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Predictive performance for population models using stochastic differential equations applied on data from an oral glucose tolerance test

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Abstract Several articles have investigated stochastic differential equations (SDEs) in PK/PD models, but few have quantitatively investigated the benefits to predictive performance of models based on real data. Estimation of first phase insulin secretion which reflects beta-cell function using models of the OGTT is a difficult problem in need of further investigation. The present work aimed at investigating the power of SDEs to predict the first phase insulin secretion (AIR_{0-8}) in the IVGTT based on parameters obtained from the minimal model of the OGTT, published by Breda et al. (Diabetes 50(1):150–158, 2001). In total 174 subjects underwent both an OGTT and a tolbutamide modified IVGTT. Estimation of parameters in the oral minimal model (OMM) was performed using the *FOCE*-method in NONMEM VI on insulin and C-peptide measurements. The suggested SDE models were based on a continuous AR(1) process, i.e. the Ornstein-Uhlenbeck process, and the extended Kalman filter was implemented in order to estimate the parameters of the models. Inclusion of the Ornstein-Uhlenbeck (OU) process caused improved description of the variation in the data as measured by the auto-correlation function (ACF) of one-step prediction errors. A main result was that application of SDE models improved the correlation between the individual first phase indexes obtained from OGTT and AIR_{0-8} ($r = 0.36$ to $r = 0.49$ and $r = 0.32$ to $r = 0.47$ with C-peptide and insulin measurements, respectively). In addition to the increased correlation also the properties of the indexes obtained using the SDE

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models more correctly assessed the properties of the first phase indexes obtained from the IVGTT. In general it is concluded that the presented SDE approach not only caused autocorrelation of errors to decrease but also improved estimation of clinical measures obtained from the glucose tolerance tests. Since, the estimation time of extended models was not heavily increased compared to basic models, the applied method is concluded to have high relevance not only in theory but also in practice.

Keywords Pharmacokinetic (PK) · Oral glucose tolerance test (OGTT) · Intravenous glucose tolerance test (IVGTT) · Acute insulin response (AIR) · Oral minimal model (OMM) · Autocorrelation function (ACF) · Stochastic differential equations (SDEs) · Ornstein-Uhlenbeck (OU) · Extended Kalman filter (EKF)

Introduction

The present article deals with the application of mathematical models for the description of the dynamics of insulin response following an oral glucose tolerance test (OGTT) [1]. Traditionally the parameters in these models are estimated using single subject estimation as performed in [2]. In this paper the data was instead modelled using non-linear mixed-effects (NLME) population models. This approach handles the data from various patients as a population which enables simultaneous estimation of inter- and intra-subject variability, influence of measured concomitant effects, and covariates on the fixed effects parameters. This way of estimating parameters is the preferred method in population PK/PD modeling because it provides reliable predictions of variability and is the only practical method for analyzing data from multiple patients in a single data analysis. As a result of this, the models become cornerstones in the simulation of future trials and thus have high value for the pharmaceutical companies. Compared to a single-subject estimation, the population method is also less time consuming and has been shown in [3–5] to provide more correct and robust estimates of metabolic indices.

In the development of PK/PD models a correct determination of the magnitude of unexplained variability is of great importance. Clearly the efficacy and safety of the drug might decrease as unexplained variability increases [6]. Mathematical models applied to time-dependent data are in general said to be falsified if the prediction errors have a systematic trend across the time-scale [7]. In line with this it was found in [8] that misspecification of the residual error impacts the type I error rate in inclusion of covariates. In population analysis this is not an uncommon phenomenon and various examples can be found in [9]. One way to account for time-correlated prediction errors is to use a more complex error structure or introduce stochastic differential equations in the model building as performed in [9, 10], respectively.

In the application of SDEs the differences between individual predictions and observations are explained not by one, but by two fundamentally different types of noise [11].

- The measurement noise, which represents the serial uncorrelated part of the residual variability that may be due to assay error or if the sample concentration is not representative for the true concentration in plasma.
- The dynamic noise, which enters through the dynamics of the system and may originate from model deficiencies, true random fluctuations within the system, or simply unknown system inputs.

Quantification of the dynamic component is thus a unique tool to tell if the proposed PK/PD model is precise enough to satisfactorily describe the underlying system. An estimate of large dynamic noise could be an indication that a model is too simple or simply describing the system badly.

