:

$$\dot{X}(t) = p_2\left[-X(t) + S_I I(t)\right], \tag{10}$$

$$\dot{I}(t) = -nI(t) + \frac{S_2(t)}{WV_I t_{1\max}}, \tag{11}$$

where $W[Kg]$ is the bodyweight and $V_I[\frac{\text{ml}}{\text{Kg}}]$ is the distribution volume of insulin. To take the meal intake and the time delays of meal absorption into account, the following two-compartment model is used which is inspired by (Deichmann and Kaltenbach, 2021):

$$\dot{M}_1(t) = \frac{-M_1(t)}{t_{2\max}} + D(t), \tag{12}$$

$$\dot{M}_2(t) = \frac{M_1(t) - M_2(t)}{t_{2\max}}, \tag{13}$$

where $t_{2\max}[min]$ is the rate of absorption and $D[mg/min]$ is the ingested glucose. Futhermore $\dot{G}(t)$ changes to:

$$\dot{G}(t) = -S_G\left(G(t) - G_b\right) - X(t)\,G(t) + \frac{M_2(t)}{t_{2\max}WV_G}, \tag{14}$$

with $V_G[\frac{1}{dL}]$ as the distribution volume of glucose. Between the measured glucose obtained from the *Continuous Glucose Monitoring System* and the actual plasma glucose level, there is also a lag behavior. It can be described with (Deichmann and Kaltenbach, 2021)

$$\dot{G}_I(t) = \frac{G(t) - G_I(t)}{\tau}, \tag{15}$$

where $G_I(t)$ is the measured glucose and $G(t)$ is the glucose in plasma.

2.2 Extended Kalman Filter for Two Compartment Minimal Model

For the EKF (Welch and Bishop, 1995) the discrete-time form of the state equations are needed. The explicit euler method is used for the time discretization. The state vector is constructed as

$$\mathbf{x}(k) = \begin{bmatrix} G(k) \\ X(k) \\ I(k) \\ D(k) \\ S_1(k) \\ S_2(k) \\ G_I(k) \\ M_1(k) \\ M_2(k) \\ S_I(k) \end{bmatrix}, \tag{16}$$

where S_I is estimated as a Gaussian variable. The measured output $G_I = \mathbf{Hx}$ determines the output map

$$\mathbf{H} = [0\ 0\ 0\ 0\ 0\ 0\ 1\ 0\ 0\ 0]. \tag{17}$$

In the prediction step, the process model of the system is used to predict the states and predicted states' covariance matrix forward in time:

$$\hat{\mathbf{x}}_{k|k-1} = \mathbf{f}(\hat{\mathbf{x}}_{k-1|k-1}, \mathbf{u}_{k-1}, \mathbf{w}_{k-1}), \tag{18}$$

$$\mathbf{P}_{k|k-1} = \mathbf{A}_k\mathbf{P}_{k-1|k-1}\mathbf{A}_k^T + \mathbf{Q}_k, \tag{19}$$

where dynamics field $\mathbf{f}$ is the vector of state update equations based on the discretized system ODEs, $\hat{\mathbf{x}}_{k-1|k-1}$ is the a-posteriori state vector, $\mathbf{u}_{k-1}$ are the inputs, and $\mathbf{w}_{k-1}$ is the process noise (which is unknown and assumed to be zero in implementation of the prediction step). $\mathbf{Q}_k$ is the process covariance matrix, quantifying the prediction uncertainty, and $\mathbf{A}_k$ is the Jacobian of the system. $\mathbf{P}_{k-1|k-1}$ the corrected covariance of the previous step and $\mathbf{P}_{k|k-1}$ is the predicted covariance of the present time step. Then the EKF has to be updated:

$$\mathbf{K}_k = \mathbf{P}_{k|k-1}\mathbf{H}^T\left(\mathbf{H}\mathbf{P}_{k|k-1}\mathbf{H}^T + \mathbf{R}_k\right)^{-1}, \tag{20}$$

