

A stochastic framework for parameter estimation and uncertainty quantification in colon cancer-induced angiogenesis

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Abstract

In this paper, a new stochastic framework for parameter estimation and uncertainty quantification in colon cancer-induced angiogenesis, using patient data, is presented. The dynamics of colon cancer is given by a stochastic process that captures the inherent randomness in the system. The stochastic framework is based on the Fokker-Planck equation that represents the evolution of the probability density function corresponding to the stochastic process. An optimization problem is formulated that takes input individual patient data with randomness present, and is solved to obtain the unknown parameters corresponding to the individual tumor characteristics. Furthermore, sensitivity analysis of the optimal parameter set is performed to determine the parameters that need to be controlled, thus, providing information of the type of drugs that can be used for treatment.

Keywords: non-smooth PDE optimization, non-linear conjugate gradient, Weibull distribution, anti-angiogenic drugs.

MSC: 35R30, 49J20, 49K20, 62D99, 65M08, 82C31

1 Introduction

Colon cancer is one of the leading causes of worldwide cancer related deaths [13]. Detection of colon cancer usually occurs at an advanced stage in patients when the cancer becomes metastatic, due to the lack of early symptoms [34]. Thus, for devising effective treatment strategies, a proper understanding of the dynamics of relevant biomarkers are required to track the progression of colon

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cancer in an individual, and, correspondingly, determine the tumor-sensitive biological factors that needs to be controlled. In this context, angiogenesis is an important biomarker that describes the formation of blood vessels, where new vasculature develops in order to support the tumor as it increases in size. Angiogenesis has been found to be a crucial prognostic factor in colon cancer [14, 15]. In the past, there have been numerous experimental studies related to the investigation of the angiogenesis induced by colon cancer in order to develop targeted therapies [3]. For e.g., the authors in [11] study the dynamics of vascular endothelial growth factor (VEGF), which belongs to the class of tumor angiogenic factors (TAF) that promotes angiogenesis. In [12], the authors investigate the role of a humanized monoclonal antibody targeting VEGF, known as Bevacizumab, as an anti-angiogenic drug. In [35], the authors consider two different treatment strategies with low and high doses of Bevacizumab in experimental mice, and track the effects on tumor growth. In addition to Bevacizumab, effects of another anti-angiogenic drug called ziv-aflibercept was studied in [36]. Recently, the authors in [40] analyzed the role of HIF-1 α , VEGF and microvascular density in primary and metastatic tumors. For a comprehensive discussion on the angiogenesis pathway and some important biomarker discoveries for colon cancer, we refer the readers to [25].

Since anti-angiogenic drugs are quite costly, it is expensive to perform these protein-based in-vitro and in-vivo experimental studies for testing effects of such drugs. Also, it is important to consider the maximum allowable drug amount while designing treatment strategies. An alternate cost effective option is to develop computational frameworks for testing optimal drug dosages. For this purpose, it is important to understand the angiogenesis pathway mechanisms through mathematical models. In this context, dynamical modeling provides a rich computational framework to understand the process of angiogenesis and identify potential targets for treatments. Usually, dynamical models are represented by a set of differential equation systems that govern the dynamics of a biological process and are, usually, complex in nature with varying non-linearities. Several dynamical models have been developed that describe the process of angiogenesis in colon cancer. The authors in [2] describe a diffusion-based model for TAF and growth of capillaries. In [7], the authors describe the diffusion of the TAF into the surrounding host tissue and the response of the endothelial cells to the chemotactic stimulus through a system of partial differential equations (PDE). Another PDE-based model was used [8] to describe the features of a growing capillary network. In [4], a PDE system is used to describe the migration of capillary sprouts in response to a chemoattractant field set up by TAF. Furthermore, a successful or failed neovascularization of the tumor is described through the existence of traveling wave solutions of this system. The authors in [39] develop a PDE-based model for vascular regression and regrowth. Some stochastic models have also been developed to describe the process of angiogenesis. In [24], the authors develop a Markov chain model to investigate the changes of microvessel densities in tumor. A simplified stochastic geometric model was built by the authors in [5] to describe a spatially distributed angiogenic processes. For a detailed review of the other available dynamical models for angiogenesis, we refer the readers to the review papers [9, 29, 30].

The dynamical models contain numerous unknown parameters appearing as coefficients of the differential equation systems that represent the tumor characteristics of an individual patient. Since, the properties of tumor vary from patient to patient, it becomes crucial to accurately estimate these unknown parameters based on individual patient data. Traditionally, the process

of parameter estimation has not been given its due importance, and is often done using assembled data from disparate sources, such as multiple biological studies and clinical assays. This results in the lack of validation of these parameters and, thus, cannot be used for developing personalized treatment strategies.

In this paper, we present a new parameter estimation method using the framework of differential equation-based optimal control approach. The starting point of this estimation process is to consider a recent dynamical model for angiogenesis, given in [10]. The model describes the evolution of three variables: the proliferating tumor volume, the vasculature volume in tumor and the dynamics of tumor angiogenic factors (TAF). We extend the dynamical model in [10] to a new Itô stochastic process that takes into account the randomness of the tumor-induced angiogenesis dynamics. The aim is to determine the unknown coefficients of this stochastic process, representing individual-specific parameters, from given data by solving a constrained optimization problem. However, in this case, the presence of random variables in the dynamical model enforces us to choose cost functionals to be optimized as expectation functionals. To solve for the parameters, one can use the method of dynamic programming to determine the necessary Hamilton-Jacobi-Bellman (HJB) equations. The solution of such HJB equations pose a severe challenge due to the complex nature of the underlying dynamical models.

On the other hand, a more convenient framework is to formulate an optimization problem in a deterministic setup. For this purpose, we note that the state of a stochastic process can be completely determined by its probability density function (PDF). The evolution of the PDF of the stochastic dynamical model is governed by the Fokker-Planck (FP) equation. The number of variables in the dynamical model corresponds to the spatial dimension of the FP equation. Usually, the experimental data contains random noise that arises due to the inherent error present in the methods for various types of cell measurement methods such as flow cytometry and deconvolution. For e.g., identifying apoptotic cells as live cells results in a perturbed death rate measurement, which eventually changes the number of live cells. The FP framework has the potential to encompass a wide range of objective functionals that can incorporate noisy data measurements, and yet provide accurate estimates of the unknown parameters of the stochastic model, represented as optimization variables. The aim of this work is to consider a FP optimization framework for parameter estimation in colon cancer using noisy data of individual patients. Once the parameters are estimated, it is important to study how a small perturbation of these parameters may affect an output of interest, where the output is a function of these parameters. In this way, we can study the sensitivity of each of these parameters with respect to the output. For this purpose, we aim to use a Monte Carlo-based sampling technique, called latin hypercube sampling (LHS), together with partial rank correlation coefficient (PRCC) analysis to determine the most sensitive parameters.

In the next section, we describe a FP parameter estimation framework by formulating a data-driven optimization problem to recover the unknown parameters. Section 3 is concerned with the theoretical properties of the FP parameter estimation problem. In Section 4, we present a numerical scheme based on a combined splitting technique for time discretization and Chang-Cooper scheme for spatial discretization for the FP equations. We prove the properties of conservativeness, positivity, and second order convergence of the scheme. Section 5 is devoted to the theory

of the uncertainty quantification and sensitivity analysis of the estimated parameter set using the LHS-PRCC technique. In Section 6, we validate our FP parameter estimation framework using synthetically generated data and real data from [10, 35]. Furthermore, we apply the LHS-PRCC technique on both generated data and real data to identify the most sensitive parameters with respect to an output of our interest. A section of conclusion completes the exposition of our work.

2 A Fokker-Planck parameter estimation problem

To describe the role of angiogenesis in tumor growth, we use a coupled system of ordinary differential equations (ODEs). These equations are based on the model given in [10]. The following are the variables associated with different types of cell populations whose evolution we track over time.

1. $V(t)$ - the total tumor cell volume (cm^3)
2. $B(t)$ - the vasculature volume in the tumor (cm^3)
3. $T(t)$ - the concentration of tumor angiogenic factors (TAF) in the tumor (mg/ml).

The governing system of ODEs, representing the dynamics of the above defined variables are given as follows

$$\begin{aligned}\frac{dV}{d\tau} &= c\gamma V, \quad V(0) = V_0, \\ \frac{dB}{d\tau} &= c_e c\gamma V + c_v T B, \quad B(0) = B_0, \\ \frac{dT}{d\tau} &= c_T(1 - \gamma) - q_T T, \quad T(0) = T_0.\end{aligned}\tag{1}$$

The unknown patient parameters that need to be determined is the parameter vector $\boldsymbol{\theta} = (c, c_e, c_v, c_T, q_T, \gamma)$, defined as follows

1. c - growth rate of tumor (day^{-1})
2. c_e - rate of internalization of new vasculature from the environment
3. c_v - rate of formation of new blood vessels due to TAF ($\text{ml mg}^{-1} \text{ day}^{-1}$)
4. c_T - rate of production of TAF ($\text{mg ml}^{-1} \text{ day}^{-1}$)
5. q_T - rate of removal of TAF from tumor (day^{-1})
6. γ - ratio of well-supported tumor cells inside the tumor volume

The parameter γ is one of the important parameters of interest as it determines the ratio of the tumor cells inside the tumor volume that receive nutrients from outside the tumor. In [10], γ is a function of t that initially decreases when the tumor volume is close to zero but stabilizes quickly

after the volume reaches a threshold level. We consider our modeling framework with a non-zero starting tumor volume and, thus, we assume that γ is constant.

