A Stochastic Analysis of the One Compartment Pharmacokinetic Model Considering Optimal Controls

QIANNING LIU and QINGSONG SHAN
Department of Statistics, Jiangxi University of Finance and Economics, Nanchang 330013, China
Corresponding author: Qingsong Shan (shanqingsong@jxufe.edu.cn)

This work was supported in part by the Education Department of Jiangxi Province under Grant GJJ190253 and Grant GJJ190259.

ABSTRACT
First-order 1-compartment pharmacokinetic model for extravascular administered drugs can be used to derive many useful quantities by comparing the predicted values with actual data. However, less research has been done in actually formulating them as optimal control problems. Moreover, 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 models’ (pharmacokinetic/pharmacodynamic models’) parameters and the derived conclusions. Therefore there is an increasing need to extend the deterministic models to models including a stochastic component. In our study, we modify the 1-compartment pharmacokinetic model to a stochastic differential equation model based on an optimal control problem. A schedule of optimal dosing and timing has been given from our proposed model.

INDEX TERMS
Stochastic differential equation, optimal control, pharmacokinetics, stability, E-M method.

I. INTRODUCTION
Pharmacokinetics (PK) is the study of what the body does to a drug. It studies the absorption, distribution, metabolism, and excretion of the medicine (ADME), as well as bioavailability. PK analysis forms a major part of the understanding and development of the Investigation Medicinal Product (IMP), and can also contribute heavily to the prescription once a drug has been approved.

There are three approaches that have been suggested for pharmacokinetic modeling: compartmental, physiological and model-independent. The first one is an empirical approach, which is based on simple compartmental models. These compartments have no strict physiological or anatomical basis. The compartment simply represents a body volume, or just as easily it could represent a chemical state, for example a metabolite of the drug. Usually this approach uses one or two compartments. Despite its simplistic nature, many useful quantities can be derived using this approach, and by comparing predicted values with actual data.

In [1], Sophie Donnet and Adeline Samson (2013) reviewed the examination of the pertinence of stochastic differential equations (SDEs) for pharmacokinetic/pharmacodynamic models. A natural extension of deterministic differential equations model is a system of SDEs, where relevant parameters have been modeled as suitable stochastic processes, or stochastic processes have been added to the driving system equations [2]. The first papers encouraging the introduction of random fluctuations in PK/PD were authored by D’Argenio [3] and Ramanathan [4], [5]. 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, Ramanathan [5] proposes a stochastic one-compartment PK model with a variable elimination rate. More sophisticated PK/PD models then have been proposed with multiple compartments, non-linear or time-inhomogeneous absorption or elimination (seen for example Ferrante et al. [6]; Tornøe et al. [7]; Ditlevsen and De Gaetano [8]; Ditlevsen et al. [9]; Picchini et al. [10]).

Although lots of mathematical models for pharmacokinetics has been build, less research has been done in actually formulating them as optimal control problems. Actually, suitable control such as food intake, special exercises, some vitamin, can affect the drug absorption. As in [11], the authors studied significant effect of infection and food intake on sirolimus pharmacokinetics and exposure in pediatric patients with acute lymphoblastic leukemia. A mathematical model for the depletion of bone marrow under cancer chemotherapy...
is analyzed as an optimal control problem in [12]. Reference [13] investigated multiscale tumor modeling that integrates drug pharmacokinetic and pharmacodynamic (PK/PD) information using stochastic hybrid system modeling framework. Reference [14] presented a new model to describe the single-dose pharmacokinetics of bevacizumab and predict its multiple-dose pharmacokinetics in beagle dogs. Reference [15] combined health record informatics and pharmacokinetic modeling and got a powerful translational approach to detect high dimensional drug-drug interactions. Through clinical trial, [16] proposed a model based optimization of G-CSF treatment during cytotoxic chemotherapy and showed validity of model predictions regarding alternative G-CSF schedules.

In this study, we investigate to combine optimal control theory and stochastic methods to propose a novel pharmacokinetic model. Our aim is to find the optimal drug dosing schedule and predict the absorption rate and concentration rate. We added a control vector to the pharmacokinetic model and optimal control theory was used to analyze the model. We found the optimal dosing timing schedule and an equilibrium point of the dynamic system. Near the stationary point, white noise was added to the modified model, and the ensuing stochastic differential equations (SDEs) were presented. We proved existence, uniqueness and stability of the SDE system and found an explicit solution. Finally, the model was simulated and parameters of the model was estimated by using the R language and the stability of the numerical method was proven.

A. A BRIEF REVIEW OF FIRST-ORDER 1-COMPARTMENT UNCONTROLLED MODEL (Extravascular Administration)

This approach models the entire body as a single compartment into which a drug is added by a rapid single dose, or bolus. It is assumed that the drug concentration is uniform in the body compartment at all times, and is eliminated by a first order process that is described by a first order rate constant $K_{10}$:

$$\begin{align*}
\frac{dA_a}{dt} &= -K_\alpha A_a, \\
\frac{dA_c}{dt} &= K_\alpha A_a - K_{10} A_c,
\end{align*}$$

where $A_a =$ Amount of drug absorption deposit, $A_c =$ Amount of drug in central compartment, $K_\alpha =$ Absorption rate constant, $K_{10} =$ first-order elimination rate, indicating elimination of drug out of the central compartment into urine, feces, etc.

It’s easy to get the solution of the system (1):

$$\begin{align*}
A_a(t) &= A_a(0)e^{-K_\alpha t}, \\
A_c(t) &= \frac{K_\alpha A_a(0)}{K_\alpha - K_{10}} (e^{-K_{10}t} - e^{-K_\alpha t}),
\end{align*}$$

where $A_a(0)$ is the initial amount of drug in the gastrointestinal tract.

B. STABILITY OF THE SDES

Definition 1: [17] Let $(\Omega, F, P)$ be a complete probability space with a filtration $\{F_t\}_{t\geq 0}$ satisfying the usual conditions. Let $B_t = (B_1^t, \ldots, B_n^t)_{t\geq 0}$ be a $d$-dimensional Brownian motion defined on the space. Let $0 \leq t_0 < T < \infty$. Let $x(t) = (x_1(t), \ldots, x_n(t))^T$ be a $d$-dimensional Itô process on $t \geq 0$ and $x_0$ be an $F_{t_0}$-measurable $\mathbb{R}^d$-valued random variable such that $E|x_0|^2 \leq \infty$. Let $f : \mathbb{R}^d \times [0, T] \to \mathbb{R}^d$ and $g : \mathbb{R}^d \times [0, T] \to \mathbb{R}^{d \times m}$ be both Borel measurable. Consider the $d$-dimensional stochastic differential equation of Itô type

$$dx(t) = f(x(t), t)dt + g(x(t), t)dB_t, \quad t_0 \leq t \leq T \quad (2)$$

with initial value $x(t_0) = x_0$. Assume that for any initial value $x(t_0) = x_0 \in \mathbb{R}^d$, equation (2) has a unique global solution which is denoted by $x(t; t_0, x_0)$. We know that the solution has continuous sample paths and its every moment is finite. Assume furthermore that

$$f(0, t) = 0 \quad \text{and} \quad g(0, t) = 0 \quad \text{for all } t \geq t_0.$$

So equation (2) has the solution $x(t) \equiv 0$ corresponding to the initial value $x(t_0) = 0$. This solution is called the trivial solution or equilibrium position.

