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ORIGINAL ARTICLE

Model Identification Using Stochastic Differential Equation Grey-Box Models in Diabetes

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Abstract

Background:

The acceptance of virtual preclinical testing of control algorithms is growing and thus also the need for robust and reliable models. Models based on ordinary differential equations (ODEs) can rarely be validated with standard statistical tools. Stochastic differential equations (SDEs) offer the possibility of building models that can be validated statistically and that are capable of predicting not only a realistic trajectory, but also the uncertainty of the prediction. In an SDE, the prediction error is split into two noise terms. This separation ensures that the errors are uncorrelated and provides the possibility to pinpoint model deficiencies.

Methods:

An identifiable model of the glucoregulatory system in a type 1 diabetes mellitus (T1DM) patient is used as the basis for development of a stochastic-differential-equation-based grey-box model (SDE-GB). The parameters are estimated on clinical data from four T1DM patients. The optimal SDE-GB is determined from likelihood-ratio tests. Finally, parameter tracking is used to track the variation in the "time to peak of meal response" parameter.

Results:

We found that the transformation of the ODE model into an SDE-GB resulted in a significant improvement in the prediction and uncorrelated errors. Tracking of the "peak time of meal absorption" parameter showed that the absorption rate varied according to meal type.

Conclusion:

This study shows the potential of using SDE-GBs in diabetes modeling. Improved model predictions were obtained due to the separation of the prediction error. SDE-GBs offer a solid framework for using statistical tools for model validation and model development.

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Abbreviations: (ACF) autocorrelation function, (BG) blood glucose, (BW) body weight, (CHO) carbohydrate, (CSII) continuous subcutaneous insulin infusion, (IVP) Identifiable Virtual Patient, (ODE) ordinary differential equation, (PD) pharmacodynamic, (PK) pharmacokinetic, (SDE) stochastic differential equation, (SDE-GB) stochastic-differential-equation-based grey-box model, (T1DM) type 1 diabetes mellitus

Keywords: autocorrelation, blood glucose dynamics, statistical model building, stochastic differential equations, stochastic grey-box modeling, type 1 diabetes mellitus

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Introduction

Several studies have shown promising potential for automatic insulin delivery in the treatment of type 1 diabetes mellitus (T1DM) patients. In the development of control algorithms for an artificial pancreas, virtual T1DM patients are a useful tool for preclinical testing and verification. The advantages are several: acceleration of the development process, lower costs, and the possibility of testing extreme treatment strategies without having to deal with the ethical aspects. The acceptance of virtual preclinical testing is growing and thus also the need for robust and reliable models for simulation. Currently, several dynamic models of the blood glucose (BG)–insulin system in T1DM patients exist.[1–4] The simplest models are used for simulating BG response after an intravenous glucose tolerance test, and the most advanced and complex models are used for simulating BG response to a meal [in terms of amount of ingested carbohydrates (CHOs)] and to continuous subcutaneous insulin infusion (CSII) from a pump. One of the most complex models has been approved for preclinical *in silico* testing of control algorithms by the U.S. Food and Drug Administration.[5]

The existing models can be categorized as white-box models based on ordinary differential equations (ODEs). White-box models are mainly constructed on the basis of physiological knowledge about the system. Solutions to ODEs are deterministic functions of time, and hence these models are built on the assumption that future concentrations and effects can be predicted exactly.

An essential part of model validation is the analysis of the residual errors (the deviation between the true observations and the one-step predictions provided by the model). This validation method is based on the fact that a correct model leads to uncorrelated residuals. This is rarely obtainable for white-box models. Hence, in these situations, it is not possible to validate ODE models using standard statistical tools. However, by using a slightly more advanced type of differential equations, this problem can be solved. By replacing ODEs with stochastic differential equations (SDEs), we can obtain uncorrelated residuals both by systematically improving the model and because of the way the stochasticity enters the system.

Stochastic-differential-equation-based models are referred to as grey-box models because the structure of the model is built on a combination of physiological knowledge, as white-box models, and on statistical information based on the observations, as black-box models, which are entirely built on data. Hence, stochastic-differential-equation-based grey-box models (SDE-GBs) can be seen as a mix of white-box and black-box models as sketched in **Figure 1**. An SDE-GB can be written as

$$dx_t = f(x_t,u_t,t,\theta)dt + \sigma(u_t,t,\theta)d\omega \quad (1)$$

$$y_k = h(x_k,u_k,t_k,\theta) + e_k \quad (2)$$

The equations describing the dynamics of the states of the system, x_t, are formulated in continuous time and are separated in a drift term, $f(x_t,u_t,t,\theta)$, and a diffusion term, $\sigma(u_t,t,\theta)d\omega$. The observations, y_k, are linked to the states through the observation equations, **Equation (2)**, which are typically formulated in discrete time and include the measurement error, e_k. u_t represents the inputs and θ the parameters of the system.

