Optimizing Angiogenic Inhibition for Precise Tumor Growth Control: A Nonlinear Control Approach

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BTP Report

by

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CERTIFICATE

This is to certify that the project entitled **"Optimizing Angiogenic Inhibition for Precise Tumor Growth Control: A Nonlinear Control Approach"** is an authentic bona fide record of the work carried out by **Gopal Gupta** under my supervision and guidance in fulfillment of the requirements for the degree of Dual in Chemical Engineering at the Indian Institute of Technology Kharagpur.

Date: /11/2023

Place: Kharagpur

Professor Amiya Kumar Jana

Department of Chemical Engineering

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Declaration

I hereby affirm that:

1. The content presented in this thesis is entirely original and has been conducted by me under the supervision of my mentor.
2. This work has not been presented to any other educational institution for the purpose of obtaining any degree or diploma.
3. I have diligently adhered to the guidelines stipulated by the institution in the preparation of this thesis.
4. I have strictly adhered to the ethical code of conduct outlined by the institution, ensuring compliance with established norms and guidelines.
5. In instances where I have incorporated materials such as data, theoretical analyses, figures, and text from external sources, proper acknowledgment has been given. I have appropriately cited these sources within the thesis text and provided detailed references.

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Abstract

This project navigates the complexities of cancer treatment, specifically focusing on anti-angiogenic chemotherapy, a promising avenue to mitigate the drawbacks associated with traditional cytotoxic methods. We delve into the literature, exploring pivotal studies in model-based approaches to angiogenic inhibition, dynamical theories of tumor growth, and endogenous inhibitors like Endostatin. The core of our work involves the model depicting the dynamic progression of tumor growth under angiogenic inhibition proposed by Hahnfeldt et al. (1999). We optimize model parameters through various methods, scrutinizing their efficacy in controlling tumor growth. Notably, our investigation extends to the optimization of drug delivery rates using a Nonlinear Model Predictive Controller (MPC). While we encounter challenges in Simulink integration, the study offers insights into future enhancements for both simulation and control methodologies.

Lexicons

In this segment, concise explanations are provided for key terms commonly used in medical terminology.

1. **Endothelial Cells:** Cells composing a delicate layer along the interior of blood vessels.
2. **Interstitium:** The region between cells within a tissue.
3. **Angiogenesis:** The process of generating new blood vessels, often referenced in the context of vessels supplying tumor cells.
4. **Angiogenic Inhibition:** The hindrance of new blood vessel formation, leading to a therapeutic approach known as anti-angiogenic therapy.
5. **Vascular System:** The network of channels facilitating the flow of nutrient fluids within the body, typically referring to vessels conveying blood.
6. **Inhibitor:** A substance impeding a chemical reaction, growth, or other biological activities. Angiogenic inhibitors are frequently naturally occurring proteins.
7. **Endostatin:** A naturally existing antiangiogenic protein that hampers the development of blood vessels nourishing tumors.
8. **Boli:** The plural form of 'bolus.' In medical contexts, a bolus denotes a single, substantial dose of a drug administered to a patient for immediate release, often via intravenous delivery for swift efficacy.

Acknowledgement

I would like to express my sincere gratitude to **Professor Amiya Kumar Jana** for their invaluable guidance and unwavering support throughout my bachelor's Thesis Project (BTP). Their expertise, encouragement, and insightful feedback have played a pivotal role in shaping the trajectory of my research. I am truly thankful for the opportunity to learn under his guidance, and his commitment to fostering academic growth has been instrumental in the successful completion of this project.

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I. Introduction

Cancer is a deadly disease that has become increasingly prevalent in recent times. This project examines a tumor treatment known as anti-angiogenic chemotherapy that has emerged in the past decades. Conventional cytotoxic chemotherapy is designed to directly target tumor cells; however, it may inadvertently affect healthy cells, resulting in diverse side effects. Additionally, the development of resistance in tumor cells to chemotherapy drugs often requires the exploration and deployment of novel therapeutic agents. In contrast, anti-angiogenic therapy presents fewer side effects and prevents the development of resistance in tumor cells to angiogenic drugs. This is attributed to its focus on endothelial cells rather than tumor cells. When tumors grow beyond a specific size, they require a vascular system for supplies because they can no longer obtain enough nutrients from the interstitium. Tumor cells stimulate angiogenesis to achieve this. Anti-angiogenic therapy inhibits angiogenesis, causing the tumor to die. Kerbel (1997) and Kerbel and Folkman (2002) offer a comprehensive analysis of the clinical dimensions of angiogenic inhibition. Hahnfeldt et al. (1999) formulated a model for tumor growth under angiogenic inhibition, validating it through experiments on mice afflicted with lung cancer. Ledzewicz and Schatler (2005) designed optimal bang-bang control for a simplified model. Ergun et al. (2003) explored the integration of anti-angiogenic therapy with radiotherapy.

Based on our understanding, Endostatin stands out as the most potent drug in anti-angiogenic therapy (O'Reilly et al., 1997). However, the drawback of this therapy lies in the elevated cost of the drug, necessitating its careful and efficient use. The objective of this project is to develop a nonlinear controller for optimizing the delivery rate of the drug, aiming to enhance the effectiveness of cancer treatment.

