One-compartment stochastic pharmacokinetic model

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Abstract

In this work, we consider a pharmacokinetic (PK) model with first-order drug absorption and first-order elimination that represent the concentration of drugs in the body, including both the absorption and elimination parts, and we also add a random factor to describe the variability between patients and the environment. Using Itô's lemma and the Laplace transform, we obtain the solutions in integral form for a single and constant dosage regimen in time. Moreover, formulas for the expected value and the variance for each case of study are presented, which allows the statistical assessment of the proposed models, as well as predicting the ideal path of drug concentration and its uncertainty. These results are important in the long-term analysis of drug concentration and the persistence of therapeutic level. Further, a numerical method for the solution of the stochastic differential equation (SDE) is introduced and developed.

Keywords: Stochastic differential equations; Itô's lemma; analytic solutions; PK model.

1. Introduction

Drug concentration levels in the body vary among different patients according to their weight, age, stress, or genetic factors [1]. In addition, it has also been observed that the food intake, special excercises and some vitamin can affect the drug absorption [2]. Due to the variability and uncertainty of such factors, several researches have introduced stochastic corrections on the well known compartmental pharmacokinetics deterministic models [3].

The mathematical modeling of stochastic compartmental systems has received great attention in the literature and has produced many useful mathematical models. For example, an analysis of a one-compartment model to describe the spontaneous erratic variations of drug concentration decay with a single dose administration [4, 5], where the elimination rate fluctuates according a Wiener motion. More recently the same case is studied in [6] where stochastic differential equations (SDE) driven by the Liu process (see [7]) are proposed and this model presents the uncertainty that the drug concentration is larger than the minimum effective concentration. In contrast to [6], in this paper we include the drug absorption phenomena under two kinds of dosage forms and the elimination using a Wiener motion.

Another approach is presented in [4] and [8] using a Vasicek model to study the stochastic variability for continuous dosing. Some recent studies have proposed more complex compartments models [9, 10, 11, 12, 13, 14]. These works consider the noise term as a constant and focus on

parameter estimation techniques. However, in such works closed expressions for the solution, the expected value, and the time-dependent variance are not derivated. The aim of this article is to determine such formulas.

In addition, the problem to determine an optimal dosing timing schedule to control the blood drug concentration is studied in [2]. The authors combine optimal control theory and stochastic methods, prove existence, uniqueness of the solution and present the corresponding stability analisys. In such work the goal is to determine the source term of the SDEs system. On the other hand, in this paper we are interested in determining the terapeutic range of the drug when dosification function is known.

In this article, we consider an one-compartment PK model where drug is absorbed according to a first-order process and first order elimination. Such situation is described by a differential equation coupled with a SDE, that takes into account the variability among individuals under dose regimen. In order to solve such system, we employ Itô's calculus and Laplace transformation to obtain a solution in Riemann integral form. The advantage is that one can approximate numerically the realistic trajectory of the drug concentration by standard quadrature rules. To determine the therapeutic range of the drug, it is necessary to know the expected value and the time-dependent variance of the drug concentration. In order to find them, it is possible to solve the differential equations for the first moment (i.e. the expected value) and for the second moment (and so find the variance), this is usefull when an exact solution of the corresponding SDE is not known. However, in this work we obtain an explicit formula for the solution of SDE in an integral form, this allow us to directly calculate the expected value and variance for this solution.

2. Mathematical model

In order to describe mathematically the absorption and elimination of a drug in the body, we consider the following hypotheses in the deterministic part of the model [3]:

a) The absorbed drug concentration decreases proportionally to the amount of drug at site of administration at the time t.

b) The drug is rapidly and uniformly distributed throughout the body, i.e., when the body behaves as a single central compartment.

c) The drug elimination is considered as a first-order process, ie, is proportional to the amount of drug in the body

The classical model, which describes drug absorption in a one-compartment and relates the changes in drug concentration in the blood with time to the absorption and the elimination rates is based on the Wagner-Nelson method [15]:

$$\begin{cases} \dfrac{\mathrm{d}X_a(t)}{\mathrm{d}t} = -r_a X_a(t) + f(t) \\ \dfrac{\mathrm{d}X(t)}{\mathrm{d}t} = r_a X_a(t) - r_e X(t) \\ s.t. \quad X_a(0) = X_{a0}, \quad X(0) = 0, \end{cases} \tag{1}$$

where $\mathrm{d}X/\mathrm{d}t$ is the rate (mg h^{-1}) of change of drug concentration in the blood, $X(t)$ is the concentration of drug in the blood or body at time t, X_a is the concentration of absorbable drug at the absorption site at time t, r_a and r_e are the first-order absorption and elimination constants
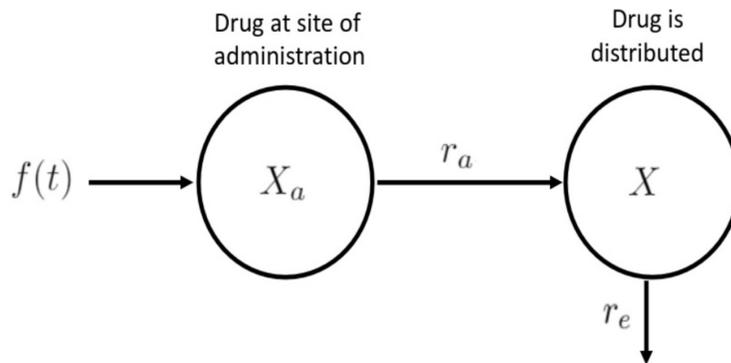
Figure 1. Compartmental Model.

rates, respectively (e.g., h^{-1}), $r_a X_a$ is the first-order rate of absorption (mg h^{-1}, $\mu g\ h^{-1}$, etc.), $r_e X(t)$ is the first-order rate of elimination (e.g., mg h^{-1}), X_{a0} is the initial dose of drug and for the dosage regimen of the drug per unit of time $f(t)$. We consider the following two cases:

- Single dose: $f(t) = 0$ with $X_{a0} \neq 0$.

- Constant dosage: $f(t) = r_a X_p$, with X_p positive constant.

However, model (1) does not take into account that drug concentration levels vary among different patients according to their weight, age, stress or genetic factors ([16] and [1]). Therefore, we consider that the elimination rate r_e is not constant in time but randomly fluctuates around a mean value as $r_e - \zeta_t$, where ζ_t is a Gaussian white noise process. Then $\zeta_t\ dt$ can be written as $c\ dW(t)$, where $W(t)$ is a standard Wiener motion and the positive constant c is a diffusion coefficient.

