Advanced Mathematical Models & Applications
Vol.9, No.3, 2024, pp.454-474
https://doi.org/10.62476/amma93454

WELL-POSEDNESS AND CONVERGENCE ANALYSIS OF THE MULTI-LEVEL MONTE CARLO METHOD FOR A SYSTEM OF PDEs WITH RANDOM COEFFICIENTS MODELING DRUG TRANSPORT IN TUMORS

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Abstract. In this paper, we consider a mathematical model of drug transport in tumors given by a system of PDEs with random coefficients and initial data. The existence of a strong solution to this model in any dimension is proved under the assumption that the random coefficients are uniformly bounded. Along with the finite difference method (FD), we applied a multilevel Monte Carlo method to simulate these random PDEs. We also derived the overall convergence rate and estimated the total computation cost. Finally, some numerical results are presented to confirm our theoretical results. Additionally, we provide a comparison between the stochastic and deterministic approaches for solving the drug transport equation, demonstrating the efficiency of the method we adopted.

Keywords: Drug transport equation, random coefficients, finite difference method, multilevel Monte Carlo.
AMS Subject Classification: 93A30, 91G60, 65L12.
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Received: 15 May 2024; Revised: 7 September 2024; Accepted: 20 September 2024; Published: 4 December 2024.

1 Introduction

In recent years, numerical simulations have increasingly been used to produce predictions of the behavior of complex engineering and physical systems due to the rapid growth in computational power, the sources of errors arising in computer simulations can be reduced or controlled, by now, using some techniques such as mesh adaptivity and the more recent modeling error analysis (Oden & Prudhomme, 2002; Oden & Vemaganti, 2000; Braack & Ern, 2003), a posteriori error estimation (Ainsworth & Oden, 2000; Babuska & Strouboulis, 2001; Verfurth, 1996). All this has increased the accuracy of numerical predictions as well as our confidence in them.

However, in fields such as drug transport in tumors, uncertainties in input data can critically impact the reliability of predictions. Parameters such as model coefficients, boundary conditions, and geometric features are often uncertain and can influence the outcomes substantially. Properly managing this uncertainty is crucial for ensuring that numerical predictions are robust enough to guide clinical decisions and develop effective treatments.

How to cite (APA): Essarrout, S., Raghay, S., & Mahani Z. (2024). Well-Posedness and convergence analysis of the multi-level Monte Carlo method for a system of PDEs with random coefficients modeling drug transport in tumors. *Advanced Mathematical Models & Applications*, *9*(3), 454-474 https://doi.org/10.62476/amma93454

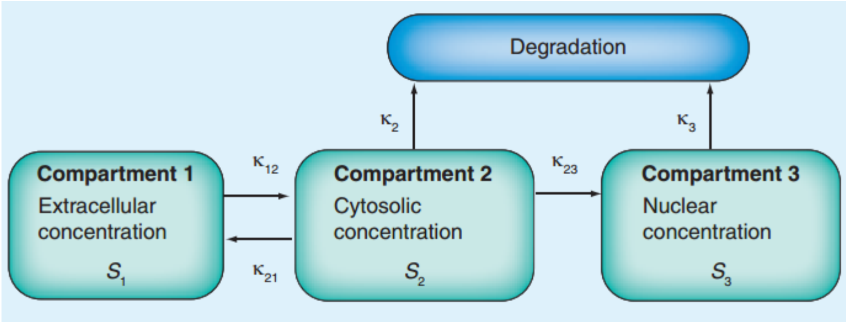


Figure 1: Multicompartmental models of drug distribution

There are various methods to quantify uncertainty, including worst-case scenario analysis, fuzzy set theory, probabilistic frameworks, and evidence theory (Hlavacek et al., 2004; Sandeep et al., 2006). In this study, we focus on a model for drug transport within tumors, employing a probabilistic approach to handle uncertainties in input data. The model is represented by a system of partial differential equations (PDEs) which is capable of tracking the amount of drugs both spatially and temporally through three compartments : the extracellular space, the cytosol, and the nucleus (see Figure 1). The model is formulated as follows:

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

In the model, S_1 denotes the Extracellular concentration, S_2 represents the Cytosolic concentration, and S_3 stands for Nuclear concentration. The parameter D_s signifies the diffusivity of the drug through interstitial space, while k_{ij} denotes the transfer rate from compartment i to j. The rates k'_{ij}, which are primed in the first equation, are related to their unprimed counterparts via $k'_{ij} = k_{ij}/F$, where F signifies the extracellular fraction of the entire tissue. Additionally, k_i represents a rate of permanent removal from compartment i, and V_c denotes the volume of a cell (further details are available in Sinek et al. (2008a); El-Kareh & Secomb (2003)). These parameters encapsulate significant phenomena, including efflux pumps, cell permeability, and DNA repair. Their values are derived from experimental data and lack certainty. Consequently, we regard these inferred parameters as stochastic processes or random variables rather than constants or deterministic functions. Therefore, it proves advantageous to conceptualize the equations describing such models as stochastic rather than deterministic.

Here we will focus on the case where the probability space has a low dimensionality, that means, the stochastic problem depends only on a small number of random variables. A possible way to describe such random fields consists in using a Polynomial Chaos (PC) expansion (Wiener, 1938; Xiu & Karniadakis, 2002) or Karhunen Loéve (Loeve, 1977). The former uses polynomial expansions in terms of independent random variables, while the latter represents the random field as a linear combination of an infinite number of uncorrelated random variables.

The first main result of this paper concerns the existence and uniqueness of strong solutions to system 1, when the imputed parameters are considered as random field rather than constants, using Leray-schauder's fixed point theorem .

The secondary objective of this paper involves investigating a multilevel approach that combines Monte Carlo (MC) sampling with a "pathwise" finite difference method (FDM) to estimate the mean of stochastic solutions for 1. This approach, termed the multilevel Monte Carlo finite difference method (MLMCFDM) for (1), is non-intrusive, requiring only repeated application of existing solvers for input data samples, and is straightforward to implement and parallelize. Our analysis encompasses establishing convergence rates for both the MCFDM and MLMCFDM towards the mean of the stochastic solution of (1). Additionally, we determine the optimal number of MC samples necessary to minimize computational effort for a given error tolerance.

The remainder of this paper is organized as follows. In Section 2, we introduce the mathematical problem and the main notations used throughout. In Section 3, we provide the existance and uniqueness of the solution of our problem using Leray-schauder's fixed point theorem. In section 4 we focus on the discretization of our problem and we prove an a priori estimate for the L^2-error then we deduce the error analysis of the solution and use it to to derive the complexity analysis of the MLMC method for our system of PDEs with random coefficients. In Section 5 we perform some numerical experiments to validate our error estimates. Finally, we summarize the findings of this paper in Section 6.

2 Problem setting and notation

We consider the following stochastic problem: for $k \in \{1, 2, 3\}$ find a random function S_k : $([0, T] \times D \times \Omega) \longrightarrow \mathbb{R}$ satisfying almost surely(a.s)

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

subject to random initial conditions

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

and boundary conditions

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

Where $D \subset \mathbb{R}^2$ is a Lipschitz polyhedral domain, $(\Omega, \mathcal{F}, \mathbb{P})$ is the complete probability space with the set of outcomes Ω, σ-algebra $\mathcal{F}$ and probability mesure $\mathbb{P}$. For Y in $(\Omega, \mathcal{F}, \mathbb{P})$ we denote by $\mathbb{E}(Y)$ the expected value wich is defined by $\mathbb{E}(Y) = \int_\Omega Y(\omega) d\mathbb{P}(\omega)$ and these soboleve spaces $L^2(D)$ and $L^2([0, T], L^2(D))$ are equiped respectively with the norm

$$\|v\|_{L^2(\Omega, L^2(D))} = \left(\int_\Omega \int_D |v(x, \omega)|^2 dx d\mathbb{P}(\omega) \right)^{\frac{1}{2}},$$

$$\|v\|_{L^2([0,T], L^2(D))} = \left(\int_{[0,T]} \int_D |v(x, t)|^2 dx dt \right)^{\frac{1}{2}},$$

In the rest of these work we make the following assumptions to the random coefficients D_s, $k_{i,j}$, $k'_{i,j}$, V_c, k_i for i and $j \in \{1, 2, 3\}$.

H. There exist the constants such that for almost surely (a.s.):

$$0 < D_s^- < D_s(x, \omega) < D_s^+ < +\infty$$

$$0 < k_{i,j}^- < k_{i,j}(x, \omega) < k_{i,j}^+ < +\infty$$

$$0 < k_{i,j}^{',-} < k'_{i,j}(x, \omega) < k_{i,j}^{',+} < +\infty$$

$$0 < V_c^- < V_c(x, \omega) < V_c^+ < +\infty$$

$$0 < k_i^- < k_i(x, \omega) < k_i^+ < +\infty$$

for all x in D and ω in Ω.

