Advancing Personalised Cancer Treatment: Integrating Optimal Control with Evolutionary Algorithms for Drug Administration.

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ABSTRACT

This study aims to advance personalized cancer treatment by integrating optimal control techniques with evolutionary algorithms for drug administration. The primary objectives of this research are to minimize tumor growth and reduce damage to normal cells through personalized chemotherapy for two patients, Patient A and Patient B, each with distinct parameters and initial conditions. The methodology employed in this study involves the use of discretization and nonlinear programming techniques, supported by the Applied Modeling Programming Language (AMPL) linked with the Interior-Point Optimization solver (IPOPT) to determine the most optimal solution for drug administration. The results obtained from the application of optimal control solutions demonstrate impressive outcomes for both patients, as evidenced by the quantification of adaptability through objective function evaluation and tumor cell count reduction. In conclusion, optimal control techniques consistently deliver the desired results in personalized cancer treatment. This study showcases the effectiveness of optimal control in improving the efficiency and efficacy of cancer treatment, reducing medication requirements, and enhancing patient health. Furthermore, it expands our understanding of the practical applications of mathematical modeling in the field of healthcare.

1. Introduction

Cancer poses a significant global health challenge, leading to millions of deaths worldwide. Personalized treatment approaches are necessary due to the complexity and variability of the disease. While various therapeutic methods have been developed, improving their effectiveness for individual patients remains a challenge. In recent years, there has been a growing focus on using computational methods and mathematical models in cancer treatment. These models provide a framework for understanding tumor dynamics, treatment response, and the interaction between cancer cells and the immune system. By integrating mathematical modeling, the aim is to enhance the accuracy and individualization of cancer treatment techniques. This research project aims to enhance personalized cancer treatment by employing optimal control and evolutionary algorithms. The objective is to develop an efficient control model using mathematical models specifically designed for different categories of cancer patients. By combining optimal control theory with evolutionary algorithms, the goal is to optimize treatment methods and improve patient outcomes. The research focuses on investigating mathematical approaches for cancer treatment, utilizing comprehensive mathematical models that consider tumor growth and the immune response. By utilizing optimal control theory and an evolutionary algorithm, personalized treatment strategies for different types of cancer will be developed. The optimization method considers multiple objectives, such as reducing tumor size and extending patient survival. By combining mathematical modeling with clinical data, the aim is to develop more accurate and individualized cancer treatment plans.

(dePillis and Radunskaya, 2001), aimed to find the most effective chemotherapy schedule. They used a cost function to minimize the number of tumor cells remaining after treatment. However, their proposed regimen showed variations in the tumor cell population throughout the treatment. To address this issue, (dePillis and Radunskaya, 2003) conducted further research and proposed an improved cost function that considered multiple variables, including the total tumor cell population, cumulative population during treatment, and the highest population observed. Building on this work, (dePillis et al., 2007) developed an updated mathematical model of cancer and investigated optimal medicine delivery by integrating quadratic and linear controls. They explored the use of singular control to optimize linear control in chemotherapy treatment. The objective of chemotherapy is to minimize side effects while achieving significant tumor reduction and efficient medication delivery. The model described in the article includes immune cells, lymphocytes, medicines, and tumor cells. It also considers side effects as a direct influence on Circulating Lymphocytes. The article further explains the optimal control for both linear and quadratic controllers using the Pontryagin Maximum/Minimum Principle, addressing the single arc, higher-order differential equations, and first-order condition in the optimal control problem.

In another study by (Rostami and Jafarpour, 2015), they present a mathematical model for cancer therapy that considers tumor proliferation, immunological reaction, and treatment outcomes. Using optimal control theory, the authors determine the most

beneficial drug dosage and treatment plan that promote tumor response while minimizing negative consequences. This study provides insights into using optimal control methods to develop personalized treatment plans for cancer patients.

(Swaminathan and Venkataraman, 2012) propose a mathematical model that describes tumor growth and response to treatment. Their model incorporates cell proliferation, mortality rates, and the impact of treatment on cancer cells. The authors use optimal control theory to adjust chemotherapy dosage and duration to enhance tumor response while reducing damage. This study demonstrates the potential of optimal control strategies in customizing chemotherapy regimens for individual patients and improving treatment outcomes.

An optimal control problem is examined in the analysis of a mathematical model that represents the reduction of bone marrow after cancer chemotherapy. The control reflects the drug dosage of a solitary chemotherapeutic agent, and it includes pharmacokinetic equations that simulate its plasma concentration. The pharmacological dosages are administered in a linear manner. (Vinter, 2021) discusses Pontryagin's Maximum Principle, which is a set of circumstances that offer insights into solutions for optimal control issues. These issues involve optimization with constraints defined by differential equations. The Maximum Principle unifies and expands upon several essential requirements derived from the calculus of variations. (Ledzewicz and Schättler, 2007) demonstrates that the most effective controls involve alternating drug dosages at full strength with rest periods in between, a strategy known as bang-bang control.

(Rehman and Siddiqui, 2020) present an extensive examination of mathematical models used in the field of cancer therapy. The review encompasses many modeling methodologies, such as ordinary differential equations, partial differential equations, and agent-based models. The authors examine the integration of several elements, including tumor growth, drug pharmacokinetics, immune response, and therapeutic options. This article provides a comprehensive survey of the many mathematical modeling methods employed in cancer research and their potential utility in individualized therapy.

(Mehmet İtik et al., 2009) propose an optimal control approach for nonlinear systems, with a specific emphasis on its implementation in cancer treatment through medication therapy. The authors utilise a set of equations developed from population dynamics to depict the concept of tumour growth. This model considers the interplay between normal cells and tumour cells, as well as the impact of the immune system in the context of cancer. The authors suggest a method for approximating the optimal control strategy of a system that varies over time in a linear manner. This technique is not only suitable for tiny disturbances around the equilibrium point, but also applies to the overall behaviour of the system. The simulated model employs the optimal control strategy to eradicate cancer cells while minimising the dosage of the drugs administered. The simulations indicate that an adequate delivery of the therapy can lead to the efficient elimination of cancer cells in a short time frame, while minimising the need of drugs.