Incorporating this assumption into the deterministic model (1), we obtain the following SDE system

$$\begin{cases} dX_a(t) = \big(-r_a X_a(t) + f(t)\big)\, dt \\ dX(t) = \big(r_a X_a(t) - r_e X(t)\big)\, dt + c X(t)\, dW(t) \\ s.t. \quad X_a(0) = X_{a0}, \quad X(0) = 0. \end{cases} \tag{2}$$

Theorem 2.1. The solution to the initial value problems (2) with $f(t) = r_a X_p$ and X_p a positive constant is given by

$$X(t) = e^{-\frac{1}{2}c^2 t + cW(t)}\, \mathcal{L}^{-1} \left\{ \frac{r_a}{s + r_e} \int_0^\infty e^{-(s - \frac{1}{2}c^2)u}\, e^{-cW(u)} X_a(u)\, du \right\} \tag{3}$$

where $\mathcal{L}^{-1}$ is the inverse Laplace transform operator, s is the Laplace transform parameter and $X_a(t)$ is the solution of first equation from (2) which is given by the indefinite integral form:

$$X_a(t) = e^{-r_a t}\left(X_{a0} + \int_0^t e^{r_a u} f(u)du \right). \tag{4}$$

Proof. To determine the solution to problem (2), we use the integration factor method (see [17]) as follows:

1. We solve the non-deterministic part of equation (2), i.e

$$dX(t) = c X(t) \, dW(t). \tag{5}$$

Using Itô formula [18] with $F(X, t) = \ln(X)$ and after some calculations, we get

$$X(t) = K e^{-\frac{1}{2}c^2 t + c W(t)}. \tag{6}$$

2. Applying the method of variation of parameters, we make the constant K of the non-deterministic solution (6) vary as a function of time, so $X(t)$ is of the form

$$X(t) = K(t) e^{-\frac{1}{2}c^2 t + c W(t)} = K(t) G(t), \tag{7}$$

where $G(t)$ satisfies equation (5). Then,

$$dX(t) = d\big[K(t)G(t)\big]$$
$$\big(r_a X_a(t) - r_e X(t)\big) \, dt + c X(t) \, dW(t) = G(t) \, dK(t) + K(t) \, dG(t).$$

By substituting (7) into the above equation, we have

$$\big(r_a X_a(t) - r_e K(t) G(t)\big) \, dt + c K(t) G(t) \, dW(t) = G(t)\big[dK(t) + c K(t) \, dW(t)\big]$$

By cancelling the similar terms and dividing by $G(t)$ in both sides of above equation, we get the following initial value problem

$$\begin{cases} \dfrac{dK(t)}{dt} + r_e K(t) = \dfrac{r_a X_a(t)}{G(t)} \\ s.t. \quad K(0) = 0, \end{cases} \tag{8}$$

where $X_a(t)$ is given by (4). To solve the initial value problem (8) we use the Laplace transform, then

$$\mathscr{L}\left\{\frac{dK(t)}{dt}\right\} + r_e \mathscr{L}\{K(t)\} = \mathscr{L}\left\{\frac{r_a X_a(t)}{G(t)}\right\}$$

$$s\mathbb{K}(s) - K(0) + r_e \mathbb{K}(s) = r_a \int_0^\infty e^{-(s - \frac{1}{2}c^2)t} \, e^{-c W(t)} X_a(t) \, dt$$

$$(s + r_e)\mathbb{K}(s) = r_a \int_0^\infty e^{-(s - \frac{1}{2}c^2)t} \, e^{-c W(t)} X_a(t) \, dt$$

$$\mathbb{K}(s) = \frac{r_a}{s + r_e} \int_0^\infty e^{-(s - \frac{1}{2}c^2)t} \, e^{-c W(t)} X_a(t) \, dt.$$

Now, we apply the inverse Laplace transformation on both sides:

$$K(t) = \mathscr{L}^{-1}\left\{\frac{r_a}{s + r_e} \int_0^\infty e^{-(s - \frac{1}{2}c^2)t} \, e^{-c W(t)} X_a(t) \, dt\right\}. \tag{9}$$

We plug equation (9) into (7) to obtain the general solution of (2)

$$X(t) = e^{-\frac{1}{2}c^2 t + c W(t)} \, \mathscr{L}^{-1}\left\{\frac{r_a}{s + r_e} \int_0^\infty e^{-(s - \frac{1}{2}c^2)u} \, e^{-c W(u)} X_a(u) \, du\right\},$$

where u is an auxiliary variable. $\qquad\square$

3. Drug dose regimens

In this section, we analyze the behavior of the drug concentration in the body under constant dosage (infusion) regimen and the single dose (push) administration.

3.1. Continuous dosage (infusion) of the drug

A constant amount of the drug is supplied continuously for long periods of time, in the treatment of some chronic diseases. Such types of administration are: intravenous infusion, certain oral formulations based on the phenomenon of osmosis and certain transdermal patches.

Remark 3.1. When the source function $f(t) = r_a X_p$ with X_p a positive constant, the solution of the first equation of (2) given by (4) is

$$X_a(t) = X_p + (X_{a0} - X_p)e^{-r_a t}. \tag{10}$$

Theorem 3.1. Let $f(t) = r_a X_p$ be the source function with X_p a positive constant that represents the concentration of the drug that is administered at all time $t > 0$. Then, the concentration of the drug is given by the integral form:

$$X(t) = \int_0^t \kappa_1(t-u)\, e^{c(W(t)-W(u))}\, \mathrm{d}u + \int_0^t \kappa_2(t-u)\, e^{c(W(t)-W(u))}\, \mathrm{d}u, \tag{11}$$

where

$$\kappa_1(t-u) := r_a X_p\, e^{-(r_e + \frac{1}{2}c^2)(t-u)}, \tag{12}$$

and

$$\kappa_2(t-u) := r_a (X_{a0} - X_p)\, e^{-r_a u - (r_e + \frac{1}{2}c^2)(t-u)}. \tag{13}$$

