A Data-driven Stochastic Framework for Treatment Assessment in Colon Cancer

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AMiTaNS'21

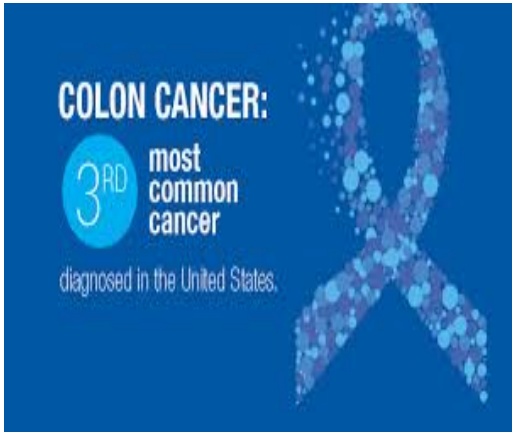
June 25, 2021

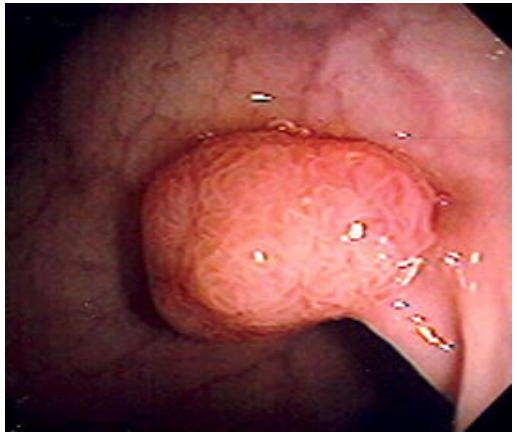
Acknowledgement

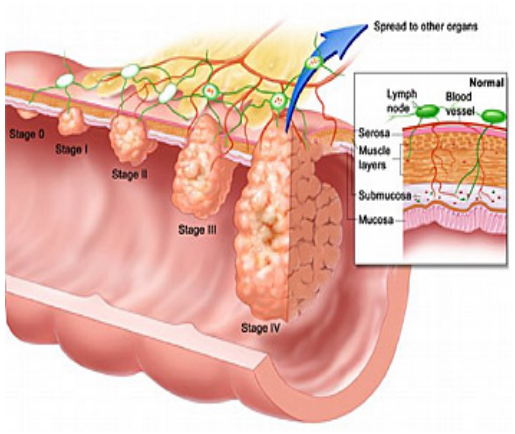
This is a joint work with Suvra Pal, Achyuth Manoj, Susanth Kakarla, Juan Villegas and Mesfer Alajmi (University of Texas at Arlington).

The work was funded by NCI-NIH (Award Number R21 CA242933).

Colon cancer







- Colon cancer is the 3^{rd} leading cause of cancer deaths in USA.
- Colon cancer begins in the large intestine (colon), which is the final part of the digestive tract.
- Though colon cancer usually affects older adults, it can happen to people of any age.
- It usually begins as small, noncancerous (benign) clumps of cells called polyps that form on the inside of the colon. Over time some of these polyps develop into colon cancers.
- Since polyps are usually small, and produce very few symptoms, colon cancer gets diagnosed at a very later stage.

Some challenges in clinical cancer research

- It is essential to understand pharmaceutical concepts, such as physiological effects, tumor shrinkage, pharmacokinetics and pharmacodynamics (PK/PD), therapeutic window, maximum tolerable dose (MTD).
- A large number of clinical studies are often required to understand such complex mechanisms of cancers and associated treatments.
- Another major clinical challenge is to obtain an effective treatment strategy for each patient or at least identify a subset of patients who could benefit from a particular treatment.
- It is very expensive to test even one therapy during clinical trials, let alone testing combination therapies that are far more effective.
- In this context, mathematical and computational methods provide a fast and effective framework for treatment assessments.

