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Exact Solution of a Stochastic Differential Model for Repeated Dose Pharmacokinetics

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Abstract. This paper examines the dynamics of drug concentration in the body accounting for random factors like patient and environmental variability. We develop an explicit solution for drug concentration using a Stochastic Differential Equation (SDE) model. We calculate formulas for the expected value and variance, enabling statistical evaluation and prediction of the drug's concentration trajectory and its uncertainty. The unknown parameters in the model are estimated using the method of moments. We apply our proposed methods to a real-world dataset, providing useful insights analysis of drug concentration and the determination of its therapeutic range.

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1. Introduction

In the study and planning of effective and safe therapies in drug administration to a patient, the development of mathematical models that describe the time evolution of the absorption, distribution, metabolism and elimination of the drug plays a very important role. This area of knowledge is known as pharmacokinetics (PK).

In general, these phenomena are modeled by differential equations [16] and are based on the following assumptions:

a) The body as a whole is considered as a single compartment or a network of compartments that represent the different organs of the body where the drug is distributed, absorbed and degraded.
b) Drug input is instantaneous.
c) The distribution of the drug throughout the body is uniform and homogeneous.
d) The elimination of the drug is proportional to the amount of drug present in the body (i.e. a first-order process).

However, these models do not take into account that drug concentration levels vary among different patients according to their weight, age, stress or genetic factors [21] and [19].

Since these factors can not be explicitly incorporated into the models, some authors have used stochastic differential equations by grouping all of them in a random term. To model the concentration decay of a drug administered in a single dose and distributed instantaneously, Ramanathann [14] used a geometric Brownian motion (GBM), noting that this description gives insight into why drugs concentration are distributed log normally. Next, in [15] the same author proposed an in-homogeneous geometric Brownian motion (IGBM) for the study of continuous dosing; furthermore, in order to design drug therapeutic regimens, closed-form expressions for expected value and time-dependent variance are derived by solving the auxiliary differential moment equations.

On the other hand, to model continuous dosing. In [5], the intensity factor of the noise term is considered as a constant in the stochastic differential equations (SDE), leading to the Vasicek model [23]. Further, a maximum likelihood procedure is given to obtain the model parameter estimators constructed from observations. In [12] the Ornstein-Uhlenbeck process is used as the PK model with intravenous (IV) bolus dose for each individual and combine the First-Order Conditional Estimation (FOCE) method and the Extended Kalman Filter for model identification. In similar line of research, more complex compartments models in which drug elimination or absorption over time have been considered, for example in: [3], [5], [10], [13], [17] and [22]. Most of these works do not consider a state-dependent noise term in the SDE model and parameter estimators are obtained by maximizing the likelihood [4].

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In this paper, we propose a one compartment model based on SDE that takes into account the variability among individuals under a multiple doses regimen, which has not been considered in the literature. In this respect, the results presented here complements works of [14] and [15] for a one compartment model under a single dose regimen and a constant dose, both models will be revisited for the sake of completeness. From a mathematical point of view, these models correspond to an autonomous linear SDE whose solutions are well known and are obtained by the parameter variation formula (See [9] and [20]). However, when we analyze the case of multiple doses, the source term in our model is a piecewise continuous function of exponential order for $t > 0$, so we use a combination of the Laplace transform and Itô calculus to obtain the exact solution. Furthermore, the exact solution allows us to deduce closed-form expressions for the expected value and variance, that are very useful in establishing the therapeutic range of a drug, as well as, to estimate model parameters from empirical data. The advantage of the proposed models is that they can be statistically validated and offer the possibility not only of predicting the realistic trajectory of the drug concentration but also the uncertainty of prediction.

The paper is organized as follows: In Section 2, we present the exact solutions of SDE model. In Section 3, we used the obtained exact general solution to analyze the drug concentration under some specifics dosage regimens (constant dosage, unique dosage and repeated doses), also, we determine expressions for the expected value and variance for each regimen. The adjustment methodology of our proposed model to real data via the method of moments and numerical simulation are shown in Section 4. In Section 5, we present some conclusions and finally, in the appendices we show the deduction details of closed formulas for the expected value and variance for each case of study instead of solving the corresponding moment equations and avoiding the use of simulations.

2. Mathematical model and general solution

Based on the assumptions described in the introduction, we consider the following stochastic differential equation (SDE)

$$\begin{cases} dX(t) = \big(-rX(t) + f(t)\big)\,dt + cX(t)\,dW(t) \\ \text{s.t.} \quad X(0) = X_0, \end{cases} \tag{2.1}$$

where $X(t)$ represents the drug concentration in the body at time t, r the mean rate at which the drug is removed from the body, $W(t)$ is the Brownian motion, $cX(t)\,dW(t)/dt$ random fluctuations of the concentration due to the environmental variation, the positive constant c is the diffusion coefficient, X_0 is the initial dose of drug which depends of the body mass index (BMI) and $f(t)$

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the dosage regimen of the drug per unit of time, we will consider the following three cases:

C1. Single dose: $f(t) = 0$.

C2. Constant dosage: $f(t) = rX_p$, with X_p positive constant.

C3. Repeated dose: $f(t) = X_0 \sum_{k=1}^{n} \delta(t - k\tau)$, where the drug is provided every τ hours and $\delta(\cdot)$ is the Dirac's delta "function".

Since the source function $f(t)$ is continuous or piecewise continuous for $t > 0$ and of exponential order γ, we employ Laplace transform to solve in general way the equation (2.1). Another approach to solve the SDE (2.1) can be found in [9].

Theorem 2.1. *Let be the SDE* (2.1) *for some $f(t)$ continuous and of exponential order. The solution to this SDE that satisfies the initial condition is given by*

$$X(t) = X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + e^{-\frac{1}{2}c^2t+cW(t)}\, \mathcal{L}^{-1}\left\{ \frac{1}{s+r} \int_0^{\infty} e^{-(s-\frac{1}{2}c^2)u}\, e^{-cW(u)} f(u)\, du \right\}, \quad (2.2)$$

where $\mathcal{L}^{-1}$ is the inverse Laplace transform operator and s is the Laplace transform parameter.

Proof. To determine the solution to problem (2.1), we use the integration factor method (see [7]) as follows:

(1) We solve the non-deterministic part of equation (2.1). That is,

$$\begin{aligned} dX(t) &= cX(t)\, dW(t) \quad (2.3)\\ \frac{dX(t)}{X(t)} &= c\, dW(t)\\ d\big[\ln X(t)\big] &= c\, dW(t). \end{aligned}$$

Applying Itô formula [11] with $F(X,t) = \ln(X)$ it follows that

$$dF(X,t) = F_t\, dt + F_X\, dX + \frac{1}{2} F_{XX}\, (dX)^2, \quad (2.4)$$

where

$$F_t = 0,\ F_X = \frac{1}{X(t)},\ F_{XX} = -\frac{1}{X(t)^2}. \quad (2.5)$$

By substituting (2.5) into (2.4), we get

$$\begin{aligned} dF &= \frac{1}{X(t)}\big(cX(t)\, dW(t)\big) + \frac{1}{2}\left(-\frac{1}{X^2(t)}\right)\big(cX(t)\, dW(t)\big)^2\\ &= c\, dW(t) - \frac{1}{2}c^2\, dt. \quad (2.6) \end{aligned}$$

