

# Bayesian analysis for mixed-effects model defined by stochastic differential equations

Yan Fangrong<sup>1,2,4</sup> Zhang Ping<sup>2,4</sup> Lu Tao<sup>3,4</sup> Lin Jinguan<sup>1</sup>

<sup>1</sup>Department of Mathematics, Southeast University, Nanjing 210096, China)

<sup>2</sup>Department of Mathematics, China Pharmaceutical University, Nanjing 210009, China)

<sup>3</sup>Laboratory of Molecular Design and Drug Discovery, China Pharmaceutical University, Nanjing 210009, China)

<sup>4</sup>State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China)

**Abstract:** The nonlinear mixed-effects model with stochastic differential equations (SDEs) is used to model the population pharmacokinetic (PPK) data that are extended from ordinary differential equations (ODEs) by adding a stochastic term to the state equation. Compared with the ODEs, the SDEs can model correlated residuals which are ubiquitous in actual pharmacokinetic problems. The Bayesian estimation is provided for nonlinear mixed-effects models based on stochastic differential equations. Combining the Gibbs and the Metropolis-Hastings algorithms, the population and individual parameter values are given through the parameter posterior predictive distributions. The analysis and simulation results show that the performance of the Bayesian estimation for mixed-effects SDEs model and analysis of population pharmacokinetic data is reliable. The results suggest that the proposed method is feasible for population pharmacokinetic data.

**Key words:** population pharmacokinetics; mixed-effects models; stochastic differential equations; Bayesian analysis  
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Population pharmacokinetic (PPK) models play a pivotal role in quantitative pharmacology study. They combine the classic pharmacokinetic (PK) analysis with population statistical models, which make them able to investigate the determined factors of drug concentration in patients group quantitatively, to guide the adjustment of administration and to provide comprehensive quantitative information for a more rational and effective clinical administration regimen. In recent years, with the trend that model-based drug development (MBDD) is promoted and strongly advocated by the FDA, the population pharmacokinetic theory and practical research have been greatly

developed.

Nonlinear mixed-effects modeling (NONMEM) has been proved to be a kind of widely used and effective tool for describing the pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs<sup>[1-2]</sup>. The flexibility of modeling correlation structures, with the total variation separated into inter- and intra-individual variation contributes to the rapidly growing quantity of nonlinear mixed-effects models. This modeling approach usually leads to more accurate estimation of population parameters, especially in pharmacokinetic/pharmacodynamic (PK/PD) models including random effects. However, the traditional nonlinear mixed-effects models are most frequently based on ordinary differential equations (ODEs), assuming that the inter-individual variation is independent with the measurement errors, which means that the residuals are uncorrelated, ignoring the parts of the related dynamics that we cannot predict or explain. This assumption is well-functioning to the expected distribution of assay error, but when other sources of error appear in the distribution error, a good estimator cannot be obtained in the case of ignoring the correlation which is between the structural model parameters<sup>[3]</sup>. In fact, in the actual pharmacokinetic problems, correlations between residuals are ubiquitous, the result may not be obtained exactly under the basic statistical assumption in PK modeling<sup>[4]</sup>. The NONMEM<sup>[5]</sup> is the most commonly used software for PK/PD analysis using nonlinear mixed-effects models, and it is possible to deal with correlated residual errors using an AR model<sup>[4]</sup>. The simulation results show that the introduction of a correlated residuals model may lead to better estimates of the inter-individual variations and the structural parameters.

The other approach to modeling correlated residuals is stochastic differential equations (SDEs) in the model setup. SDEs are an extension of ODEs and facilitate the ability to split the intra-individual error into two fundamentally different types: One is a serially uncorrelated measurement error, which is mainly caused by operation mistakes; the other is system error, which may be caused by mis-specified models or true random behavior of the system. This model structure includes the statistical function of the AR model, but it is more flexible with respect

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**Biographies:** Yan Fangrong (1978—), male, doctor; Lin Jinguan (corresponding author), male, professor, jglin@seu.edu.cn.