2. Literature review

Cancer, marked by the unregulated growth and proliferation of cells, has been a prominent subject of research owing to its pervasive occurrence and profound repercussions on human health. A noteworthy approach in cancer treatment involves targeting angiogenesis, the process of forming new blood vessels that becomes vital for tumor expansion beyond a specific size threshold. This literature review delves into pivotal studies that enrich our comprehension and management of tumor growth under the influence of angiogenic inhibition.

I. Model-Based Approaches to Angiogenic Inhibition

A pivotal study by Kovács et al. (2014) introduces a model-based approach to angiogenic inhibition, leveraging modern robust control methods. The researchers propose a comprehensive model that considers the dynamic interactions between tumor growth, angiogenesis, and therapeutic interventions.

The utilization of robust control methods enhances the model's predictive accuracy, providing a foundation for optimizing anti-angiogenic treatments (Kovács et al., 2014).

II. Dynamical Theory of Tumor Growth

Hahnfeldt et al. (1999) contribute a dynamical theory of tumor growth under angiogenic signaling. Their work delves into the intricate dynamics of tumor development, treatment response, and postvascular dormancy. The study provides valuable insights into the temporal aspects of tumor progression and the effects of angiogenic inhibition on the tumor microenvironment (Hahnfeldt et al., 1999).

III. Case Study on Tumor Growth Analysis and Synthesis

Drexler et al. (2011) offer a case study focusing on the analysis and synthesis of tumor growth under angiogenic inhibition. Through their model-based methodology, they conduct a thorough investigation of the tumor system, adding depth to our comprehension of the inherent dynamics and exploring potential strategies for control (Drexler et al., 2011).

IV. Endostatin: An Endogenous Inhibitor

O'Reilly et al. (1997) identify endostatin as an endogenous inhibitor of angiogenesis and tumor growth. This seminal work sheds light on a natural mechanism to inhibit angiogenesis, offering a potential avenue for therapeutic intervention. The study emphasizes the significance of endostatin as a potent inhibitor and its implications for anti-angiogenic cancer treatment (O'Reilly et al., 1997).

V. Nonlinear Adaptive Optimal Controller Design

Nath et al. (2023) present a novel approach in cancer treatment through nonlinear adaptive optimal controller design. Their study focuses on anti-angiogenic tumor treatment, emphasizing the importance of adaptability and optimization in controlling tumor growth. The research introduces innovative control strategies with potential implications for personalized cancer therapies (Nath et al., 2023).

VI. Utilizing Robust Fixed-Point Transformation in Nonlinear Model Predictive Control for Tumor Growth Regulation

The investigation by Czakó and Kovács (2018) delves into the application of nonlinear model predictive control with a robust fixed-point transformation, aiming to effectively regulate tumor growth. The study introduces robust control strategies that leverage fixed-point transformations to enhance the precision of control interventions. The research contributes to the development of advanced control methodologies in the context of cancer treatment (Czakó & Kovács, 2018).

3. Work Progress & Achievement

I. Tumor Growth Dynamics

Introduction

n 1999, Hahnfeldt et al. introduced a dynamic model aimed at understanding and controlling tumor growth, with a specific emphasis on the impact of angiogenic stimulation and inhibition [1].

Model Formulation

The nonlinear model that characterizes tumor growth under angiogenic inhibition is expressed through the following system of nonlinear differential equations:

$$\dot{x_1} = -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) \quad \ldots\ldots(1)$$

$$\dot{x_2} = bx_1 - dx_1^{\frac{2}{3}}x_2 - ex_2x_3 \quad \ldots\ldots..(2)$$

$$x_3 = \int_0^t u(t')e^{-\lambda_3(t-t')}dt' \quad \ldots\ldots..(3)$$

$$y = x_1$$

State Vector and Input

The state vector and input components are outlined as follows:

• x_1 - tumor volume (measured in mm^3)

• x_2 - endothelial volume (measured in mm^3)

• x_3 - administered inhibitor concentration (measured in mg/kg)

• $u(t)$ - rate of inhibitor administration (measured in mg/kg/day)

Model Parameters

The model parameters include:

• λ_1 - rate of tumor growth (expressed in 1/day)

• b - rate of vascular birth (expressed in 1/day)

• d - rate of vascular death (expressed in 1/ ($mm^{2/3}\cdot$ day))

• e - parameter for drug-induced cell death (expressed in 1/ (day · mg/kg)

• λ_3 - clearance of drug (expressed in 1/day)

Note: The original model incorporates an additional term $+\lambda_2 x_2$ in equation (2), nevertheless, empirical evidence indicates that λ_2 is practically zero. The unit of concentration (conc.) is determined by the proportion of the inhibitor's mass relative to the patient's body mass and is expressed in milligrams per kilogram (mg/kg) [2].

Inhibitor Administration

Inhibitors were administered as bolus doses, employing the model equation (3) with Dirac delta functions. The concentration (x_3) of the administered inhibitor at a particular time *t* encompasses contributions from prior administrations at all preceding times *t'* < *t*.