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Integrating (2.6) with respect to t, results

$$F(X,t) = A - \frac{1}{2}c^2 t + cW(t).$$

Thus,

$$X(t) = Ke^{-\frac{1}{2}c^2 t + cW(t)}. \tag{2.7}$$

(2) Applying the method of variation of parameters, we make the constant K of the non-deterministic solution (2.7) vary as a function of time, so $X(t)$ is of the form

$$X(t) = K(t)e^{-\frac{1}{2}c^2 t + cW(t)} = K(t)G(t), \tag{2.8}$$

where $G(t)$ satisfies equation (2.3). Then,

$$dX(t) = d\big[K(t)G(t)\big]$$
$$\big(-rX(t) + f(t)\big)\,dt + cX(t)\,dW(t) = G(t)\,dK(t) + K(t)\,dG(t).$$

By substituting (2.8) in the above equation, we have

$$\big(-rK(t)G(t) + f(t)\big)\,dt + cK(t)G(t)\,dW(t) = G(t)\big[dK(t) + cK(t)\,dW(t)\big].$$

In this way, we get the following initial value problem

$$\begin{cases} \dfrac{dK(t)}{dt} + rK(t) = \dfrac{f(t)}{G(t)} \\ \text{s.t.} \quad K(0) = X_0. \end{cases} \tag{2.9}$$

Therefore, to solve the initial value problem (2.9) we use the Laplace transform, then

$$\mathcal{L}\left\{\frac{dK(t)}{dt}\right\} + r\mathcal{L}\{K(t)\} = \mathcal{L}\left\{\frac{f(t)}{G(t)}\right\}$$
$$s\mathbb{K}(s) - K(0) + r\mathbb{K}(s) = \int_0^\infty e^{-(s-\frac{1}{2}c^2)t}\, e^{-cW(t)} f(t)\,dt$$
$$(s+r)\mathbb{K}(s) = X_0 + \int_0^\infty e^{-(s-\frac{1}{2}c^2)t}\, e^{-cW(t)} f(t)\,dt$$
$$\mathbb{K}(s) = \frac{X_0}{s+r} + \frac{1}{s+r}\int_0^\infty e^{-(s-\frac{1}{2}c^2)t}\, e^{-cW(t)} f(t)\,dt.$$

Applying Laplace inverse transform,

$$K(t) = X_0\, e^{-rt} + \mathcal{L}^{-1}\left\{\frac{1}{s+r}\int_0^\infty e^{-(s-\frac{1}{2}c^2)t}\, e^{-cW(t)} f(t)\,dt\right\}. \tag{2.10}$$

By substituting (2.10) into (2.8), finally we obtain the general solution of equation (2.1)

$$X(t) = X_0\, e^{-(r+\frac{1}{2}c^2)t + cW(t)}$$
$$+ e^{-\frac{1}{2}c^2 t + cW(t)}\,\mathcal{L}^{-1}\left\{\frac{1}{s+r}\int_0^\infty e^{-(s-\frac{1}{2}c^2)u}\, e^{-cW(u)} f(u)\,du\right\},$$

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where u is a dummy variable. That's what we wanted to prove. □

Remark 2.2. Observe that the integral (2.2) can not be computed explicitly due to the Brownian Motion in some cases. For example, when $f(t) = rX_p$ we need to evaluate $X(t)$ numerically, as we can see in section 4.1.

3. Dosage regimens

In this section, we analyze the behavior of the drug concentration in the body under the three different dosage regimens presented in the introduction.

3.1. **Constant dosage of the drug.**

Some chronic diseases treatments require the administration of a drug for extended periods of time, for this, a constant amount of the drug is supplied continuously. Examples of this type of administration are: intravenous infusion, certain oral formulations based on the phenomenon of osmosis and certain transdermal patches.

Theorem 3.1. *Let the source function $f(t) = rX_p$ be such that X_p is a positive constant and represents the concentration of the drug that is administered at all time $t > 0$. Then the concentration of the drug is given by*

$$X(t) = a(t)\, e^{cW(t)} + \int_0^t \kappa(t-u)\, e^{c(W(t)-W(u))}\, du, \tag{3.1}$$

where

$$a(t) := X_0\, e^{-(r+\frac{1}{2}c^2)t}, \tag{3.2}$$

and

$$\kappa(t-u) := rX_p\, e^{-(r+\frac{1}{2}c^2)(t-u)}. \tag{3.3}$$

Proof. Replacing $f(t)$ in (2.2) we get

$$\begin{aligned} X(t) =& X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + \mathcal{L}^{-1}\left\{\frac{rX_p}{s+r}\int_0^\infty e^{-(s-\frac{1}{2}c^2)u}\, e^{-cW(u)}\, e^{-\frac{1}{2}c^2t+cW(t)}\, du\right\} \\ =& X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + \mathcal{L}^{-1}\left\{\frac{rX_p}{s+r}\int_0^\infty e^{-su}\, e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\, du\right\}, \end{aligned}$$

applying theorem of convolution, we get

$$\begin{aligned} X(t) =& X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + rX_p\left\{e^{-rt} * e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\right\} \\ =& X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + rX_p\int_0^t e^{-r(t-u)}\, e^{-\frac{1}{2}c^2(t-u)}\, e^{c(W(t)-W(u))}\, du \\ =& X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + rX_p\int_0^t e^{-(r+\frac{1}{2}c^2)(t-u)}\, e^{c(W(t)-W(u))}\, du \\ =& X_0\, e^{-(r+\frac{1}{2}c^2)t+cW(t)} + \int_0^t rX_p\, e^{-(r+\frac{1}{2}c^2)(t-u)}\, e^{c(W(t)-W(u))}\, du. \end{aligned}$$

Finally, we obtain

$$X(t) = a(t)\, e^{cW(t)} + \int_0^t \kappa(t-u)\, e^{c(W(t)-W(u))}\, du,$$

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where $a(t-u)$ and $\kappa(t-u)$ are given in (3.2) and (3.3). □

If $X_p = 0$ in equation (3.3), we obtain the following result.

Corollary 3.2. ***Single dose administration*** *If $X_p = 0$, i.e, $f(t) = 0$ and the dose is supplied at the initial time ($t = 0$). From equation (3.1) the concentration is given by*

$$X(t) = X_0\, e^{-(r+\frac{1}{2}c^2)t} e^{cW(t)}. \tag{3.4}$$

Proof. The corollary is an immediate consequence of the theorem. □

3.1.1. *Expected value and variance.* In this section we determine the mean and variance of the process given by (3.1).

Proposition 3.3. *The expected value and variance of the stochastic process $X(t)$ are defined as*

$$\mathbb{E}\big[X(t)\big] = X_p - (X_p - X_0)\, e^{-rt}, \tag{3.5}$$

and

$$\begin{aligned} Var\big[X(t)\big] = \big(X_p - X_0\big)^2 e^{-2rt}\big(e^{c^2 t} - 1\big) + \frac{c^2 X_p^2}{c^2 - 2r}\big(e^{(c^2-2r)t} - 1\big) \\ - \frac{2c^2 X_p}{c^2 - r}\big(X_p - X_0\big)e^{-rt}\big(e^{(c^2-r)t} - 1\big). \end{aligned} \tag{3.6}$$

Proof. To determine the expected value of (3.1), is it necessary to determine first $a(t)\, e^{cW(t)}$ by using the fact that $\mathbb{E}\big[e^{cW(t)}\big]$ is the moment-generating function $M_{W(t)}(c)$ of the random variable $W(t)$. By doing that we get

$$\begin{aligned} \mathbb{E}\big[a(t)\, e^{cW(t)}\big] &= X_0\, e^{-(r+\frac{1}{2}c^2)t}\mathbb{E}\left[e^{cW(t)}\right] = X_0\, e^{-(r+\frac{1}{2}c^2)t} M_{W(t)}(c) \\ &= X_0\, e^{-(r+\frac{1}{2}c^2)t}\, e^{\frac{1}{2}c^2 t} = X_0\, e^{-rt}. \end{aligned} \tag{3.7}$$

