ADVANCING PERSONALISED CANCER TREATMENT: INTEGRATING OPTIMAL CONTROL WITH EVOLUTIONARY ALGORITHMS FOR DRUG ADMINISTRATION

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DEPARTMENT OF ELECTRICAL ENGINEERING
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THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF BACHELOR OF ELECTRICAL ENGINEERING

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ADVANCING PERSONALISED CANCER TREATMENT: INTERGRATING OPTIMAL CONTROL WITH EVOLUTIONARY ALGORITHMS FOR DRUG ADMINISTRATION.

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. Evolutionary Algorithm is then applied to solve the optimization of multi-objective problem by using Non-dominated Sorting Genetic Algorithm (NSGA-II) to get the best solution. 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.

Keywords: Cancer treatment, Optimal control, Evolutionary Algorithms, Drug administration.

MEMAJUKAN RAWATAN KANSER PERIBADI: MENGINTEGRASIKAN KAWALAN OPTIMAL DENGAN ALGORITMA EVOLUSI UNTUK PENTADBIRAN UBAT.

ABSTRAK

Kajian ini bertujuan untuk memajukan rawatan kanser yang dipersonalisasi dengan mengintegrasikan teknik kawalan optimal dengan algoritma evolusi untuk pentadbiran ubat. Objektif utama penyelidikan ini adalah untuk meminimumkan pertumbuhan tumor dan mengurangkan kerosakan kepada sel normal melalui kemoterapi yang dipersonalisasi untuk dua pesakit, Pesakit A dan Pesakit B, setiap satu dengan parameter dan keadaan awal yang berbeza. Metodologi yang digunakan dalam kajian ini melibatkan penggunaan teknik diskritisasi dan pemrograman tak linear, yang disokong oleh Bahasa Pengaturcaraan Model Terapan (AMPL) yang disambungkan dengan penyelesaian Pengoptimuman Titik Dalaman (IPOPT) untuk menentukan penyelesaian yang paling optimum untuk pentadbiran ubat. Algoritma Evolusi kemudian digunakan untuk menyelesaikan optimasi masalah pelbagai objektif dengan menggunakan Algoritma Genetik Pengisihan Tak-Dominasi (NSGA-II) untuk mendapatkan penyelesaian terbaik. Keputusan yang diperoleh daripada aplikasi penyelesaian kawalan optimal menunjukkan hasil yang mengagumkan untuk kedua-dua pesakit, seperti yang dibuktikan oleh pengukuran adaptabiliti melalui penilaian fungsi objektif dan pengurangan bilangan sel tumor. Kesimpulannya, teknik kawalan optimal secara konsisten memberikan hasil yang diinginkan dalam rawatan kanser yang dipersonalisasi. Kajian ini mempamerkan keberkesanan kawalan optimal dalam meningkatkan kecekapan dan keberkesanan rawatan kanser, mengurangkan keperluan ubat, dan meningkatkan kesihatan pesakit. Selain itu, ia meluaskan pemahaman kita tentang aplikasi praktikal pemodelan matematik dalam bidang penjagaan kesihatan.

Keywords: Rawatan kanser peribadi, Kawalan optimal, Algoritma evolusi, Pentadbiran ubat.

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LIST OF SYMBOLS AND ABBREVIATIONS

AMPL	:	Applied Modeling Programming Language
CMOOP	:	Constrained Multi-Objective Optimization Problems
EA	:	Evolutionary Algorithm
HV	:	Hypervolume
I	:	Immune cell
IPOPT	:	Interior-Point Optimization solver
M	:	Drug concentration in blood stream or tissue in tumor site
MODE	:	Multi-objective Optimization Differential Evolution
MOEA	:	Multi-Objective Evolutionary Algorithm
MOEA/D	:	Multi-Objective Evolutionary Algorithm based on Decomposition
MOOCP	:	Drug concentration in blood stream or tissue in tumor site
N	:	Normal cell
NLP	:	Non-linear programming
NSGA-II	:	Non-dominated Sorting Genetic Algorithm-II
NSGA-III	:	Non-dominated Sorting Genetic Algorithm-III
OCPs	:	Optimal Control Problems
PMP	:	Pontryagin Maximum Principle
pymoo	:	Multi-Objective Optimization in Python
T	:	Tumor cell
u	:	Drug dose administered

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 Introduction

Cancer, an affliction marked by unregulated cellular proliferation, continues to be a prominent contributor to global mortality. Nearly 10 million deaths worldwide are caused by cancer (World Health Organization, 2020). Personalized treatment options are required to successfully target the unique characteristics of individual patients due to the complexity and variety of cancer. Medical research progress has resulted in the emergence of several therapeutic methods, including surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy. Although these methods have demonstrated encouraging outcomes, the task of enhancing their efficacy for individual patients remains a considerable obstacle.