The $u(t)$ in the model Eq. 3 was considered as $u(\delta(t'-t_1)+\delta(t'-t_2)+\ \delta(t'-t_3)+\cdots)$, where *u* represents the dose concentration administered, and t_i are the injection days [2].

Refined Model for Dynamic Examination

To facilitate dynamic analysis and simulations, we adjusted the Hahnfeldt model by substituting equation (3) with a one-compartment model [3]:

$$\dot{x_3} = -\lambda_3 * x_3 + u(t) \ldots\ldots (4)$$

This modification is justified using a input characterized by a step function, corresponding to infusion therapy, in contrast to the Dirac deltas used in the original Hahnfeldt model.

Therefore, for dynamic examination and simulations, we employ our adapted Hahnfeldt model –

$$\dot{x_1} = -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) \quad \ldots (5)$$

$$\dot{x_2} = bx_1 - dx_1^{\frac{2}{3}}x_2 - ex_2x_3 \quad \ldots (6)$$

$$\dot{x_3} = -\lambda_3 x_3 + u(t) \quad \ldots (7)$$

Model Simulation

Using the modified model, we conducted dynamic analysis and simulations. The simulated results under the following experimental conditions were obtained [2]:

- Experimental Condition:
    - Implantation of Lewis lung carcinoma in C57BL/6 mice.
    - Treatment initiation on day 0 (5 days post-implantation) when the tumor size reached approximately 200 mm^3.
    - Subsequent tumor measurements were conducted on days 0, 4, and every third day thereafter.
- Parameter Values for Simulation:

	λ_1	*b*	*d*	x_{20}	*e*	λ_3
Model Parameter	0.192	5.85	0.00873	625	0.66	1.7

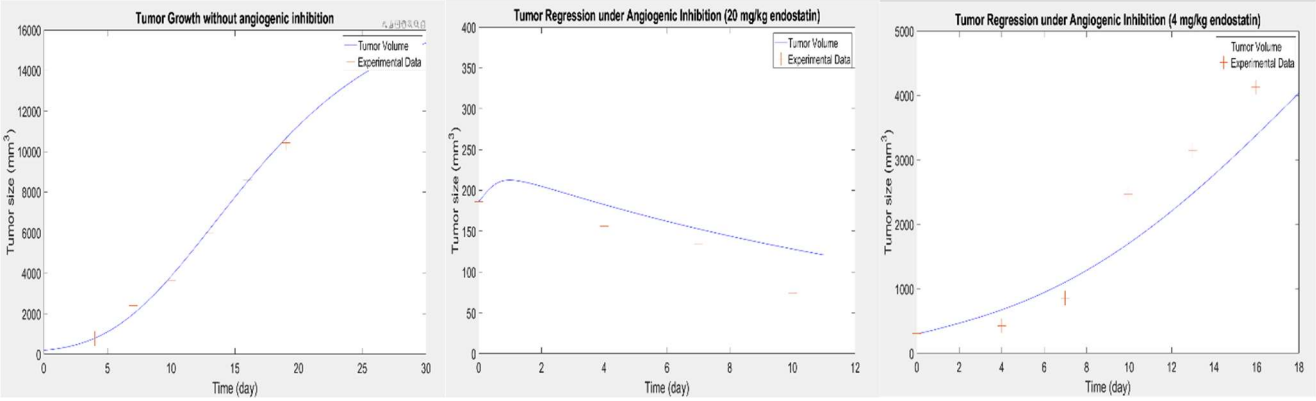

Figure 1: (a) Tumor Growth in the Absence of Angiogenic Inhibition, (b) Tumor Suppression with Angiogenic Inhibition (Endostatin at 20 mg/kg/day), (c) Tumor Suppression with Angiogenic Inhibition (Endostatin at 4 mg/kg/day)

II. Model Parameter Optimization

Introduction

The focus of this section is on the optimization of model parameters for tumor growth, specifically in the absence and presence of Angiogenic Inhibition (Endostatin). The goal is to refine parameter estimates to enhance the model's predictive accuracy.

Curve Fitting for Control Tumor Growth

Due to the limited number of data points (only 6) for regulating tumor growth without the presence of angiogenic inhibition, a curve-fitting approach is employed. The Lorentz function, among various curve models tested, demonstrated superior fitting performance compared to other functions like Boltzmann, SGompertz, Slogistics, GaussMod, and logistic.

The Lorentz Function Mathematical Equation is given as –

$$V = y_0 + \frac{2A}{\pi}\left[\frac{w}{4(time - x_c)^2 + w^2}\right]$$

Where – V = Tumor Growth

	y_0	x_c	w	A
Co-efficient	**-3329.55**	**20.8**	**21.64**	**482269**

Fitness –

$R^2 = 0.99855$

Adj. $R^2 = 0.99637$

Optimization Methods:

Various optimization techniques are explored to refine parameters (λ_1, b, d) of the tumor growth model, aiming to minimize the Root Mean Square Error (RMSE). The methods include:

1. lsqnonlin/lsqcurvefit:

- Utilizes a local minimum approach.
- Commonly used for minimizing the sum of squares of nonlinear functions.