(Krabs and Pick, 2010) examine a mathematical model that addresses the regulation of tumour cell proliferation through the application of optimal control theory. The model especially concentrates on the implementation of chemotherapeutic treatment for cancer, with the goal of reducing the growth of the tumour within a specified treatment period, while taking into account the constraint of the medications that are now accessible. Drug administration is regulated based on the dosage administered within a specific time frame, with a predetermined maximum limit. The authors establish that the most effective controls for this problem have a bang-bang behaviour, signifying that they alternate between the upper limit and alternative values. In addition, they determine that choosing the upper limit as the best control is feasible when the total quantity of medications is sufficiently substantial.

The application of evolutionary algorithms (EA) to real-world situations has demonstrated its efficacy and popularity in tackling multi-objective optimization challenges. This population-based approach use heuristics to steer the best answer through the Pareto front and identify the optimal collection of solutions to the optimization issue (Maier et al., 2019). For imbalanced optimal problems, a MOEA can yield solution sets that are significantly degraded. Consequently, in order to address the imbalanced optimal problem, a multi-objective evolutionary method based on decomposition was presented in (Liu et al., 2014). As a single-objective problem, MOEA/D converts MOOCP using the cluster method and then applies population-based algorithms to solve it. This is in contrast to MOEA, where the algorithms' primary selection process is based on the Pareto front. Chemotherapy and EA have been the subjects of several cooperative investigations. In a similar vein, (Lobato et al., 2016) sought to successfully reduce tumor cell growth without endangering the patient's health. In order to do this, proposed a multi-objective optimum control approach based on Differential Evolution for the administration of medication to cancer patients. The suggested algorithm is a member of the EA family, although its recombination and mutation strategies are different. As a result of this study, the optimal drug administration method is described by the Pareto's curve obtained using the MODE algorithm.

(Lobato et al., 2016) emphasize the importance of mathematical modeling in comprehending physical and biological systems behavior, specifically in relation to tumor dynamics. The benefits of utilizing mathematical models are highlighted, particularly in relation to their use in optimization and inverse problem methodologies. The authors observe that conventional Optimal Control Problems (OCPs) in cancer treatment predominantly concentrate on limiting the number of tumor cells, while frequently disregarding the potential influence of optimal drug concentrations on patients' well-being. In order to overcome this constraint, the authors state their aim of developing an optimal drug delivery regimen for cancer patients that simultaneously reduces the concentration of malignant cells and the recommended drug concentration. The Multi-objective Optimization Differential Evolution (MODE) algorithm is suggested as a solution to this multi-objective problem. It produces a Pareto Curve that offers a variety of optimal protocols. An ideal drug administration method can be chosen based on a

given criterion by analyzing this curve. Their work advances the creation of patient-centered, personalised strategies for the optimization of cancer treatment.

(Shindi et al., 2020) mainly focuses around addressing the difficulties associated with establishing the most suitable dosage of pharmaceuticals to efficiently decrease tumor size, while also minimizing the harmful effects of chemotherapy on patients. An important area of study focuses on addressing Constrained Multi-Objective Optimization Problems (CMOOP) within the field of cancer chemotherapy. In an effort to determine the best drug regimens that minimize tumor size and drug concentration while maintaining patient health within acceptable bounds, a number of research offer hybrid approaches that blend optimal control theory with multi-objective swarm and evolutionary algorithms. Overall, these proposed methodologies present encouraging solutions for minimizing chemotherapy administration while ensuring effective tumor eradication. They offer valuable insights to oncologists in determining optimal chemotherapy dosage schedules that prioritize tumor reduction while safeguarding patient well-being.

(Amir Ebrahimi Zade et al., 2021) suggest a top-down approach that utilises artificial neural networks (ANN) and genetic algorithm (GA) to forecast the survival of GBM patients. A feed-forward undercomplete Autoencoder network, together with a neuro-evolutionary (NE) method, to derive a condensed representation of the input clinical data. This approach use a Genetic approach (GA) to identify the most efficient structure for a multi-layer perceptron (MLP). The authors utilise the Taguchi L16 orthogonal design of experiments to optimise the parameters of the NE algorithm. Ultimately, the optimised Multilayer Perceptron (MLP) is employed to forecast the survival results of individuals with Glioblastoma Multiforme (GBM). The proposed approach offers a potential way to improve the precision of survival forecasts in GBM patients by utilising the capabilities of artificial neural networks (ANN) and genetic algorithms (GA) in a hierarchical manner.

(Jang, Kim, and Kang, 2021) investigate the fusion of mathematical models and machine learning techniques in personalised cancer treatment. The authors analyze the utilization of mathematical models to comprehend tumor dynamics and treatment response. Additionally, they emphasize the implementation of machine learning algorithms to forecast treatment outcomes and enhance therapy. The work highlights the capacity to merge mathematical modeling and machine learning to create customized treatment approaches that take into account specific patient attributes and enhance treatment effectiveness.