QSP parameter estimation

- One of the main computational tools used to discover, test, and predict dose exposure response is quantitative systems pharmacology (QSP) modeling.
- These models help us to understand biological processes, identify targets and biomarkers, predict treatment outcomes, and discover mechanisms of drug resistance.
- QSP models are represented by a set of differential equations that describe the dynamical properties of the cancer mechanism and interaction with drugs.
- Traditionally, parameters have been commonly estimated using the data that are often assembled from disparate sources rather than a single curated dataset.
- These may span multiple biological studies, in vitro, in vivo, and clinical assays, and may be qualitative. As a result, they cannot be easily validated or used for personalized treatments.
- Since each tumor has its own unique characteristics, they respond differently to different treatments.
- Therefore, we need parameter estimation methods that take into account each individual's tumor characteristics.

A new framework

- In this work, we contribute to the field of cancer research by a new parameter estimation framework using optimization, and sensitivity analysis approach to obtain and analyze the unknown parameters of the QSP model from the patient data.
- The results obtained from the parameter estimation and sensitivity analysis process is used to obtain information about appropriate type of drugs that can be used to control colon cancer.
- This leads to personalized treatment regimes.

A QSP model for colon cancer

- We start off with a QSP model formulated by the authors in DePillis '14.
- The QSP model describes the tumor growth and response of various immune cells in a colon cancer patient.
- The model variables are as follows
  1. $T(t)$- the total tumor cell population (cells).
  2. $N(t)$- the concentration of Natural Killer (NK) cells per liter of blood (cells/L).
  3. $L(t)$- the concentration of cytotoxic T lymphocytes ($CD8^+$) per liter of blood (cells/L).
  4. $C(t)$- the concentration of lymphocytes per liter of blood, not including NK cells and active $CD8^+$ T cells (cells/L).

The ODE system I

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

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT,\ T(0) = T_0,$$
$$\frac{dN}{dt} = eC - fN - pNT,\ N(0) = N_0,$$
$$\frac{dL}{dt} = -mL + j\frac{T}{k+T}L - qLT + (r_1N + r_2C)T - uNL^2,\ L(0) = L_0,$$
$$\frac{dC}{dt} = \alpha - \beta C,\ C(0) = C_0,$$

where $D = d\frac{(L/T)^l}{s + (L/T)^l}$.

The ODE system II

- The unknown parameters that needs to be determined are the patient specific parameter vector $\boldsymbol{\theta} = (d, l, s, p, k, q)$ defined as follows
  1. d- immune system strength coefficient.
  2. l- immune system strength scaling coefficient.
  3. s- the value of $(L/T)^l$ required for half-maximal $CD8^+$ T cell effectiveness against tumor.
  4. p- rate of NK cell death due to tumor interaction.
  5. k- tumor size for half-maximal $CD8^+$ T cell lysed tumor debris $CD8^+$ T cell activation.
  6. q- rate of $CD8^+$ T cell death due to tumor interaction.

A stochastic differential dynamical model for angiogenesis I

- We extend the non-dimensional form of the QSP model to the following Itó stochastic ODE

$$
\begin{aligned}
\frac{dT}{dt} &= T(1-bT) - cNT - DT + \sigma_1\, dW_1(t),\ T(0) = T_0,\\
\frac{dN}{dt} &= C - fN - pNT + \sigma_2\, dW_2(t),\ N(0) = N_0,\\
\frac{dL}{dt} &= j\frac{T}{k+T}L - qLT + (r_1N + r_2C)T + \sigma_3\, dW_3(t),\ L(0) = L_0,\\
\frac{dC}{dt} &= 1 - \beta C + \sigma_4\, dW_4(t),\ C(0) = C_0,
\end{aligned}
$$

  where $dW_i,\ i = 1, 2, 3, 4$ are one-dimensional Wiener processes and $\sigma_i,\ i = 1, 2, 3, 4$, are positive constants.