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to specifying models for different residuals. Some PK/PD modeling books also show that the adoption of the nonlinear mixed-effects models based on SDEs rather than ODEs may be more appropriate to model intra-individual variations<sup>[6]</sup>.

However, estimating parameters in nonlinear mixed-effects models with SDE is a difficult problem and not straightforward, except for simple cases. A natural approach would be likelihood inference, but the transition densities are rarely known, and thus the explicit likelihood function is usually hard to write. Actually, there is hardly any theory for SDE models at present. Kristensen et al.<sup>[7]</sup> proposed the maximum likelihood method and maximized a posteriori to estimate the parameters in PK models with SDE; however, they only focused on single subject modeling where no inter-individual variance components were estimated. Overgaard et al.<sup>[8]</sup> suggested applying the Kalman filter to approximate the likelihood function for a SDE model with a nonlinear drift term and a constant diffusion term. Tornøe et al.<sup>[9]</sup> made this algorithm to be used in NONMEM for estimating SDEs, but the NONMEM implementation cannot be used to form Kalman smoothing estimates, which is an important feature of the SDE approach, where all data is used to give optimal estimates at each sampling point. Donnet et al.<sup>[10]</sup> proposed a Bayesian inference to analyze growth curves using mixed-effects models based on stochastic differential equations and obtained good results. Struthers et al.<sup>[11]</sup> applied the Bayesian method to the multicenter AIDS cohort study. Inspired by these, we introduce the Bayesian inference to pharmacokinetic models, estimate the parameters in the nonlinear mixed-effects models based on the stochastic differential equation and help to direct the clinical test.

The present work describes the implementation of SDEs in a nonlinear mixed-effects model with parameters estimation performed by the Bayesian analysis.

## 1 Models and Notation

### 1.1 Nonlinear mixed-effects model based on ordinary

Let  $y = (y_i)_{1 \leq i \leq n} = (y_{ij})_{1 \leq i \leq n, 1 \leq j \leq n_i}$ ,  $i = 1, 2, \dots, n$ ,  $j = 0, 1, \dots, n_i$  be the true observations. Here,  $y_{ij}$  is measurement for individual  $i$  at time  $t_{ij}$ ;  $n$  is the number of individuals and  $n_i$  is the number of measurements for individual  $i$ . Traditional nonlinear mixed-effects models usually model this process by the nonlinear mixed-effects model based on the ordinary differential equation. Formally, the classical nonlinear mixed-effects model is written as

$$\frac{\partial f(\varphi, t)}{\partial t} = F(f, \varphi, t) \quad (1)$$

$$y_{ij} = f(\varphi_i, t_{ij}) + \varepsilon_{ij} \quad \varepsilon_{ij} \stackrel{\text{i.i.d.}}{\sim} N(0, \sigma^2) \quad (2)$$

$$\varphi_i \sim N(\mu, \Omega) \quad (3)$$

where  $f$  is the possibly nonlinear function and  $\phi = (\varphi_i)_{1 \leq i \leq n}$  are the individual parameter vectors.  $\varphi_i$  are assumed to be independently and identically normally distributed with expectation  $\mu$  and variance  $\Omega$ .  $\varepsilon_{ij}$  are the measurement errors, and they are also assumed to be independently and identically normally distributed with null mean and variance  $\sigma^2$ .

### 1.2 Nonlinear mixed-effects model based on stochastic differential equation

Under the framework of ordinary differential equations, noise is only introduced through the measurement equation (see Eq. (2)). This allows the measurement noise term to absorb the whole error due to model miss-specification or true random fluctuations of the states that may ignore the correlated residuals. Considering the correlated residuals, a stochastic process is added to the state space model (see Eq. (1)). Such that the nonlinear mixed-effects model based on SDEs can be written as

$$\begin{aligned} dZ_t(\varphi_i) &= F(Z_t, \varphi_i, t) dt + \Gamma(Z_t, \varphi_i, \gamma^2) dW_t \\ Z(t=0) &= Z_0(\varphi) \end{aligned} \quad (4)$$