Using the Karhunen-Loéve (KL) expansion (Loeve, 1977) 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 (2) can be described by just a finite number of random variables, that is, $S_k(x,t,\xi) = S_k(x,t,\xi_1(\omega),\xi_2(\omega),\ldots,\xi_N(\omega))$ where the random vector $\xi = (\xi_1(\omega),\xi_2(\omega),\ldots,\xi_N(\omega))$ has a joint probability density function $\rho : \Gamma \longrightarrow \mathbb{R}_+$ that factorizes $\rho(\xi) = \prod_{n=1}^{N} \rho_n(\xi_n)$ for all $\xi \in \Gamma \subset \mathbb{R}^{\mathbb{N}}$ with $\Gamma = \Gamma_1 \times \Gamma_2 \times, \ldots, \Gamma_N$, where Γ_n is the bounded image set of the random variables $\xi_n(\Omega)$. Then we can rewrite our problem with an $N-$dimensional parameter as follows:

$$\begin{cases} \dfrac{\partial S_1}{\partial t}(x,t;\xi) = D_s(x,\xi)\Delta S_1(x,t;\xi) - k'_{12}(x,\xi)S_1(x,t;\xi) + \dfrac{k'_{21}(x,\xi)}{V_c(x,\xi)}S_2(x,t;\xi), \\ \dfrac{\partial S_2}{\partial t}(x,t;\xi) = k_{12}(x,\xi)V_c(x,\xi)S_1(x,t;\xi) - \big(k_{21}+k_2+k_{23}\big)(x,\xi)S_2(x,t;\xi), \\ \dfrac{\partial S_3}{\partial t}(x,t;\xi) = k_{23}(x,\xi)S_2(x,t;\xi) - k_3(x,\xi)S_3(x,t;\xi), \end{cases} \tag{5}$$

subject to random initial conditions

$$\begin{cases} S_1(x,t=0;\xi) = S_{01}(x,\xi) \\ S_2(x,t=0;\xi) = S_{02}(x,\xi) \\ S_3(x,t=0;\xi) = S_{03}(x,\xi) \end{cases} \tag{6}$$

and boundary conditions

$$S_k = 0 \quad on\ \partial D \quad for\ k = 1,2,3. \tag{7}$$

3 Global existence and uniqueness of solutions

The main result of this section concerns the existence and uniqueness of bounded strong solution to system 2-4 using the following fixed Point theorem (Leray-schauder's theorem):

Theorem 1. *Let B be a Banach space and let T be a compact mapping of $B \times [0,1]$ into B such that $T(x,0) = 0$ for all $x \in B$, suppose there exists a constant M such that*

$$||x||_B < M$$

for all $(x,\sigma) \in B \times [0,1]$ satisfying $x = T(x,\sigma)$, then the mapping T_1 of B into itself given by $T_1 x = T(x,1)$ has a fixed point.

Proof. see Gilbarg & Trudinger (2015) Theorem 10.3. □

And the Gronwall lemma

Lemma 1. *If $h(t)$ satisfies $\frac{\partial h(t)}{\partial t} \leq ah(t) + b$ some constant $a \neq 0$ and b, then we have*

$$h(t) \leq e^{at}(h(0) + \frac{b}{a}), \quad t \geq 0.$$

3.1 Existence

In this subsection, we show the existence of solutions to the stochastic problem (2)–(4)

Theorem 2. *Let D be a smooth bounded connected open subset of $\mathbb{R}^n$(for $n \in \mathbb{N} - \{0\}$), and D_s, $k_{i,j}$, $k'_{i,j}$, V_c,k_i for i and $j \in \{1,2,3\}$ satisfy the assumptions H, and consider initial data*

$(S_{01}, S_{02}, S_{03}) \in \left(L^2(\Omega, H_0^1(D))\right)^3$. *Then, for each* $\omega \in \Omega$ *the system 2-4 has a unique strong solution* $(S_1, S_2, S_3) \in \left(L^2([0,T], L^2(D))\right)^3$ *for all* $T > 0$ *such that*

$$C_T := Tk_{12}V_c < 1.$$

$$C_T^{'} := T\frac{k_{21}^{'}}{V_c} < 1.$$

$$C_T^{''} := Tk_{23} < 1.$$

Proof. We will prove, thanks to Leray-schauder's theorem that for each $\omega \in \Omega$ the system 2-4 has a solution:
To this end we define:

$$\eta := L^2([0,T], L^2(D)) \quad and \quad \mathfrak{X} := \eta \times \eta.$$

and

$$\mathcal{F} : \mathfrak{X} \times [0,1] \to \mathfrak{X} \quad \text{via} \quad \mathcal{F}(S_1, S_3, \lambda) := (\lambda \mathfrak{S}_1, \lambda \mathfrak{S}_3),$$

where $(\mathfrak{S}_1, \mathfrak{S}_3)$ is given (in a unique way) by solving first an ODE (for S_2), and then successively (for $\mathfrak{S}_1$ and $\mathfrak{S}_3$, in that order) . More precisely, $(\mathfrak{S}_1, \mathfrak{S}_3)$ is the (unique) solution on $[0,T] \times \Omega \times D$ of the system

$$\begin{cases} \frac{\partial \mathfrak{S}_1}{\partial t} = D_s \Delta \mathfrak{S}_1 - k_{12}' \mathfrak{S}_1 + \frac{k_{21}'}{V_c} S_2, \\ \frac{\partial S_2}{\partial t} = k_{12} V_c S_1 - (k_{21} + k_2 + k_{23}) S_2, \\ \frac{\partial \mathfrak{S}_3}{\partial t} = k_{23} S_2 - k_3 \mathfrak{S}_3, \end{cases} \tag{8}$$

subject to random initial conditions

$$\begin{cases} \mathfrak{S}_1(w, t=0, x) = S_{01}(w, x) \\ S_2(w, t=0, x) = S_{02}(w, x) \\ \mathfrak{S}_3(w, t=0, x) = S_{03}(w, x) \end{cases} \tag{9}$$

and boundary conditions

$$\mathfrak{S}_k = 0 \quad for \quad k = 1, 3 \quad and \quad S_2 = 0 \quad on \quad \partial\Omega \tag{10}$$

Note that $F(S_1, S_3, 0) = 0$.

Similarly as in Lemma 2,3 and Lemma 4 Saadeddine et al. (2020) we can prove that there is $C_1 > 0$ depending on $(T, \mathfrak{S}_{01}, \mathfrak{S}_{03}, k_{i,j}, \nabla k_{i,j}, k_i, \nabla k_i, k_i^{'}, \nabla k_i^{'}, D_s, V_c, \nabla V_c)$ such that for $i = 1, 3$

$$||\mathfrak{S}_i||_{L^2([0,T], L^2(D))} < C_1$$

$$||\nabla \mathfrak{S}_i||_{L^2([0,T], L^2(D))} < C_1$$

$$||\frac{\partial \mathfrak{S}_i}{\partial t}||_{L^2([0,T], L^2(D))} < C_1$$

then for $i = 1, 3$ we have $\mathfrak{S}_i \in H^1([0,T], L^2(D)) \cap L^2([0,T], H^1(D))$ then because $H^1(D) \hookrightarrow L^2(D)$ compactly and using theorem 2.4.1 Droniou (2001) we see that, the map $\mathcal{F}$ sends bounded sets in $\mathfrak{X}$ into relatively compact sets of $\mathfrak{X}$.