$$\mathbf{P}_{k|k} = (\mathbf{I}_{10\times10} - \mathbf{K}_k\mathbf{H})\mathbf{P}_{k|k-1}, \tag{21}$$

$$\hat{\mathbf{x}}_{k|k} = \hat{\mathbf{x}}_{k|k-1} + \mathbf{K}_k(\mathbf{y}_m - \mathbf{H}\hat{\mathbf{x}}_{k|k-1}), \tag{22}$$

in which $\mathbf{K}_k$ is the Kalman gain matrix at time step k. $\mathbf{R}_k$ is related to the observation noise covariance. $\mathbf{y}_m$ is the observation at time step k and $\mathbf{I}$ is a identity matrix. The corrected estimates $\hat{\mathbf{x}}_{k|k}$ arise by combining the prediction $\hat{\mathbf{x}}_{k|k-1}$ with measurements $\mathbf{y}_m$. (Welch and Bishop, 1995)

3. SIMULATION

The parameters of the model are in the following range and are taken from Gallardo-Hernández et al. $u(t)$ is a non-negative rectangular function. Furthermore following parameters can be used (Gallardo-Hernández et al., 2022):

$n \in [0.02, 0.3]$, $p_1 \in [0.01, 0.1]$, $p_2 \in [0.01, 0.2]$,

$p_3 \in [10^{-5}, 10^{-3}]$, $u_B \in [1000, 30000]$, see Table 1.

The parameters have to be fitted to the specific patient and can differ slightly. For patients with diabetes mellitus, the parameter glucose effectiveness $S_G = 0$ and the rate of the pancreatic β-cells release insulin $\gamma = 0$. (Sylvester et al., 2017) Besides insulin, the glucose effectiveness can cause the glucose to disappear from blood without changes of insulin. (Ahrén B, 2021) The simulation is implemented for a female diabetes mellitus type 1 patient, where the insulin sensitivity changes in the different phases of the menstrual cycle, to analyse the influence of the hormones on the insulin sensitivity and with this effect also the influence on the glucose levels. The values of the insulin sensitivity are as followed:

$$S_{I_{\text{menstruation}}} = 0.7S_I, \tag{23}$$

$$S_{I_{\text{follicular}}} = 1.2S_I, \tag{24}$$

$$S_{I_{\text{ovulatory}}} = 0.8S_I, \tag{25}$$

$$S_{I_{\text{luteal}}} = 0.6S_I. \tag{26}$$

The course of the insulin sensitivity are based on the observations of Toor et al. (2023), but the values of the factors were chosen based on the simulation study. The values between the phases are interpolated. Furthermore the meal input is randomized, see Fig. 7. Every 300 minutes a meal is taken with a value between:

$$D(t) = \text{randomized}([1500, 4000])\,\frac{\text{mg}}{\text{dl}}, \tag{27}$$

and the insulin bolus is calculated as:

$$u(t) = 1000D(t) + \text{randomized}([-0.2, 0.2])\,\frac{\mu\text{U}}{\text{ml}}, \tag{28}$$

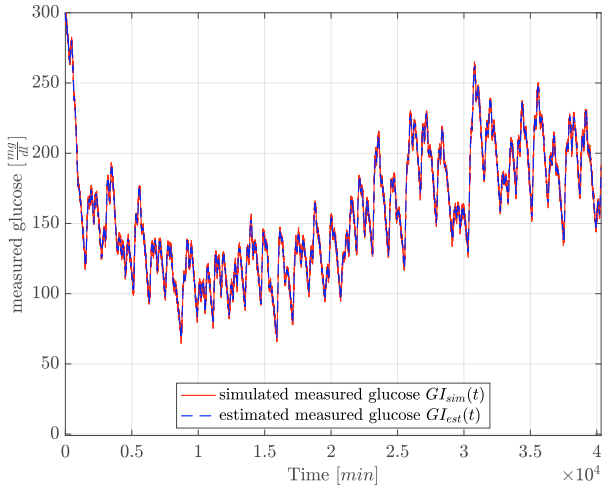

Fig. 1. $G_{\text{sim}}(t)$ and $G_{\text{est}}(t)$ for a female diabetes mellitus type 1 patient