Similarly, the variance of $X(t)$, is given by

$$\begin{aligned} Var\big[a(t)\, e^{cW(t)}\big] &= \mathbb{E}\big[a^2(t)\, e^{2cW(t)}\big] - \big(\mathbb{E}\big[a(t)\, e^{cW(t)}\big]\big)^2 \\ &= \mathbb{E}\left[X_0^2\, e^{-2(r+\frac{1}{2}c^2)t + 2cW(t)}\right] - X_0^2\, e^{-2rt} \\ &= X_0^2\, e^{-2(r+\frac{1}{2}c^2)t}\mathbb{E}\big[e^{2cW(t)}\big] - X_0^2\, e^{-2rt} \\ &= X_0^2\, e^{-2(r+\frac{1}{2}c^2)t} M_{W(t)}(2c) - X_0^2\, e^{-2rt} \\ &= X_0^2\, e^{-2(r+\frac{1}{2}c^2)t} e^{2c^2 t} - X_0^2\, e^{-2rt} \\ &= X_0^2\, e^{-2rt}\big(e^{c^2 t} - 1\big). \end{aligned} \tag{3.8}$$

It is well-known that, if $S \sim N(0,t)$, then its moment-generating function is $\mathbb{E}\left[e^{cS}\right] = e^{\frac{1}{2}c^2 t}$. Therefore, since $W(t) - W(u) \sim N(0, t-u)$ and $e^{c(W(t)-W(u))}$ is a log-normal distribution, it follows that

$$\mathbb{E}\big[e^{c(W(t)-W(u))}\big] = e^{\frac{1}{2}c^2(t-u)}$$

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$$Var\big[e^{c(W(t)-W(u))}\big] = e^{c^2(t-u)}\big(e^{c^2(t-u)}-1\big).$$

Then, the expected value of $X(t)$ in (3.1) is given by

$$\begin{aligned}\mathbb{E}\big[X(t)\big] &= a(t)\,\mathbb{E}\big[e^{cW(t)}\big] + \int_0^t \kappa(t-u)\,\mathbb{E}\big[e^{c(W(t)-W(u))}\big]\,du \\ &= a(t)\,e^{\frac{1}{2}c^2t} + \int_0^t \kappa(t-u)\,e^{\frac{1}{2}c^2(t-u)}\,du \\ &= X_0e^{-rt} + rX_p\left(\frac{e^{-r(t-u)}}{r}\Big|_{u=0}^{u=t}\right) \\ &= X_0e^{-rt} + X_p\big(1-e^{-rt}\big) = X_p - \big(X_p - X_0\big)e^{-rt},\end{aligned}$$

and the variance is given by

$$\begin{aligned}Var\big[X(t)\big] =& \left(X_0^2 + \frac{2rX_p\big(X_p-X_0\big)}{r-c^2} - \frac{2rX_p^2}{2r-c^2}\right)e^{-2(r-\frac{1}{2}c^2)t} + \frac{c^2X_p^2}{2r-c^2} \\ &- \frac{2c^2}{r}\frac{rX_p}{r-c^2}\big(X_p-X_0\big)e^{-rt} - \big(X_p-X_0\big)^2e^{-2rt}.\end{aligned} \tag{3.9}$$

We obtain the formula (3.9) from the mathematical definition of the variance, in contrast to the method of differential equations of moments employed in [14]. Details of our calculation of $Var\big[X(t)\big]$ can be seen in appendix A. □

Remark 3.4. Note that expression (3.7) coincides with the solution of (2.1) in the absence of the stochastic term and $f(t) = 0$. In addition, the uncertain measure that the drug can produce a desired pharmacological effect in most patients with the minimum effective concentration X_0, at any given time t is

$$\begin{aligned}P(X_t > X_0) =& P\big(X_0\,e^{-(r+\frac{1}{2}c^2)t}e^{cW(t)} > X_0\big) = P\big(e^{cW(t)} > e^{(r+\frac{1}{2}c^2)t}\big) \\ =& P\left(cW(t) > \left(r+\frac{1}{2}c^2\right)t\right) = P\left(\frac{W(t)}{\sqrt{t}} > \frac{\sqrt{t}}{c}\left(r+\frac{1}{2}c^2\right)\right) \\ =& 1-\Phi\left(\left(\frac{r}{c}+\frac{c}{2}\right)\sqrt{t}\right)\end{aligned}$$

where $\Phi(.)$ is the cumulative distribution function of the standard normal distribution.

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 (3.5) and (3.6) 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

$$X_{\min} \le X_p - 2\,\sigma_{X(t)} \le X(t) \le X_p + 2\,\sigma_{X(t)} \le X_{\max},$$

where $\sigma_{X(t)} = \dfrac{cX_p}{\sqrt{2r-c^2}}$ when $t \to \infty$.

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3.2. **Repeated doses administration.** We consider the case when the drug is administered periodically. That is, the first dose is made at time $t = 0$, the drug is taken repeatedly every τ units of time. Then, if $t = n\tau$ there have been provided $n + 1$ drug doses. The following results state what is the drug concentration at time t.

Theorem 3.6. *Let define the source function in* (2.1) *as follows*

$$f(t) = X_0 \sum_{k=1}^{n} \delta(t - k\tau), \tag{3.10}$$

where n is the number of periods and $\delta(\cdot)$ is the Dirac's delta "function". Then the concentration is given by

$$X(t) = X_0 \left(e^{-(r+\frac{1}{2}c^2)t+cW(t)} + \sum_{k=1}^{n} e^{-\left(r+\frac{1}{2}c^2\right)(t-k\tau)+c(W(t)-W(k\tau))}\, U_{k\tau}(t) \right) \tag{3.11}$$

where U is the step function ($U_{k\tau}(t) = 1$ for $t \geq k\tau$ and $U_{k\tau}(t) = 0$ for $t < k\tau$).

Proof. Substituting (3.10) into (2.10), we get

$$K(t) = X_0 e^{-rt} + \mathcal{L}^{-1}\left\{ \frac{\mathbb{H}(s)}{s+r} \right\}, \tag{3.12}$$

where

$$\begin{aligned} \mathbb{H}(s) &= \int_0^\infty e^{-st} \Big(X_0 \sum_{k=1}^{n} \delta(t - k\tau) \Big) e^{\frac{1}{2}c^2 t - cW(t)}\, dt \\ &= X_0 \sum_{k=1}^{n} \int_0^\infty e^{-(s-\frac{1}{2}c^2)t} \delta(t - k\tau)\, e^{-cW(t)}\, dt \\ &= X_0 \sum_{k=1}^{n} e^{-(s-\frac{1}{2}c^2)k\tau - cW(k\tau)}. \end{aligned} \tag{3.13}$$

Substituting (3.13) into (3.12), we have

$$\begin{aligned} K(t) &= X_0 \left(e^{-rt} + \sum_{k=1}^{n} e^{\frac{1}{2}c^2 k\tau - cW(k\tau)}\, \mathcal{L}^{-1}\left\{ \frac{e^{-sk\tau}}{s+r} \right\} \right) \\ &= X_0 \left(e^{-rt} + \sum_{k=1}^{n} e^{\frac{1}{2}c^2 k\tau - cW(k\tau)}\, e^{-r(t-k\tau)} U_{k\tau}(t) \right), \; t \geq k\tau. \end{aligned} \tag{3.14}$$

Therefore, from (2.2) and (3.14), we obtain that the concentration of the drug after $n + 1$ doses is

$$X(t) = X_0 \left(e^{-(r+\frac{1}{2}c^2)t+cW(t)} + \sum_{k=1}^{n} e^{-\left(r+\frac{1}{2}c^2\right)(t-k\tau)+c(W(t)-W(k\tau))}\, U_{k\tau}(t) \right).$$

□

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3.2.1. *Expected value and variance.* Now, we find the mean and variance for the stochastic process given in (3.11).

