MATHEMATICAL MODELING AND COMPUTING, Vol. 9, No. 3, pp. 567–578 (2022)

Quantifying uncertainty of a mathematical model of drug transport in tumors

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(Received 28 October 2021; Accepted 23 March 2022)

This paper presents a numerical simulation in the two-dimensional for a system of PDE governing drug transport in tumors with random coefficients, which is described as a random field. The continuous stochastic field is approximated by a finite number of random variables via the Karhunen–Loève expansion and transform the stochastic problem into a determinate one with a parameter in high dimension. Then we apply a finite difference scheme and the Euler–Maruyama Integrator in time. The Monte Carlo method is used to compute corresponding simple averages. We compute the error estimate using the Central Limits Theorem (CLT) and the error estimate for the finite difference method. Some numerical results are simulated to illustrate the theoretical analysis. We also propose a comparison between the stochastic and determinate solving processes of our system where we show the efficiency of our adopted method.

Keywords: *mathematical models of drug transport in tumors, Monte Carlo method, finite difference method, uncertainty quantification.*

2010 MSC: 93A30, 91G60, 65L12 **DOI:** 10.23939/mmc2022.03.567

1. Introduction

In the last two decades, there has been a large interest in the numerical analyses of the random and stochastic differential equations, due to the increasing need for modeling the uncertainties that arise in many research domains. These uncertainties appear for various reasons, such as the lack of knowledge on the properties of the environments, errors in the measurements, or the lack and insufficiency of measurements in the data, such as boundary conditions, model coefficients, forcing terms, the geometry of the medium, etc. Therefore, many methods have seen a lot of activity to increase the precision of the numerical predictions and to obtain fairly reliable pre-visions on the model at hand. For example Stochastic Galerkin method (see [1–3]), the Multilevel Monte Carlo method (see [4–6]) and Stochastic Collocation method (see [7–9]).

Monte Carlo (MC) method or one of its variants is one of the most commonly used method, because of its simplicity in implementation. Moreover it is suitable for parallelization. Using a spatial discretization of the partial differential equations, given for example by a finite volume method, finite difference method or a Galerkin finite elements method, they generate a set of independent identically distributed approximations of the solutions by sampling the random coefficients of the equation. Then the sample averages of desired statistics can be computed through these approximations. The stochastic Galerkin method is preferred if the noise is described by a small number of random parameters or if the accuracy requirement is sufficiently strict; otherwise, an MC method still seems to be the best choice.

In this paper, we focus our study on the multi-compartment pharmacokinetics model, which is capable of tracking the amount of drugs (Cisplatin) both spatially and temporally through the compartments. There are three compartments for Cisplatin corresponding to (1) Extracellular fluid/matrix, (2) Cytosolic, and (3) DNA-bound drugs. The system of equations governing transport for Cisplatin takes the following form,

$$\begin{cases} \dfrac{\partial S_1}{\partial t} = D_s \Delta S_1 - k'_{12} S_1 + \dfrac{k'_{21}}{V_c} S_2, \\ \dfrac{\partial S_2}{\partial t} = k_{12} V_c S_1 - k_{21} S_2 - k_2 S_2 - k_{23} S_2, \\ \dfrac{\partial S_3}{\partial t} = k_{23} S_2 - k_3 S_3, \end{cases}$$

for $i = 1, 2, 3$, S_i represents the drug concentration in compartment i. The term D_s is the diffusivity of the drug through interstitial space, the parameters k_{ij} represent a transfer rate from compartment i to j. The primed rates k'_{ij} appearing in the first equation are related to their unprimed counterparts via $k'_{ij} = k_{ij}/F$, where F is the extracellular fraction of the whole tissue, V_c is the volume of a cell. The term k_i represents a rate of permanent removal from compartment i (more details can be found in [10–12]). These parameters account for important phenomena, such as cell permeability, efflux pumps, and DNA repair. Their values are obtained through experimental data and are not known with certainty. An efficient and well-established way to deal with this problem is to adopt the probabilistic approach, i.e., consider these imputed parameters as random variables or stochastic processes rather than constants or deterministic functions. Therefore, it is advantageous to consider the equations that describe such models as stochastic rather than deterministic. And so, we aim in this note to analyze numerically the above system of equations with *random coefficients* in 2D using the Monte Carlo method as an attempt to predict the influence of the so-called incertitudes on the system.

The rest of the paper is organized as follows. In Section 2, we introduce the mathematical problem and the main notations used throughout. In Section 3, we present the numerical method and analyze the error. We illustrate the theoretical results by few numerical simulations in Section 4. Finally, we make a conclusion to this work in Section 5.

2. The problem setting and notation

Let D be a convex bounded polygonal domain in $\mathbb{R}^2$, and let $(\Omega, \mathfrak{F}, \mathbb{P})$ be a complete probability space. Here Ω is the set of outcomes, $\mathfrak{F}$ is the σ-algebra of events, and $\mathbb{P} \colon \mathfrak{F} \to [0, 1]$ is a probability measure. Consider the following stochastic system of equation governing transport for both drugs: find the stochastic concentration $S_i \colon D \times (0, T) \times \Omega \longrightarrow \mathbb{R}$ for $i = 1, 2, 3$ such that $\mathbb{P}$-almost everywhere in Ω, i.e., almost surely (a.s.) satisfy the following equations:

$$\begin{cases} \dfrac{\partial S_1}{\partial t} = D_s(x, y, \omega) \Delta S_1 - k'_{12}(x, y, \omega) S_1 + \dfrac{k'_{21}(x, y, \omega)}{V_c(x, y, \omega)} S_2, \\ \dfrac{\partial S_2}{\partial t} = k_{12}(x, y, \omega) V_c(x, y, \omega) S_1 - (k_{21} + k_2 + k_{23})(x, y, \omega) S_2, \\ \dfrac{\partial S_3}{\partial t} = k_{23}(x, y, \omega) S_2 - k_3(x, y, \omega) S_3, \end{cases} \tag{1}$$

subject to random initial conditions

$$\begin{cases} S_1(x, y, t = 0, \omega) = S_{01}(x, y, \omega), \\ S_2(x, y, t = 0, \omega) = S_{02}(x, y, \omega), \\ S_3(x, y, t = 0, \omega) = S_{03}(x, y, \omega), \end{cases} \tag{2}$$

and boundary conditions

$$S_i = 0 \quad \text{on} \quad \partial D \quad \text{for} \quad i = 1, 2, 3. \tag{3}$$