- Using a compact notation, we can write the above equation as

$$
\frac{d\boldsymbol{X}}{dt} = \boldsymbol{F}(\boldsymbol{X}, \boldsymbol{\theta}) + \boldsymbol{\sigma}\, d\boldsymbol{W}(t),\ \boldsymbol{X}(0) = \boldsymbol{X}_0,
$$

A stochastic differential dynamical model for angiogenesis II

- Here

$$d\boldsymbol{W}(t) = \begin{pmatrix} dW_1(t) \\ dW_2(t) \\ dW_3(t) \\ dW_4(t) \end{pmatrix}$$

is a 4-dimensional Wiener process with stochastically independent components and

$$\boldsymbol{\sigma} = \begin{pmatrix} \sigma_1 & 0 & 0 & 0 \\ 0 & \sigma_2 & 0 & 0 \\ 0 & 0 & \sigma_3 & 0 \\ 0 & 0 & 0 & \sigma_4 \end{pmatrix}$$

is the dispersion matrix.

- Aim: Given time series data for $\boldsymbol{X}$, find the unknown parameter set $\boldsymbol{\theta}$.

The Fokker-Planck equation I

- The state of a random process can be characterized by the shape of the corresponding probability density function (PDF).
- The evolution of the PDF, denoted with $f = f(x,t)$, associated to the stochastic process is modeled by the Fokker-Planck (FP) equation.

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

- Here $f(x,t)$ is the probability that $X(t) = x$, where $x \in \Omega \subset \mathbb{R}^4_+ = \{x \in \mathbb{R}^4 : x_i \geq 0,\ i = 1,2,3,4\}$.
- Notice that the FP equation can be written in flux form: $\partial_t f(x,t) = \nabla \cdot F$ where the flux F is given by

$$\mathcal{F}_j(x,t;f) = \frac{\sigma_j^2}{2}\partial_{x_j} f - \boldsymbol{F}_j(x,\boldsymbol{\theta}) f,\ j = 1,2,3,4.$$

- We chose non-reflecting boundary conditions as follows

$$F \cdot n = 0 \qquad \text{on } \partial\Omega \times (0,T).$$

- Our goal is to use the FP optimization framework to accurately and robustly obtain $\boldsymbol{\theta}$.

Results with the FP optimization framework I

The FP optimization has been successfully applied to Itō processes, subdiffusion processes, PDP processes arising in applications related to pedestrian motion, game theory, collective motion.

- M. Annunziato and A. Borzì, *A Fokker-Planck control framework for multidimensional stochastic processes*, Journal of Computational and Applied Mathematics, 237 (2013), 487–507.
- M. Annunziato and A. Borzì, *Optimal control of piecewise deterministic processes*, European Journal of Applied Mathematics, 25 (2014), 1–25.
- M. Annunziato, A. Borzì, M. Magdziarz, A. Weron, *A fractional Fokker-Planck control framework for subdiffusion processes*, Optimal Control, Applications and Methods, 2015.
- Souvik Roy, Mario Annunziato and Alfio Borzì. A Fokker–Planck feedback control-constrained approach for modelling crowd motion, *Journal of Computational and Theoretical Transport*, 45(6): 452–458, 2016.
- Souvik Roy, Alfio Borzì and Abderrahmane Habbal. Pedestrian motion constrained by FP-constrained Nash games, *Royal Society Open Science*, 4(9):170648, 2017.

Results with the FP optimization framework II

- Souvik Roy, Mario Annunziato, Alfio Borzì and Christian Klingenberg. A Fokker-Planck approach to control collective motion, *Computational Optimization and Applications*, 69(2):423–459, 2018.
- Souvik Roy. A sparsity-based Fokker-Planck optimal control framework for modeling traffic flows, *AIP Conference Proceedings*, 2302:110007, 2020.

To the best of our knowledge, this is the first work on FP optimization frameworks in colon cancer-induced immune response.

We formulate a FP optimization framework that takes into account inconsistencies and inaccuracies in data measurement, yet can provide an accurate estimate of the unknown parameter set $\boldsymbol{\theta}$.

We then carry out a sensitivity analysis of the optimal parameter set to determine the parameters that need to be controlled, thus, providing information of the type of drugs that can be used for treatment.