2. Global Optimization Methods:
    - Genetic Algorithm (GA): The GA operates by evolving a population of potential solutions over numerous generations. Through selection, crossover, and mutation, it explores and adapts the parameter values to obtain an optimal fit with the experimental data. The GA effectively balances exploration and exploitation, gradually improving the model's predictive accuracy.
    - Pattern Search: Pattern Search operates by iteratively exploring the parameter space while intelligently adjusting the step size. By evaluating multiple points and iteratively refining the search pattern, it navigates the complex landscape of potential solutions. This method balances precision with computational efficiency, ensuring a comprehensive exploration of the solution space.
    - Surrogate Optimization: Surrogate Optimization constructs a surrogate model from limited data points, approximating the complex relationship between parameters and the objective function. Through iterative sampling and surrogate refinement, it efficiently explores the parameter space. The surrogate guides the search, enabling the algorithm to converge toward optimal parameter.
    - Particle Swarm Optimization (PSO)**:** PSO operates through a population of particles, each representing a potential solution. These particles iteratively adjust their positions based on their own best-known solutions and the collective knowledge of the swarm. By adapting and fine-tuning parameters collaboratively.

Methodology:

The objective function is constructed based on the tumor growth model and experimental data. Different optimization techniques iteratively adjust parameters to minimize discrepancies between model predictions and observations.

$$obj = \sum_{i=1}^{N} \left(\text{interp1}(t_m, V_m(:,1), \text{t}_{se,i}) - V_{se,i}\right)^2$$

In this equation:

- N represents the number of data points in the simulated experimental data from the curve fit of Lorentz function mentioned above
- t_m – Model Simulated time Vector and $\text{V}_\text{m}(:,1)$ – Tumor Volume Vector
- $\text{interp1}(\text{t}_\text{m}, \text{V}_\text{m}(:,1), \text{t}_{\text{e,i}})$ – calculates the interpolated model prediction at the i^{th} simulated time point ($\text{t}_{\text{se,i}}$)
- $\text{V}_{\text{se,i}}$ represents the i^{th} simulated experimental Tumor Volume

III. Controller Design for Drug Delivery Optimization

Model Predictive Controller (MPC)

Model Predictive Control (MPC) is a powerful control technique that proves particularly effective for optimizing complex and nonlinear systems with multiple inputs and outputs (MIMO), time delays, and dynamic constraints. In the context of cancer treatment through drug delivery optimization, MPC offers a systematic approach to dynamically adjust the inhibitor administration rate, ensuring effective tumor growth control while considering the high cost associated with the drug.

Parameters of MPC Design:

- **Sample Time**: The sample time in the MPC controller is crucial for capturing the dynamics of the system and actuator. A smaller sample time enhances control performance but increases computational costs. The choice of sample time should balance the need for precision with computational efficiency.
- **Prediction Horizon**: The forecasting horizon dictates the extent into the future the controller anticipates the system's behavior. It should be long enough to capture the impact of the control input on the system output. However, an excessively long prediction horizon may lead to unnecessary computational burden and increased uncertainty.
- **Control Horizon**: The control horizon specifies the number of future steps over which the MPC controller optimizes the control input. It should be equal to or shorter than the prediction horizon. A shorter control horizon can enhance computational efficiency and robustness but may limit control performance.
- **Constraints**: Constraints are essential for preventing the system from operating in undesirable regions. In the context of cancer treatment, constraints may include limits on tumor volume, endothelial volume, and inhibitor concentration. Handling both hard and soft constraints allows the MPC controller to adapt to varying scenarios while avoiding infeasibility or suboptimal solutions.
- **Weights**: Weights in the MPC controller represent the trade-off between different objectives. Tuning these weights is critical to achieving optimal performance. Objectives may include minimizing tracking errors, controlling effort, or ensuring smooth control inputs. Weight adjustments can be made to improve the overall performance and robustness of the MPC controller.

Working Principle of MPC in Drug Delivery Optimization

The MPC controller functions by addressing an optimization challenge at each time step, derived from the nonlinear model depicting the dynamic progression of tumor growth and the cost function that incorporates weights and constraints. The optimization problem determines the optimal inhibitor administration rate over the prediction horizon, considering the dynamic nature of the tumor growth system. The MPC controller then applies only the first element of the optimal control input to the system and iteratively repeats this process at each subsequent time step, adapting to updated measurements and predictions.

Controllability Analysis

In the endeavour to apply our developed controller to the nonlinear system, it becomes essential to evaluate the controllability of the system. Let's examine the nonlinear model articulated in (5) – (7) in the format of –

$$\dot{x} = f(x) + g(x)u(t) \quad \ldots\ldots(8)$$

Where the output is $(y = x_1)$. To ensure the feasibility of control application, we perform a controllability check on the nonlinear model.

As per Isidori (1995), the controllability of the nonlinear system is ascertained through the Lie algebra rank condition. The system attains controllability if the distribution Δ_0, constituted by the drift vector field (f) and the control vector field (g) augmented with the Lie brackets $[f, g]$ and $[f, [f, g]]$ reaches full rank.