$$y_{ij} = Z_{t_{ij}}(\varphi_i) + \varepsilon_{ij} \quad \varepsilon_{ij} \stackrel{\text{i.i.d.}}{\sim} N(0, \sigma^2) \quad (5)$$

$$\varphi_i \sim N(\mu, \Omega) \quad (6)$$

where  $\Gamma(X_t, \varphi, \gamma^2) dW_t$  is called the diffusion term and describes the stochastic part of the system;  $W_t$  is the standard Wiener process defined by  $w_{t_2} - w_{t_1} \sim N(0, |t_2 - t_1| I)$ .  $F(X_t, \varphi, t) dt$  is called the drift term and describes the deterministic part. The stochastic dynamics of the system is defined by the drift and diffusion terms together.

In the nonlinear mixed-effects model based on SDEs (see Eqs. (4) to (6)), the total variance is distinguished into three fundamentally different noises: the inter-individual variability  $\Omega$  describing the individual difference, the system noise  $\gamma^2$  reflecting the random fluctuations around the corresponding dynamic model, and the measurement noise  $\sigma^2$  representing the uncorrelated residuals originating from measurement assay or sampling errors.

## 2 Bayesian Estimation

### 2.1 Prior specification

The Bayesian approach allows prior distributions to be incorporated with the likelihood function to evaluate the posterior distribution of the population parameters  $(\mu, \Omega, \sigma^2, \gamma^2)$  in the SDE model. Thus the first step is the choice of the prior distributions. Usual diffuse prior distributions can be chosen but the resulting posterior distributions may not be proper. Therefore, we propose to use standard prior distributions suggested by Cruz-Mesia and Marshall<sup>[12]</sup>:

$$\mu_k \sim N(m_k^{\text{prior}}, v_k^{\text{prior}}) \quad k = 1, 2, \dots, p$$

$$\Omega^{-1} \sim W(R, p + 1) \quad 1/\sigma^2 \sim \Gamma(\alpha_\sigma^{\text{prior}}, \beta_\sigma^{\text{prior}}) \quad (7)$$

where  $W$  and  $\Gamma$  are the Wishart distributions and Gamma distributions, respectively. We select a uniform prior on  $\gamma^2$ . In practice, the specification of hyper parameters  $m_k^{\text{prior}}, v_k^{\text{prior}}, R, \alpha_\sigma^{\text{prior}}, \beta_\sigma^{\text{prior}}$  may be very difficult. Therefore, we choose the non-informative priors for the hyper parameters.

## 2.2 Posterior computation

For the ODE model (see Eqs. (1) to (3)), the Gibbs sampling algorithms are proposed in Ref. [13]. These algorithms will not be detailed here. For the SDE model, (see Eqs. (4) to (6)), we propose to use the Gibbs algorithm, including the sampling of the auxiliary random variables  $\varphi_i$  and vector  $X_i$  of realizations of process  $X_i$  for each individual at each observation time. Let  $\mathbf{X} = (X_1, \dots, X_n) \in \mathbf{R}^{(n_1+1) + \dots + (n_n+1)}$  denote the vector of  $n$  realizations. Hence the Gibbs sampling algorithm for the SDE model is outlined as follows:

**Step 1** Initialize the iteration counter of the chain  $k = 1$  and start with initial values  $\sigma^{-2(0)}, \gamma^{2(0)}, \mu^{(0)}, \varphi^{(0)}, \mathbf{X}^{(0)}$ .

**Step 2** Obtain  $\sigma^{-2(k)}, \gamma^{2(k)}, \mu^{(k)}, \varphi^{(k)}, \mathbf{X}^{(k)}$  from  $\sigma^{-2(k-1)}, \gamma^{2(k-1)}, \mu^{(k-1)}, \varphi^{(k-1)}, \mathbf{X}^{(k-1)}$ .

**Step 3** Change  $k$  to  $k + 1$  and return to Step 2 until convergence is reached.

In the case when the SDE has an explicit solution, we describe an easily implemented Gibbs algorithm. When the conditional distribution of the parameter has no explicit form, we propose to approximate it using the Metropolis-Hastings random walks.

