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ESTIMATION OF THE GEOMETRIC BROWNIAN MOTION WITH RANDOM EFFECT USING SOLUTION OF FOKKER-PLANCK EQUATION AND STOCHASTIC DIFFERENTIAL MIXED EFFECTS MODEL THEORY

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ABSTRACT:

Abstract— in this paper, we are interested in the application of the theory of stochastic and mixed effects models on the Geometric Brownian Motion (GBM) with random effect, due to its importance in real studies. Actually, in many modelling studies, it is preferred to consider stochastic processes instead of deterministic, because the majority of real processes are always exposed to influences that are not completely understood or that it is impossible to model explicitly, and ignoring these phenomena in the modelling may affect the estimation result. Moreover, in order to take account of the all population comportment simultaneously, we incorporate two types of parameters in the model: fixed effects to capture general and common behavior for the whole population, and random effects varying between individuals to account for individual deviation. However, the obtained mixed-effects model with stochastic differential equations (SDEs), known by the Stochastic Differential Mixed Effects (SDME) model, is an extremely poorly estimated estimation problem. In fact, in general, the transition density of the stochastic process is usually unknown and therefore the likelihood function cannot be obtained in a closed form. Thus, many numerical approximation methods may be necessary to estimate model parameters. So, here, we consider a framework estimate for the Geometric Brownian Motion incorporating random effect under the Ito formula, by deriving its transition density from the solution of the Fokker-Planck equation.

Keywords: Index Terms— Stochastic process, stochastic differential equations, random effects, transition density, Brownian Motion, Fokker-Planck, likelihood function.

1. INTRODUCTION

In many pharmacokinetic/pharmacodynamic (PK/PD) applications and in biomedical researches, the experiment requires data on an entire population and not only on a single individual to obtain complete information on the phenomenon, as well as several repeated measurements of a quantitative variable for each unit, in order to model correctly the progression and the development of a disease or an economic or a financial aggregate. Thus, for each individual, many repeated measurements are taken at different points of time, it allows, therefore, to model the global behavior of a phenomenon for a group of units and also its dynamic side. Thus, this kind of modelling leads to describe the common side of the phenomenon in a whole population and the specificity of each individual, which leads to an increasing popularity and an extreme need for stochastic models with mixed effects. It is often reasonable to consider that responses follow the same model structure for all experimental units, while model parameters vary randomly among individuals, and both variations within and between groups are modeled, leading to a more precise estimation of population parameters. So, mixed-effects models have become an increasingly popular choice for modeling real processes, due to its inherent incorporation of uncertainty, allowing simultaneous representations of randomness in
dynamics of real processes and variability between experimental units.
See a rich and developed resources for mixed-effects models in [3], [4], [5], [6] and [7], also, see many applications in biomedical field in [8], [9] and [10] and in pharmacokinetic field in [11], [12], and [13]. So, all these points of advantage constituted a motivation to develop this article where we are interested in the estimation of the GBM containing a random effect.
A SDME model is established from the SDEs with the incorporation of random effects and stochastic components driven by the Wiener process, which is an extension of an ordinary differential equation model. For a deterministic differential equation model, the solution is a deterministic function, while the solution of a SDE is a continuous time Markov process. The behavior of a diffusion process is governed by its transition density, that is in turn governed by the values of the parameters in the SDME model. In the theory, the stochastic differential equations (SDE)s have proved to be more useful than deterministic differential equations (ODE)s to describe the dynamic side of real processes in, e.g., the PK/PD phenomenon, finance studies [14], and other processes in different fields, See: [15], [16], [17], [18]. In [19], some examples of the application of the SDEs in the biomedical field are treated by the author, as well as other examples in pharmacokinetic field are discussed in [20]. However, statistical inference for SDME models is not straightforward, it provides a powerful modeling tool with immediate applications, since a closed form solution to many SDME models used in practice is not known, except for a few cases. Moreover, to obtain an explicit expression of the maximum likelihood estimators, we need to solve the integral in the marginal likelihood function of the parameters given the random effects. However, in general, it is not possible to solve analytically and explicitly this integral, and the more the dimension of random effects vector increases, the more the difficulties increase. So, a closed-form expression of the likelihood function is rarely available. Hence, exact maximum likelihood estimation is generally unrealizable. In this paper, we deal with a generic and feasible estimation approach based on maximum likelihood estimation, which can be implemented in the absence of a closed expression of the transition density. In the literature, we propose a review on estimation methods of SDME models in [21], [22] and [23]. Moreover, to strengthen knowledge on estimation methods of SDME models, we refer to [24] and [25] that propose an example of stochastic mixed effects model with random effects log-normally distributed with a constant diffusion term. Also, several solutions have been proposed to approximate the transition density and have shown their effectiveness despite certain limitations. For example, the transition density could be approximated by the solution of the partial differential equations of Kolmogorov [26]; or by the derivation of an Hermite expansion of closed form at the transition density [27], [28], [29], this method has been reviewed and applied for many known stochastic processes for