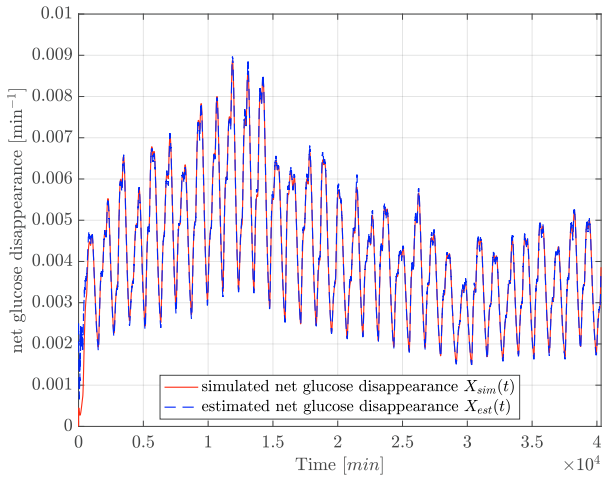

Fig. 2. $X_{\text{sim}}(t)$ and $X_{\text{est}}(t)$ for a female diabetes mellitus type 1 patient

which get infused randomized($[1, 30]$) mins after the meal intake, see Fig. 8. Furthermore the basal rate $u_B(t)$ has a typical pattern from morning to the night, see Fig. 9.

$$n = 0.1, \quad S_G = 0, \quad S_I = 5^{-4}, \quad p_2 = 0.02,$$
$$\gamma = 0, \quad t_1 = 120, \quad \gamma = t_2 = 150,$$
$$V_G = 0.16, \quad V_I = 125, \quad W = 65.$$

The initial conditions are:

$$x_{\text{init}} = [300 \ 1e-7 \ 100 \ 0 \ 0 \ 300 \ 0 \ 0 \ 5e-4]^T. \quad (29)$$

Figures 1, 2, 3, and 4 show the result of a female diabetes type 1 patient with changing insulin sensitivity through the menstrual cycle. Figures 5 and 6 depict the evolution of the intermediate state variables S_2, M_2 for insulin and glucose processing within the human body. For the $u(t)$ and $u_b(t)$, Rapid acting insulin is infused for every meal $D(t)$. Rapid acting insulins begin to work between 10 to 20 minutes after injection and have their peak 30 to 90 minutes after the injection. (Wong and Kroon, 2021) It can be seen in (Fig. 1), with decreasing insulin sensitivity, the patient has a higher glucose level because the calculation of the bolus is based on a strict rule without knowledge of the insulin sensitivity. Furthermore the insulin sensitivity can be estimated throughout the menstrual cycle (Fig. 4).

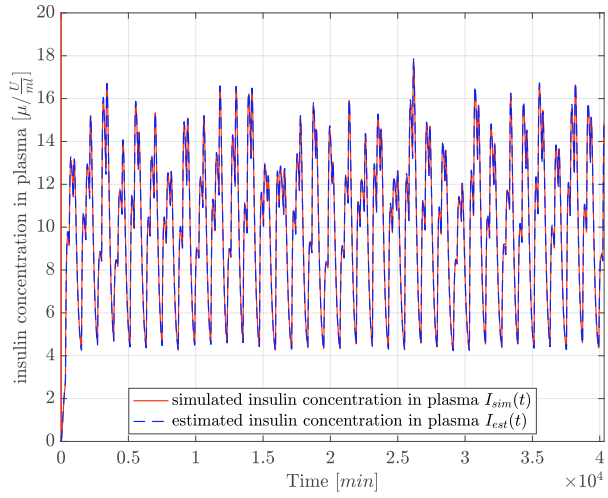

Fig. 3. $I_{\text{sim}}(t)$ and $I_{\text{est}}(t)$ for a female diabetes mellitus type 1 patient