For stabilization and scalability of the numerical algorithms, we non-dimensionalize the ODE system (1) using the following non-dimensionalized state and time variables, and parameters

$$\begin{aligned}\bar{V} &= k_1 V, \quad \bar{B} = k_2 B, \quad \bar{T} = k_3 T, \quad t = k_4 \tau, \\ \bar{c} &= \frac{c}{k_4}, \quad \bar{c}_e = \frac{c_e k_2}{k_1}, \quad \bar{c}_v = \frac{c_v}{k_3 k_4}, \quad \bar{c}_T = \frac{c_T k_3}{k_4}, \quad \bar{q}_T = \frac{q_T}{k_4}.\end{aligned}\tag{2}$$

Then, the transformed non-dimensional ODE system is given as follows

$$\begin{aligned}\frac{d\bar{V}}{dt} &= \bar{c}\gamma\bar{V}, \quad \bar{V}(0) = \bar{V}_0, \\ \frac{d\bar{B}}{dt} &= \bar{c}_e\bar{c}\gamma\bar{V} + \bar{c}_v\bar{T}\bar{B}, \quad \bar{B}(0) = \bar{B}_0, \\ \frac{d\bar{T}}{dt} &= \bar{c}_T(1 - \gamma) - \bar{q}_T\bar{T}, \quad \bar{T}(0) = \bar{T}_0.\end{aligned}\tag{3}$$

The system of ODEs given in (3) can be written in a compact form as follows

$$\begin{aligned}\frac{d\mathbf{X}}{dt} &= \mathbf{F}(\mathbf{X}, \boldsymbol{\theta}), \\ \mathbf{X}(0) &= \mathbf{X}_0,\end{aligned}\tag{4}$$

where $\mathbf{X}(t) = (\bar{V}(t), \bar{B}(t), \bar{T}(t))^T$.

We extend the ODE system (1) to include stochasticity present in the dynamics. This leads to the following system of Itô stochastic differential equation corresponding to (3)

$$\begin{aligned}\frac{d\bar{V}}{dt} &= \bar{c}\gamma\bar{V} + \sigma_1 dW_1(t), \quad \bar{V}(0) = \bar{V}_0, \\ \frac{d\bar{B}}{dt} &= \bar{c}_e\bar{c}\gamma\bar{V} + \bar{c}_v\bar{T}\bar{B} + \sigma_2 dW_2(t), \quad \bar{B}(0) = \bar{B}_0, \\ \frac{d\bar{T}}{dt} &= \bar{c}_T(1 - \gamma) - \bar{q}_T\bar{T} + \sigma_3 dW_3(t), \quad \bar{T}(0) = \bar{T}_0.\end{aligned}\tag{5}$$

where dW_i , $i = 1, 2, 3$ are one-dimensional Wiener processes and σ_i , $i = 1, 2, 3$, are positive constants. Using a compact notation, we can write (5) as

$$\begin{aligned}\frac{d\mathbf{X}}{dt} &= \mathbf{F}(\mathbf{X}, \boldsymbol{\theta}) + \boldsymbol{\sigma} d\mathbf{W}(t), \\ \mathbf{X}(0) &= \mathbf{X}_0,\end{aligned}\tag{6}$$

where

$$d\mathbf{W}(t) = \begin{pmatrix} dW_1(t) \\ dW_2(t) \\ dW_3(t) \end{pmatrix}$$

is a 3-dimensional Wiener process with stochastically independent components and

$$\boldsymbol{\sigma} = \begin{pmatrix} \sigma_1 & 0 & 0 \\ 0 & \sigma_2 & 0 \\ 0 & 0 & \sigma_3 \end{pmatrix}$$

is the dispersion matrix.

We now characterize the state of the stochastic process, describing the evolution of $\mathbf{X}(t)$ through (6), by its probability density function (PDF). For this purpose, we first assume that the process (6) is constrained to stay in a bounded convex domain with Lipschitz boundaries, thus $X(t) \in \Omega \subset \mathbb{R}_+^3 = \{x \in \mathbb{R}^3 : x_i \geq 0, i = 1, 2, 3\}$, by virtue of a reflecting barrier on $\partial\Omega$. This is due to the maximum cell carrying capacity inside a human being. Let $x = (x_1, x_2, x_3)^T$. Now define $f(x, t)$ as the PDF for the stochastic process described by (6), i.e., $f(x, t)$ is the probability of $\mathbf{X}(t)$ assuming the value x at time t . Then, the evolution of the PDF of the process modeled by (6) is given through the following Fokker-Planck (FP) equations

$$\begin{aligned} \partial_t f(x, t) + \nabla \cdot (\mathbf{F}(x, \boldsymbol{\theta}) f(x, t)) &= \frac{1}{2} \nabla \cdot (\boldsymbol{\sigma}^2 \nabla f(x, t)), \\ f(x, 0) &= f_0(x), \end{aligned} \quad (7)$$

where $f_0(x)$ represents the initial PDF distribution that satisfies the following

$$f_0 \geq 0, \quad \int_{\Omega} f_0(x) dx = 1, \quad (8)$$

and $\boldsymbol{\theta} \in U_{ad} = \{y \in \mathbb{R}^6 : 0 \leq y_i \leq M_i, i = 1, \dots, 6, M_i > 0\}$. The function $f_0(x)$ represents the distribution of the initial state X_0 of the process and the domain of definition of the FP problem is $Q = \Omega \times (0, T)$, where T is the final time of observation. The reflecting barrier conditions assumed on the process correspond to flux zero boundary conditions for the FP equation (7). For this purpose, we write (7) in flux form as

$$\partial_t f(x, t) = \nabla \cdot \mathcal{F}, \quad f(x, 0) = f_0(x), \quad (9)$$

where the flux F is given component-wise by

$$\mathcal{F}_j(x, t; f) = \frac{\sigma_j^2}{2} \partial_{x_j} f - \mathbf{F}_j(x, \boldsymbol{\theta}) f, \quad j = 1, 2, 3. \quad (10)$$

Then, the flux zero boundary conditions can be formulated as follows

$$\mathcal{F} \cdot \hat{n} = 0 \quad \text{on } \partial\Omega \times (0, T), \quad (11)$$

where \hat{n} is the unit outward normal on $\partial\Omega$. We now use a FP optimization framework to estimate the patient specific unknown parameter vector $\boldsymbol{\theta}$, given the values of $f(x, t)$ at specific time instants t_1, \dots, t_N as $f_i^*(x)$, $i = 1, \dots, N$, by solving the following optimization problem

$$\boldsymbol{\theta}^* = \arg \min_{\boldsymbol{\theta} \in U_{ad}} J(f, \boldsymbol{\theta}) := \frac{\alpha}{2} \int_Q (f(x, t) - f^*(x, t))^2 dx + \frac{\beta}{2} \|\boldsymbol{\theta}\|_{l^2}^2, \quad (12)$$

subject to the FP system (7),(8),(11), where $f^*(x, t)$ is the data function formed by interpolating the patient data $f_i^*(x)$.

3 Theory of the Fokker-Planck parameter estimation problem

In this section, we discuss some theoretical results related to FP system (7) and the existence of solutions of the optimization problem (12). For this purpose, we denote the FP system (7),(8),(11) as $\mathcal{E}(f_0, \boldsymbol{\theta}) = 0$. We first discuss the existence of weak solutions of $\mathcal{E}(f_0, \boldsymbol{\theta}) = 0$. We have the following proposition.

Proposition 1. *Let $f_0 \in H^1(\Omega)$, $f_0 \geq 0$, and $\boldsymbol{\theta} \in U$. Then, there exists a unique non-negative solution of $\mathcal{E}(f_0, \boldsymbol{\theta}) = 0$ given by $f \in L^2(0, T; H^1(\Omega)) \cap C([0, T]; L^2(\Omega))$.*

We remark that using classical techniques [37], one can get the $H^2(\Omega)$ regularity in space. Next, because of (9) and (11), we can prove the following proposition that states conservation of the total probability.

Proposition 2. *The FP system given in (7),(8),(11) is conservative.*

Proof. Multiplying (7) by $\psi \in H^1(\Omega)$, integrating by parts, and using the flux zero boundary conditions (11), we obtain the following

$$\begin{aligned} \int_{\Omega} \frac{\partial f}{\partial t} \psi dx &= -\frac{1}{2} \int_{\Omega} \boldsymbol{\sigma}^2 \nabla f \cdot \nabla \psi dx + \int_{\Omega} (\mathbf{F} f) \cdot \nabla \psi dx, \\ &= -\frac{1}{2} \int_{\Omega} \boldsymbol{\sigma} \nabla f \cdot \boldsymbol{\sigma} \nabla \psi dx + \int_{\Omega} (\mathbf{F} f) \cdot \nabla \psi dx. \end{aligned} \quad (13)$$

Choosing $\psi = 1$, we obtain $\int_{\Omega} f(x, t) dx = \int_{\Omega} f_0(x) dx = 1$ for all $t \in (0, T]$ and this proves the result. \square

The following proposition gives a stability property of our FP system.