Definition 2: [17] Let $K$ denote the family of all continuous nondecreasing functions $\mu : \mathbb{R}_+ \to \mathbb{R}_+$ such that $\mu(0) = 0$ and $\mu(r) > 0$ if $r > 0$. For $h > 0$, let $S_h = \{x \in \mathbb{R}^d : |x| < h\}$. A continuous function $V(x, t)$ defined on $S_h \times [t_0, \infty)$ is said to be positive-definite (in the sense of Lyapunov) if $V(0, t) \equiv 0$ and, for some $\mu \in K$,

$$V(x, t) \geq \mu(|x|) \quad \text{for all } (x, t) \in S_h \times [t_0, \infty).$$

A function $V(t)$ is said to be negative-definite if $-V$ is positive-definite. A continuous non-negative function $V(x, t)$ is said to be decrescent (i.e. to have an arbitrarily small upper bound) if for some $\mu \in K$,

$$V(x, t) \leq \mu(|x|) \quad \text{for all } (x, t) \in S_h \times [t_0, \infty).$$

A function $V(x, t)$ defined on $\mathbb{R}^d \times [t_0, \infty)$ is said to be radially unbounded if

$$\lim_{|x| \to \infty} \inf_{t \geq t_0} V(x, t) = \infty.$$

Definition 3: [17] The trivial solution of equation (2) is said to be

(i) stochastically stable or stable in probability if for every pair of $\epsilon \in (0, 1)$ and $r > 0$, there exists a $\delta = \delta(\epsilon, r, t_0) > 0$ such that

$$P(|x(t; t_0, x_0)| < r \text{ for all } t \geq t_0) \geq 1 - \epsilon$$

whenever $|x_0| < \delta$. Otherwise, it is said to be stochastically unstable.

(ii) stochastically asymptotically stable if it is stochastically stable and, moreover, for every $\epsilon \in (0, 1)$, there exists a $\delta_0 = \delta_0(\epsilon, t_0) > 0$ such that

$$P\left(\lim_{t \to \infty} x(t; t_0, x_0) = 0\right) \geq 1 - \epsilon$$

whenever $|x_0| < \delta_0$. 
(iii) stochastically asymptotically stable in the large if it is stochastically stable and, moreover, for all \( x_0 \in \mathbb{R}^d \),

\[
P \left( \lim_{t \to \infty} x(t; t_0, x_0) = 0 \right) = 1.
\]

Let \( 0 < h \leq \infty \). Denote by \( C^2(\mathbb{S}_h \times [t_0, \infty); \mathbb{R}_+) \) the family of all nonnegative functions \( V(x, t) \) defined on \( \mathbb{S}_h \times \mathbb{R}_+ \) such that they are continuously twice differentiable in \( x \) and once in \( t \). Define the differential operator \( L \) associated with equation (2) by

\[
L = \frac{\partial}{\partial t} + \sum_{i=1}^d f_i(x, t) \frac{\partial}{\partial x_i} + \frac{1}{2} \sum_{i,j=1}^d [g(x, t)g^T(x, t)]_{ij} \frac{\partial^2}{\partial x_i \partial x_j}.
\]

If \( L \) acts on a function \( V \in C^2(\mathbb{S}_h \times [t_0, \infty); \mathbb{R}_+) \), then

\[
LV(x, t) = V_t(x, t) + V_x(x, t)f(x, t) + \frac{1}{2} \text{trace}[g^T(x, t)V_{xx}(x, t)g(x, t)].
\]

**Theorem 1:** [17] If there exists a positive-definite function \( V(x, t) \in C^2(\mathbb{S}_h \times [t_0, \infty); \mathbb{R}_+) \) such that \( LV(x, t) \leq 0 \) for all \( (x, t) \in \mathbb{S}_h \times [t_0, \infty) \), then the trivial solution of equation (2) is stochastically stable.

**Definition 4:** [17] The Euler–Maruyama approximate solutions are defined as follows: For every integer \( n \geq 1 \), define \( x_n(t_0) = x_0 \), and then for \( t_0 + (k-1)/n < t \leq (t_0 + k/n) \wedge T, k = 1, 2, \cdots \),

\[
x_n(t) = x_n(t_0) + \int_{t_0+(k-1)/n}^t f(x_n(t_0 + (k-1)/n), s) ds + \int_{t_0+(k-1)/n}^t g(x_n(t_0 + (k-1)/n), s) dB(s).
\]

**Theorem 2:** [18] If \( \sum_{i=1}^d B_i^T B_i + A + A^T \) is negative-definite, then for any sufficiently small stepsize \( \Delta \), the Euler–Maruyama (EM) approximate solution of the linear SDE

\[
dy(t) = [Ay(t) + a] dt + \sum_{i=1}^d [B_i y(t) + b_i] dB_i(t), \quad t \geq 0
\]

(where the initial value \( y(0) = x \in \mathbb{R}^d \)). Here \( A \) and \( B_i \)s are all the \( d \times d \) matrices while \( a \) and \( b_i \)s are \( d \)-dimensional vectors.) is stable in distribution. In particular, for a scalar linear SDE

\[
dy(t) = [ay(t) + a] dt + \sum_{i=1}^d [b_i y(t) + b_i] dB_i(t), \quad t \geq 0,
\]

where \( a, \alpha, \beta, b \) are all real numbers, its EM approximate solution is stable in distribution if \( 2\alpha + \sum_{i=1}^d \beta_i^2 < 0 \) and the stepsize \( \Delta \) is sufficiently small.

Let \( \Omega \) be the set of all possible outcomes (or realisations) at the point \( t \), and define the random variable \( Y_t \) as the function \( Y_t : \Omega \to \mathbb{R} \). Define the set of possible outcomes over all time as \( \Omega = \bigotimes_{t=0}^{\infty} \Omega_t \), and the random variables \( X_t : \Omega \to \mathbb{R} \), where for every \( \omega \in \Omega \), with \( \omega = (\omega_0, \omega_1, \cdots) \), we have \( X_t(\omega) = Y_t(\omega_t) \). Hence we have a sequence of random variables \( \{X_t\} \) (which we call a random process). When we observe \( \{x_t\}_t \), this means there exists an \( \omega \in \Omega \), such that \( X_t(\omega) = x_t \). To complete things we have a sigma-algebra \( \mathcal{F} \) whose elements are subsets of \( \Omega \) and a probability measure \( P : \mathcal{F} \to [0, 1] \).

**Definition 5:** We say that the sequence \( \{X_t\} \) converges almost sure to \( \mu \), if there exists a set \( M \subset \Omega \), such that \( P(M) = 1 \) and for every \( \omega \in M \), we have

\[
X_t(\omega) \to \mu, \quad \text{as } t \to \infty.
\]

In other words for every \( \epsilon > 0 \), there exists an \( N(\omega) \) such that

\[
|X_t(\omega) - \mu| < \epsilon,
\]

for all \( t > N(\omega) \). We denote \( X_t \to \mu \) almost surely, as \( X_t \to \mu, \quad \mathbb{P} - \text{a.s.} \).

