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Regularity analysis and numerical resolution of the Pharmacokinetics (PK) equation for cisplatin with random coefficients and initial conditions

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Abstract. In this paper, we study the pharmacokinetics equation for cisplatin (PKC) with random coefficients and initial conditions using the Stochastic Collocation method. We analyze the regularity of the solution with respect to the random variables. The error estimate for the Stochastic Collocation method is proved using the regularity result and the error estimate for the Finite Difference method. Then, we provide the overall errors estimate and convergence is achieved as a direct result. Some numerical results are simulated to illustrate the theoretical analysis. We also propose a comparison between the stochastic and determinate solving process of PKC equation where we show the efficiency of our adopted method.

Keywords: Pharmacokinetics (PK) equation for cisplatin, stochastic collocation, finite difference method, uncertainty quantification.
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1 Introduction

In recent years, numerical analysis of stochastic and random partial differential equations have gained a lot of interest because of ever increasing needs

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for modeling the uncertainties that arise in many research domains. These uncertainties appear in the models because of 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 model coefficients, forcing terms, boundary conditions, geometry of the medium etc. For that, many methods has seen a lot of activity to increase the precision of the numerical predictions and to obtain fairly reliable pre-visions on the model in hand. For example the Multilevel Monte-Carlo method [1,2,10], Sthocastic Galerkin method [8,12,13] and Sthocastic Colocation method [5–7].

In this paper, we focus our attention on the pharmacokinetics PDE system of equation for cisplatin which is capable of tracking the amount of drugs both spatially and temporally through three compartments: 1. Extracellular fluid/matrix, 2. Cytoplasm and 3. Nuclear/DNA-bound. This is based on governing rate parameters (see Figure 1). The equation takes the following form,

$$\begin{cases} \dfrac{\partial S_1}{\partial t} = D_s \Delta S_1 - k_{12}^{'} S_1 + \dfrac{k_{21}^{'}}{V_c} S_2, \\ \dfrac{\partial S_2}{\partial t} = k_{12} V_c S_1 - k_{21} S_2 - k_2 S_2 - k_{23} S_2, \\ \dfrac{\partial S_3}{\partial t} = k_{23} S_2 - k_3 S_3, \end{cases} \tag{1}$$

where S_1, S_2 and S_3 are respectively the Extracellular concentration, Cytosolic concentration and Nuclear concentration. The term D_s is the diffusivity of the drug through interstitial space, V_c is the volume of a cell, the parameters k_{ij} represents 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. The term k_i represents a rate of permanent removal from compartment i (more details can be found in [9,15]. These parameters account for important phenomenas, such as efflux pumps, cell permeability and DNA repair. Their values are obtained through experimental data and are not known with certainty. This prompts us to 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.

If we are to compare relative works for similar problems and up to our knowledge, there are no existing investigations on numerical methods for solving stochastic Pharmacokinetics (PK) equation for Cisplatin. And so, we aim in this note to analyze numerically the PKC equation with **random**

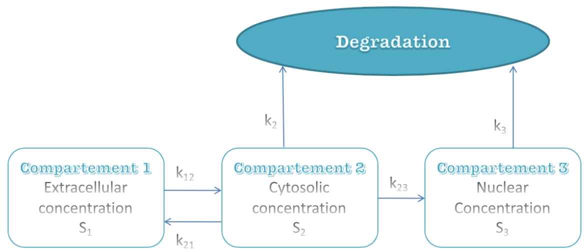

Figure 1: Multicompartmental pharmacokinetics modeling.

coefficients in 2D using the Collocation method as an attempt to predict the influence of the so called incertitudes on the equation.

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 provide some regularity results on the solution of our problem. In Section 4, we give a complete convergence result for the Collocation method. We illustrate the theoretical results by few numerical simulations in Section 5. Finally, we make a conclusion to this work in Section 6.

2 The problem setting and Notation

Let D be a convex bounded polygonal domain in $\mathbb{R}^2$, let $x \in D$ and $t \in [0, T]$ be respectively the spatial and temporal coordinates. Consider $(\Omega, \mathcal{A}, \mathcal{P})$ a complete probability space equipped with σ-algebra $\mathcal{A}$, where Ω is the event space and $\mathcal{P}$ is a probability measure. Let $\rho : \Gamma \longrightarrow \mathbb{R}^+$ be a bounded joint probability density function of the $\mathbb{R}^d$-valued random variable $\xi = [\xi_1(\omega), \ldots, \xi_d(\omega)]$, $\omega \in \Omega$, where $\Gamma := \Pi_{d=1}^{n} \Gamma_n$, $\Gamma_n = \xi_n(\Omega) \in \mathbb{R}$ is the image of ξ .

Consider the stochastic Pharmacokinetics equation for Cisplatin (PKC): Find the random Extra-cellular concentration $S_1(x, t, \xi)$, random Cytosolic concentration $S_2(x, t, \xi)$ and random Nuclear concentration $S_3(x, t, \xi)$, with $(x, t, \xi) \in D \times (0, T) \times \Omega$ such that P-almost everywhere in Ω, i.e., almost surely (a.s.) satisfy the following equations

$$\begin{cases} \dfrac{\partial S_1}{\partial t} = D_s \varDelta S_1 - k'_{12}\big(x, \xi(\omega)\big) S_1 + \dfrac{k'_{21}\big(x, \xi(\omega)\big)}{V_c\big(x, \xi(\omega)\big)} S_2, \\ \dfrac{\partial S_2}{\partial t} = k_{12}\big(x, \xi(\omega)\big) V_c\big(x, \xi(\omega)\big) S_1 - \big(k_{21} + k_2 + k_{23}\big)\big(x, \xi(\omega)\big) S_2, \\ \dfrac{\partial S_3}{\partial t} = k_{23}\big(x, \xi(\omega)\big) S_2 - k_3\big(x, \xi(\omega)\big) S_3, \end{cases} \tag{2}$$

subject to random initial conditions

$$\begin{cases} S_1\big(x, t=0, \xi(\omega)\big) = S_{01}\big(x, \xi(\omega)\big), \\ S_2\big(x, t=0, \xi(\omega)\big) = S_{02}\big(x, \xi(\omega)\big), \\ S_3\big(x, t=0, \xi(\omega)\big) = S_{03}\big(x, \xi(\omega)\big), \end{cases} \tag{3}$$

and boundary conditions

$$S_i = 0 \quad \text{on } \partial D \quad \text{for } i = 1, 2, 3, \tag{4}$$

where S_{0i} for $i = 1, 2, 3$ are some given functions. To account for uncertainties about the problem data, we assume that the parameters k_{ij}, $k_{ij}^{'}$, k_i and V_c are all random and D_s is a positive constant.

Note that in this work, the Laplacien Δ and Gradient ∇ notations mean only the differentiation with respect to the spatial variable x.

Remark 1. The value of the parameter D_s is also not known with certainty. Yet, we can not consider D_s as a random field. In fact, if one considers D_s as such, we will face regularity analysis problems (In particular, Lemma 2 becomes impossible to achieve). For that, we shall consider D_s a constant.

We aim to build a numerical approximation of the exact solution of (2)-(4) by Lagrange Interpolation approach [5, 14, 16]. We choose a set of Gauss-Lobatto collocation points $\{\xi_k\}_{k=1}^{(N+1)^d} \in \Gamma$ where $N+1$ is the number of collocation points in each random variable space. Then, at each collocation point $\xi_k, k = 1, ..., (N+1)^d$, we solve the following system,

$$\begin{cases} \dfrac{\partial \hat{S}_1}{\partial t}(x, t; \xi_k) = D_s \Delta \hat{S}_1(x, t; \xi_k) - k_{12}^{'}(x, \xi_k)\hat{S}_1(x, t; \xi_k) + \dfrac{k_{21}^{'}(x, \xi_k)}{V_c(x, \xi_k)}\hat{S}_2(x, t; \xi_k), \\ \dfrac{\partial \hat{S}_2}{\partial t}(x, t; \xi_k) = k_{12}(x, \xi_k)V_c(x, \xi_k)\hat{S}_1(x, t; \xi_k) \\ \qquad\qquad\qquad - \big(k_{21} + k_2 + k_{23}\big)(x, \xi_k)\hat{S}_2(x, t; \xi_k), \\ \dfrac{\partial \hat{S}_3}{\partial t}(x, t; \xi_k) = k_{23}(x, \xi_k)\hat{S}_2(x, t; \xi_k) - k_3(x, \xi_k)\hat{S}_3(x, t; \xi_k), \end{cases} \tag{5}$$

subject to random initial conditions

$$\begin{cases} \hat{S}_1(x, t=0, \xi_k) = \hat{S}_{01}(x, \xi_k), \\ \hat{S}_2(x, t=0, \xi_k) = \hat{S}_{02}(x, \xi_k), \\ \hat{S}_3(x, t=0, \xi_k) = \hat{S}_{03}(x, \xi_k), \end{cases} \tag{6}$$

and boundary conditions

$$\hat{S}_i(x, t; \xi_k) = 0 \quad \text{on } \partial D \quad \text{for} \quad i = 1, 2, 3. \tag{7}$$

We can simply denote the approximate solution as

$$S_i^N(x,t;\xi) = \sum_{k=1}^{(N+1)^d} \hat{S}_i(x,t,\xi_k)\mathcal{L}_k(\xi) \quad \text{for} \quad i=1,2,3, \tag{8}$$

where the functions $\mathcal{L}_k(\xi)$ are the tensor-product Lagrange interpolation polynomials.