2. Tumor model

2.1 Cancer Mathematical Model with Drug Administration.

In this paper, we utilize the parameter sets and variation range of the parameters as suggested by dePillis and Radunskaya (2003), which are provided in Table 1. A set of differential equations was used to build a mathematical model of the pharmaceutical influence of cancer treatment on the patient's body. Two patients involve in this research, which are reference patient and unknown patient. Given that chemotherapy kills three cell groups at varying rates, the impact of chemotherapy in the presence of the medication is analyzed by incorporating an extra state, M(t), which represents the concentration of the drug in the bloodstream or tissue at the tumor site. Conversely, in this system, the drug dose administered at time t is denoted as u(t) and regarded as the system's control input. The administration of a dose of drug u(t) results in varying degrees of fractional cell death, denoted as F(u(t)), for each kind of cell in the tissue as follows:

$$F_i(u(t)) = a_i(1 - \exp(-M(t))), \qquad (i = 1,2,3).$$

The parameters a_i, i=1,2,3, represent unique positive constant values that describe the reaction of coefficients of immune, tumor, and normal cells to the administered

medicine, respectively. The concentration of the drugs at the tumor location can be described by the following dynamics:

$$\dot{u} = u(t) - d_2M(t),$$

Where u(t) is the drug dose administered externally through blood veins or orally, and d_2 is the degradation rate of the drug in the blood stream or tumor site. Thus, the tumor's mathematical model incorporating the drug's action can be expressed as:

$$\dot{N}(t) = r_2N(t)(1 - b_2N(t)) - c_4T(t)N(t) - a_3(1 - \exp(-M(t)))N(t),$$

$$\dot{T}(t) = r_1T(t)(1 - b_2T(t)) - c_2I(t)T(t) - c_3T(t)N(t) - a_2(1 - \exp(-M(t)))T(t),$$

$$\dot{I}(t) = s + \frac{\rho I(t)T(t)}{\alpha + T(t)} - c1I(t)T(t) - d1I(t) - a1(1 - exp(-M(t)))I(t),$$

$$\dot{M}(t) = u(t) - d_2M(t)$$

N: Normal cell

T: Tumor cell

I: Immune cell

M: Drug concentration in blood stream or tissue in tumor site

The positive initial condition for N(0), T(0) and I(0) as in Table. The normal, tumor and immune cell evolve from the initial conditions for reference patient and unknown patient with the influence of the parameters. Both patients have their personalized initial conditions and parameters. Table shows the different initial conditions and Table shows the different parameters for both patients.

Table 2.1: Normal parameters value and their variation range (dePillis and Radunskaya, 2003)

Parameters	Description	Normal value	Unit	Consideration
a_1	Immune cell kill by chemotherapy	0.2	mg^{-1} L day^{-1}	$0 \leq a_i \leq 0.5$ $a_3 \leq a_1 \leq a_2$
a_2	Tumor cell kill by chemotherapy	0.3	mg^{-1} L day^{-1}	
a_3	Normal cell kill by chemotherapy	0.1	mg^{-1} L day^{-1}	
b_1	Tumor cell carrying capacity	1.0	$cell^{-1}$	$b_1^{-1} \leq b^{-1}_2$
b_2	Normal cell carrying capacity	1.0	$cell^{-1}$	
c_1	Fractional immune cell kill by tumor cells	1.0	$cell^{-1}$ L day^{-1}	$c_i > 0$
c_2	Fractional tumor cell kill by immune cells	0.5	$cell^{-1}$ L day^{-1}	
c_3	Fractional tumor cell kill by normal cells	1.0	$cell^{-1}$ L day^{-1}	
c_4	Fractional normal cell kill by tumor cells	1.0	$cell^{-1}$ L day^{-1}	

Table 2.1 continued

d_1	Per capita death rate of immune cells	0.2	day^{-1}	
d_2	Per capita death rate of chemotherapy drug	1.0	day^{-1}	
r_1	Per unit tumor cells growth rate	1.5	day^{-1}	$r_1 > r_2$, $r_1 < \frac{c_2 s}{d} + c_3$
r_2	Pre unit normal cells growth rate	1.0	day^{-1}	
s	Immune cells steady source rate	0.33	cell day^{-1}	$0 \leq s \leq 0.5$
α	Immune threshold rate	0.3	cell	a>0
ρ	Immune response rate	0.01	day^{-1}	$0 \leq \rho \leq 2.5$

Table 2.2: Initial normal, tumor and immune cells population for patient A and patient B.

	Patient A	Patient B
N(0)	1	0.8
T(0)	0.2	0.3
I(0)	0.15	0.15

Table 2.3: Parameters value for patient A and patient B.

Parameter	Patient A	Patient B
a_1	0.2	0.1
a_2	0.3	0.5
a_3	0.1	0.06
b_1	1.0	1.0
b_2	1.0	1.0
c_1	1.0	1.0
c_2	0.5	0.58
c_3	1.0	1.0
c_4	1.0	1.0
d_1	0.2	0.2
d_2	1.0	1.0
r_1	1.5	1.7
r_2	1.0	1.3
s	0.33	0.33
α	0.3	0.5
ρ	0.01	0.06

2.1 **Pontryagin Maximum Principle (PMP) and Bang Control**

The Pontryagin Maximum Principle (PMP) is a powerful tool used to determine the optimal control strategy in problems with a cost function and a constraint expressed as a differential equation. The Pontryagin Maximum Principle (PMP) is a method used in optimum control to minimize the Hamiltonian equation of a model by employing both single controls and Bang control. This study utilizes the PMP (Pontryagin's Maximum Principle) to tackle a stochastic optimal control problem. The approach involves doing

preparation measures, such as describing the optimization problem and establishing suitable nomenclature.