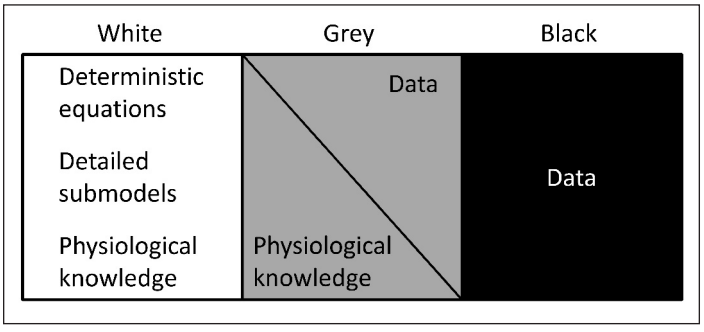

Figure 1. Illustration of the concept of grey-box modeling. White-box models are based mainly on knowledge about the system. Black-box models are built on statistical information from the data. Grey-box modeling combines the two approaches.

As seen in **Equations (1)** and **(2)**, the SDE-GB separates the residual error into two separate error terms:

- The diffusion, $\sigma(u_t,t,\theta)d\omega$, representing model approximations and noise originating from unknown disturbances to the system, e.g., changes in metabolism due to physical activity, altered stress level, hormone cycle, or simply true stochastic behavior and

- The measurement noise, e_k, representing the serially uncorrelated error occurring due to imperfect accuracy and precision of the analyzing equipment.

Solutions to SDEs are stochastic processes that are described by probability distributions. This property allows for maximum likelihood estimation.[6]

In physiological modeling, SDE-GBs are obvious choices from a theoretical point of view due to their ability to describe the stochastic, complex, and unpredictable nature of these systems. The separation of the residual error into diffusion and measurement noise results in a more correct description of the prediction error. If the model is describing the data properly, this formulation will lead to uncorrelated residuals.

Inclusion of the diffusion has another advantage, mainly related to the model building itself. By investigating the diffusion terms, one can retrieve information about how to improve an insufficient model. Diffusion terms that are estimated to be relatively large indicate a model mismatch for the relevant part of the model. Accordingly, the diffusion terms can help in the search for a more reliable model.[7] SDE-GBs have been found to be useful within many areas of mathematical modeling of biological and physiological systems.[8–12]

This article focuses on the advantages of using SDE-GBs when modeling the glucoregulatory system in T1DM patients. We start out from a previously published ODE-based model[3] and use SDEs and statistical analysis to extend the model by adding significant diffusion terms.

Methods

Data

Data from a clinical study conducted at Hvidovre University Hospital as a part of the DIACON project were used.[13] Four CSII-treated T1DM patients performed four different study sequences, including standardized meals and insulin boluses. During each study day, three events took place. The first event took place after at least 120 min of BG stabilization. It consisted of a standardized solid meal [1 g CHO/kg body weight (BW)] with either a half-meal-size insulin bolus calculated on the basis of the patient's insulin sensitivity factor and insulin-to-carbohydrate ratio or with no bolus at all. The second event was introduced 150 min after the meal and was a small or large bolus defined as a bolus that would lower BG by 54 or 108 mg/dl, respectively. Finally, after another 150 min, the patient was given a standardized liquid snack (event 3; 0.4 g CHO/kg BW). The combination of events on the four study days is depicted in **Table 1**. Patients spent the day in bed and received their normal basal rate of insulin during the whole study day. Blood glucose samples were obtained every 10 min (YSI2300 STAT plus, Yellow Springs Instruments, Yellow Springs, OH) and plasma insulin concentration was sampled nonequidistantly 23 times during the trial day.

The Initial White-Box Model

We used the Identifiable Virtual Patient (IVP)[3,14] as an initial white-box basis for formulating our grey-box model. The IVP model is an extended minimal model, including meal absorption and CSII. This initial model will be presented as an SDE-GB with diffusion. The insulin pharmacokinetic (PK) model is a two-compartmental model:

$$dI_{subc} = \frac{1}{\tau_1}\left(\frac{ID}{C_I} - I_{subc}\right)dt + \sigma_{Isubc}d\omega_1 \quad (3)$$