3 Regularity analysis

In this section, we establish the regularity for the solution of our model problem (2)-(4). This result is essential to prove the convergence of the scheme given above, in the next section. First, we recall the following Gronwall inequality for its useful use in our demonstration.

Lemma 1. *Gronwall inequality. If $h(t)$ satisfies $\dfrac{dh(t)}{dt} \le ah(t)+b$ for some constant $a \neq 0$ and b, then we have*

$$h(t) \le e^{at}\Big(h(0)+\frac{b}{a}\Big), \quad \forall\, t \ge 0.$$

We have the following Lemmas concerning the regularity of the system (2)-(4).

Lemma 2. *Let $t \in [0,T]$. We have*

$$\int_\Gamma\int_D \Big(\sum_{i=1}^{3}|S_i|^2\Big)\rho(\xi)(t)dxd\xi \le e^{C_1T}\int_\Gamma\int_D \Big(\sum_{i=1}^{3}|S_{0i}|^2\Big)\rho(\xi)dxd\xi,$$

where

$$C_1 := \max_{\bar{D}\times\bar{\Gamma}}\Big\{\Big(\frac{k'_{21}}{V_c}\Big)^2+\Big(k_{12}V_c\Big)^2,\Big(k_{23}\Big)^2+2\Big\}.$$

Proof. We multiply the equations in (2) by $2\rho(\xi)S_1$, $2\rho(\xi)S_2$ and $2\rho(\xi)S_3$ respectively, then we integrate over D and Γ. The following equation is a direct result of using Green formula and the boundary conditions

$$\frac{d}{dt}\int_\Gamma\int_D |S_1|^2\rho(\xi)dxd\xi + \int_\Gamma\int_D 2D_s|\nabla S_1|^2\rho(\xi)dxd\xi$$
$$+\int_\Gamma\int_D 2k'_{12}(x,\xi)|S_1|^2\rho(\xi)dxd\xi = \int_\Gamma\int_D 2\frac{k'_{21}(x,\xi)}{V_c(x,\xi)}S_1S_2\rho(\xi)dxd\xi.$$

By the Cauchy-Schwarz inequality, it is easy to see that

$$\frac{d}{dt}\int_\Gamma\int_D |S_1|^2\rho(\xi)dxd\xi \leq \int_\Gamma\int_D \Big(\Big(\frac{k_{21}^{'}(x,\xi)}{V_c(x,\xi)}\Big)^2|S_1|^2+|S_2|^2\Big)\rho(\xi)dxd\xi. \quad (9)$$

Similarly, we obtain

$$\frac{d}{dt}\int_\Gamma\int_D |S_2|^2\rho(\xi)dxd\xi \leq \int_\Gamma\int_D \Big(\Big(k_{12}(x,\xi)V_c(x,\xi)\Big)^2|S_1|^2+|S_2|^2\Big)\rho(\xi)dxd\xi \quad (10)$$

and

$$\frac{d}{dt}\int_\Gamma\int_D |S_3|^2\rho(\xi)dxd\xi \leq \int_\Gamma\int_D \Big(\Big(k_{23}(x,\xi)\Big)^2|S_2|^2+|S_3|^2\Big)\rho(\xi)dxd\xi. \quad (11)$$

According to Eqs. (9), (10) and (11), we have

$$\frac{d}{dt}\int_\Gamma\int_D \Big(\sum_{i=1}^3|S_i|^2\Big)\rho(\xi)dxd\xi \leq C_1\int_\Gamma\int_D \Big(\sum_{i=1}^3|S_i|^2\Big)\rho(\xi)dxd\xi. \quad (12)$$

Applying the Gronwall inequality yields

$$\int_\Gamma\int_D \Big(\sum_{i=1}^3|S_i|^2\Big)\rho(\xi)(t)dxd\xi \leq e^{C_1T}\int_\Gamma\int_D \Big(\sum_{i=1}^3|S_{0i}|^2\Big)\rho(\xi)dxd\xi,$$

which completes the proof. □

Lemma 3. *Let $t\in[0,T]$, we have*

$$\int_\Gamma\int_D \Big(\sum_{i=1}^3\Big|\frac{\partial S_i}{\partial t}\Big|^2\Big)\rho(\xi)(t)dxd\xi \leq C_2e^{C_1T}\int_\Gamma\int_D \Big(|\Delta S_{01}|^2+\sum_{i=1}^3|S_{0i}|^2\Big)\rho(\xi)dxd\xi,$$

where, $C_2 := \max_{\bar{D}\times\bar{\Gamma}}\Big\{4D_s^2, K_1, K_2, K_3\Big\}$ with K_i, for $i=1,2,3$ defined as

$$\begin{aligned} K_1 &= 16\Big(k_{12}^{'}\Big)^2+4\Big(k_{12}V_c\Big)^2,\\ K_2 &= 16\Big(\frac{k_{21}^{'}}{V_c}\Big)^2+4\Big(k_{21}+k_2+k_{23}\Big)^2+4\Big(k_{23}\Big)^2,\\ K_3 &= 4\Big(k_3\Big)^2. \end{aligned} \quad (13)$$

Proof. Taking the time derivative of Eq. (2), we obtain

$$\begin{cases} \dfrac{\partial^2 S_1}{\partial t^2} = D_s \Delta(\dfrac{\partial S_1}{\partial t}) - k'_{12}(x,\xi)\dfrac{\partial S_1}{\partial t} + \dfrac{k'_{21}(x,\xi)}{V_c(x,\xi)}\dfrac{\partial S_2}{\partial t}, \\ \dfrac{\partial^2 S_2}{\partial t^2} = k_{12}(x,\xi)V_c(x,\xi)\dfrac{\partial S_1}{\partial t} - k_{21}(x,\xi)\dfrac{\partial S_2}{\partial t} - k_2(x,\xi)\dfrac{\partial S_2}{\partial t} \\ \qquad -k_{23}(x,\xi)\dfrac{\partial S_2}{\partial t}, \\ \dfrac{\partial^2 S_3}{\partial t^2} = k_{23}(x,\xi)\dfrac{\partial S_2}{\partial t} - k_3(x,\xi)\dfrac{\partial S_3}{\partial t}. \end{cases} \tag{14}$$

Following the same steps as in the proof of Lemma 2, by multiplying this time the equations of (14) by $2\rho(\xi)\dfrac{\partial S_1}{\partial t}$, $2\rho(\xi)\dfrac{\partial S_2}{\partial t}$ and $2\rho(\xi)\dfrac{\partial S_3}{\partial t}$, respectively, one gets

$$\int_\Gamma \int_D \Big(\sum_{i=1}^3 \Big|\frac{\partial S_i}{\partial t}\Big|^2\Big)\rho(\xi)(t)dxd\xi \le e^{C_1 T}\int_\Gamma \int_D \Big(\sum_{i=1}^3 \Big|\frac{\partial S_i}{\partial t}\Big|^2\Big)\rho(\xi)(0)dxd\xi.$$