An equivalent definition, in terms of probabilities, is for every \( \epsilon > 0 \), \( X_t \to \mu, \quad \mathbb{P} - \text{a.s.} \) if

\[
P(\omega; \cap_{t=1}^{\infty} \cup_{t=1}^{\infty} \{|X_t(\omega) - \mu| > \epsilon\}) = 0.
\]

**II. USING OPTIMAL CONTROL THEORY TO STUDY THE FIRST-ORDER 1-COMPARTMENT MODEL**

Pharmacokinetic (PK) equations model the time evolution of the drug’s concentration in the body/plasma. Let \( u \) denote the drug dosage with \( u = 1 \) corresponding to a maximal dose and \( u = 0 \) denoting no treatment. Simple models considered in the literature (for example, see [19], [20]) use a first-order linear system

\[
\dot{c} = fc + hu, \quad c(0) = 0,
\]

where \( f \) and \( h \) are positive constants to represent the dynamics for the drug concentration \( c \) in the plasma. The model itself is one of exponential growth/decay as it is commonly used as model for continuous infusions.

As in [12], a more generally bilinear system of the form was proposed

\[
\dot{c} = (f + ug)c + hu, \quad c(0) = 0
\]

with an additional parameter \( g \) added.

Here we add a control vector to equation (1) of the first-order 1-compartment model, and derive the following first-order 1-compartment dynamic system,

\[
\begin{aligned}
\frac{dA_u}{dt} &= -K_{10}A_u + \alpha u, \\
\frac{dA_c}{dt} &= K_{10}A_u - K_{10}A_c + \beta u,
\end{aligned}
\]

where \( \alpha \) and \( \beta \) are positive constants representing the dynamics for the drug and concentration in absorption deposit \( A_u \) and central compartment \( A_c \) in the plasma, respectively.
Let \( A := \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} \) and \( B := \begin{bmatrix} b_1 \\ b_2 \end{bmatrix} \).

Then, we can write (3) in matrix notation as \( \dot{x} = Ax + Bu \).

By Von Karman controllability, the necessary condition for controllability is that the matrix \([B AB]\) has full rank, i.e., \(|B AB| \neq 0\), i.e.,
\[
\begin{pmatrix}
\alpha \\
\beta
\end{pmatrix}
\begin{bmatrix}
-K_a & 0 \\
K_a & -K_{10}
\end{bmatrix}
\begin{pmatrix}
\alpha \\
\beta
\end{pmatrix}
\neq 0,
\]
i.e., \(K_a \alpha^2 - (K_{10} - K_a) \alpha \beta\) which implies \(\alpha \neq 0\) and \(K_a \alpha \neq (K_{10} - K_a) \beta\).

The fact is that maximizing the Hamiltonian function \(H\) with respect to \(u\), is only possible if \(u\) is bounded, i.e., \(|u| \leq u_0\) for some \(u_0\).

As we mentioned above, in our system, the drug dosage \(u\) is between 0 and 1 which surely satisfies the above bounded condition. In order to avoid drug side effects, we hope to achieve the best possible therapeutic effect with as few medications as possible. So in this paper we consider to a performance index in the form
\[
J = r_1 A_a (T) + r_2 A_c (T) + \int_0^T [q_1 A_a (t) + q_2 A_c (t) + b(1-u(t))] dt,
\]
where \(T\) represents the time between two treatments, \(r_1, r_2 > 0\), \(q_1, q_2 \geq 0\), and \(b > 0\) are constants.

In the objective (4), we have incorporated a term \(q_1 A_a (t) + q_2 A_c (t)\) in the Lagrangian in an effort to achieve the best possible therapeutic effect. At the same time, in order to avoid drug side effects, we also want to schedule as few drug dosage as possible by including a term \(b(1-u(t))\) in the objective. In addition we have added a terminal term \(r_1 A_a (T) + r_2 A_c (T)\) which represents a weighted average of the total drug concentration at the end of an assumed fixed therapy interval \([0, T]\) in order to prevent that the drug concentration would be too low to keep certain effectiveness towards the end of the therapy interval.

The mathematical problem therefore can be formulated as to maximize (4) over all Lebesgue measurable functions \(u\) which take values in \([0, 1]\) subject to the dynamics (1) respectively (3) and given initial conditions. By (4) and (3) respectively, we denote \(f_0(x_1, x_2, u) = q_1 A_a (x_1) + q_2 A_c (x_2) + b(1-u)\), \(f_1(x_1, x_2, u) = -K_a x_1 + \alpha u\), and \(f_2(x_1, x_2, u) = K_a x_1 - K_{10} x_2 + \beta u\). We form the augmented
\[
J^* = \int_0^T [f_0 + \psi_1 (f_1 - x_1') + \psi_2 (f_2 - x_2')] dt,
\]
where \(\psi_1\) and \(\psi_2\) are the adjoint functions associated with constraints (3) and the given initial conditions. We will obtain them from the following discussion.

Define the Hamiltonian
\[
H = f_0 + \psi_1 f_1 + \psi_2 f_2 = q_1 A_a (t) + q_2 A_c (t) + b - \psi_1 K_a x_1 + \psi_2 (K_a x_1 - K_{10} x_2) + (\psi_1 \alpha + \psi_2 \beta - b) u.
\]

By the Pontryagin’s maximum principle [21] [22], if \(u^*\) is the optimal control (optimal controls \(u^*\) maximize the Hamiltonian \(H\), i.e., \((\psi_1 + \psi_2 - b) u^* = \max_0^{10} (\psi_1 + \psi_2 - b) u\)), and \(x^*\) is the state trajectory, then there exists an absolutely continuous function \(\psi(t) := (\psi_1(t), \psi_2(t))\) defined on \([0, T]\) satisfying the adjoint equations with transversality condition,
\[
\psi_1 = -\frac{\partial H}{\partial x_1} = \psi_1 K_a - \psi_2 K_a, \quad \psi_1 (T) = r_1,
\]
\[
\psi_2 = -\frac{\partial H}{\partial x_2} = \psi_2 K_{10}, \quad \psi_2 (T) = r_2,
\]
such that the following condition is satisfied: the optimal control \(u^*\) maximizes the Hamiltonian \(H\) (see (5)) over the control set \([0, 1]\) along \((\psi_1(t), \psi_2(t), A^u_a, A^u_c, u^*)(t)\).

We call a pair \((A_a, A_c, u)\) consisting of an admissible control \(u\) with corresponding trajectory \((A_a, A_c)\) for which there exist multipliers \((\psi_1, \psi_2)\) such that the conditions of the Maximum Principle are satisfied an extremal (pair) and the triple \((A_a, A_c, u, (\psi_1, \psi_2))\) is an extremal lift (to the cotangent bundle).