Proof. By replacing (10) in (3) we get

$$\begin{aligned}
X(t) =& \mathcal{L}^{-1}\left\{ \frac{r_a X_p}{s + r_e} \int_0^\infty e^{-(s-\frac{1}{2}c^2)u}\, e^{-cW(u)}\, e^{-\frac{1}{2}c^2 t + cW(t)}\, \mathrm{d}u \right\} \\
&+ \mathcal{L}^{-1}\left\{ \frac{r_a (X_{a0} - X_p)}{s + r_e} \int_0^\infty e^{-(s+r_a-\frac{1}{2}c^2)u}\, e^{-cW(u)}\, e^{-\frac{1}{2}c^2 t + cW(t)}\, \mathrm{d}u \right\} \\
=& \mathcal{L}^{-1}\left\{ \frac{r_a X_p}{s + r_e} \int_0^\infty e^{-su}\, e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\, \mathrm{d}u \right\} \\
&+ \mathcal{L}^{-1}\left\{ \frac{r_a (X_{a0} - X_p)}{s + r_e} \int_0^\infty e^{-su}\, e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\, e^{-r_a u}\, \mathrm{d}u \right\},
\end{aligned}$$

using the convolution theorem, we obtain

$$\begin{aligned}
X(t) =& r_a X_p \int_0^t e^{-r_e(t-u)}\, e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\, \mathrm{d}u \\
&+ r_a (X_{a0} - X_p) \int_0^t e^{-r_e(t-u)}\, e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\, e^{-r_a u}\, \mathrm{d}u
\end{aligned}$$

Finally, we get the integral form

$$X(t) = \int_0^t \kappa_1(t-u)\, e^{c(W(t)-W(u))}\, \mathrm{d}u + \int_0^t \kappa_2(t-u)\, e^{c(W(t)-W(u))}\, \mathrm{d}u,$$

where $\kappa_1(t-u)$ and $\kappa_2(t-u)$ are defined as in (12) and (13) respectively. $\qquad\qquad\square$

Remark 3.2. In conclusion, the solution of the system (2) with $f(t) = r_a X_p$ is

$$\begin{cases} X_a(t) = X_p + (X_{a0} - X_p)e^{-r_a t}, \\ X(t) = \int_0^t \kappa_1(t-u)\, e^{c(W(t)-W(u))}\, \mathrm{d}u + \int_0^t \kappa_2(t-u)\, e^{c(W(t)-W(u))}\, \mathrm{d}u, \end{cases}$$

with $\kappa_1(t-u)$ and $\kappa_2(t-u)$ as in (12) and (13).

Corollary 3.1. Single dose (push) administration Let $X_p = 0$ in equation (10) and the dose is supplied at the initial time ($t = 0$). Then the concentration is given by the integral form

$$X(t) = r_a X_{a0} \int_0^t e^{-r_a u - (r_e + \frac{1}{2}c^2)(t-u)}\, e^{c(W(t)-W(u))}\, \mathrm{d}u \qquad (14)$$

Proof. As $X_p = 0$, it follows from (12) and (13) that

$$\kappa_1(t-u) = 0, \qquad \text{and} \qquad \kappa_2(t-u) = r_a X_{a0}\, e^{-r_a u - (r_e + \frac{1}{2}c^2)(t-u)}.$$

Thus, immediately from (11) the result is obtained. $\qquad\qquad\square$

3.1.1. *Expected value and variance for constant dose*

In this section we obtain explicit formulas for the expected value and the variance of the drug concentration $X(t)$. Having these formulas, we can identify the model parameters from observed data and to establish therapeutic ranges of the drug for each dosing regimen. At this point, it is important to differentiate the case when the absorption constant rate r_a is equal to the elimination constant rate r_e to determine the relevant pharmacokinetic parameters (see **3.3**). In the deterministic model similar results have been obtained in [23] and [24].

Proposition 3.1. The expected value of the stochastic process $X(t)$ given by (11) is

$$\mathbb{E}[X(t)] = \begin{cases} \dfrac{r_a}{r_e} X_p\left(1 - e^{-r_e t}\right) + \dfrac{(X_{a0} - X_p)}{1 - r_e/r_a}(e^{-r_e t} - e^{-r_a t}) & \text{if } r_e \neq r_a \\ X_p\left(1 - e^{-r_a t}\right) + (X_{a0} - X_p)r_a t e^{-r_a t} & \text{if } r_e = r_a. \end{cases} \qquad (15)$$

Proof. Since $W(t) - W(u) \sim N(0, t-u)$ then $\exp\{c(W(t) - W(u))\}$ has a log-normal distribution with parameters

$$\mathbb{E}\left[e^{c(W(t)-W(u))}\right] = e^{\frac{1}{2}c^2(t-u)} \qquad \text{and} \qquad \mathrm{Var}\left[e^{c(W(t)-W(u))}\right] = e^{c^2(t-u)}\left(e^{c^2(t-u)} - 1\right).$$

- If $r_e \neq r_a$ the expected value of $X(t)$ in (11) is given by

$$
\begin{aligned}
\mathbb{E}\big[X(t)\big] &= \int_0^t \kappa_1(t-u)\,\mathbb{E}\big[e^{c(W(t)-W(u))}\big]\,\mathrm{d}u + \int_0^t \kappa_2(t-u)\,\mathbb{E}\big[e^{c(W(t)-W(u))}\big]\,\mathrm{d}u \\
&= \int_0^t \kappa_1(t-u)\,e^{\frac{1}{2}c^2(t-u)}\,\mathrm{d}u + \int_0^t \kappa_2(t-u)\,e^{\frac{1}{2}c^2(t-u)}\,\mathrm{d}u \\
&= \int_0^t r_a X_p\, e^{-r_e(t-u)}\,\mathrm{d}u + \int_0^t r_a\big(X_{a0} - X_p\big)\, e^{-r_a u - r_e(t-u)}\,\mathrm{d}u \qquad (16) \\
&= \frac{r_a}{r_e} X_p\big(1 - e^{-r_e t}\big) + \frac{r_a}{r_a - r_e}\big(X_{a0} - X_p\big)\big(e^{-r_e t} - e^{-r_a t}\big).
\end{aligned}
$$

- For the case that $r_e = r_a$, the result is obtained easily from equation (16). $\qquad\square$

Proposition 3.2. If $r_e \neq \{r_a, r_a + c^2, r_a + c^2/2, c^2, c^2/2\}$, the variance of the stochastic process $X(t)$ given by (11) is

$$
\begin{aligned}
\mathrm{Var}\big[X(t)\big] =& \frac{2r_a^2 X_p^2}{r_e(2r_e - c^2)}\big(1 - e^{-2(r_e - \frac{1}{2}c^2)t}\big) - \frac{2r_a^2 X_p^2}{r_e(r_e - c^2)}\big(1 - e^{-(r_e - c^2)t}\big)e^{-r_e t} \\
& - \frac{2r_a^2 X_p(X_{a0} - X_p)}{(r_a - r_e)(r_e - c^2)}\big(e^{-r_a t} - e^{-r_e t}\big)\left(1 - e^{-(r_e - c^2)t}\right) \\
& + \frac{2r_a^2}{r_a - r_e}\frac{(X_{a0} - X_p)^2}{2(r_a - r_e) + c^2}\left(e^{-2r_a t} - e^{-2(r_e - \frac{1}{2}c^2)t}\right) \qquad (17) \\
& - \frac{2r_a^2}{r_a - r_e}\frac{(X_{a0} - X_p)^2}{r_a - r_e + c^2}\left(e^{-(r_e + r_a)t} - e^{-2(r_e - \frac{1}{2}c^2)t}\right) \\
& - \left[\frac{r_a}{r_e} X_p\big(1 - e^{-r_e t}\big) + \frac{r_a(X_{a0} - X_p)}{r_a - r_e}\big(e^{-r_e t} - e^{-r_a t}\big)\right]^2.
\end{aligned}
$$