In summary, the inclusion of a diffusion term, representing dynamic noise, allows the SDE model to explain a larger portion of the variation in a given data set compared to a basic ODE approach. Additionally, estimation of this component provides information on model uncertainties and can be used in general model building as performed in [10]. In agreement it was suggested in [12] that the variability between occasions in PK/PD modelling may be more appropriately modelled using SDEs rather than ODEs.

The application of SDEs in describing the glucose/insulin system has been successfully performed in only few studies. These include modelling data from an euglycaemic clamp study, first in [13] and later in [14], data from an IVGTT [3], and finally also data from a 24-h profile in [15, 16]. In spite of the different applications of SDEs in PK/PD model development it generally holds, that the direct benefits seen on practical applications are scarce and evaluation of these e.g. to predictive performance of parameters on real data has not been performed.

In this paper we investigated the predictive performance of population PK/PD models based on ODEs and SDEs built on data obtained from an OGTT. Various models have been built with the purpose of describing the observed dynamics and a major part of them is presented in [1, 2, 17–24]. The purpose of using these models is to create a metabolic portrait of the subjects under investigation. A complete assessment of all models is beyond the scope and here we used the oral minimal model (OMM) described by Breda et al. [1] which is widely used.

We focused solely on the part of the metabolic portrait concerned as the beta-cell function index. Estimation of this measure was used to evaluate the performance of the studied models through a comparison with the standard beta-cell function index obtained from an IVGTT (AIR_{0-8}). Besides measuring the correlation between the index obtained from the OGTT and AIR_{0-8}, we also investigated their respective relation to different covariates. It was thus not the goal to obtain maximal correlation with AIR_{0-8} as in [24], but rather to investigate how well the beta-cell function index obtained from the applied OGTT model relates to AIR_{0-8} and how application of SDEs can effect these relations.

In the selection of a beta-cell function index from the OGTT models, as stated above, a reasonable goal could be to obtain a measure that reflects the properties of the widely used index obtained from the IVGTT, AIR_{0-8}. This measure can be interpreted as the response to an impulse of glucose. Strictly speaking it is a measure

describing the magnitude of the direct insulin response to a rapid increase in glucose. In [2] a correlation of 0.28 was obtained between a dynamic beta-cell function index (Φ_d) and AIR_{0-10}, using single-subject modelling applied to 17 nondiabetic subjects. An extended OGTT model was presented in [22] which also takes incretin effects into account. The obtained correlation between the different indices was 0.67 and estimation was performed using a population approach on 40 healthy subjects. In [24] a regression based approach using measurements from the OGTT and subject specific covariates as independent variables and AIR_{0-8} as dependent variable was used. A correlation equal to 0.74 from the estimation dataset and a value of 0.67 on an internal validation set was obtained. Based on these results it seems reasonable to assume that some information on the first phase index on IVGTT can be derived from models of the OGTT.

Methods

Research design

In this study we applied the dataset originally described in [24] where each subject underwent an oral glucose tolerance test (OGTT) (18 samples during 240 min) and a tolbutamide-modified intravenous glucose tolerance test (IVGTT) (33 samples during 180 min). The cleaned dataset applied here consisted of samples taken from 174 individuals. The condition of subjects was categorized according to the level of fasting plasma glucose (FPG) and level 2 h after glucose ingestion ($OGTT_{120}$) measured in mmol/l. The classification criteria applied, agreed with the ones described in [25] and resulted in a distribution of subjects as presented in Table 1. The study was approved by Ethical Committee of Copenhagen and was in accordance with the principles of the Declaration of Helsinki.

IVGTT

All subjects underwent a 33-point tolbutamide-modified, frequently sampled IVGTT within 1 week after the OGTT examination except for a few individuals who underwent an IVGTT within 4 weeks. The trials were carried out after 12 h of

Table 1 Study population

Mean and standard deviation (SD) of demographic characteristics of the studied population

	NGT	IFG-IGT-T2D	Total
Age (years)	42.19 (11.55)	44.45 (12.55)	42.45 (11.65)
BMI (kg $^{-2}$)	25.70 (4.238)	30.77 (4.715)	26.28 (4.577)
FPG (mmol L^{-1})	5.084 (0.436)	6.025 (0.693)	5.192 (0.558)
C_b-Ins (pmol L^{-1})	37.76 (20.98)	78.86 (55.38)	42.48 (29.98)
C_b-Cpep (pmol L^{-1})	497.3 (169.4)	725.0 (250.2)	523.5 (193.8)
Number of subjects	154	20	174

fasting and samples were drawn at −30, −5 and 0 min before the IVGTT, and at 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min after glucose ingestion. Measurements were taken on serum insulin, plasma glucose and serum C-peptide. At $t = 0$, the glucose was injected intravenously. At $t = 20$ min, a bolus of 3 mg tolbutamide/(kg body-weight) was injected in 5 s.