From Pontryagin’s Maximum Principle [21] [22], the optimal control \(u^*\) maximizes \(H\) as a function of \(u\). Since \(H\) is linear in \(u\) and \(u \in [0, 1]\), the maximum value of \(H\) is at \(u^* = 1\) if \(\alpha \psi_1 (t) + \beta \psi_2 (t) - b > 0\), and at \(u^* = 0\) if \(\psi_1 (t) + \psi_2 (t) - b < 0\); that is
\[
u^* = \begin{cases}
1, & \text{if } \alpha \psi_1 (t) + \beta \psi_2 (t) - b > 0, \\
0, & \text{if } \alpha \psi_1 (t) + \beta \psi_2 (t) - b < 0.
\end{cases}
\]

Since \(u = 1\) represents maximal dosage and \(u = 0\) corresponds to no drug dosed, we have that, in principle, optimal controls alternate between sessions of “full control” or rest periods and partial controls are not optimal. Next we aim to find the switching time.

Claim: There is one and only one switch in the control.

Proof: Firstly, since the switching function \(\Phi(t) = \alpha \psi_1 (t) + \beta \psi_2 (t) - b\) is continuous on the compact interval \([0, T]\) and there exist two points which have different signs on \([0, T]\), by intermediate value theorem, there is at least one solution for \(\Phi(t) = \alpha \psi_1 (t) + \beta \psi_2 (t) - b = 0\).

Secondly, by the adjoint equations (6), we have \(\dot{\psi}_1 = -\frac{\partial H}{\partial x_1} = \psi_1 K_a - \psi_2 K_a\), we get \(\dot{\psi}_1 = -\psi_1 K_a = -C_2 K_a e^{K_{10} t}\).

By solving the above ODE, we get \(\psi_1 = -\frac{C_2 K_a e^{K_{10} t}}{K_{10} - K_a} - C_1 K_a e^{K_{10} t}\), where \(C_1\) is a constant.

By the transversality condition \(\psi_2 (T) = r_2\), we get \(C_2 = r_2 e^{-K_{10} T}\). So \(\psi_2 = r_2 e^{K_{10} (T-t)}\).
By the transversality condition $\psi_1(T) = r_1$, and $C_2 = r_2 e^{-K_{10}T}$, we obtain

$$r_1 = \psi_1(T) = -\frac{r_2 K_a}{K_{10} - K_a} - C_1 r_2 K_a e^{(K_a - K_{10})T}.$$ 

It implies $C_1 = -\frac{r_2 K_a}{r_2 K_a e^{(K_a - K_{10})T}}$. The necessary condition for $t$ being a switching time is that $t$ satisfies

$$\psi_1(t) \alpha + \psi_2(t) \beta - b = 0,$$

i.e.,

$$\left(\frac{C_2 K_a e^{K_{10}t}}{K_{10} - K_a} - C_1 C_2 K_a e^{K_{10}t}\right) \alpha + C_2 e^{K_{10}t} \beta - b = 0,$$

where $C_1 = -\frac{r_2 K_a}{r_2 K_a e^{(K_a - K_{10})T}}$ and $C_2 = r_2 e^{-K_{10}T}$. 

Since

$$\left[\left(\frac{C_2 K_a e^{K_{10}t}}{K_{10} - K_a} - C_1 C_2 K_a e^{K_{10}t}\right) \alpha + C_2 e^{K_{10}t} \beta - b \right] \neq 0 \text{ on } [0,T],$$

i.e., the switching function $\Phi(t) = \alpha \psi_1(t) + \beta \psi_2(t) - b$ is strictly monotonous on $[0,T]$, there’s no other one switch. Therefore, by the above two conclusions, there is only one switch in the control.

The switching time can be obtained by solving

$$\left(\frac{C_2 K_a e^{K_{10}t}}{K_{10} - K_a} - C_1 C_2 K_a e^{K_{10}t}\right) \alpha + C_2 e^{K_{10}t} \beta - b = 0,$$

using numerical method.

Optimal trajectories satisfy

$$\dot{x} = Ax + Bu^*. $$

The equilibrium point $P$ is

$$P := \left( \begin{array}{c} x_1 \\ x_2 \end{array} \right) = \left( \begin{array}{c} \frac{a u^*}{K_a} \\ \frac{a u^*}{(\alpha + \beta) u^*} \end{array} \right) = \left( \begin{array}{c} \frac{\alpha u^*}{K_a} \\ \frac{\alpha u^*}{(\alpha + \beta) u^*} \end{array} \right). $$

Since both eigenvectors of matrix $A$, $\lambda_1 = -K_a$ and $\lambda_2 = -K_{10}$, are negative, the positive-plane has stable node at $P = \left( \frac{\alpha u^*}{K_a} \frac{\alpha u^*}{(\alpha + \beta) u^*} \right)$.

### III. THE FIRST-ORDER 1-COMPARTMENT STOCHASTIC MODEL

From the above discussion, we see that the optimal control occurs at $u^*$. Thus, we revise the first-order compartment optimal control model (3) as

$$\begin{cases}
\frac{dA_u}{dt} = -K_a A_u + \alpha u^*, \\
\frac{dA_c}{dt} = K_a A_u - K_{10} A_c + \beta u^*.
\end{cases}$$

We assume that the stochastic perturbations of the variables around their values given in (8), $P := \left( \begin{array}{c} \frac{a u^*}{K_a} \\ \frac{\alpha u^*}{(\alpha + \beta) u^*} \end{array} \right) = \left( \begin{array}{c} A_u^* \\ A_c^* \end{array} \right)$, are white noise type, which are proportional to the distances of $A_u, A_c$ from the values $A_u^*, A_c^*$. We then arrive to the system

$$\begin{cases}
dA_u = (-K_a A_u + \alpha u_0)dt + \sigma_1(A_u - A_u^*)d\xi_1^1, \\
dA_c = (K_a A_u - K_{10} A_c + \beta u_0)dt + \sigma_2(A_c - A_c^*)d\xi_1^2,
\end{cases}$$

where $\sigma_1$ and $\sigma_2$ are real constants, and can be defined as the intensities of stochasticity, and $\xi_1 = (\xi_1^1, \xi_1^2)$ is a 2-dimensional white noise process. We wonder whether the dynamical behaviour of model (9) is robust with respect to such a kind of stochastic perturbations by investigating the asymptotic stochastic stability behavior of equilibrium $P$ for (10), and comparing the results with those obtained from the system (9).

Let $X_1 = A_u - A_u^* = A_u - \frac{\alpha u^*}{K_a}$ and $X_2 = A_c - A_c^* = A_c - \frac{(\alpha + \beta) u^*}{K_{10}}$, then $A_u = X_1 + \frac{\alpha u^*}{K_a}$ and $A_c = X_2 + \frac{(\alpha + \beta) u^*}{K_{10}}$. Substituting them into the above system (10), and after simplification, we arrive to a first order 1-compartment SDE model:

$$\begin{cases}
dx_1 = -K_a x_1 dt + \sigma_1 x_1 d\xi_1^1, \\
dx_2 = (K_a x_1 - K_{10} x_2) dt + \sigma_2 x_2 d\xi_1^2.
\end{cases}$$

Using Itô’s formula [23], it’s easy to solve $dx_1 = -K_a x_1 dt + \sigma_1 x_1 d\xi_1^1$ and get $X_1 = X_1(0) \exp\left(1 + \frac{\sigma_1^2}{2}\right) t$, which is a so-called geometric Brownian motion (GBM).