Notice that,

$$\begin{aligned} \Big|\frac{\partial S_1}{\partial t}\Big|^2(0) &= \Big|D_s\Delta S_{01} - k'_{12}(x,\xi)S_{01} + \frac{k'_{21}(x,\xi)}{V_c(x,\xi)}S_{02}\Big|^2 \\ &\le 4D_s^2|\Delta S_{01}|^2 + 16\Big(k'_{12}(x,\xi)\Big)^2|S_{01}|^2 + 16\Big(\frac{k'_{21}(x,\xi)}{V_c(x,\xi)}\Big)^2|S_{02}|^2, \\ \Big|\frac{\partial S_2}{\partial t}\Big|^2(0) &\le 4\Big(k_{12}(x,\xi)V_c(x,\xi)\Big)^2|S_{01}|^2 \\ &\quad +4\Big(k_{21}(x,\xi) + k_2(x,\xi) + k_{23}(x,\xi)\Big)^2|S_{02}|^2, \end{aligned}$$

and

$$\Big|\frac{\partial S_3}{\partial t}\Big|^2(0) \le 4\Big(k_{23}(x,\xi)\Big)^2|S_{02}|^2 + 4\Big(k_3(x,\xi)\Big)^2|S_{03}|^2.$$

finally with the notation of the lemma we gets

$$\begin{aligned} \int_\Gamma \int_D \Big(\sum_{i=1}^3 \Big|\frac{\partial S_i}{\partial t}\Big|^2\Big)\rho(\xi)(t)dxd\xi &\le e^{C_1 T}\int_\Gamma \int_D \Big(4D_s^2|\Delta S_1^0|^2 + K_1(x,\xi)|S_{01}|^2 \\ &\quad + K_2(x,\xi)|S_{02}|^2 + K_3(x,\xi)|S_{03}|^2\Big)\rho(\xi)dxd\xi. \end{aligned}$$

This concludes the proof. □

Theorem 1. *Let $t \in [0,T]$, we have*

$$\int_\Gamma \int_D \sum_{i=1}^{3} \Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2 (t)\rho(\xi)dxd\xi \\ \leq e^{C_3 T} \int_\Gamma \int_D \Big(\sum_{i=1}^{3} \Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2 (0) + \frac{C_4}{C_3} e^{C_1 T} \sum_{i=1}^{3} |S_{0i}|^2 \Big)\rho(\xi)dxd\xi,$$

where

$$C_3 := \max_{\bar\Gamma \times \bar D} \Big\{ |k_{12}V_c|^2 + 3, |k_{23}|^2 + \Big|\frac{k'_{21}}{V_c}\Big|^2 + 5 \Big\}$$

and

$$C_4 := \max_{\bar\Gamma \times \bar D} \Big\{ \Big|\frac{\partial k'_{12}}{\partial \xi_k}\Big|^2 + \Big|\frac{\partial (k_{12}V_c)}{\partial \xi_k}\Big|^2, \\ \Big|\frac{\partial}{\partial \xi_k}\Big(\frac{k'_{21}}{V_c}\Big)\Big|^2 + \Big|\frac{\partial k_{21}}{\partial \xi_k}\Big|^2 + \Big|\frac{\partial k_2}{\partial \xi_k}\Big|^2 + 2\Big|\frac{\partial k_{23}}{\partial \xi_k}\Big|^2 + \Big|\frac{\partial k_3}{\partial \xi_k}\Big|^2 \Big\}.$$

Proof. Differentiating (2) with respect to any ξ_k, $k = 1, 2, \dots, d$, we obtain

$$\begin{cases} \dfrac{\partial}{\partial t}\dfrac{\partial S_1}{\partial \xi_k} = D_s \Delta\Big(\dfrac{\partial S_1}{\partial \xi_k}\Big) - \dfrac{\partial k'_{12}}{\partial \xi_k} S_1 - k'_{12}\dfrac{\partial S_1}{\partial \xi_k} + \dfrac{\partial}{\partial \xi_k}\Big(\dfrac{k'_{21}}{V_c}\Big) S_2 + \dfrac{k'_{21}}{V_c}\dfrac{\partial S_2}{\partial \xi_k}, \\ \dfrac{\partial}{\partial t}\dfrac{\partial S_2}{\partial \xi_k} = \dfrac{\partial (k_{12}V_c)}{\partial \xi_k} S_1 + k_{12}V_c \dfrac{\partial S_1}{\partial \xi_k} - \Big(\dfrac{\partial k_{21}}{\partial \xi_k} + \dfrac{\partial k_2}{\partial \xi_k} + \dfrac{\partial k_{23}}{\partial \xi_k}\Big) S_2 \\ \qquad - \Big(k_{21} + k_2 + k_{23}\Big)\dfrac{\partial S_2}{\partial \xi_k}, \\ \dfrac{\partial}{\partial t}\dfrac{\partial S_3}{\partial \xi_k} = \dfrac{\partial k_{23}}{\partial \xi_k} S_2 + k_{23}\dfrac{\partial S_2}{\partial \xi_k} - \dfrac{\partial k_3}{\partial \xi_k} S_3 - k_3 \dfrac{\partial S_3}{\partial \xi_k}. \end{cases} \tag{15}$$

By multiplying the equations in (15) by $2\rho(\xi)\frac{\partial S_1}{\partial \xi_k}$, $2\rho(\xi)\frac{\partial S_2}{\partial \xi_k}$ and $2\rho(\xi)\frac{\partial S_3}{\partial \xi_k}$, respectively, then integrating over D and Γ, then using the boundary conditions, Green formula and Cauchy Schwartz inequality, we get

$$\frac{d}{dt}\int_\Gamma \int_D \Big|\frac{\partial S_1}{\partial \xi_k}\Big|^2 \rho(\xi)dxd\xi \leq \int_\Gamma \int_D \Big(\Big|\frac{\partial k'_{12}}{\partial \xi_k}\Big|^2 |S_1|^2 + \Big|\frac{\partial S_1}{\partial \xi_k}\Big|^2 \Big)\rho(\xi)dxd\xi \\ + \int_\Gamma \int_D \Big(\Big|\frac{\partial}{\partial \xi_k}\Big(\frac{k'_{21}}{V_c}\Big)\Big|^2 |S_2|^2 + \Big|\frac{\partial S_1}{\partial \xi_k}\Big|^2 \Big)\rho(\xi)dxd\xi \\ + \int_\Gamma \int_D \Big(\Big|\frac{k'_{21}}{V_c}\Big|^2 \Big|\frac{\partial S_2}{\partial \xi_k}\Big|^2 + \Big|\frac{\partial S_1}{\partial y_i}\Big|^2 \Big)\rho(\xi)dxd\xi.$$

By the same fashion, when applied to the second and third equations in (15), we get the second and third inequalities, then by adding the three inequaltities we obtain

$$\frac{d}{dt}\int_\Gamma\int_D\sum_{i=1}^{3}\Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2\rho(\xi)dxd\xi \le \int_\Gamma\int_D\Big[C_3\sum_{i=1}^{3}\Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2 + C_4\sum_{i=1}^{3}|S_i|^2\Big]\rho(\xi)dxd\xi.$$

Gronwall inequality and Lemma 2 implies

$$\int_\Gamma\int_D\sum_{i=1}^{3}\Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2(t)\rho(\xi)dxd\xi \le e^{C_3T}\int_\Gamma\int_D\Big[\sum_{i=1}^{3}\Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2(0) + \frac{C_4}{C_3}e^{C_1T}\sum_{i=1}^{3}|S_{0i}|^2\Big]\rho(\xi)dxd\xi.$$

which conclude the proof. □

Lemma 4. *Let $t\in[0,T]$. We have*

$$\int_\Gamma\int_D\sum_{i=1}^{3}|\nabla S_i|^2(t)\rho(\xi)dxd\xi \le e^{C_3T}\int_\Gamma\int_D\Big[\sum_{i=1}^{3}|\nabla S_i|^2(0) + \frac{C_5}{C_3}e^{C_1T}\sum_{i=1}^{3}|S_{0i}|^2\Big]\rho(\xi)dxd\xi,$$

where

$$C_5 = \max_{\bar D\times\bar\Gamma}\Big\{|\nabla k_{12}'|^2 + |\nabla(k_{12}V_c)|^2, \Big|\nabla\frac{k_{21}'}{V_c}\Big|^2 + |\nabla k_{21}|^2 + |\nabla k_2|^2 + 2|\nabla k_{23}|^2 + |\nabla k_3|^2\Big\}.$$