The computation of the Lie bracket between the drift and control vector fields is expressed as:

$$[f, g] = \begin{bmatrix} 0 \\ ex_2 \\ \lambda_3 \end{bmatrix} \quad \ldots\ldots(9)$$

The distribution Δ_0 augmented with the Lie bracket $[f, g]$ is:

$$\Delta = \{f, g, [f, g]\} = \begin{bmatrix} -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) & 0 & 0 \\ bx_1 - dx_1^{\frac{2}{3}} x_2 - ex_2 x_3 & 0 & ex_2 \\ -\lambda_3 x_3 & 1 & \lambda_3 \end{bmatrix} \ldots\ldots(10)$$

Achieving full rank, this distribution indicates system controllability when both x_1 and x_2 are non-zero, implying effectiveness in controlling the system away from the steady stated$(x_1 = 0, x_2 = 0)$. Notably, distribution (11) retains full rank but experiences a two-rank drop when either x_1 or x_2 equals zero. Therefore, it is crucial to prevent the states from approaching zero to maintain system controllability.

MPC Control Design

In the pursuit of optimizing drug delivery for effective cancer treatment, the application of a Nonlinear Model Predictive Controller (MPC) in a Single-Input Single-Output (SISO) system stands as a promising approach. This section outlines the MPC design parameters, its integration into our tumor growth model, and the practical implementation within Simulink.

Our controller utilizes a simplified version of the tumor growth under angiogenic inhibition model to minimize computational costs. The modified model, used for prediction within the MPC framework, is expressed as –

$$\dot{x_1} = -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) \quad \ldots(8)$$

$$\dot{x_2} = bx_1 - dx_1^{\frac{2}{3}} x_2 - ex_2 u(t) \quad \ldots(9)$$

This simplified representation allows the MPC controller to efficiently predict the system's future behavior, facilitating real-time adjustments to the inhibitor administration rate.

To enhance the controller's effectiveness, an Extended Kalman Filter (EKF) is employed as a state estimator. The EKF refines the predictions by incorporating measurements from the system, enhancing the accuracy of the control strategy.

The entire system is implemented within Simulink, where the rigorous tumor growth model is utilized for dynamic analysis and simulation. The error between the predicted and actual system states is computed and fed back into the MPC control loop. The set-point reference is established as a linearly decreasing line, representing the desired tumor growth trajectory.

Simulink Design –

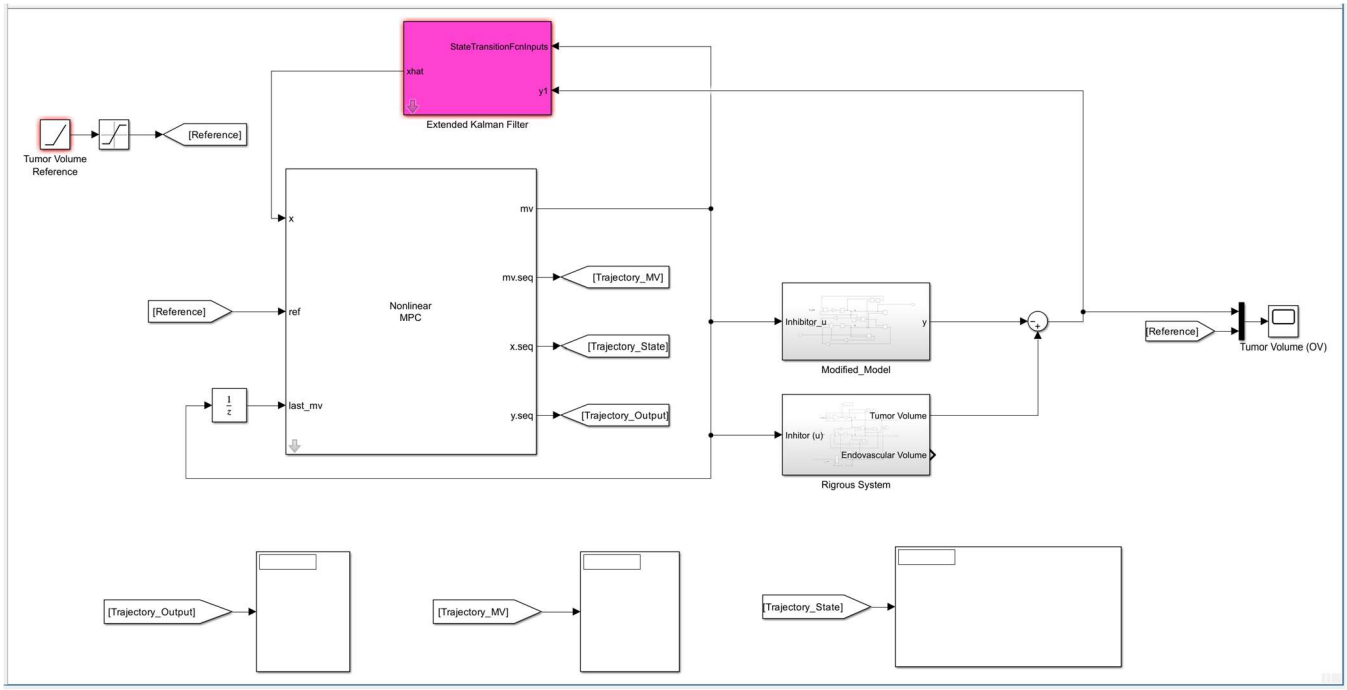

Fig – 2: Simulink Design of the control system block

Need further exploration on the Control design because it is no giving output yet.