$$dI_p = \frac{1}{\tau_2}(I_{subc} - I_p)dt + \sigma_{Ip}d\omega_2 \quad (4)$$

Table 1.
Description of the Four Study Sequences

Patient	Event 1	Event 2	Event 3
1	Meal + ½ bolus 65 g CHO + 3.3 U	Small bolus 0.9 U	Snack 28 g CHO
2	Meal without bolus 75 g CHO	Small bolus 1.6 U	Snack 31 g CHO
3	Meal + ½ bolus 105 g CHO + 8.8 U	Large bolus 5.0 U	Snack 44 g CHO
4	Meal without bolus 65 g CHO	Large bolus 2.2 U	Snack 27 g CHO

where I_{subc} represents the subcutaneous concentration of insulin (mU/liter) and ID is the input from CSII (mu/min) representing the insulin basal delivery rate and boluses. I_p represents the plasma insulin concentration (mU/liter). In this

study, the diffusion term parameterized as $\sigma d\omega$. σ is a scaling parameter for the diffusion, and $d\omega$ is assumed to be a Wiener process for which the increments are normally distributed.[15] The remaining parameter definitions are given in **Table 2**. The glucose–insulin dynamics are described as

$$dI_{eff} = p_2(S_I I_p - I_{eff})dt + \sigma_{Ieff} d\omega_3 \quad (5)$$

$$dG_p = \left(-(GEZI + I_{eff})G_p + EGP + \frac{D_2}{\tau_m} + \frac{G_{IV}}{\tau_g V_g} \right) dt + \sigma_{Gp} d\omega_4 \quad (6)$$

where I_{eff} is the pharmacodynamic (PD) effect of insulin (min^{-1}) on the BG level, G_p (mg/dl). G_{IV} is the intravenous glucose input (mg) administrated during the stabilization period if needed and is modeled as a vector of zeros except at the time instants where glucose was given during the clinical study. The meal absorption is described as a two-compartment model:

$$dD_1 = \left(\frac{AgCHO}{V_g} + \frac{D_1}{\tau_m} \right) dt + \sigma_{D1} d\omega_5 \quad (7)$$

$$dD_2 = \frac{1}{\tau_m}(D_1 - D_2)dt + \sigma_{D2} d\omega_6 \quad (8)$$

where CHO is the rate of ingestion of carbohydrates (mg/min). D_1 (mg) and D_2 (mg) represent the digestive system.

Table 2.
Identifiable Virtual Patient Model Parameters

Name	Unit	Description	Nominal value[a]
τ_1	min	Time constant related to the insulin movement between the subcutaneous layer and plasma	40–131
τ_2	min	Time constant related to the insulin movement between the subcutaneous layer and plasma	10–70
C_l	liter/min	Insulin clearance	0.54–2.01
p_2	1/min	Delayed insulin action on BG level	8.14×10^{-3}–2.33×10^{-2}
S_I	liter/(mU × min)	Insulin sensitivity	9.64×10^{-5}–1.73×10^{-3}
$GEZI$	1/min	Glucose effectiveness at zero insulin	1.00×10^{-8}-6.39×10^{-3}
EGP	mg/(dl × min)	Endogenous glucose production rate at zero insulin	0.6–3.45
τ_m	min	Peak time of meal absorption	27–107
τ_g	min	Time constant for the intravenous glucose administration	1
Ag	Dimensionless	Bioavailability for carbohydrates	0.9
V_G	dl/kg BW	Volume of distribution for glucose	1.93–4.14

[a] The values are obtained from Kanderian and coauthors[3] except Ag and τ_g, which were fixed during the estimation.

To specify which states we observe and to introduce measurement error, we construct two observation equations linking the observations to the actual state—one for each type of observation: YSI (representing the BG level) and I_A (representing the insulin level in plasma). For our model, the set of observation equations can be written as

$$YSI = G_p + \exp(e_{YSI}), \quad \exp(e_{YSI}) \in N(0, S_{YSI}) \quad (9)$$

$$I_A = I_p + \exp(e_{I_A}), \quad \exp(e_{I_A}) \in N(0, S_{I_A}) \quad (10)$$

where S represents the variance of the measurement noise for each of the two types of observations. The sequence of measurement errors, e, is assumed to be independent and identically distributed. If we expect time correlated errors,

e.g., if we used observations from a continuous glucose monitor, the correlated noise could be implemented in the model as a state.