We now show that for any $\lambda \in [0,1]$, $\mathcal{F}(.,.,\lambda)$ is continuous from $\mathfrak{X}$ to $\mathfrak{X}$. For that let (S_1, S_3) , $(\hat{S}_1, \hat{S}_3)$ and $(\lambda \mathfrak{S}_1, \lambda \mathfrak{S}_3) = \mathcal{F}(S_1, S_3, \lambda)$, $(\lambda \hat{\mathfrak{S}}_1, \lambda \hat{\mathfrak{S}}_1) = \mathcal{F}(\hat{S}_1, \hat{S}_3, \lambda)$, we have

$$\frac{\partial S_2}{\partial t} = k_{12} V_c S_1 - (k_{21} + k_2 + k_{23}) S_2,$$

and

$$\frac{\partial \hat{S}_2}{\partial t} = k_{12} V_c \hat{S}_1 - (k_{21} + k_2 + k_{23}) \hat{S}_2,$$

then we have

$$\frac{\partial(S_2-\hat{S}_2)}{\partial t}=k_{12}V_c(S_1-\hat{S}_1)-(k_{21}+k_2+k_{23})\,(S_2-\hat{S}_2),$$

we multiply this equation by $(S_2-\hat{S}_2)$ we obtain

$$\frac{\partial(S_2-\hat{S}_2)^2}{\partial t}\leq 2k_{12}V_c(S_1-\hat{S}_1)(S_2-\hat{S}_2),$$

then using the inequality $2ab\leq a^2+b^2$ for all $(a,b)\in\mathbb{R}^2$ we get the following inequality

$$\frac{\partial(S_2-\hat{S}_2)^2}{\partial t}\leq k_{12}V_c\big((S_1-\hat{S}_1)^2+(S_2-\hat{S}_2)^2\big),$$

for a fixed $\omega\in\Omega$ we integrate this inequality over D and $[0,s]$ for $s\in[0,T]$ we obtain

$$\int_0^s\frac{\partial}{\partial t}\int_D(S_2-\hat{S}_2)^2\leq k_{12}V_c\Big(\int_0^s\int_D(S_1-\hat{S}_1)^2+\int_0^s\int_D(S_2-\hat{S}_2)^2\Big),$$

then

$$||S_2(.,s)-\hat{S}_2(.,s)||^2_{L^2(D)}\leq k_{12}V_c\Big(\int_0^T\int_D(S_1-\hat{S}_1)^2+\int_0^T\int_D(S_2-\hat{S}_2)^2\Big),$$

and by integrating this inequality over $[0,T]$ we have

$$||S_2-\hat{S}_2||^2_{L^2([0,T],L^2(D))}\leq Tk_{12}V_c\big(||S_1-\hat{S}_1||^2_{L^2([0,T],L^2(D))}+||S_2-\hat{S}_2||^2_{L^2([0,T],L^2(D))}\big),$$

we denote by $C_T:=Tk_{12}V_c$ and here we choise T small enough such that $C_T<1$ wet get

$$||S_2-\hat{S}_2||^2_{L^2([0,T],L^2(D))}\leq\frac{C_T}{1-C_T}||S_1-\hat{S}_1||^2_{L^2([0,T],L^2(D))}\tag{11}$$

similarly we have

$$\frac{\partial\mathfrak{S}_1}{\partial t}=D_s\Delta\mathfrak{S}_1-k'_{12}\mathfrak{S}_1+\frac{k'_{21}}{V_c}S_2\tag{12}$$

and

$$\frac{\partial\hat{\mathfrak{S}}_1}{\partial t}=D_s\Delta\hat{\mathfrak{S}}_1-k'_{12}\hat{\mathfrak{S}}_1+\frac{k'_{21}}{V_c}\hat{S}_2\tag{13}$$

then we have

$$\frac{\partial(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)}{\partial t}=D_s\Delta(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)-k'_{12}(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)+\frac{k'_{21}}{V_c}(S_2-\hat{S}_2)\tag{14}$$

Multiply this equation by $(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)$ we get

$$\frac{\partial(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)^2}{\partial t}=2D_s\Delta(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)-2k'_{12}(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)^2+2\frac{k'_{21}}{V_c}(S_2-\hat{S}_2)(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)\tag{15}$$

we obtain that

$$\frac{\partial(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)^2}{\partial t}\leq 2D_s\Delta(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)+2\frac{k'_{21}}{V_c}(S_2-\hat{S}_2)(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)\tag{16}$$

we integrate this inequality over D and $[0,s]$ for $s\in[0,T]$ and using the green formula and the boundary condition and then using the inequality $2ab\leq a^2+b^2$ we have that

$$||\mathfrak{S}_1(.,s)-\hat{\mathfrak{S}}_1(.,s)||^2_{L^2(D)}\leq\frac{k'_{21}}{V_c}(||(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)||^2_{L^2([0,T],L^2(D))}+||S_2-\hat{S}_2||^2_{L^2([0,T],L^2(D))})\tag{17}$$

integrating this inequality over $[0,T]$ we have

$$||\mathfrak{S}_1-\hat{\mathfrak{S}}_1||^2_{L^2([0,T],L^2(D))}\leq T\frac{k'_{21}}{V_c}(||(\mathfrak{S}_1-\hat{\mathfrak{S}}_1)||^2_{L^2([0,T],L^2(D))}+||S_2-\hat{S}_2||^2_{L^2([0,T],L^2(D))}) \tag{18}$$

then if we denote $C'_T:=T\frac{k'_{21}}{V_c}$ and chose T such that $C'_T<1$ we get

$$||\mathfrak{S}_1-\hat{\mathfrak{S}}_1||^2_{L^2([0,T],L^2(D))}\leq\frac{C'_T}{1-C'_T}||S_2-\hat{S}_2||^2_{L^2([0,T],L^2(D))} \tag{19}$$

finally using the inequality 11 we have

$$||\mathfrak{S}_1-\hat{\mathfrak{S}}_1||^2_{L^2([0,T],L^2(D))}\leq\frac{C'_T}{1-C'_T}\frac{C_T}{1-C_T}||S_1-\hat{S}_1||^2_{L^2([0,T],L^2(D))} \tag{20}$$

Similarly we have that

$$||\mathfrak{S}_3-\hat{\mathfrak{S}}_3||^2_{L^2([0,T],L^2(D)))}\leq\frac{C"_T}{1-C"_T}\frac{C_T}{1-C_T}||S_1-\hat{S}_1||^2_{L^2([0,T],L^2(D))} \tag{21}$$

where $C"_T:=Tk_{23}$.
It follow from (20)-(21) that for any $\lambda\in[0,1]$, $\mathcal{F}(.,.,\lambda)$ is continuous from $\mathfrak{X}$ to $\mathfrak{X}$.We now check the last assumption in Leray-schauder's theorem for that we Consider therefore

$$Z:=\{(S_1,S_3)\in\mathfrak{X}:(S_1,S_3)=\mathcal{F}(S_1,S_3,\lambda)\ where\ 0<\lambda\leq1\} \tag{22}$$

and we will show that Z is bounded in $\mathfrak{X}$.

Note that if $(S_1,S_3)\in Z$,then $(S_1,S_3)=(\lambda\mathfrak{S}_1,\lambda\mathfrak{S}_3)$ where $(\mathfrak{S}_1,\mathfrak{S}_3)$ solves $(8)-(10)$, therefore by multiplying the equations in $(8)-(10)$ by λ, we obtain for $(S_1,S_3)\in Z$

$$\begin{cases}\frac{\partial S_1}{\partial t}=D_s\Delta S_1-k'_{12}S_1+\lambda\frac{k'_{21}}{V_c}S_2,\\ \frac{\partial S_2}{\partial t}=k_{12}V_cS_1-\lambda\left(k_{21}+k_2+k_{23}\right)S_2,\\ \frac{\partial S_3}{\partial t}=\lambda k_{23}S_2-k_3S_3,\end{cases} \tag{23}$$

subject to random initial conditions

$$\begin{cases}S_1(x,\omega,t=0)=\lambda S_{01}(x,\omega)\\ S_2(x,\omega,t=0)=S_{02}(x,\omega)\\ S_3(x,\omega,t=0)=\lambda S_{03}(x,\omega)\end{cases} \tag{24}$$

In order to show that Z is bounded , we multiply the equation in (23) by $2S_1$, $2S_2$ and $2S_3$ respectively, then we integrate over D. The following equation is a direct result of using Green formula and the boundary conditions

$$\frac{\partial}{\partial t}\int_D|S_1|^2dx+\int_D2D_s|\nabla S_1|^2dx+\int_D2k'_{12}|S_1|^2=\int_D2\lambda\frac{k'_{21}}{V_c}S_2S_1dx$$

then

$$\frac{\partial}{\partial t}\int_D|S_1|^2dx\leq\int_D2\lambda\frac{k'_{21}}{V_c}S_2S_1dx$$

and by Cauchy Schwartz inequality, it is easy to see that

$$\frac{\partial}{\partial t}\int_D|S_1|^2dx\leq\int_D\left((\lambda\frac{k'_{21}}{V_c})^2|S_1|^2+|S_2|^2\right)dx \tag{25}$$

$$\leq \int_D \big((\frac{k'_{21}}{V_c})^2|S_1|^2 + |S_1|^2\big)dx$$

because $0 < \lambda \leq 1$,Similarly ,we obtain

$$\frac{\partial}{\partial t}\int_D |S_2|^2 dx \leq \int_D \big((k_{12}V_c)^2|S_1|^2 + |S_2|^2\big)dx \tag{26}$$

and

$$\frac{\partial}{\partial t}\int_D |S_3|^2 dx \leq \int_D \big((k_{23})^2|S_3|^2 + |S_2|^2\big)dx \tag{27}$$

then according to (25)-(26) we have

$$\frac{\partial}{\partial t}\int_D (\sum_{i=1}^{3}|S_i|^2)(t)dx \leq C_1 \int_D \sum_{i=1}^{3}|S_i|^2)(t)dx$$

where

$$C_1 = \max\{k_{23})^2, k_{12}V_c)^2, \frac{k'_{21}}{V_c})^2, 3\}$$

Applying Gronwall inequality yields

$$\int_D (\sum_{i=1}^{3}|S_i|^2)(t)dx \leq e^{C_1T}\int_D \sum_{i=1}^{3}|S_{0i}|^2)dx$$

$$= e^{C_1T}\sum_{i=1}^{3}||S_{0i}||^2_{L^2(D)}$$

Then integrating this inequality over $[0,T]$ we get

$$||S_i||^2_{L^2([0,T],L^2(D))} \leq Te^{C_1T}\sum_{i=1}^{3}||S_{0i}||^2_{L^2(D)} \leq Te^{C_1T}M = M_T \tag{28}$$

Because of for $i \in \{1,2,3\}$, $S_{0i} \in L^2(D)$.