Proof. Details of the calculation of $\mathrm{Var}\big[X(t)\big]$ can be seen in **Appendix B**. $\qquad\square$

Proposition 3.3. If $r_e = r_a$, the variance of the stochastic process $X(t)$ given by (11) is

$$
\begin{aligned}
\mathrm{Var}\big[X(t)\big] =& \frac{2r_a^2}{c^2}\big(X_p - X_{a0}\big)^2 e^{-2r_a t}\left(\frac{1}{c^2}(e^{c^2 t} - 1) - t\right) - \frac{2r_a X_p^2}{2r_a - c^2}\left(e^{(c^2 - 2r_a)t} - 1\right) \\
& + \frac{2r_a X_p e^{-r_a t}}{r_a - c^2}\big(X_p + r_a(X_p - X_{a0})\,t\big)\big(e^{-(r_a - c^2)t} - 1\big) \\
& - \left(X_p\big(e^{-r_a t} - 1\big) + r_a t e^{-r_a t}\big(X_p - X_{a0}\big)\right)^2.
\end{aligned}
$$

Proof. The result can be obtained from the variance definition and equation (23) in Appendix B. $\qquad\square$

Remark 3.3. The expected value given in (15) satisfies the ordinary differential equation given in (1) when $f(t) = r_a X_p$, since if we differentiate (15) with respect to t and substitute into (1), it is satisfied. Furthermore, if $X_p = 0$ in (15), this expression coincides with the exact solution of (1), that is, in the absence of the stochastic term.

Remark 3.4. To compute the variance of process $X(t)$ in presence of flip-flop kinetics ($r_e > r_a$), we consider the cases $r_e = r_a + c^2$ and $r_e = r_a + c^2/2$ (see Appendix B).

Remark 3.5. In pharmacology is very important to determine the therapeutic range of a drug, which is the range in which the drug can be used without causing toxic or lethal effects on the individual. From equations (15) and (17) we obtain that in the stationary state ($t \to \infty$), the minimum effective concentration $X_{\min}$ and the concentration maximum admissible $X_{\max}$ must be such that

$$X_{\min} \leq \frac{r_a}{r_e} X_p - 2\,\sigma_{X(t)} \leq X(t) \leq \frac{r_a}{r_e} X_p + 2\,\sigma_{X(t)} \leq X_{\max},$$

where $\sigma_{X(t)} = \dfrac{c\,r_a X_p}{r_e\sqrt{2r_e - c^2}}$ when $t \to \infty$.

4. Numerical simulation

Several numerical schemes have been used to solve SDEs (for example [19] and [20]). However, in this work we propose an alternative method to simulate the evolution of the drug concentration, when a single dose or constant dose are administrated. To compute numerically an approximation of the solution (11), let us denote by $\alpha := r_e + c^2/2$, $\beta := \alpha - r_a$, when $X_p \neq 0$ then $h(t) := r_a X_p e^{-\alpha t + c w(t)}$ and $g(t) := (X_{a0}/X_p - 1)h(t)$. Hence the solution (11) can be written as follows

$$X(t) = h(t) \int_0^t e^{\alpha u} e^{-cw(u)}\,du + g(t) \int_0^t e^{\beta u} e^{-cw(u)}\,du. \tag{18}$$

Note that the integrals in (18) are just Riemann Integrals, then in order to evaluate $X(t)$. First, we divide the interval $[0, t_{max}]$ into N sub-intervals of equal length $\Delta t := t_{max}/N$. This defines a set of discrete times $t_i = i\,\Delta t, i = 1, \ldots, N$. Next, we discretize the Wiener process with a time step Δt and interpolate linearly the term $e^{-cw(u)}$ on the interval $[t_{i-1}, t_i]$. Then, an approximation of $X(t_k)$ for $k = 1, \ldots, N$ is

$$X(t_k) = \frac{h(t_k)}{\Delta t} \sum_{i=1}^{k} \left[\frac{\int_{t_{i-1}}^{t_i} e^{\alpha u}(t_i - u)\,du}{e^{cw(t_{i-1})}} + \frac{\int_{t_{i-1}}^{t_i} e^{\alpha u}(u - t_{i-1})\,du}{e^{cw(t_i)}} \right]$$

$$+ \frac{g(t_k)}{\Delta t} \sum_{i=1}^{k} \left[\frac{\int_{t_{i-1}}^{t_i} e^{\beta u}(t_i - u)\,du}{e^{cw(t_{i-1})}} + \frac{\int_{t_{i-1}}^{t_i} e^{\beta u}(u - t_{i-1})\,du}{e^{cw(t_i)}} \right], \tag{19}$$

where $X(t_0) = X(0) = 0$ and the integrals are computed exactly.

4.1. Single dosage (push) administration

We consider the experimental data of Theophylline concentrations (in mg/L) for 12 subjects following a single oral dose of 320 mg. The data is reported in [21] and its time series graphs are shown in **Figure 2(a)**. From this data we identify the parameters r_e, r_a, X_{a0} and c (see Figure 2(a)) by the method of moments (see [22]). We found that elimination rate, absorption rate, coefficient of variance, and initial absorption concentration are $r_e = 0.0782$, $r_a = 1.7603$, $c = 0.1004$ and $X_{a0} = 9.5206$ respectively. **Figure 2(b)** shows a simulation of the drug concentration decay. As we can observe, computational simulations are consistent with the experimental measurements. Furthermore, in both figures, the sample paths are in between the strip formed by $\mathbb{E}[X(t)] \pm 2\sigma_{X(t)}$.

4.2. Continuous dosage (infusion) of the drug

We will now study the Propofol concentration behavior during 60 minutes infusion dose administration with an infusion rate of 25 μg kg^{-1} min^{-1} . Experimental data are taken from [25]. We estimate the parameters of the model by the method of moments, we find that $r_a = 0.8261, r_e = 0.1247, c = 0.1435, X_p = 0.0029$ and $X_{a0} = 0.0137$.

