Random Effects In Stochastic Differential Equation Models

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Abstract

A class of statistical models is proposed where random effects are incorporated into a stochastic differential equations model and an expression for the likelihood function is derived. In general, though, it is not possible to find an explicit expression for the likelihood function, but in a very simple example it is derived and explicit maximum likelihood estimators are found.

Key words : Maximum likelihood, pharmacokinetics, population estimates, random effects, repeated measurements, stochastic processes.

Mathematics Subject Classification : **39A50.**

1. Introduction

In recent years, Mathematical models have gained importance in describing, analyzing, Optimizing and controlling all kinds of systems. In biomedical research, studies in which repeated measurements are taken on a series of individuals or experimental animals play an important role. Models including random effects to model this kind of data enjoy an increasing popularity. In these models it is assumed that all responses follow a similar functional form, but with parameters that vary among individuals.The increasing popularity of random effects models lies in the flexible modeling of correlation structures where the total variation is specially split in withingroup and between-group variation. This will often lead to more precise estimation of population parameters. Especially in pharmacokinetic/pharmacodynamic (PK/PD) modeling most studies include random effects in the models, thereby improving population parameter estimation.

Continuous biological processes are often described by systems of ordinary differential equations (ODE), which unfortunately cannot account for noisy components often present in biological systems, representing the parts of the dynamics that we cannot predict or understand, or that we choose not to include in the explicit modeling. A natural extension is given by systems of stochastic differential equations (SDE), where system noise is modeled by including a diffusion term of some suitable form in the driving

equations. In PK/PD modeling the focus is most often on the infinitesimal changes of substances, which naturally leads to a ODE system. The inter-individual variability is modeled with the random effect, and the intra-individual variability with an additive noise term (possibly after some convenient transformation). Noise in the differential equations describing the behavior of the system requires an extension of the model class to SDE models.

The theory for mixed-effects models is well developed for deterministic models (without system error), both linear and non-linear [2,3,14,25], and standard software for model fitting is available, see e.g. [18] and references therein. Early and important references in the pharmacokinetic field are [21,22].Estimating parameters in SDE models is not straightforward, except for simple cases.

A natural approach would be likelihood inference, but the transition den- sities are rarely known, and thus it is usually not possible to write the likelihood function explicitly. A variety of methods for statistical inference in discretely observed diffusion processes has been developed during the past decades, see e.g. [1,4,5,6,7,9,10, 13,16,17,19,20,23,24]. However, to our knowledge there is practically no theory at present for SDE models with random effects. In [15] it is suggested to apply the Kalman filter to approximate the likelihood function for SDE model with random effects, with a non-linear drift term and a constant diffusion term. As SDE models will be more commonly applied to biomedical data, there will be an increasing need for developing a theory including mixed effects, and for results on the estimation of model parameters. In [8] methods for PK/PD population modeling are reviewed, but the authors regret that system noise is not considered since it is difficult to estimate, and that there exits no software at present in the pharmacokinetic field.

In this paper a class of statistical models is proposed where random effects are incorporated into a diffusion model, and an expression for the likelihood function is derived. In general, though, it is not possible to find an explicit expression for the likelihood function, but in a very simple example it is derived and explicit maximum likelihood estimators are found.

2. The Model

Consider the one-dimensional SDE model for some continuous process evolving in M different subjects randomly chosen from a population :

$$dX^i_t = g(X^i_t,\theta,b^i)\,dt + \sigma(X^i_t,\theta,b^i)dW^i_t; \quad i = 1,...,M$$

$$b^i \sim N(0,\Sigma)$$

$$X^i_0 = x^i_0 \qquad (2.1)$$

Where θ is a p-dimensional fixed effects parameter (the same for the entire population) and b^i is a q-dimensional random effects parameter (subject specifc), which is assumed to follow a normal distribution in the population, with covariance matrix Σ that is assumed known up to the parameter vectorψ. The W_t^i are standard Brownian motions. The W_t^i and b^{ij} are assumed mutually independent for all $1 \leq i, j \leq M$, and independent of X_o^i.

The drift and the diffusion coefficient functions g (.) and σ (.) are assumed known up to the parameters, and are assumed sufficiently regular to ensure a unique solution. Let $E \subseteq R$ denote the state space of X_t^i. Assume that the distribution of X_t^i given b^i and $X_s^i = x$, $t > s$, has a strictly positive density w.r.t. the Lebesgue measure on E, which we denote by

$$y \rightarrow p(y,x,t-s\backslash b^i, \theta) > 0 \quad y \in E. \tag{2.2}$$

Assume the M subjects each are observed at the $(n_i + 1)$ discrete time points $(t_o^i, t_1^i, ..t_n)$. Let y^i be the $(n_i + 1)$ -dimensional response vector for the i'th subject :
$y^i = (y_o^i ..... y_{ni}^i)$, $y(t_j^i) = y_{tj}^i = y_j^i$ and let y be the N-dimensional total response vector,

$N = \sum_{I=1}^{M} (n_i+1)$. Write $t^i_j - t^i_{j-1} = \Delta^i_j$ for the distance between observation j - 1 and j for subject i.