2.2 **Regularity of State Constraints and Boundary Control.**

In order to ensure the patient's well-being throughout the course of treatment, it is essential to maintain the normal cells at a level that exceeds a specified threshold. A state constraint was implemented as follows:

Using the state constraint value and parameters from table, the boundary arc $N(t) = 0.74$ is defined by the equation below:

$$0 = \dot{N} = r_2 N(t)\big(1 - b_2 N(t)\big) - c_4 T(t) N(t) - a_3\big(1 - \exp\big(-M(t)\big)\big)N(t)$$

Since there is no control variable in the equation above, $\dot{M}(t)$ is considered because the equation have u(t) and M is in the equation of $\dot{N}$.

$$\dot{M}(t) = u(t) - d_2 M(t)$$

$$d_2 = 1$$

$$\dot{M}(t) = u(t) - M(t)$$

To replace the $\dot{M}(t)$, second time derivative of N is required and can be defined as equation below:

$$0 = \ddot{N} = r_2 \dot{N}(t)\left(1 - b_2 \dot{N}(t)\right) - c_4 \dot{T}(t)\dot{N}(t) - a_3\big(1 - \exp\big(-M(t)\big)\big)\dot{N}(t)$$

$$0 = \ddot{N} = r_2 \dot{N}(t)\left(1 - b_2 \dot{N}(t)\right) - c_4 \dot{T}(t)\dot{N}(t) - a_3\big(1 + \dot{M}\exp\big(-M(t)\big)\big)\dot{N}(t)$$

$$0 = \ddot{N} = r_2 \dot{N}(t)\left(1 - b_2 \dot{N}(t)\right) - c_4 \dot{T}(t)\dot{N}(t) - a_3 \dot{N}(t) + a_3 \dot{N}(t)(u(t) - M(t))\exp\left(-M(t)\right)$$

The regularity condition satisfied since,

$$\frac{\partial}{\partial u}\ddot{N}(t) = a_3\dot{N}(t)\exp\left(-M(t)\right) \neq 0$$

The boundary control is derived from the equation $\ddot{N} = 0$,

$$u(t) = -\frac{r_2\left(1 - b_2\dot{N}(t)\right) - c_4\dot{T}(t) - a_3(1 + M(t)\exp\left(-M(t)\right))}{a_3\exp\left(-M(t)\right)}$$

3. Optimal Control Model of Cancer Chemotherapy.

Cancer mathematical model is considered in this paper to construct Hamiltonian equation. It is a fundamental equation to express relationship of the dynamic system. The Hamiltonian equation used to analyze and optimized the behavior of the system and can be used to derive optimal control strategies that minimize or maximize the Hamiltonian function under certain constraints to achieve desired objective.

$$H = J + \lambda_1 \dot{x}_1 + \lambda_2 \dot{x}_2 + \lambda_3 \dot{x}_3 + \lambda_4 \dot{x}_4$$

The Hamiltonian formulation establishes the link between the state variables $(\dot{x}_1, \dot{x}_2, \dot{x}_3, \dot{x}_4)$ and the co-state variables $(\dot{\lambda}_1, \dot{\lambda}_2, \dot{\lambda}_3, \dot{\lambda}_4)$. From the equation ?, replace the state variable $(\dot{x}_1, \dot{x}_2, \dot{x}_3, \dot{x}_4)$ to $\dot{N}, \dot{T}, \dot{I}, \dot{M}$.

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial N(t)}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial T(t)}$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial I(t)}$$

$$\dot{\lambda}_4 = -\frac{\partial H}{\partial M(t)}$$

$$switching\ function = \frac{\partial H}{\partial u(t)}$$

By applying the equation obtained co-state variable, the Hamiltonian formulation and the costate variable equation can be obtain as follows:

$$\begin{aligned} H = T(t) &+ \lambda_1(r_2 N(t)\big(1 - b_2 N(t)\big) - c_4 T(t)N(t) - a_3\big(1 - \exp\big(-M(t)\big)\big)N(t)) \\ &+ \lambda_2(r_1 T(t)\big(1 - b_2 T(t)\big) - c_2 I(t)T(t) - c_3 T(t)N(t) \\ &- a_2\big(1 - \exp\big(-M(t)\big)\big)T(t)) + \lambda_3(s + \frac{\rho I(t)T(t)}{\alpha + T(t)} - c_1 I(t)T(t) - d_1 I(t) \\ &- a_1\big(1 - \exp\big(-M(t)\big)\big)I(t)) + \lambda_4(u(t) - d_2 M(t)) \end{aligned}$$

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial N(t)} = \lambda_1(r_2\big(1 - b_2 N(t)\big) - c_4 T(t) - a_3\big(1 - \exp\big(-M(t)\big)\big)) - \lambda_2 c_3 T(t)$$

$$\begin{aligned} \dot{\lambda}_2 = 1 - \frac{\partial H}{\partial T(t)} \\ &= -\lambda_1 c_4 N(t) + \lambda_2(r_1\big(1 - b_2 T(t)\big) - c_2 I(t) - c_3 N(t) \\ &- a_2\big(1 - \exp\big(-M(t)\big)\big)T(t)) - \lambda_3 c_1 I(t) \end{aligned}$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial I(t)} = -\lambda_2 c_2 T(t) + \lambda_3 (s + \frac{\rho I(t) T(t)}{\alpha + T(t)} - c_1 I(t) T(t) - d_1 I(t)$$

$$- a_1 \big(1 - \exp\big(-M(t)\big)\big))$$

$$\dot{\lambda}_4 = -\frac{\partial H}{\partial M(t)} = -\lambda_1 a_3 \exp(-M)\, N(t) - \lambda_2 a_2 \big(\exp\big(-M(t)\big)\big) T(t)$$

$$- \lambda_3 a_1 \big(\exp\big(-M(t)\big)\big) I(t) - d_2$$

$$switching\ function = \frac{\partial H}{\partial u(t)} = \lambda_4$$

4. Simulation

Applied Modeling Programming Language (AMPL), combined with the Interior-Point Optimization solver (IPOPT) has been chosen to do simulation. The platform for the simulation is Google Colaboratory, a cloud-based platform that allows user to write, execute and share Python code. The platform offers a Jupyter Notebook interface that enables users to generate and execute Python code cells, compose explanatory text, and present data visually.

Both simulation workflow can be presented as the Figure 3.1 and Figure 3.2.