Where S_{0i} for $i = 1, 2, 3$ are some given functions. We assume that the parameters k_{ij}, k'_{ij}, k_i, V_c and D_s are all stochastic functions with continuous and bounded covariance function, to account for uncertainties about the problem data. Our goal is to compute for any $(t, \omega) \in [0, T] \times \Omega$ the quantity of interest (QoI):

$$Q(S_i)(t, \omega) := \int_D S_i(x, y, t, \omega) \, dx \, dy \quad \text{for} \quad i = 1, 2, 3.$$

Using the Karhunen–Loève (KL) expansion [13] for each parameter of our problem considered as stationary random field with continuous covariance function. The solution corresponding to the system of stochastic partial differential equation (1) can be described by just a finite number of random variables, that is, $S_i(x,y,t,Z) = S_i(x,y,t,Z_1(\omega),Z_2(\omega),\dots,Z_N(\omega))$ where the random vector $Z = (Z_1(\omega),Z_2(\omega),\dots,Z_N(\omega))$ has a joint probability density function $\rho\colon \Gamma \to \mathbb{R}_+$ that factorizes $\rho(Z) = \prod_{n=1}^{N}\rho_n(Z_n)$ for all $Z \in \Gamma \subset \mathbb{R}^{\mathbb{N}}$ with $\Gamma = \Gamma_1 \times \Gamma_2\times,\dots,\Gamma_N$, where Γ_n is the bounded image set of the random variables $Z_n(\Omega)$. Then we can rewrite our problem with an N-dimensional parameter as follows:

$$\begin{cases} \dfrac{\partial S_1}{\partial t}(x,y,t;Z) = D_s(x,y,Z)\varDelta S_1(x,y,t;Z) - k'_{12}(x,y,Z)S_1(x,y,t;Z) + \dfrac{k'_{21}(x,y,Z)}{V_c(x,y,Z)}S_2(x,y,t;Z),\\ \dfrac{\partial S_2}{\partial t}(x,y,t;Z) = k_{12}(x,y,Z)V_c(x,y,Z)S_1(x,y,t;Z) - \big(k_{21}+k_2+k_{23}\big)(x,y,Z)S_2(x,y,t;Z),\\ \dfrac{\partial S_3}{\partial t}(x,y,t;Z) = k_{23}(x,y,Z)S_2(x,y,t;Z) - k_3(x,y,Z)S_3(x,y,t;Z), \end{cases} \tag{4}$$

subject to random initial conditions

$$\begin{cases} S_1(x,y,t=0;Z) = S_{01}(x,y,Z),\\ S_2(x,y,t=0;Z) = S_{02}(x,y,Z),\\ S_3(x,y,t=0;Z) = S_{03}(x,y,Z), \end{cases}$$

and boundary conditions

$$S_i = 0 \quad \text{on} \quad \partial D \quad \text{for} \quad i=1,2,3.$$

3. Numerical method and error analysis

We consider the partition of space domain D and time interval $[0,T]$ as a uniform grids

$$\begin{aligned} x_i &= i\varDelta x, \quad i=0,1,\dots,N_x+1,\\ y_j &= j\varDelta y, \quad j=0,1,\dots,N_y+1,\\ t^n &= n\varDelta t, \quad n=0,1,\dots,N_t+1, \end{aligned}$$

with $\varDelta x$, $\varDelta y$, and $\varDelta t$ are respectively the mesh sizes along the x, y directions and the time step size, N_x, N_y, and N_t are three integers.

Denote by $S^{n,z}_{1,i,j}$, $S^{n,z}_{2,i,j}$ and $S^{n,z}_{3,i,j}$ the approximation of the extra-cellular concentration field $S_1(t^n,x_i,y_j,Z)$, cytosolic concentration field $S_2(t^n,x_i,y_j,Z)$, and the nuclear concentration field $S_3(t^n,x_i,y_j,Z)$ respectively. We denote also $k'^{i,j,z}_{lk} = k'_{lk}(x_i,y_j,Z)$, $k^{i,j,z}_{lk} = k_{lk}(x_i,y_j,Z)$, $k^{i,j,z}_{l} = k_l(x_i,y_j,Z)$, $D^{i,j,z}_s = D_s(x_i,y_j,Z)$ and $V^{i,j,z}_c = V_c(x_i,y_j,Z)$ for any fixed random vector Z.

For any fixed random vector Z, the explicit finite difference (FD) scheme for the system (4) is defined as follows

$$\begin{aligned} S^{n+1,z}_{1,i,j} &= \left(1 - \varDelta t\left(k'^{i,j,z}_{12} + D^{i,j,z}_s\left(\frac{2}{\varDelta x^2}+\frac{2}{\varDelta y^2}\right)\right)\right)S^{n,z}_{1,i,j} + D^{i,j,z}_s\frac{\varDelta t}{\varDelta x^2}\left(S^{n,z}_{1,i+1,j} - S^{n,z}_{1,i-1,j}\right) \\ &\quad + D^{i,j,z}_s\frac{\varDelta t}{\varDelta y^2}\left(S^{n,z}_{1,i,j+1} - S^{n,z}_{1,i,j-1}\right) + \varDelta t\frac{k'^{i,j,z}_{21}}{V^{i,j,z}_c}S^{n,z}_{2,i,j}, \end{aligned} \tag{5}$$

$$S^{n+1,z}_{2,i,j} = \left(1 - \varDelta t\left(k^{i,j,z}_{21} + k^{i,j,z}_{2} + k^{i,j,z}_{23}\right)\right)S^{n,z}_{2,i,j} + \varDelta t\, k^{i,j,z}_{12}V^{i,j,z}_c S^{n,z}_{1,i,j}, \tag{6}$$

$$S^{n+1,z}_{3,i,j} = \left(1 - \varDelta t\, k^{i,j,z}_{3}\right)S^{n,z}_{3,i,j} + \varDelta t\, k^{i,j,z}_{23}S^{n,z}_{2,i,j}. \tag{7}$$

The boundary values for scheme (5)–(7) can be derived explicitly using boundary conditions as,

$$S^{n,z}_{k,0,j} = S^{n,z}_{k,N_x+1,j} = S^{n,z}_{k,i,0} = S^{n,z}_{k,i,N_y+1} = 0 \quad \text{for} \quad k=1,2,3.$$

The initial values $S^{0,z}_{k,i,j}$ for $k=1,2,3$ are given as

$$S^{0,z}_{k,i,j} = S_{0k}(x_i,y_i,Z).$$

For grid functions $M := \{M_{i,j}, i = 0, 1, \dots, N_x + 1, j = 0, 1, \dots, N_y + 1\}$, we introduce the following norm

$$\|M\|_{l^2(D)} = \left(\sum_{i=0}^{N_x+1} \sum_{j=0}^{N_y+1} (M_{i,j})^2 \Delta x \Delta y \right)^{1/2}.$$

Throughout the rest of this work, in particular for the theoretical analysis, we will assume that the solution of the system (1)–(3) acquires the following regularity property: for any fixed random vector Z,

$$S_k \in C^1\left([0,T], C^3(\bar{D})\right) \quad \text{for} \quad k = 1, 2, 3. \tag{8}$$

Theorem 1. *Let Z be a fixed random vector and*

$$S_k^n := \{S_{k,i,j}^{n,z}, i = 0, 1, \dots, N_x + 1, j = 0, 1, \dots, N_y + 1\} \quad \text{for} \quad k = 1, 2, 3 \quad \text{and} \quad n \geqslant 0 \tag{9}$$

the solution of the FD scheme (5)–(7).