A FP optimization problem for parameter estimation

- We will estimate the patient specific unknown parameter vector $\boldsymbol{\theta}$, given the values of $f(x,t)$ at specific time instants $t_1, \cdots, t_N$ as $f_i^*(x),\ i = 1, \cdots, N$, i.e, the data is given as PDFs that helps account for inconsistencies and inaccuracies in data measurements.
- We solve the following constrained optimization problem

$$\boldsymbol{\theta}^* = \underset{\boldsymbol{\theta} \in U_{ad}}{\operatorname{argmin}}\, J(f, \boldsymbol{\theta}) := \frac{\alpha}{2} \int_Q \left(f(x,t) - f^*(x,t)\right)^2 \, dx + \frac{\beta}{2} \|\boldsymbol{\theta}\|_{l^2}^2,$$

  subject to the FP system, where U_{ad} is an admissible set for the range of values of $\boldsymbol{\theta}$.
- The function $f^*(x,t)$ is the data function formed by interpolating the patient data $f_i^*(x)$ for all times t.
- The first term in J is a least-squares data fitting term whereas the second term is a l^2 regularization term that is based on the fact that the biological parameter values are bounded.
- We denote the FP equation above as $\mathcal{E}(f_0, \boldsymbol{\theta}) = 0$

Theory of the FP optimization problem I

Proposition (Solution of FP equation)

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

Proposition (Conservation of total probability)

The FP system is conservative.

Proposition ($L^2(\Omega)$ stability)

The solution f of the FP system satisfies the following stability estimate

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

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

Theory of the FP optimization problem II

Proposition (Other stability results)

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

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

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

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

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

where c_4 is a positive constant.

Theorem (Existence of an optimal parameter set)

Let $f_0 \in H^1(\Omega)$. 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}.

First-order necessary optimality condition

The optimality conditions can now be written as

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

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

$$\left\langle \beta\boldsymbol{\theta} - \int_\Omega \nabla_{\boldsymbol{\theta}} \boldsymbol{F} \cdot \nabla p, \boldsymbol{\psi} - \boldsymbol{\theta} \right\rangle_{l^2} \geq 0, \qquad \forall \boldsymbol{\psi} \in \mathbb{R}^6. \tag{OPT}$$

Discretization of the FP equation and of its adjoint I

- We implement and analyze a time splitting Douglas-Gunn (DG4) scheme combined with the positive and conservative second-order Chang-Cooper (CC) space-discretization scheme.
- At each step, the DG4-CC scheme is implicit in 1 direction and explicit in the other 3 directions.
- The discrete scheme for the adjoint FP equation is obtained using a combination DG4 scheme for the time discretization, one sided finite difference discretization for the advection term, and central difference for the diffusion term.

Numerical analysis of the DG4-CC scheme I

We assume that $\boldsymbol{F}$ is Lipschitz continuous with Lipshitz constant Γ.

Theorem (Positivity)

The DG4-CC scheme is positive under the Courant-Friedrichs-Lewy (CFL)-like condition

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

where

$$V = \frac{h\underline{B}}{e^{2h\underline{B}/\overline{C}} - 1} + \frac{h\overline{B}}{1 - e^{-2h\overline{B}/\overline{C}}},$$

$$\underline{B} = \min_{x,t}\{\boldsymbol{F}(x,t)\},\ \overline{B} = \max_{x,t}\{\boldsymbol{F}(x,t)\},\ \overline{C} = \max_{i}\sigma_i^2$$

Numerical analysis of the DG4-CC scheme II

Define the discrete L^1 norm as

$$\|f\|_1 = h^4 \sum_{i,j,k,l=0}^{N_x} |f_{i,j,k,l}|,$$

Lemma (Conservativeness)

The DG4-CC scheme is conservative, i.e., $\|f^m\|_1 = \|f^0\|_1$.

Theorem (Stability)

The solution $f^m_{i,j,k,l}$ *obtained using the DG4-CC scheme for the FP equation with a source* $g(x,t)$*, under the CFL-like condition given above, satisfies the following* L^1 *stability result*

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

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

Numerical analysis of the DG4-CC scheme III

Lemma (Truncation error)

The truncation error of the DG4-CC scheme is of order $\mathcal{O}(\delta t^2 + h^2)$ under the aforementioned CFL-like condition.