If $\xi_1^1$ is independent of $X_1(0)$, we have that

$$E(X_1(t)) = X_1(0) e^{-K_a t},$$

and

$$\text{Var}(X_1(t)) = X_1(0)^2 e^{-2K_a t} (e^{2\sigma^2} - 1).$$

The probability density function of $X_1(t)$ is $f_{x_1}(x, K_a, \sigma_1, t)$

$$= \frac{1}{\sqrt{2\pi \sigma_1 t}} \exp\left(-\frac{(\ln x - \ln X_1(0) - K_a t_{\frac{\sigma_1^2}{2}})^2}{2\sigma_1^2 t}\right).$$

If $K_a + \frac{\sigma_1^2}{2} > 0$, then $X_1(t) \rightarrow 0$ as $t \rightarrow \infty$, $P - a.s.$

If $K_a + \frac{\sigma_1^2}{2} < 0$, then $X_1(t) \rightarrow \infty$ as $t \rightarrow \infty$, $P - a.s.$

If $K_a + \frac{\sigma_1^2}{2} = 0$, then $X_1(t)$ will fluctuate between arbitrary large and arbitrary small values as $t \rightarrow \infty$, $P - a.s.$

For $dx_2 = (K_a x_1 - K_{10} x_2) dt + \sigma_2 x_2 d\xi_2^1$, we let $X_2 = g(t, \xi_2^1)$, and use Itô’s formula [23] to derive

$$dx_2 = \left(\frac{\partial g}{\partial t} + \frac{1}{2} \frac{\partial^2 g}{\partial (\xi_2^1)^2}\right) dt + \frac{\partial g}{\partial \xi_2^1}(t, \xi_2^1) d\xi_2^1.$$ 

Thus,

$$\frac{\partial g}{\partial t} + \frac{1}{2} \frac{\partial^2 g}{\partial (\xi_2^1)^2} = K_a x_1 - K_{10} g,$$

$$\frac{\partial g}{\partial \xi_2^1} = \sigma_2 g.$$
From $\frac{dx}{dt} = \sigma_2 g$, we get $X_2 = g(t, \xi_2^t) = C(t)e^{\sigma_2 \xi_2^t}$. and substituting it into $\frac{dx}{dt} + \frac{1}{2} \frac{\sigma_2^2}{\alpha(\xi_1^t)^2} = K_a X_1 - K_{10} g$, we gather

$$K_a X_1 - K_{10} X_2 = K_a X_1 - K_{10} C(t)e^{\sigma_2 \xi_2^t} = \frac{\sigma_2}{\alpha(\xi_1^t)^2} = C'(t)e^{\sigma_2 \xi_2^t} + \frac{\sigma_2^2}{2} C(t)e^{\sigma_2 \xi_2^t}.$$ 

So $K_a X_1 - K_{10} C(t)e^{\sigma_2 \xi_2^t} = C'(t)e^{\sigma_2 \xi_2^t} + \frac{\sigma_2^2}{2} C(t)e^{\sigma_2 \xi_2^t}$, i.e.,

$$C'(t) + \left(\frac{\sigma_2^2}{2} + K_{10}\right) C(t) = K_a X_1 e^{-\sigma_2 \xi_2^t}.$$ 

$$C(t) = X_2(0)e^{-\left(\frac{\sigma_2^2}{2} + K_{10}\right) t} + e^{-\left(\frac{\sigma_2^2}{2} + K_{10}\right) t} \int_0^t X_1(0)e^{-\left(\frac{\sigma_2^2}{2} + K_{10}\right) s} e^{-\sigma_2 \xi_2^s} ds.$$ 

Therefore,

$$X_2(t) = C(t)e^{\sigma_2 \xi_2^t} = X_2(0)e^{-\frac{\sigma_2^2}{2} + K_{10} t} + K_a X_1(0)e^{-\frac{\sigma_2^2}{2} + K_{10} t} \int_0^t e^{-\frac{\sigma_2^2}{2} + K_{10} s} e^{-\sigma_2 \xi_2^s} ds.$$ 

In conclusion, the solution of the system (11) is

$$X_1(t) = X_1(0) \exp\left(\sigma_1 \xi_1^t - K_a t + \frac{\sigma_1^2}{2} t\right),$$

$$X_2(t) = X_2(0) e^{-\sigma_2 \xi_2^t - \left(K_a + \frac{\sigma_1^2}{2}\right)t} + K_a X_1(0) e^{-\sigma_2 \xi_2^t - \left(K_a + \frac{\sigma_1^2}{2}\right)t} \int_0^t e^{\sigma_1 \xi_1^t - \sigma_2 \xi_2^t + \left(\frac{\sigma_1^2}{2} + K_{10}\right) s} e^{-\sigma_2 \xi_2^s} ds.$$ 

IV. QUALITATIVE ANALYSIS OF THE FIRST-ORDER 1-COMPARTMENT STOCHASTIC MODEL

Theorem 3: The solution of the stochastic model (11) is unique.

Since the stochastic system model (11) is a linear system, the uniqueness of its solution can be obtained directly from Theorem 2.1 in Reference [17].

Theorem 4: If $\sigma_1$ and $\sigma_2$ satisfies

$$A = \begin{bmatrix} \frac{K_a}{2K_{10}(K_a + K_{10})} + \frac{1}{2K_a} & \frac{\sigma_1^2}{2K_{10}} \\ \frac{\sigma_2^2}{2K_{10}} & 1 \end{bmatrix} \sigma_1^2 < 1,$$

$$B = \begin{bmatrix} \frac{K_a}{2K_{10}(K_a + K_{10})} + \frac{1}{2K_a} & \frac{\sigma_2^2}{2K_{10}} \\ \frac{\sigma_2^2}{2K_{10}} & 1 \end{bmatrix} \sigma_2^2 < 1,$$

then the trivial solution of the stochastic model (11) is stochastically stable.

Proof: Let the Lyapunov function be $V(x, t) = x^T Q x$, where $A = \begin{bmatrix} -K_a & 0 \\ K_a & -K_{10} \end{bmatrix}$, $x = [X_1, X_2]^T$ and

$$Q = \begin{bmatrix} q_{11} & q_{12} \\ q_{12} & q_{22} \end{bmatrix}$$

is symmetric and satisfies $A^T Q + QA = -I$ which implies

$$\begin{cases} 2K_a (q_{12} - q_{11}) = -1, \\ K_a (q_{22} - q_{12}) - K_{10} q_{12} = 0, \\ -2K_{10} q_{22} = -1. \end{cases}$$

Solve this system, we obtain

$$Q = \begin{bmatrix} \frac{K_a}{2K_{10}(K_a + K_{10})} + \frac{1}{2K_a} & \frac{K_a}{2K_{10}(K_a + K_{10})} \\ \frac{K_a}{2K_{10}(K_a + K_{10})} & \frac{1}{2K_{10}} \end{bmatrix}.$$

By the application, we know $K_a > 0$ and $K_{10} > 0$, hence

$$q_{11} = \frac{K_a}{2K_{10}(K_a + K_{10})} + \frac{1}{2K_a} > 0.$$ 

Moreover,

$$|Q| = \frac{1}{4K_a K_{10}} + \frac{K_a}{4K_{10}(K_a + K_{10})^2} > 0.$$ 

Thus, $Q$ is a symmetric positive-definite matrix as required. Moreover, since $V(x, t) = x^T Q x$ is positive-definite if and only if $Q$ is positive-definite, we have that $V(x, t)$ is positive-definite.