OGTT

All subjects furthermore underwent a standardized and extended 75-g frequently sampled OGTT. After a 12-h overnight fast, venous blood samples were drawn in duplicate at −30, −10, 0 before the glucose intake and at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 140, 160, 180, 210, 240 after. As for the IVGTT, serum insulin, plasma glucose, and serum C-peptide were measured.

Generally the glucose tolerance study was modelled using the glucose measured in mmol/l, the insulin in pmol/l, and the C-peptide in pmol/l.

Mathematical and statistical methods

Structural models

The structural oral glucose models applied in this study are closely related to the oral minimal model (OMM) presented in [1]. The hypothesis is that the insulin secretion is controlled by a static and a dynamic glucose component. The static component consist of a delayed version of the glucose level above a given threshold whereas the dynamic component consist of direct change in the glucose level. The static and the dynamic components are presented in the model by sr_s and sr_d respectively. Applying the model on C-peptide measurements thus leads to the following equations

$$\begin{aligned} \frac{dC_1}{dt} &= sr_s + sr_d - k_1 C_1 + k_2 C_2 - k_3 C_1 \\ \frac{dC_2}{dt} &= k_1 C_1 - k_2 C_2 \end{aligned} \tag{1}$$

in which k_1, k_2, and k_3 are the standard C-peptide kinetic parameters as calculated by Cauter et al. [26]. C_1 and C_2 are the C-peptide concentration above baseline in the central and peripheral compartments. The dynamics of the static secretion component sr_s are described by

$$\frac{dsr_s}{dt} = -\tau^{-1}(sr_s - \Phi_s[G - G_{0'}]^+) \tag{2}$$

where $[G - G_{0'}]^+$ equals $G - G_{0'}$ if $G > G_{0'}$ and 0 otherwise. After a stepwise increase of glucose, sr_s approaches a steady-state value linearly related through the parameter Φ_s, with a rate constant equal to τ^{-1} which corresponds to a delay equal

to τ (min). The dynamic secretion sr_d corresponds to the secretion of promptly releasable insulin stored in the beta-cells, and is proportional to the rate of increase of glucose through a parameter Φ_d

$$sr_d = \begin{cases} \Phi_d \frac{dG}{dt} & \text{if} \quad \frac{dG}{dt} > 0 \\ 0 & \text{Otherwise} \end{cases} \tag{3}$$

For simplicity, parameters and units are summarised in Table 2.

Compared to the minimal model presented in [1] the presented model differs in the following ways

1. The glucose threshold is not estimated but instead fixed to $G_{0'}$
2. The glucose signal ($G - G_{0'}$) is forced to be non-negative
3. The baseline secretion (sr_b) is not estimated as a parameter. Instead baseline concentration is added in the measurement equation.

All these assumptions are applied in order to gain robust population estimation for all parameters in the model.

The corresponding model applied to the insulin data is

$$\frac{dsr_s}{dt} = -\tau^{-1}(sr_s - \Phi_s[G - G_{0'}]^+) \tag{4}$$

$$\frac{dC_2}{dt} = sr_s + sr_d - k_e C_2 \tag{5}$$

where $k_e = 0.161$ [24] is the elimination constant of insulin and corresponds to $t_{1/2} \approx 4.3$ (min). Insulin concentration above baseline is presented by the state of the central compartment (C_2). The other parameters are interpreted as in the model for C-peptide as explained above. Compared to the C-peptide model which was described using three differential equations (ODEs) the insulin model can be described using only two differential equations.