Proposition 3. *The solution f of the FP system (7),(8),(11) satisfies the following stability estimate*

$$\|f(t)\|_{L^2(\Omega)} \leq \|f_0\|_{L^2(\Omega)} \exp(\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 t), \quad (14)$$

where $N = \sup_{\Omega \times U} |F(x, \boldsymbol{\theta})|$.

Proof. Choosing $\psi = f(\cdot, t)$ in (13), we have

$$\frac{\partial}{\partial t} \|f(t)\|_{L^2(\Omega)}^2 = -\|\boldsymbol{\sigma} \nabla f(t)\|_{L^2(\Omega)}^2 + 2 \int_{\Omega} (\mathbf{F} f(t)) \cdot \boldsymbol{\sigma}^{-1} \boldsymbol{\sigma} \nabla f(t) dx. \quad (15)$$

To estimate the last term in (15), we use the Young's inequality, $2bd \leq kb^2 + d^2/k$ with $k = \|\boldsymbol{\sigma}^{-1}\|_2$, the L^2 matrix norm of $\boldsymbol{\sigma}^{-1}$, and obtain the following

$$\frac{\partial}{\partial t} \|f(t)\|_{L^2(\Omega)}^2 \leq \|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 \|f(t)\|_{L^2(\Omega)}^2.$$

Using Gronwall's inequality, we arrive at the desired result. \square

Next, we state and prove some further properties of the solution to (7) that is needed for proving the existence of an optimal parameter set $\boldsymbol{\theta}^*$. For this purpose, we have the following proposition.

Proposition 4. *Let $f_0 \in H^1(\Omega)$, $f_0 \geq 0$, and $\boldsymbol{\theta} \in U_{ad}$. Then, if f is a solution to $\mathcal{E}(f_0, \boldsymbol{\theta}) = 0$, the following inequalities hold*

$$\|f\|_{L^\infty(0,T;L^2(\Omega))} \leq c_1 \|f_0\|_{L^2(\Omega)}, \quad (16)$$

$$\|\partial_t f\|_{L^2(0,T;H^{-1}(\Omega))} \leq (c_2 + c_3 N) \|f_0\|_{L^2(\Omega)}, \quad (17)$$

where c_1, c_2, c_3 are positive constants and N is defined in Proposition 3. Further, if $\|\boldsymbol{\sigma}^{-1}\|_2^2 > \frac{1}{N}$, then the following inequality holds

$$\|f\|_{L^2(0,T;H^1(\Omega))} \leq c_4 \|f_0\|_{L^2(\Omega)}, \quad (18)$$

where c_4 is a positive constant.

Proof. The inequality (16) follows from (14), with

$$c_1 = \exp\left(\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 t\right).$$

To prove inequality (17), we define the dual of the $H^1(\Omega)$ norm, given by $H^{-1}(\Omega)$, as follows

$$\|\partial_t f\|_{H^{-1}(\Omega)} = \sup_{\substack{\psi \in H_0^1(\Omega) \\ \psi \neq 0}} \frac{\langle \partial_t f, \psi \rangle_{L^2(\Omega)}}{\|\psi\|_{H_0^1(\Omega)}}.$$

From (13), using (14) we get

$$\langle \partial_t f, \psi \rangle_{L^2(\Omega)} \leq (c_2 + c_3 N) \|f_0\|_{L^2(\Omega)} \|\psi\|_{H_0^1(\Omega)},$$

where

$$c_2 = \frac{\|\boldsymbol{\sigma}\|_2^2}{2}, \quad c_3 = c_1^2.$$

To prove (18), we first integrate (15) in $(0, T)$ to obtain

$$\|f(T)\|_{L^2(\Omega)}^2 - \|f_0\|_{L^2(\Omega)}^2 = - \int_0^T \|\boldsymbol{\sigma} \nabla f(t)\|_{L^2(\Omega)}^2 dt + 2 \int_0^T \int_\Omega (\mathbf{F} f(t)) \cdot \nabla f(t) dx dt.$$

Using the Young's inequality, we have

$$\int_0^T \|\boldsymbol{\sigma} \nabla f(t)\|_{L^2(\Omega)}^2 dt \leq \|f_0\|_{L^2(\Omega)}^2 + \int_0^T \left(N \|f(t)\|_{L^2(\Omega)}^2 + N \|\boldsymbol{\sigma}^{-1}\|_2^2 \|\boldsymbol{\sigma} \nabla f(t)\|_{L^2(\Omega)}^2 \right) dt.$$

This implies

$$(N\|\boldsymbol{\sigma}^{-1}\|_2^2 - 1) \int_0^T \|\nabla f(t)\|_{L^2(\Omega)}^2 dt \leq \|f_0\|_{L^2(\Omega)}^2 + N \int_0^T \|f(t)\|_{L^2(\Omega)}^2 dt. \quad (19)$$

Adding $(N\|\boldsymbol{\sigma}^{-1}\|_2^2 - 1) \int_0^T \|f(t)\|_{L^2(\Omega)}^2 dt$ to (19) we have the following

$$(N\|\boldsymbol{\sigma}^{-1}\|_2^2 - 1) \int_0^T \left(\|f(t)\|_{L^2(\Omega)}^2 + \|\nabla f(t)\|_{L^2(\Omega)}^2 \right) dt \leq \|f_0\|_{L^2(\Omega)}^2 + N \int_0^T \|f(t)\|_{L^2(\Omega)}^2 dt. \quad (20)$$

Using (14), we have

$$\int_0^T \|f(t)\|_{L^2(\Omega)}^2 dt \leq \|f_0\|_{L^2(\Omega)}^2 \int_0^T \exp(\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 t) dt = \frac{1}{\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2} \left[\exp(\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 T) - 1 \right] \|f_0\|_{L^2(\Omega)}^2. \quad (21)$$

Therefore, we obtain

$$\begin{aligned} & (N\|\boldsymbol{\sigma}^{-1}\|_2^2 - 1) \int_0^T \left(\|f(t)\|_{L^2(\Omega)}^2 + \|\nabla f(t)\|_{L^2(\Omega)}^2 \right) dt \\ & \leq \frac{1}{\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2} \left[\exp(\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 T) - 1 + \|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 \right] \|f_0\|_{L^2(\Omega)}^2. \end{aligned} \quad (22)$$

This proves (18) with $c_4 = \sqrt{\frac{1}{(N\|\boldsymbol{\sigma}^{-1}\|_2^2 - 1)\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2} \left[\exp(\|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 T) - 1 + \|\boldsymbol{\sigma}^{-1}\|_2^2 N^2 \right]}$. \square

From the results above, we obtain that the mapping $\Lambda : U_{ad} \rightarrow C([0, T]; H^1(\Omega))$, $\boldsymbol{\theta} \rightarrow f = \Lambda(\boldsymbol{\theta})$ is continuous. Further, using arguments given in [1], we can prove that this mapping is also Fréchet differentiable. In the next proposition, we discuss some properties of the cost functional J given in (12), which can be proved using the fact that the PDF f is non-negative.

Proposition 5. *The objective functional J given in (12) is sequentially weakly lower semicontinuous (w.l.s.c.), bounded from below, coercive on U , and it is Fréchet differentiable.*

We now state and prove the existence of the optimal parameter set $\boldsymbol{\theta}^*$ in the following theorem.

Theorem 3.1. *Let $f_0 \in H^1(\Omega)$ satisfy (8) and let J be given as in (12). Then, there exists a pair $(f^*, \boldsymbol{\theta}^*) \in C([0, T]; H^1(\Omega)) \times U_{ad}$ such that f^* is a solution to $\mathcal{E}(f_0, u^*) = 0$ and $\boldsymbol{\theta}^*$ minimizes J in U_{ad} .*

Proof. Since J is bounded below, there exists a minimizing sequence $(\boldsymbol{\theta}^m) \in U_{ad}$. Since $U_{ad} \subset \mathbb{R}^6$, and J is sequentially w.l.s.c. as well as coercive in U_{ad} , this sequence is bounded. Therefore, it contains a convergent subsequence $(\boldsymbol{\theta}^{m_i})$ in U_{ad} such that $u^{m_i} \rightarrow \boldsymbol{\theta}^*$. Correspondingly, the

sequence (f^{m_i}) , where $f^{m_i} = \Lambda(\boldsymbol{\theta}^{m_i})$, is bounded in $L^2(0, T; H^1(\Omega))$, while the sequence of the time derivatives, $(\partial_t f^{m_i})$, is bounded in $L^2(0, T; H^{-1}(\Omega))$. Therefore, both the sequences converge weakly to f^* and $\partial_t f^*$, respectively. Next, we use the compactness result of Aubin-Lions [21] to obtain strong convergence of a subsequence (f^{m_k}) in $L^2(0, T, L^2(\Omega))$. From the above discussion, we obtain weak convergence of the sequence $(\mathbf{F}(\boldsymbol{\theta}^{m_k})f^{m_k})$ in $L^2(0, T, L^2(\Omega))$. It now follows that $f^* = \Lambda(\boldsymbol{\theta}^*)$, and the pair $(f^*, \boldsymbol{\theta}^*)$ minimizes J . \square

We now introduce the reduced functional, given as follows

$$\hat{J}(\boldsymbol{\theta}) = J(\Lambda(\boldsymbol{\theta}), \boldsymbol{\theta}). \quad (23)$$

The following proposition shows the differentiability of the reduced functional \hat{J} that can be proved using similar arguments as in [38].