## 3 Model Used for Simulation

### 3.1 Classical one-compartment PK model

We shall simulate experiments using a one-compartment PK model, and the compound metabolism is modeled by the following single exponential attenuation modeling:

$$\frac{dZ_i}{dt} = -kaZ_i \quad (8)$$

In classical mixed-effects models, the process is modeled by a deterministic function, depending on individual random parameters. Formally, the classical nonlinear mixed-effects model is written as

$$\begin{aligned} \log y_{ij} &= \log Z_0 - ka_i t + \varepsilon_{ij} \quad \varepsilon_{ij} \stackrel{\text{i.i.d.}}{\sim} N(0, \sigma^2) \\ i &= 1, 2, \dots, n; j = 0, 1, \dots, n_i \\ ka_i &\sim N(ka, \sigma_{ka}^2) \quad i = 1, 2, \dots, n \end{aligned} \quad (9)$$

For simplicity, we model on the logarithm of the noisy observed measurements.

### 3.2 Stochastic one-compartment PK model

We propose to introduce a stochastic term in the ODE

model (see Eqs. (9)) and extend it to the SDE model with the volatility function  $\Gamma(Z_i, \varphi, \gamma^2) = \gamma Z_i$ .

$$dZ_{ii} = -ka_i Z_{ii} dt + \gamma Z_{ii} dW_i \quad (10)$$

Set  $X_{ij} = \log(Z_{ij})$ , and by Itô's formula, we obtain a Brownian motion with linear drift:

$$dX_{ii} = -\left(ka_i + \frac{1}{2}\gamma^2\right)dt + \gamma dW_i \quad (11)$$

with solution

$$X_{ii} = X_{i,0} - \left(ka_i + \frac{1}{2}\gamma^2\right)t + \gamma W_i \quad (12)$$

By discretizing the SDE, the realization  $X_{ij}$  of the SDE is Markovian:

$$\begin{aligned} X_{i,t_{ij}} | X_{i,t_{ij-1}} &\sim N\left(X_{i,t_{ij-1}} - \left(ka_i + \frac{1}{2}\gamma^2\right)(t_{ij} - t_{ij-1}), \gamma^2(t_{ij} - t_{ij-1})\right) \\ X_{i,0} &= \log Z_0 \end{aligned} \quad (13)$$

Therefore, the SDE model on the logarithm of data is defined as

$$\begin{aligned} (\log y_{i0}, \log y_{i1}, \dots, \log y_{in_i})^T &= (X_{i,0}, X_{i,1}, \dots, X_{i,n_i})^T + \varepsilon_i \\ \varepsilon_i &\stackrel{\text{i.i.d.}}{\sim} N(0, \sigma^2 I_{n_i+1}) \\ (X_{i,1}, \dots, X_{i,n_i})^T &= \\ &\left(X_{i,0} - \left(ka_i + \frac{1}{2}\gamma^2\right)t_{i1}, \dots, X_{i,0} - \left(ka_i + \frac{1}{2}\gamma^2\right)t_{in_i}\right)^T + \eta_i \\ \eta_i &\stackrel{\text{i.i.d.}}{\sim} N(0, \gamma^2 T_i), T_i = (\min(t_{ij}, t_{ij'}))_{1 \leq j, j' \leq n_i} \\ ka_i &\sim N(ka, \sigma_{ka}^2) \end{aligned} \quad (14)$$

### 3.3 Posterior computation and inference

We propose the condition posterior distribution for the nonlinear mixed-effects model based on the SDE in details. The prior distributions of the parameters to be estimated are defined as

$$\begin{aligned} ka &\sim N(m_{ka}^{\text{prior}}, v_{ka}^{\text{prior}}) \\ 1/\sigma_{ka}^2 &\sim \Gamma(\alpha_{\sigma_{ka}^{\text{prior}}}, \beta_{\sigma_{ka}^{\text{prior}}}) \\ 1/\sigma^2 &\sim \Gamma(c^{\text{prior}}, d^{\text{prior}}) \end{aligned}$$