Suppose that the exact solutions S_1, S_2 and S_3 satisfy the regularity property (8). For any $0 \leqslant i \leqslant N_x + 1$ and $0 \leqslant j \leqslant N_y + 1$, if we assume the following inequalities to hold true

$$\left|1 - \Delta t\big(k_{21}^{i,j,z} + k_2^{i,j,z} + k_{23}^{i,j,z}\big)\right|^2 + 8\Delta t^2 \left|\frac{k'_{21} i, j, z}{V_c^{i,j,z}}\right|^2 + 2\Delta t^2 |k_{23}^{i,j,z}|^2 \leqslant 1/2,$$

$$\left|1 - \Delta t\left(k_{12}'^{i,j,z} + D_s^{i,j,z}\left(\frac{2}{\Delta x^2} + \frac{2}{\Delta x^2}\right)\right)\right|^2 + 8\left|D_s^{i,j,z}\frac{\Delta t}{\Delta x^2}\right|^2 + 16\left|D_s^{i,j,z}\frac{\Delta t}{\Delta y^2}\right|^2 + 2\big|\Delta t\, k_{12}^{i,j,z} V_c^{i,j,z}\big|^2 \leqslant \frac{1}{2},$$

$$\big|1 - \Delta t\, k_3^{i,j,z}\big|^2 \leqslant \frac{1}{2}, \qquad \Delta t \leqslant \frac{1}{16}.$$

Then, for any fixed $T > 0$ there exists a positive constant C_T independent on Δx, Δy and Δt such that

$$\max_{0 \leqslant n \leqslant N_T} \left(\sum_{k=1}^{3} \left\|S_k(t^n) - S_k^n\right\|_{l^2(D)}^2 \right)^{1/2} \leqslant C_T\big(\Delta t + \Delta x^2 + \Delta y^2\big).$$

Proof. Let

$$L_{1,i,j}^n = S_1(t^n, x_i, y_j, Z) - S_{1,i,j}^{n,z}, \quad L_{2,i,j}^n = S_2(t^n, x_i, y_j, Z) - S_{2,i,j}^{n,z}, \quad L_{3,i,j}^n = S_3(t^n, x_i, y_j, Z) - S_{3,i,j}^{n,z}.$$

Subtracting (5)–(7) from three equations of (1), we obtain the following error equations

$$\begin{aligned}
L_{1,i,j}^{n+1} &= \left(1 - \Delta t\left(k_{12}'^{i,j,z} - D_s^{i,j,z}\left(\frac{2}{\Delta x^2} + \frac{2}{\Delta y^2}\right)\right)\right) L_{1,i,j}^n + D_s^{i,j,z}\frac{\Delta t}{\Delta x^2}\big(L_{1,i+1,j}^n - L_{1,i-1,j}^n\big) \\
&\quad + D_s^{i,j,z}\frac{\Delta t}{\Delta y^2}\big(L_{1,i,j+1}^n - L_{1,i,j-1}^n\big) + \Delta t\,\frac{k_{21}'^{i,j,z}}{V_c^{i,j,z}} L_{2,i,j}^n + \Delta t\,\tau_{1,i,j}^n, \\
L_{2,i,j}^{n+1} &= \left(1 - \Delta t\left(k_{21}^{i,j,z} + k_2^{i,j,z} + k_{23}^{i,j,z}\right)\right) L_{2,i,j}^n + \Delta t\, k_{12}^{i,j,z} V_c^{i,j,z} L_{1,i,j}^n + \Delta t\,\tau_{2,i,j}^n, \\
L_{3,i,j}^{n+1} &= \big(1 - \Delta t\, k_3^{i,j,z}\big) L_{3,i,j}^n + \Delta t\, k_{23}^{i,j,z} L_{2,i,j}^n + \Delta t\,\tau_{3,i,j}^n.
\end{aligned}$$

Where $\tau_{1,i,j}^n$, $\tau_{2,i,j}^n$ and $\tau_{3,i,j}^n$ are the truncation errors which can be written as

$$\begin{aligned}
\tau_{1,i,j}^n &= \frac{\Delta t}{2}\frac{\partial^2 S_1}{\partial t^2}(\alpha_{1,n}, x_i, y_j, z) - \frac{\Delta x^2}{4!}\frac{\partial^4 S_1}{\partial x^4}(t^n, \beta_i, y_j, z) - \frac{\Delta y^2}{4!}\frac{\partial^4 S_1}{\partial y^4}(t^n, x_i, \gamma_j, z), \\
\tau_{2,i,j}^n &= \frac{\Delta t}{2}\frac{\partial^2 S_2}{\partial t}(\alpha_{2,n}, x_i, y_j, z), \\
\tau_{3,i,j}^n &= \frac{\Delta t}{2}\frac{\partial^2 S_3}{\partial t^2}(\alpha_{2,n}, x_i, y_j, z).
\end{aligned}$$

Where $t^n \leqslant \alpha_{l,n} \leqslant t^{n+1}$ for $l \in \{1, 2, 3\}$, $x_i \leqslant \beta_i \leqslant x_{i+1}$ and $y_j \leqslant \gamma_j \leqslant y_{j+1}$. Notice that

$$|\tau_{1,i,j}^n| \leqslant \frac{\Delta t}{2}\left\|\frac{\partial^2 S_1}{\partial t^2}\right\|_\infty + \frac{\Delta x^2}{4!}\left\|\frac{\partial^4 S_1}{\partial x^4}\right\|_\infty + \frac{\Delta y^2}{4!}\left\|\frac{\partial^4 S_1}{\partial y^4}\right\|_\infty \leqslant M\big(\Delta t + \Delta x^2 + \Delta y^2\big),$$

$$|\tau^n_{2,i,j}| \leqslant \frac{\Delta t}{2}\left\|\frac{\partial^2 S_2}{\partial t^2}\right\|_\infty \leqslant M\big(\Delta t+\Delta x^2+\Delta y^2\big),$$
$$|\tau^n_{3,i,j}| \leqslant \frac{\Delta t}{2}\left\|\frac{\partial^2 S_3}{\partial t^2}\right\|_\infty \leqslant M\big(\Delta t+\Delta x^2+\Delta y^2\big).$$