Proposition 6. *The reduced functional $\hat{J}(u)$ is differentiable and its derivative is given by*

$$d\hat{J}(\boldsymbol{\theta}) \cdot \boldsymbol{\psi} = \left\langle \beta \boldsymbol{\theta} - \nabla_{\boldsymbol{\theta}} \mathbf{F} \cdot \nabla p, \boldsymbol{\psi} \right\rangle_{L^2}, \quad \forall \boldsymbol{\psi} \in \mathbb{R}^6,$$

where p is the solution to the adjoint equation

$$\begin{aligned} -\partial_t p(x, t) - f(x, t)(\mathbf{F}(x, \boldsymbol{\theta}) \cdot \nabla p(x, t)) - \frac{1}{2} \nabla \cdot (\boldsymbol{\sigma}^2 \nabla p(x, t)) &= -\alpha(f(x, t) - f^*(x, t)), \\ \frac{\partial p}{\partial n} &= 0, \quad \text{on } \partial\Omega \times (0, T), \end{aligned}$$

with $p(x, T) = 0$.

The optimality conditions corresponding to the minimization problem (12) can now be written as

$$\begin{aligned} \partial_t f(x, t) + \nabla \cdot (\mathbf{F}(x, \boldsymbol{\theta}) f(x, t)) &= \frac{1}{2} \nabla \cdot (\boldsymbol{\sigma}^2 \nabla f(x, t)), \quad \text{in } \Omega \times (0, T), \\ f(x, 0) &= f_0(x), \quad \text{in } \Omega, \\ \mathcal{F} \cdot \hat{n} &= 0, \quad \text{on } \partial\Omega \times (0, T). \end{aligned} \quad (\text{FOR})$$

$$\begin{aligned} -\partial_t p(x, t) - f(x, t)(\mathbf{F}(x, \boldsymbol{\theta}) \cdot \nabla p(x, t)) - \frac{1}{2} \nabla \cdot (\boldsymbol{\sigma}^2 \nabla p(x, t)) &= -\alpha(f(x, t) - f^*(x, t)), \quad \text{in } \Omega \times (0, T), \\ p(x, T) &= 0, \quad \text{in } \Omega, \\ \frac{\partial p}{\partial n} &= 0, \quad \text{on } \partial\Omega \times (0, T). \end{aligned} \quad (\text{ADJ})$$

$$\left\langle \beta \boldsymbol{\theta} - \nabla_{\boldsymbol{\theta}} \mathbf{F} \cdot \nabla p, \boldsymbol{\psi} - \boldsymbol{\theta} \right\rangle_{L^2} \geq 0, \quad \forall \boldsymbol{\psi} \in \mathbb{R}^6. \quad (\text{OPT})$$

4 Numerical discretization schemes for solving the FP optimality system

4.1 Discretization of the forward and adjoint FP equations

In this section, we describe the numerical discretization schemes for solving the forward and adjoint FP equations given in (FOR), (ADJ). For this purpose, we consider a sequence of uniform grids $\{\Omega_h\}_{h>0}$ given by

$$\Omega_h = \{(x_1, x_2, x_3) \in \mathbb{R}^3 : (x_{1i}, x_{2j}, x_{3k}) = (x_{10} + ih, x_{20} + jh, x_{30} + kh)\},$$

where $(i, j, k) \in \{0, \dots, N_{x_1}\} \times \{0, \dots, N_{x_2}\} \times \{0, \dots, N_{x_3}\} \cap \Omega$ and N_{x_i} represents the number of grid points along the i^{th} coordinate direction. We also define $\delta t = T/N_t$ to be the time step, where N_t denotes the maximum number of time steps. With this setting, we now consider the discretized domain for Ω as follows

$$Q_{h,\delta t} = \{(x_{1i}, x_{2j}, x_{3k}, t_m) : (x_{1i}, x_{2j}, x_{3k}) \in \Omega_h, t_m = m\delta t, 0 \leq m \leq N_t\}.$$

We denote the value of $f(x, t)$ on the discrete domain $Q_{h,\delta t}$ as $f_{i,j}^m$.

For the spatial discretization, we will use the Chang-Cooper (CC) scheme [6], which is represented by the following discretization of the flux term in (FOR) at time t_m

$$\nabla \cdot \mathcal{F} = \frac{1}{h} \left[(\mathcal{F}_{i+\frac{1}{2},j,k}^m - \mathcal{F}_{i-\frac{1}{2},j,k}^m) + (\mathcal{F}_{i,j+\frac{1}{2},k}^m - \mathcal{F}_{i,j-\frac{1}{2},k}^m) + (\mathcal{F}_{i,j,k+\frac{1}{2}}^m - \mathcal{F}_{i,j,k-\frac{1}{2}}^m) \right],$$

where $\mathcal{F}_{i+\frac{1}{2},j,k}^m$, $\mathcal{F}_{i,j+\frac{1}{2},k}^m$, $\mathcal{F}_{i,j,k+\frac{1}{2}}^m$ represent the numerical flux in the i, j, k directions, respectively, at the point (x_{1i}, x_{2j}, x_{3k}) . The numerical flux $\mathcal{F}_{i+\frac{1}{2},j,k}^m$ in the i^{th} direction is given as follows

$$\mathcal{F}_{i+\frac{1}{2},j,k}^m = \left[(1 - \delta_i) B_{i+\frac{1}{2},j,k,m} + \frac{\sigma_i^2}{2h} \right] f_{i+1,j}^m - \left[\frac{\sigma_i^2}{2h} - \delta_i B_{i+\frac{1}{2},j,k,m} \right] f_{i,j}^m, \quad (24)$$

where

$$B_{i+\frac{1}{2},j,m} = -\mathbf{F}_1(x_{1i+\frac{1}{2}}, x_{2j}, x_{3k}, \boldsymbol{\theta}), \quad (25)$$

and

$$\delta_i = \frac{1}{w_{i+\frac{1}{2},j}^m} - \frac{1}{\exp(w_{i+\frac{1}{2},j,k}^m) - 1}, \quad w_{i+\frac{1}{2},j,k}^m = 2h B_{i+\frac{1}{2},j,k} / \sigma_i^2. \quad (26)$$

A similar formulae also holds true for the fluxes in the other directions.

For discretizing the time derivative, we will use the Douglas-Gunn (D-G) scheme. The D-G scheme is a three-step method that gives a consistent discretization of the FP equation at each step. At every step, the scheme is implicit in one direction only that results in a simpler system to solve. The D-G scheme is coupled with the CC scheme that results in a fully discretized scheme for solving the FP equation (FOR). We call this scheme as the DG3-CC scheme. Below, we describe the formulation of the fully discrete DG3-CC scheme. We introduce an auxiliary time

steps $t_{m^*}, t_{m^{**}}$. For notational convenience, we only use indices in the flux \mathcal{F} that represent the flux in the corresponding direction and drop the other indices. For e.g., $\mathcal{F}_{i+\frac{1}{2}}$ represents $\mathcal{F}_{i+\frac{1}{2},j,k}$, the flux in the i^{th} direction.

$$\begin{aligned}
\frac{f_{i,j,k}^{m^*} - f_{i,j,k}^m}{\delta t} &= \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^{m^*} - \mathcal{F}_{i-\frac{1}{2}}^{m^*}) \\
&\quad + \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^m - \mathcal{F}_{i-\frac{1}{2}}^m) + \frac{1}{h}(\mathcal{F}_{j+\frac{1}{2}}^m - \mathcal{F}_{j-\frac{1}{2}}^m) + \frac{1}{h}(\mathcal{F}_{k+\frac{1}{2}}^m - \mathcal{F}_{k-\frac{1}{2}}^m), \\
\frac{f_{i,j,k}^{m^{**}} - f_{i,j,k}^m}{\delta t} &= \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^{m^*} - \mathcal{F}_{i-\frac{1}{2}}^{m^*}) + \frac{1}{2h}(\mathcal{F}_{j+\frac{1}{2}}^{m^{**}} - \mathcal{F}_{j-\frac{1}{2}}^{m^{**}}) \\
&\quad + \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^m - \mathcal{F}_{i-\frac{1}{2}}^m) + \frac{1}{2h}(\mathcal{F}_{j+\frac{1}{2}}^m - \mathcal{F}_{j-\frac{1}{2}}^m) + \frac{1}{h}(\mathcal{F}_{k+\frac{1}{2}}^m - \mathcal{F}_{k-\frac{1}{2}}^m), \\
\frac{f_{i,j,k}^{m+1} - f_{i,j,k}^m}{\delta t} &= \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^{m^*} - \mathcal{F}_{i-\frac{1}{2}}^{m^*}) + \frac{1}{2h}(\mathcal{F}_{j+\frac{1}{2}}^{m^{**}} - \mathcal{F}_{j-\frac{1}{2}}^{m^{**}}) + \frac{1}{2h}(\mathcal{F}_{k+\frac{1}{2}}^{m+1} - \mathcal{F}_{k-\frac{1}{2}}^{m+1}) \\
&\quad + \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^m - \mathcal{F}_{i-\frac{1}{2}}^m) + \frac{1}{2h}(\mathcal{F}_{j+\frac{1}{2}}^m - \mathcal{F}_{j-\frac{1}{2}}^m) + \frac{1}{2h}(\mathcal{F}_{k+\frac{1}{2}}^m - \mathcal{F}_{k-\frac{1}{2}}^m),
\end{aligned} \tag{27}$$