Stochastic Differential Equation Grey-Box Model Construction

Because of the complex structure of SDEs, estimation of parameters in an SDE-GB is not trivial except for some simple cases. Instead, a maximum likelihood method in combination with an extended Kalman filter is used to estimate the parameters.[12,15] The likelihood function is formulated using the one-step prediction errors, $\varepsilon_{k,}$ and the associated variances, $R_{k|k-1}$:[15]

$$L(\theta;Y_N) = p(Y_N|\theta) \tag{11}$$

$$= \left(\prod_{k=1}^{N} \frac{\exp(-\frac{1}{2}\varepsilon_k^T R_{k|k-1}^{-1}\varepsilon_k)}{\sqrt{\det(R_{k|k-1})}(\sqrt{2\pi})^{\dim(Y_N)}} \right) p(y_0|\theta) \tag{12}$$

Y_N is the set of observations, and y_0 is the initial conditions. For a given set of parameters and initial states, ε_k and $R_{k|k-1}$ are computed by a continuous-discrete extended Kalman filter as described previously.[8,15] The parameter estimates are found by maximizing the log-likelihood:

$$\hat{\theta} = \text{argmax}\{\log(L(\theta;Y_N|y_0))\}. \tag{13}$$

The corresponding value of the log-likelihood is the observed maximum likelihood value for that data set and model. All computations were done using the free statistical software, R (version 2.15.1), and the "CTSMR-package" (Continuous Time Stochastic Modeling in R).[16]

To improve the IVP model using SDEs, the following forward selection strategy was used:

Step 1: The parameters of the ODE version of the model were estimated for each data set. The following parameters were fixed: $Ag = 0.9$ as in Dalla Man and coauthors,[1] $\tau_g = 1$ min, and all diffusion terms were fixed to zero. All initial conditions were fixed except for I_{eff}.

Step 2: One diffusion term at a time was now estimated together with the parameters estimated in step 1 for each data set. This was done six times corresponding to the six diffusion terms in **Equations (3)–(8)**.

Step 3: A likelihood-ratio test was used to identify the SDE-GB resulting in the most significant improvement compared with the ODE. The test statistic is[6]

$$D = 2(\log(\sum_i L) - \log(\sum_i L_0)) \tag{14}$$

where $i = 1$–4, corresponding to each of the four data sets. L and L_0 are the likelihood values obtained in **Equation (13)** for the SDE-GB and ODE model, respectively. D is $\chi^2(f)$ distributed, where f is the difference in number of parameters between the two models—in this case, $f = 1$.

Step 4: The model found in step 3 was extended by repeating the procedure in step 2. This time, yet another diffusion term was estimated. Hereby, the procedure was repeated five times. The best model now including two nonzero diffusion terms was identified with a likelihood-ratio test against the best SDE-GB identified in step 3. Analysis showed that it was not feasible to estimate more than two diffusion terms in the IVP model, given the limited size of each data set.

Step 5: In order to illustrate another method for systematic model improvement, we performed parameter tracking to pinpoint model deficiencies.[8] Parameter tracking can be used to identify parameters with systematic variation due to factors or disturbances not included in the model, e.g., changing hormone levels or other unknown factors influencing

the system. By changing the parameter of interest into a state and by setting the drift term to zero, the parameter is allowed to vary as a random walk as dictated by the data. This will reveal any presence of a systematic structure that can be included in the model subsequently.

Results

Model Evaluation

The performance of the models is evaluated from the likelihood-ratio tests and by examining the one-step predictions and the autocorrelation function (ACF) for the standardized residuals. One step corresponds to the time between two samples. The ACF of the residuals shows whether the residuals are correlated.[9,17] The standard deviations given in the following figures are equal to $\sqrt{diag(R_{k|k-1})}$.

A one-step prediction of the BG level from the ODE model and the ACF for the YSI residuals are seen in **Figure 2**. The one-step prediction is inaccurate, and especially after the bolus at 150 min, the predictions clearly deviate from the observations. The ACF shows that the YSI residuals are highly correlated and thus cannot be considered as independent. The same holds for the three other patients. The prediction of the insulin level from the ODE model and the corresponding ACF for the insulin residuals are shown in **Figure 3** for patient 1. The prediction seems acceptable, although the limited number of observations (n = 23) makes it hard to assess. Based on the corresponding ACF, the residuals appear to be correlated. The next step in the model development was to estimate the model parameters, including one nonzero diffusion term. **Table 3** shows the results from the likelihood-ratio test performed in steps 3 and 4. As seen from the six likelihood-ratio tests in step 3, we found that the largest improvement was achieved with a nonzero diffusion term on the PD effect of insulin on the BG level, I_{eff} in **Equations (5)** and **(6)**.