one-dimensional [9] and multi-dimensional [30] timehomogeneous SDME model; or by simulating the process to Monte-Carlo integrate the transition density, see [31], [32], [33]. These techniques are very useful and can solve the problem, but unfortunately, they involve intense calculations which make the problem always complicated.
In this work, we focus on two fundamental issues concerning the implementation of SDME models. The first is to incorporate mixed effects in the GBM model, and the second is about the estimation of the model parameters by deriving simulation issues. Then, many artificial data were generated using moderate and different values of M (the number of subjects) and n (the number of observations for each experimental unit data), and the obtained estimates are often close to the true values of the parameters. This is relevant to the proposed estimation methodology and its application in situations where large data are not available, e.g. in biomedical applications, where mixed effects theory is widely applied.

I. THEORETICAL TOOLS

A. Stochastic Differential Mixed-Effects Models

For a N-multidimensional continuous stochastic process
, evolving in M different exper-imental units, the SDME model in the sense of Ito is defined as follows [34]:

$$dY^i(t) = \mu(Y^i(t), t, \theta, b^i)dt + \sum(Y^i(t), \theta, b^i)dW^i(t) \quad (1)$$

$Y_0^i = y_0^i, \quad i = 1,...,M$

where $\theta \in \Theta \subset \mathrm{R}^p$ is the common p-dimensional parameters vector to all individuals and $b^i \in B \subseteq \mathrm{R}^q$ is the qdimensional random effects vector of individual i distributed with a density P_B depending on a population parameter Ψ specifying the marginal distributions of the components of b_i, each component $b_i^l, l = 1, ..., q$ may follows different distribution with a joint density function P_B, the standard choice is a Gaussian distribution, but it could be any other continuous or discrete distribution such as Gamma distributions to ensure the positivity of the parameters:

$$b^i \sim i.iP_B(.|\Psi) \quad (2)$$

and $(W^i(t))_{0\leq i\leq M}$ are M independent Wiener process trajectories assumed mutually independent with b^j for all $i \neq j$, the different realizations of the two vectors give different paths for each subject and describe the intra- and intervariability between different units of the population. Therefore, to ensure the existence of solution Y_t^i to (1), the functions $\mu(\cdot) : E \times \mathrm{R} \times \Theta \times B \longrightarrow \mathrm{R}$ and $\Sigma(\cdot) : E \times \Theta \times B \longrightarrow \mathrm{R}^+$, representing the drift and diffusion term respectively, are supposed to verify sufficient properties, see: [35], [36], [37], with $E \subseteq \mathrm{R}^N$ is the space state of the process Y_t^i. Therefore, we assume that the solution Y_t^i of (1) have a strict positive density with respect to the Lebesgue measure on E given (b_i, θ) and $Y^i(s) = y_s^0$, $s < t$, however, this assumption does not imply the existence of an explicit transition density:

$$y \rightarrow P_Y(y, t-s|y_s, b^i, \theta) > 0, \quad y \in E \quad (3)$$

Also, the equation (1) can be understood under the following integral form:

$$Y^i(t) = Y_i(t_0) + \int_{t_0}^{t} \mu(Y^i(s), s, \theta, b^i)ds + \int_{t_0}^{t} \sum(Y^i(s), \theta, b^i)dW^i(s)$$