Proof. Taking $\nabla\times$ of Eq. (2), we repeat the same steps as in the previous proof where this time we use $2\rho(\xi)\nabla S_1$, $2\rho(\xi)\nabla S_2$ and $2\rho(\xi)\nabla S_3$ for the multiplication. The rest of the development is quite similar where we obtain three inequalities for each S_i, $i=1,2,3$. Summing these inequalities yields the above result where Gronwall inequality and Lemma 2 are used. □

Lemma 5. *Let $t\in[0,T]$. We have*

$$\int_\Gamma\int_D\Big(\sum_{i=1}^{3}\Big|\nabla\frac{\partial S_i}{\partial t}\Big|^2\Big)(t)\rho(\xi)dxd\xi \le e^{C_6T}\int_\Gamma\int_D\Big[\sum_{i=1}^{3}\Big|\nabla\frac{\partial S_i}{\partial t}\Big|^2(0) + L\Big(|\Delta S_{01}|^2 + \sum_{i=1}^{3}|S_{0i}|^2\Big)\Big]\rho(\xi)dxd\xi,$$

where

$$L := \frac{C_7}{C_6} C_2 e^{C_3 T}, \quad C_6 := \max_{\bar{D}\times\bar{\Gamma}} \Big\{ \Big| \frac{k_{21}^{'}}{V_c} \Big|^2 + |k_{23}|^2 + 4, |k_{21} V_c|^2 + 3 \Big\},$$

$$C_7 := \max_{\bar{D}\times\bar{\Gamma}} \Big\{ |\nabla k_{12}^{'}|^2 + |\nabla (k_{12} V_c)|^2, \Big| \nabla \frac{k_{21}^{'}}{V_c} \Big|^2 + |\nabla k_{21}|^2 + |\nabla k_2|^2 + |\nabla k_{23}|^2 + |\nabla k_3|^2 \Big\}.$$

Proof. The proof is exactly the same fashion as the previous one. We take $\frac{\partial}{\partial t}\nabla$ of Eq. (2), we use $2\rho(\xi)\nabla \frac{\partial S_1}{\partial t}$, $2\rho(\xi)\nabla\frac{\partial S_2}{\partial t}$ and $2\rho(\xi)\nabla\frac{\partial S_3}{\partial t}$ for multiplication and we conclude by Lemma 3 instead of Lemma 2. □

Theorem 2. *For any* $t \in [0, T]$ *and* $k = 1, 2, \ldots, d$, *we have*

$$\begin{aligned} &\int_\Gamma \int_D \Big(\sum_{i=1}^3 \Big| \nabla \frac{\partial S_i}{\partial \xi_k} \Big|^2 \Big)(t) \rho(\xi) dx d\xi \\ &\le e^{C_8 T} \Big[\int_\Gamma \int_D \Big(\sum_{i=1}^3 \Big| \nabla \frac{\partial S_i}{\partial \xi_k} \Big|^2 + \frac{C_9}{C_8} e^{C_3 T} \sum_{i=1}^3 |\nabla S_i|^2 \Big)(0) \rho(\xi) dx d\xi \\ &+ \int_\Gamma \int_D \Big(M \sum_{i=1}^3 |S_{0i}|^2 + \frac{C_{10}}{C_8} e^{C_3 T} \Big(\sum_{i=1}^3 \Big| \frac{\partial S_i}{\partial \xi_k} \Big|^2 \Big)(0) \Big) \rho(\xi) dx d\xi \Big], \end{aligned}$$

where

$$\begin{aligned} M &= \frac{C_5 C_9}{C_8 C_3} e^{(C_1 + C_3)T} + \frac{C_{10} C_4}{C_8 C_3} e^{(C_1+C_3)T} + \frac{C_{11}}{C_8} e^{C_1 T}, \\ C_8 &:= \max_{\bar{D}\times\bar{\Gamma}} \Big\{ |k_{12} V_c|^2 + 7, \Big| \frac{k_{21}^{'}}{V_c} \Big|^2 + |k_{23}|^2 + 13 \Big\}, \\ C_9 &:= \max_{\bar{D}\times\bar{\Gamma}} \Big\{ \Big| \frac{\partial k_{12}^{'}}{\partial \xi_k} \Big|^2 + \Big| \frac{\partial (k_{12} V_c)}{\partial \xi_k} \Big|^2, \\ &\qquad \Big| \frac{\partial}{\partial \xi_k} \Big(\frac{k_{21}^{'}}{V_c} \Big) \Big|^2 + \Big| \frac{\partial k_{21}}{\partial \xi_k} \Big|^2 + \Big| \frac{\partial k_2}{\partial \xi_k} \Big|^2 + 2 \Big| \frac{\partial k_{23}}{\partial \xi_k} \Big|^2, \Big| \frac{\partial k_3}{\partial \xi_k} \Big|^2 \Big\}, \\ C_{10} &:= \max_{\bar{D}\times\bar{\Gamma}} \Big\{ |\nabla k_{12}^{'}|^2 + |\nabla (k_{12} V_c)|^2, \\ &\qquad \Big| \nabla \frac{k_{21}^{'}}{V_c} \Big|^2 + |\nabla k_{21}|^2 + |\nabla k_2|^2 + 2|\nabla k_{23}|^2, |\nabla k_3|^2 \Big\}, \\ C_{11} &:= \max_{\bar{D}\times\bar{\Gamma}} \Big\{ \Big| \nabla \frac{\partial k_{12}^{'}}{\partial \xi_k} \Big|^2 + \Big| \nabla \frac{\partial (k_{12} V_c)}{\partial \xi_k} \Big|^2, \Big| \nabla \frac{\partial}{\partial \xi_k} \Big(\frac{k_{21}^{'}}{V_c} \Big) \Big|^2 + \Big| \nabla \frac{\partial k_{21}}{\partial \xi_k} \Big|^2 \\ &\qquad + \Big| \nabla \frac{\partial k_2}{\partial \xi_k} \Big|^2 + 2 \Big| \nabla \frac{\partial k_{23}}{\partial \xi_k} \Big|^2, \Big| \nabla \frac{\partial k_3}{\partial \xi_k} \Big|^2 \Big\}. \end{aligned}$$

Proof. For each $k = 1, 2, \ldots, d$, we take $\nabla \frac{\partial}{\partial \xi_k}$ of Eq. (2). Then, we multiply the obtained equations by $2\rho(\xi)\nabla\frac{\partial S_1}{\partial \xi_k}$, $2\rho(\xi)\nabla\frac{\partial S_2}{\partial \xi_k}$ and $2\rho(\xi)\nabla\frac{\partial S_3}{\partial \xi_k}$ respectively. By the same principal as above, we obtain three inequalities which we sum up to

$$\frac{d}{dt}\int_\Gamma\int_D\Big(\sum_{i=1}^3\Big|\nabla\frac{\partial S_i}{\partial \xi_k}\Big|^2\Big)\rho(\xi)dxd\xi \leq C_8\int_\Gamma\int_D\Big(\sum_{i=1}^3\Big|\nabla\frac{\partial S_i}{\partial \xi_k}\Big|^2\Big)\rho(\xi)dxd\xi$$
$$+ C_9\int_\Gamma\int_D\Big(\sum_{i=1}^3|\nabla S_i|^2\Big)\rho(\xi)dxd\xi + C_{10}\int_\Gamma\int_D\Big(\sum_{i=1}^3\Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2\Big)\rho(\xi)dxd\xi$$
$$+ C_{11}\int_\Gamma\int_D\Big(\sum_{i=1}^3|S_i|^2\Big)\rho(\xi)dxd\xi.$$

The result is a direct result of Lemma 2, Lemma 4 and Theorem 1 by a simple implication of the Gronwall inequality. □

In the Theorem 3, we will prove the boundedness of the second derivative with respect to the random variables according to the Lemma 2 and Theorem 1.