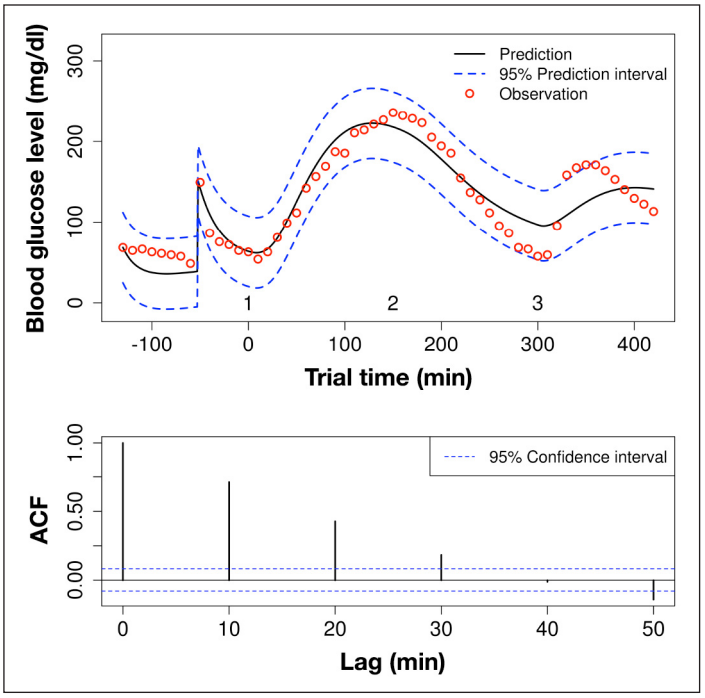

Figure 2. (Top) One-step prediction and 95% prediction interval from the ODE model and YSI observations for patient 2. The starting time of each event is indicated by 1, 2, and 3. The prediction is not in total agreement with the observations, particularly after the bolus at 150 min. **(Bottom)** The ACF for the YSI residuals from the ODE model. The sketched 95% confidence interval corresponds to an uncorrelated process. If more than 5% is outside this region, the process cannot be assumed to be uncorrelated. The residuals are strongly correlated in this case.

In the following, we define this model as SDE-GB 1. The one-step prediction of the BG level from SDE-GB 1

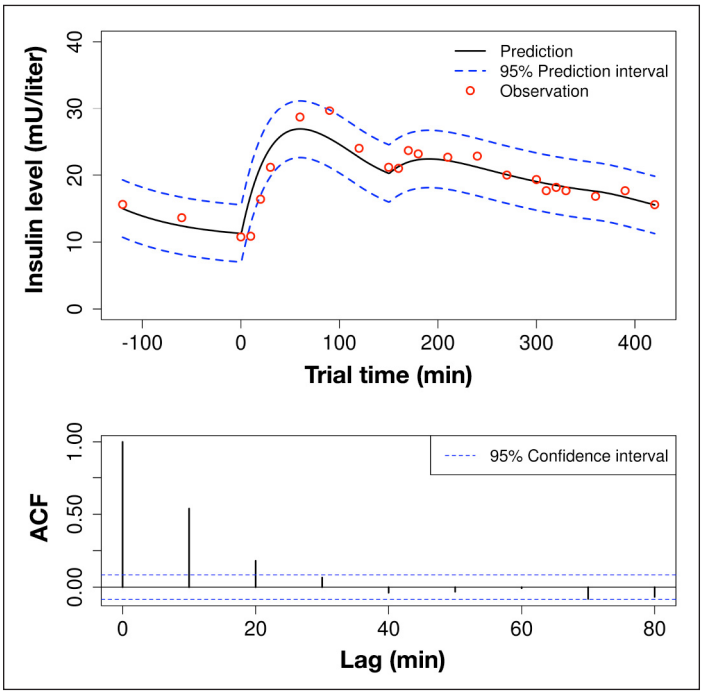

Figure 3. (Top) One-step prediction and 95% prediction interval from the ODE model and observations of the insulin plasma level for patient 1. The prediction is acceptable. **(Bottom)** The ACF for the insulin residuals from the ODE model. Despite the acceptable fit, the residuals are correlated.

for patient 4 is seen in **Figure 4**. The prediction has improved markedly, and the prediction uncertainty has also decreased substantially.

The ACF for the YSI residuals in **Figure 4** shows that the residuals now can be considered as almost independent only by the inclusion of a single nonzero diffusion term in the state representing I_{eff} in **Equations (5)** and **(6)**. Subsequently, SDE-GB 1 was extended as described in step 4. From the sequence of likelihood-ratio tests, we concluded that the largest improvement was achieved with an additional nonzero diffusion term on the state describing the insulin plasma level, I_p in **Equations (3)** and **(4)** as stated in **Table 3**. This model is named SDE-GB 2 and includes two nonzero diffusion terms in total. Based on the individual likelihood values (for each data set) found in **Equation (13)**, we saw that the obtained likelihood value had improved significantly only for patients 1 and 2. Thus we consider this model only for these two patients.