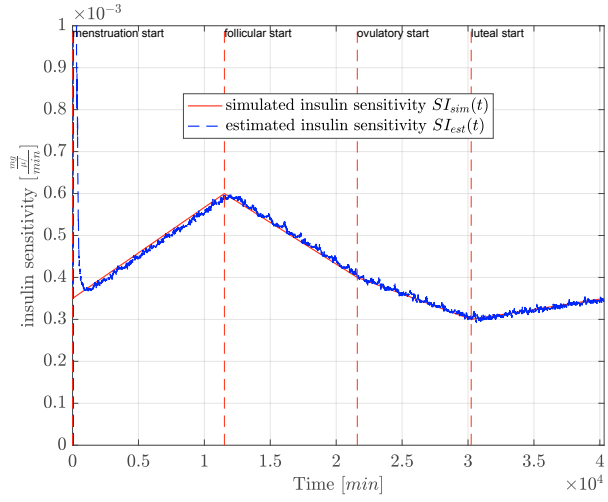

Fig. 4. $SI_{\text{sim}}(t)$ and $SI_{\text{est}}(t)$ for a female diabetes mellitus type 1 patient

Since the strategy for the insulin bolus does not change over the simulation time with changing insulin sensitivity, the glucose level in the ovulatory and the luteal phase is higher because the bolus $u(t)$ is not administrated.

4. CONCLUSION

Studies of diabetes, especially type 1 diabetes in the context of menstruation, emphasize the critical need for individualized insulin dosing. Alterations in insulin sensitivity through menstruation lead to elevated glucose levels if insulin is not administered properly. This study further suggests the application of the extended Kalman filter (EKF) to an extended version the Bergman minimal model to address the challenge of adjusting insulin dose to overcome changes in insulin sensitivity throughout the menstrual cycle. The findings in two studies reveal that the phases of the menstrual cycle can influence insulin sensitivity, making an adaptive insulin administration necessary to maintain glucose levels within a target range. To estimate the insulin sensitivity with this approach, it is necessary to track the meal intake, insulin bolus, insulin basal rate and have proper knowledge about the insulin type. Simulation

results with MATLAB/Simulink show the possibility of estimating the insulin sensitivity with simulating meals and insulin boluses. This approach can lead to a more accurate method of insulin dosing and so to reduce the risk of hyperglycemia. In future work, an approach will be developed to estimate insulin sensitivity without tracking meals and calculate adaptive boluses based on the estimated parameters.

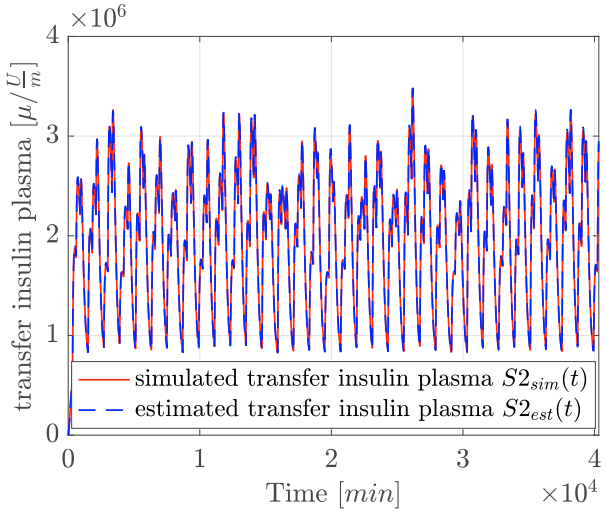

Fig. 5. $S_{2_{\text{sim}}}(t)$ and $S_{2_{\text{est}}}(t)$ for a female diabetes mellitus type 1 patient