With

$$M := \max\left\{\frac{1}{2}\left\|\frac{\partial^2 S_1}{\partial t^2}\right\|_\infty, \frac{1}{2}\left\|\frac{\partial^2 S_2}{\partial t^2}\right\|_\infty, \frac{1}{2}\left\|\frac{\partial^2 S_3}{\partial t^2}\right\|_\infty, \frac{1}{4!}\left\|\frac{\partial^4 S_1}{\partial x^4}\right\|_\infty, \frac{1}{4!}\left\|\frac{\partial^4 S_1}{\partial y^4}\right\|_\infty\right\}.$$

We have

$$|L^{n+1}_{1,i,j}| \leqslant \left|1-\Delta t\left(k'^{i,j,z}_{12}+D^{i,j,z}_s\left(\frac{2}{\Delta x^2}+\frac{2}{\Delta y^2}\right)\right)\right||L^n_{1,i,j}| + D_s\frac{\Delta t}{\Delta x^2}\left(|L^n_{1,i+1,j}|+|L^n_{1,i-1,j}|\right) + D^{i,j,z}_s\frac{\Delta t}{\Delta y^2}\left(|L^n_{1,i,j+1}|+|L^n_{1,i,j-1}|\right)+\Delta t\left|\frac{k'^{i,j,z}_{21}}{V^{i,j,z}_c}\right|\left|L^n_{2,i,j}\right|+\Delta t|\tau^n_{1,i,j}|. \quad (10)$$

Squaring both sides of the inequality (10) and by means of the inequality $(a+b)^2 \leqslant 2(a^2+b^2)$

$$|L^{n+1}_{1,i,j}|^2 \leqslant 2\left|1-\Delta t\left(k'^{i,j,z}_{12}+D^{i,j,z}_s\left(\frac{2}{\Delta x^2}+\frac{2}{\Delta y^2}\right)\right)\right|^2\left|L^n_{1,i,j}\right|^2+8\left(D^{i,j,z}_s\frac{\Delta t}{\Delta x^2}\right)^2\left(|L^n_{1,i+1,j}|^2+|L^n_{1,i-1,j}|^2\right) + 16\left(D^{i,j,z}_s\frac{\Delta t}{\Delta y^2}\right)^2\left(|L^n_{1,i,j+1}|^2+|L^n_{1,i,j-1}|^2\right)+16\Delta t^2\left|\frac{k'^{i,j,z}_{21}}{V^{i,j,z}_c}\right|^2\left|L^n_{2,i,j}\right|^2+\Delta t^2|\tau^n_{1,i,j}|^2. \quad (11)$$

Similarly,

$$|L^{n+1}_{2,i,j}|^2 \leqslant 2\left|1-\Delta t\big(k^{i,j,z}_{21}+k^{i,j,z}_{2}+k^{i,j,z}_{21}\big)\right|^2|L^n_{2,i,j}|^2+4\Delta t^2\left|k^{i,j,z}_{12}V^{i,j,z}_c\right|^2|L^n_{1,i,j}\big|^2+4\Delta t^2\big|\tau^n_{2,i,j}\big|^2 \quad (12)$$

and

$$\big|L^{n+1}_{3,i,j}\big|^2 \leqslant 2\big|1-\Delta t\, k^{i,j,z}_3\big|^2\big|L^n_{3,i,j}\big|^2+4\Delta t^2\big|k^{i,j,z}_{23}\big|^2\big|L^n_{2,i,j}\big|^2+4\Delta t^2\big|\tau^n_{3,i,j}\big|^2. \quad (13)$$

Adding up the inequalities (11), (12), and (13) then multiplying by $\Delta x\Delta y$ and summing up on $\{i,j\} \in [1,\dots,N_x]\times[1,\dots,N_y]$, we get

$$\big\|L^{n+1}_1\big\|^2_{l^2(D)}+\big\|L^{n+1}_2\big\|^2_{l^2(D)}+\big\|L^{n+1}_3\big\|^2_{l^2(D)} \leqslant \big\|L^n_1\big\|^2_{l^2(D)}+\big\|L^n_2\big\|^2_{l^2(D)}+\big\|L^n_3\big\|^2_{l^2(D)} + \Delta t\big(\big\|\tau^n_1\big\|^2_{l^2(D)}+\big\|\tau^n_2\big\|^2_{l^2(D)}+\big\|\tau^n_3\big\|^2_{l^2(D)}\big), \quad (14)$$

where the hypothesis of the theorem has been used. The inequality (14) and the estimates of truncation errors conclude the proof. ■

Given a number of realization M, we can compute discretization solution $S_{i,h,\Delta t}(Z(\omega_m))$ for each $m=1,2,\dots,M$ and $i=1,2,3$, by the scheme (5)–(7). Then we can compute the empirical mean and variance estimators by the Monte Carlo method $E_M(S_{i,h,\Delta t}) := \frac{1}{M}\sum_{m=1}^M S_{i,h,\Delta t}(Z(\omega_m))$, $E_M(Q(S_{i,h,\Delta t})) := \frac{1}{M}\sum_{m=1}^M Q(S_{i,h,\Delta t}(Z(\omega_m))$, $\mathrm{Var}_M(S_{i,h,\Delta t}) := \frac{1}{M}\sum_{m=1}^M |S_{i,h,\Delta t}(Z(\omega_m)) - E_M(S_{i,h,\Delta t})|^2$ and $\mathrm{Var}_M(Q(S_{i,h,\Delta t})) := \frac{1}{M}\sum_{m=1}^M |Q(S_{i,h,\Delta t})(Z(\omega_m)) - E_M(Q(S_{i,h,\Delta t}))|^2$ to approximate respectively $\mathbb{E}(S_i)$, $\mathbb{E}(Q(S_i))$, $\mathrm{Var}(S_i)$ and $\mathrm{Var}(Q(S_i))$.

In the rest of this section, we fixed the time at $t=T$. Using the triangular inequality the computational error is then separated into two parts:

$$\left|\mathbb{E}\big(Q(S_i)(Z)\big)-\frac{1}{M}\sum_{m=1}^M Q\big(S_{i,h,\Delta t}\big)\big(Z(\omega_m)\big)\right| \leqslant \big|\mathbb{E}\big(Q(S_i)(Z)\big)-\mathbb{E}\big(Q(S_{i,h,\Delta t})(Z)\big)\big| + \left|\mathbb{E}\big(Q(S_{i,h,\Delta t})(Z)\big)-\frac{1}{M}\sum_{m=1}^M Q\big(S_{i,h,\Delta t}\big)\big(Z(\omega_m)\big)\right| = \xi_{h,\Delta t}+\xi_s,$$

where the size of the spatial and temporal discretization $h:=(\Delta x,\Delta y)$ and Δt controls the discretization error $\xi_{h,\Delta}$ while the number of realizations M of $S_{i,h,\Delta t}$ controls the statistical error ξ_s.