Note that the bounded (28) do not depend on $\lambda \in [0,1]$, this means that the set Z defined in (22) is bounded in $\mathfrak{X}$ this shows that the last assumption of Leray-Schauder fixed theorem holds, and therefore that the mapping $\mathcal{F}$ has a fixed point which satisfies as a consequence system $23-24$, which give also the solution to the original system $2-4$ for ($T > 0$ *small*) . □

Remark 1. *The overall existence in time for all $T' > 0$ is obtained by taking as initial condition the value at T thus we cover the horizon T'.*

3.2 Uniqueness

Proposition 1. *Let $T > 0$, under the assumption of 2, We consider two sets of initial data (S_{01}, S_{02}, S_{03}) and $(S'_{01}, S'_{02}, S'_{03})$ in $(L^2(\Omega, H^1_0(D)))^3$, and two sets of strong solution (in the sense of the theorem 2) (S_1, S_2, S_3) and (S'_1, S'_2, S'_3) to system 2-4 (with corresponding initial data) on $[0,T] \times \Omega \times D$, for each $\omega \in \Omega$ there is $C^*_T > 0$ such that*

$$\sum_{i=1}^{3}||S_i - S'_i||_{L^2([0,T],L^2(D))} \leq C^*_T \sum_{i=1}^{3}||S_{0i} - S'_{0i}||_{L^2(D)}$$

Proof. Substracting the equation satisfied by S_1 , $S_1^{'}$ and S_2 , $S_2^{'}$ and finally S_3 , $S_3^{'}$, we obtain

$$\begin{cases} \frac{\partial(S_1-S_1^{'})}{\partial t} = D_s\Delta(S_1-S_1^{'}) - k_{12}'(S_1-S_1^{'}) + \frac{k_{21}'}{V_c}(S_2-S_2^{'}), \\ \frac{\partial(S_2-S_2^{'})}{\partial t} = k_{12}V_c(S_1-S_1^{'}) - (k_{21}+k_2+k_{23})(S_2-S_2^{'}), \\ \frac{\partial(S_3-S_3^{'})}{\partial t} = k_{23}(S_2-S_2^{'}) - k_3(S_3-S_3^{'}), \end{cases} \tag{29}$$

as in the proof of the theorem we multiply the equation in (29) by $2(S_1 - S_1^{'})$, $2(S_2 - S_2^{'})$ and $2(S_2 - S_2^{'})$ respectively, then integrate over D then using the Chauchy-Schwarz inequality and Applying Gronwall inequality yields

$$\int_D \big(\sum_{i=1}^{3}|S_i - S_i^{'}|^2(t)\big)dx \leq e^{C_1 T}\int_D \big(\sum_{i=1}^{3}|S_{0i} - S_{0i}^{'}|^2\big)dx$$

then integrate this last inequality over $[0, T]$ we obtain

$$\sum_{i=1}^{3}||S_i - S_i^{'}||^2_{L^2([0,T],L^2(D))} \leq C_T^*\sum_{i=1}^{3}||S_{0i} - S_{0i}^{'}||_{L^2(D)}.$$

□

Note that uniqueness in theorem 2 is a direct consequence of proposition 1.

4 Numerical Analysis

4.1 Finite difference Method

Let the partition of space domain $D = [0, l]^2$ and time interval $[0, T]$ be a uniform grids defined as

$$x_i = i\Delta x, i = 0, 1 \ldots, N_x + 1,$$
$$y_j = j\Delta y, j = 0, 1 \ldots, N_y + 1,$$
$$t^n = n\Delta t, n = 0, 1 \ldots, N_t + 1,$$

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 $k^{',i,j,\xi}_{lk} = k^{'}_{lk}(i\Delta x, j\Delta y, \xi)$, $k^{i,j,\xi}_{lk} = k_{lk}(i\Delta x, j\Delta y, \xi)$, $k^{i,j,\xi}_{l} = k_l(i\Delta x, j\Delta y, \xi)$, $V^{i,j,\xi}_c = V_c(i\Delta x, j\Delta y, \xi)$ and $D^{i,j,\xi}_S = D_s(i\Delta x, j\Delta y, \xi)$ for any fixed random vector ξ.

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

$$\begin{aligned} S^{n+1,\xi}_{1,i,j} = &\Big(1 - \Delta t\Big(k^{',i,j,\xi}_{12} + D^{i,j,\xi}_s\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta y^2}\Big)\Big)S^{n,\xi}_{1,i,j} + D^{i,j,\xi}_S\frac{\Delta t}{\Delta x^2}\Big(S^{n,\xi}_{1,i+1,j} - S^{n,\xi}_{1,i-1,j}\Big) \\ &+ D_s\frac{\Delta t}{\Delta y^2}\Big(S^{n,\xi}_{1,i,j+1} - S^{n,\xi}_{1,i,j-1}\Big) + \Delta t\frac{k^{',i,j,\xi}_{21}}{V^{i,j,\xi}_c}S^{n,\xi}_{2,i,j}, \end{aligned} \tag{30}$$

$$S^{n+1,\xi}_{2,i,j} = \Big(1 - \Delta t\Big(k^{i,j,\xi}_{21} + k^{i,j,\xi}_{2} + k^{i,j,\xi}_{23}\Big)\Big)S^{n,\xi}_{2,i,j} + \Delta t k^{i,j,\xi}_{12}V^{i,j,\xi}_c S^{n,\xi}_{1,i,j}, \tag{31}$$

$$S^{n+1,\xi}_{3,i,j} = \Big(1 - \Delta t k^{i,j,\xi}_3\Big)S^{n,\xi}_{3,i,j} + \Delta t k^{i,j,\xi}_{23}S^{n,\xi}_{2,i,j}. \tag{32}$$

Using boundary conditions, the boundary values for scheme (30)-(32) can be derived explicitly as,

$$S^{n,\xi}_{k,0,j} = S^{n,\xi}_{k,N_x+1,j} = S^{n,\xi}_{k,i,0} = S^{n,\xi}_{k,i,N_y+1} = 0 \quad for \quad k = 1, 2, 3. \tag{33}$$

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

$$S_{k,i,j}^{0,\xi} = S_{0k}(x_i, y_i, \xi). \tag{34}$$

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

$$\|M\|_{l^2(D)} = \Big(\sum_{i=0}^{N_x+1} \sum_{j=0}^{N_y+1} (M_{i,j})^2 \Delta x \Delta y \Big)^{1/2}. \tag{35}$$

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

$$S_k \in C^1\Big([0, T], C^3(\bar{D})\Big), \quad for \quad k = 1, 2, 3. \tag{36}$$