Theorem (Convergence)

The DG4-CC scheme is convergent with an error of order $\mathcal{O}(\delta t^2 + h^2)$ under the aforementioned CFL condition in the discrete L^1 norm.

A projected NCG scheme

Algorithm (Projected NCG Scheme)

1. *Input: initial approx.* $\boldsymbol{\theta}_0$. *Evaluate* $d_0 = -\nabla_{\boldsymbol{\theta}} \hat{J}(\boldsymbol{\theta}_0)$, *index* $k = 0$, *maximum* $k = k_{max}$, *tolerance =* tol.
2. *While* $(k < k_{max})$ *do*
3. *Set* $\boldsymbol{\theta}_{k+1} = P_U\left[\boldsymbol{\theta}_k + \alpha_k\, d_k\right]$, *where* α_k *is obtained using a line-search algorithm.*
4. *Compute* $g_{k+1} = \nabla_{\boldsymbol{\theta}} \hat{J}(\boldsymbol{\theta}_{k+1})$.
5. *Compute* β_k^{HG} *using Hager-Zhang formula.*
6. *Set* $d_{k+1} = -g_{k+1} + \beta_k^{HG} d_k$.
7. *If* $\|\boldsymbol{\theta}_{k+1} - \boldsymbol{\theta}_k\|_{l^2} < tol$, *terminate.*
8. *Set* $k = k + 1$.
9. *End while.*

Sensitivity analysis using LHS-PRCC

- We next perform a sensitivity analysis of the optimal parameter set with respect to the tumor cell count.
- For this purpose, we use a Latin hypercube sampling - Partial rank correlation coefficient (LHS-PRCC) method.
- The LHS samples are drawn from PDF's corresponding to the Weibull distribution for each uncertain parameter in the model.
- Then the PRCC values along with the p-values (using the student's t test statistic) are computed.
- We then identify parameters with large PRCC values $(> 0.5$ or $< -0.5)$ and corresponding small p-values (say, < 0.05 at 5% significance level).
- Finally, rank the sensitive parameters based on the magnitude of their PRCC values.

Numerical setup

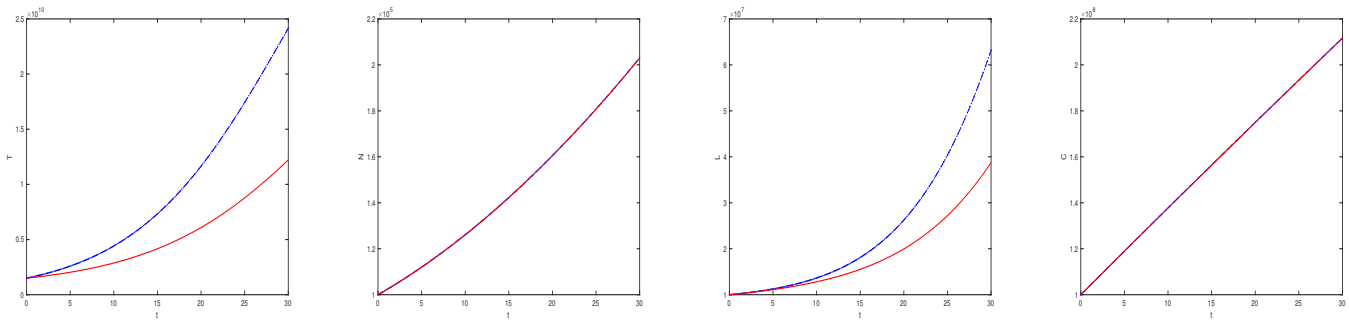
- We choose our domain $\Omega = (0, 6)^4$ and discretize it using $N_{x_i} = 51$ points for $i = 1, 2, 3, 4$.
- The final time t is chosen to be 30 and the maximum number of time steps N_t is chosen to be 100.
- The patient data is represented by the target PDFs $f_i^*(x),\ i = 1, \cdots, N$ with $N = 10$, 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 5D interpolation to obtain the data function $f^*(x, t)$ at all discrete times $t_k,\ k = 1, \cdots, N_t$.
- The values of $\sigma_1, \sigma_2, \sigma_3, \sigma_4$ are chosen to be 0.2 to account for the measurement errors.
- The regularization parameters are chosen to be $\alpha = 1,\ \beta = 0.02$.