Scientific research has been concentrating more and more on using computational methods and mathematical models in cancer treatment in recent years. These mathematical models offer a theoretical framework for comprehending the dynamics of tumour growth, reaction to treatment, and the interplay between cancer cells and the immune system. Scientists strive to enhance the accuracy and individualization of treatment techniques in cancer research by integrating mathematical modelling.

The aim of this Final Year Project (FYP) is to enhance individualised treatment for cancer patients by employing optimum control and evolutionary algorithms. Our objective is to create an efficient control model utilising the mathematical models put forth by (dePillis and Radunskaya, 2003), specifically designed for two distinct categories of cancer patients. The objective for this research is to enhance the likelihood of good outcomes for individual patients by combining optimal control theory with evolutionary algorithms to optimise treatment methods.

The rationale behind this FYP rests in the desire to increase cancer treatment effectiveness by adapting medicines to the unique characteristics of each patient. Presently, therapy selections frequently rely on broad recommendations rather than individualised considerations, leading to less than optimal outcomes for numerous individuals. Through the utilisation of mathematical modelling, optimal control theory, and evolutionary algorithms, we may determine treatment protocols that are tailored to individual patients, aiming to maximise the effectiveness of therapy while minimising any adverse effects.

The scientific research pertaining to this Final Year Project (FYP) is based on the investigation of mathematical approaches for cancer treatment. Mathematical models offer a numerical depiction of the intricate dynamics occurring within a tumour and its environs. These models incorporate variables such as cell proliferation, apoptosis, angiogenesis, and immune response, enabling researchers to simulate and forecast the behaviour of cancer cells in relation to various treatment regimens.

Optimal control theory is a valuable tool in this situation, as it allows for the determination of treatment plans that maximise desired outcomes. By framing the situation as an optimal control problem, we may precisely establish the objective function, constraints, and control variables linked to the treatment process in a mathematical manner. The evolutionary algorithm, a computational optimisation technique inspired by natural selection, enhances optimal control theory by effectively exploring the vast solution space to find the most optimal treatment procedures.

This FYP will utilise the (dePillis and Radunskaya, 2003) cancer mathematical model, which offers a thorough depiction of tumour growth and the immune response. The model integrates essential biological components and their interconnections, enabling a more accurate simulation of the tumor's response to different treatment settings. We will utilise

optimal control theory and an evolutionary algorithm to include this model and develop personalised treatment strategies for two distinct cancer kinds.

The optimisation method will take into account multiple objectives, including reducing tumour size and extending patient survival. By combining optimal control theory and the evolutionary algorithm, we aim to find treatment plans that effectively meet these goals, taking into consideration specific patient characteristics, such as tumour stage, genetic factors, and overall health.

This research endeavours to overcome the shortcomings of present cancer therapies by creating individualised treatment regimens. These therapies generally employ standardised methods that may not completely consider the distinct attributes of each patient's disease. Mathematical modelling and computer optimisation approaches provide a methodical examination of the therapy options, leading to the discovery of customised best treatments for particular patients.

Moreover, this Final Year Project (FYP) makes a valuable contribution to the wider domain of mathematical oncology. This subject aims to utilise mathematical and computational techniques to acquire a deeper understanding of cancer biology and enhance the effectiveness of cancer treatments. By combining mathematical models with clinical data, we can improve our comprehension of the fundamental mechanisms that influence cancer growth and how it responds to treatment. Our aim is to make a valuable contribution to the expanding field of cancer research by developing more accurate and individualised cancer treatment plans.

This Final Year Project (FYP) aims to enhance personalised therapy for patients with cancer by employing the theory of optimal control and evolutionary algorithms. The goal is to improve the effectiveness of cancer treatments and reduce side effects by using

mathematical modelling and computational optimisation approaches to optimise treatment procedures for each patient. With this research, our aim is to make a valuable contribution to the expanding field of mathematical oncology and establish a foundation for the development of more accurate and individualised approaches to cancer treatment. The objective is to enhance treatment outcomes and, in turn, cancer patients' quality of life by customising care to each patient's unique characteristics.