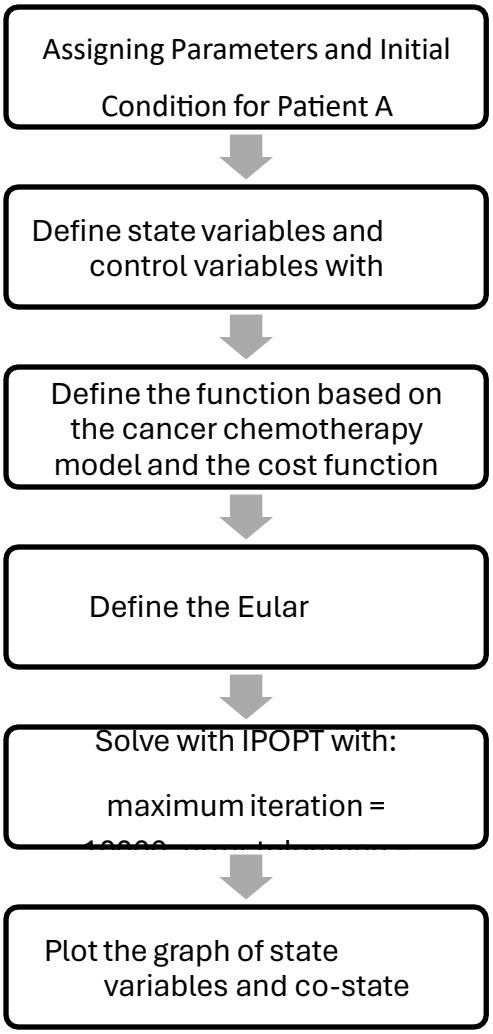

Figure 4.1: Workflow of simulation for patient A using AMPL and IPOPT.

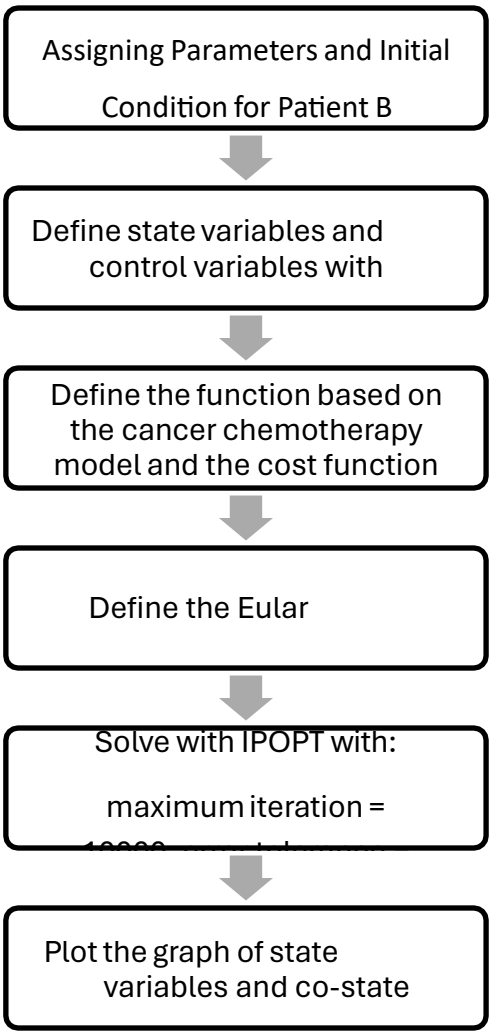

Figure 4.2: Workflow of simulation for patient B using AMPL and IPOPT.

5. Result and Discussion

The discretization techniques were implemented. Applied Modeling Programming Language (AMPL) was used because it can efficiently encode the nonlinear programming problem (NLP) and offers many optimization algorithms. The Interior-Point optimization solution (IPOPT) was employed in this scenario with error tolerance of e^{-8}.

The Implicit Euler method was applied with small interval of 0.01 to solve the optimal control problem for the drug administered cancer mathematical model of both patients. The objective of this study was to minimize the developing tumor and damaged cells.

5.1 Result for Patient A

The results for the personalized chemotherapy for reference patient can be shown at Figure 5.1. Figure 5.1 shows the normal cell for 140 days of treatment. The normal cell increases rapidly until day 25 and reaches 1.00. After that, the normal cell experiences a sudden drop until day 50 to 0.95 and became slightly consistent until day 140. It shows that the number of normal cells increase for 25 days during the treatment period but decrease until day 50. The normal cell was slightly damaged. Since the decrement is minimized, it can be considered that the patient has a healthy number of tumor cell until the last day of the treatment. Figure 5.1 shows the pattern of the tumor cell from day 0 to 140. The tumor cell number decreases from day 0 to day 25. The tumor cell can be concluded to be extinct from day 25 until day 140. The objective to minimize the tumor cell is achieved. 25 Figure 4.1 shows the immune cell number trend for the period of treatment. The immune cell increases from 0.15, which is the initial condition, to above 1.6. The immune cell decreases after day 25

to day 50 and becomes constant until the last day of treatment. This indicates a significant increase in immune cells, but the cell faces minor damage and decreases. However, the number of immune cells is still healthy. This shows that the damaged to immune cells was minimized. From Figure 5.1, it can be seen that the drug dose is given on the first day of treatment. After that the chemotherapy dose is stopped until day 25 and the dose continues until day 140. From this result, it can be concluded that the reference patient body reacts to the chemotherapy treatment instantly after some day of treatment. The tumor cells decrease rapidly until day 25. The patient needs to have consistent chemotherapy dose from day 50 until day 140, to avoid the tumor cell to developed. This shows that the drug needed is still within the administered dose and effectively can kill the tumor cell and minimize the damaged to the other cell. This result demonstrates the effectiveness of the chemotherapy treatment in preventing the development and survivability of cancer cells.