with the initial condition $f_{i,j,k}^0 = f_0(x_{1i}, x_{2j}, x_{3k})$, for all $(i, j, k) \in \{1, \dots, N_x - 1\}$. The flux zero boundary conditions in the i^{th} direction is given as follows

$$\mathcal{F}(N_x - 1/2, j, k) = 0, \quad \mathcal{F}(1/2, j, k) = 0, \quad \forall j, k = 0, \dots, N_x. \tag{28}$$

A similar condition holds for flux zero boundary condition in the other directions. We now analyze some properties of the DG3-CC scheme (27)-(28). The following lemma shows that the DG3-CC scheme is conservative.

Lemma 4.1. *The DG3-CC scheme (27)-(28) is conservative in the discrete sense.*

Proof. Summing over all i, j in the last equation of (27), we obtain

$$\begin{aligned}
\sum_{i,j,k} \frac{f_{i,j,k}^{m+1} - f_{i,j,k}^m}{\delta t} &= \sum_{i,j,k} \left[\frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^{m^*} - \mathcal{F}_{i-\frac{1}{2}}^{m^*}) + \frac{1}{2h}(\mathcal{F}_{j+\frac{1}{2}}^{m^{**}} - \mathcal{F}_{j-\frac{1}{2}}^{m^{**}}) + \frac{1}{2h}(\mathcal{F}_{k+\frac{1}{2}}^{m+1} - \mathcal{F}_{k-\frac{1}{2}}^{m+1}) \right. \\
&\quad \left. + \frac{1}{2h}(\mathcal{F}_{i+\frac{1}{2}}^m - \mathcal{F}_{i-\frac{1}{2}}^m) + \frac{1}{2h}(\mathcal{F}_{j+\frac{1}{2}}^m - \mathcal{F}_{j-\frac{1}{2}}^m) + \frac{1}{2h}(\mathcal{F}_{k+\frac{1}{2}}^m - \mathcal{F}_{k-\frac{1}{2}}^m) \right].
\end{aligned} \tag{29}$$

The right hand side of (29) is a telescoping series and, thus, we have

$$\sum_{i,j} \frac{f_{i,j,k}^{m+1} - f_{i,j,k}^m}{\delta t} = 0. \tag{30}$$

This gives us

$$\sum_{i,j,k} f_{i,j,k}^{m+1} = \sum_{i,j,k} f_{i,j,k}^m, \quad \forall m = 0, \dots, N_t - 1, \tag{31}$$

which proves that the DG3-CC scheme is conservative in the discrete sense. \square

Next, we show the positivity of the DG-CC scheme, i.e. $f^0 \geq 0$ implies $f^m \geq 0$ for all $m > 0$. For this purpose, we assume that \mathbf{F} is Lipschitz continuous with Lipschitz constant Γ independent of t , i.e.,

$$\|\mathbf{F}(x, t) - \mathbf{F}(y, t)\| \leq \Gamma \|x - y\|, \quad \forall x, y \in \Omega, \quad t \in [0, T]. \quad (32)$$

Such a condition also ensures unique solvability of the underlying ODE system (4). Then, we can use similar arguments as in [32, Th. 4.1] to obtain the following result

Theorem 4.1. *The DG3-CC scheme is positive under the Courant-Friedrichs-Lewy (CFL)-like condition*

$$\delta t < \min \left\{ \frac{2}{\Gamma}, \frac{2h^2}{V} \right\}, \quad (33)$$

where Γ is the Lipschitz constant given in (32) and

$$V = \frac{h\underline{B}}{e^{2h\underline{B}/\overline{C}} - 1} + \frac{h\overline{B}}{1 - e^{-2h\overline{B}/\overline{C}}}, \quad \text{where } \underline{B} = \min_{x,t} \{\mathbf{F}(x, t)\}, \quad \overline{B} = \max_{x,t} \{\mathbf{F}(x, t)\}, \quad \overline{C} = \max_i \sigma_i^2 \quad (34)$$

Next, we state a discrete stability property of the DG3-CC scheme that can be proved using similar arguments as in [32, Th. 4.3].

Theorem 4.2. *The solution $f_{i,j,k}^m$ obtained using the DG3-CC scheme for the FP equation (FOR) with a source $g(x, t)$, under the CFL-like condition (33), satisfies the following L^1 stability result*

$$\|f^m\|_1 \leq \|f^0\|_1 + \delta t \sum_{n=0}^m \max(\|g^n\|_1, \|g^{n-1/2}\|_1), \quad m = 0, \dots, N_t - 1,$$

where $\|\cdot\|_1$ is the discrete L^1 norm.

We now analyze the consistency properties of the DG3-CC scheme. For this purpose, we note that the the DG3-CC scheme given in (27)-(28) can be written in one step as we obtain

$$\begin{aligned} \frac{f_{i,j,k}^{m+1} - f_{i,j,k}^m}{\delta t} &= \frac{1}{2h} [(\bar{D}_x^1 + \bar{D}_x^2 + \bar{D}_x^3)(f_{i,j,k}^m + f_{i,j,k}^{m+1})] \\ &\quad - \frac{\delta t}{4h^2} [(\bar{D}_x^1 \bar{D}_x^2 + \bar{D}_x^1 \bar{D}_x^3 + \bar{D}_x^2 \bar{D}_x^3)(f_{i,j,k}^{m+1} - f_{i,j,k}^m)] \\ &\quad + \frac{\delta t^2}{8h^3} [(\bar{D}_x^1 \bar{D}_x^2 \bar{D}_x^3)(f_{i,j,k}^{m+1} - f_{i,j,k}^m)], \end{aligned} \quad (35)$$

where

$$\begin{aligned} \bar{D}_x^1 f_{i,j,k}^m &= D_+ C_{i-\frac{1}{2},j,k}^{m*} D_- f_{i,j,k}^m + D_+ B_{i-\frac{1}{2},j,k}^{m*} M_\delta f_{i,j,k}^m, \\ \bar{D}_x^2 f_{i,j,k}^m &= D_+ C_{i,j-\frac{1}{2},k}^{m**} D_- f_{i,j,k}^m + D_+ B_{i,j-\frac{1}{2},k}^{m**} M_\delta f_{i,j,k}^m, \\ \bar{D}_x^3 f_{i,j,k}^m &= D_+ C_{i,j,k-\frac{1}{2},l}^{m***} D_- f_{i,j,k}^m + D_+ B_{i,j,k-\frac{1}{2},l}^{m***} M_\delta f_{i,j,k}^m, \end{aligned} \quad (36)$$

and for an index $r \in \{i, j, k\}$

$$\begin{aligned} D_+ f_r &= (f_{r+1} - f_r)/h, \\ D_- f_r &= (f_r - f_r)/h, \\ M_\delta f_r &= (1 - \delta_{r-1})f_r + \delta_{r-1}f_{r-1}. \end{aligned}$$

The first term on the right hand side of (35) corresponds to the Crank-Nicholson method with CC discretization for the spatial operator. Using similar arguments as in [23, Lemma 3.2 and Th. 3.6], using a Taylor series expansion, one can show that under the CFL condition (33), the truncation error corresponding to the first term on the right hand side of (35) is $\mathcal{O}(\delta t^2 + h^2)$. For the other two terms, using similar arguments as in [23, Lemma 3.2 and Th. 3.6] and [32, Lemma 4.2], one can show that the truncation error is $\mathcal{O}(\delta t^2 + \delta t^2 h^2)$. Defining the overall truncation error as

$$\begin{aligned} \varphi_{i,j,k}^{m+1} &:= \frac{f_{i,j,k}^{m+1} - f_{i,j,k}^m}{\delta t} - \frac{1}{2h} [(\bar{D}_x^1 + \bar{D}_x^2 + \bar{D}_x^3)(f_{i,j,k}^m + f_{i,j,k}^{m+1})] \\ &\quad + \frac{\delta t}{4h^2} [(\bar{D}_x^1 \bar{D}_x^2 + \bar{D}_x^1 \bar{D}_x^3 + \bar{D}_x^2 \bar{D}_x^3)(f_{i,j,k}^{m+1} - f_{i,j,k}^m)] - \frac{\delta t^2}{8h^3} [(\bar{D}_x^1 \bar{D}_x^2 \bar{D}_x^3)(f_{i,j,k}^{m+1} - f_{i,j,k}^m)], \end{aligned} \quad (37)$$

we obtain the following result for the truncation error estimate of the DG3-CC scheme

Lemma 4.2. *The truncation error (37) of the DG3-CC scheme (27)-(28) is of order $\mathcal{O}(\delta t^2 + h^2)$ under the CFL-like condition (33).*

Using Lemma 4.2, Theorem 4.2 and arguments as in [31, 32], we obtain the following convergence error estimate of the DG3-CC scheme

Theorem 4.3. *The DG3-CC scheme (27)-(28) is convergent with an error of order $\mathcal{O}(\delta t^2 + h^2)$ under the CFL condition (33) in the discrete L^1 norm.*

For the adjoint equation (ADJ), we use the D-G scheme for the time discretization in the first term, one sided finite difference discretization for the second term, and central difference for the third term on the left hand side of (ADJ).