SDE extension

One argument for using the SDEs compared to ODEs is that correlation between the prediction errors at time s and t can be taken into account. In this paper we have applied an Ornstein-Uhlenbeck (OU) process which can improve model performance and to a certain extent remove the correlation and "push" the model in the

Table 2 Parameter units

Symbols	Unit
sr_s, sr_d, sr_b	(pmol l^{-1} min^{-1})
Φ_s	(10^{-9} min^{-1})
Φ_d	(10^{-9})
τ	(min)
C_1, C_2	(pmol l^{-1})
k_1, k_2, k_3	(min^{-1})

Units of applied parameters and variables

direction of less correlated prediction errors. This is obtained as the OU process itself has correlation between points at time s and t and—by obtaining optimal parameter estimates—the correlation in the process will counterbalance that of the original errors thus cancelling some of the correlation already present.

The OU-process is a so-called continuous version of the AR(1)-process, as previously introduced in PK/PD modelling by Karlsson et al. [9] (See [7] for mathematical details) and is described by an SDE which evolves according to

$$dU = -\gamma U dt + \sigma_{w_1} dw_1 \tag{6}$$

where γ is the drift coefficient, σ_{w1} the diffusion coefficient, and w_1 a standard Wiener process. In general the process has the following covariance structure

$$Cov[U_s, U_t] = Var(U_t) exp(-\gamma|s - t|) \tag{7}$$

which corresponds to an exponential decaying correlation with rate constant γ, decreasing with the distance between timepoint s and t. In general correlation between prediction errors for models based on ODEs can be interpreted as either a symptom of inadequate structural model or true fluctuations in parameters. This is one of the reasons why we find it important to use SDEs in PKPD models.

Model implementation

All models were implemented as non-linear mixed-effects models in NONMEM VI using *FOCE* with interaction. Fixed effects parameters τ, Φ_s, Φ_d, and estimates for inter-subject variabilities $\eta_\tau, \eta_{\Phi_s}, \eta_{\Phi_d}$ were estimated according to the formula $\theta_i = \theta \exp(\eta_i)$ where θ represent the fixed effect parameter. In the SDE models parameter values for correlation decay rate γ and magnitude of Wiener process σ_{w1} were estimated according to the method presented by Tornøe et al. [27], and were assumed equal across subjects. A general interpretation of parameters is presented in Table 3.

Data from the OGTT and the IVGTT was treated individually such that no false correlation was introduced for the first-phase and the indices in the OGTT models. Due to skewness, the dependent variables were log-transformed thus causing an error model of the form

$$log(OBS) = log(C_{pred} + C_b) + \epsilon \tag{8}$$

Table 3 Description of parameters; interpretation of parameters

Symbols	Description
Φ_s	Static secretion index
Φ_d	Dynamic secretion index
τ	Delay between glucose input and insulin/C-peptide feedback
$\eta_{\Phi_s}, \eta_{\Phi_d}, \eta_\tau$	Inter-subject variability of Φ_s, Φ_d and τ
γ	Correlation decay rate
σ_{w_1}	Magnitude of Wiener process

where C_{pred} is the individual predicted concentration of either C-peptide or insulin above baseline, C_b is the corresponding individual baseline level, and OBS, the individual observation.

In the extended SDE models the OU-process is added, thus causing the prediction

$$log(OBS) = log(C_{pred} + C_b) + U + \epsilon \tag{9}$$

where U is the OU-process as presented in Eq. 6. Estimation in these extended models was performed in NONMEM using the extended Kalman filter with equations for mean and covariance as described in [27].

Autocorrelation function

Graphical presentations of prediction errors and their corresponding autocorrelation function (ACF) are used in validation of model assumptions. In general the ACF describes the serial correlation present in a time series calculated for different time lags and is a useful tool to identify insufficient error structure of mathematical models (See also [7]). In this paper the ACF was calculated from the vector of the prediction errors obtained by appending the errors at different timepoints from each individual thus causing a vector with $16 \cdot 174 = 2{,}784$ elements. Estimating the ACF in this way can lead to slightly underestimated correlations as it does not take into account the changes present in the transition from one subject to the other where points from the different subjects usually not are correlated. In spite of this it still provides valuable information about where the model is consistently over and under estimating at the various time points.