Theorem 3. *Let ξ a fixed random vector and*

$$S_k^n := \{S_{k,i,j}^{n,\xi}, i = 0, 1..., N_x + 1, j = 0, 1..., N_y + 1\} \quad for \quad k = 1, 2, 3 \quad and \quad n \geq 0 \tag{37}$$

the solution of the FD scheme (30)-(32). Suppose that the exact solutions S_1, S_2 and S_3 satisfy the regularity property (36). For any $0 \leq i \leq Nx + 1$ and $0 \leq j \leq Ny + 1$, if we assume the following inequalities to hold true

$$2\Big|1 - \Delta t\Big(k_{21}^{i,j,\xi} + k_2^{i,j,\xi} + k_{23}^{i,j,\xi}\Big)\Big|^2 + 16\Delta t^2 \Big|\frac{k_{21}^{',i,j,\xi}}{V_c^{i,j,\xi}}\Big|^2 + 4\Delta t^2 |k_{23}^{i,j,\xi}|^2 \leq 1, \tag{38}$$

$$2\Big|1 - \Delta t\Big(k_{12}^{',i,j,\xi} + D_S^{i,j,\xi}\Big(\frac{2}{\Delta x^2} + \frac{2}{\Delta x^2}\Big)\Big)\Big|^2 + 16\Big|D_S^{i,j,\xi}\frac{\Delta t}{\Delta x^2}\Big|^2 + 32\Big|D_S^{i,j,\xi}\frac{\Delta t}{\Delta y^2}\Big|^2 + 4|\Delta t k_{12}^{i,j,\xi} V_c^{i,j,\xi}|^2 \leq 1, \tag{39}$$

$$2|1 - \Delta t k_3^{i,j,\xi}|^2 \leq 1, \tag{40}$$

$$\Delta t \leq 1/16. \tag{41}$$

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

$$\max_{0 \leq n \leq N_T} \Big(\sum_{i=1}^{3} \|S_i(t^n) - S_i^n\|_{l^2(D)}^2 \Big)^{1/2} \leq C_T\Big(\Delta t + \Delta x^2 + \Delta y^2\Big). \tag{42}$$

Proof. Is similar to the proof in Saadeddine et al. (2020); Essarrout et al. (2022) just here the diffusion coefficient is given as a random field. □

4.2 Multilevel Monte Carlo Method

4.2.1 Monte Carlo finite difference method

Let $S \in L^2(\Omega; L^2(D))$ be a random field. The expectation $\mathbb{E}[S]$ is approximated by the sample average $E_M[S]$, which is defined by

$$E_M[S] := \frac{1}{M} \sum_{i=1}^{M} S_{\omega_i}$$

where $S_{\omega_i} := S(\omega_i, \cdot), i = 1, \ldots, M$ are independent identically distributed (i.i.d.) realizations of the random field S. The following lemma give statistical error of the sample average $E_M[S]$.

Lemma 2. *Let $S \in L^2(\Omega; L^2(D))$. Then, we have for any $M \in \mathbb{N}$:*

$$\|\mathbb{E}[S] - E_M[S]\|_{L^2(\Omega; L^2(D))} \leq M^{-1/2} \|S\|_{L^2(\Omega; L^2(D))}.$$

Proof. Considering that $S_{\omega_i} := S(\omega_i, \cdot), i = 1, \ldots, M$ are i.i.d. samples of the random field S, we have:

$$\begin{aligned}
&\mathbb{E}\left[\|\mathbb{E}[S] - E_M[S]\|^2_{L^2(D)}\right] \\
&= \mathbb{E}\left[\left\|\mathbb{E}[S] - \frac{1}{M}\sum_{i=1}^{M} S_{\omega_i}\right\|^2_{L^2(D)}\right] = \frac{1}{M^2}\mathbb{E}\left[\left\|\sum_{i=1}^{M}\left(\mathbb{E}[S] - S_{\omega_i}\right)\right\|^2_{L^2(D)}\right] \\
&= \frac{1}{M^2}\sum_{i=1}^{M}\mathbb{E}\left[\|\mathbb{E}[S] - S_{\omega_i}\|^2_{L^2(D)}\right] = \frac{1}{M}\mathbb{E}\left[\|\mathbb{E}[S] - S\|^2_{L^2(D)}\right] \\
&= \frac{1}{M}\left(\mathbb{E}\left[\|S\|^2_{L^2(D)}\right] - \|\mathbb{E}[S]\|^2_{L^2(D)}\right) \le \frac{1}{M}\mathbb{E}\left[\|S\|^2_{L^2(D)}\right]
\end{aligned}$$

Taking the square root of both sides of the inequality, we complete the proof. □

It is difficult in practice to take samples from the random field S, since we do not know it most of time. To overcome this difficulty, we choose samples from the FD approximation S_{k,h_L} for $k \in \{1, 2, 3\}$ with h_L and Δt_L , where $L \in \mathbb{N}$ is a given level, and Δt_L satisfy the CFL condition $\Delta t_L \le C h_L^2$. We define the the classical MC estimator:

$$E_M\left[S_{k,h_L}\right] := \frac{1}{M}\sum_{i=1}^{M} S_{k,\omega_i,h_L}$$

where $S_{k,\omega_i,h_L} := S_{k,h_L}(\omega_i, \cdot), i = 1, \ldots, M$ are i.i.d. realizations of the random field S_{k,h_L}.

Theorem 4. *Let $t \in [0, T]$ and Suppose assumptions H hold, then for $k \in \{1, 2, 3\}$ we have:*

$$\|\mathbb{E}[S_k] - E_M\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} \le C_T\left(h_L^2 + M^{-1/2}\right)$$

where the constant C_T is independent of h_L and M.

Proof. By the triangle inequality, we have:

$$\begin{aligned}
&\|\mathbb{E}[S_k] - E_M\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} \\
&\le \|\mathbb{E}[S_k] - \mathbb{E}\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} + \|\mathbb{E}\left[S_{k,h_L}\right] - E_M\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))}
\end{aligned}$$

Using the Cauchy-Schwarz inequality, we have:

$$\begin{aligned}
\|\mathbb{E}[S_k] - \mathbb{E}\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} &= \|\mathbb{E}\left[S_k - S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} \le \mathbb{E}\left[\|S_k - S_{k,h_L}\|_{L^2(D)}\right] \\
&\le \|S_k - S_{k,h_L}\|_{L^2(\Omega;L^2(D))} \le C_T^1 h_L^2
\end{aligned}$$

where the third inequality follows from Theorem 3, and the CFL condtion $\Delta t_L \le C h_L^2$. For term $\|\mathbb{E}\left[S_{k,h_L}\right] - E_M\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))'}$ applying Lemma 2, we obtain:

$$\|\mathbb{E}\left[S_{k,h_L}\right] - E_M\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} \le M^{-1/2}\|S_{k,h_L}\|_{L^2(\Omega;L^2(D))}.$$

Hence there is C_T such that:

$$\|\mathbb{E}[S_k] - E_M\left[S_{k,h_L}\right]\|_{L^2(\Omega;L^2(D))} \le C_T\left(h_L^2 + M^{-1/2}\right)$$

The proof is complete. □

Theorem 4 suggests that the total error outcome can be separated into two components: statistical error with an order of $M^{-1/2}$ and discretization error with an order of h_L^2. To achieve a fixed error level, the optimal number of samples M should be balanced with the spatial mesh size h_L, indicating:

$$M^{-1/2} = \mathcal{O}\left(h_L^2\right) = \mathcal{O}\left(N_L^{-1}\right)$$

where $N_L = 2^{2L}$. Hence, the total computational cost is:

$$Cost(L) = \mathcal{O}\left(\frac{M \cdot N_L}{\Delta t_L}\right).$$

4.2.2 Multilevel Monte Carlo finite difference method

In this subsection, we provide a detailed explanation of the corresponding multilevel approach the multilevel Monte Carlo finite difference method. This method relies on conducting Monte Carlo sampling concurrently across different resolution levels of the finite difference scheme, with varying numbers of MC samples denoted as M_l, dependent on each level.

To that end, for $t \in [0,T]$ and $k \in \{1,2,3\}$ let $(S_{k,h_l}(\cdot,t))_{l=0}^{L}$ be a sequence of finite difference approximations on grids with cell sizes $h_l = \Delta x_l = \Delta y_l$ and time steps Δt_l (subject to the CFL condition $\Delta t_l \leq C h_l^2$) . Then, the random field S_{k,h_L} for $k \in \{1,2,3\}$ can be written as

$$S_{k,h_L} = \sum_{l=1}^{L} \left(S_{k,h_l} - S_{k,h_{l-1}}\right)$$

where $S_{k,h_0} = 0, l = 0, \ldots, L$. The linearity of the expectation operator yields:

$$\mathbb{E}\left[S_{k,h_L}\right] = \sum_{l=1}^{L} \mathbb{E}\left[S_{k,h_l} - S_{k,h_{l-1}}\right]$$

We approximate $\mathbb{E}\left[S_{k,h_l} - S_{k,h_{l-1}}\right]$ by the MC estimator with M_l i.i.d. samples on sub-level l. Hence, we estimate $\mathbb{E}[S_k]$ for $k \in \{1,2,3\}$ by

$$E^L\left[S_{k,h_L}\right] := \sum_{l=1}^{L} E_{M_l}\left[S_{k,h_l} - S_{k,h_{l-1}}\right]$$

where the samples over all levels are independent of each other.