4.2 A projected NCG optimization scheme

For solving the optimization problem (12), we use a projected non-linear conjugate gradient (NCG) scheme (see for e.g., [26, 27, 31, 32]). It falls in the class of non-linear optimization schemes where the objective functional is differentiable with respect to the optimization variables. For non-linear optimization schemes involving non-differentiable objective functionals, one can use proximal methods or semi-smooth Newton schemes (see for e.g., [16, 17, 33]). We start with an initial guess θ_0 for the unknown parameter vector and, correspondingly, calculate

$$d_0 = g_0 := \nabla_{\theta} \hat{J}(\theta_0),$$

where $\nabla \hat{J}$ is given by (OPT). The search directions are then obtained recursively as

$$d_{k+1} = -g_{k+1} + \beta_k d_k, \quad (38)$$

where $g_k = \nabla \hat{J}(u_k)$, $k = 0, 1, \dots$ and the parameter β_k is chosen according to the formula of Hager-Zhang [19] given by

$$\beta_k^{HG} = \frac{1}{d_k^T y_k} \left(y_k - 2d_k \frac{\|y_k\|_{l^2}^2}{d_k^T y_k} \right)^T g_{k+1}, \quad (39)$$

where $y_k = g_{k+1} - g_k$. The parameter vector θ is updated using a conjugate gradient descent scheme

$$u_{k+1} = u_k + \alpha_k d_k, \quad (40)$$

where k is an index of the iteration step and $\alpha_k > 0$ is a steplength obtained using a line search algorithm. For this line search, we use the following Armijo condition of sufficient decrease of \hat{J}

$$\hat{J}(\theta_k + \alpha_k d_k) \leq \hat{J}(\theta_k) + \delta \alpha_k \langle \nabla_{\theta} \hat{J}(\theta_k), d_k \rangle_{l^2}, \quad (41)$$

where $0 < \delta < 1/2$ and the scalar product $\langle u, v \rangle_{l^2} = \sum_{m=1}^6 u_m v_m$. The gradient update step is combined with a projection step onto U_{ad} in the following way

$$\theta_{k+1} = P_U [\theta_k + \alpha_k d_k], \quad (42)$$

where

$$P_U [\theta] = (\max\{0, \min\{M_1, \theta_1\}\}, \dots, \max\{0, \min\{M_6, \theta_6\}\}).$$

The projected NCG scheme can be summarized in the following algorithm:

Algorithm 4.1 (Projected NCG Scheme).

1. *Input: initial approx. θ_0 . Evaluate $d_0 = -\nabla_{\theta} \hat{J}(\theta_0)$, index $k = 0$, maximum $k = k_{max}$, tolerance $= tol$.*
2. *While $(k < k_{max})$ do*
3. *Set $\theta_{k+1} = P_U [\theta_k + \alpha_k d_k]$, where α_k is obtained using a line-search algorithm.*
4. *Compute $g_{k+1} = \nabla_{\theta} \hat{J}(\theta_{k+1})$.*
5. *Compute β_k^{HG} using (39).*
6. *Set $d_{k+1} = -g_{k+1} + \beta_k^{HG} d_k$.*
7. *If $\|\theta_{k+1} - \theta_k\|_{l^2} < tol$, terminate.*
8. *Set $k = k + 1$.*
9. *End while.*

5 Global uncertainty and sensitivity analysis of optimal parameter set

The question of accuracy of results from mathematical models of biological systems is an important one and such accuracies are often complicated due to the presence of uncertainties in experimental data that are used to estimate the parameter values [28]. Thus, it is important to understand the effects of model parameter values on the outcome measures or the outputs of interest. Uncertainty in the chosen parameter values may result in variability in the model's prediction of resulting dynamics. Furthermore, the significance of the variability introduced depends on the degree of uncertainty [20]. Thus, uncertainty analysis is important to investigate the uncertainty in the model output that is a result of the uncertainty in the input parameters. It is important to note that sensitivity analysis naturally follows uncertainty analysis since it helps in assessing how variations in model outputs can be allocated to different input sources. The goal of carrying out uncertainty and sensitivity analyses is to single out the key parameters, from the set of input parameters, whose uncertainties significantly contribute to prediction imprecision and to rank these identified key parameters by the magnitude in which they contribute to this imprecision.

Instead of carrying out a single-parameter or local sensitivity analysis, where all other parameters are kept fixed at their baseline values and that may result in inaccuracies in assessing uncertainties [18], we study here a multi-dimensional parameter space globally which facilitates simultaneous identification of all uncertainties. For this purpose, we make use of two efficient and powerful statistical tools: (i) a Monte Carlo based Latin hypercube sampling (LHS) scheme and (ii) partial rank correlation coefficient (PRCC) analysis [22]. The main idea of the LHS scheme is to start with k input model parameters (also called the uncertain parameters) corresponding to the underlying mathematical model and then use Monte Carlo simulation to generate M values for each of the k uncertain parameters. This creates a $(M \times k)$ matrix, known as the LHS matrix. Here, M is the simulation size and is chosen such that $M > (\frac{4}{3})k$. Now, all k values in each row of the LHS matrix can be used as input values to generate the output measure, which is a function of k input parameters and is unidimensional. Since there are M rows in the LHS matrix, we have M different sets of inputs that can generate M different output values. Thus, the output variable is a vector with dimension $(M \times 1)$. The main idea of the PRCC analysis is to calculate the PRCC between each uncertain parameter and the output variable and then identify the parameters with significant PRCC values. The necessary steps involved in carrying out the LHS-PRCC analysis can be summarized in the following algorithm

Algorithm 5.1 (LHS-PRCC Scheme).

- S1: Specify a PDF for each uncertain parameter in the model so that the variability in the pdf becomes a direct measure of the variability of the uncertain parameter.*
- S2: Divide each pdf into M non-overlapping and equiprobable intervals. In this way, the sampling distribution of the values for each parameter reflects the shape of the chosen pdf.*
- S3: For each uncertain parameter, randomly sample every equiprobable interval exactly once so*

that the entire range of each parameter is explored. Each parameter is sampled independently to make sure that the parameters are uncorrelated.

- S4: S3 guarantees that each of the k uncertain parameters will have M values. Using these values, create the LHS matrix whose dimension is $(M \times k)$. The values for each column of this LHS matrix are random and are not arranged in any particular order. Interestingly, this readily implies that each row of the LHS matrix consists of k random values, where each value corresponds to a specific uncertain parameter.*
- S5: Use each row (consisting of k values) of the LHS matrix to generate the output. Since there are M rows in the LHS matrix, this will generate a vector of output values whose dimension is $(M \times 1)$.*
- S6: Rank all k columns of the LHS matrix and call the resulting ranked matrix as $X_R = [X_{1R}, X_{2R}, \dots, X_{kR}]$, where each X_{iR} , $i = 1, \dots, k$, is a vector of dimension $(M \times 1)$ representing the rank transform for the i -th parameter. In a similar way, also rank the output vector of dimension $(M \times 1)$, and call the resulting ranked vector of output values as Y_R .*
- S7: For the i -th uncertain parameter ($i = 1, 2, \dots, k$), run two multiple linear regression (MLR) models. The first one is the MLR of X_{iR} on all $\{X_{jR} : j = 1, 2, \dots, k \text{ and } j \neq i\}$ and the second one is the MLR of Y_R on all $\{X_{jR} : j = 1, 2, \dots, k \text{ and } j \neq i\}$.*
- S8: Calculate the residuals from both MLR models. The PRCC value for the i -th parameter is the Pearson's correlation coefficient between these two sets of residuals. In this way, calculate the PRCC values for all k uncertain parameters.*
- S9: For each uncertain parameter, perform test of significance to assess if the corresponding PRCC value is significantly different from zero. This can be done using the student's t statistic and then calculating the corresponding p -value.*
- S10: Identify parameters with large PRCC values (> 0.5 or < -0.5) and corresponding small p -values (say, < 0.05 at 5% significance level). These are the sensitive parameters, i.e., the ones that contribute to uncertainty and hence model's prediction imprecision. A negative sign of a PRCC value would imply that the corresponding parameter is inversely proportional to the outcome measure.*
- S11: Finally, rank the sensitive parameters based on the magnitude of their PRCC values.*

6 Numerical results

In this section, we present the results of numerical simulations that validate the effectiveness of the FP framework. For this purpose, we choose our domain $\Omega = (0, 6)^3$ and discretize it using $N_{x_i} = 51$ points for $i = 1, 2, 3$. The final time t is chosen to be 4 and the maximum number of time steps N_t is chosen to be 50. The patient data is represented by the target PDFs $f_i^*(x)$, $i = 1, \dots, N$

with $N = 10, 20$, where f_i^* are described by a normal distribution about the measured mean value $\mathbb{E}[f_i^*]$ and variance 0.05. We perform a 4D interpolation to obtain the data function $f^*(x, t)$ at all discrete times t_k , $k = 1, \dots, N_t$. The values of $\sigma_1, \sigma_2, \sigma_3$ are chosen to be 0.2 to account for the measurement errors. The regularization parameters are chosen to be $\alpha = 1$, $\beta = 0.02$. For the set U_{ad} , the value of the vector $M = (M_1, \dots, M_6)$ is given as $(1.5, 0.05, 0.2, 1.5, 0.5, 1)$. The initial guess of the parameter set θ in the NCG algorithm is given by $\theta_0 = (0.1, 0.1, 0.1, 0.1, 0.1, 0.1)$.