3.1. Discretization error

Since the measure of D is assumed to be finite, there are C_1 and C_2 positive constants such that:

$$\|\cdot\|_{L^1(D)} \leqslant C_1\|\cdot\|_{L^2(D)} \leqslant C_2\|\cdot\|_{l^2(D)}, \tag{15}$$

using this inequality we have any $Z \in \Gamma$:

$$\begin{aligned}\big|Q(S_i)(Z) - Q(S_{i,h,\Delta t})(Z)\big| &= \left|\int_D \big(S_i(x,y,T,Z) - S_{i,h,\Delta t}(x,y,T,Z)\big)dx\,dy\right| \\ &\leqslant \int_D \big|S_i(x,y,T,Z) - S_{i,h,\Delta t}(x,y,T,Z)\big|dx\,dy \\ &\leqslant C_2\big\|S_i(T,Z) - S_{i,h,\Delta t}(T,Z)\big\|_{l^2(D)},\end{aligned}$$

by the inequality (15) together with Theorem 1

$$\begin{aligned}\xi_{h,\Delta t} &= |\mathbb{E}(Q(S_i)(Z)) - \mathbb{E}(Q(S_{i,h,\Delta t})(Z))| \\ &= |\mathbb{E}(Q(S_i)(Z) - Q(S_{i,h,\Delta t})(Z))| \\ &\leqslant C_2||S_i(T,Z) - S_{i,h,\Delta t}(T,Z)||_{l^2(D)} \\ &\leqslant C_2C_T(\Delta t + \Delta x^2 + \Delta y^2).\end{aligned}$$

3.2. The statistical error

To analyze the statistics error, we first recall the following theorem for its reasonable use in our demonstration.

Theorem 2 (CLT). *Assume ξ_k, $k = 1,2,\dots$ are i.i.d and $\mathbb{E}(\xi_k) = 0$, $\mathbb{E}(\xi_k^2) = 1$ then*

$$\sum_{k=1}^{M} \frac{\xi_k}{\sqrt{M}} \rightharpoonup \lambda, \tag{16}$$

where λ is $N(0,1)$ and $\rightharpoonup$ denotes the weak convergence; that is, the convergence (16) means that the following limit holds as $M \to +\infty$:

$$\mathbb{E}\left(g\bigg(\sum_{k=1}^{M}\frac{\xi_k}{\sqrt{M}}\bigg)\right) \longrightarrow \mathbb{E}\big(g(\lambda)\big), \tag{17}$$

for all bounded and continuous function g.

Proof. See [14], page 23. ∎

We have for $i = 1,2,3$

$$\begin{aligned}\xi_s(M) &= \left|\mathbb{E}\big(Q(S_{i,h,\Delta t})(Z)\big) - \frac{1}{M}\sum_{m=1}^{M} Q\big(S_{i,h,\Delta t}\big)\big(Z(\omega_m)\big)\right| \\ &= \left|\frac{1}{M}\sum_{m=1}^{M}\left\{\mathbb{E}\big(Q(S_{i,h,\Delta t})(Z)\big) - Q\big(S_{i,h,\Delta t}\big)\big(Z(\omega_m)\big)\right\}\right|,\end{aligned}$$

then $\mathbb{E}(\xi_s(M)) = 0$ and $\mathrm{Var}(\xi_s(M)) = \frac{1}{M}\mathrm{Var}(Q(S_{i,h,\Delta t}))$ and we can estimate

$$\begin{aligned}\mathrm{Var}(Q(S_{i,h,\Delta t})) &= \mathbb{E}(Q(S_{i,h,\Delta t})^2) \\ &= \mathbb{E}\left(\left(\int_D S_{i,h,\Delta t}(x,y,T,Z)\,dx\,dy\right)^2\right) \\ &\leqslant C_1^2\mathbb{E}\big(\|S_{i,h,\Delta t}\|^2_{L^2(D)}\big) \\ &\leqslant C_1^2\big\|S_{i,h,\Delta t}\big\|^2_{L^2_\rho(\Gamma,L^2(D))}\end{aligned}$$

$$\leqslant 2C_1^2\big(\|S_i\|^2_{L^2_\rho(\Gamma,L^2(D))} + \|S_i - S_{i,h,\Delta t}\|^2_{L^2_\rho(\Gamma,L^2(D))}\big)$$
$$\leqslant 2C_1^2\big(\|S_i\|^2_{L^2_\rho(\Gamma,L^2(D))} + C_2^2\big(\Delta t + \Delta x^2 + \Delta y^2\big)^2\big)$$
$$< +\infty,$$

where $\|S\|_{L^2_\rho(\Gamma;L^2(D))} := \big(\int_\Gamma \|S(z)\|^2_{L^2(D)}\rho(z)dz\big)^{1/2}$. We conclude that

$$\mathrm{Var}\big(\xi_s(M)\big) \leqslant \frac{C}{M} \to 0, \quad M \to +\infty, \tag{18}$$

with the constant C uniformly bounded with respect to Δt, Δx, and Δy. Since $\mathrm{Var}(Q(S_{i,h,\Delta t})(Z)) \leqslant C$, by this result and using the Chebyshev inequality we have for any given $\varepsilon > 0$:

$$\mathbb{P}\big(|\xi_s(M)| > \varepsilon\big) \leqslant \frac{\mathrm{Var}(\xi_s(M))}{\varepsilon^2} \leqslant \frac{C}{\varepsilon^2}.$$

Let $Y = Q(S_{i,\Delta t,h})(Z)$, $Y_j = Q(S_{i,\Delta t,h})(Z(\omega_j))$, Y_j, $j = 1,2,3,\dots$ be i.i.d random variable with $\mu := \mathbb{E}(Y_j) < +\infty$ and $\sigma := \mathrm{Var}(Y_j) < +\infty$. We have

$$\xi_s(M) = \left|\frac{1}{M}\sum_{j=1}^{M} Y_j - \mathbb{E}(Y)\right| = \left|\sum_{j=1}^{M}\frac{Y_j - \mathbb{E}(Y)}{M}\right|,$$

let $\zeta_j = (Y_j - \mu)/\sigma$, then ζ_j, $j = 1,2,3,\dots$, are i.i.d, and $\mathbb{E}(\zeta_j) = 0$, $\mathbb{E}(\zeta_j^2) = 1$. Then by Theorem 2,