To illustrate the effect of the additional diffusion term, **Figure 5** shows the one-step prediction of the insulin level from SDE-GB 1 and the ACF for the residuals for

Table 3.
Estimated Log-Likelihood Values and Test Statistics and *P* Values from the Likelihood-Ratio Tests

	log(∑*L*)	*D*[a]	*P* value[b]
ODE model	-510.3	—	—
SDE-GB σ_{Ip}	-494.0	32.6	1.13×10^{-8}
SDE-GB σ_{Isc}	-494.3	32	1.54×10^{-8}
SDE-GB σ_{Ieff}	-326.9	366.8	0
SDE-GB σ_{G}	-357.7	305.2	0
SDE-GB σ_{D1}	-331.1	358.4	0
SDE-GB σ_{D2}	-337.1	346.4	0
SDE-GB $\sigma_{Ieff+}\sigma_{Ip}$	-319.9	14	0.00018
SDE-GB $\sigma_{Ieff+}\sigma_{Isc}$	-324.6	4.6	0.032
SDE-GB $\sigma_{Ieff+}\sigma_{G}$	-326.9	0	1
SDE-GB $\sigma_{Ieff+}\sigma_{D1}$	-326.9	0	1
SDE-GB $\sigma_{Ieff+}\sigma_{D2}$	-326.9	0	1

[a] The test statistic *D* is computed from **Equation (14)** as the likelihood ratio between the ODE model and the following six models in the table (SDE-GB $\sigma_{Ip\text{-}D2}$), and between SDE-GB σ_{Ieff} and final five models in the tables (SDE-GB $\sigma_{Ieff+Ip\text{-}Ieff+D2}$).

[b] Based on a $\chi^2(1)$ distribution.

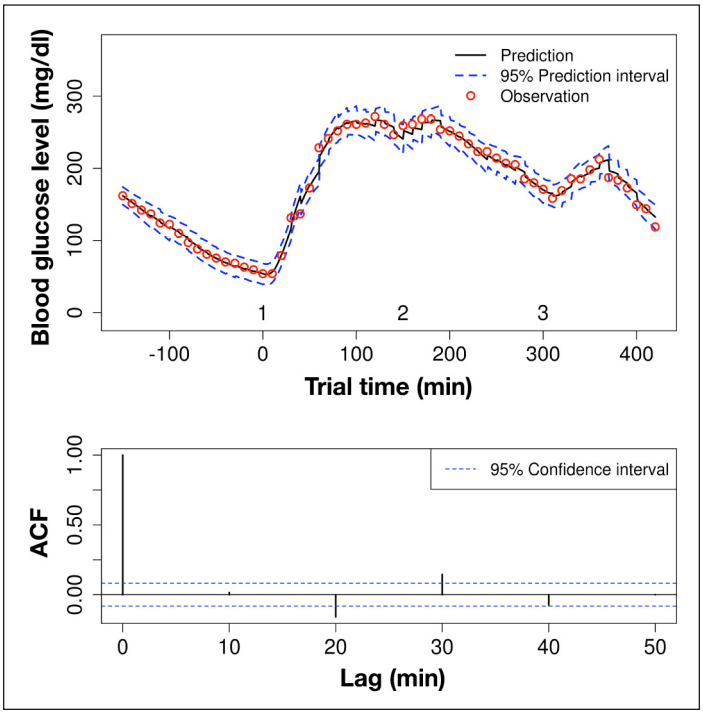

Figure 4. (Top) One-step prediction and 95% prediction interval from the SDE-GB 1 and YSI observations for patient 4. The prediction has improved from the ODE model prediction. The starting time of each event is indicated by 1, 2, and 3. **(Bottom)** The ACF for the YSI residuals from the SDE-GB 1. Almost no significant correlation is left.