From **Figure 3(a)** we see that the average mean of data (red dots) almost coincides with the expected value (black curve). Furthermore, the experimental data lie within a band around the expected value with a width of two standard deviations. **Figure 3(b)** illustrates a simulation of the drug concentration in five individuals when the dosage is continuous (infusion). Here, solution of the differential equation (2) with $f(t) = r_a X_p$, was evaluated by the numerical approximation (19).
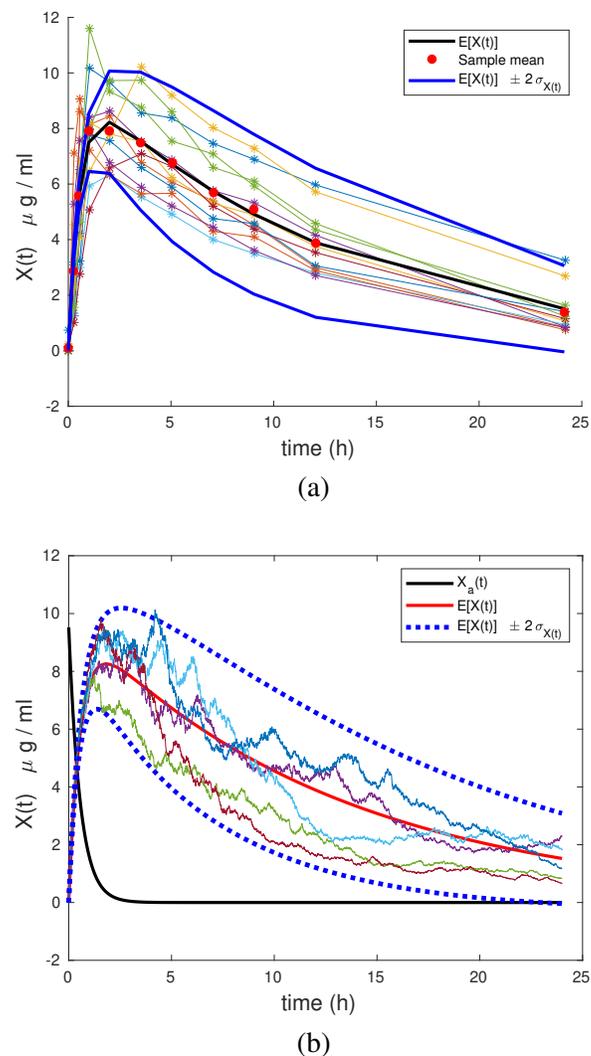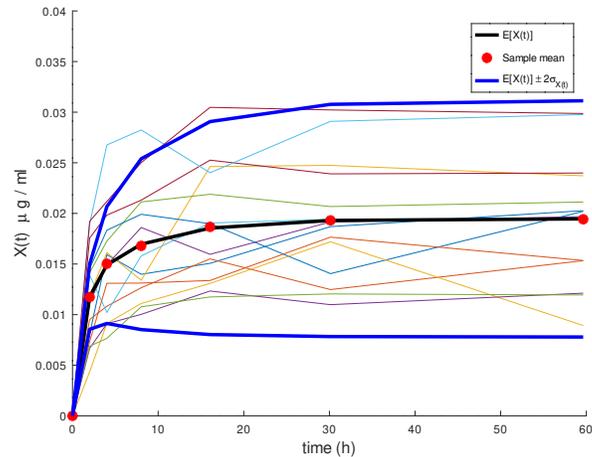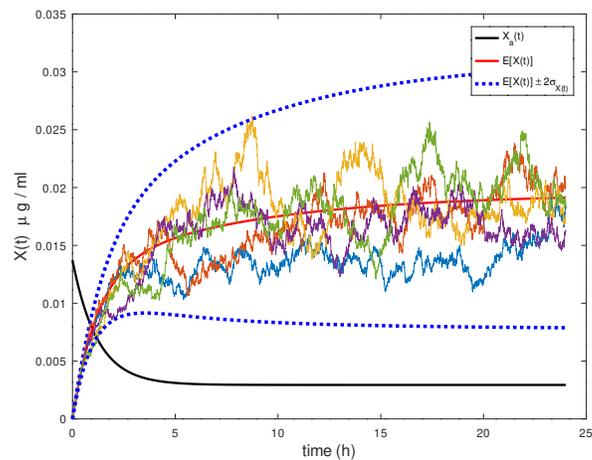

(a)

(b)

Figure 2. (a) Experimental data of the Theophylline concentrations. (b) Simulation of the decay of the Theophylline concentration after the administration of a single dose (push). Five sample paths, expected value of the process (2) and the graphs of $\mathbb{E}[X(t)] \pm 2\sigma_{X(t)}$. $r_e = 0.0782$, $r_a = 1.7603$, $c = 0.1004$, $X_0 = 0$, $X_{a0} = 9.5206$ and $f(t) = 0$.

(a)

(b)

Figure 3. (a) Experimental data of the Propofol concentrations. (b) Simulation of the drug concentration under a constant dosage regimen. Samples of five paths, expected value of the process (2) and the graphs of $\mathbb{E}\big[X(t)\big] \pm 2\sigma_{X(t)}, r_a = 0.8261, r_e = 0.1247, c = 0.1435, X_p = 0.0029$ and $X_{a0} = 0.0137$.

5. Conclusions

We study an one compartment stochastic differential model that describe absorption and elimination of a drug under a single and constant dosage regimens. We derived an integral equation for the solution, that allow to determine an explicit formulas for the expected value and variance. The model is identified using the formulas of the expected value and the variance, which allows to predict the realistic path of the solution and its uncertainty, as well as, to determine the therapeutic range of the drug. Further, a numerical method for the solution of the SDE is introduced and developed, in this case, using a quadrature rule; instead of solving the SDE system by standard numerical methods. We leave the convergence analysis of the numerical method for future work.