4. Results and Discussion

- *Simulation Results for Control Tumor Growth (Endostatin 0 mg/kg)*

Optimized parameters obtained using optimization methods is compared to the reported parameter RMSE values which is summarised in Table 2.

The Root Mean Square Error (RMSE) for the experimental data can be mathematically expressed as follows:

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\frac{\text{interp1}(t_m, V_m(:,1), t_{e,i}) - V_{e,i}}{V_{e,i}}\right)^2}$$

In this equation:

- N represents the number of data points in the actual experimental data
- t_m – Model time Vector and $V_m(:,1)$ – Model Tumor Volume Vector (obtained by solving the ODE system with the optimized parameters using the ode45 solver)
- $\text{interp1}(t_m, V_m(:,1), t_{e,i})$ – calculates the interpolated model prediction at the i^{th} time point ($t_{e,i}$)
- $V_{e,i}$ represents the i^{th} experimental Tumor Volume

Table 2 – Optimization Methods Results

Methods/Parameter	λ_1	*b*	*d*	k_0	*RMSE (%)*
Reported Parameter	*0.192*	*5.85*	*0.00873*	*625*	*8.89*
lsqnonlin Method	*0.1745*	*11.990*	*0.0170*	*625*	*8.29*
Genetic Algorithm	*0.1780*	*10.7749*	*0.0155*	*625*	*8.18*
Pattern Search	*0.1760*	*11.1617*	*0.0159*	*625*	*8.26*
Surrogate	*0.1879*	*7.7770*	*0.0116*	*625*	*8.04*
Particle Swarm	*0.1822*	*8.8169*	*0.0129*	*625*	*7.90*

**All the parameters in the above Table are estimated using the Lorentz Function Fit and kept k_0 constant for the given Methods*

Particle Swarm Optimization yields the lowest RMSE, indicating its effectiveness which can be seen in the Fig – 2.

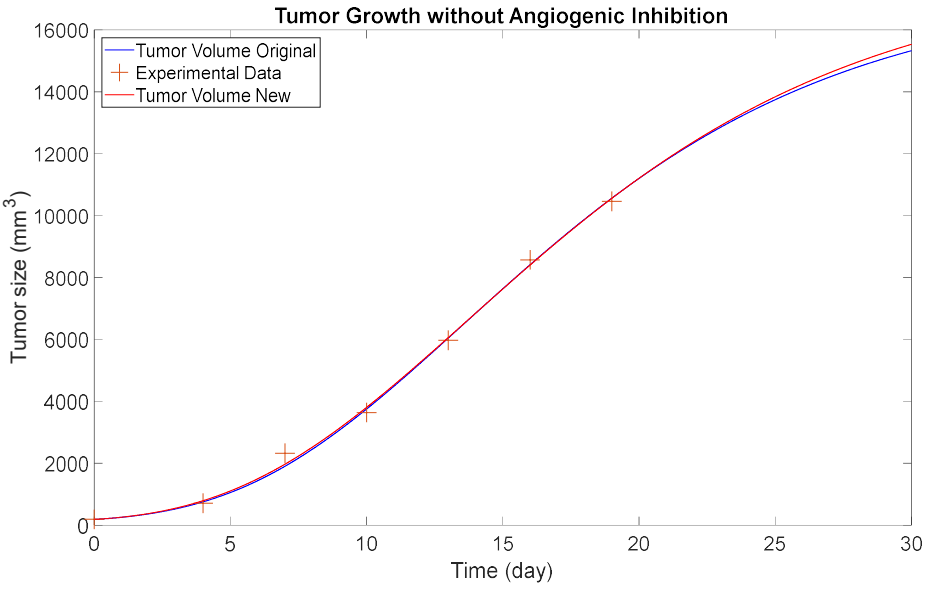

Fig – 2: Tumor Growth without Angiogenic Inhibition with Tumor Volume New (Using Optimized Parameter) and Tumor Volume Original (Using Reported Parameter)

- *Simulation Results for Endostatin (20 mg/kg)*

Optimization is extended to parameters for Angiogenic Inhibition (Endostatin) specifically the drug killing parameter (e) and drug clearance (λ_3). The data provided was based on a dosage of D = 20 mg/kg/day of Endostatin. Optimization methods such as lsqnonlin and Particle Swarm Method were employed to calculate the optimized parameters [e, λ_3] that minimized the Root Mean Square Error (RMSE).