Then the posterior distribution of the parameters is written as

$$\begin{aligned} X_i &\sim N(m_{X_i}^{\text{post}}, v_{X_i}^{\text{post}}), v_{X_i}^{\text{post}} = (\sigma^{-2} I_{n_i} + \gamma^{-2} T_i^{-1})^{-1} \\ m_{X_i}^{\text{post}} &= v_{X_i}^{\text{post}} [\sigma^{-2} (\log y_{i1}, \dots, \log y_{in_i})^T + \gamma^{-2} T_i^{-1} \mu_{X_i}] \end{aligned} \quad (15)$$

where

$$\begin{aligned} \mu_{X_i} &= X_{i,0} - \left(ka_i + \frac{1}{2}\gamma^2\right)(t_{i1}, \dots, t_{in_i})^T \\ ka_i &\sim N(m_{ka_i}^{\text{post}}, v_{ka_i}^{\text{post}}), v_{ka_i}^{\text{post}} = \\ &\left[(t_{i0}, \dots, t_{in_i}) G_i^{-1} (t_{i0}, \dots, t_{in_i})^T + \frac{1}{\sigma_{ka}^2}\right]^{-1} \end{aligned}$$

$$m_{ka_i}^{\text{post}} = v_{ka_i}^{\text{post}} \left( (t_{i0}, \dots, t_{in_i}) G_i^{-1} \mu_{ka_i} + \frac{ka}{\sigma_{ka}^2} \right)$$

where

$$G_i = \begin{bmatrix} \sigma^2 & 0 \\ 0 & \gamma^2 T_i \end{bmatrix}_{(n_i+1) \times (n_i+1)}$$

$$\mu_{ka_i} = - (X_{i0}, X_{i1}, \dots, X_{in_i})^T + X_{i0} - \frac{1}{2} \gamma^2 (t_{i0}, \dots, t_{in_i}) \quad (16)$$

$$ka \sim N(m_{ka}^{\text{post}}, v_{ka}^{\text{post}}), \quad v_{ka}^{\text{post}} = [n\sigma_{ka}^{-2} + (v_{ka}^{\text{prior}})^{-1}]^{-1}$$

$$m_{ka}^{\text{post}} = v_{ka}^{\text{post}} \left[ \sigma_{ka}^{-2} \sum_{i=1}^n ka_i + \frac{m_{ka}^{\text{prior}}}{v_{ka}^{\text{prior}}} \right] \quad (17)$$

$$1/\sigma_{ka}^2 \sim \Gamma(\alpha^{\text{post}}, \beta^{\text{post}}), \quad \alpha^{\text{post}} = \frac{n}{2} + \alpha^{\text{prior}}$$

$$\beta^{\text{post}} = \left[ \frac{\sum_{i=1}^n (ka_i - ka)^2}{2} + \frac{1}{\beta^{\text{prior}}} \right]^{-1} \quad (18)$$

$$1/\sigma^2 \sim \Gamma(c^{\text{post}}, d^{\text{post}}), \quad c^{\text{post}} = n \frac{n_i + 1}{2} + \alpha^{\text{prior}}$$

$$\beta^{\text{post}} = \left[ \frac{\sum_{i=1, j=0}^{n, n_i} (\log y_{ij} - X_{ij})^2}{2} + \frac{1}{d^{\text{prior}}} \right]^{-1} \quad (19)$$

The posterior distributions of  $\gamma^2$  have no explicit form, so we use the Metropolis-Hastings random walks. The Gibbs algorithm convergence is ensured by the classical convergence theorem proposed by Carlin and Louis<sup>[14]</sup>, the convergence of the Metropolis-Hastings algorithm is ensured by the theorem proposed by Mengersen and Tweedie<sup>[15]</sup>.