6. Acknowledgments

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A. Basic notions

1. According to [22], if $S \sim N(0, t)$, its mgf is
$$\mathbb{E}\big[e^{r_a S}\big] = e^{\frac{1}{2} t r_a^2}.$$

2. Since $W(t) \sim N(0, t)$, it follows that $dW(t) \sim N(0, dt)$. Therefore,
$$\mathrm{Var}\big[dW(t)\big] = \mathbb{E}\big[dW(t) - \mathbb{E}[dW(t)]\big]^2 = \mathbb{E}\big[dW(t)\big]^2 = dt.$$

3. Square of the sum of N real numbers
$$\left(\sum_{n=1}^{N} a_n\right)^2 = \sum_{n=1}^{N} a_n^2 + 2\sum_{j=1}^{N-1}\sum_{i=j+1}^{N} a_i a_j.$$

4. Identity
$$n \int_0^t f(u) \left(\int_0^u f(v)\, dv\right)^{n-1} du = \left(\int_0^t f(v)\, dv\right)^n \tag{20}$$
   Proof. In the left hand we make change of variable
$$z = F(u) = \int_0^u f(v)\, dv, \qquad dz = d\big[F(u)\big] = f(u)du$$
   we obtain
$$n \int_0^{F(t)} z^{n-1}\, dz = z^n \big|_0^{F(t)} = \left(\int_0^t f(v)\, dv\right)^n.$$

B. Calculation of variance for a constant dose

From equation (11) we get
$$\mathbb{E}\big[X^2(t)\big] = \mathbb{E}\big[I_1^2(t)\big] + 2\mathbb{E}\big[I_1(t)\, I_2(t)\big] + \mathbb{E}\big[I_2^2(t)\big],$$
where the integrals are
$$I_j(t) := \int_0^t \kappa_j(t-u)\, e^{c(W(t)-W(u))}\, du, \qquad j = 1, 2$$
and $\kappa_j(t-u)$ are given by the equations (12) and (13) respectively. Using the identity (20) with $n = 2$, we obtain
$$\mathbb{E}\big[I_1^2(t)\big] = \mathbb{E}\left[\left(\int_0^t \kappa_1(t-u)\, e^{c(W(t)-W(u))}\, du\right)^2\right]$$
$$= \mathbb{E}\left[2\int_0^t \kappa_1(t-u) e^{c(W(t)-W(u))}\left(\int_0^u \kappa_1(t-v)\, e^{c(W(t)-W(v))}\, dv\right) du\right]$$
$$= 2\int_0^t \int_0^u \kappa_1(t-u)\, \kappa_1(t-v)\, \mathbb{E}\left[e^{c[2(W(t)-W(u))+(W(u)-W(v))]}\right] dv\, du.$$

For simplicity, we denote the increments over different time by $\widetilde{W}(u) = W(t) - W(u)$ and $\widetilde{W}(v) = W(u) - W(v)$, then

$$\mathbb{E}\big[I_1^2(t)\big] = 2 \int_0^t \int_0^u \kappa_1(t-u)\,\kappa_1(t-v)\, M_{\widetilde{W}(u)}(2c)\, M_{\widetilde{W}(v)}(c)\, \mathrm{d}v\, \mathrm{d}u$$

$$= 2 \int_0^t \int_0^u \kappa_1(t-u)\,\kappa_1(t-v)\, e^{\frac{1}{2}(2c)^2(t-u)}\, e^{\frac{1}{2}c^2(u-v)}\, \mathrm{d}v\, \mathrm{d}u$$

$$= 2 \int_0^t \int_0^u \kappa_1(t-u)\,\kappa_1(t-v)\, e^{2c^2(t-u)}\, e^{\frac{1}{2}c^2(u-v)}\, \mathrm{d}v\, \mathrm{d}u$$

Substituting (13) in the above expression, it results

$$\mathbb{E}\big[I_1^2(t)\big] = 2 r_a^2 X_p^2 \int_0^t \int_0^u e^{r_e[2(u-t)+(v-u)]}\, e^{-c^2(u-t)}\, \mathrm{d}v\, \mathrm{d}u$$

$$= 2 r_a^2 X_p^2 \int_0^t \int_0^u e^{-2(r_e - \frac{1}{2}c^2)t}\, e^{(r_e - c^2)u}\, e^{r_e v}\, \mathrm{d}v\, \mathrm{d}u$$

$$= 2 r_a^2 X_p^2\, e^{-2(r_e - \frac{1}{2}c^2)t} \int_0^t e^{(r_e - c^2)u} \left(\int_0^u e^{r_e v}\, \mathrm{d}v \right) \mathrm{d}u \tag{21}$$

If $r_e \neq c^2$ and $r_e \neq c^2/2$ then

$$\mathbb{E}\big[I_1^2(t)\big] = 2 r_a^2 X_p^2\, e^{-2(r_e - \frac{1}{2}c^2)t} \int_0^t e^{(r_e - c^2)u} \left(\frac{e^{r_e v}}{r_e} \Big|_{v=0}^{v=u} \right) \mathrm{d}u$$

$$= 2 \frac{r_a^2 X_p^2}{r_e}\, e^{-2(r_e - \frac{1}{2}c^2)t} \int_0^t e^{(r_e - c^2)u} \left(e^{r_e u} - 1 \right) du$$

$$= \frac{2}{r_e} \frac{r_a^2 X_p^2}{2 r_e - c^2}\, e^{-2(r_e - \frac{1}{2}c^2)t} \left(e^{2(r_e - \frac{1}{2}c^2)t} - 1 \right)$$

$$\quad - \frac{2}{r_e} \frac{r_a^2 X_p^2}{r_e - c^2}\, e^{-2(r_e - \frac{1}{2}c^2)t} \left(e^{(r_e - c^2)t} - 1 \right)$$

$$= \frac{2}{r_e} \frac{r_a^2 X_p^2}{2 r_e - c^2} \left(1 - e^{-2(r_e - \frac{1}{2}c^2)t} \right) - \frac{2}{r_e} \frac{r_a^2 X_p^2}{r_e - c^2}\, e^{-r_e t} \left(1 - e^{-(r_e - c^2)t} \right). \tag{22}$$

To compute $\mathbb{E}\big[I_2^2(t)\big]$ of process is similar to previous one, then

$$\mathbb{E}\big[I_2^2(t)\big] = 2 r_a^2 \big(X_{a0} - X_p\big)^2\, e^{-2(r_e - \frac{1}{2}c^2)t} \int_0^t e^{(r_e - r_a - c^2)u} \left(\int_0^u e^{(r_e - r_a)v}\, \mathrm{d}v \right) \mathrm{d}u \tag{23}$$

If $r_e \neq r_a$ and $r_e \neq r_a + c^2$ then

$$\mathbb{E}\big[I_2^2(t)\big] = \frac{2 r_a^2}{r_a - r_e} \frac{(X_{a0} - X_p)^2}{2(r_a - r_e) + c^2} \left(e^{-2 r_a t} - e^{-2(r_e - \frac{1}{2}c^2)t} \right)$$

$$\quad - \frac{2 r_a^2}{r_a - r_e} \frac{(X_{a0} - X_p)^2}{r_a - r_e + c^2} \left(e^{-(r_e + r_a)t} - e^{-2(r_e - \frac{1}{2}c^2)t} \right). \tag{24}$$