The optimized parameter values [e,λ_3] obtained from the lsqnonlin and Particle Swarm Method can be summarized in the Table – 3 below:

Table 3 – Optimization Methods for Endostatin 20 mg/kg:

Methods/Parameter	λ_1	*b*	*d*	k_0	*e*	λ_3	*RMSE (%)*
Reported Parameter	*0.192*	*5.85*	*0.00873*	*625*	*0.66*	*1.7*	*37.07*
lsqnonlin	*0.1822*	*8.8169*	*0.0129*	*625*	*0.7992*	*1.0179*	*9.83*
Particle Swarn	*0.1822*	*8.8169*	*0.0129*	*625*	*0.7992*	*1.0163*	*9.76*

** This parameter (λ_1, b, d, k_0) are from the Particle Swarn Method optimization based on the control data*

Assessment:

Fig – 3 visually demonstrates the optimized model's improved fit for the 20 mg/kg Endostatin data compared to the reported Tumor Volume Model.

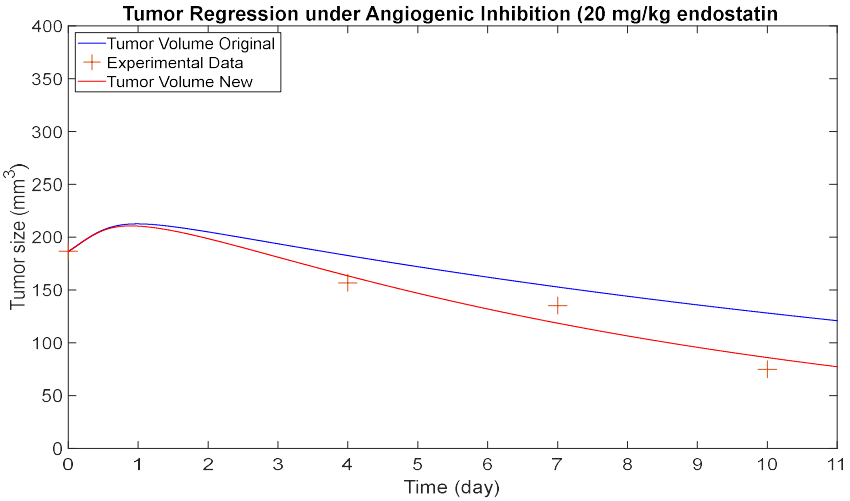

Fig – 3 Tumor Regression under Angiogenic inhibition (20 mg/kg Endostatin)

- *Simulation Results for Endostatin (4 mg/kg):*

Simulations based on the optimized parameters for Endostatin 4 mg/kg reveal notable deviations from the reported parameters. The performance of the model, originally tuned for the control data and 20 mg/kg Endostatin, does not align well with the experimental observations at 4 mg/kg. In response to these discrepancies, a meticulous exploration of optimization methods and parameter adjustments becomes imperative.

Investigation of Deviations

The simulated results, illustrated in Fig – 4, highlight substantial disparities between the model predictions using the optimized parameters and the reported Tumor Volume Model. These deviations prompt a re-evaluation of the optimization strategy to achieve a more robust and versatile parameterization that caters to diverse experimental conditions.

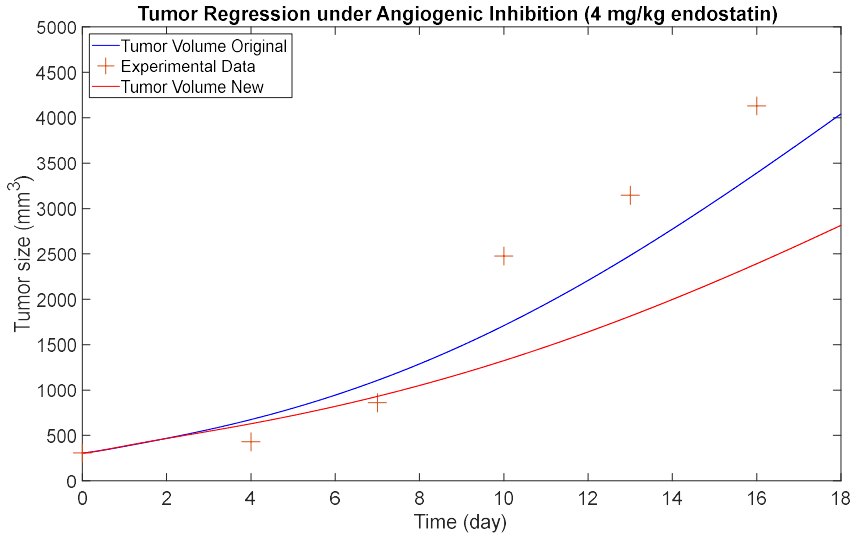

Fig – 4 Tumor Regression under Angiogenic inhibition (4 mg/kg Endostatin)

Iterative Optimization for a Balanced Model

Recognizing the limitations of the initially optimized parameters for the 4 mg/kg Endostatin condition, an iterative optimization process is initiated. The objective is to identify a set of parameters that strike a balanced fit, ensuring satisfactory performance across both the 20 mg/kg and 4 mg/kg datasets.

Best Possible Parameters

Table 4 presents a set of refined parameters deemed as the "Best Possible" configuration, carefully chosen to reconcile the model's performance for both 20 mg/kg and 4 mg/kg Endostatin conditions.