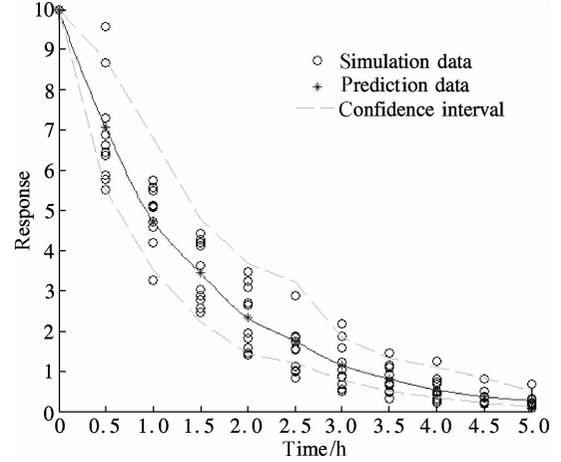
### 3.4 Simulations

To check the estimators when a simulation study is performed, we simulate datasets mimicking the one-compartment PK model with  $n = 10$  individuals and  $n_i = 10$  measurements. For all simulations, the sampling time period of the simulation interval is 5 and the observation points are obtained at equidistant time points depending on  $n_i$ . The initial values for population parameters are  $ka = 0.7$ ,  $\sigma_{ka}^2 = 0.01$ ,  $\sigma^2 = 0.04$ ,  $\gamma^2 = 0.04$ . 500 datasets are generated from the mixed-effects model with SDE (see Eqs. (14)). On the simulation datasets, parameters are estimated (see Eqs. (15) to (19)). We choose 10 000 iterations to make sure the convergence of the Gibbs algorithm. Estimators are obtained as the expectation of the parameter posterior distribution of the last 5 000 simulated trajectories of the SDE generated during the Gibbs algorithm. The true values and estimators are reported in Tab. 1, where the 95% credibility intervals are given in brackets. The results are presented in Fig. 1. Fig. 2 shows the basic goodness-of-fit graph for simulation data. The

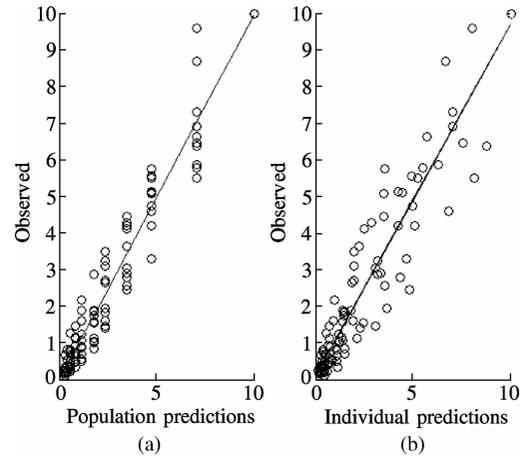
solid lines are the lines of identity. From the results, we can conclude that the parameters are well estimated.

**Tab. 1** Parameter estimation and 95% credibility interval

Parameter	True value	Estimator (95% credibility interval)
$ka$	0.7	0.713 2(0.687 5, 0.744 9)
$\sigma_{ka}^2$	0.01	0.011 7(0.007 8, 0.018 3)
$\sigma^2$	0.001 6	0.001 8(0.001 3, 0.002 0)
$\gamma^2$	0.04	0.042 9(0.036 3, 0.046 7)



**Fig. 1** The blood concentration vs. time in simulation case



**Fig. 2** Basic goodness-of-fit graph for simulation data. (a) Observed vs. population predicted values; (b) Observed vs. individual predicted value

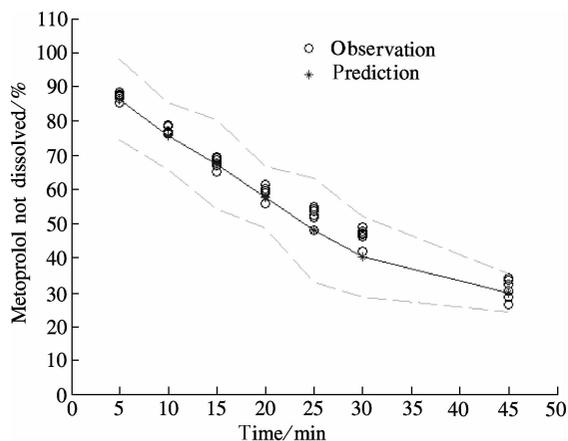
## 4 Application to Metoprolol Tartrate Dissolution Data