$$\begin{aligned}\sqrt{M}\xi_s(M) &= \left|\sqrt{M}\sum_{j=1}^{M}\frac{Y_j - \mathbb{E}(Y)}{M}\right| \\ &= \left|\sum_{j=1}^{M}\frac{Y_j - \mathbb{E}(Y)}{\sqrt{M}}\right| \\ &= \left|\sum_{j=1}^{M}\frac{Y_j - \mu}{\sqrt{M}}\right| \\ &= \left|\sum_{j=1}^{M}\frac{\sigma\zeta_j + \mu - \mu}{\sqrt{M}}\right| \\ &= \sum_{j=1}^{M}\frac{\sigma\zeta_j}{\sqrt{M}} \rightharpoonup \sigma\lambda,\end{aligned}$$

where λ is $\mathcal{N}(0,1)$, using this result and the Central Limits Theorem (CLT), that is

$$\mathbb{P}\left(\left|\frac{\sqrt{M}\xi_s(M)}{\sigma}\right| \leqslant C_0\right) \approx \mathbb{P}(|\lambda| \leqslant C_0) \mapsto 2\varphi(C_0) - 1, \quad \text{as} \quad M \mapsto +\infty,$$

with $\varphi(x) := \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{x} e^{-t^2/2}dt$. We can write the statistical error for $i = 1,2,3$ as

$$\xi_s(M) = \left|\mathbb{E}\big(Q(s_{i,h,\Delta t})(Z)\big) - \frac{1}{M}\sum_{m=1}^{M} Q(s_{i,h,\Delta t})\big(Z(\omega_m)\big)\right| \leqslant \frac{C_0\sigma}{\sqrt{M}},$$

where exact variance σ is in practice approximated by the sample variance

$$\hat{\sigma} := \frac{1}{M}\sum_{j=1}^{M}\left(Y_j - \sum_{m=1}^{M}\frac{Y_m}{M}\right)^2, \tag{19}$$

thus we have the following (CLT) error bounded

$$\xi_s(M) \leqslant \frac{C_0\hat{\sigma}}{\sqrt{M}},$$

where C_0 is an appropriate constant.

4. Results and discussion

To justify our theoretical analysis and show the efficiency of the proposed method, we will perform in this section two numerical tests with the deterministic initial condition, $S_{01}(x,y) = 0.05\,\mathrm{kg/m^3}$, $S_{02}(x,y) = 0.05\,\mathrm{kg/m^3}$ and $S_{03}(x,y) = 0.05\,\mathrm{kg/m^3}$, the parameters k_{12}, k_{21}, k'_{12}, k'_{21}, k_2, k_3, V_c and D_s are chosen as follow:

$$\begin{aligned}
V_c(x,y,Z) &= |520\cdot 10^{-6} + 10^{-4}\cdot\sin((Z_1+Z_2+Z_3)x - (Z_4+Z_5+Z_6)y)|,\\
k_{12}(x,y,Z) &= |1.48 - 0.1\cdot\sin((Z_1+Z_2+Z_3)x - (Z_4+Z_5+Z_6)y)|,\\
k'_{12}(x,y,Z) &= k_{12}(x,y,Z)/0.48,\\
k_{21}(x,y,Z) &= |0.071 + 0.1\cdot\cos((Z_1+Z_2+Z_3)x - (Z_4+Z_5+Z_6)y)|,\\
k'_{21}(x,y,Z) &= k_{21}(x,y,Z)/0.48,\\
k_2(x,y,Z) &= |1.55 + 0.5\cdot\sin((Z_1+Z_2+Z_3)x + 2(Z_4+Z_5+Z_6)y)|,\\
k_{23}(x,y,Z) &= |11.8 + 0.1\cdot\sin((Z_1+Z_2+Z_3)x - 2(Z_4+Z_5+Z_6)y)|,\\
k_3(x,y,Z) &= |0.95 + 0.2\cdot\sin((Z_1+Z_2+Z_3)x - (Z_4+Z_5+Z_6)y)|,\\
D_s(x,y,Z) &= |0.003 + 10^{-2}\cdot\sin((Z_1+Z_2+Z_3)x - (Z_4+Z_5+Z_6)y)|,
\end{aligned}$$

where $(x,y)\in D = [0,1]\times[0,1]$ and Z_k $(0\leqslant k\leqslant 6)$ is a uniform independent random variable on $[0,1]$. To guarantee the hypotheses of theorem 1 and the stability of the FD scheme applied to our system of equation (4), we use the partition size in x and y direction $h = \Delta x = \Delta y = 0.01$ and we set the time partition $\Delta t = 10^{-2}\,\mathrm{h}$.

4.1. Test 1

In this part, the influence of the number of realizations M is discussed. We define the random variables X^i_m for $i = 1, 2$ and 3 by

$$X^i_m := Q(S_i)\big(Z(\omega_m)\big) = \int_D S_i\big(x,y,T,Z(\omega_m)\big)\,dx\,dy,$$

for each realization m we calculate X^i_m using the same scheme (Simpson, etc.), the series $\{X^i_m\}_{\{m=1,2,3,\dots,M\}}$ is independently and identically distributed.

We denote by $\bar\mu$ and $\bar\sigma^2$ the corresponding expectation and variance respectively. By the Central Limit Theorem :

$$\mathbb{P}\bigg(-z\leqslant \frac{\frac{1}{M}\sum_{m=1}^M X^i_m - \bar\mu}{\bar\sigma^2/M}\leqslant z\bigg)\longrightarrow \frac{1}{\sqrt{2\pi}}\int_{-z}^{z} e^{-t^2/2}dt,\quad z\in\mathbb{R}\quad\text{and}\quad i=1,2,3.$$

The confidence interval of the expectation $\bar\mu$ at the level $1-p$ is given by:

$$\big[I_1(M), I_2(M)\big] = \left[\frac{1}{M}\sum_{m=1}^M X^i_m - z_p\sqrt{\bar\sigma^2/M}, \frac{1}{M}\sum_{m=1}^M X^i_m + z_p\sqrt{\bar\sigma^2/M}\right]\quad\text{for}\quad i=1,2,3,$$

where the unknown variance $\bar\sigma^2$ is approximated as in (19) by:

$$\bar\sigma^2 \approx \mathrm{Var}^M(X^i) := \frac{1}{M}\sum_{j=1}^M\left(X^i_j - \sum_{m=1}^M\frac{X^i_m}{M}\right)^2,$$

and z_p is such that $\frac{1}{\sqrt{2\pi}}\int_{-z_p}^{z_p} e^{-t^2/2}dt = 1-p$. If we choose 95% the confidence level, which corresponds to $z_{0.05}\approx 1.96$; then we obtain the following result in Figure 1 in which the confidence interval $[I_1(M), I_2(M)]$ and the average $E_M(X^i) := \frac{1}{M}\sum_{m=1}^M X^i_m$ are plotted as function of M.