B. Maximum Likelihood Estimation in SDME Models

Each subject is observed in several points of time $\{t_0^i, t_1^i, ..., t_{n_i}^i, i = 1, ..., M\}$, and the vector $y^i = (y_1^i, y_2^i, ..., y_{n_i}^i)$ is the repeated measurements vector for the responses of each subject i. The process Y could be observed directly or indirectly with measurement noise, which may be due to a test error or to the existence of a disturbance element. Here, we assume that $(Y_t)_{t\leq 0}$ is observed directly at discrete times $t_1,...,t_{ni}$, in this case, the likelihood function is defined as follows:

$$L(\theta,\Psi)=\prod_{i=1}^{M}P(\underline{y}^i|\theta,\Psi)=\prod_{i=1}^{M}\int_B P_{\underline{Y}}(\underline{y}^i|b^i,\theta)P_B(b^i|\Psi)db^i \quad (4)$$

where $P(\underline{Y}^i|.)$ denote the density of y^i given (θ,Ψ), and

$P_{\underline{Y}}(y^i|.)$ is defined by the Markov property as the product of the transition densities for a given realization of the random effects and for a given θ:

$$P_{\underline{Y}}(\underline{y}^i|b^i,\theta)=\prod_{j=1}^{n_i}P_{yY}(y_j^i,\Delta_j^i|y_j^i,b^i,\theta) \quad (5)$$

where $\Delta_j^i=t_j^i-t_{j-1}^i$ and $y_j=y_{tj}$ and the densities $P_Y(.)$ are as in (3). As mentioned above, the density $P_B(.|\Psi)$ is often assumed to be multinormal but it could be any other density function. When the transition density is known explicitly, the likelihood (4) have a closed form and exact maximum likelihood estimators (MLEs) can be obtained, but this is possible in a few cases, otherwise, the transition density should be approximated. But, notice that even when the transition density is known, the explicit estimation equations for the MLEs may be difficult to compute, because the integral of (4) often has no solution or is difficult to solve and the degree of difficulty increases as the dimension of B is greater. In the theory, several methods were proposed to approximate the transition density: by solving the Kolmogrov partial differential equations satisfied by the transition density [38]; or by using the approximate transition density based on Hermite expansion suggested by [39] and [40], see practical examples in [18] and [30]; or by using the Bayesian inference either for model with or without measurements errors; or by using an extension of the Kalman Filter; or by simulating the process to Monte-Carlo-integrate the transition density, see: [41], [42], [43], [44] and [45].

The MLEs obtained by maximizing (4) have usually good properties, and we assume that they are the unique maximum of the likelihood function in (4). Thus, after estimating the fixed effects, we generate the random effects using the standard method of the mixed effects theory by plugging the estimates of θ in the following individual likelihood function:

b*i* = *argminbi*(−**Σ***logqY* (*yji*,Δ*ij*|*yji*−1*,bi,θ*b))

C. Closed-form transition density and likelihood approximation

Let $q_{\underline{Y}}(\underline{y}^i|b^i,\theta)=\prod_{j=1}^{N}q_Y(y_j^i,\Delta_j^i|y_{j-1}^i,b^i,\theta)$ be the approximate transition density of (5) when the exact formula is not known, so the approximate likelihood function of (1) is defined as:

$$L^{(q)}(\theta,\Psi)=\prod_{i=1}^{M}\int_B q_{\underline{Y}}\left(\underline{y}^i|b^i,\theta\right)P_B(b^i|\Psi)db^i \quad (6)$$