Proposition 3.7. *The expected value and variance of the stochastic process* $X(t)$ *in* (3.11) *are defined as*

$$\mathbb{E}\big[X(t)\big] = X_0 e^{-rt} + X_0 e^{-rt} \sum_{k=1}^{n} e^{rk\tau}\, U_{k\tau}(t), \tag{3.15}$$

and its variance

$$\begin{aligned} Var\big[X(t)\big] = X_0^2 \Bigg\{ & e^{-2rt}\big(e^{c^2 t} - 1\big) \\ & + e^{-2(r-\frac{1}{2}c^2)t} \Bigg(\sum_{k=1}^{n} \Big(2e^{(r-c^2)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau} - e^{-c^2 t}\big(2e^{rk\tau} + e^{2rk\tau}\big) \Big)\, U_{k\tau}(t) \\ & + 2\sum_{l=2}^{n} e^{rl\tau} \Bigg(\frac{e^{(r-c^2)(l-1)\tau} - 1}{1 - e^{-(r-c^2)\tau}} - e^{-c^2 t} \Big[\frac{e^{r(l-1)\tau} - 1}{1 - e^{-r\tau}} \Big] \Big)\, U_{l\tau}(t) \Bigg) \Bigg\}. \end{aligned} \tag{3.16}$$

Proof. In this case, the expected value turns out to be

$$\begin{aligned} \mathbb{E}\big[X(t)\big] &= \mathbb{E}\Big[X_0 \Big(e^{-(r+\frac{1}{2}c^2)t + cW(t)} + \sum_{k=1}^{n} e^{-(r+\frac{1}{2}c^2)(t-k\tau) + c(W(t)-W(k\tau))}\, U_{k\tau}(t) \Big) \Big] \\ &= X_0 \Big(e^{-(r+\frac{1}{2}c^2)t} \mathbb{E}\Big[e^{cW(t)}\Big] + \sum_{k=1}^{n} e^{-(r+\frac{1}{2}c^2)(t-k\tau)} \mathbb{E}\Big[e^{c(W(t)-W(k\tau))}\Big]\, U_{k\tau}(t) \Big) \\ &= X_0 \Big(e^{-(r+\frac{1}{2}c^2)t} e^{\frac{1}{2}c^2 t} + \sum_{k=1}^{n} e^{-(r+\frac{1}{2}c^2)(t-k\tau)} e^{\frac{1}{2}c^2(t-k\tau)}\, U_{k\tau}(t) \Big) \\ &= X_0 \Big(e^{-rt} + \sum_{k=1}^{n} e^{-r(t-k\tau)}\, U_{k\tau}(t) \Big) = X_0 e^{-rt} + X_0 e^{-rt} \sum_{k=1}^{n} e^{rk\tau}\, U_{k\tau}(t). \end{aligned}$$

Derivation details of the variance (3.16) can be found in appendix B. □

Remark 3.8. Note that the first term in (3.15) shows the transient effect of the first dose and the second term indicates the persistent behaviour of the drug concentration.

3.3. **Long-term drug concentration.** Now, we consider the case when the patient receive n doses of the drug and we are interested to determine the long-term drug concentration in the body.

Proposition 3.9. *Let* $X(t)$ *be a stochastic process defined by* (3.11) *and* $t = n\tau$ *with* $n \in \mathbb{N}$*, then*

$$\lim_{n\to\infty} \mathbb{E}\big[X(n\tau)\big] = \frac{X_0}{1 - e^{-r\tau}}, \tag{3.17}$$

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and

$$\lim_{n\to\infty} Var\big[X(n\tau)\big] = X_0^2\left[\frac{1}{1-e^{-2(r-\frac{1}{2}c^2)\tau}} - \frac{1+e^{-r\tau}}{(1-e^{-r\tau})(1-e^{-2r\tau})} + \frac{2\,e^{-(r-c^2)\tau}}{(1-e^{-(r-c^2)\tau})(1-e^{-2(r-\frac{1}{2}c^2)\tau})}\right]. \tag{3.18}$$

Proof. To determine the concentration of the drug in the body when the number of doses is large enough, we first assume that $n\tau \le t < (n+1)\tau$. From (3.15) and (3.16) we get

$$\mathbb{E}\big[X(t)\big] = X_0 e^{-rt}\left(1+\sum_{k=1}^{n}(e^{r\tau})^k\right) = X_0 e^{-rt}\left(1+\frac{e^{rn\tau}-1}{1-e^{-r\tau}}\right)$$

and substituting $t = n\tau$ and making $n\to\infty$ in this expression we obtain (3.17). Now

$$\begin{aligned} Var\big[X(t)\big] =& X_0^2\Bigg\{e^{-2rt}\big(e^{c^2t}-1\big) + e^{-2(r-\frac{1}{2}c^2)t}\Bigg(2\left[\frac{e^{(r-c^2)n\tau}-1}{1-e^{-(r-c^2)\tau}}\right] \\ &+ \left[\frac{e^{2(r-\frac{1}{2}c^2)n\tau}-1}{1-e^{-2(r-\frac{1}{2}c^2)\tau}}\right] - e^{-c^2t}\left(2\left[\frac{e^{rn\tau}-1}{1-e^{-r\tau}}\right] + \left[\frac{e^{2rn\tau}-1}{1-e^{-2r\tau}}\right]\right) \\ &+ \Big(\frac{2\,e^{r\tau}}{1-e^{-(r-c^2)\tau}}\Big)\left[\frac{e^{2(r-\frac{1}{2}c^2)(n-1)\tau}-1}{1-e^{-2(r-\frac{1}{2}c^2)\tau}} - \frac{e^{r(n-1)\tau}-1}{1-e^{-r\tau}}\right] \\ &- \Big(\frac{2\,e^{r\tau-c^2t}}{1-e^{-r\tau}}\Big)\left[\frac{e^{2r(n-1)\tau}-1}{1-e^{-2r\tau}} - \frac{e^{r(n-1)\tau}-1}{1-e^{-r\tau}}\right]\Bigg)\Bigg\}. \end{aligned}$$

Again substituting $t = n\tau$ we take $n\to\infty$ to obtain (3.18). □

Remark 3.10. If the duration of treatment with multiple doses is prolonged, from expressions (3.17) and (3.18), it follows that the therapeutic range of the drug must satisfy

$$X_{\min} \le \lim_{n\to\infty}\big(\mathbb{E}\big[X(n\tau)\big] - 2\sigma_{X(n\tau)}\big) \le X(t) \le \lim_{n\to\infty}\big(\mathbb{E}\big[X(n\tau)\big] + 2\sigma_{X(n\tau)}\big) \le X_{\max}$$

where $\sigma_{X(n\tau)} = \sqrt{Var[X(n\tau)]}$.

4. Fitting an experimental data and simulations

In this section, we consider several empirical real data of drug concentrations to identify the parameters of the model for different drug regimens. Once we found them, we use these to perform some simulations to demonstrate the usefulness of our approach.

For each regimen of drug administration, the identification problem is solved by the method of moments. First, we compute the average mean $m(t)$ and variance $v(t)$ over all individuals from the real drug concentration data. Then, we estimate r and c by solving the following minimization problems

$$\min_{0<r<1} \|m(t) - \mathbb{E}[X(t)]\|_2 \qquad \text{and} \qquad \min_{c\in\mathbb{R}^+} \|v(t) - Var[X(t)]\|_2 . \tag{4.1}$$

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Where, $\mathbb{E}[X(t)]$ is the expected value and $Var[X(t)]$ is the variance of the drug concentration obtained in section 3. We solve the minimization problems using an optimization MATLAB lsqnonlin routine.