Theorem 3. *Let $t \in [0, T]$. For each $k = 1, 2, \ldots, d$, we have*

$$\int_\Gamma\int_D\Big(\sum_{i=1}^3\Big|\frac{\partial^2 S_i}{\partial \xi_k^2}\Big|^2\Big)(t)\rho(\xi)dxd\xi \leq e^{C_{12}T}\Big[\int_\Gamma\int_D\Big(\sum_{i=1}^3\Big|\frac{\partial^2 S_i}{\partial \xi_k^2}\Big|^2\Big)(0)\rho(\xi)dxd\xi$$
$$+ \frac{C_{13}}{C_{12}}e^{C_3T}\int_\Gamma\int_D\Big(\sum_{i=1}^3\Big|\frac{\partial S_i}{\partial \xi_k}\Big|^2\Big)(0)\rho(\xi)dxd\xi$$
$$+ \Big(\frac{C_{13}C_4}{C_{12}C_3} + \frac{C_{14}}{C_{12}}\Big)e^{C_1T}\int_\Gamma\int_D\Big(\sum_{i=1}^3|S_{0i}|^2\Big)\rho(\xi)dxd\xi\Big],$$

where

$$C_{12} := \max_{\bar{D}\times\bar{\Gamma}}\Big\{|k_{12}V_c|^2 + 7, \Big|\frac{k'_{21}}{V_c}\Big|^2 + |k_{23}|^2 + 9\Big\},$$
$$C_{13} := \max_{\bar{D}\times\bar{\Gamma}}\Big\{\Big|\frac{\partial k'_{12}}{\partial \xi_k}\Big|^2 + |k'_{12}|^2 + \Big|\frac{\partial(k_{12}V_c)}{\partial \xi_k}\Big|^2,$$
$$\Big|\frac{\partial}{\partial \xi_k}\Big(\frac{k'_{21}}{V_c}\Big)\Big|^2 + \Big|\frac{\partial k_{21}}{\partial \xi_k}\Big|^2 + \Big|\frac{\partial k_2}{\partial \xi_k}\Big|^2 + 4\Big|\frac{\partial k_{23}}{\partial \xi_k}\Big|^2, \Big|\frac{\partial k_3}{\partial \xi_k}\Big|^2\Big\},$$
$$C_{14} := \max_{\bar{D}\times\bar{\Gamma}}\Big\{\Big|\frac{\partial^2 k'_{12}}{\partial \xi_k^2}\Big|^2 + \Big|\frac{\partial^2(k_{12}V_c)}{\partial \xi_k^2}\Big|^2,$$
$$\Big|\frac{\partial^2}{\partial \xi_k^2}\Big(\frac{k'_{21}}{V_c}\Big)\Big|^2 + \Big|\frac{\partial^2 k_{21}}{\partial \xi_k^2}\Big|^2 + \Big|\frac{\partial^2 k_2}{\partial \xi_k^2}\Big|^2 + 2\Big|\frac{\partial^2 k_{23}}{\partial \xi_k^2}\Big|^2, \Big|\frac{\partial^2 k_3}{\partial \xi_k^2}\Big|^2\Big\}.$$

Proof. We repeat the standard proof for the lasts results by taking this time $\frac{\partial^2}{\partial \xi_k^2}$ of Eq. (2) for each $k = 1, 2, \ldots, d$ and multiply the obtained equations by $2\rho(\xi)\frac{\partial^2 S_1}{\partial \xi_k^2}$, $2\rho(\xi)\frac{\partial^2 S_2}{\partial \xi_k^2}$ and $2\rho(\xi)\frac{\partial^2 S_3}{\partial \xi_k^2}$ respectively. The proof is concluded by the use of Lemma 2 and Theorem 1 on the summed up three inequalities. □

Remark 2. If the random parameters are smooth enough, we can prove that the higher derivatives with respect to the random vector ξ, are bounded by similar techniques as in Theorems 1 - 3.

4 Convergence

In this section, we prove the convergence estimate for the stochastic collocation method using the obtained regularity results and the following interpolation error estimates.

Lemma 6. *Let $I_N^\xi u$ denote the polynomial of degree N that interpolates u at the $(N+1)$ Gauss, Gauss-Radau, or Gauss-Lobatto points $\{\xi_k\}_{k=0}^N$, i.e., $I_N^\xi u(\xi) = \sum_{k=0}^N u(\xi_k)\mathcal{L}_k(\xi)$. Then we have the interpolation error in the L_2-norm*

$$||u - I_N^\xi u||_{L_2(-1,1)} \le CN^{-m}|u|_{H^m(-1,1)}, \quad \forall u \in H^m(-1,1) \quad with \quad m \ge 1 \quad (16)$$

and the interpolation error in the H^l-norm

$$||u - I_N^\xi u||_{H^l(-1,1)} \le CN^{2l-\frac{1}{2}-m}|u|_{H^m(-1,1)}, \quad \forall u \in H^m(-1,1) \quad with \quad m \ge l \ge 1. \quad (17)$$

For the Gauss-Lobatto interpolation, we have the following optimal error estimate

$$||(u - I_N^\xi u)'||_{L_2(-1,1)} \le CN^{1-m}|u|_{H^m(-1,1)}, \quad \forall u \in H^m(-1,1) \quad with \quad m \ge 1. \quad (18)$$

Proof. See [4], pp. 289-290. □

To present the error estimate, we first recall that the mean (or expectation) of a function u is defined by

$$\mathcal{N}[u] = \int_\Gamma \int_D u(x,t,\xi)\rho(\xi)dxd\xi.$$

Its mean square is defined by

$$\mathcal{M}[u] = \Big(\int_\Gamma \int_D |u(x,t,\xi)|^2\rho(\xi)dxd\xi\Big)^{1/2}.$$

Theorem 4. *For each $i = 1, 2, 3$, let $(S_i)_i$ be the solution of Eqs. (2)-(4) and $(S_i^N)_i$ be the approximate solution given by the stochastic collocation method. If the assumptions of Theorems 1, 2 and 3 are satisfied, then the following mean and mean square errors hold: For any $0 < t \leqslant T$,*

$$\sum_{i=1}^{3} \mathcal{M}[S_i - S_i^N] \leqslant C_T N^{-2}, \tag{19}$$

$$\sum_{i=1}^{3} \mathcal{N}[S_i - S_i^N] \leqslant C_T N^{-2}, \tag{20}$$

$$\sum_{i=1}^{3} \mathcal{M}[\nabla(S_i - S_i^N)] \leqslant C_T N^{-1}, \tag{21}$$

$$\sum_{i=1}^{3} \mathcal{N}[\nabla(S_i - S_i^N)] \leqslant C_T N^{-1}. \tag{22}$$

For the Gauss-Lobatto interpolation, we have the error estimate for the derivative of the solution with respect to the random variables: For any $0 < t \leq T$, and $k = 1, ..., d$,

$$\sum_{i=1}^{3} \mathcal{M}[\partial_{\xi_k}(S_i - S_i^N)] \leqslant C_T N^{-1}, \tag{23}$$

$$\sum_{i=1}^{3} \mathcal{N}[\partial_{\xi_k}(S_i - S_i^N)] \leqslant C_T N^{-1}. \tag{24}$$

Here C_T is a constant depending on T but independent of N.

Proof. Let $m = 2$. For any fixed x, using inequality (16) of Lemma 6 for $u = S_1, S_2$ and S_3 respectively, we get

$$\int_\Gamma \Big(\sum_{i=1}^{3} |S_i - S_i^N|^2 \Big) \rho(\xi) d\xi \leqslant C N^{-4} \int_\Gamma \Big(\sum_{i=1}^{3} |\partial_\xi^2 S_i|^2 \Big) \rho(\xi) d\xi \tag{25}$$

Integrating with respect to x over D and using Theorem 3, we obtain Eq. (19). Similarly, using Eq. (18) of Lemma 6 and the higher regularity proved in Theorem 3, we obtain Eq. (23).

Let now $m = 1$. Again, by the inequality (16) of Lemma 6 for $u = \nabla S_1, \nabla S_2$ and ∇S_3, respectively, we get

$$\int_\Gamma \Big(\sum_{i=1}^{3} |\nabla(S_i - S_i^N)|^2 \Big) \rho(\xi) d\xi \leqslant C N^{-2} \int_\Gamma \Big(\sum_{i=1}^{3} |\partial_\xi \nabla S_i|^2 \Big) \rho(\xi) d\xi. \tag{26}$$

We integrate with respect to x over D and we use Theorem 2. We immediately get Eq. (21).