In the literature, the likelihood function of a nonlinear SDME model could be approximated with the likelihood of a linear mixed-effects model [46] or by using Laplacian and Gaussian quadrature approximation, see: [47], [48] and [49]. Therefore, by maximizing (6) with respect to (θ,Ψ) we obtain the approximate estimators $(\hat{\theta},\hat{\Psi})$. Moreover, as mentioned before, the integral has often no closed form solution and efficient numerical integration methods are required. See [50] and [51], for proposed and available approximation methods for multidimensional integrals for any random effects distribution, and see [18] and [30] where the integral in (6) was approximated using the Gauss-Hermite quadrature and Laplace approximation respectively. Thus, after approximating the transition density, the integration over the random parameters b^i is obtained using the proposed methods, and finally, the approximate likelihood is obtained in its approximate closed form to optimize analytically or by using optimization tools.

Here, we choose to approximate the transition density using the Risken approximation [1] based on the Fokker-Planck (FP) equation characteristics or the forward Kolmogrov equation. We notice that, a benchmark study was elaborate in order to evaluate the effectiveness of this approach using OU process, which is one of few processes with exact transition density, and that shows that this approximate transition lead to satisfactory results [2]. Let now describe the proposed methodology for approximating the transition density, which is based on the Kramers-Moyal expansion that represents a motion equation verified by the probability density. Under some assumptions, see [1], the probability density $\phi(y,t)$ of a N-dimensional SDME model obeys the Kramers-Moyal expansion:

For special initial condition, the transition density of the process in (1) is the solution of the following Fokker Planck equation:

$$\frac{\partial P_y(y_j,\Delta_j|y_{j-1},b,\theta)}{\partial t_i} = L_{FP} P_Y(y_j,\Delta_j|y_{j-1},b,\theta) \quad (7)$$

with:

$$L_{FP} = -\frac{\partial}{\partial y_i^{(l)}}\mu_{(l)}(y_j,t_j,\theta,b) + \frac{\partial^2}{\partial y_i^{(l)} Y_i^{(k)}}\sum\nolimits_{lk}(y_j,t_j,\theta,b) \quad (8)$$

The equation (7) represents the motion equation of the process Y verified by its transition probability $P_Y(y_j,\Delta_j|y_{j-1},b,\theta)$, and the resolution of this equation leads to obtain an explicit form for this density. For a small Δ_j, we have:

$$P_Y(y_j,\Delta_j|y_{j-1},b,\theta) = [1 + L_{FP}(y_j,t_j)\Delta_j + \circ(\Delta_j^2)]\delta(y_j - y_{j-1})$$

(9)

where δ is Fourier integral terms: $\delta(y_j - y_{j-1}) = \int_{-\infty}^{+\infty} e^{iu(y_j - y_{j-1})}du$.

Then, after a classical computation we get the following:

$$P_Y(y_j,\Delta_j|y_{j-1},b,\theta) = \left(2\sqrt{\prod \Delta_j}\right)^{-N}[Det\Sigma]^{-\frac{1}{2}}\exp\left(-\frac{1}{4\Delta_j}[\Sigma^{-1}]_{lk}[y_{jl}^i - y_{j-1\,l}^i - \mu_l(y_{j-1}^i,t,\theta,b^i)\Delta_j^i][y_{j\,k}^i - y_{j-1\,k}^i - \mu_k(y_{j-1}^i,t_{j-1},\theta,b^i)\Delta_j^i]\right)$$

]) (10)

We notice that the proposed approximate transition density can be applied to multidimensional SDME models having constant or non-constant and linear and non-linear diffusion term, with random effects following any continuous distribution.