Covariate effects for Φ_d

In order to estimate the effects of different covariates such as BMI, Age, FPG etc. on the first-phase index, the parameter Φ_d is presented in NONMEM by the equation

$$log(\Phi_d) = log(\theta_1) + \theta_2\left(\frac{X - \mu_X}{\sigma_X}\right) + \eta \tag{10}$$

which means that θ_2 can be interpreted as the slope between a normalised covariate X and $\log(\Phi_d)$. In the results part, this correlation is compared to the correlation between X and $\log(AIR_{0\text{–}8})$ which can be used to compare the two measures of the beta-cell function.

For clarity, the implementation of different models can be read from Table 4 indicating that each model built on C-peptide and insulin measurements were implemented in five different ways, including a basic model and the four different covariate inclusions. All models were further implemented with a more complex error structure by using the OU-process as described earlier in this section. In total results were thus obtained from 20 different models.

Table 4 Correlation estimates

Model	C-peptide (ODE)	(SDE)	Insulin (ODE)	(SDE)
No covariates	0.36	0.49	0.32	0.48
BMI	0.39	0.49	0.33	0.46
AGE	0.34	0.49	0.36	0.46
FPG	0.35	0.50	0.24	0.50
C_b	0.38	0.49	0.34	0.46
Mean	(0.36)	(0.49)	(0.32)	(0.47)

Correlation (r) between $log(\Phi_d)$ and $log(AIR_{0-8})$. Last row indicates mean for the given model presented in column header

Results

Model diagnostics

Individual model fits from the C-peptide and the insulin model using ODEs and SDEs are presented for a single subject in Fig. 1. Left plots present obtained predictions from the models based on ODEs using C-peptide and insulin respectively whereas plots to the right show fits obtained from the models including the OU error term. As seen the predictions obtained using SDEs more correctly reflect the dynamics of the system compared to those obtained using the ODEs. Note that the presence of cracks in the ODE predictions is caused by the linear interpolations of predictions.

In order to further diagnose the different models, evaluation has been based also on the ACF of one step prediction errors (PE) which equals the observation subtracted by the one step prediction obtained from the Kalman filter at the given time-point. ACF values are presented in Fig. 2 for the different models not including covariates. For models based on C-peptide and insulin, it is observed that the autocorrelation between residuals is significantly smaller for SDEs than for ODEs. Notice that for dynamic models small (or zero) values of the ACF indicate that the model provides a sufficient description of the data.

Correlation between Φ_d and AIR_{0-8}

This section evaluates the ability of the OGTT models to predict the first phase response obtained from the IVGTT. The evaluation was performed through an analysis of the correlation between $log(\Phi_d)$ derived from the implemented OGTT models and $log(AIR_{0-8})$ obtained from the IVGTT. The correlations are presented in Table 4. The value 0.36 in the first row thus indicates that the correlation between the individual parameters for $log(\Phi_d)$ obtained using the C-peptide model with no covariates included, correlates with the individual estimates of $log(AIR_{0-8})$ with a coefficient of 0.36. In all cases the correlation is increased going from the ODE to the SDE model. Furthermore the difference between correlations obtained from the models using ODEs and SDEs (Δr) and corresponding SD obtained from 1,000 bootstraps were 0.130(0.059), and 0.166(0.056) for the C-peptide and insulin