Let $f(x(t), t) = [-K_a X_1, K_a X_1 - K_{10} X_2]^T$ and $g(x(t), t) = [\sigma_1 X_1, \sigma_2 X_2]^T$, then

$$LV(x, t) = x^T Q f(x, t) + f^T(x, t) Q g(x, t) = -X_1^2 - X_2^2 + q_{11} X_1^2 + 2q_{12} \sigma_1 \sigma_2 X_1 X_2 + q_{22} \sigma_2^2 X_2^2.$$ 

Define $h(X_1, X_2) = -X_1^2 - X_2^2 + q_{11} X_1^2 + 2q_{12} \sigma_1 \sigma_2 X_1 X_2 + q_{22} \sigma_2^2 X_2^2$, then

$$h_{X_1}(X_1, X_2) = -2X_1 + 2q_{11} \sigma_1^2 X_1 + 2q_{12} \sigma_1 \sigma_2 X_2,$$

$$h_{X_2}(X_1, X_2) = -2X_2 + 2q_{22} \sigma_2^2 X_2 + 2q_{12} \sigma_1 X_1.$$ 

Denote

$$A = h_{X_1}(X_1, X_2) = -2 + 2q_{11} \sigma_1^2 = -2(1 - q_{11} \sigma_1^2),$$

$$B = h_{X_2}(X_1, X_2) = 2q_{12} \sigma_1 \sigma_2,$$

$$C = h_{X_2}(X_1, X_2) = -2 + 2q_{22} \sigma_2^2 = -2(1 - q_{22} \sigma_2^2).$$ 

and let

$$0 = h_{X_1}(X_1, X_2) = -2X_1 + 2q_{11} \sigma_1^2 X_1 + 2q_{12} \sigma_1 \sigma_2 X_2,$$

$$0 = h_{X_2}(X_1, X_2) = -2X_2 + 2q_{22} \sigma_2^2 X_2 + 2q_{12} \sigma_1 X_1.$$ 

i.e.,

$$(1 - q_{11} \sigma_1^2) X_1 = q_{12} \sigma_1 \sigma_2 X_2,$$

$$(1 - q_{22} \sigma_2^2) X_2 = q_{12} \sigma_1 \sigma_2 X_1.$$ 

It's clear that $(0, 0)$ is a solution.

$$AC - B^2 = 4(1 - q_{11} \sigma_1^2)(1 - q_{22} \sigma_2^2) - 4q_{12} \sigma_1 \sigma_2^2$$

$$= 4 \left[ 1 - \left( \frac{K_a}{2K_{10}(K_a + K_{10})} + \frac{1}{2K_a} \right) \sigma_1^2 - \frac{\sigma_2^2}{2K_{10}} \right].$$
If $\sigma_1$ and $\sigma_2$ satisfies $AC - B^2 > 0$ and $A < 0$, $C < 0$, i.e.,

\[
\begin{align*}
K_{a} \left[ \frac{1}{2K_{10}(K_{a} + K_{10})} + \frac{1}{2K_{a}} \right] \sigma_1^2 < 1, \\
\frac{\sigma_1^2}{2K_{10}} < 1, \\
\frac{K_{a}}{2K_{10}(K_{a} + K_{10})} + \frac{1}{2K_{a}} \sigma_2^2 + \frac{\sigma_2^2}{2K_{10}} < 1 + \frac{\sigma_1^2 \sigma_2^2}{4K_{a}K_{10}} + \frac{4K_{a}K_{10}}{4K_{10}(K_{a} + K_{10})^2}.
\end{align*}
\]

then $h(0, 0) = 0$ is the maximum value of $h$. It means $LV = h(X_1, X_2) \leq h(0, 0) = 0$.

Thus, by Theorem 1 (i), the trivial solution is stochastically stable.

V. QUANTITATIVE ANALYSIS OF THE FIRST-ORDER 1-COMPARTMENT MODEL (EXTRAVASCULAR ADMINISTRATION)

A. PARAMETER ESTIMATION OF THE FIRST-ORDER 1-COMPARTMENT MODEL (Extravascular Administration)

In the original ODE model,

\[
\begin{align*}
\frac{dA_{a}}{dt} &= -K_{a}A_{a}, \\
\frac{dA_{c}}{dt} &= K_{a}A_{a} - K_{10}A_{c},
\end{align*}
\]

In order to estimate the parameters $K_{a}$ and $K_{10}$ in the model, firstly, we generated sampled data with $K_{a} = 2, K_{10} = 1$ and with initial concentrations being $A_{a} = 0.957, A_{c} = 0.031$. Then we set the initial values for the optimizer as $K_{a} = K_{10} = 0.5$, and we specify the coefficients drift and diffusion as expressions. We can now use the Levenberg-marquardt routine in package minpack.lm to estimate the parameters $K_{a}$, $K_{10}$, $\alpha$ and $\beta$ of the model.

The estimated coefficients are extracted from the output object fitmod as follows:

**Parameters**:

| Parameter | Estimate | Std. | Error | $t$ value | $Pr(>|t|)$ |
|-----------|----------|------|-------|-----------|------------|
| $K_{a}$   | 2.06204  | 0.02380 | 86.63 | $< 2e - 16$ | $***$      |
| $K_{10}$  | 1.01778  | 0.01051 | 96.83 | $< 2e - 16$ | $***$      |

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Residual standard error: 0.009599 on 36 degrees of freedom
Number of iterations to termination: 6
Reason for termination: Relative error in the sum of squares is at most ‘fiml’.

B. PARAMETER ESTIMATION OF THE FIRST-ORDER 1-COMPARTMENT MODEL WITH OPTIMAL CONTROL

In our revised ODE model with optimal control,

\[
\begin{align*}
\frac{dA_{a}}{dt} &= -K_{a}A_{a} + \alpha u^*, \\
\frac{dA_{c}}{dt} &= K_{a}A_{a} - K_{10}A_{c} + \beta u^*.
\end{align*}
\]

For $u^* = 0$, we have done above. For $u^* = 1$, in order to estimate the parameters $K_{a}$, $K_{10}$, $\alpha$ and $\beta$ in the model, firstly, we generated sampled data with $K_{a} = 2, K_{10} = 1$, $\alpha = 0.16$, $\beta = 0.2$, and with initial concentrations being $A_{a} = 0.957, A_{c} = 0.031$. Then we set the initial values for the optimizer as $K_{a} = K_{10} = 0.5$, $\alpha = 0.12$, $\beta = 0.03$, and we specify the coefficients drift and diffusion as expressions. We can now use the Levenberg-marquardt routine in package minpack.lm to estimate the parameters $K_{a}$, $K_{10}$, $\alpha$ and $\beta$ of the model.