By Fubini's Theorem we have that:

$$
\mathbb{E}\big[I_1(t)\,I_2(t)\big] = \mathbb{E}\left[\left(\int_0^t \kappa_1(t-u)e^{c(W(t)-W(u))}\,\mathrm{d}u\right)\left(\int_0^t \kappa_2(t-v)\,e^{c(W(t)-W(v))}\,\mathrm{d}v\right)\right]
$$

$$
= \int_0^t \int_0^t \kappa_1(t-u)\,\kappa_2(t-v)\,\mathbb{E}\Big[e^{c[2(W(t)-W(u))+(W(u)-W(v))]}\Big]\,\mathrm{d}v\,\mathrm{d}u
$$

$$
= \int_0^t \int_0^t \kappa_1(t-u)\,\kappa_2(t-v)\,M_{\widetilde{W}(u)}(2c)\,M_{\widetilde{W}(v)}(c)\,\mathrm{d}v\,\mathrm{d}u
$$

$$
= \int_0^t \int_0^t \kappa_1(t-u)\,\kappa_2(t-v)\,e^{2c^2(t-u)}\,e^{\frac{1}{2}c^2(u-v)}\,\mathrm{d}v\,\mathrm{d}u
$$

Substituting (13) in the above expression, it results

$$
\mathbb{E}\big[I_1(t)\,I_2(t)\big] = -\,r_a^2 X_p\big(X_{a0}-X_p\big)\int_0^t \int_0^t e^{-2(r_e-\frac{1}{2}c^2)t}\,e^{(r_e-c^2)u}\,e^{-(r_a-r_e)v}\,\mathrm{d}v\,\mathrm{d}u
$$

$$
= -\,\frac{r_a^2 X_p\big(X_{a0}-X_p\big)}{e^{2(r_e-\frac{1}{2}c^2)t}}\left(\int_0^t e^{(r_e-c^2)u}\,\mathrm{d}u\right)\left(\int_0^t e^{-(r_a-r_e)v}\,\mathrm{d}v\right) \tag{25}
$$

If $r_e \neq r_a$ and $r_e \neq c^2$ then

$$
\mathbb{E}\big[I_1(t)\,I_2(t)\big] = r_a^2 X_p\big(X_{a0}-X_p\big)\,e^{-2(r_e-\frac{1}{2}c^2)t}\left(\frac{e^{(r_e-c^2)v}}{r_e-c^2}\bigg|_{u=0}^{u=t}\right)\left(\frac{e^{-(r_a-r_e)v}}{r_a-r_e}\bigg|_{v=0}^{v=t}\right)
$$

$$
= \frac{r_a^2 X_p\big(X_{a0}-X_p\big)}{(r_a-r_e)(r_e-c^2)}\,e^{-2(r_e-\frac{1}{2}c^2)t}\left(e^{(r_e-c^2)t}-1\right)\left(e^{-(r_a-r_e)t}-1\right)
$$

$$
= \frac{r_a^2 X_p\big(X_{a0}-X_p\big)}{(r_a-r_e)(r_e-c^2)}\left(1-e^{-(r_e-c^2)t}\right)\left(e^{-r_a t}-e^{-r_e t}\right). \tag{26}
$$

Thus, from (15), (22), (24) and (26) we obtain

$$
\mathrm{Var}\big[X(t)\big] = \mathbb{E}\big[X^2(t)\big]-\big(\mathbb{E}\big[X(t)\big]\big)^2
$$

$$
= -\left(\frac{r_a(r_e X_{a0}-r_a X_p)}{r_e(r_e-r_a)}\right)^2 e^{-2rt}-\left(\frac{2c^2 r_a^2 X_p}{r_e^2}\right)\left(\frac{r_e X_{a0}-r_a X_p}{(r_e-r_a)(r_e-c^2)}\right)e^{-r_e t}
$$

$$
+\left(\frac{c^2 r_a^2(X_{a0}-X_p)^2}{(r_a-r_e)^2(2(r_e-r_a)-c^2)}\right)e^{-2r_a t}-\frac{2c^2 r_a^2 X_p(X_{a0}-X_p)}{r_e(r_a-r_e)(r_e-c^2)}e^{-r_a t}
$$

$$
-\frac{2r_a(X_{a0}-X_p)}{r_e(r_e-r_a)^2}\left(\frac{c^2(r_e X_{a0}-r_a X_p)-(r_e-r_a)^2 X_p}{r_e-r_a-c^2}\right)e^{-(r_e+r_a)t}
$$

$$
+\frac{2r_a^2 X_p(X_p-X_{a0})}{(r_e-r_a)(r_e-c^2)}e^{-(r_e+r_a-c^2)t}+\frac{c^2 r_a^2 X_p^2}{r_e^2(2r_e-c^2)}
$$

$$
+\left(\frac{2r_a^2(X_p-X_{a0})^2}{(r_e-r_a-c^2)(2(r_e-r_a)-c^2)}\right.
$$

$$
\left.+\frac{2r_a^2 X_p\big[(c^2-r_e-r_a)X_p+(2r_e-c^2)X_{a0}\big]}{(r_e-r_a)(r_e-c^2)(2r_e-c^2)}\right)e^{-2(r_e-\frac{1}{2}c^2)t}
$$

Since the parameters of the model can have the same values, from expressions (21), (23) and (25), we obtain the following cases for the variance:

1. If $r_e = r_a + \frac{c^2}{2}$ then

$$
\begin{aligned}
\mathrm{Var}\big[X(t)\big] = & \frac{8}{c^4} r_a^2 e^{-2r_a t} \left(X_p - X_{a0}\right)^2 \left(e^{-\frac{1}{2}c^2 t} - 1\right) - r_a X_p^2 \frac{e^{-2r_a t} - 1}{r_a + \frac{1}{2}c^2} \\
& - \left(r_a X_p \frac{e^{-(r_a + \frac{1}{2}c^2)t} - 1}{r_a + \frac{1}{2}c^2} - \frac{2}{c^2} r_a \left(X_p - X_{a0}\right)(e^{-\frac{1}{2}c^2 t} - 1) e^{-r_a t}\right)^2 \\
& + \frac{4t}{c^2} r_a^2 e^{-2r_a t} \left(X_p - X_{a0}\right)^2 + 2r_a^2 X_p^2 e^{-(r_a + \frac{1}{2}c^2)t} \frac{e^{-(r_a - \frac{1}{2}c^2)t} - 1}{\left(r_a - \frac{1}{2}c^2\right)\left(r_a + \frac{1}{2}c^2\right)} \\
& - \frac{4}{c^2} r_a^2 X_p \left(X_p - X_{a0}\right) e^{-r_a t} \left(e^{-\frac{1}{2}c^2 t} - 1\right) \frac{e^{-(r_a - \frac{1}{2}c^2)t} - 1}{r_a - \frac{1}{2}c^2}
\end{aligned}
$$

