Advanced Drug Delivery Reviews 65 (2013) 929–939

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

A review on estimation of stochastic differential equations for pharmacokinetic/pharmacodynamic models ☆

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ARTICLE INFO

Article history:
Accepted 13 March 2013
Available online 22 March 2013

Keywords:
Stochastic differential equations
Pharmacokinetic
Pharmacodynamic
Population approach
Maximum likelihood estimation
Kalman filter
EM algorithm
Hermite expansion
Gauss quadrature
Bayesian estimation

ABSTRACT

This paper is a survey of existing estimation methods for pharmacokinetic/pharmacodynamic (PK/PD) models based on stochastic differential equations (SDEs). Most parametric estimation methods proposed for SDEs require high frequency data and are often poorly suited for PK/PD data which are usually sparse. Moreover, PK/PD experiments generally include not a single individual but a group of subjects, leading to a population estimation approach. This review concentrates on estimation methods which have been applied to PK/PD data, for SDEs observed with and without measurement noise, with a standard or a population approach. Besides, the adopted methodologies highly differ depending on the existence or not of an explicit transition density of the SDE solution.

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☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Mathematical modeling of systems pharmacogenomics towards personalized drug delivery".

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http://dx.doi.org/10.1016/j.addr.2013.03.005

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1. Introduction

Pharmacokinetics (PK) aims at describing the relationship between the dose administered and the exposure to the drug, i.e. the total concentration of drug in the body. Pharmacodynamics (PD) quantifies the relationship between the drug exposure and the response to this exposure. PK/PD models are often described by differential systems derived from physiology. In general, the proposed models are deterministic, that is, the observed kinetic/dynamic is driven exclusively by internal deterministic mechanisms. However, real pharmacological processes are always exposed to influences that are not completely understood or not feasible to model explicitly. Ignoring these phenomena in the modeling may affect the estimation of PK/PD parameters and the derived conclusions. Therefore there is an increasing need to extend the deterministic models to models including a stochastic component. A natural extension of deterministic differential equations model is a system of stochastic differential equations (SDEs), where relevant parameters have been modeled as suitable stochastic processes, or stochastic processes have been added to the driving system equations [12].

The first papers encouraging the introduction of random fluctuations in PK/PD were published by [7,41,42]. The authors underline that PK/PD have contributions from both deterministic and stochastic components: drug concentrations follow determinable trends but the exact concentration at any given time is not completely determined. For example [42] proposes a stochastic one-compartment PK model with a variable elimination rate. More sophisticated PK/PD models have then been proposed with multiple compartments, nonlinear or time-inhomogeneous absorption or elimination (see for example [21,46,11,13,37]).

Parameter estimation for SDE has been highly tackled in the statistical literature, often motivated by financial applications (see [44], for a review). However, many suggested solutions require high frequency data and are not suited for PK/PD data where designs are usually sparse. Especially, estimation methods based on approximations of the continuous-time observation likelihood (namely the Girsanov formula), which require a high number of data and a small time step between two successive observations, are not adapted. Moreover, PK/PD data are more and more analyzed through a population approach when data from several subjects are considered simultaneously. This yields to PK/PD models with random parameters. Combining SDE with a population approach is quite appealing but raises inference challenges.

In this paper, we concentrate our review on estimation methods adapted to the particular characteristics of PK/PD data. After a short presentation of some examples of PK/PD SDEs in Section 2, we introduce some preliminary comments on the likelihood functions depending on the considered observation model (with and without measurement noise) in Section 3. Section 4 is about estimation methods for standard PK/PD SDE: when SDEs are directly observed, the reader is introduced to techniques based on (i) exact maximum likelihood estimator when explicit solution is available or (ii) Hermite expansion of the transition density, (iii) approximation of the spectral density if the SDE has no explicit solution. When the SDE is observed with an additive measurement error, methods are based on (iv) Kalman filter and its extended version or (v) Monte Carlo approximation of the likelihood. Section 5 discusses estimation methods within population approach: we detail methods based on (i) exact maximum likelihood estimator when linear SDE with random effect and no measurement noise are considered, (ii) Gauss-Hermite quadrature to approximate the likelihood, possibly coupled with (iii) Hermite expansion of the transition density, (iv) Bayesian approach, (v) Kalman filter and linearization of the likelihood, and (vi) Expectation-Maximization algorithm. The paper finishes with some discussion (Section 6).

2. Stochastic PK/PD models

In this section, we present some stochastic compartmental PK/PD models that have been proposed in the literature. This list is far from being exhaustive but aims at presenting typical situations, each of them involving a different level of statistical inference difficulty. We refer to [12] for a construction of the Brownian motion and stochastic integrals and for usual stochastic processes (geometric Brownian motion, Ornstein-Uhlenbeck process, etc.) that are presented in this section.

2.1. From deterministic to stochastic model in PK

Let us first consider a very simple PK model proposed by [41], namely a one compartment PK model with first-order elimination k_e and an injected intravenous bolus dose D of drug. The kinetic of the drug concentration C_t in the body at time $t > 0$ is described by the following deterministic differential equation:

$$\frac{dC_t}{dt} = -k_e C_t, \quad C_0 = \frac{D}{V},$$

where V is the volume of the compartment. This equation has an explicit solution: $C_t = \frac{D}{V} e^{-k_e t}$. Now, assume that k_e is not constant in time but randomly fluctuates around a mean value as $k_e + \xi_t$, where ξ_t is a Gaussian white noise process. Then $\xi_t dt$ can be written as γdB_t, where B_t is a Brownian motion and γ is a constant parameter. Incorporating this noise into the deterministic model, C_t becomes a stochastic process, solution of the following SDE:

$$dC_t = -k_e C_t dt + \gamma C_t dB_t, \quad C_0 = \frac{D}{V}. \tag{1}$$

This process – known as geometric Brownian motion – has an explicit expression

$$C_t = \frac{D}{V} e^{-k_e t} exp\left(-\frac{\gamma^2}{2} t + \gamma B_t\right).$$

This stochastic process, which is log-normal, only takes positive values, which is noticeable when modeling concentration. Parameters to be estimated are $\theta = (k_e, V, \gamma)$.

A stochastic one compartment PK model with first-order absorption has also been considered by [21]:

$$dC_t = (k_a/V - k_e C_t)dt + \gamma dB_t, \quad C_0 = \frac{D}{V}, \tag{2}$$

where k_a is the absorption rate. This process – known as an Ornstein-Uhlenbeck process – has an explicit expression

$$C_t = \frac{D}{V} e^{-k_e t} + \frac{k_a}{V k_e}\left(1 - e^{-k_e t}\right) + \gamma \int_0^t e^{-k_e (t-s)} dB_s,$$