Theorem 5. *Let $t \in [0,T]$ and assumptions H hold, then for $k \in \{1,2,3\}$*

$$\left\|\mathbb{E}[S_k] - E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \leq C_T \left(\Delta t_L + h_L^2 + \sum_{l=1}^{L} M_l^{-1/2}(\Delta t_l + h_l^2)\right)$$

where the constant C_T is independent of h_l and $M, l = 1, \ldots, L$.

Proof. By the triangle inequality, we obtain:

$$\begin{aligned}
&\left\|\mathbb{E}[S_k] - E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \\
&= \left\|\mathbb{E}[S_k] - \mathbb{E}\left[S_{k,h_L}\right] + \mathbb{E}\left[S_{k,h_L}\right] - E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \\
&\leq \left\|\mathbb{E}[S_k] - \mathbb{E}\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} + \left\|\mathbb{E}\left[S_{k,h_L}\right] - E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \\
&\leq \left\|\mathbb{E}[S_k] - \mathbb{E}\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} + \left\|\sum_{l=1}^{L} \left(\mathbb{E}\left[S_{k,hl} - S_{k,h_{l-1}}\right] - E_{M_l}\left[S_{k,h_l} - S_{k,h_{l-1}}\right]\right)\right\|_{L^2(\Omega;L^2(D))} \\
&:= I + II.
\end{aligned}$$

For estimating I, similarly to the proof of Theorem 3, we have:

$$\left\|\mathbb{E}[S_i] - \mathbb{E}\left[S_{i,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \leq C_T\left(2h_L^2 + \Delta t_L\right)$$

For II, using the triangle inequality, we obtain:

$$\begin{aligned}
&\left\|\sum_{l=1}^{L}\left(\mathbb{E}\left[S_{k,h_l}-S_{k,h_{l-1}}\right]-E_{M_l}\left[S_{k,h_l}-S_{k,h_{l-1}}\right]\right)\right\|_{L^2(\Omega;L^2(D))}\\
&\le \sum_{l=1}^{L}\left\|\mathbb{E}\left[S_{k,h_l}-S_{k,h_{l-1}}\right]-E_{M_l}\left[S_{k,h_l}-S_{k,h_{l-1}}\right]\right\|_{L^2(\Omega;L^2(D))}\\
&= \sum_{l=1}^{L}\left\|(\mathbb{E}-E_{M_l})\left[S_{k,h_l}-S_{k,h_{l-1}}\right]\right\|_{L^2(\Omega;L^2(D))}\\
&\le \sum_{l=1}^{L}M_l^{-1/2}\left\|S_{k,h_l}-S_{k,h_{l-1}}\right\|_{L^2(\Omega;L^2(D))}\\
&\le \sum_{l=1}^{L}M_l^{-1/2}\Big(\|S_k-S_{k,h_l}\|_{L^2(\Omega;L^2(D))}+\left\|S_k-S_{k,h_{l-1}}\right\|_{L^2(\Omega;L^2(D))}\Big)\\
&\le C_T\sum_{l=1}^{L}M_l^{-1/2}\left(\Delta t_l+h_l^2+h_{l-1}^2\right)\\
&\le C_T\sum_{l=1}^{L}M_l^{-1/2}(\Delta t_l+h_l^2).
\end{aligned}$$

Combing the estimates of I and II, we obtain the desired result:

$$\left\|\mathbb{E}[S_k]-E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))}\le C_T\left(\Delta t_L+h_L^2+\sum_{l=1}^{L}M_l^{-1/2}(\Delta t_l+h_l^2)\right).$$

The proof is complete. □

Here, we present the error bounds of the multilevel Monte Carlo finite difference method approximation for any distribution $\{M_l\}_{l=1}^{L}$ across mesh levels. Similar to the single-level MC-FD approximation, our focus lies on determining the optimal ratio of sample size to grid size at each level. To attain the overall convergence rate, the selection of the sampling number M_l is crucial. We aim to minimize the computational workload of the MLMCFDM while ensuring convergence within a specified error tolerance $\epsilon > 0$. This optimization process is elucidated in the following theorem.

Theorem 6. *Let $t \in [0,T]$ and suppose assumptions H hold and $h_l = 2^{-l}h_0$. Then given an error tolerance $\epsilon > 0$, the optimal sample numbers M_l minimizing the computational work given the error tolerance ϵ are given by:*

$$M_l \simeq \left(\frac{2^{2/3}L^2}{(\epsilon-2^{-2L}h_0^2)^2}\right)2^{-2\frac{(6l+1)}{3}}h_0^4 \tag{43}$$

where $\simeq$ indicates that this is the number of sample, up to a constant which is independent of l and L. And the total cost for computing $E^L[S_k]$ is:

$$Cost(L) := W_{MLMC}^{\text{FDM}}(L) \le C\frac{L^3}{(\epsilon-2^{-2L}h_0^2)^2}. \tag{44}$$

In particular, for $\epsilon = 2^{-2L+1}h_0^2$ we have

$$\left\|\mathbb{E}[S_k]-E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))}\le C_T h_L^2. \tag{45}$$

and

$$Cost(L) \le CL^3h_L^{-4}. \tag{46}$$

Proof. As result of the theorem (5), for each $t \in [0,T]$ we have:

$$\left\|\mathbb{E}[S_k] - E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \le C_T\left(\Delta t_L + h_L^2 + \sum_{l=1}^{L} M_l^{-1/2}(\Delta t_l + h_l^2)\right)$$

where the constant C_T is independent of h_l and $M, l = 1, \ldots, L$. Then using the CFL condition $\Delta t_L \le C\Delta x_L^2$ we get:

$$\left\|\mathbb{E}[S_k] - E^L\left[S_{k,h_L}\right]\right\|_{L^2(\Omega;L^2(D))} \le C_T'(h_L^2 + \sum_{l=0}^{L} M_l^{-1/2} h_l^2).$$

So the approximation error scales as

$$Er_L := C_T'(h_L^2 + \sum_{l=0}^{L} M_l^{-1/2} h_l^2)$$

know it is important to give an estimate of the computational work which is needed to compute one approximation of the solution using the deterministic FDM and how it increases with respect to mesh refinement. By computational work, we understand the number of floating point operations performed when executing an algorithm and we assume that this in turn is proportional to the runtime of the algorithm. For a bounded domains $D \subset \mathbb{R}^2$ the number of grid cells scales as $1/h^2$ where $h = \Delta x = \Delta y$. For the deterministic FDM the number of floating point operations per time step and the number of cells in the spatial domain are proportional , hence the computational work can be bounded by $C\Delta t^{-1}h^{-2}$. Considering the CFL condition $(\Delta t \le Ch^2)$, we thus obtain the computational work estimate

$$W^{\mathrm{FDM}}(h) \le Ch^{-4}. \tag{47}$$

Given the Multilevel Monte Carlo finite difference method at level l, M_l deterministic finite difference approximations are computed, each necessitating effort as described in (47). Consequently, the cumulative effort of the MLFDM at level L is determined.

$$W_{MLMC}^{\mathrm{FDM}}(L) = C\sum_{l=0}^{L} M_l h_l^{-4}.$$

Know if we use a Lagrange multiplier λ, we get for

$$\begin{aligned}\mathcal{L} :&= W_{MLMC}^{\mathrm{FDM}}(L) - \lambda(\epsilon - Er_L)\\ &= \sum_{l=0}^{L} M_l 2^{4l} h_0^{-4} - \lambda\big(\epsilon - (2^{-2L}h_0^2 + \sum_{l=0}^{L} M_l^{-1/2} 2^{-2l} h_0^2)\big)\end{aligned}$$

the first order conditions

$$\frac{\partial \mathcal{L}}{\partial M_l} = 0, \quad l = 0, 1, \ldots, L$$

then

$$\begin{aligned}\frac{\partial \mathcal{L}}{\partial M_l} := 0 \quad &\iff 2^{4l}h_0^{-4} - \lambda(\frac{1}{2}M_l^{-3/2}2^{-2l}h_0^2) = 0\\ &\iff M_l = \lambda^{2/3}2^{-2\frac{(6l+1)}{3}}h_0^4.\end{aligned}$$

Using the constraint

$$Er_L = \epsilon,$$

we get

$$\epsilon = 2^{-2L}h_0^2 + \sum_{l=0}^{L} M_l^{-1/2}2^{-2l}h_0^2.$$

$$= 2^{-2L}h_0^2 + \sum_{l=0}^{L}(\lambda^{2/3}2^{-2\frac{(6l+1)}{3}}h_0^4)^{-1/2}2^{-2l}h_0^2.$$