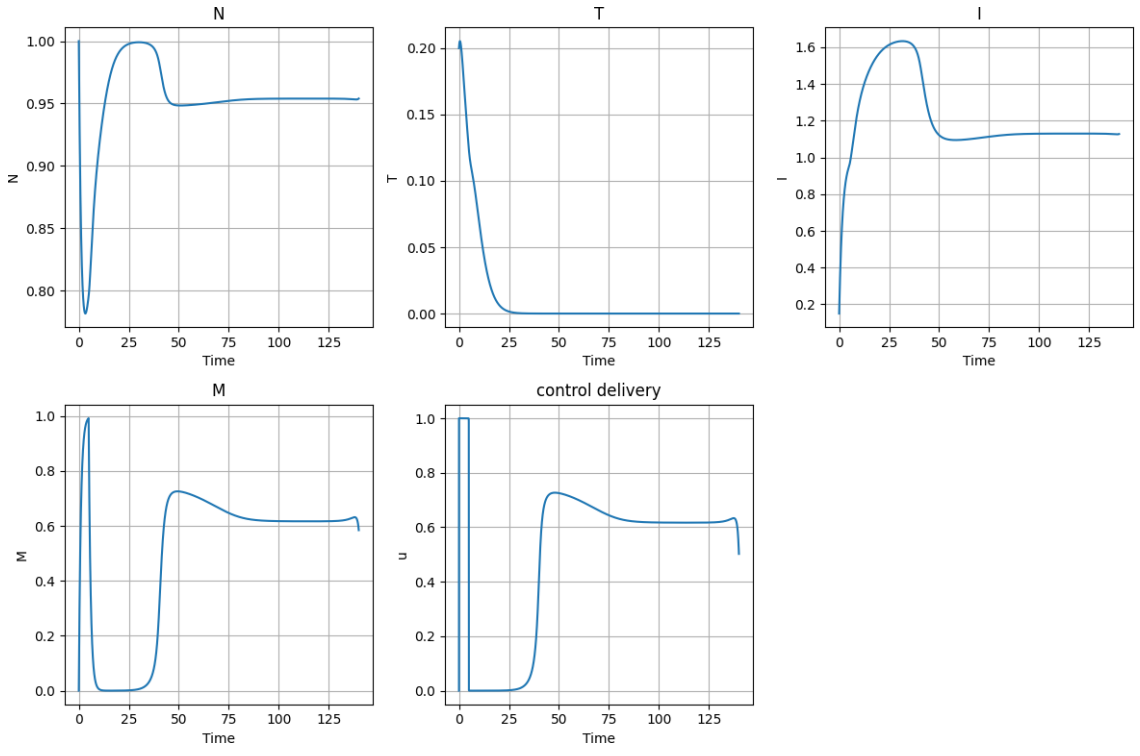

Figure 5.1: Optimal result for N, T, I, M and control variable, u, for patient A.

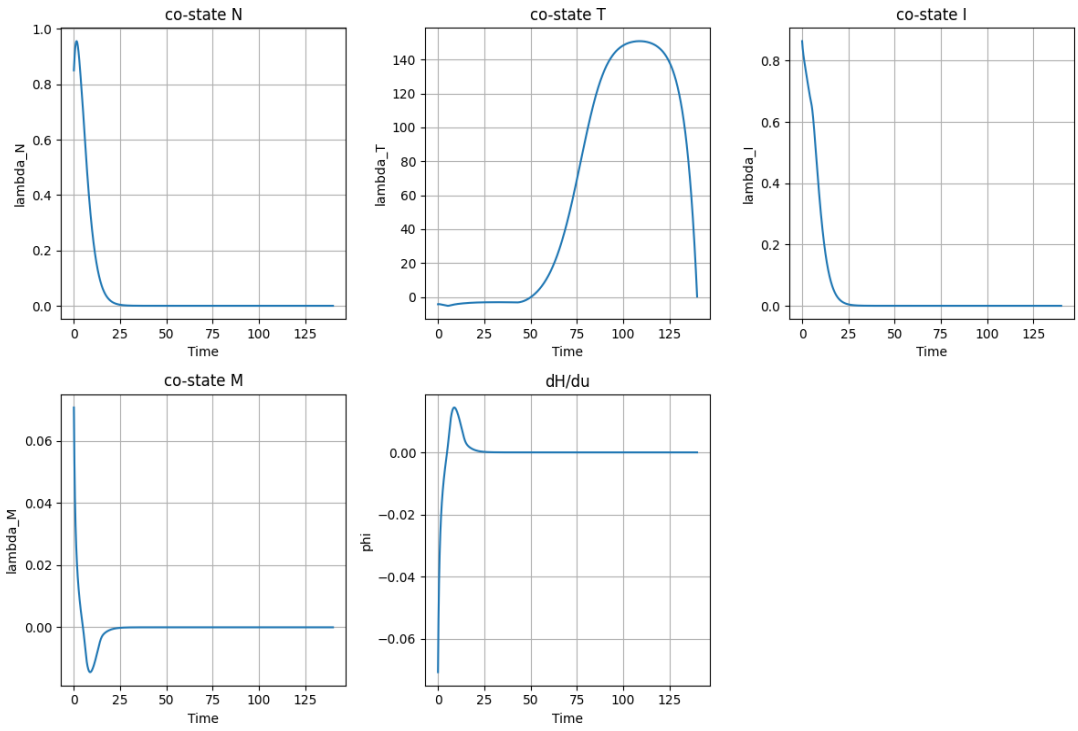

Figure 5.2: Co-state variables result with switching function $\frac{\partial H}{\partial u}$, for patient A

In Figure 5.2, shows the results of the co-state variables and the switching function. The co-state variables are related to the cancer chemotherapy model. The variables are crucial in optimizing drug administration to achieve desired outcomes. The behavior of the variables can be observed and identified so that the control variable can be modified. The switching function becomes zero because the boundary of the drug concentration constraint is satisfied.