Table 4 – Best Possible Parameters:

Methods/Parameter	λ_1	b	d	k_0	e	λ_3	*RMSE (%)*
Reported Parameter	0.192	5.85	0.00873	625	0.66	1.7	37.07
Best possible parameters	0.1822	8.8169	0.0129	625	0.8939	1.5121	37.05

** 20 mg/kg endostatin condition*

Assessing the Balanced Model

Fig – 5 visualizes the model's performance under the "Best Possible" parameters for the 20 mg/kg Endostatin condition. The simulation results demonstrate a promising alignment with the reported Tumor Volume Model.

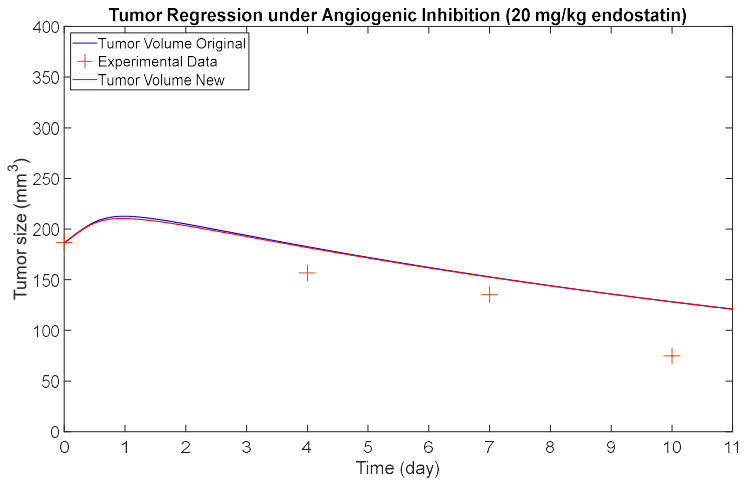

Fig – 6 Tumor Regression under Angiogenic inhibition (20 mg/kg Endostatin)

Final Considerations

While the optimized parameters improve the model's fit for both the control data and 20 mg/kg Endostatin, achieving a seamless transition to the 4 mg/kg condition remains challenging as observed from Fig – 6. The "Best Possible" parameters provide a compromise, minimizing the Root Mean Square Error (RMSE) and enhancing the model's ability to capture the dynamics of tumor growth under diverse experimental conditions.

In summary, the iterative optimization process aims to strike a balance between different datasets, fostering a more comprehensive and adaptable model. Further refinements and considerations may be necessary to address the nuances of varying experimental scenarios.

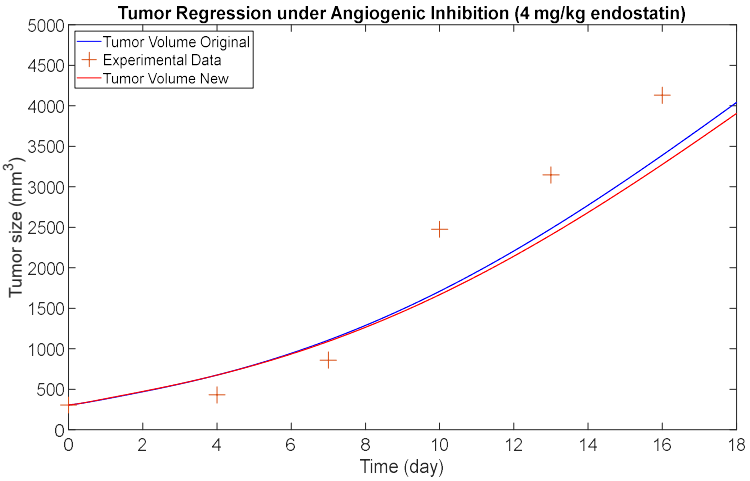

Fig – 7 Tumor Regression under Angiogenic inhibition (4 mg/kg Endostatin)

5. Conclusion

In summary, our exploration of the nonlinear model characterizing tumor growth under angiogenic inhibition involved optimizing parameters using Particle Swarm Algorithm. While achieving optimized parameters, discrepancies emerged during testing with 4 mg/kg of Endostatin. Subsequently, our focus shifted to controller design for optimal drug delivery rates, employing a nonlinear Model Predictive Control (MPC) approach. Despite efforts to implement this controller in Simulink, challenges were encountered in getting the Output which I ensure to look into the future.

6. Future work

I. **Enhanced Simulink Integration**: Delve into an in-depth exploration of Simulink to overcome challenges and obtain results from the implemented controller design. Investigate potential modifications or optimizations to enhance the Simulink setup.

II. To deal with deviation in 4 mg/kg/day endostatin we will explore Nonlinear controller which incorporate the parameter in controller itself to get the optimize drug delivery rate.

III. **Nonlinear Controller Diversity**: Broaden the scope by exploring alternative nonlinear controllers beyond MPC. Investigate the applicability and efficiency of diverse control strategies for optimizing drug delivery rates. Assess how different controllers influence not only drug efficacy but also the overall cost-effectiveness of the treatment.

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