1.2 Objective

- Apply optimal control theory to determine the optimal scheduling, dosing, and sequencing of cancer therapies for each individual patient, with the goal of minimizing the tumor cell.
- Employ a hybrid approach combining optimal control theory and evolutionary algorithms to systematically explore the complex solution space and identify the most effective personalized treatment strategies that can minimize both tumor cell and drug concentration in the blood for each cancer patient.
- Enhance the efficiency and effectiveness of cancer treatment, reduce negative side effects by minimizing tumor cell and drug concentrations in the tumor site and bloodstream respectively, and improve personalized cancer therapy by developing an integrated framework that applies both optimal control and the hybrid optimization method to tailor comprehensive treatment plans for individual patients.

1.3 Problem Statement

Current cancer treatments frequently fail to provide the critical need for tailored and individualized care. Existing treatment regimens are generally based on broad guidelines and recommendations that fail to take into account each patient's specific traits and

circumstances. This standardized approach to cancer therapy typically results in poor outcomes because people respond differently to different treatment modalities based on their unique genetic profiles, illness stages, overall health state, and other individual characteristics.

Cancer treatment lacks customization, which has a negative impact on patient outcomes. Standardized treatment approaches, while useful to some extent, frequently fail to address the unique subtleties and complexities of each patient's condition. As a result, many cancer patients have inadequate treatment efficacy, which can lead to increased side effects and a lower quality of life.

This research effort seeks to solve this essential issue by creating advanced mathematical models and computational optimization approaches that can tailor treatment strategies to specific cancer patients. Using the ideas of optimal control theory and evolutionary algorithms, the project aims to provide a complete framework for identifying the most successful and individualized treatment solutions for each patient.

1.4 Scope of Research

Several important issues in the field of personalised cancer therapy are covered by the scope of this study. Initially, the research will entail the creation and improvement of mathematical models that precisely represent the intricate dynamics of tumour growth, response to treatment, and the interplay between tumour cells and the immune system.

Secondly, the research will utilise optimal control theory to structure the treatment planning issue as an optimization challenge. Optimal control theory enables the creation of treatment plans that maximise desired outcomes, such as reducing tumour growth and extending patient survival, by explicitly defining objective functions, constraints, and control variables associated with the treatment process. This method will facilitate the

creation of customised treatment regimens that maximise the effectiveness of therapy for each patient.

Furthermore, the research will employ evolutionary algorithms as computer optimisation methods to systematically investigate the extensive range of possible solutions and determine the most optimal treatment protocols for individual patients. These algorithms, which are influenced by natural selection, will effectively explore treatment regimens that satisfy various objectives, taking into account the distinct attributes of each patient. Integrating evolutionary algorithms with optimal control theory will improve the accuracy and customisation of treatment techniques.

Additionally, the study will prioritise two distinct groups of cancer patients in order to devise individualised therapeutic approaches that are precisely adapted to their requirements. The mathematical models and optimisation methods will be improved to develop precise treatment regimens that cater to the unique characteristics and needs of different cancer kinds. This approach recognises the diversity of cancer and highlights the significance of individualised treatment.

The project's ultimate goal is to optimise treatment results and elevate the well-being of cancer patients by personalising therapy to their unique qualities. The research aims to surpass the constraints of present standardised treatment approaches by incorporating mathematical modelling, optimal control theory, and evolutionary algorithms. The primary objective is to create precise and customised treatment strategies that optimise the effectiveness of therapy while minimising negative consequences. This contributes to the growing field of mathematical oncology and promotes the advancement of personalised methods for treating cancer.

The scope does not explicitly encompass the consideration of the toxicity level of the delivered dose as a parameter in treatment optimisation. The research largely focuses on the development of mathematical models, optimal control theory, and evolutionary algorithms to customise treatment regimens based on criteria such as tumour features and general health. The objective is to enhance treatment effectiveness and minimise adverse effects. Nevertheless, this study does not encompass the detailed examination of toxicity levels in dose optimisation.