5.2 Result for Patient B

The results for the personalised chemotherapy for unknown patient can be shown at Figure 5.3. Figure 5.3 shows the normal cell for 140 days of treatment. The normal cell increases rapidly from day 0 until day 25 and becomes a bit consistent above 0.95. It shows that the number of normal cells increase for 25 days during the treatment period. The normal cell can be assumed to not have decreased from day 25 until day 140, which fulfills part of the objective. Figure 5.3 shows the pattern of the tumor cell from day 0 to 140. The tumor cell

number decreases from day 0 to day 25. The tumor cell can be concluded to be extinct from day 25 until day 140. The objective to minimize the tumor cell is achieved. Figure 5.3 shows the immune cell number trend for the period of treatment. The immune cell increases from 0.15, which is the initial condition, to above 1.2. The immune cells increase slightly from day 25 to day 50 and became constant from day 75 to day 140. This indicates a significant increase to immune cell and the objective is accomplished. From Figure 5.3, it can be seen that the drug dose is consistently given with the same rate until day 25. After that the dose is decreased until day 50. From this result, it can be concluded that the reference patient needs to have full dose of chemotherapy until day 25, which significantly increase the normal cells and immune cells. The tumor cells also decrease rapidly until day 25. This shows that the drug 28 needed is still within the administered dose and effectively can kill the tumor cell and minimize the damaged to the other cell. This result demonstrates the survivability cells.

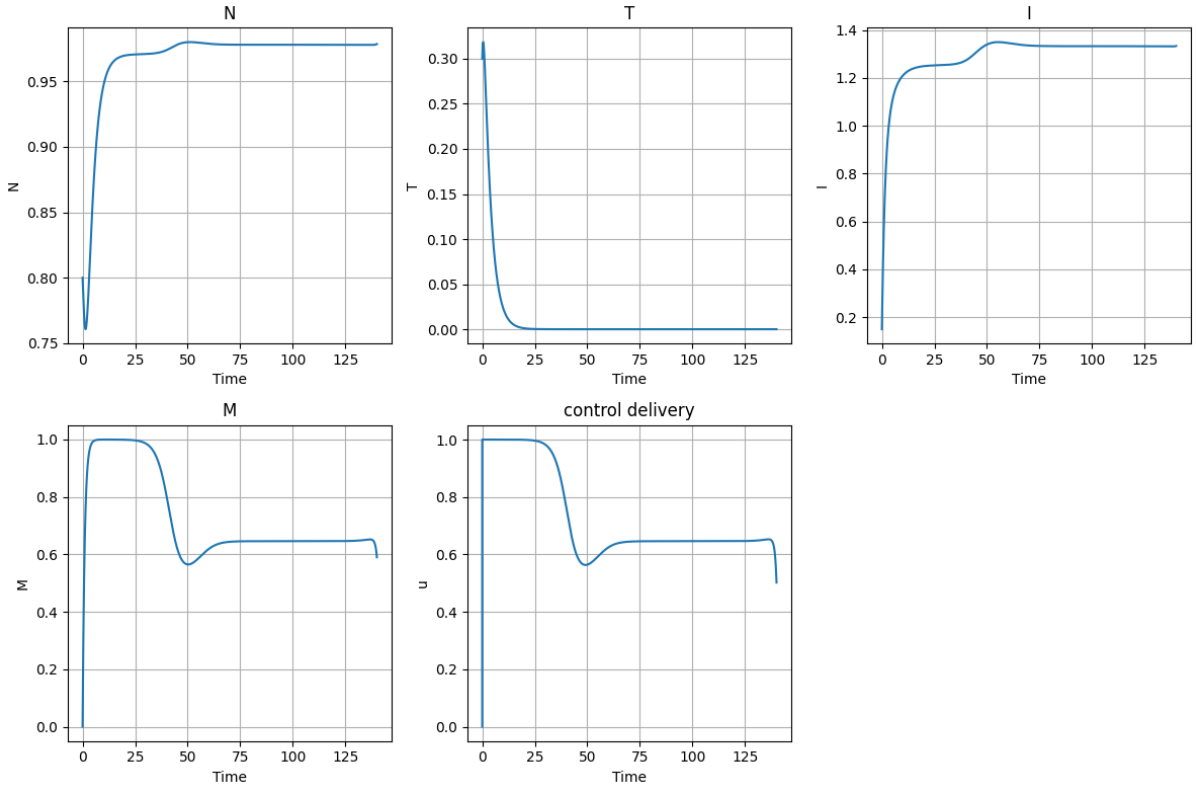

Figure 5.3: Optimal result for N, T, I, M and control variable, u, for patient B.