Datasets

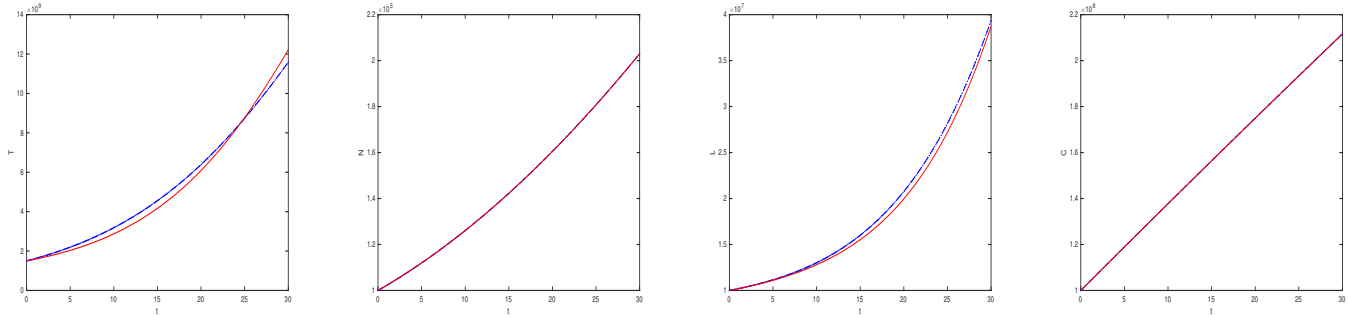
We use 2 synthetic data measurements by solving the original ODE in the time interval $t = [0, 30]$

- Moderately strong immune system patient: The non-dimensional parameter set $\boldsymbol{\theta} = (1.1, 1.6, 1.0, 1.0, 0.1, 1.0)$.
- Strong immune system patient: The non-dimensional parameter set $\boldsymbol{\theta} = (1.3, 1.3, 0.5, 1.0, 0.1, 1.0)$.

Test Case: Moderately strong immune system



(a) T (b) N (c) L (d) C



(e) T (f) N (g) L (h) C

Figure: Test Case 1: Parameter estimation ODE vs FP.

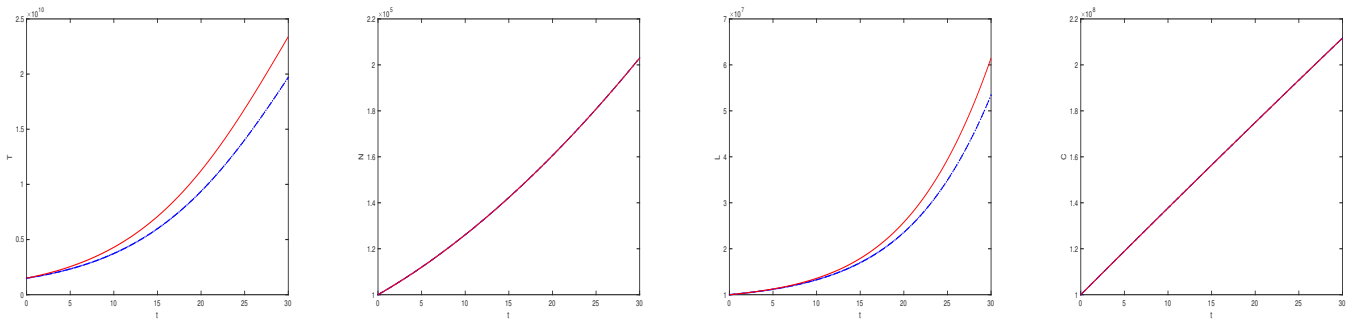
Sensitivity analysis

The obtained optimal parameter set $\boldsymbol{\theta}^*$ with the ODE setup is $(2, 1.5, 0.7, 1.8, 0.4, 1.6)$ and with the FP setup is $(1.0, 1.56, 1.12, 0.6, 0.2, 1.5)$