Finally, Eqs. (20), (22) and (24) follow from the standard inequality $||u||_{L_1} \leqslant C^{'}||u||_{L_2}$ and the estimates (19), (21) and (23). □

5 Numerical analysis

Let the partition of space domain D and time interval $[0, T]$ be a uniform grids defined as

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

where Δx and Δy are respectively the mesh sizes along the x and y directions, Δt is the time step size and N_x, N_y and N_t are three integers. Denote by $S^{n,\xi}_{1,i,j}$, $S^{n,\xi}_{2,i,j}$ and $S^{n,\xi}_{3,i,j}$ the approximation of the Extra-cellular concentration field $S_1(t^n, x_i, y_j, \xi)$, Cytosolic concentration field $S_2(t^n, x_i, y_j, \xi)$ and the Nuclear concentration field $S_3(t^n, x_i, y_j, \xi)$ respectively. Also we denote $k^{',i,j,\xi}_{lk} = k^{'}_{lk}(i\Delta x, j\Delta y, \xi)$, $k^{i,j,\xi}_{lk} = k_{lk}(i\Delta x, j\Delta y, \xi)$, $k^{i,j,\xi}_{l} = k_l(i\Delta x, j\Delta y, \xi)$ and $V^{i,j,\xi}_c = V_c(i\Delta x, j\Delta y, \xi)$ for any fixed random vector ξ.

The explicit FD scheme for PKC equation (2) for any fixed random vector ξ is defined as follows

$$\begin{aligned} S^{n+1,\xi}_{1,i,j} &= \Big(1 - \Delta t\Big(k^{',i,j,\xi}_{12} + D_s\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta y^2}\Big)\Big)S^{n,\xi}_{1,i,j} \\ &\quad + D_s\frac{\Delta t}{\Delta x^2}\Big(S^{n,\xi}_{1,i+1,j} - S^{n,\xi}_{1,i-1,j}\Big) \\ &\quad + D_s\frac{\Delta t}{\Delta y^2}\Big(S^{n,\xi}_{1,i,j+1} - S^{n,\xi}_{1,i,j-1}\Big) + \Delta t\frac{k^{',i,j,\xi}_{21}}{V^{i,j,\xi}_c}S^{n,\xi}_{2,i,j}, \end{aligned} \tag{27}$$

$$S^{n+1,\xi}_{2,i,j} = \Big(1 - \Delta t\Big(k^{i,j,\xi}_{21} + k^{i,j,\xi}_{2} + k^{i,j,\xi}_{23}\Big)\Big)S^{n,\xi}_{2,i,j} + \Delta t k^{i,j,\xi}_{12}V^{i,j,\xi}_c S^{n,\xi}_{1,i,j}, \tag{28}$$

$$S^{n+1,\xi}_{3,i,j} = \Big(1 - \Delta t k^{i,j,\xi}_{3}\Big)S^{n,\xi}_{3,i,j} + \Delta t k^{i,j,\xi}_{23}S^{n,\xi}_{2,i,j}. \tag{29}$$

Using boundary conditions, the boundary values for scheme (27)-(29) can be derived explicitly as,

$$S^{n,\xi}_{k,0,j} = S^{n,\xi}_{k,N_x+1,j} = S^{n,\xi}_{k,i,0} = S^{n,\xi}_{k,i,N_y+1} = 0 \quad \text{for} \quad k = 1, 2, 3. \tag{30}$$

Finally, the initial values $S^{0,\xi}_{k,i,j}$ for $k = 1, 2, 3$ are easily given as

$$S^{0,\xi}_{k,i,j} = S_{0k}(x_i, y_i, \xi). \tag{31}$$

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

$$\|M\|_{l^2(D)} = \Big(\sum_{i=0}^{N_x+1} \sum_{j=0}^{N_y+1} (M_{i,j})^2 \Delta x \Delta y \Big)^{1/2}. \tag{32}$$

We will assume throughout the rest of this work, in particular the theoretical analysis, that the solution of the PKC equations (2)-(4) acquires the following regularity property, for any fixed random vector ξ, we have

$$S_k \in C^1\Big([0,T], C^3(\bar{D})\Big), \quad for \quad k = 1, 2, 3. \tag{33}$$

Theorem 5. *Let ξ be a fixed random vector and*

$$S_k^n := \{S_{k,i,j}^{n,\xi}, i = 0, 1, \ldots, N_x + 1, j = 0, 1, \ldots, N_y + 1\}, \tag{34}$$

for $k = 1, 2, 3$ and $n \geq 0$, the solution of the FD scheme (27)-(29). Suppose that the exact solutions S_1, S_2 and S_3 satisfy the regularity property (33). For any $0 \leq i \leq Nx + 1$ and $0 \leq j \leq Ny + 1$, if we assume the following inequalities to hold true

$$\begin{aligned}
&2\Big|1 - \Delta t\Big(k_{21}^{i,j,\xi} + k_{2}^{i,j,\xi} + k_{23}^{i,j,\xi}\Big)\Big|^2 + 16\Delta t^2\Big|\frac{k_{21}^{',i,j,\xi}}{V_c^{i,j,\xi}}\Big|^2 + 4\Delta t^2 |k_{23}^{i,j,\xi}|^2 \leq 1,\\
&2\Big|1 - \Delta t\Big(k_{12}^{',i,j,\xi} + D_s\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta x^2}\Big)\Big)\Big|^2 + 16\Big|D_s\frac{\Delta t}{\Delta x^2}\Big|^2 + 32\Big|D_s\frac{\Delta t}{\Delta y^2}\Big|^2\\
&\qquad\qquad + 4|\Delta t k_{12}^{i,j,\xi} V_c^{i,j,\xi}|^2 \leq 1,\\
&2|1 - \Delta t k_3^{i,j,\xi}|^2 \leq 1,\\
&\Delta t \leq 1/16.
\end{aligned}$$

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

$$\max_{0 \leq n \leq N_T} \Big(\sum_{i=1}^{3} \|S_i(t^n) - S_i^n\|_{l^2(D)}^2 \Big)^{1/2} \leq C_T\Big(\Delta t + \Delta x^2 + \Delta y^2\Big). \tag{35}$$

Proof. Let

$$Z_{1,i,j}^n = S_1(t^n, x_i, y_j, \xi) - S_{1,i,j}^{n,\xi}, \tag{36}$$

$$Z_{2,i,j}^n = S_2(t^n, x_i, y_j, \xi) - S_{2,i,j}^{n,\xi}, \tag{37}$$

$$Z_{3,i,j}^n = S_3(t^n, x_i, y_j, \xi) - S_{3,i,j}^{n,\xi}. \tag{38}$$

Subtracting (27)-(29) from the three equations of (2), we obtain the following error equations

$$
\begin{aligned}
Z_{1,i,j}^{n+1} &= \Big(1 - \Delta t\Big(k_{12}^{\prime,i,j,\xi} - D_s\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta y^2}\Big)\Big)\Big) Z_{1,i,j}^{n} \\
&\quad + D_s \frac{\Delta t}{\Delta x^2}\Big(Z_{1,i+1,j}^{n} - Z_{1,i-1,j}^{n}\Big) + D_s \frac{\Delta t}{\Delta y^2}\Big(Z_{1,i,j+1}^{n} - Z_{1,i,j-1}^{n}\Big) \\
&\quad + \Delta t \frac{k_{21}^{\prime,i,j,\xi}}{V_c^{i,j,\xi}} Z_{2,i,j}^{n} + \Delta t \tau_{1,i,j}^{n}, \qquad (39) \\
Z_{2,i,j}^{n+1} &= \Big(1 - \Delta t\Big(k_{21}^{i,j,\xi} + k_{2}^{i,j,\xi} + k_{23}^{i,j,\xi}\Big)\Big) Z_{2,i,j}^{n} + \Delta t k_{12}^{i,j,\xi} V_c^{i,j,\xi} Z_{1,i,j}^{n} \\
&\quad + \Delta t \tau_{2,i,j}^{n}, \qquad (40) \\
Z_{3,i,j}^{n+1} &= \Big(1 - \Delta t k_{3}^{i,j,\xi}\Big) Z_{3,i,j}^{n} + \Delta t k_{23}^{i,j,\xi} Z_{2,i,j}^{n} + \Delta t \tau_{3,i,j}^{n} \qquad (41)
\end{aligned}
$$