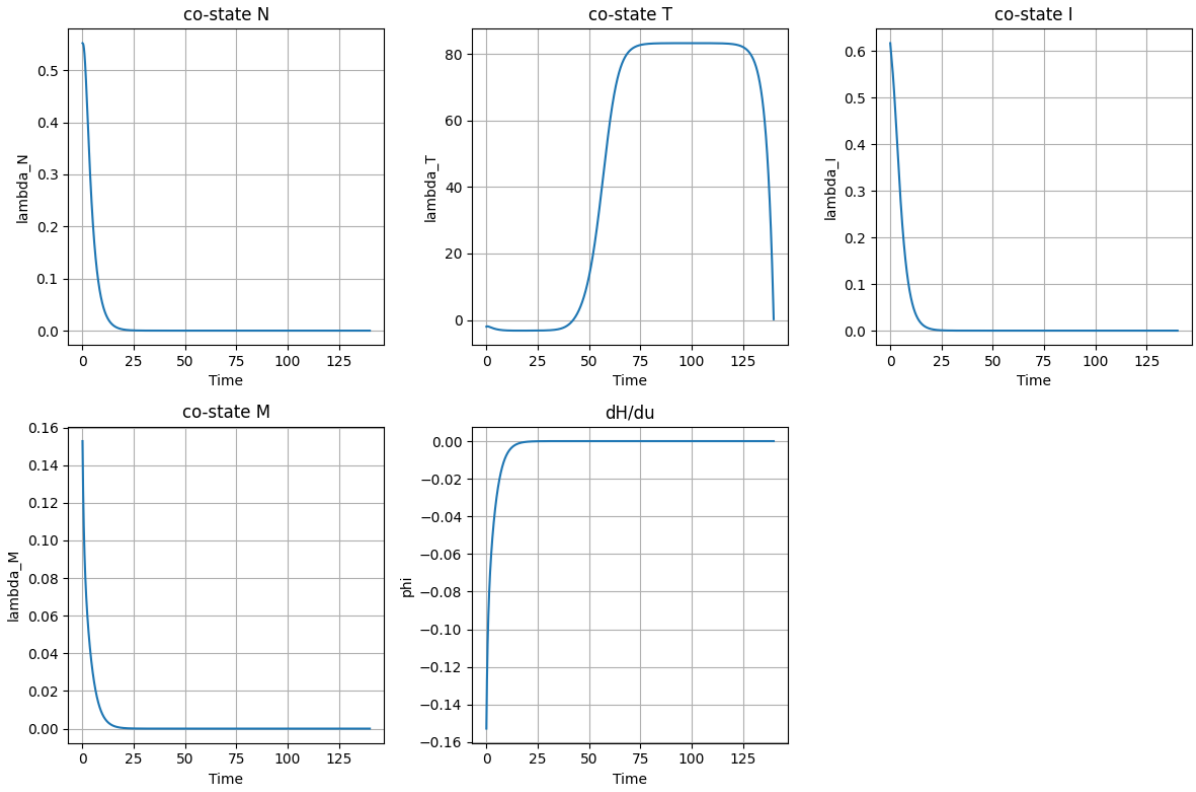

Figure 5.4: Co-state variables result with switching function $\frac{\partial H}{\partial u}$, for patient B

In Figure 5.4, shows the results of the co-state variables and the switching function. The co-state variables are related to the cancer chemotherapy model. Similar to patient A, the variables are crucial in optimizing drug administration to achieve desired outcomes. The behavior of the variables can be observed and identified so that the control variable can be modified. The switching function becomes zero because the boundary of the drug concentration constraint is satisfied.

4.3 Discussion

The study effectively employed discretization techniques with the assistance of the Applied Modeling Programming Language (AMPL) and the Interior-Point optimization solver (IPOPT) to achieve numerical solutions for the optimal control of patients with varying parameters and initial conditions. By verifying the essential optimality conditions, we can ensure that the solution obtained using the Implicit Euler technique, with a time step of 0.01 and accuracy as much as five decimal places, is the most optimal outcome possible for the given issue.

The primary outcome of the research was the similar findings observed from the results for patient A and patient B. By utilizing the cancer model with different parameters and initial conditions from Table 2.2 and Table 2.3, the cumulative tumor which is the objective function for both patients are very low. The result for patient A is $objective = 1.65316$ and $T(t) = 1.18067e^{-12}$. For patient B is $objective = 1.42722$ and $T(t) = 8.12705e^{-9}$.

The approach relies on patient A, whose treatment protocol is formulated using a well-established nonlinear mathematical model that necessitates meticulous examination to ascertain the most effective medication delivery. Once the treatment plan for patient A is established, it can be readily ascertained for another patient B utilizing the suggested methodology. Within this framework, solely the patient's states, including the quantities of

normal, malignant, and immune cell populations, are essential for determining the individualized dosage of medications.

The analysis of chemotherapy drug doses administered over a period of 140 days demonstrated the effectiveness of the bang-bang optimal control method. This strategy involves minimizing the objective function, which is inversely related to tumor mass, significant improvements were observed until the optimal point was reached. Importantly, toxicity levels remained below the acceptable threshold, ensuring the safety of patients undergoing cancer treatment.

This study emphasizes the potential of employing optimum control techniques for numerical solutions in biological field, such as cancer chemotherapy mathematical models. While the results of this study are promising, additional research is required to authenticate these techniques and outcomes across a broader spectrum of cancer models and circumstances. This study establishes a foundation for future investigations into optimal administration of chemotherapy drugs, which could potentially enhance treatment outcomes and improve the quality of life for patients.

6. Conclusion

This research proposed an integration of optimal control with evolutionary algorithm for drug administration in cancer treatment using cancer chemotherapy mathematical model presented by dePillis and Radunskaya. The goal of this research is to minimize the drug and tumor concentrations while maintaining normal cell concentrations above a safe threshold.

The optimal control model was developed by using Hamiltonian equation and determining the regularity state constraints and boundary control. The model was derived from cancer chemotherapy model results to similar outcomes for patient A and patient B.

Furthermore, we confirmed that the numerical results remained constant across several parameter settings within the identical model, hence enhancing the dependability of our discoveries. The consistency of this method enhances its practical applicability in the domain of cancer treatment.

The findings of this study highlight the capacity of optimal control techniques to address intricate biological systems such as cancer chemotherapy models. Nevertheless, additional investigation is required to authenticate these techniques across a broader spectrum of chemotherapeutic models and clinical scenarios.

Our research on optimizing chemotherapy medication administration has the potential to improve treatment outcomes and enhance the quality of life for cancer patients. Subsequent research can further investigate advanced control strategies and expand the use of optimal control techniques in personalized medicine approaches.

In summary, this study offers useful insights into the efficacy and suitability of

optimal control in cancer chemotherapy, which can lead to further progress in optimizing therapeutic treatments for improved patient health.

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