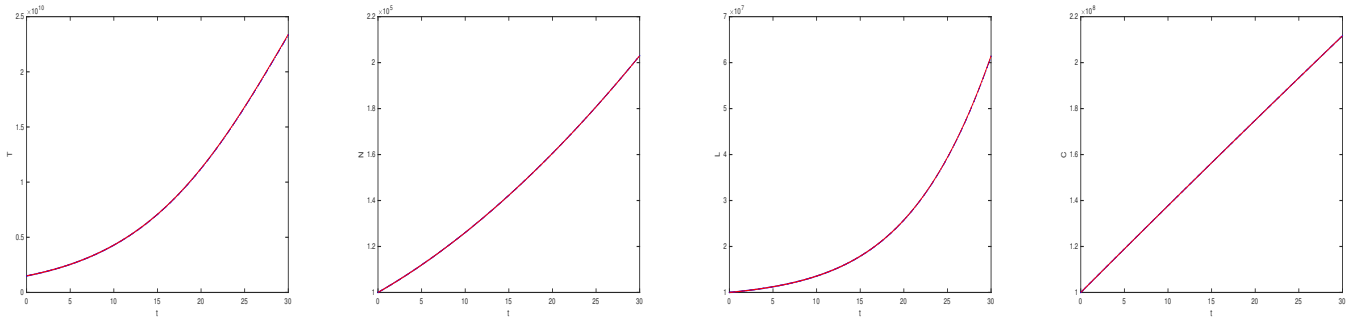
Parameter	$p-$value	PRCC value
d	6.3e-8	-0.77
l	1.0e-27	0.99
s	7.0e-6	0.72
p	0.058	-0.07
k	0.70	-0.34
q	0.07	0.18

Table: $p-$values and PRCC values for the optimal parameter set $\boldsymbol{\theta}^*$

Test Case: Strong immune system



(a) T (b) N (c) L (d) C



(e) T (f) N (g) L (h) C

Figure: Test Case 2: Parameter estimation ODE vs FP.

Sensitivity analysis

The obtained optimal parameter set $\boldsymbol{\theta}^*$ with the ODE setup is $(2.1, 2.0, 1.0, 1.5, 0.5, 1.5)$ and with the FP setup is $(1.1, 1.0, 0.7, 0.8, 0.2, 0.9)$

Parameter	$p-$value	PRCC value
d	5.4e-5	-0.85
l	7.0e-6	0.89
s	0.0054	0.6791
p	0.55	-0.1697
k	0.89	0.04
q	0.56	0.17

Table: $p-$values and PRCC values for the optimal parameter set $\boldsymbol{\theta}^*$

Treatment assessment

- We observe that for a patient with moderately strong immune system, the parameters d, l, s are the most sensitive ones with respect to the tumor cell count T at the final time.
- For a patient with a strong immune system, the parameters d, l are the most sensitive ones with respect to the tumor cell count T at the final time.
- This indicates that for a patient with moderately strong immune system, an optimal combination therapy of chemotherapy drug like FOLFIRI and monoclonal antibodies (mAb) like Cetuximab and Panitumumab would be ideal.
- For a patient with a strong immune system response, FOLFIRI is enough to control the cancer.

Conclusions

- We have presented a new stochastic framework for parameter estimation and uncertainty quantification in colon cancer-induced immune response.
- 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.
- We presented robust discretization schemes to solve for the parameter estimation problem.
- Numerical results with synthetic data demonstrates that the unknown parameters can be estimated real-time with high accuracy.
- An ongoing work is to determine optimal drug dosages based on the immune system response of the patients.

THANK YOU FOR YOUR ATTENTION