4.1. **Numerical approximation.** Due to the Brownian motion in formula (3.1), it can not be computed explicitly, then we approximate this solution numerically. Let us denote by $\alpha := r + \frac{1}{2}c^2$, $g(t) := X_0 e^{-\alpha t + cw(t)}$ and $h(t) := rX_p e^{-\alpha t + cw(t)}$, then the solution (3.1) can be written as follows:

$$X(t) = g(t) + h(t) \int_0^t e^{\alpha u} e^{-cw(u)} du. \tag{4.2}$$

In order to evaluate $X(t)$, 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 $t_i = i\Delta t, i = 0, ..., N$. Next, we discretize the Brownian 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

$$X(t_k) = g(t_k) + \frac{h(t_k)}{\Delta t} \sum_{i=1}^{k} \left[e^{-cw(t_{i-1})} \int_{t_{i-1}}^{t_i} e^{\alpha u}(t_i - u) du \right.$$
$$\left. + e^{-cw(t_i)} \int_{t_{i-1}}^{t_i} e^{\alpha u}(u - t_{i-1}) du \right] \tag{4.3}$$

where $X(t_0) = X(0) = 0$ and the integrals are computed exactly. This formula has the same order that the composite trapezoidal rule $\mathcal{O}(\Delta t^2)$.

4.2. **Single dosage 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 [1] and its time series graphs are shown in Figure 1a. Since the one compartment model (2.1) assumes that the drug distribution is instantaneous and its elimination is of first-order, we only consider the data on the elimination phase to identify the parameters r and c (see fig. 1a). We found that elimination rate and coefficient of variation are $r = 0.0776$ and $c = 0.1004$ respectively. Figure 1b shows a simulation of the drug concentration decay. As we can observe, computational simulations are consistent with the experimental measurements.

4.3. **Constant dosage 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 [18]. By solving the corresponding minimization problems given in (4.1), we find that $r = 0.3975$ and $c = 0.2609$. From figure 2a we see that the average mean of data (red curve) almost coincides with the expected value (blue curve). Furthermore, the experimental data lie within a band around the expected value

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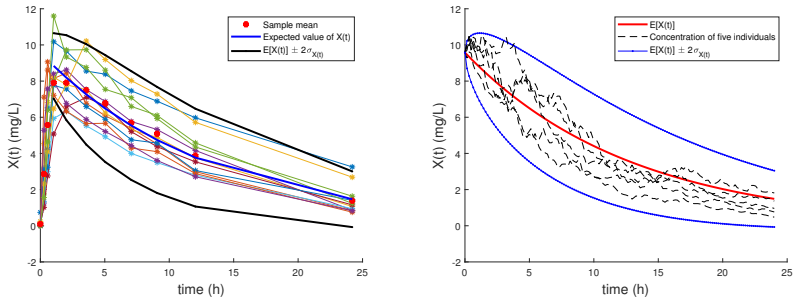
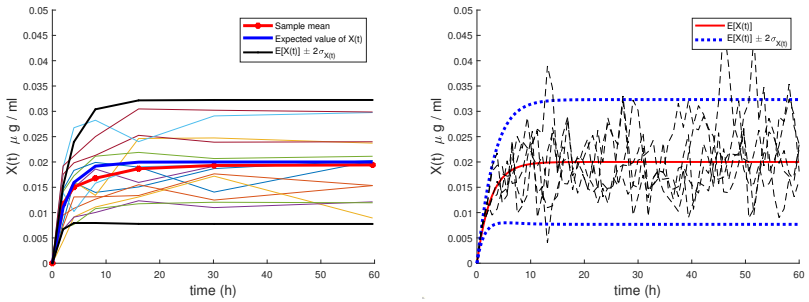


(a) (b)

FIGURE 1. (a) Experimental data of the Theophylline concentrations (b) Simulation of the decay of the Theophylline concentration after the administration of a single dose. Five sample paths, expected value of the process (2.1) and the graphs of $\mathbb{E}\big[X(t)\big] \pm 2\sigma_{X(t)}$. $X_0 = 9.5788, r = 0.0776$, $c = 0.1004, f(t) = 0$.

with a width of two standard deviations. Figure 2b illustrates a simulation of the drug concentration in five individuals when the dosage is constant. Here, solution of the differential equation (2.1) with $f(t) = rX_p$, was evaluated by the numerical approximation (4.3).



(a) (b)

FIGURE 2. (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 (2.1) and the graphs of $\mathbb{E}\big[X(t)\big] \pm 2\sigma_{X(t)}, X_0 = 0, X_p = 0.02, r = 0.3975, c = 0.2609$.

4.4. **Repeated doses administration.** We will consider the concentration X(t) in (3.11) for multiple dosage. We use experimental data of Meclizine hydrochloride [8], here a 25 mg tablet is administered orally to 6 subjects twice a day every 10 hours. Recall that in (3.11), we assume that the elimination

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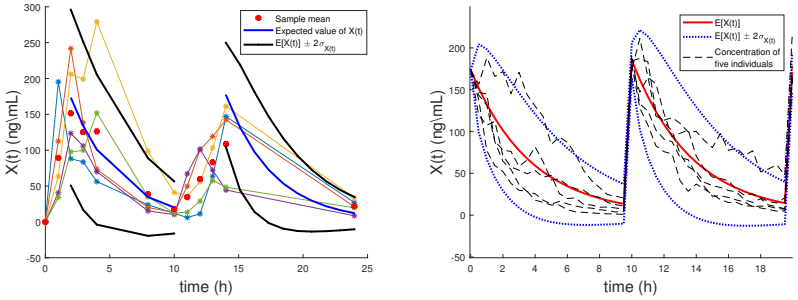
rate r and the coefficient of variation c are the same every time the drug is administrated, then, to estimate X_0, r and c, we only use the given data for the first dosage period and the expectation value (3.15) and the variance (3.16). The parameters values obtained were $X_0 = 173.4344, r = 0.2686$ and $c = 0.2443$.



(a) (b)

FIGURE 3. (a) Experimental data of the Meclizine concentrations (b) Accumulation of the drug concentration after administration of 2 doses every 10 hours. Five sample paths, expected value of the process (2.1) and the graphs of $\mathbb{E}\big[X(t)\big] \pm 2\sigma_{X(t)}$, $X_0 = 173.4344, r = 0.2686, c = 0.2443$.

We observe that the concentration curves of our model (fig. 3b) have similar behavior to the concentration curves representing real data (fig. 3a). The shift to the left (about 4 hours) of simulated curves is due to the assumption that the drug is distributed instantly throughout the body at the time the dose is administrated (i.e every 10 hours). However, equation (3.11) may be used to ensure an exposure to the drug within the therapeutic range over a prolonged time.

5. Conclusions

- We propose a SDE model for the concentration of a drug under a multiple dosage regimens not previously considered in the literature.
- We studied three models based on SDE that describe three dosage regimens and that consider the variability of both the patient and the environment that are generally ignored in deterministic models.
- We obtained explicit formulas for the concentration of the drug, its expected value and the variance. They allow to:
  i) Predict the realistic path of the solution and the uncertainty of the prediction.
  ii) Formulate the therapeutic range of the drug in each dosage regimen.

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iii) Easily calculate the parameters of the models from observed data.

- From the real study cases, we observe that the concentration curves of our model have similar behavior to the concentration curves representing real data. Moreover the experimental data lie within a band around the expected value with a width of two standard deviations, which is very important to establish an effective and safe treatment of the drug administration. It is noteworthy that the model presented here assumes that the drug is rapidly mixes with the blood supply and produces a high concentration of the drug every where in the blood. However, the absorption phenomena in the tissues was not considered, the inclusion of such phenomena implies to pose a system of SDE that will be study in a future work.