II. GEOMETRIC BROWNIAN MOTION WITH RANDOM EFFECT

A. Definition

The Geometric Brownian process has relevant applications for modeling in pharmacokinetics as well as for modeling the growth of a population of bacterial or tumor cells, and is also used in mathematical finance to model stock prices. Here we include a random effect in the model in order to improve the real side of these processes, as already mentioned, which allows us to consider both system noise and individual differences. A SDME model of the Geometric Brownian motion is defined as follows:

$$dY_t^i = (\beta + \beta^i)Y_t^i dt + \sigma Y_t^i dW_t^i, \quad Y_0^i = y_0^i, \quad i = 1,\dots,M$$

(11)

where Ito solution is given as follows:

$$Y_t^i = Y_0^i exp((\beta + \beta^i - \frac{\sigma^2}{2})t + \sigma W_t^i), \quad i = 1,\dots,M \quad (12)$$

with $\beta^i \sim N(0,\sigma_\beta^2)$, for this example we have: $b^i = \beta^i$, $\theta = (\beta,\sigma^2)$ and $\psi = \sigma_\beta^2$. We which to estimate $(\beta,\sigma^2,\sigma_\beta^2)$ given a set $\underline{y} = (\underline{y}^1,\underline{y}^2,...,\underline{y}^M)$ of observations.

B. Maximum Likelihood

Assume equidistant observations and that each subject has the same number of observations, that is, assume $\Delta_j^i = \Delta$
and $n^i = n$ for all $1 \le i \le M, 1 \le j \le n_i$. The likelihood function of (11) using (6) and (10) is reported in the Appendix.

The integral in (14) is solved analytically using the gauss integral, and then, we obtain an exact estimator of the parameter β while we need a numerical optimization tool to obtain estimates of σ and σ_β, see the following section:

$$\hat{\beta} = \frac{\sum_{i=1}^{M}\left(\frac{-1}{2}\sum_{j=1}^{n}(Y_j^i - Y_{j-1}^i) + \frac{\sum_{j=1}^{n} Y_j^i (Y_j^i - Y_{j-1}^i)}{\frac{2\Delta^2}{\sigma}\sum_{j=1}^{n} Y_j^i + \frac{8\Delta^2}{\sigma_\beta^2}}\right)}{\sum_{i=1}^{M}\left(\frac{-\Delta}{2}\sum_{j=1}^{n} Y_j^i - \frac{\sum_{j=1}^{n} {Y_j^i}^2}{\frac{2\Delta}{\sigma}\sum_{j=1}^{n} Y_j^i + \frac{8}{\sigma_\beta^2}}\right)} \quad (13)$$

III. IMPLEMENTATION ISSUES

This section reports the results of applying our estimation method to geometric Brownian motion that we perturb with random effects. Using Matlab software, we generate for different sets of parameter values and for different choices of M and n, 1000 data sets of dimensions $n \times M$ from (12) using true values of parameters, i.e. for large data , or for small samples where we have a small number of subjects with a small number of repetitions of the experiment on each subject, as is often the case in biomedical applications. All the observations were generated by the following code algorithm:

```
W = wienerproc(M ∗ n);
for i = 1 : M
Data(n ∗ (i − 1) + 1) = 100;
for j = 2 : n
Data(n∗(i−1)+j) = 100∗exp((β +β^i −σ^2/2)∗j +σ^2 ∗ W(n ∗ (i − 1) + j));
end
end
```

So, we obtain 1000 sets of estimates of $\hat{\beta}$ from (13). Then, for numerical optimization reasons, the approximated estimators $\hat{\sigma}$ and $\hat{\sigma}_\beta$ are obtained by minimizing the negative log-likelihood function (14) giving $\hat{\beta}$ using genetic algorithm (GA) see: [52], then we get 1000 estimates of $\hat{\sigma}$ and $\hat{\sigma}_\beta$. Note that there were no boundary input arguments or initial values when using the GA function: $(\hat{\sigma}^2,\hat{\sigma}_\beta^2) = ga(@(\beta,\sigma^2,\sigma_\beta^2)(-log(L(\sigma^2,\sigma_\beta^2)(M,n,\beta,\sigma^2,\sigma_\beta^2,Data,\Delta)),2)$, and that the results were obtained by searching solutions on the set **R**. We repeat this for different possibilities of data size: (n;M) = (50; 10) and (10; 50). Then, we report the mean of each parameter in Table 1.