The estimated coefficients are extracted from the output object fitmod as follows:

**Parameters**:

| Parameter | Estimate | Std. | Error | $t$ value | $Pr(>|t|)$ |
|-----------|----------|------|-------|-----------|------------|
| $K_{a}$   | 2.07126  | 0.03118 | 66.419 | $< 2e - 16$ | $***$      |
| $K_{10}$  | 1.03649  | 0.03128 | 33.131 | $< 2e - 16$ | $***$      |
| $\alpha$  | 0.83755  | 0.03572 | 23.447 | $< 2e - 16$ | $***$      |
| $\beta$   | 0.21409  | 0.07052 | 3.036  | $0.00444 *$ |

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Residual standard error: 0.009599 on 36 degrees of freedom
Number of iterations to termination: 6
Reason for termination: Relative error in the sum of squares is at most ‘fiml’.

C. SIMULATIONS OF THE THREE FIRST-ORDER 1-COMPARTMENT MODELS

Using the above estimated parameters in V.A and V.B, we solved the three models numerically and plotted the simulation curves (Figure 1, 2, 3), then compared the three models visually.

For $0 < u(t) < 1$, all of the curves of $(A_{a}, A_{c})$ are between curves on Figure 1 and Figure 2. It’s clear that our revised ODE model with optimal control increased the amount of drug absorption deposit $(A_{a})$ and drug in central compartment $(A_{c})$, and SDE with optimal control model did the same improvement but with consideration of the influences that are not completely understood or not feasible to model explicitly. So the SDE with optimal control model improves the model and is more reasonable than the original ODE model and our revised ODE model with optimal control. If we keep the same $(A_{a}, A_{c})$, then we need less drug dosage.
1) USING NUMERICAL METHOD TO VERIFY THE EXPLICIT SOLUTION OF THE FIRST ORDER 1-COMPARTMENT SDE MODEL

In this section, we’ll give a theorem for the stability of the EM method [24], [25] for our SDE with optimal control model (11). Then we’ll verify our explicit solutions of our SDE with optimal control model through comparing the explicit solution with the numerical solution from Euler-Maruyama(E-M) method.

**Theorem 5:** If \( \frac{\sigma^2}{\sigma^2 - 2K_a} > K^2_a \), then for any sufficiently small step size \( \Delta \), the E-M approximate solution of the SDE model (11) is stable in distribution.

**Proof:** Let \( X(t) = \begin{bmatrix} \sigma_X(t) \\ X(t) \end{bmatrix} \), \( A = \begin{bmatrix} -K_a & 0 \\ K_a & -K_{10} \end{bmatrix} \), \( B_1 = \begin{bmatrix} \sigma_1 \\ 0 \end{bmatrix} \), \( B_2 = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \), \( \xi(t) = \begin{bmatrix} \xi_1(t) \\ \xi_2(t) \end{bmatrix} \). Then
\[
\frac{\sigma^2}{\sigma^2 - 2K_a} < K^2_a.
\]
\[
\left( \frac{\sigma^2}{\sigma^2 - 2K_a} \right) \left( \frac{\sigma^2}{\sigma^2 - 2K_{10}} \right) > K^2_a.
\]

\[
U = B_1^T B_1 + B_2^T B_2 + A + A^T = \begin{bmatrix} \sigma^2 - 2K_a & K_a \\ K_a & \sigma^2 - 2K_{10} \end{bmatrix}.
\]

If
\[
\frac{\sigma^2}{\sigma^2 - 2K_a} < 0,
\]
\[
\left| U \right| = \left( \frac{\sigma^2}{\sigma^2 - 2K_a} \right) \left( \frac{\sigma^2}{\sigma^2 - 2K_{10}} \right) - K^2_a > 0,
\]

then \( U \) is negative-definite, so by Theorem 2 for any sufficiently small step size \( \Delta \), the E-M approximate solution of the SDE with optimal control model (11) is stable in distribution.

In our SDE with optimal control model (11), \( K_a = 2.07126 \), \( K_{10} = 1.03649 \), \( \sigma_1 = 0.5 \), and \( \sigma_2 = 0.1 \), so
\[
\frac{\sigma^2}{\sigma^2 - 2K_a} = 0.5^2 - 2(2.07126) = -3.89252 < 0,
\]
\[
\left( \frac{\sigma^2}{\sigma^2 - 2K_a} \right) \left( \frac{\sigma^2}{\sigma^2 - 2K_{10}} \right) = (-3.89252)(-2.06298) = 8.03019091 > 4.290117988 = 2.07126^2 = K^2_a.
\]

Thus for any sufficiently small step size \( \Delta \), the E-M approximate solution of our SDE with optimal control model (11) is stable in distribution.

In order to compare the explicit \( A_a \) and the numerical \( A_{an} \), we draw them on the same set of axes (Figure 5), and to show the explicit \( A_a \) and the numerical \( A_{an} \) overlap each other, we also draw them on the same set of axes (Figure 7). In order to compare the explicit \( A_a \) and the numerical \( A_{an} \), we draw them on the same set of axes (Figure 5), and to show the explicit \( A_a \) and the numerical \( A_{an} \) overlap each other, we also draw them on the same set of axes (Figure 7).

From Figure 4 and Figure 5, we can see the two curves of explicit \( A_a \) and the numerical \( A_{an} \) completely overlap each other, thus the explicit solution of \( A_a \) is correct. From Figure 6
and Figure 7, we can see the two curves of explicit totally \( A_c \) and the numerical \( A_c \) also overlap each other, thus the explicit solution of \( A_c \) is also correct.

VI. CONCLUSION

In this paper, we combined optimal control theory and stochastic differential equation and proposed an optimal controlled pharmacokinetic SDE model which provides an optimal dosing and timing schedule. The original ODE PK model was augmented through optimal control analysis and moreover, in order to make the model more reasonable, the optimal control model further was augmented into SDE model by considering the stochastic perturbations of the variables around their values at optimal control equilibrium point being white noise type, which are proportional to the distances of \( A_c \) and \( A_c \) from values at the optimal control equilibrium point.

We got the explicit solution of our SDE model with optimal control and proved the uniqueness and stability of explicit solution. In part V, we discussed our model quantitatively. We estimated the parameters of the model and compared the simulation curves of the three model and found that our SDE model with optimal control increased the amount of drug absorption deposit \( (A_d) \) and drug in central compartment \( (A_c) \) and SDE more reasonable. Then we provided the condition of stability of E-M method and used it to get the numerical solutions. Then we verified our explicit solution is correct through comparing the curves of simulated the explicit and numerical solution.

Reference [12] analyzed a model for cancer chemotherapy that aims at minimizing the damage done to bone marrow cells during the chemotherapy, and concluded that partial doses are not optimal and in principle optimal controls alternate between chemotherapy sessions of “full dose” and rest-periods. Reference [16] established a biomathematical model of human granulopoiesis under chemotherapy which allows predictions of yet untested G-CSF schedules, comparisons between them, and with it, optimization of filgrastim and pegfilgrastim treatment, and showed validity of model predictions regarding alternative G-CSF schedules by clinical trial results. From our study, we conclude theoretically that optimal dosing alternate between sessions of “full dose” or rest periods and partial dosage are not optimal through analyzing the PK model as an optimal control problem. Moreover, we found the switching time of “full dose” and rest-periods which can be used for drug dosage schedule easily. We can see that appropriate control can achieve the best possible therapeutic effect with as few medications as possible so that we can avoid drug side effects. And the stochastic differential equation makes the model more reasonable and the predictions about drug concentration more accurate.