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Appendix A. Calculation of variance for a constant dose

From the equation (3.1) we get

$$\mathbb{E}\big[X^2(t)\big] = \mathbb{E}\big[I^2(t)\big] + 2\mathbb{E}\big[a(t)\, e^{cW(t)} I(t)\big] + \mathbb{E}\big[a^2(t)\, e^{2cW(t)}\big],$$

where

$$I(t) := \int_0^t \kappa(t-u)\, e^{c(W(t)-W(u))}\, du$$

and $a(t)$, $\kappa(t-u)$ are given by the equations (3.2) and (3.3) respectively. Using the identity (see [2])

$$n \int_0^t h(u) \left(\int_0^u h(v)\, \mathrm{d}v \right)^{n-1} \mathrm{d}u = \left(\int_0^t h(v)\, \mathrm{d}v \right)^n, \tag{A.1}$$

with $n = 2$, we obtain

$$\begin{aligned}
\mathbb{E}\big[I^2(t)\big] &= \mathbb{E}\left[\left(\int_0^t \kappa(t-u)\, e^{c(W(t)-W(u))}\, du \right)^2 \right] \\
&= \mathbb{E}\left[2 \int_0^t \kappa(t-u) e^{c(W(t)-W(u))} \left(\int_0^u \kappa(t-v)\, e^{c(W(t)-W(v))}\, dv \right) du \right] \\
&= 2 \int_0^t \int_0^u \kappa(t-u)\, \kappa(t-v)\, \mathbb{E}\Big[e^{c[2(W(t)-W(u))+(W(u)-W(v))]} \Big]\, dv\, du \\
&= 2 \int_0^t \int_0^u \kappa(t-u)\, \kappa(t-v)\, M_{\widetilde{W}(u)}(2c)\, M_{\widetilde{W}(v)}(c)\, dv\, du
\end{aligned}$$

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$$= 2\int_0^t \int_0^u \kappa(t-u)\,\kappa(t-v)\,e^{\frac{1}{2}(2c)^2(t-u)}\,e^{\frac{1}{2}c^2(u-v)}\,dv\,du$$
$$= 2\int_0^t \int_0^u \kappa(t-u)\,\kappa(t-v)\,e^{-2c^2(u-t)}\,e^{\frac{1}{2}c^2(u-v)}\,dv\,du.$$

Substituting (3.3) in the above expression results

$$\begin{aligned}
\mathbb{E}\big[I^2(t)\big] =& 2\big(rX_p\big)^2 \int_0^t \int_0^u e^{r[2(u-t)+(v-u)]}\,e^{-c^2(u-t)}\,dv\,du \\
=& 2\big(rX_p\big)^2 \int_0^t \int_0^u e^{-2(r-\frac{1}{2}c^2)t}\,e^{(r-c^2)u}\,e^{rv}\,dv\,du \\
=& 2\big(rX_p\big)^2 e^{-2(r-\frac{1}{2}c^2)t} \int_0^t e^{(r-c^2)u}\left(\int_0^u e^{rv}\,dv\right) du \\
=& 2\big(rX_p\big)^2 e^{-2(r-\frac{1}{2}c^2)t} \int_0^t e^{(r-c^2)u}\left(\frac{e^{rv}}{r}\bigg|_{v=0}^{v=u}\right) du \\
=& 2\frac{(rX_p)^2}{r}\,e^{-2(r-\frac{1}{2}c^2)t} \int_0^t e^{(r-c^2)u}\,(e^{ru}-1)\,du \\
=& \left[\frac{2}{r}\frac{(rX_p)^2}{2r-c^2}\left(e^{2(r-\frac{1}{2}c^2)t}-1\right) - \frac{rX_p^2}{r-c^2}\big(e^{(r-c^2)t}-1\big)\right] e^{-2(r-\frac{1}{2}c^2)t} \\
=& \frac{2}{r}\frac{(rX_p)^2}{2r-c^2}\left(1-e^{-2(r-\frac{1}{2}c^2)t}\right) - \frac{rX_p^2}{r-c^2}\,e^{-rt}\left(1-e^{-(r-c^2)t}\right). \quad \text{(A.2)}
\end{aligned}$$

In addition,

$$\begin{aligned}
2\mathbb{E}\big[a(t)\,e^{cW(t)}I(t)\big] &= 2a(t)\,\mathbb{E}[e^{cW(t)}I(t)] \\
&= 2a(t)\,\mathbb{E}\left[e^{cW(t)}\int_0^t \kappa(t-u)\,e^{c(W(t)-W(u))}\,du\right] \\
&= 2a(t)\mathbb{E}\left[\int_0^t \kappa(t-u)\,e^{2cW(t)}e^{-cW(u)}\,du\right] \\
&= 2a(t)\int_0^t \kappa(t-u)\,\mathbb{E}\Big[e^{2c(W(t)-W(u))+c(W(u)-W(0))}\Big]\,du \\
&= 2a(t)\int_0^t \kappa(t-u)\,M_{\widetilde{W}(u)}(2c)\,M_{W(u)}(c)\,du \\
&= 2a(t)\int_0^t \kappa(t-u)\,e^{\frac{1}{2}(2c)^2(t-u)}\,e^{\frac{1}{2}c^2u}\,du.
\end{aligned}$$

Again substituting (3.2) and (3.3) in the above expression results

$$\begin{aligned}
2\mathbb{E}\big[a(t)\,e^{cW(t)}I(t)\big] &= 2rX_0X_p\,e^{-2(r+\frac{1}{2}c^2)t}\int_0^t e^{(r-c^2)u}\,e^{2c^2t}\,du \\
&= 2rX_0X_p\,e^{-2(r+\frac{1}{2}c^2)t}\,e^{2c^2t}\left(\frac{e^{(r-c^2)t}-1}{r-c^2}\right)
\end{aligned}$$

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$$= \frac{2rX_0X_p}{r-c^2}\left(e^{-rt} - e^{-2(r-\frac{1}{2}c^2)t}\right). \tag{A.3}$$

Finally, we get

$$\begin{aligned}\mathbb{E}\big[a^2(t)\,e^{2cW(t)}\big] &= a^2(t)\,\mathbb{E}\big[e^{2cW(t)}\big]\\ &= a^2(t)\,M_{W(t)}(2c)\\ &= X_0^2\,e^{-2(r+\frac{1}{2}c^2)t}\,e^{\frac{1}{2}(2c)^2t}\\ &= X_0^2\,e^{-2(r-\frac{1}{2}c^2)t}. \end{aligned}\tag{A.4}$$