The method is used to model the Metoprolol Tartrate dissolution data taken from Polli et al<sup>[16]</sup>. Complete data is the percentage of released drug of four types of tablet formulations of 100-mg Metoprolol Tartrate, and each experiment is repeated six times. The data were also analyzed by Lánský et al. using the fractional differential rate equation model in 2003 and 2004<sup>[17–18]</sup>. They found that the slow dissolving test formulation was the closest to an exponential behavior, which is used here to illustrate the methods. We only use the data up to 45 min.

The percentage of Metoprolol that has not yet dissolved is modeled as Eq. (14), where  $y$  is the measurements for experiment  $i$  at time point  $j$ . Estimators and their standard deviation are reported in Tab. 2. The estimator of  $ka$  is in agreement with comparable values found in Ref. [18]. From Tab. 2, we see that there is clear difference in the performance of different methods. The SDE method performs better than the fractional differential rate equation. Fig. 3 shows the percentage of Metoprolol that has not yet dissolved data and the prediction data.

**Tab. 2** Parameters estimations for Metoprolol Tartrate dissolution data

Parameter	Estimator by stochastic differential equation(std)	Estimator by fractional differential rate equation(std)
$ka$	0.023 2(0.000 2)	0.024(0.039)
$\gamma^2$	0.074 (0.009)	0.08(0.005 4)
$\sigma_{ka}^2$	0.014 (0.01)	
$\sigma^2$	0.041 (0.025)	



**Fig. 3** Percentage of Metoprolol that has not dissolved data and the prediction data

From Fig. 3, we can conclude that the predicted trajectory is in good agreement with the actual data. The credibility interval includes most of the actual data, implying the feasibility of the Bayesian approach to nonlinear mixed-effects models based on the SDE, and the Bayesian inference has a good practical application value.

## 5 Conclusion

We propose a Bayesian approach to nonlinear mixed models defined by stochastic differential equations. These models are the extension to the classical nonlinear mixed-effects models whose error structures are too restrictive to model some unexplained processes. The introduction of the SDE model results in a clear validation of the model which is not the case in the standard model, by adding the new stochastic term. The proposed model is proved to be useful for the pharmacokinetic modeling. An interesting area for future research is the exploration of the model with covariate. Moreover, the extension of this work to multidimensional SDEs would also be an interesting work.

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## 混合效应随机微分方程的贝叶斯分析

言方荣<sup>1,2,4</sup> 张萍<sup>2,4</sup> 陆涛<sup>3,4</sup> 林金官<sup>1</sup>

(<sup>1</sup> 东南大学数学系, 南京 210096)

(<sup>2</sup> 中国药科大学数学系, 南京 210009)

(<sup>3</sup> 中国药科大学分子设计与药物发现实验室, 南京 210009)

(<sup>4</sup> 中国药科大学天然药物活性组分与药效国家重点实验室, 南京 210009)

**摘要:** 采用带有随机微分方程的非线性混合效应模型对群体药物代谢动力学数据建模, 通过在状态方程中引入随机项, 将常微分方程扩展到随机微分方程. 和常微分方程相比, 随机微分方程可解决群体药物代谢动力学模型中相关残差问题. 利用贝叶斯估计对非线性混合效应随机微分方程模型参数进行估计, 给出群体参数及个体参数的精确后验分布, 将 Gibbs 和 Metropolis-Hastings 算法相结合, 给出参数估计值. 通过计算机模拟和实例分析验证了方法的可靠性, 结果表明利用非线性混合效应随机微分方程模型及贝叶斯估计方法分析群体药物代谢动力学数据是可行的.

**关键词:** 群体药物代谢动力学; 混合效应模型; 随机微分方程; 贝叶斯分析

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