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

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

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

$$
\begin{aligned}
|\tau_{1,i,j}^{n}| &\le \frac{\Delta t}{2}\Big\|\frac{\partial^2 S_1}{\partial t^2}\Big\|_\infty + \frac{\Delta x^2}{4!}\Big\|\frac{\partial^4 S_1}{\partial x^4}\Big\|_\infty + \frac{\Delta y^2}{4!}\Big\|\frac{\partial^4 S_1}{\partial y^4}\Big\|_\infty \\
&\le M\Big(\Delta t + \Delta x^2 + \Delta y^2\Big), \\
|\tau_{2,i,j}^{n}| &\le \frac{\Delta t}{2}\Big\|\frac{\partial^2 S_2}{\partial t^2}\Big\|_\infty \le M\Big(\Delta t + \Delta x^2 + \Delta y^2\Big), \\
|\tau_{3,i,j}^{n}| &\le \frac{\Delta t}{2}\Big\|\frac{\partial^2 S_3}{\partial t^2}\Big\|_\infty \le M(\Delta t + \Delta x^2 + \Delta y^2),
\end{aligned}
$$

with

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

We have

$$|Z_{1,i,j}^{n+1}| \leq \Big|1 - \Delta t\Big(k_{12}^{',i,j,\xi} + D_s\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta y^2}\Big)\Big)\Big||Z_{1,i,j}^n| \\ + D_s\frac{\Delta t}{\Delta x^2}\Big(|Z_{1,i+1,j}^n| + |Z_{1,i-1,j}^n|\Big) + D_s\frac{\Delta t}{\Delta y^2}\Big(|Z_{1,i,j+1}^n| + |Z_{1,i,j-1}^n|\Big) \\ + \Delta t\Big|\frac{k_{21}^{',i,j,\xi}}{V_c^{i,j,\xi}}\Big||Z_{2,i,j}^n| + \Delta t|\tau_{1,i,j}^n|. \tag{42}$$

Squaring both sides of the inequality (42) and by means of the inequality $(N + M)^2 \leq 2(N^2 + M^2)$ we obtain

$$|Z_{1,i,j}^{n+1}|^2 \leq 2\Big|1 - \Delta t\Big(k_{12}^{',i,j,\xi} + D_s\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta y^2}\Big)\Big)\Big|^2|Z_{1,i,j}^n|^2 \\ + 8\Big(D_s\frac{\Delta t}{\Delta x^2}\Big)^2\Big(|Z_{1,i+1,j}^n|^2 + |Z_{1,i-1,j}^n|^2\Big) \\ + 16\Big(D_s\frac{\Delta t}{\Delta y^2}\Big)^2\Big(|Z_{1,i,j+1}^n|^2 + |Z_{1,i,j-1}^n|^2\Big) \\ + 16\Delta t^2\Big|\frac{k_{21}^{',i,j,\xi}}{V_c^{i,j,\xi}}\Big|^2|Z_{2,i,j}^n|^2 + \Delta t^2|\tau_{1,i,j}^n|^2. \tag{43}$$

Similarly we have,

$$|Z_{2,i,j}^{n+1}|^2 \leq 2\Big|1 - \Delta t\Big(k_{21}^{i,j,\xi} + k_2^{i,j,\xi} + k_{21}^{i,j,\xi}\Big)\Big|^2|Z_{2,i,j}^n|^2 \\ + 4\Delta t^2|k_{12}^{i,j,\xi}V_c^{i,j,\xi}|^2|Z_{1,i,j}^n|^2 + 4\Delta t^2|\tau_{2,i,j}^n|^2, \tag{44}$$

and

$$|Z_{3,i,j}^{n+1}|^2 \leq 2|1 - \Delta t k_3^{i,j,\xi}|^2|Z_{3,i,j}^n|^2 + 4\Delta t^2|k_{23}^{i,j,\xi}|^2|Z_{2,i,j}^n|^2 + 4\Delta t^2|\tau_{3,i,j}^n|^2. \tag{45}$$

Adding up the last three inequalities then multiplying by $\Delta x\Delta y$ and summing up on $\{i, j\} \in [1, \ldots, Nx] \times [1, \ldots, Ny]$, we get

$$\|Z_1^{n+1}\|_{l^2(D)}^2 + \|Z_2^{n+1}\|_{l^2(D)}^2 + \|Z_3^{n+1}\|_{l^2(D)}^2 \leq \|Z_1^n\|_{l^2(D)}^2 + \|Z_2^n\|_{l^2(D)}^2 + \|Z_3^n\|_{l^2(D)}^2 \\ + \Delta t\Big(\|\tau_1^n\|_{l^2(D)}^2 + \|\tau_2^n\|_{l^2(D)}^2 + \|\tau_3^n\|_{l^2(D)}^2\Big),$$

where the hypothesis of the theorem have been used. The last inequality together with the estimates of truncation errors, conclude the proof. □

Next we give the main result of the section where we present the overall errors for solving the PKC equation with random coefficients and random initial datum by the FD scheme. To this purpose, for $k = 1, 2, 3$, denote S_k^N the solutions of the FD scheme for any fixed random vector ξ and $S_{k,h}^{N,\Delta t}$

the fully-discrete solution by the imposed stochastic collocation method. Then, the discrete mean square error is given by

$$\begin{aligned}\Big(\int_\Gamma \|S_k - S_{k,h}^{N,\Delta t}\|^2_{l^2(D)}\rho(\xi)d\xi\Big)^{\frac{1}{2}} \\ &\leq \Big(\int_\Gamma 2\Big(\|S_k - S_k^N\|^2_{l^2(D)} + \|S_k^N - S_{k,h}^{N,\Delta t}\|^2_{l^2(D)}\Big)\rho(\xi)d\xi\Big)^{\frac{1}{2}} \\ &\leq C_T\Big[N^{-2} + (\Delta t + \Delta x^2 + \Delta y^2)\Big].\end{aligned}$$

The above is easily achieved by Theorems 4 and 5.

5.1 Numerical results

5.1.1 Test 1

We test the convergence of the collocation method for the PKC equations with random coefficients and initial condition in two dimensions to justify our theoretical analysis whose governing equations are

$$\begin{cases} \dfrac{\partial S_1}{\partial t} = D_s\Delta S_1 - k'_{12}S_1 + \dfrac{k'_{21}}{V_c}S_2 + f_1, \\ \dfrac{\partial S_2}{\partial t} = k_{12}V_cS_1 - k_{21}S_2 - k_2S_2 - k_{23}S_2 + f_2, \\ \dfrac{\partial S_3}{\partial t} = k_{23}S_2 - k_3S_3 + f_3, \end{cases} \tag{46}$$

where the parameters k'_{12}, k'_{21}, V_c, k_{12}, k_{21}, k_{23}, k_2 and k_3 are functions of the spatial variable (x, y) and the random vector ξ. Functions f_1, f_2 and f_3 are added source terms used to construct exact solutions to check the convergence. The exact solution is given by

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

where our choice of the parameters reads

$$\begin{aligned} k'_{12}(x,y,\xi) &= 1 + 0.01\sin((\xi_1+\xi_2+\xi_3)x + (\xi_4+\xi_5+\xi_6)y), \\ k'_{21}(x,y,\xi) &= 1 + 0.01\cos((\xi_1+\xi_2+\xi_3)x + (\xi_4+\xi_5+\xi_6)y), \\ V_c(x,y,\xi) &= 1 + 0.1\sin((\xi_1+\xi_2+\xi_3)x - (\xi_4+\xi_5+\xi_6)y), \\ k_{12}(x,y,\xi) &= 1 - 0.1\sin((\xi_1+\xi_2+\xi_3)x - (\xi_4+\xi_5+\xi_6)y), \\ k_{21}(x,y,\xi) &= 1 - 0.1\cos((\xi_1+\xi_2+\xi_3)x - (\xi_4+\xi_5+\xi_6)y), \\ k_2(x,y,\xi) &= 1 - 0.1\sin((\xi_1+\xi_2+\xi_3)x + 2(\xi_4+\xi_5+\xi_6)y), \\ k_{23}(x,y,\xi) &= 1 - 0.1\sin((\xi_1+\xi_2+\xi_3)x - 2(\xi_4+\xi_5+\xi_6)y), \\ k_3(x,y,\xi) &= 1 - 0.2\sin((\xi_1+\xi_2+\xi_3)x - (\xi_4+\xi_5+\xi_6)y), \end{aligned}$$

Table 1: The error of the solutions in the discrete $\mathcal{N}[.]$ and $\mathcal{M}[.]$.

mesh	1/10	1/20	1/40	1/60
$\mathcal{N}[\lvert S_1 - S_1^h\rvert]$	$7.751205E{-}03$	$1.055841E{-}03$	$4.797782E{-}04$	$8.159386E{-}05$
$\mathcal{M}[\lvert S_1 - S_1^h\rvert]$	$1.164287E{-}02$	$6.053139E{-}03$	$8.300205E{-}04$	$4.950215E{-}05$
$\mathcal{N}[\lvert S_2 - S_2^h\rvert]$	$6.967211E{-}03$	$1.001005E{-}03$	$4.011205E{-}04$	$7.950235E{-}05$
$\mathcal{M}[\lvert S_2 - S_2^h\rvert]$	$9.841208E{-}03$	$5.651205E{-}03$	$6.951201E{-}04$	$3.851205E{-}05$
$\mathcal{N}[\lvert S_3 - S_3^h\rvert]$	$8.001215E{-}03$	$1.261215E{-}03$	$5.031215E{-}04$	$8.651245E{-}05$
$\mathcal{M}[\lvert S_3 - S_3^h\rvert]$	$1.211235E{-}02$	$6.151227E{-}03$	$8.451005E{-}04$	$5.051201E{-}05$

The variables ξ_k $(1 \le k \le 6)$ are uniform independent random variables on $[0, 1]$.