In Test Case 1, we generate synthetic data measurements by solving the ODE (3) in the time interval $t = [0, 4]$ with $N = 10, 20$, and with the non-dimensional parameter set $\theta = (1.3400, 0.0350, 0.1200, 1.1400, 0.2473, 0.5000)$. The values of the constants used in converting the ODE system (1) to its non-dimensional form given in (3) are given as $k_1 = \frac{1}{10}$, $k_2 = 3$, $k_3 = 100$, $k_4 = \frac{1}{10}$. The data is given as $(\bar{V}_i, \bar{B}_i, \bar{T}_i) = (\bar{V}(t_i), \bar{B}(t_i), \bar{T}(t_i))$, $i = 1, \dots, N$, for specified times t_i , with $(\bar{V}(0), \bar{B}(0), \bar{T}(0)) = (1, 1, 1)$. The corresponding PDFs f_i^* are given by normal distribution functions with mean \bar{V}_i and variance 0.05.

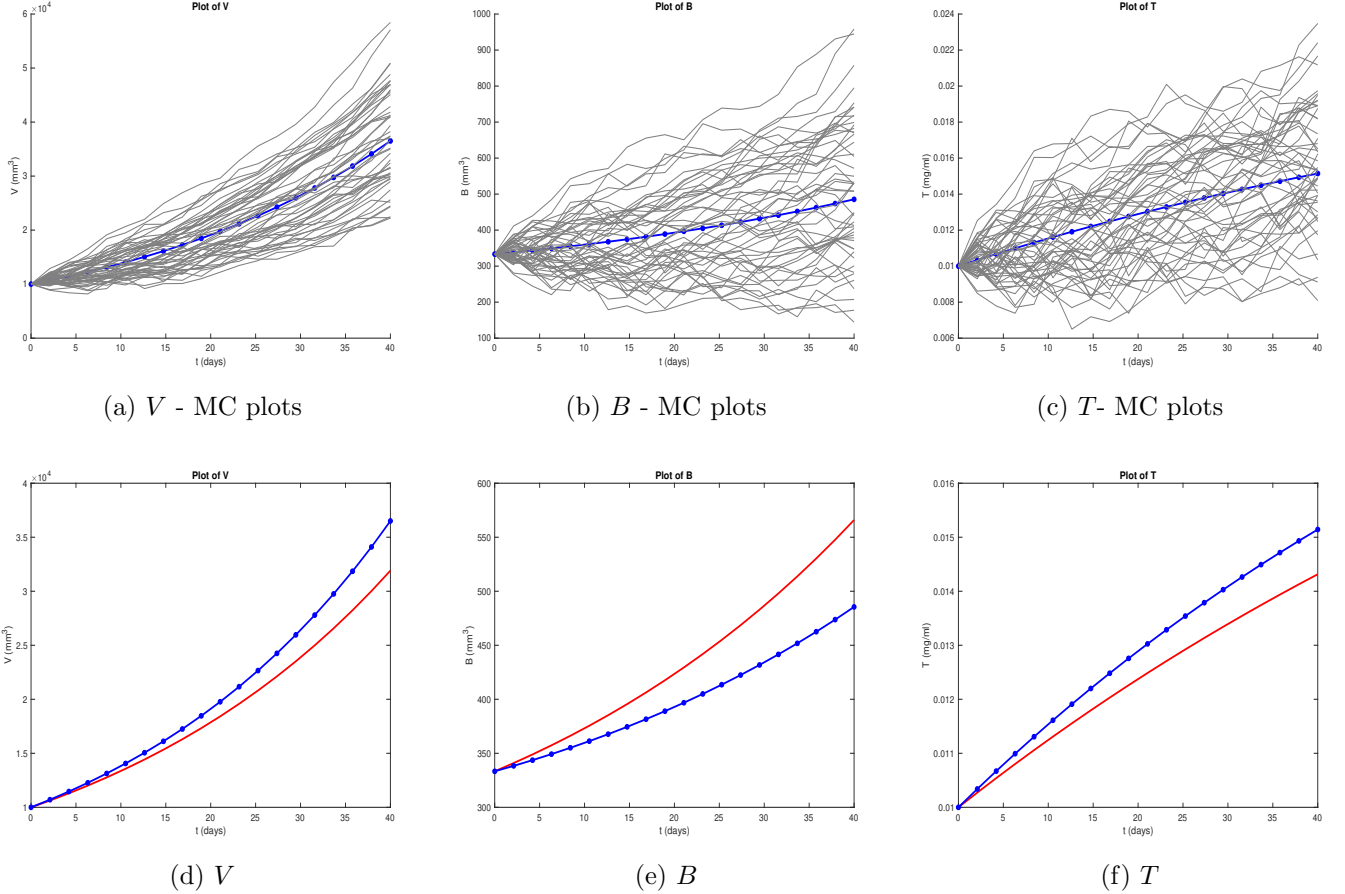
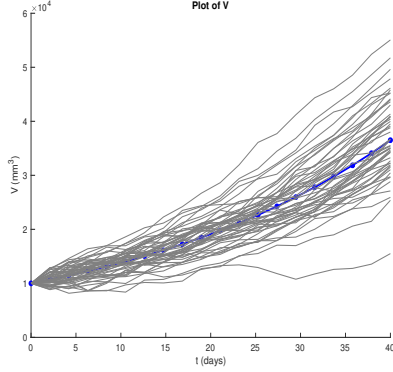
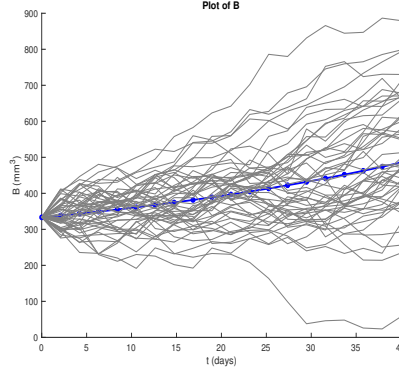


Figure 1: Test Case 1: Monte-Carlo simulation and mean trajectory plots of the profiles of V, B, T with $N = 10$.

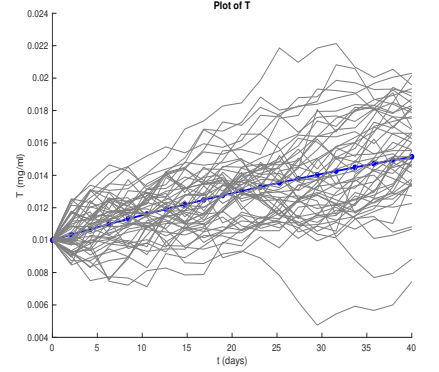
The obtained optimal parameter set θ^* for $N = 10$ is (0.9349, 0.042, 0.1478, 0.8505, 0.18, 0.6726) and with $N = 20$ is (1.0359, 0.0383, 0.1940, 1.0877, 0.2000, 0.5775). We observe that the optimal parameter estimates get closer to the true parameter values with the increase in N , which is expected due to availability of additional data. Figure 1 shows the 50 Monte-Carlo (MC) simulation plots and profiles of V, B, T with $N = 10$. The plots in the first row show the Monte-Carlo simulations for the solution of the stochastic ODE (5) with the true parameter set. The plots in the second row show the mean trajectories of V, B, T with the true and optimal parameter set. The blue curve in each of the figures show the plot of the true mean value of the corresponding random variables (V, B, T). The red curve shows the plot of the mean value of the corresponding variables obtained by solving the (5) with the optimal parameter set. The Monte-Carlo simulation shows a large variance in the data due to measurement errors. Using such a data and the FP framework, the optimal parameter set θ^* leads to the mean value of the variables being close to the true mean value. This demonstrates that even in the presence of significant variations in the measurement data, the obtained optimal parameter set is close to the true values and provides accurate mean values of the random variables (V, B, T).