A. TABLE I

TABLE1: GEOMETRIC BROWNIAN MOTION MAXIMUM LIKELIHOOD ESTIMATES (MEAN AND STD()), FROM SIMULATIONS OF MODEL (11), SOLVING THE INTEGRAL ANALYTICALLY

β	Parameter values $\sigma 2$	$\sigma_\beta 2$		$\hat{\beta}$	$\hat{\sigma}^2$	$\hat{\sigma}\beta 2$
				M=10 n=50		
-0.3	0.5	0.5	Mean Std()	-0.401 (0.106)	0.500 (0.023)	0.510 (0.017)
				M=50 n=10		
-0.3	0.5	0.5	Mean	-0.281	0.500	0.500

			Std()	(0.145)	(0.011)	(0.032)
					M=10 n=50	
-0.1	0.4	0.5	Mean Std()	-0.126 (0.174)	0.411 (0.003)	0.500 (0.019)
					M=50 n=10	
-0.1	0.4	0.5	Mean Std()	-0.261 (0.011)	0.400 (0.045)	0.500 (0.112)

In all simulations we fixed $X_0^i = 100$ for all i. From I it is seen that the true parameter values are well identified using the exact maximum likelihood estimators of (14). The parameters σ^2 and $\sigma_\beta{}^2$ are well closed to the true value in particular in the cases (M, n) = (50, 10) where the estimates are better than the cases (M, n) = (10, 50), and that, in all cases β is well determined.

2. CONCLUSION

In this paper, we are interested in SDME models, because we believe that such a class of models will experience increasing popularity, because it combines the interesting features of mixed effects theory (within-subject and between-subject variation), with the ability to disrupt the process dynamics by considering random variability within the subject, thus providing a very flexible modeling approach. Then, we take the example of GBM as an application in order to estimates the model parameters when we include random effects in the model.

Therefore, we adopt an estimation method as a flexible modeling framework to regularize the ill-posed problem of the SDME models, that we apply to the GBM with random effect. The proposed parameter estimation method is based on the classical statistical inference by maximizing the likelihood function of the model. Therefore, we propose to derive the transition density of the process by solving the Fokker Planck equation and using the equation solution proposed in [1], that we perform otherwise in order to get an explicit form of the likelihood function. The proposed approach is addressed by simulation studies on large and small data, since in the epidemic field the data are not sufficiently large and are usually sparse. However, it may be difficult to numerically evaluate the integral in (4) when the dimension of B increases, and efficient numerical algorithms are needed.

Finally, simulation studies are addressed to estimate the model parameters of GBM with random effect on different artificial data sizes, the simulation results show that the estimates obtained by minimizing $-logL(\beta,\sigma,\sigma_\beta)$, are close to the true parameter values, and this result can be achieved using even moderate values of M (the number of subjects) and n (the number of observation for a given subject). This result is relevant for applications of GBM in situations where large data sets are unavailable, as in biomedical applications, and where Mixed-Effects theory is widely applied

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APPENDIXHere, we report the explicit expression of the likelihood function of (11) using (6) and (10):

$$L(\beta,\sigma,\sigma_\beta)=(\frac{1}{\sqrt{2\pi\sigma_\beta}})^M(2\sqrt{\pi\Delta})^{-nM}\prod_{i=1}^{M}(\prod_{j=1}^{n}\mid\sigma Y_j^i\mid^{-\frac{1}{2}}$$

$$exp(\frac{-1}{4\Delta Y_j^i}(Y_j^i-Y_{j-1}^i-Y_j^i\Delta\beta)^2)exp(\frac{\sum_{j=1}^{n}(Y_j^i-Y_{j-1}^i-Y_j^i\Delta\beta)^2}{\frac{4\Delta^3}{\sigma}\sum_{j=1}^{n}Y_j^i+\frac{8\Delta^2}{\sigma_\beta^2}})$$

$$\sqrt{\frac{\pi}{\frac{\Delta}{4\sigma}\sum_{j=1}^{n}Y_j^i+\frac{1}{2\sigma_\beta^2}}}$$

(14)