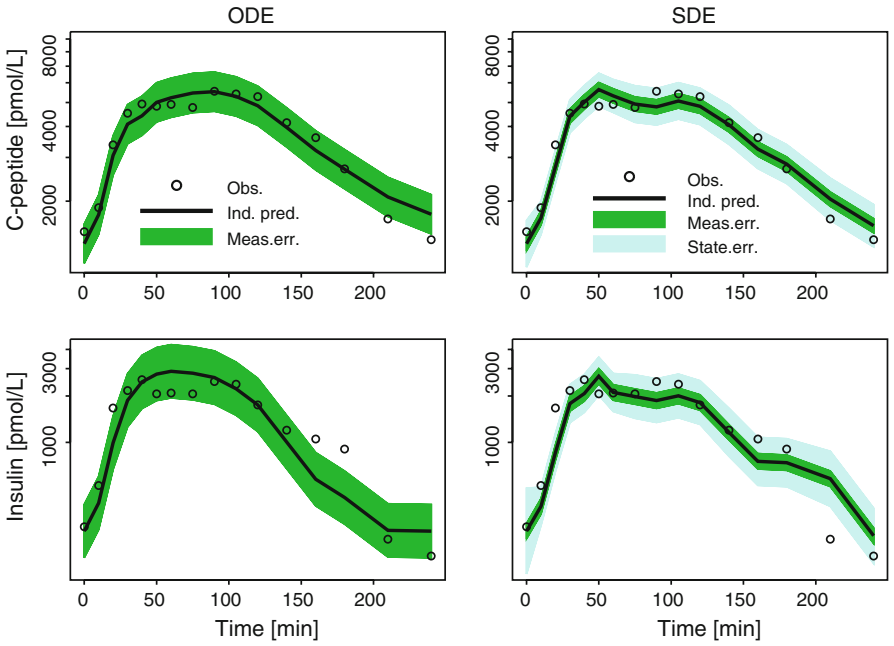

Fig. 1 Individual predictions for implemented OGTT models of C-peptide and insulin using ODEs and SDEs. *Dark* band identifies measurement error whereas *light* band identifies the state error obtained from the extended Kalman filter

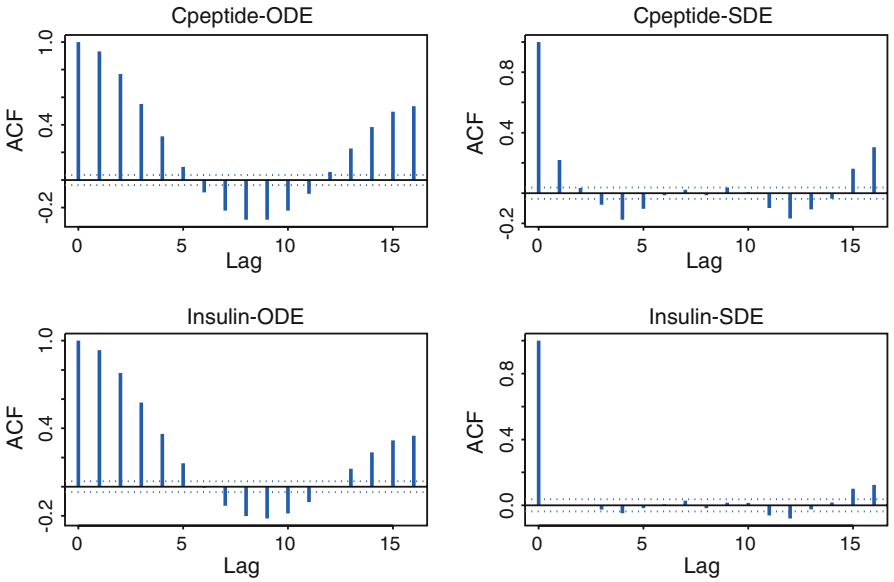

Fig. 2 Autocorrelation functions (ACFs) of one step prediction errors (PEs)

models without covariates and was concluded to be significant as $\Delta r > 2SD$. The bootstrap was performed by picking 174 random parameter estimates 1,000 times from each model. Afterwards the distributions of correlation coefficients obtained from each model were compared.

Covariate relationships for Φ_d and AIR_{0-8}

In addition to estimating the correlation between $log(\Phi_d)$ and $log(AIR_{0-8})$, the predictive performance of the models was also analysed through the ability of Φ_d to describe properties in the AIR_{0-8} as presented by relations to given covariates. This was measured through covariate relationships as presented in Table 5. Values in the second column were calculated as the slope between $log(AIR_{0-8})$ and the corresponding covariate indicated in the first column normalized according to Eq. 10. Last four columns present parameter values obtained for θ_2 (See also Eq. 10) indicating the relationship between $log(\Phi_d)$ and the given covariate. The value 0.273 in first row thus indicates that the slope between normalized BMI and $log(\Phi_d)$ in the basic C-peptide model equals 0.273. Equality between slopes obtained for the AIR_{0-8} and Φ_d indicates that the index obtained using the OGTT model has same relation as AIR_{0-8} to the given covariate. These slopes are thus applied as a measure for the similarity between model derived index and AIR_{0-8}. We believe this gives a clearer picture of the similarities between the two beta-cell function indexes compared to using only the correlation. In all cases the extended error structure based on the OU process caused the slopes for the covariates to better reflect the ones observed for the $log(AIR_{0-8})$. It shall be noted that we did not expect to get exactly equal values for $log(\Phi_d)$ and $log(AIR_{0-8})$ as the physiological interpretations of these parameters are different. Note also that a full covariate analysis on first phase indexes was determined to be out of the scope of this paper but is subject for future research.