Then

$$\epsilon - 2^{-2L}h_0^2 = \sum_{l=0}^{L}\big(\lambda^{2/3}2^{-2\frac{(6l+1)}{3}}h_0^4\big)^{-1/2}2^{-2l}h_0^2.$$

$$= \lambda^{-1/3}\big(\sum_{l=0}^{L}2^{\frac{(6l+1)}{3}}2^{-2l}\big).$$

That give

$$\lambda = \frac{2L^3}{(\epsilon - 2^{-2L}h_0^2)^3},$$

then, we obtain

$$M_l \approx \big(\frac{2L^3}{(\epsilon - 2^{-2L}h_0^2)^3}\big)^{2/3}2^{-2\frac{(6l+1)}{3}}h_0^4$$

$$M_l \approx \big(\frac{2^{2/3}L^2}{(\epsilon - 2^{-2L}h_0^2)^2}\big)2^{-2\frac{(6l+1)}{3}}h_0^4.$$

Finally, we have the following bound of overall work at level L :

$$W_{MLMC}^{\text{FDM}}(L) \leq C\sum_{l=0}^{L}M_l h_l^{-4}$$

$$\leq C\sum_{l=0}^{L}\big(\frac{2^{2/3}L^2}{(\epsilon - 2^{-2L}h_0^2)^2}\big)2^{-2\frac{(6l+1)}{3}}hh_0^4 2^{4l}h_0^{-4}$$

$$\leq C\frac{L^3}{(\epsilon - 2^{-2L}h_0^2)^2}.$$

The bounded 45 and 46 is a direct result using $\epsilon = 2^{-2L+1}h_0^2$. □

5 Numerical simulation

In this section, we numerically verify the assertion of Theorem 6, specifically the order of convergence 45 and the upper bound on the computational cost 46. The problem is then solved using two distinct sets of determined parameters, presented in Table 2. The results obtained are subsequently compared to those of our proposed method, as illustrated in Figure 5. For this purpose, we consider the following system

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

where the parameters $k'_{12}, k'_{21}, V_c, k_{12}, k_{21}, k_{23}, k_2$, k_3 and D_s 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

$$S_1(x,y,t,\xi) = xy(1-x)(1-y)\exp\big(D_s + \big(k'_{12} + k'_{21}\big)(x,y,\xi)\big)\exp\left(-2V_c(x,y,\xi)t\right)$$
$$S_2(x,y,t,\xi) = xy(1-x)(1-y)\exp\left(\left(k_{12}V_c - k_{21} - k_2\right)(x,y,\xi)\right)\exp\left(-2k_{23}(x,y,\xi)t\right)$$
$$S_3(x,y,t,\xi) = xy(1-x)(1-y)\exp\left(k_{23}(x,y,\xi) + x + y\right)\exp\left(-2k_3(x,y,\xi)t\right)$$

The parameters are modeled as random functions, varying within an interval around their experimental values given in Table 2. In other words, they fluctuate randomly within a defined range centered on the experimentally observed values, as follows:

$$\begin{aligned}
V_c(x,y,\xi) &= \left|520 \times 10^{-6} + 10^{-4} \times \sin\left(\left(\xi_1+\xi_2+\xi_3\right)x - \left(\xi_4+\xi_5+\xi_6\right)y\right)\right|, \\
k_{12}(x,y,\xi) &= \left|1.48 - 0.1 \times \sin\left(\left(\xi_1+\xi_2+Z_3\right)x - \left(\xi_4+\xi_5+\xi_6\right)y\right)\right|, \\
k'_{12}(x,y,\xi) &= k_{12}(x,y,\xi)/0.48, \\
k_{21}(x,y,\xi) &= \left|0.071 + 0.1 \times \cos\left(\left(\xi_1+\xi_2+\xi_3\right)x - \left(\xi_4+\xi_5+\xi_6\right)y\right)\right|, \\
k'_{21}(x,y,\xi) &= k_{21}(x,y,\xi)/0.48, \\
k_2(x,y,\xi) &= \left|1.55 + 0.5 \times \sin\left(\left(\xi_1+\xi_2+\xi_3\right)x + 2\left(\xi_4+\xi_5+\xi_6\right)y\right)\right|, \\
k_{23}(x,y,\xi) &= \left|11.8 + 0.1 \times \sin\left(\left(\xi_1+\xi_2+\xi_3\right)x - 2\left(\xi_4+\xi_5+\xi_6\right)y\right)\right|, \\
k_3(x,y,\xi) &= \left|0.95 + 0.2 \times \sin\left(\left(\xi_1+\xi_2+\xi_3\right)x - \left(\xi_4+\xi_5+\xi_6\right)y\right)\right|, \\
D_s(x,y,\xi) &= \left|0.003 + 10^{-2} \times \sin\left(\left(\xi_1+\xi_2+\xi_3\right)x - \left(\xi_4+\xi_5+\xi_6\right)y\right)\right|,
\end{aligned}$$

The variables $\xi_p(1 \leq p \leq 6)$ are uniform independent random variables on $[0,1]$.

Consider sequences $\{\mathcal{T}_{h_l}\}_{l=0}^{L}$, where L ranges from 1 to 5, representing rectangular meshes over the domain $D=[0,1]\times[0,1]$ and time domain $[0,1]$ (i.e $T=1$) . We set the mesh size h_0 of $\mathcal{T}_{h_0}$ to $h_0 = 2^{-2}$. Finally, for any given value of L, we derive the sequence $\{M_l\}_{l=0}^{L}$ indicating the number of samples per refinement level using 43.

In Table 1, we present the needed sequences $\{M_l\}_{l=0}^{L}$, for $L=1,\dots,4$, used in computing $E^L\left[S_{k,h_L}\right]$ for $k\in\{1,2,3\}$, where M_l is the number of samples for a refinement level with mesh size $h_l = 2^{-l}h_0$, $\Delta t_l = 0.01 \times h_l^2$ and $\epsilon = 2\times h_L$. Consistent with the choice of M_l in Theorem 6 we see that the number of samples M_l decreases with increasing ℓ for a fixed final level L.

Table 1: The sequences $\{M_l\}_{l=0}^{L}$, for $L=1,\dots,4$, used in computing $E^L\left[S_{k,h_L}\right]$ for $k\in\{1,2,3\}$, where M_l is the number of samples over a refinement level with mesh size $h_l = 2^{-(2+l)}$

L	M_0	M_1	M_2	M_3	M_4
1	160	12			
2	2089	263	71		
3	383612	23971	1498	193	
4	6501159	406324	25360	12873	1103

we shows in Figure 2 the optimal number of sample for each level according to the formula given in (43) for different values of $\epsilon = 0.01, 0.001$, and 0.0001 , the optimal number of sample in each level l in order to achieve the desired accuracy.

Figure 3 presents the plot of the CPU-time (in seconds) for the computation of $E^L\left[S_{k,h_L}\right]$ versus the number $N_l \approx h_l^{-2}$ with mesh size $h_L = 2^{-(2+L)}$ for $L=1,\dots,4$. It is clear from the figure that the computational cost is asymptotically bounded by $O\left(L^3 N_L^2\right)$ as $L\to\infty$. this confirms the theoretical cost bound in 46

In addition we report the error associated with $E^L\left[S_{k,h_L}\right]$ in Figure 4. We can see clearly that the best fitting curve for the error behaves like $O\left(h_L^2\right)$ as $L\to\infty$. This confirms the bound 45 in Theorem 6.

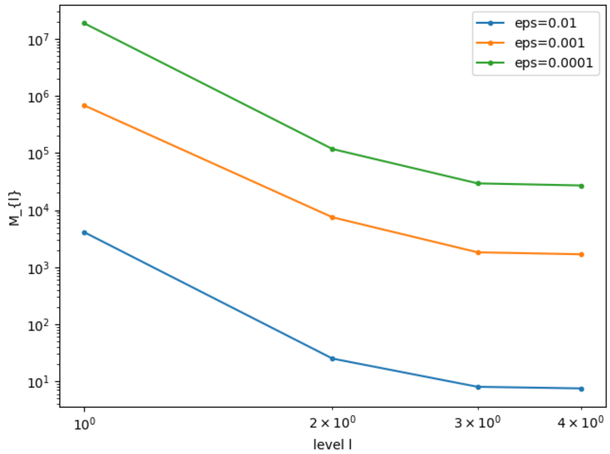


Figure 2: Optimal number of sample paths per level l, i.e.,M_l , in MLMC method for $\epsilon \in \{10^{-2}, 10^{-3}, 10^{-4}\}$ with $L = 4$