1. If $r_e = r_a + c^2$ then

$$
\begin{aligned}
\mathrm{Var}\big[X(t)\big] = & -\frac{2r_a^2 t}{c^2} \left(X_p - X_{a0}\right)^2 e^{-(2r_a + c^2)t} + 2r_a X_p^2 e^{-(r_a + c^2)t} \frac{e^{-r_a t} - 1}{r_a + c^2} \\
& - \left(\frac{r_a}{c^2} \left(X_p - X_{a0}\right)\left(e^{-(r_a + c^2)t} - e^{-r_a t}\right) - r_a X_p \frac{e^{-(r_a + c^2)t} - 1}{r_a + c^2}\right)^2 \\
& - \frac{2r_a^2}{c^4} \left(X_p - X_{a0}\right)^2 \left(e^{-c^2 t} - 1\right) e^{-2r_a t} - 2r_a^2 X_p^2 \frac{e^{-(2r_a + c^2)t} - 1}{\left(2r_a + c^2\right)\left(r_a + c^2\right)} \\
& - \frac{2r_a}{c^2} X_p \left(X_p - X_{a0}\right)\left(e^{-r_a t} - 1\right)\left(e^{-c^2 t} - 1\right) e^{-r_a t}
\end{aligned}
$$

1. If $r_e = \frac{c^2}{2}$ then

$$
\begin{aligned}
\mathrm{Var}\big[X(t)\big] = & r_a \left(X_p - X_{a0}\right)^2 \frac{e^{-2r_a t} - 1}{r_a - \frac{1}{2}c^2} - \frac{8}{c^4} r_a^2 X_p^2 e^{-\frac{1}{2}c^2 t} \left(e^{\frac{1}{2}c^2 t} - 1\right) \\
& - \left(r_a \left(X_p - X_{a0}\right) \frac{e^{-r_a t} - e^{-\frac{1}{2}c^2 t}}{r_a - \frac{1}{2}c^2} - \frac{2}{c^2} r_a X_p \left(e^{-\frac{1}{2}c^2 t} - 1\right)\right)^2 \\
& + \frac{4t}{c^2} r_a^2 X_p^2 - 2r_a^2 \left(X_p - X_{a0}\right)^2 \frac{e^{-(r_a + \frac{1}{2}c^2)t} - 1}{\left(r_a - \frac{1}{2}c^2\right)\left(r_a + \frac{1}{2}c^2\right)} \\
& + \frac{4}{c^2} r_a^2 X_p \left(X_p - X_{a0}\right) \frac{e^{-r_a t} - e^{-\frac{1}{2}c^2 t}}{r_a - \frac{1}{2}c^2} \left(e^{\frac{1}{2}c^2 t} - 1\right)
\end{aligned}
$$

1. If $r_e = c^2$ then

$$
\begin{aligned}
\mathrm{Var}\big[X(t)\big] =\, & 2r_a \frac{\left(X_p - X_{a0}\right)^2}{r_a - c^2} \left(e^{-c^2 t} - e^{-(r_a + c^2)t}\right) - \frac{2}{c^4} r_a^2 X_p^2 \left(e^{-c^2 t} - 1\right) \\
& - \left(\frac{1}{c^2} r_a X_p \left(e^{-c^2 t} - 1\right) + r_a \left(X_p - X_{a0}\right) \frac{e^{-c^2 t} - e^{-r_a t}}{r_a - c^2}\right)^2 \\
& - \frac{2t}{c^2} r_a^2 X_p^2 e^{-c^2 t} - 2r_a^2 \left(X_p - X_{a0}\right)^2 \frac{e^{-c^2 t} - e^{-2r_a t}}{\left(r_a - c^2\right)\left(2r_a - c^2\right)} \\
& - 2r_a^2 X_p t \left(X_p - X_{a0}\right) \frac{e^{-c^2 t} - e^{-r_a t}}{r_a - c^2}
\end{aligned}
$$

Modelo farmacocinético estocástico de un compartimento

Resumen: En este trabajo, consideramos un modelo farmacocinético (PK) con absorción de fármacos de primer orden y eliminación de primer orden que representa la concentración de fármacos en el cuerpo, incluyendo tanto la parte de absorción como la de eliminación, y también agregamos un factor aleatorio para describir la variabilidad entre los pacientes y el medio ambiente. Utilizando el lema de Itô y la transformada de Laplace, obtenemos las soluciones en forma integral para un régimen de dosificación único y constante en el tiempo. Además, se presentan fórmulas para el valor esperado y la varianza para cada caso de estudio, lo que permite evaluar estadísticamente los modelos propuestos, así como predecir la trayectoria ideal de concentración del fármaco y su incertidumbre. Estos resultados son importantes en el análisis a largo plazo de la ruta de concentración del fármaco y la persistencia del nivel terapéutico. Adicionalmente, se introduce y desarrolla un método numérico para la solución de la ecuación diferencial estocástica (SDE).

Palabras Clave: soluciones analíticas; lema de Itô; modelo PK; ecuaciones diferenciales estocásticas.

Modelo farmacocinético estocástico de um compartimento

Resumo: Neste trabalho, consideramos um modelo farmacocinético (PK) com absorção de drogas de primeira ordem e eliminação de primeira ordem que representa a concentração de drogas no corpo, incluindo as partes de absorção e eliminação, e também adicionamos um fator aleatório para descrever a variabilidade entre os pacientes e o ambiente. Utilizando o lema de Itô e a transformada de Laplace, obtemos as soluções na forma integral para um regime de dosagem único e constante no tempo. Além disso, são apresentadas fórmulas do valor esperado e da variância para cada caso de estudo, o que permite avaliar estatisticamente os modelos propostos, bem como prever a trajetória ideal de concentração do fármaco e sua incerteza. Esses resultados são importantes na análise a longo prazo da concentração da droga e da persistência do nível terapêutico. Adicionalmente, um método numérico para a solução da equação diferencial estocástica (SDE) é introduzido e desenvolvido.

Palavras-chave: soluções analíticas; lema de Itô; modelo PK; equações diferenciais estocásticas.

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