In Figure 1 it is clear that if we chose the number of realization M larger enough the confidence interval begin small enough as shown in the left hand of the figure, in right hand the first 100 realization is shown for three-compartment concentration of drug.

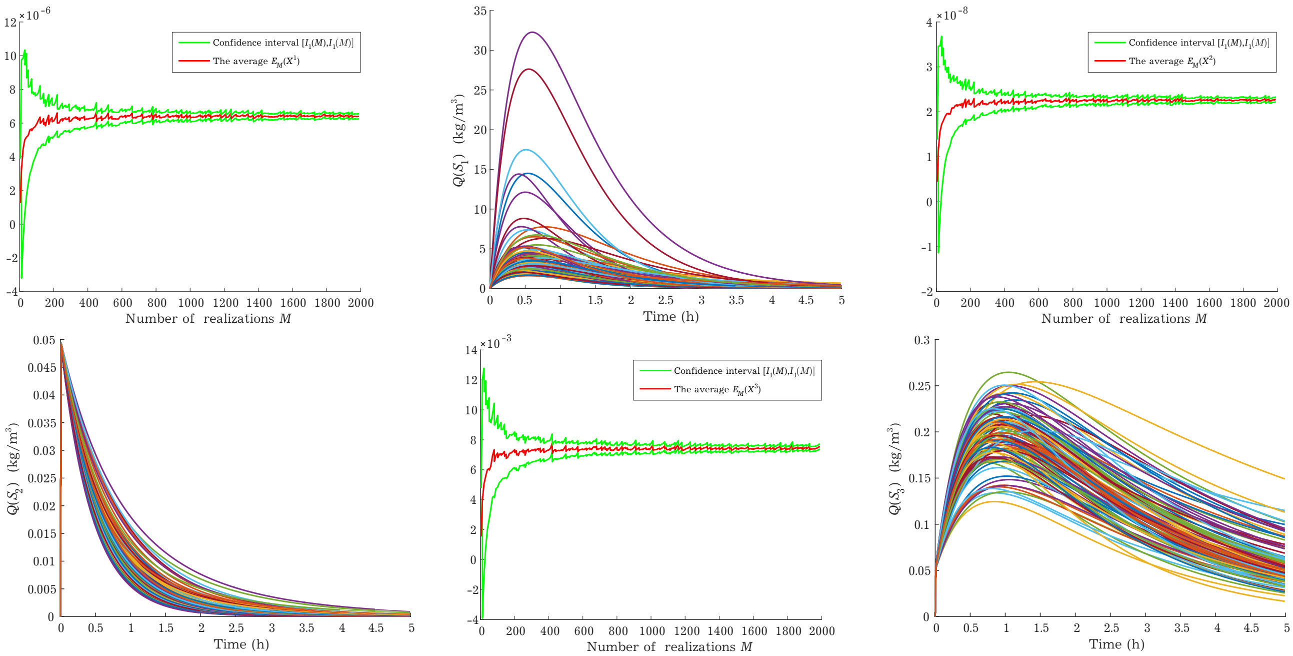

Fig. 1. The confidence interval of $\bar{\mu}$ at level 0.95 and the (QoI) of the drug concentration in the three-compartment versus time for the first $M = 100$ realizations.

Next, to check the convergence of the proposed method, we solve the following system

$$\begin{cases} \dfrac{\partial S_1}{\partial t} = D_s \Delta S_1 - k'_{12} S_1 + \dfrac{k'_{21}}{V_c} S_2 + h_1, \\ \dfrac{\partial S_2}{\partial t} = k_{12} V_c S_1 - k_{21} S_2 - k_2 S_2 - k_{23} S_2 + h_2, \\ \dfrac{\partial S_3}{\partial t} = k_{23} S_2 - k_3 S_3 + h_3, \end{cases}$$

where the functions h_1, h_2, and h_3 are the added source terms used to construct exact solutions. The exact solutions are given by

$$\begin{aligned} S_1(x,y,t,Z) &= xy(1-x)(1-y)\exp\left(D_s + (k'_{12} + k'_{21})(x,y,Z)\right)\exp\left(-V_c(x,y,Z)t\right), \\ S_2(x,y,t,Z) &= xy(1-x)(1-y)\exp\left((k_{12}V_c - k_{21} - k_2)(x,y,Z)\right)\exp\left(-k_{23}(x,y,Z)t\right), \\ S_3(x,y,t,Z) &= xy(1-x)(1-y)\exp\left(k_{23}(x,y,Z) + x + y\right)\exp\left(-k_3(x,y,Z)t\right), \end{aligned}$$

the error for the mean and the variance of the solution for different values of number realization M and different values of the parameter of the difference scheme Δx and Δy are given in the following tables.

First, we consider the case where $M = 100$ with different values of Δx and Δy.

Table 1. The error at time $T = 1$ (h).

mesh ($\Delta x = \Delta y$)	1/10	1/100	1/1000
$\lvert\mathbb{E}(Q(S_1)) - \mathbb{E}(Q(S_1^h))\rvert$	0.951205	0.901005	0.894203
$\lvert\mathrm{Var}(Q(S_1)) - \mathrm{Var}(Q(S_1^h))\rvert$	0.914287	0.900119	0.863578
$\lvert\mathbb{E}(Q(S_2)) - \mathbb{E}(Q(S_2^h))\rvert$	0.967211	0.920312	0.900531
$\lvert\mathrm{Var}(Q(S_2)) - \mathrm{Var}(Q(S_2^h))\rvert$	0.898208	0.880701	0.810739
$\lvert\mathbb{E}(Q(S_3)) - \mathbb{E}(Q(S_3^h))\rvert$	0.971215	0.948019	0.902060
$\lvert\mathrm{Var}(Q(S_3)) - \mathrm{Var}(Q(S_3^h))\rvert$	0.911235	0.8891508	0.811951

Next, we consider the case where $M = 1000$ with different values of Δx and Δy.

Table 2. The error at time $T = 1$ (h).

mesh ($\Delta x = \Delta y$)	1/10	1/100	1/1000
$\lvert\mathbb{E}(Q(S_1)) - \mathbb{E}(Q(S_1^h))\rvert$	0.856082	0.414461	0.116250
$\lvert\mathrm{Var}(Q(S_1)) - \mathrm{Var}(Q(S_1^h))\rvert$	0.822850	0.411057	0.112267
$\lvert\mathbb{E}(Q(S_2)) - \mathbb{E}(Q(S_2^h))\rvert$	0.870497	0.423345	0.118076
$\lvert\mathrm{Var}(Q(S_2)) - \mathrm{Var}(Q(S_2^h))\rvert$	0.808386	0.405129	0.105494
$\lvert\mathbb{E}(Q(S_3)) - \mathbb{E}(Q(S_3^h))\rvert$	0.873991	0.436080	0.117274
$\lvert\mathrm{Var}(Q(S_3)) - \mathrm{Var}(Q(S_3^h))\rvert$	0.820115	0.409016	0.106553

Finally, the result for the case where $M = 10000$ with different values of Δx and Δy.