CHAPTER 2: LITERATURE REVIEW

2.1 Cancer Model

(dePillis and Radunskaya, 2001) conducted research with the objective of determining the most effective chemotherapy schedule. They employed a cost function to minimise the number of tumour cells remaining at the conclusion of the recovery phase. Nevertheless, their suggested regimen displayed notable variations in the population of tumour cells throughout the duration of the treatment. In order to overcome this constraint and minimise the fluctuation of the tumour cell population, (dePillis and Radunskaya, 2003) conducted more study and proposed an enhanced cost function. The revised cost function encompasses multiple variables, including the amalgamation of tumour cell population at the end time, the cumulative tumour cell population during the treatment duration, and the highest tumour population seen during treatment. Building upon this work, (dePillis et al., 2007) offered an updated and augmented mathematical model of cancer. In addition, they investigated the most effective approach of providing medicine by integrating quadratic and linear controls, considering limits associated with immune cell numbers. The application of singular control was explored to address the linear control optimization problem in chemotherapy treatment. The objective of chemotherapy is to minimize the adverse effects induced by the treatment while achieving significant reduction in tumor size and efficient medication delivery. The described model includes immune cells, lymphocytes, medicines, and tumor cells. Furthermore, the model characterizes side effects as a direct influence on Circulating Lymphocytes. In this article, the optimal control for both linear and quadratic controllers is further explained using the Pontryagin Maximum/Minimum Principle. In addition, when addressing the optimal control problem, the single arc, higher-order differential equations, and first-order condition were considered.

(Rostami and Jafarpour, 2015) provide a mathematical model for cancer therapy that takes into account tumor proliferation, immunological reaction, and treatment outcomes. The authors utilize optimal control theory to ascertain the most advantageous drug dosage and treatment plan that promotes tumor response while minimising the negative consequences of therapy. The study offers valuable insights into the utilization of optimal control methods for developing tailored treatment plans for cancer patients.

(Swaminathan and Venkataraman, 2012) present a mathematical model to describe the process of tumor growth and the subsequent response to treatment. The model integrates cell proliferation, mortality rates, and the impact of treatment on cancer cells. The authors employ optimal control theory to adjust the dosage and duration of chemotherapy in order to enhance the response of the tumor while reducing damage. The study showcases the capacity of optimum control strategies in customizing chemotherapy regimens for specific patients and enhancing treatment outcomes.

2.2 Pontryagin Maximum Principle, Singular and Bang Control

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.

2.3 Optimal Control in Cancer Treatment

(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.

(Babaei and Salamci, 2015) present a novel Model Reference Adaptive Control (MRAC) strategy to address the nonlinear regulation challenge in cancer treatment through chemotherapy. They address the task of identifying the most effective methods of administering drugs to cancer patients, even without any prior understanding of the

complex model structure and characteristics. The authors propose a solution for individualized medicine delivery by integrating the State-Dependent Riccati Equation (SDRE) technique with Model Reference Adaptive Control (MRAC). The authors emphasize that current methods for eliminating malignant cells in nonlinear tumor growth models generally necessitate knowledge of the nonlinear model parameters, which is typically inaccessible to clinicians in practical settings. In order to address this constraint, they propose utilizing the SDRE technique to establish the drug delivery scenario for a reference patient with a defined mathematical model and parameters. Subsequently, utilizing their suggested methodology, they modify the medication administration scenario for a different cancer patient, even in the absence of knowledge regarding the nonlinear model structure and parameters. The authors highlight the usefulness of their method in stabilizing the nonlinear model of tumor growth and demonstrate its success in eliminating tumor masses of varying sizes in different patients using numerical simulations. In summary, their Model Reference Adaptive Control (MRAC) technique shows great potential for delivering individualized medication delivery in cancer therapy. This research is referred to for the purpose of optimizing therapy for two distinct patient.

(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.

2.4 Optimal Control Chemotherapy with Evolutionary Algorithm

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.

NSGA-II (Non-dominated Sorting Genetic Algorithm-II) is a popular multi-objective evolutionary algorithm that has been extensively researched and utilized in the literature. It was introduced by (Deb et al., 2002), NSGA-II overcomes the limitations of the original NSGA algorithm by employing an efficient non-dominated sorting approach, a crowding distance metric to retain variety, and an elitist selection strategy to conserve the best solutions. These features enable NSGA-II to converge on the genuine Pareto-optimal front while still providing a wide set of options. NSGA-II has been praised for its simplicity, effectiveness, and ability to handle a wide range of multi-objective optimization problems across various domains, including engineering design (Deb & Jain, 2014) and scheduling (Konak et al., 2006).

(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.

CHAPTER 3: METHODOLOGY

The methodology is executed in accordance with the project's objectives. To fulfill both objectives, an optimal model was developed from cancer chemotherapy model propose by (dePillis and Radunskaya, 2003).