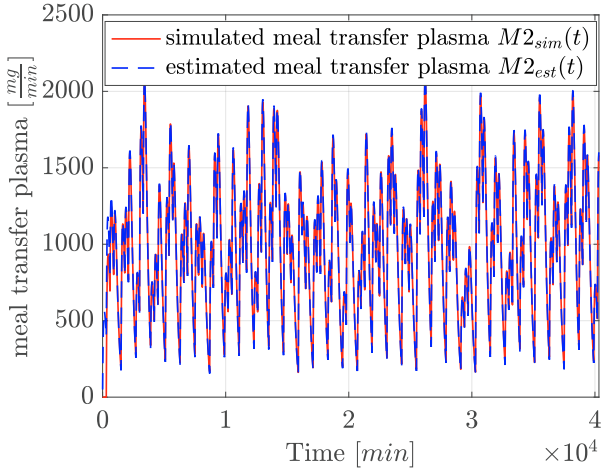

Fig. 6. $M_{2_{\text{sim}}}(t)$ and $M_{2_{\text{est}}}(t)$ for a female diabetes mellitus type 1 patient

REFERENCES

Agrawal, S., Makuch, S., Dróżdż, M., Dudzik, T., Domański, I., Poręba, R., and Mazur, G. (2022). The impact of hypoglycemia on patients with diabetes mellitus: A cross-sectional analysis. *Journal of Clinical Medicine*, 11(3), 626. doi:10.3390/jcm11030626. URL https://doi.org/10.3390/jcm11030626.

Ahrén B, P.G. (2021). Glucose effectiveness: Lessons from studies on insulin-independent glucose clearance in mice. *Journal of diabetes investigation*, 12(5), 675–685. doi:https://doi.org/10.1111/jdi.13446.

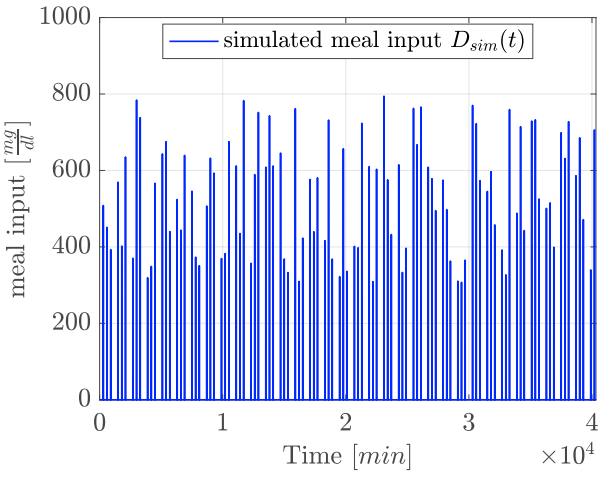

Fig. 7. $D_{\text{sim}}(t)$ and $D_{\text{est}}(t)$ for a female diabetes mellitus type 1 patient

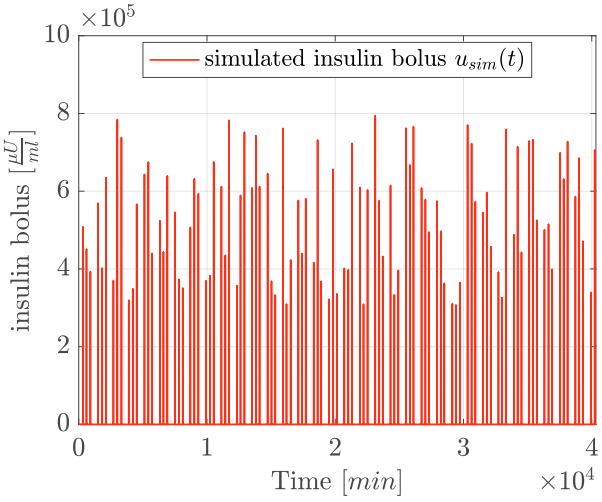

Fig. 8. $u_{\text{sim}}(t)$ and $u_{\text{est}}(t)$ for a female diabetes mellitus type 1 patient