In Table 1, we represent the errors of all three components (S_1, S_2, S_3) in the discrete $\mathcal{N}[.]$ and $\mathcal{M}[.]$ by the FD scheme applied to Equation (46) on space domain $[0, 1]^2$ and time domain $[0, 1]$. We use the same partition size in x and y directions $(h = \Delta x = \Delta y)$ varying from $1/10$ to $1/60$ and we set the time partition $\Delta t = 10^{-2}h$ and $D_s = 0.01$ to guarantee the hypotheses of Theorem 5 and the stability of the scheme.

It's clear that the estimated approximation error decreases exponentially as the partition size decreases and all solutions show second order convergence which confirm our theoretical result. This is due to two facts. First, the exact solution in this case is infinitely smooth to both spatial and random variables. Then, the overall error is dominated by the numerical scheme error.

5.1.2 Test 2

The second test envelops solving the problem by two different sets of determinate parameters present in Table 2. Then, the two obtained results are compared to our proposed method as illustrated in Figure 2. In particular, the solution we used for comparison is exactly the mean approximated solution by different random parameters than the first test and which reads

$$
\begin{aligned}
V_c(x, y, \xi) &= 0.24 \times (3.2 - \xi_1^2 - \xi_2^2)E - 03, \\
k_{12}(x, y, \xi) &= 0.7 \times (\xi_2^2 + \xi_3^2 + 2.4), \\
k_{21}(x, y, \xi) &= 0.06 \times (\xi_3^2 + \xi_4^2 + 0.2), \\
k_{12}^{'}(x, y, \xi) &= 1.46 \times (\xi_2^2 + \xi_3^2 + 2.4), \\
k_{21}^{'}(x, y, \xi) &= 0.13 \times (\xi_3^2 + \xi_4^2 + 0.2), \\
k_2(x, y, \xi) &= 0.8 \times (3 - \xi_3^2 - \xi_6^2), \\
k_{23}(x, y, \xi) &= 0.1 + (\xi_4 + \xi_5)^2, \\
k_3(x, y, \xi) &= 2.1 - \xi_5^2 - \xi_6^2.
\end{aligned}
$$

The mesh is again uniform and equivalent to $h = \Delta x = \Delta y = 1/20$ and the time step size satisfies $\Delta t = 10^{-2}h$. For all $(x, y) \in [0, 1]^2$ and $\xi \in \Gamma$, we have $S_{01}(x, y, \xi) = 0.05(\sin(x^2+y^2))^2$, $S_{02}(x, y, \xi) = 0.05(\cos(x^2+y^2))^2$ and $S_{03}(x, y, \xi) = 0.05(1-\sin(x^2+y^2))^2$ is the initial concentration of drug in the three compartments. The values of k_{12}, k_{21}, k_{23} and k_3 can be found

Table 2: 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	[9]	520	[9]
F	Interstitial Fraction	0.48	-	0.48	-
D_s	Drug diffusivity ($\mu m^2\ min^{-1}$)	30E3	-	30E3	-
k_2	Inactivation rate (min^{-1})	1.7	-	1.7	-
k_{12}	Drug uptake (min^{-1})	0.043	[17]	0.00545	[11]
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	-

in [3] (Table 3 (Peak-bound intracellular model)), and k'_{12} and k'_{21} obtained using the formula $k'_{ij} = k_{ij}/F\ i, j \in \{1, 2\}$.

Figure 2 shows the general behavior of variation of Cisplatin concentration in the three compartments versus time for two determinate case and the stochastic case. The best-fit parameters given by the two cases in Table 2 are reasonably well, but not with enough accuracy because of the variation from case-1 to case-2 as clearly shown by the red and yellow curves. To solve this problem we use the stochastic collocation method which give the result represented by the blue curve.

6 Conclusion

In this work, we developed the stochastic collocation method to solve the pharmacokinetics equation for cisplatin with random coefficients and random initial datum. We established the regularity analysis for this equation with respect to the random variables and proved the error estimate using the regularity result. We also established error estimate for space discretization by Finite Difference method. Then, an overall error estimate is written. Some numerical simulations illustrate the theoretical analysis where we also compared between the stochastic and determinate solving process. It is worth mentioning that another important parameter is the

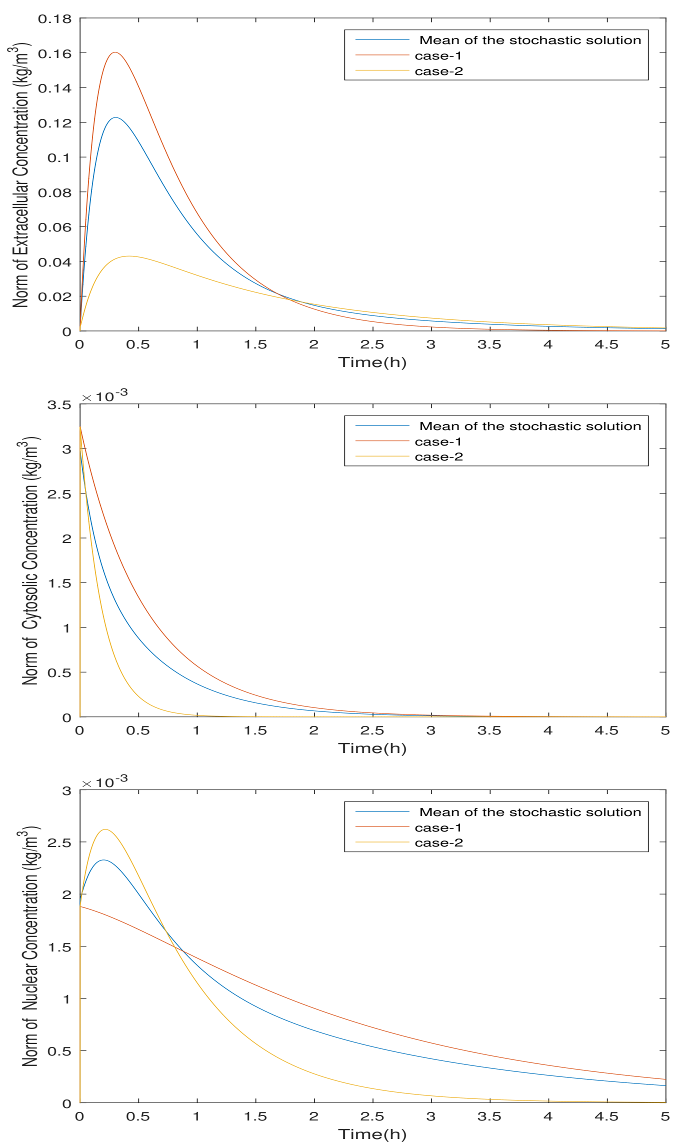

Figure 2: *Comparison of the stochastic and the determinate results.* The concentration-versus-time curve for cisplatin. The curves represent the concentration of cisplatin using the stochastic collocation method (Blue) and the parameters given in case 1 (Red) and case 2 (Yellow) of Table 2.

diffusivity of the drug through interstitial space D_s. Through this note, it was considered as a constant, as mentioned before, to ease the obtaining of certain regularity results. However, an ideal solver would take in consideration the inconsistency of such parameters. We aim to construct an even more powerful solver combining the stochastic collocation method and machine learning to predict its physical value.

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