Thus, from (3.5), (A.2), (A.3) and (A.4) we obtain

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

$$\begin{aligned}Var\big[X(t)\big] =& \frac{2rX_p^2}{2r-c^2}\left(1-e^{-2(r-\frac{1}{2}c^2)t}\right) - \frac{rX_p^2}{r-c^2}\left(1-e^{-(r-c^2)t}\right)e^{-rt}\\ &+ \frac{2rX_0X_p}{r-c^2}\left(e^{-rt}-e^{-2(r-\frac{1}{2}c^2)t}\right) + X_0^2\,e^{-2(r-\frac{1}{2}c^2)t}\\ &- \big(X_p + (X_0-X_p)e^{-rt}\big)^2\\ =& \frac{2rX_p^2}{2r-c^2} - \frac{2rX_p^2}{2r-c^2}\,e^{-2(r-\frac{1}{2}c^2)t} - \frac{rX_p^2}{r-c^2}\,e^{-rt}\\ &+ \frac{rX_p^2}{r-c^2}\,e^{-2(r-\frac{1}{2}c^2)t} + \frac{2rX_0X_p}{r-c^2}\left(e^{-rt}-e^{-2(r-\frac{1}{2}c^2)t}\right)\\ &+ X_0^2\,e^{-2(r-\frac{1}{2}c^2)t} - \big(X_p + (X_0-X_p)e^{-rt}\big)^2\\ =& e^{-2(r-\frac{1}{2}c^2)t}\left(X_0^2 + \frac{rX_p^2}{r-c^2} - \frac{2rX_0X_p}{r-c^2} - \frac{2rX_p^2}{2r-c^2}\right)\\ &+ \frac{2rX_p^2}{2r-c^2} - \frac{rX_p^2}{r-c^2}e^{-rt} + \frac{2rX_0X_p}{r-c^2}e^{-rt}\\ &- X_p^2 + 2X_p\Big(X_p-X_0\Big)e^{-rt} - \Big(X_p-X_0\Big)^2e^{-2rt}\\ =& e^{-2(r-\frac{1}{2}c^2)t}\left(X_0^2 + \frac{2rX_p}{r-c^2}\Big(X_p-X_0\Big) - \frac{2rX_p^2}{2r-c^2}\right)\\ &- 2X_p\left(\frac{rX_p}{r-c^2} - \frac{rX_0}{r-c^2} - \Big(X_p-X_0\Big)\right)e^{-rt}\\ &+ \frac{2rX_p^2}{2r-c^2} - X_p^2 - \Big(X_p-X_0\Big)^2e^{-2rt}\\ =& \left(X_0^2 + \frac{2rX_p\big(X_p-X_0\big)}{r-c^2} - \frac{(2r-c^2+c^2)X_p^2}{2r-c^2}\right)e^{-2(r-\frac{1}{2}c^2)t} + \frac{c^2X_p^2}{2r-c^2}\\ &- \frac{2c^2X_p}{r-c^2}(X_p-X_0)e^{-rt} - (X_p-X_0)^2e^{-2rt}\\ =& \left(X_0^2 + \frac{2rX_p}{r-c^2}(X_p-X_0) - X_p^2 - \frac{c^2X_p^2}{2r-c^2}\right)e^{-2(r-\frac{1}{2}c^2)t} + \frac{c^2X_p^2}{2r-c^2}\\ &- \frac{2c^2X_p}{r-c^2}(X_p-X_0)e^{-rt} - (X_p-X_0)^2e^{-2rt}\end{aligned}$$

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$$
\begin{aligned}
=&\left(\frac{2rX_p}{r-c^2}\big(X_p-X_0\big)-\big(X_p^2-X_0^2\big)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-2(r-\frac{1}{2}c^2)t}+\frac{c^2X_p^2}{2r-c^2}\\
&-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}-\big(X_p-X_0\big)^2e^{-2rt}\\
=&\left(\big(X_p-X_0\big)\left(\frac{2rX_p}{r-c^2}-\big(X_p+X_0\big)\right)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-(2r-c^2)t}+\frac{c^2X_p^2}{2r-c^2}\\
&-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}-\big(X_p-X_0\big)^2e^{-2rt}\\
=&\left(\big(X_p-X_0\big)\left(\frac{2(r-c^2+c^2)X_p}{r-c^2}-\big(X_p+X_0\big)\right)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-(2r-c^2)t}\\
&+\frac{c^2X_p^2}{2r-c^2}-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}-\big(X_p-X_0\big)^2e^{-2rt}\\
=&\left(\big(X_p-X_0\big)\left(\big(X_p-X_0\big)+\frac{2c^2X_p}{r-c^2}\right)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-(2r-c^2)t}+\frac{c^2X_p^2}{2r-c^2}\\
&-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}-\big(X_p-X_0\big)^2e^{-2rt}\\
=&\left(\big(X_p-X_0\big)^2+\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-(2r-c^2)t}+\frac{c^2X_p^2}{2r-c^2}\\
&-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}-\big(X_p-X_0\big)^2e^{-2rt}\\
=&\big(X_p-X_0\big)^2e^{-(2r-c^2)t}+\left(\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-(2r-c^2)t}\\
&+\frac{c^2X_p^2}{2r-c^2}-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}-\big(X_p-X_0\big)^2e^{-2rt}\\
=&\left(\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)-\frac{c^2X_p^2}{2r-c^2}\right)e^{-(2r-c^2)t}+\big(X_p-X_0\big)^2e^{-2rt}\big(e^{c^2t}-1\big)\\
&+\frac{c^2X_p^2}{2r-c^2}-\frac{2c^2X_p}{r-c^2}\big(X_p-X_0\big)e^{-rt}.
\end{aligned}
$$

After some calculations and simplifying we have

$$
\begin{aligned}
Var\big[X(t)\big]=&\big(X_p-X_0\big)^2e^{-2rt}\big(e^{c^2t}-1\big)-\frac{2c^2X_p}{c^2-r}\big(X_p-X_0\big)e^{-rt}\big(e^{(c^2-r)t}-1\big)\\
&+\frac{c^2X_p^2}{c^2-2r}\big(e^{(c^2-2r)t}-1\big).
\end{aligned}
$$

Appendix B. Variance calculation for $n+1$ doses

From equation (3.11) and applying the formula of the square of the sum of N real numbers

$$
\left(\sum_{k=1}^{N}a_k\right)^2=\sum_{k=1}^{N}a_k^2+2\sum_{j=1}^{N-1}\sum_{i=j+1}^{N}a_ia_j.
$$

We obtain

$$
X^2(t)=X_0^2\left[e^{-2\alpha t+2cW(t)}+\left(\sum_{k=1}^{n}e^{-\alpha(t-k\tau)+c(W(t)-w(k\tau))}\,U_{k\tau}(t)\right)^2\right.
$$

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$$
\begin{aligned}
&+ 2e^{-\alpha t+cW(t)} \sum_{k=1}^{n} e^{-\alpha(t-k\tau)+c(W(t)+W(k\tau))}\, U_{k\tau}(t)\Big] \\
=&X_0^2\Big[e^{-2\alpha t+2cW(t)} + 2\sum_{k=1}^{n} e^{-2\alpha t+\alpha k\tau+2cW(t)-cW(k\tau)}\, U_{k\tau}(t) \\
&+ \sum_{k=1}^{n} e^{-2\alpha(t-k\tau)+2c(W(t)-W(k\tau))}\, U_{k\tau}(t) \\
&+ 2\sum_{l=1}^{n-1}\sum_{k=l+1}^{n} e^{-\alpha(2t-(l+k)\tau)+2cW(t)-c(W(l\tau)+W(k\tau))}\, U_{l\tau}(t)\, U_{k\tau}(t)\Big],
\end{aligned}
$$