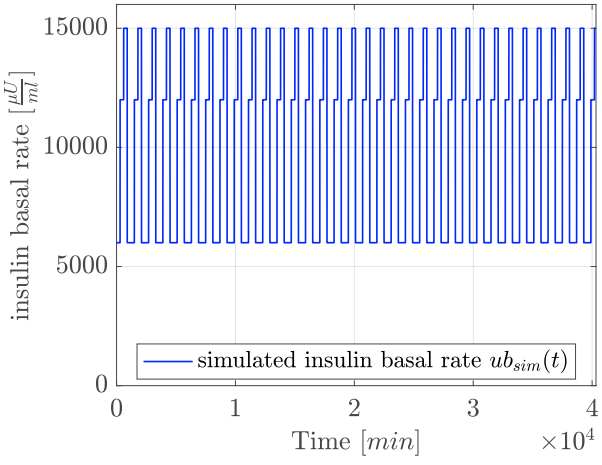

Fig. 9. $u_{B_{\text{sim}}}(t)$ and $u_{B_{\text{est}}}(t)$ for a female diabetes mellitus type 1 patient

Aloke, C., Egwu, C.O., Aja, P.M., Obasi, N.A., Chukwu, J., Akumadu, B.O., Ogbu, P.N., and Achilonu, I. (2022). Current advances in the management of diabetes mellitus. *Biomedicines*, 10(10). doi:10.3390/biomedicines10102436. URL https://www.mdpi.com/2227-9059/10/10/2436.

Andersen, K.E. and Højbjerre, M. (2003). A bayesian approach to bergman's minimal model. In C.M. Bishop and B.J. Frey (eds.), *Proceedings of the Ninth International Workshop on Artificial Intelligence and Statistics*, volume R4 of *Proceedings of Machine Learning Research*, 1–8. PMLR. URL https://proceedings.mlr.press/r4/andersen03a.html. Reissued by PMLR on 01 April 2021.

Choudhury, A.A. and Rajeswari, V.D. (2021). Gestational diabetes mellitus - a metabolic and reproductive disorder. *Biomedicine and Pharmacotherapy*, 143, 112183. doi:https://doi.org/10.1016/j.biopha.2021.112183. URL https://www.sciencedirect.com/science/article/pii/S0753332221009677.

Deichmann, J. and Kaltenbach, H.M. (2021). Estimating insulin sensitivity after exercise using an unscented kalman filter**this work was supported by the two cantons of basel through project grant pmb-01-17 granted by the eth zurich. *IFAC-PapersOnLine*, 54(15), 472–477. doi:https://doi.org/10.1016/j.ifacol.2021.10.301. URL https://www.sciencedirect.com/science/article/pii/S2405896321017067. 11th IFAC Symposium on Biological and Medical Systems BMS 2021.

DK, A.D.D. (2022). Extended kalman filter state estimation-based nonlinear explicit model predictive control design for blood glucose regulation of 1 diabetic patient. *Medical and biological engineering and computing*, 60(5), 1347–1361. doi:doi:10.1007/s11517-022-02511-5.

Eigner, G., Siket, M., and Kovács, L. (2018). Kalman filtering of discrete lpv diabetes mellitus model for control purposes. 000119–000124. doi:10.1109/CINTI.2018.8928205.

Freckmann, G. (2020). Basics and use of continuous glucose monitoring (CGM) in diabetes therapy. *Journal of Laboratory Medicine*, 44(2), 71–79. doi:10.1515/labmed-2019-0189. URL https://doi.org/10.1515/labmed-2019-0189.

Freckmann, G., Buck, S., Waldenmaier, D., Kulzer, B., Schnell, O., Gelchsheimer, U., Ziegler, R., and Heinemann, L. (2021). Insulin pump therapy for patients with type 2 diabetes mellitus: Evidence, current barriers, and new technologies. *Journal of Diabetes Science and Technology*, 15(4), 901–915. doi:10.1177/1932296820928100. URL https://doi.org/10.1177/1932296820928100. PMID: 32476471.