Parameters of the model are θ andψ which we wish to estimate.

3. Maximum Likelihood Estimation in SDE Mixed Effects Models

To obtain the marginal density, we integrate the conditional density of the data given the non-observable random effects b^i with respect to the marginal density of the random effects, using the fact that W_t^i and b^i are independent. This yields the likelihood function

$$L(\theta, \psi \mid y) = \prod_{i=1}^{M} P(y^i \mid \theta, \psi) = \prod_{i=1}^{M} \int (y^i \mid b^i, \theta)\, p(b^i \mid \psi)\, db^i \tag{3.1}$$

where L(.) is the likelihood and p(.) are densities. Now

$$p(y^i \mid b^i, \theta) = \prod_{j=1}^{n_i} p(y^i_j, y^i_{j-1}, \Delta^i_j \mid b^i, \theta) \tag{3.2}$$

since X^i_t given b^i is Markov, where the transition densities are as in equn.(2.2), and, by hypothesis,

$$p(b^i \mid \psi) = \frac{\exp\{-(b^i)^T \psi^{-1} b^i / 2\}}{\sqrt{|\psi| (2\pi)^q}} \tag{3.3}$$

where ^{T} denotes transposition. Substituting (3.2) and (3.3) into (3.1) we obtain

$$L(\theta, \psi \mid y) = \prod_{i=1}^{M} \int \prod_{j=1}^{n_i} p(y^i_j, y^i_{j-1}, \Delta^i_j \mid b^i, \theta) \frac{\exp\{-(b^i)^T \psi^{-1} b^i / 2\}}{\sqrt{|\psi| (2\pi)^q}} db^i \tag{3.4}$$

Solving the integral yields the marginal likelihood of the parameters, independent of the random effects b^i. In general it will not be possible to find an explicit solution, but in simple cases we can find an explicit expression for the likelihood, and even find explicit estimating equations for the maximum likelihood estimators.

3.1. A random effect in Brownian motion with drift

In the simplest pharmacokinetic situation, the metabolism of a compound is modeled as a mono-exponential decay in the following way (first-order kinetics) :

$$\frac{dC(t)}{dt} = -kC(t) \; ; \; C(0) = D/V \tag{3.5}$$

with solution $C(t) = C(0)\, e^{-kt}$

where C(t) is the concentration of the compound in plasma at time t after a bolus injection, k is the (positive) rate elimination constant, D is the injected dose at time t = 0, and V the apparent volume of distribution of the compound. Now assume that we want to model the erratic behavior of the metabolic processes responsible for the removal of the compound from plasma, by allowing k to vary randomly as k+»(t), where »(t) is a white noise process. Then $\xi(t)\, dt = \sigma\, dW(t)$ where W(t) is Brownian motion and σ a scaling parameter. Incorporating this into (3.5), writing $X_t = C(t)$ and $\beta = -k$, we obtain the equation

$$dX_t = \beta X_t dt + \sigma X_t\, dW_t$$

which is the equation of geometric Brownian motion. The state space E is given by the positive real line. By applying Ito's formula to the transformation: $Y_t = \log X_t$, we obtain a Brownian motion with linear drift :

$$dY_t = (\beta - \frac{1\sigma^2}{2})\, dt + \sigma\, dW_t$$

With Solution

$$Yt = Y_o + (\beta - \frac{1\sigma^2}{2})t + \sigma\, dW_t$$

Assume an experiment is conducted on different subjects where the concentration of a compound in plasma is measured at different time points after a bolus injection. We are interested in estimating the parameters in the population, but expect individual differences in the metabolic processes, and would therefore consider a random effect in β, which leads to the model :

$$Y^i_t = Y^i_0 + (\beta + \beta^i - \frac{1}{2}\sigma^2)t + \sigma W^i_t \qquad (3.6)$$

$$\beta^i \sim N(0, \sigma^2_\beta)$$

4. Conclusion

In the present paper we propose to extend random effects techniques to the estimation of parameters in SDE models. We believe this extension to be both relevant and needed. It is relevant because as the sophistication of builders and users of mathematical models of biological processes increases, there will be a progressive growth of the use of stochastic differential equations to represent noisy processes. When only few observations can be collected from any given human or animal experimental subject, as is usually the case, recourse to random or mixed effects models will be necessary.

Statistical inference for this class of models is not straightforward. In the present work, a very simple model gave rise to explicit expressions for the likelihood function and for the maximum likelihood estimators. This model is in its deterministic version frequently employed in pharmacokinetics (e.g. to represent drug elimination from plasma or initial tumor cell population growth).

Unfortunately, in general it will not be possible to find an explicit expression for the likelihood function given by equn (3.4) since the transition densities are rarely known. One possibility could be to approximate the likelihood function numerically, and then optimize the approximated likelihood function directly.

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