and the expected value is

$$
\begin{aligned}
\mathbb{E}\big[X^2(t)\big] =&X_0^2\Big[e^{-2\alpha t}\mathbb{E}\big[e^{2cW(t)}\big] + 2\sum_{k=1}^{n} e^{-\alpha(2t-k\tau)}\mathbb{E}\big[e^{2c(W(t)-W(k\tau))+c(W(k\tau)-W(0))}\big]\, U_{k\tau}(t) \\
&+ \sum_{k=1}^{n} e^{-2\alpha(t-k\tau)}\mathbb{E}\big[e^{2c(W(t)-W(k\tau))}\big]\, U_{k\tau}(t) \\
&+ 2\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{-\alpha(2t-(l+k)\tau)}\mathbb{E}\big[e^{2c(W(t)-W(k\tau))+c(W(k\tau)-W(l\tau))}\big]\, U_{k\tau}(t)\, U_{l\tau}(t)\Big] \\
=&X_0^2\Big[e^{-2\alpha t}M_{W(t)}(2c) + 2\sum_{k=1}^{n} e^{-\alpha(2t-k\tau)}M_{W(t)-W(k\tau)}(2c)M_{W(k\tau)}(c)\, U_{k\tau}(t) \\
&+ \sum_{k=1}^{n} e^{-2\alpha(t-k\tau)}M_{W(t)-W(k\tau)}(2c)\, U_{k\tau}(t) \\
&+ 2\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{-\alpha(2t-(l+k)\tau)}M_{W(t)-W(k\tau)}(2c)\, M_{W(k\tau)-W(l\tau)}(c)\, U_{k\tau}(t)\, U_{l\tau}(t)\Big] \\
=&X_0^2\Big[e^{-2\alpha t}e^{2c^2t} + 2\sum_{k=1}^{n} e^{-\alpha(2t-k\tau)}e^{2c^2(t-k\tau)}e^{\frac{1}{2}c^2k\tau}\, U_{k\tau}(t) \\
&+ \sum_{k=1}^{n} e^{-2\alpha(t-k\tau)}e^{2c^2(t-k\tau)}\, U_{k\tau}(t) \\
&+ 2\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{-\alpha(2t-(l+k)\tau)}e^{2c^2(t-k\tau)}e^{\frac{1}{2}c^2(k\tau-l\tau)}\, U_{l\tau}(t)\Big].
\end{aligned}
$$

Replacing $\alpha = r + \frac{1}{2}c^2$, we get

$$
\begin{aligned}
\mathbb{E}\big[X^2(t)\big] =&X_0^2\Big[e^{-2(r-\frac{1}{2}c^2)t} + 2e^{-2(r-\frac{1}{2}c^2)t}\sum_{k=1}^{n} e^{(r-c^2)k\tau}\, U_{k\tau}(t) \\
&+ e^{-2(r-\frac{1}{2}c^2)t}\sum_{k=1}^{n} e^{2(r-\frac{1}{2}c^2)k\tau}\, U_{k\tau}(t) \\
&+ 2e^{-2(r-\frac{1}{2}c^2)t}\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{r(l+k)\tau-c^2k\tau}\, U_{l\tau}(t)\Big] \\
=&X_0^2e^{-2(r-\frac{1}{2}c^2)t}\Big[1 + \sum_{k=1}^{n}\Big(2e^{(r-c^2)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau}\Big)\, U_{k\tau}(t)
\end{aligned}
$$

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$$+ 2\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{r(l+k)\tau - c^2 k\tau}\, U_{l\tau}(t)\Big]. \tag{B.1}$$

Thus, from (3.15) and (B.1) we have

$$\begin{aligned}
Var[X(t)] =& \mathbb{E}[X^2(t)] - (\mathbb{E}[X(t)])^2 \\
=& X_0^2 e^{-2(r-\frac{1}{2}c^2)t}\Big[1 + \sum_{k=1}^{n}\Big(2e^{\left(r-c^2\right)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau}\Big)\, U_{k\tau}(t) \\
&+ 2\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{r(l+k)\tau - c^2 k\tau}\, U_{l\tau}(t)\Big] \\
&- X_0^2 e^{-2rt}\Big[1 + 2\sum_{k=1}^{n} e^{rk\tau}\, U_{k\tau}(t) + \Big(\sum_{k=1}^{n} e^{rk\tau}\, U_{k\tau}(t)\Big)^2\Big] \\
=& X_0^2 e^{-2rt}(e^{c^2 t} - 1) + 2X_0^2 e^{-2(r-\frac{1}{2}c^2)t}\Big[\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{r(l+k)\tau}(e^{-c^2 k\tau} - e^{-c^2 t})\, U_{l\tau}(t) \\
&+ X_0^2 e^{-2(r-\frac{1}{2}c^2)t}\Big[\sum_{k=1}^{n}\Big(2e^{\left(r-c^2\right)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau} - e^{-c^2 t}(2e^{rk\tau} + e^{2rk\tau})\Big)\, U_{k\tau}(t)\Big]\Big] \\
=& X_0^2\Big[e^{-2rt}(e^{c^2 t} - 1) + 2\sum_{k=1}^{n-1}\sum_{l=k+1}^{n} e^{r(l+k)\tau}(e^{-c^2 k\tau} - e^{-c^2 t})\, U_{l\tau}(t)\Big) \\
&+ e^{-2(r-\frac{1}{2}c^2)t}\Big(\sum_{k=1}^{n}\Big(2e^{\left(r-c^2\right)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau} - e^{-c^2 t}(2e^{rk\tau} + e^{2rk\tau})\Big)\, U_{k\tau}(t)\Big].
\end{aligned}$$

Exchanging sums results in

$$\begin{aligned}
Var[X(t)] =& X_0^2\Big\{e^{-2rt}(e^{c^2 t} - 1) + 2\sum_{l=2}^{n}\sum_{k=1}^{l-1} e^{rl\tau} e^{rk\tau}(e^{-c^2 k\tau} - e^{-c^2 t})\, U_{l\tau}(t)\Big) \\
&+ e^{-2(r-\frac{1}{2}c^2)t}\Big(\sum_{k=1}^{n}\Big(2e^{(r-c^2)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau} - e^{-c^2 t}(2e^{rk\tau} + e^{2rk\tau})\Big)\, U_{k\tau}(t)\Big\} \\
=& X_0^2\Big\{e^{-2rt}(e^{c^2 t} - 1) + 2\sum_{l=2}^{n} e^{rl\tau}\Big(\frac{e^{(r-c^2)(l-1)\tau} - 1}{1 - e^{-(r-c^2)\tau}} - e^{-c^2 t}\Big[\frac{e^{r(l-1)\tau} - 1}{1 - e^{-r\tau}}\Big]\Big)\, U_{l\tau}(t)\Big) \\
&+ e^{-2(r-\frac{1}{2}c^2)t}\Big(\sum_{k=1}^{n}\Big(2e^{(r-c^2)k\tau} + e^{2(r-\frac{1}{2}c^2)k\tau} - e^{-c^2 t}(2e^{rk\tau} + e^{2rk\tau})\Big)\, U_{k\tau}(t)\Big\}.
\end{aligned}$$

If $n\tau \le t \le (n+1)\tau$ and using the sum of the first n terms of a geometric series, it results

$$\begin{aligned}
Var\big[X(t)\big] =& X_0^2\Big\{e^{-2rt}\big(e^{c^2 t} - 1\big) + e^{-2(r-\frac{1}{2}c^2)t}\Big(2\Big[\frac{e^{(r-c^2)n\tau} - 1}{1 - e^{-(r-c^2)\tau}}\Big] \\
&+ \Big[\frac{e^{2(r-\frac{1}{2}c^2)n\tau} - 1}{1 - e^{-2(r-\frac{1}{2}c^2)\tau}}\Big] - e^{-c^2 t}\Big(2\Big[\frac{e^{rn\tau} - 1}{1 - e^{-r\tau}}\Big] + \Big[\frac{e^{2rn\tau} - 1}{1 - e^{-2r\tau}}\Big]\Big) \\
&+ \Big(\frac{2\,e^{r\tau}}{1 - e^{-(r-c^2)\tau}}\Big)\Big[\frac{e^{2(r-\frac{1}{2}c^2)(n-1)\tau} - 1}{1 - e^{-2(r-\frac{1}{2}c^2)\tau}} - \frac{e^{r(n-1)\tau} - 1}{1 - e^{-r\tau}}\Big] \\
&- \Big(\frac{2\,e^{r\tau - c^2 t}}{1 - e^{-r\tau}}\Big)\Big[\frac{e^{2r(n-1)\tau} - 1}{1 - e^{-2r\tau}} - \frac{e^{r(n-1)\tau} - 1}{1 - e^{-r\tau}}\Big]\Big)\Big\}.
\end{aligned}$$

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