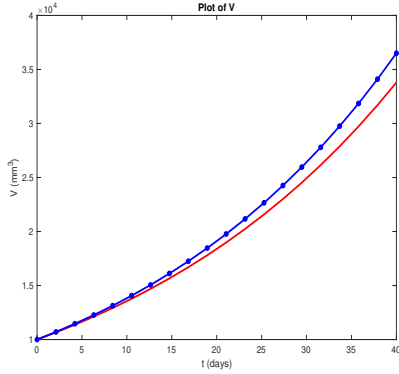
(a) V - MC plots



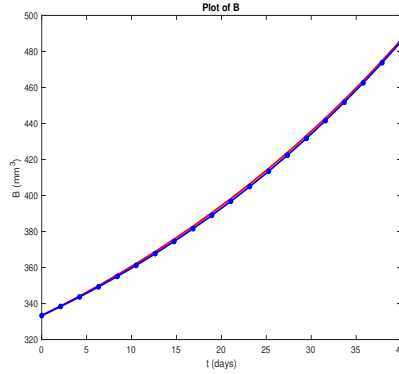
(b) B - MC plots



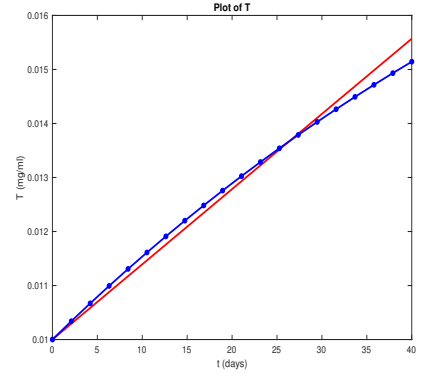
(c) T - MC plots



(d) V



(e) B



(f) T

Figure 2: Test Case 1: Monte-Carlo simulation and mean trajectory plots of the profiles of V, B, T with $N = 20$.

Furthermore, in Figure 2, we have the simulations for $N = 20$. We observe that with an increase in the number of data points, the obtained mean value of the random variables get closer to the true mean value.

Next, we run the LHS-PRCC algorithm and investigate the sensitivity of the optimal parameter set with respect to the tumor volume V at the final time $T = 4$. For this purpose, we assume each parameter to follow a Weibull distribution [26, 27] and consider the number of equiprobable intervals, M , to be 100. The p -values and the PRCC values for the cases $N = 10$ and $N = 20$ are given in Table 1.

Parameter	$N = 10$		$N = 20$	
	p -value	PRCC value	p -value	PRCC value
c	2.652e-30	0.870	1.842e-29	0.864
c_e	0.629	-0.050	0.913	0.011
c_v	0.302	0.107	0.622	-0.051
c_T	0.840	0.021	0.368	0.093
q_T	0.696	0.041	0.125	0.158
γ	1.301e-44	0.938	2.933e-48	0.949

Table 1: p -values and PRCC values for the optimal parameter set θ^*

We observe that the parameters c and γ have p -values close to 0 and high PRCC values, which make them the most sensitive variables with respect to the tumor volume V . This is expected as these two parameters directly influence the rate of increase of V . As far as the other parameters are concerned, we note that their p -values are high and PRCC values are low. Hence, these parameters are not sensitive to the output V . Between the parameters c and γ , since the PRCC value of γ is higher than that of c , we can say that the parameter γ is more sensitive to V than the parameter c .

In Test Case 2, we use real data based on experiments in [10, 35]. In [35], mice specimens were transplanted subcutaneously with C38 colon adenocarcinoma, and small animal MRI was used to measure the tumor volume \bar{V} in days 3, 5, 7, 9, 11, 15, 17, 19, 21, 23. The corresponding data for \bar{B} and \bar{T} were taken from [10]. With each of the the data points $(\bar{V}_i, \bar{B}_i, \bar{T}_i)$ as the mean of PDFs f_i^* , with variance 0.05, the mathematical data function $f^*(x, t)$ was generated using 4D interpolation. For implementing our NCG algorithm, we used the time interval $t = [0, 2.3]$. The values of the constants used in converting the ODE system (1) to its non-dimensional form given in (3) are given as $k_1 = \frac{1}{4}$, $k_2 = 50$, $k_3 = 100$, $k_4 = \frac{1}{10}$.

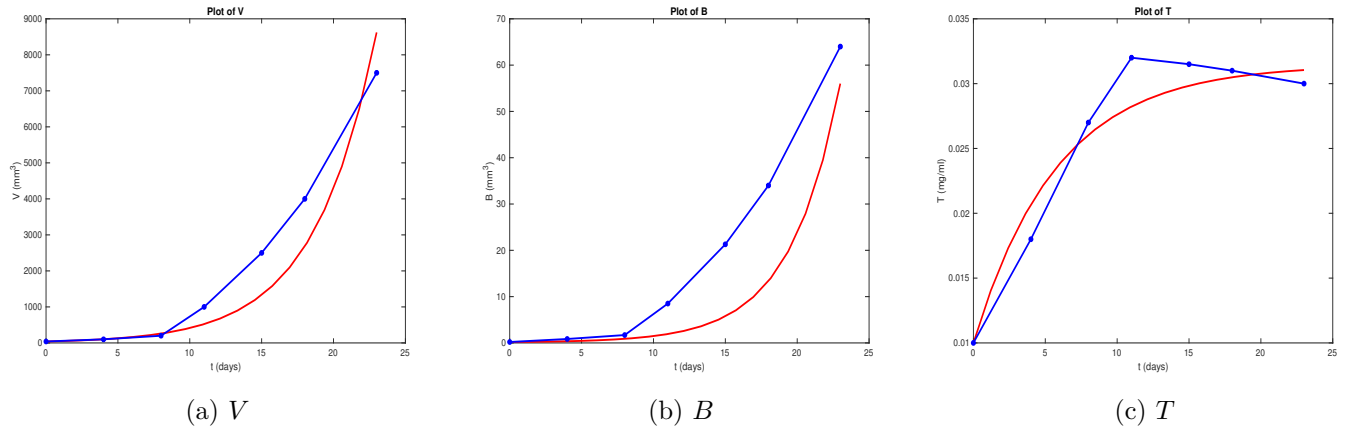


Figure 3: Test Case 2: Mean trajectory plots of the profiles of V, B, T with 10 real data set points.

The obtained value of the optimal parameter set is $\theta^* = (1.5000, 0.067, 0.2000, 1.2227, 0.3855, 0.6000)$. Figure 3 shows the plots of the mean value of the variables V, B, T using the optimal parameter set (red curve) and the true dataset points linearly interpolated (blue curve). We again observe that the obtained optimal parameter values lead to a good fit of the mean variable values to the dataset. The results of the LHS-PRCC analysis, based on Weibull density for each parameter and number of equiprobable intervals to be 100, are presented in Table 2. From the p -values, it is clear that the parameters c and γ are highly sensitive to the tumor volume V at the final time. From the PRCC values, we can conclude that the parameter γ is more sensitive to V than the parameter c .

Parameter	p -value	PRCC value
c	7.166e-33	0.886
c_e	0.557	-0.061
c_v	0.287	0.110
c_T	0.179	0.139
q_T	0.311	-0.105
γ	3.040e-66	0.979

Table 2: p -values and PRCC values for the optimal parameter set θ^* corresponding to the real data

From the test cases 1 and 2, we observe that the parameters c and γ are the most sensitive ones with respect to the tumor volume V at the final time. This indicates that we need to consider a combination of anti-angiogenic drugs that can control the colon cancer growth rate c and ratio of well-supported tumor cells γ . Choices of such combination therapies include a mix of angiogenic inhibitors Bevacizumab, Ramucirumab, Regorafenib, Ziv-aflibercept and the chemotherapy drug FOLFIRI. A challenging question is to obtain the optimal dosage for such combination therapies such that the toxicity levels and drug costs are minimized. A future work would be to formulate an optimal control problem for obtaining different optimal combination therapies in colon cancer that can help the clinicians in their decision making.

7 Conclusion

In this paper, we present a new stochastic framework for parameter estimation and uncertainty quantification in colon cancer-induced angiogenesis. We consider the angiogenic pathway dynamics proposed in [10] and extend it to a stochastic process to account for the random perturbations. We characterize the stochastic process using the PDF, whose evolution is governed by the FP equation. The coefficients in the FP equation represent the unknown patient specific parameters that we estimate using the patient data, by formulating a PDE-constrained optimization problem. The numerical discretization of the FP equations are done using a time-splitting scheme and Chang-Cooper spatial discretization method. We prove the properties of conservativeness, positivity and second order convergence of the numerical scheme. We solve the optimality system using

a projected NCG scheme. Furthermore, we study the uncertainty quantification of the optimal parameters with respect to the tumor volume using the LHS-PRCC method. Numerical results with synthetic data and real data using experimental mice demonstrates that the unknown parameters can be estimated real-time with high accuracy. Also, the rate of tumor growth and the ratio of well-supported tumor cells are the most sensitive parameters that need to be controlled using anti-angiogenic drugs. A work in the further direction would be to incorporate a combination of anti-angiogenic and chemotherapeutic drugs as parameters in the FP model and determine the optimal drug dosages.

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