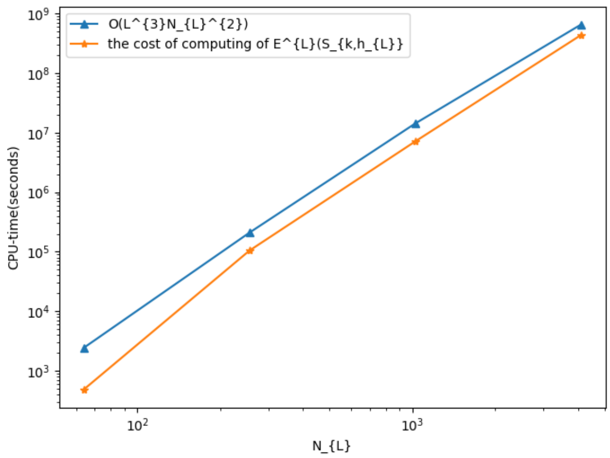


Figure 3: The computational cost upper bound for the MLMC estimator $E^L[S_{k,h_L}]$ for $k \in \{1, 2, 3\}$. We plot the cost (CPU-time in seconds) of computing $E^L[S_{k,h_L}]$ versus the number of degrees of freedom N_L when $h_L = 2^{-(L+2)}$ for $L = 1, \ldots, 4$

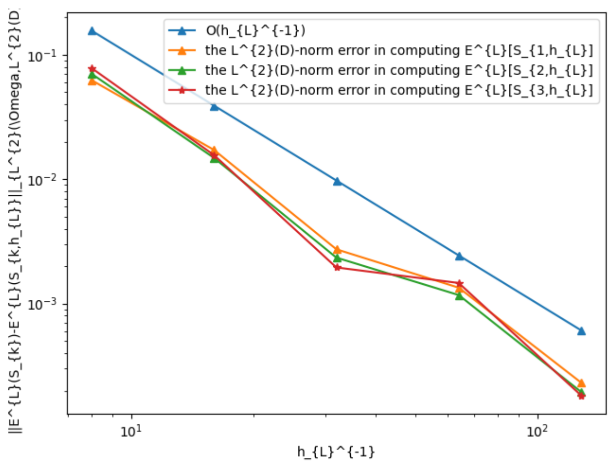


Figure 4: the error associated with $E^L[S_{k,h_L}]$ and $O(h_L^2)$ versus h_L^{-1}

To assess the performance of the proposed method, its numerical results are compared to those obtained from experimental values found in the literature. To achieve this, the problem is solved using two distinct sets of deterministic parameters, as outlined in Table 2. The initial concentration of the drug in the three compartments is represented by the following expressions: For all $(x, y) \in [0, 1]^2$ and $\xi \in \Gamma$:

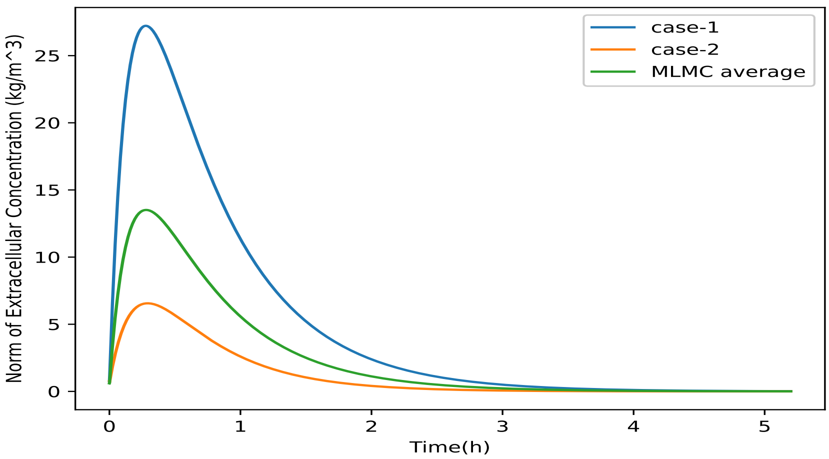
$$S_{01}(x, y, \xi) = 0.06(\sin(x^2 + y^2))^2,$$
$$S_{02}(x, y, \xi) = 0.06(\cos(x^2 + y^2))^2,$$
$$S_{03}(x, y, \xi) = 0.06(1 - \sin(x^2 + y^2))^2.$$

The results obtained are then compared to those from the proposed method, as illustrated in Figure 5.

Figure 5 illustrates the general behavior of the variation in drug concentration across the three compartments over time for two deterministic cases and the stochastic case. The adjusted parameters for the two cases shown in Table 2 are reasonably accurate, but lack precision due to variations between case 1 and case 2, as clearly shown by the blue and yellow curves. To address this issue, we use the Multilevel Monte Carlo finite difference method at level $L = 4$, which produces the result represented by the green curve.

Table 2: Valued of parameter (from Sinek et al., (2008b); Troger et al., (1992); Lavasseur et al. (1998) and associated references)

Parameter	Description	Case 1		Case 2	
		value	reference	value	reference
V_C	Cell volume (fL $cell^{-1}$)	520	Levasseur et al. (1998).	520	Levasseur et al. (1998).
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	Sinek et al. (2008b).	0.00545	Troger et al. (1992).
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	-



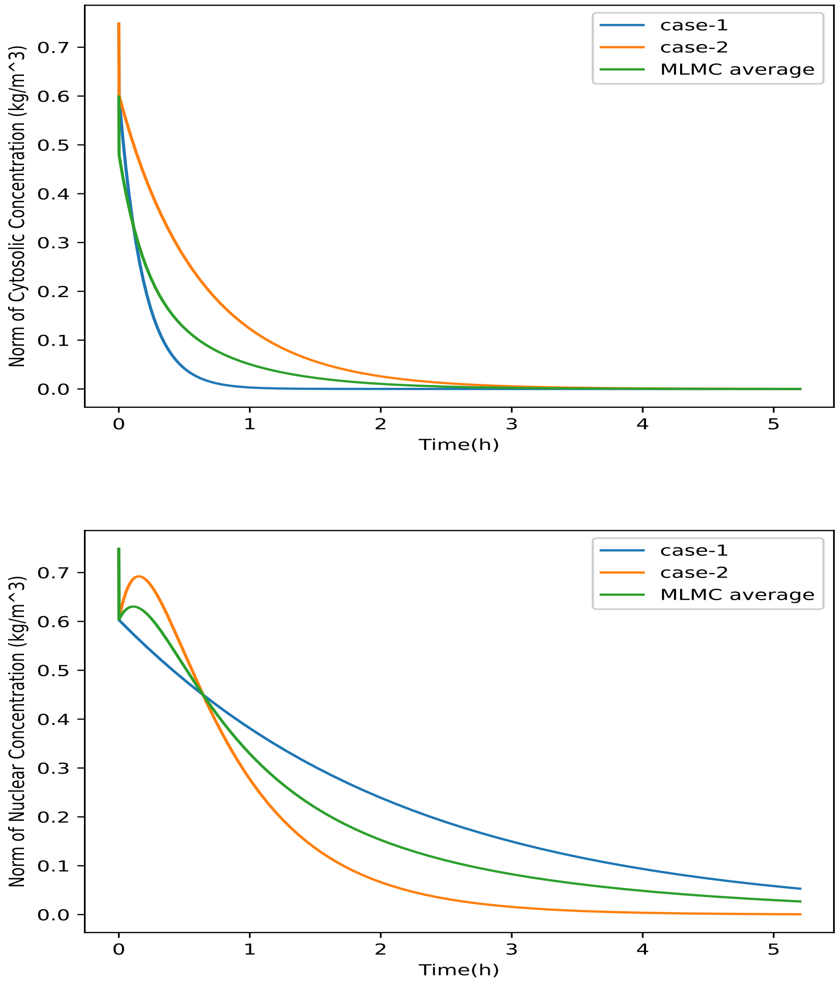


Figure 5: *Comparison of the stochastic and the determinate results.* The concentration-versus-time curve for the drug. The curves represent the concentration of the drug using the MLMC method at level $L = 4$ (green) and the parameters given in case 1 (Blue) and case 2 (Yellow) of Table 2.

6 Conclusion

In this paper, we have considered a Mathematical model of drug transport in the tumor, where the model parameters and the initial data are uncertain. we proved the existence and uniqueness of the random solution of this model in any dimension under some assumption.

Numerically to approximate the mean of the solution of our problem, we have proposed the Monte Carlo and the Multi-level Monte Carlo method coupled with finite difference method. then we proved the convergence rate estimates and established a cost bound for the Multi-level Monte Carlo estimator in 2D space . We have presented numerical experiments to verify our theoretical results concerning convergence rates and the bound cost of the multilevel Monte Carlo finite difference method. we also compared between the stochastic and determinate solving process.In the future, we aim to design an even more powerful solver by combining stochastic methods and machine learning to solve this type of problem.

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