REFERENCES

[1] S. Donnet and A. Samson, “A review on estimation of stochastic differential equations for pharmacokinetic/pharmacodynamic models,” Adv. Drug Del. Rev., vol. 65, no. 7, pp. 929–939, Jun. 2013.
[2] S. Ditlevsen and A. Samson, “Introduction to stochastic models in biology,” in Stochastic Biomathematical Models. Berlin, Germany: Springer, 2013, pp. 3–35.
[3] D. Z. D’Argenio, “Uncertain Pharmacokinetic/Pharmacodynamic systems: Design, estimation and control,” IFAC Proc. Volumes, vol. 30, no. 2, pp. 121–122, Mar. 1997.
[4] M. Ramanathan, “An application of ito’s lemma in population pharmacokinetics and pharmacodynamics,” Pharmaceutical Res., vol. 16, no. 4, pp. 584–586, 1999.
[5] M. Ramanathan, “A method for estimating pharmacokinetic risks of concentration-dependent drug interactions from preclinical data,” Drug Metabolism Disposition, vol. 27, pp. 1479–1487, Dec. 1999.
[6] L. Ferrante, S. Bompadre, and L. Leone, “A stochastic compartmental model with long lasting infusion,” Biometrical J., vol. 45, no. 2, pp. 182–194, Mar. 2003.
[7] C. W. Torné, J. L. Jacobsen, and H. Madsen, “Grey-box pharmacokinetic/pharmacodynamic modelling of a euglycaemic clamp study,” J. Math. Biol., vol. 48, no. 6, pp. 591–604, Jun. 2004.
[8] S. Ditlevsen and A. Degaetano, “Stochastic vs. Deterministic uptake of dodecanedioic acid by isolated rat livers,” Bull. Math. Biol., vol. 67, no. 3, pp. 547–561, May 2005.
[9] S. Ditlevsen and A. Degaetano, “Mixed effects in stochastic differential equation models,” REVSTAT-Stat. J., vol. 3, no. 2, pp. 157–163, 2005.
[10] U. Picchini, S. Ditlevsen, and A. De Gaetano, “Modeling the euglycemic hyperinsulinemic clamp by stochastic differential equations,” J. Math. Biol., vol. 53, no. 5, pp. 771–796, Nov. 2006.
[11] T. Mizuno, M. M. O’Brien, and A. A. Vinks, “Significant effect of infection and food intake on sirolimus pharmacokinetics and exposure in pediatriic patients with acute lymphoblastic leukemia,” Eur. J. Pharmaceutical Sci., vol. 128, pp. 209–214, Feb 2019.
[12] U. Ledzewicz and H. Schättler, “Optimal controls for a model with pharmacokinetics maximizing bone marrow in cancer chemotherapy,” Math. Biosci., vol. 206, no. 2, pp. 320–342, Apr. 2007.
[13] M. Saqlain, M. Alam, D. Brandt, L. Rönnegård, and J. Westin, “Stochastic differential equations modelling of levodopa concentration in patients with parkinson’s disease,” in Proc. 40th Conf. Stochastic Processes App., Gothenburg, Sweden, Jun. 2018, pp. 1–5.
[14] M. Li, W. Qiang, Z. Wen, L. Li, L. Wang, and Z. Cheng, “A new model to describe the single-dose pharmacokinetics of bevacizumab and predict its multiple-dose pharmacokinetics in beagle dogs,” *Iranian J. Pharmaceuti- cal Res.*, vol. 18, no. 3, pp. 1147–1155, 2019.

[15] C.-W. Chiang, P. Zhang, X. Wang, L. Wang, S. Zhang, X. Ning, L. Shen, S. K. Quinney, and L. Li, “Translational high-dimensional drug interaction discovery and validation using health record databases and pharmacokinetics models,” *Clin. Pharmacol. Therapeutics*, vol. 103, no. 2, pp. 287–295, Feb. 2018.

[16] S. Schirm, C. Engel, S. Loibl, M. Loefller, and M. Scholz, “Model-based optimization of G-CSF treatment during cytotoxic chemotherapy,” *J. Cancer Res. Clin. Oncol.*, vol. 144, no. 2, pp. 343–358, Feb. 2018.

[17] X. Mao, *Stochastic Differential Equations and Applications*. Amsterdam, The Netherlands: Elsevier, 2007.

[18] C. Yuan and X. Mao, “Stability in distribution of numerical solutions for stochastic differential equations,” *Stochastic Anal. Appl.*, vol. 22, no. 5, pp. 1133–1150, Jan. 2004.

[19] G. W. Swan, “Role of optimal control theory in cancer chemotherapy,” *Math. Biosciences*, vol. 101, no. 2, pp. 237–284, Oct. 1990.

[20] J. M. Murray, “Optimal drug regimens in cancer chemotherapy for single drugs that block progression through the cell cycle,” *Math. Biosci.*, vol. 123, no. 2, pp. 183–213, Oct. 1994.

[21] A. Bryson and Y. Ho, *Applied Optimal Control: Optimization, Estimation and Control*. Washington, DC, USA: Hemisphere, 1975.

[22] R. Gamkrelidze, L. S. Pontrjagin, and V. G. Boltjanskij, *The Mathematical Theory of Optimal Processes*. New York, NY, USA: Macmillan Company, 1964.

[23] B. Øksendal, *Stochastic Differential Equations*. Springer, 2003.

[24] D. Talay, “Numerical solution of stochastic differential equations,” *Stochastics Stochastics Rep.*, vol. 47, nos. 1–2, pp. 121–126, 2007.

[25] D. J. Higham, “An algorithmic introduction to numerical simulation of stochastic differential equations,” *SIAM Rev.*, vol. 43, no. 3, pp. 525–546, Jan. 2001.

QIANNING LIU received the B.S. degree in applied mathematics from the China University of Mining and Technology, Xuzhou, China, in 2002, and the M.S. and Ph.D. degrees in mathematical statistics from New Mexico State University, Las Cruces, NM, USA, in 2014 and 2018, respectively. Since 2018, she has been an Assistant Professor with the Department of Statistics, Jiangxi University of Finance and Economics, Nanchang, China. Her research interests include machine learning, high dimensional data analysis, nonlinear differential equations, and nonlinear stochastic differential equations that arise in biology and finance. She was a recipient of the NMSU Anna Schrufer Kist Endowed Scholarship, from 2015 to 2017, and the National Science Foundation of USA, travel grant to attend the Seminar on Stochastic Processes, in 2017.

QINGSONG SHAN received the B.S. degree in applied mathematics from the China University of Mining and Technology, Xuzhou, China, in 2002, and the M.S. and Ph.D. degrees in mathematical statistics from New Mexico State University, Las Cruces, NM, USA, in 2010 and 2015, respectively. From 2015 to 2017, he was a Visiting Assistant Professor with the Department of Statistics, Indiana University, Bloomington, IN, USA. Since 2017, he has been an Assistant Professor with the Department of Statistics, Jiangxi University of Finance and Economics, Nanchang, China. His research interests include non-parametric methods, statistical learning methods, and copulas.