Table 3. The error at time $T = 1$ (h).

mesh ($\Delta x = \Delta y$)	1/10	1/100	1/1000
$\lvert\mathbb{E}(Q(S_1)) - \mathbb{E}(Q(S_1^h))\rvert$	0.214023	0.065591	0.007871
$\lvert\mathrm{Var}(Q(S_1)) - \mathrm{Var}(Q(S_1^h))\rvert$	0.205718	0.065225	0.007653
$\lvert\mathbb{E}(Q(S_2)) - \mathbb{E}(Q(S_2^h))\rvert$	0.217662	0.066573	0.008016
$\lvert\mathrm{Var}(Q(S_2)) - \mathrm{Var}(Q(S_2^h))\rvert$	0.202178	0.064567	0.007759
$\lvert\mathbb{E}(Q(S_3)) - \mathbb{E}(Q(S_3^h))\rvert$	0.218451	0.067973	0.008164
$\lvert\mathrm{Var}(Q(S_3)) - \mathrm{Var}(Q(S_3^h))\rvert$	0.209013	0.064995	0.007813

These results allow us to conclude that the estimated approximation errors decreases exponentially as the partition size decreases and the number of realization M non-decreasing, which confirms our theoretical result.

4.2. Test 2

Now, we will try to solve our problem using two different sets of determinate parameters presented in Table 4 and we compared it with the obtained result by the proposed method as illustrated in Figure 2.

Table 4. Valued of parameter for Cisplatin (from Sinek et al., Troger et al., Lavasseur et al. and associated references).

Parameter	Description	Case 1		Case 2	
		value	reference	value	reference
V_C	Cell volume (fL cell^{-1})	520	Sinek et al. [11]	520	Sinek et al. [11]
F	Interstitial Fraction	0.48	—	0.48	—
D_s	Drug diffusivity (μm^2 min^{-1})	30E3	—	30E3	—
k_2	Inactivation rate (min^{-1})	1.7	—	1.7	—
k_{12}	Drug uptake (min^{-1})	0.043	Troger et al. [15]	0.00545	Lavasseur et al. [16]
k_{21}	Drug efflux (min^{-1})	0.00197	—	0.0004	—
k_{23}	Drug-DNA binding (min^{-1})	0.00337	—	0.06242	—
k_3	Drug-DNA repair (min^{-1})	0.00785	—	0.02402	—

The value of k'_{12} and k'_{21} are obtained using the formula $k'_{ij} = k_{ij}/F$ for $i, j \in \{1, 2\}$.

As shown in Figure 2 the behavior variation's of Cisplatin concentration in three compartments with respect to time-variable for two determinate cases in Table 4 the best-fit parameters are not reasonable which is seen from the non-accuracy of the obtained results. To overcome this issue, we have considered the stochastic version of the problem, then we manipulated Monte Carlo method; which gives us the result represented in Figure 2.

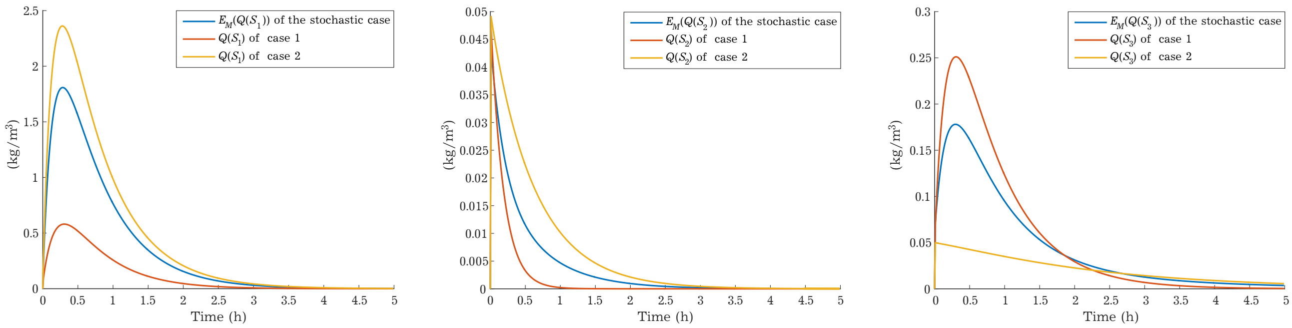

Fig. 2. Comparison of the stochastic and the determinate results. The concentration–versus–time curve for Cisplatin. The curves represent the concentration of Cisplatin using the Monte Carlo method with $M = 10^5$ (blue) and the parameters are given in case 1 (red) and case 2 (yellow) of Table 4.

5. Conclusion

In this work, we have used Karhunen–Loève expansion of the coefficients for a system of PDE governing drug transport in tumors. We transform the initial stochastic problem into a deterministic one albeit with the parameter in high dimensions. We design finite difference method in the physical space, which is efficient and has reasonable accuracy, and we use Monte Carlo method in random space. Moreover, we established the error estimate using the Central Limits Theorem as well as the error estimate for space discretization by finite difference method. Some numerical simulations are illustrated the theoretical analysis where we also compared the stochastic and determinate solving processes. Finally, it is worth mentioning that this proposed method can be used to quantifying the uncertainty of similar problems.

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Кількісна оцінка невизначеності математичної моделі транспортування ліків у пухлинах

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У цій роботі представлено чисельне моделювання в двовимірному режимі для системи диференціальних у частинних похідних, що регулює транспортування ліків у пухлинах із випадковими коефіцієнтами, що описується як випадкове поле. Неперервне стохастичне поле апроксимується скінченною кількістю випадкових величин за допомогою розкладання Кархунена–Лоева і перетворює стохастичну задачу в детерміновану з параметром великої вимірності. Після цього застосовуємо скінченну різницеву схему та інтегратор Ейлера–Маруями в часі. Метод Монте-Карло використовується для обчислення відповідних простих середніх. Обчислюємо оцінку похибки, використовуючи центральну граничну теорему та оцінку похибки для методу скінченних різниць. Деякі числові результати симулюються для ілюстрації теоретичного аналізу. Також пропонуємо порівняння між стохастичним і детермінованим процесами розв'язування нашої системи, де показуємо ефективність прийнятого нами методу.

Ключові слова: *математичні моделі транспорту ліків у пухлинах, метод Монте–Карло, метод скінченних різниць, кількісна оцінка невизначеності.*