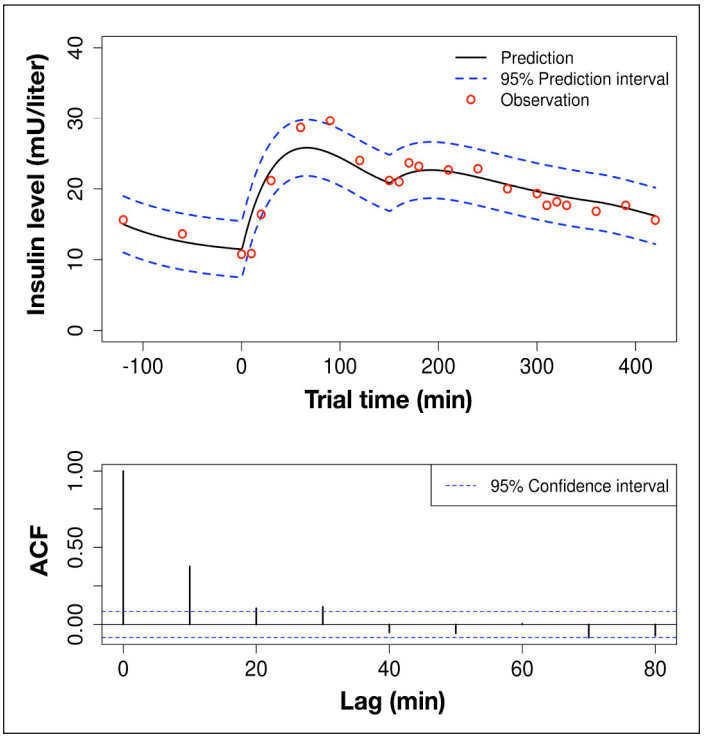

Figure 5. (Top) One-step prediction and 95% prediction interval from SDE-GB 1 and observations of the insulin plasma level for patient 1. The prediction is acceptable. **(Bottom)** The ACF for the insulin residuals from SDE-GB 1. Some correlation is still present.

patient 1. The ACF has improved from the ODE model, but some correlation is still present. **Figure 6** shows the one-step prediction of the insulin level from SDE-GB 2 together with the ACF for the residuals. The extra nonzero diffusion term removes the correlation between the residuals.

Parameter tracking

Kanderian and coauthors[3] introduced intraday variation by separating data in time windows and estimating some of the parameters within these windows. The time windows are found on the basis of subjective predefined criteria for the model fit. Using the SDE-GB approach, we do not need to define such criteria to be able to investigate parameter variation. By changing a parameter into a state, we allow the parameter to vary over time. We can then track the variation in the parameter value.

As the patients are served two types of meals (solid and liquid), we would expect the peak time of meal absorption, τ_m, to differ for the two meals. We expanded SDE-GB 1 by adding a state representing τ_m. The state was modeled as a random walk:

$$d\tau_m = \sigma_{\tau_m} d\omega_7 \tag{15}$$

With this formulation, we could track τ_m and identify the possible factors affecting the variation of this parameter. In **Figure 7**, a result of this tracking is seen. As expected, τ_m is estimated to be shorter after a liquid snack than after a solid meal. A future step would be to replace the random walk with an equation including meal type as the explanatory variable. We were not able to do this due to the limited size of the data sets. However, another case using parameter tracking for model expansion is presented elsewhere.[8]

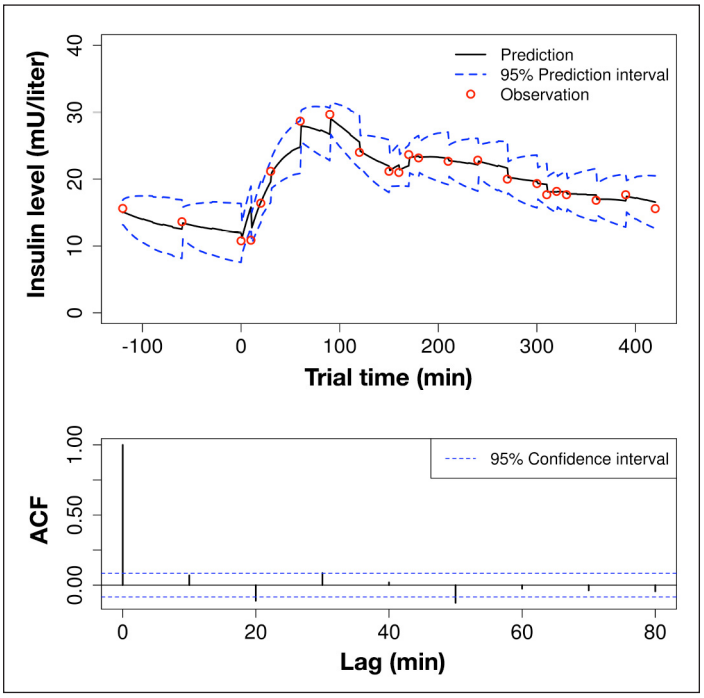

Figure 6. (Top) One-step prediction and 95% prediction interval from SDE-GB 2 and observations of the insulin plasma level for patient 1. The prediction has improved from the ODE model and SDE-GB 1. **(Bottom)** The ACF for the insulin residuals from SDE-GB 2. No significant correlation is left.