Table 5 Covariate estimates

Index	$log(AIR_{0-8})$	$log(\Phi_d)$			
Data		C-peptide		Insulin	
Model		ODE	SDE	ODE	SDE
BMI	0.176(0.052)	0.273	0.106	0.490	0.196
AGE	−0.017(0.053)	0.030	−0.017	0.207	0.033
FPG	−0.199(0.052)	0.030	−0.105	0.177	−0.050
$I_{0'}$	0.159(0.052)	0.287	0.147	0.543	0.271

Relationship between beta-cell indices and selected covariates for C-peptide and insulin models built using ODEs and SDEs

(.) Indicate standard error (SE)

Discussion

In this paper we applied population PK/PD modelling with an error description which can take correlation of model errors between different time points into account. During early model development our approach was to use SDEs with additive system noise as done in [11]. We experienced that an inadequate description of insulin concentrations at high levels was obtained which we speculate was due to the non-state dependent inclusion of the system noise. As there is no standard solution to the problem of implementing SDEs with state-dependent system noise we instead chose to add an extra state with dynamics described by an SDE of the Ornstein-Uhlenbeck type. By adding this state to the measurement equation we obtained an error model following a continuous AR-process as presented in Karlsson et al. [9]. As shown, the solution help describe the correlation between prediction errors also at high insulin concentrations. The drawback using this approach compared to a setup with state-dependent noise entering the original system equations is that it can not be directly linked to a physiological description. However, it is a mathematical technique to better explain the correlation in the measurements compared to a standard ODE approach. The method was applied to a real data set obtained from an OGTT which enabled a study of model performance based on various measures other than those obtained from basic residual plots. These measures all relate to the predictive performance of the first-phase index Φ_d compared to AIR_{0-8}.

Today various experimental methods and modelling approaches have been developed to assess beta-cell function. Some of these include hyperglycaemic clamp [28], minimal model of C-peptide secretion during the IVGTT test [29], and homeostasis model assessment [30]. In this paper we have focused on Φ_d obtained from the oral minimal model and AIR obtained from the IV test as these measures are widely used in various applications both in research and in the pharmaceutical industry. Correlation between beta-cell function indexes calculated from IVGTT and OGTT have been performed recently in [22, 24]. In both articles a correlation around 0.67 is obtained.

In this paper we applied a fairly simple OGTT model and correlation was estimated to be around 0.4 using ODEs compared to 0.5 using SDEs. In general we believe that models using the whole time scale (as the ones presented here) seem most promising as they contain more information than the regression based models. We further believe that the models concerned here serve as a good basis, but should be extended also to include incretins as done in [24]. For a systematic improvement of the models the SDEs provide an attractive tool as shown in [10].

In the study we analysed the oral minimal model applied to either C-peptide or insulin measurements. The half-life of C-peptide is much larger than that of insulin causing a less marked first pass effect through liver. In the application of the insulin model the obtained secretion rates thus reflects post-hepatic secretion. In spite of this we found it interesting to apply a model based on insulin measurements as the higher elimination rate causes changes in secretion to produce more pronounced changes in plasma concentration compared to C-peptide.

Concerning the model development it was first attempted to implement the OMM exactly as presented in [1]. From experimental research it was observed that allowing the glucose signal to go below baseline in general caused unstable population models which caused NONMEM errors in the integration routine. Furthermore, setting the glucose threshold equal to the threshold minus the glucose baseline caused extremely low estimated values and was thus substituted by the glucose baseline. Finally, it was observed that adding the insulin baseline to the prediction instead of having baseline secretion as a parameter caused more stable models with approximately same prediction performance as for the basic OMM.

In conclusion, we showed that improved model performance can be obtained using a more complex error structure where time-correlated prediction errors are taken into account by the use of an SDE of the Ornstein-Uhlenbeck type as a part of the total state space model. Furthermore we have shown that estimation of covariate effects was highly dependent on how correlated the prediction errors are for the given model. In practice we thus recommend to check the serial correlation e.g. through an inspection of the ACF calculated for the prediction errors before concluding on the estimated covariate effects. As the SDE extension presented here not only provided less serially correlated errors, but also provided better estimation of clinical measures, the method is concluded to have high relevance not only in theory but also in practice.

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