Gallardo-Hernández, A.G., González-Olvera, M.A., Castellanos-Fuentes, M., Escobar, J., Revilla-Monsalve, C., Hernandez-Perez, A.L., and Leder, R. (2022). Minimally-invasive and efficient method to accurately fit the bergman minimal model to diabetes type 2. *Cellular and Molecular Bioengineering*, 15(3), 267–279. doi:10.1007/s12195-022-00719-x. URL https://doi.org/10.1007/s12195-022-00719-x.

Gianluca Nucci, C.C. (2000). Models of subcutaneous insulin kinetics. a critical review. *Computer Methods and Programs in Biomedicine*, 62(3), 249–257. doi:10.1016/S0169-2607(00)00071-7. URL https://doi.org/10.1016/S0169-2607(00)00071-7.

Kartono, A., Arjuna, D.W., and Wahyudi, S.T. (2020). Kinetics modeling studies of type 1 diabetes mellitus treatment with the function of exogenous glucose and insulin injection. *Journal of Physics: Conference Series*, 1572(1), 012041. doi:10.1088/1742-6596/1572/1/012041. URL https://doi.org/10.1088/1742-6596/1572/1/012041.

Kharroubi, A.T. (2015). Diabetes mellitus: The epidemic of the century. *World Journal of Diabetes*, 6(6), 850. doi:10.4239/wjd.v6.i6.850. URL https://doi.org/10.4239/wjd.v6.i6.850.

Laimer, M., Melmer, A., Mader, J.K., Schütz-Fuhrmann, I., Engels, H.R., Götz, G., Pfeifer, M., Hermann, J.M., Stettler, C., and Holl, R.W. (2016). Variability of basal rate profiles in insulin pump therapy and association with complications in type 1 diabetes mellitus. *PLOS ONE*, 11(3), e0150604. doi:10.1371/journal.pone.0150604. URL https://doi.org/10.1371/journal.pone.0150604.

Mandal, S. and Sutradhar, A. (2023). Robust controller for artificial pancreas for patients with type-1 diabetes. *Research on Biomedical Engineering*, 39(2), 437–450. doi:10.1007/s42600-023-00285-9. URL https://doi.org/10.1007/s42600-023-00285-9.

Shimoda, S., Nishida, K., Sakakida, M., Konno, Y., Ichinose, K., Uehara, M., Nowak, T., and Shichiri, M. (1997). Closed-loop subcutaneous insulin infusion algorithm with a short-acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas. *Frontiers of medical and biological engineering : the international journal of the Japan Society of Medical Electronics and Biological Engineering*, 8(3), 197—211. URL http://europepmc.org/abstract/MED/9444512.

Sylvester, D.D., Munje, R.K., and Wagh, K.K. (2017). Back stepping smc for blood glucose control of type-1 diabetes mellitus patients. *International Journal of Engineering Technology Science and Research*, 4(5), 1–7.

Toor, S., Yardley, J.E., and Momeni, Z. (2023). Type 1 diabetes and the menstrual cycle: Where/how does exercise fit in? *International Journal of Environmental Research and Public Health*, 20(4), 2772. doi:10.3390/ijerph20042772. URL https://doi.org/10.3390/ijerph20042772.

Turksoy, K., Samadi, S., Feng, J., Littlejohn, E., Quinn, L., and Cinar, A. (2016). Meal detection in patients with type 1 diabetes: A new module for the multivariable adaptive artificial pancreas control system. *IEEE Journal of Biomedical and Health Informatics*, 20(1), 47–54. doi:10.1109/jbhi.2015.2446413. URL https://doi.org/10.1109/jbhi.2015.2446413.

Welch, G. and Bishop, G. (1995). An introduction to the kalman filter. Technical Report 95-041, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. URL http://www.cs.unc.edu/~welch/kalman/kalmanIntro.html.

Wong, E.Y. and Kroon, L. (2021). Ultra-rapid-acting insulins: How fast is really needed? *Clinical Diabetes*, 39(4), 415–423. doi:10.2337/cd20-0119. URL https://doi.org/10.2337/cd20-0119.