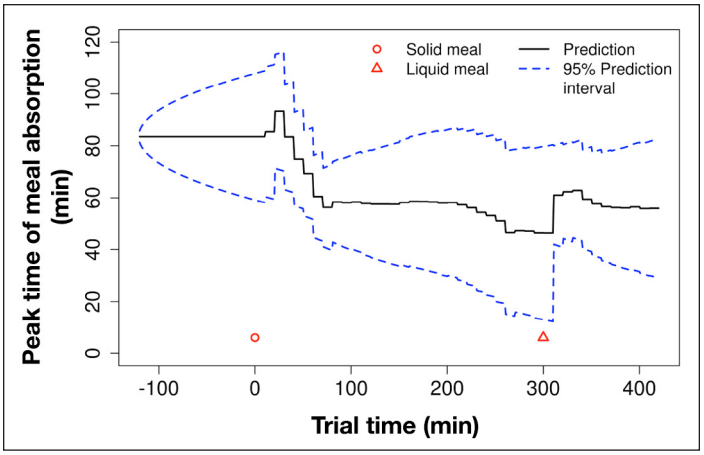

Figure 7. A result of parameter tracking. The one-step prediction and 95% prediction interval of the peak time of the meal absorption shows that the peak time is shorter for the liquid meal than the solid meal as expected.

Discussion

In this article, a systematic approach for formulating SDE-based glucoregulatory grey-box models has been described. Using an ODE-based model as basis, the approach consists of a sequential method for obtaining a statistical validated SDE-based model. The steps include identification of the needed diffusion terms from a combination of forward selection, model testing, and model validation. The final model provides a robust and validated description of the data and provides much more accurate and realistic predictions.

We have focused on short-term prediction, which is relevant if the model is to be used for prediction in model predictive control of T1DM. In this case, the prediction is updated every time a new observation is available and cannot drift far away. SDE-GBs will be superior to ODE models for pure simulation as well, although this requires a careful investigation of the diffusion, which is out of the scope of this article.[18]

The fact that the diffusion term was found to be significant for the state describing the PD effect of insulin on the BG level could indicate that the drift term of this part of the model is too simple to explain the true physiological relation. It might, however, also indicate that this part of the system is exposed to true physiological variation.

The advantages of SDE modeling are several. The most important is the possibility to use statistical tools for model selection and validation. Very few physiological systems, if any, contain states that can be predicted exactly. Since most statistical test principles rely on a full description (probabilistic distribution) of the future state values of the system, such statistical test procedures will lead to wrong conclusions about parameters and effects if they are based on an ODE model. The fact that SDE-GBs provide improved parameter estimates for models describing systems influenced by disturbances, i.e., nondeterministic states, has been shown elsewhere.[19]

Another advantage is the ability to pinpoint model deficiencies and to explore where and how to improve the model, as shown here with the peak time of meal absorption parameter τ_m. Parameter tracking with SDE-GBs is a strong tool in investigating how physiological variation influences the parameters of the models. This is recognized as the largest technical challenge in the development of simulation models.[20] A systematic method for SDE-GB development is described by Kristensen and coauthors.[7]

The main disadvantage with SDE modeling is that it requires more complex estimation methods, which are not a part of standard modeling software tools. A full establishment of SDEs in diabetic modeling requires, first of all, an implementation of the estimation algorithms in commonly used software. Additionally, the computational burden is significantly larger for SDE-GBs, which puts demands on the researcher's computer capacities. A first step toward fully recognizing the potential of SDE models is to use the ACF of the residuals as model validation as we have shown here. This is a fruitful way to test for independence.

The presence of the diffusion term in a state representing, e.g., a concentration can make the concentration drop below zero and thereby conflict with the physical understanding. To avoid this, a state-dependent diffusion term can be used to force the noise to decrease to zero when the concentration decreases to zero.[10]

To construct a reliable and robust virtual T1DM patient, the underlying model should not only represent an individual patient; it should ideally be a population SDE model based on clinical data from a large population. Population models include population parameters and random effects representing the intersubject variability in the parameter values.[21,22] This type of model has shown great potential within PK/PD modeling.[9]

Conclusion

The aim of this article was to use clinical data and an existing ODE model of a T1DM patient to illustrate the most important aspects and advantages of SDE-GB modeling. Data from four patients were used to estimate parameters in an ODE model and two SDE-GBs. Addition of a single diffusion term resulted in significant improvements in the ODE model in terms of predictions and prediction uncertainty. The ACF of the residuals confirmed that the SDE-GBs were statistically valid as opposed to the ODE model.

We have shown that SDE-GBs offer a solid framework for using statistical tools for model building and validation. Parameter tracking proved to be a useful tool to reveal the variation in the parameter describing the time to peak absorption of the meal. More reliable model predictions and the possibility to evaluate the uncertainty of the predictions as provided by the SDE-GBs will improve the reliability and potential of virtual T1DM patients.

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