3.1 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:

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

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:

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

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:

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

$$\dot{T}(t) = r_1 T(t)\big(1 - b_2 T(t)\big) - c_2 I(t) T(t) - c_3 T(t) N(t) - a_2\big(1 - \exp\big(-M(t)\big)\big)T(t),$$

$$\dot{I}(t) = s + \frac{\rho I(t) T(t)}{\alpha + T(t)} - c_1 I(t) T(t) - d_1 I(t) - a_1\big(1 - \exp\big(-M(t)\big)\big)I(t),$$

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

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 3.1: 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	$cell^{-1}$	$b_1^{-1} \leq b_2^{-1}$
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 3.1 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 3.2: 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 3.3: 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

3.2 Pontryagin Maximum Principle (PMP).

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.

3.3 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:

$$N(t) \geq 0.74$$

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:

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

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

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

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 $\ddot{N} = 0$,

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

3.4 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 the relationship of the dynamic system. The Hamiltonian equation is used to analyze and optimize 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 Hamiltonian 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:

$$H = T(t) + \lambda_1(r_2N(t)\big(1 - b_2N(t)\big) - c_4T(t)N(t) - a_3\big(1 - \exp\big(-M(t)\big)\big)N(t))$$
$$+ \lambda_2(r_1T(t)\big(1 - b_2T(t)\big) - c_2I(t)T(t) - c_3T(t)N(t)$$
$$- a_2\big(1 - \exp\big(-M(t)\big)\big)T(t)) + \lambda_3(s + \frac{\rho I(t)T(t)}{\alpha + T(t)} - c_1I(t)T(t)$$
$$- d_1I(t) - a_1\big(1 - \exp\big(-M(t)\big)\big)I(t)) + \lambda_4(u(t) - d_2M(t))$$

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial N(t)} = \lambda_1(r_2\big(1 - b_2N(t)\big) - c_4T(t) - a_3\big(1 - \exp\big(-M(t)\big)\big)) - \lambda_2c_3T(t)$$

$$\dot{\lambda}_2 = 1 - \frac{\partial H}{\partial T(t)}$$
$$= -\lambda_1c_4N(t) + \lambda_2(r_1\big(1 - b_2T(t)\big) - c_2I(t) - c_3N(t)$$
$$- a_2\big(1 - \exp\big(-M(t)\big)\big)T(t)) - \lambda_3c_1I(t)$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial I(t)} = -\lambda_2c_2T(t) + \lambda_3(s + \frac{\rho I(t)T(t)}{\alpha + T(t)} - c_1I(t)T(t) - d_1I(t)$$
$$- a_1\big(1 - \exp\big(-M(t)\big)\big))$$

$$\dot{\lambda}_4 = -\frac{\partial H}{\partial M(t)} = -\lambda_1a_3\exp(-M)\,N(t) - \lambda_2a_2\big(\exp\big(-M(t)\big)\big)T(t)$$
$$- \lambda_3a_1\big(\exp\big(-M(t)\big)\big)I(t) - d_2$$

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

3.5 Evolutionary Algorithm in Optimization of Multiple Objective Function.

Multi-objective optimization is the simultaneous optimization of two or more conflicting objectives, yielding a group of Pareto-optimal solutions that represent the optimum trade-offs between the objectives, rather than a single optimal solution. In a multi-objective problem, the objectives are frequently at odds with one another; that is, achieving one goal could cause another to deteriorate. The solutions are assessed according to a variety of objectives inside a multi-dimensional objective space. Scalarization techniques that reduce the multi-objective problem to a single-objective problem, preference-based methods that take the decision-maker's priorities into account during the optimization process, and evolutionary algorithms such as NSGA-II and Constrained Multi-Objective Optimization Problem (CMOOP), which can effectively explore the search space and find a diverse set of Pareto-optimal solutions, are common approaches for solving multi-objective optimization problems. For this CMOOP problem there are two objective functions with a constraint. The aim is to minimize tumor cell, T, and drug concentration in blood stream, M as follows:

$$\min \int T \, dt$$

$$\min \int M \, dt$$

With states constraint,

$$N \geq 0.74$$

The theory of evolutionary algorithms is based on natural selection and evolution principles, in which a population of candidate solutions evolves over successive generations to find the optimal or near-optimal solution to a given issue. The population-based structure, which evaluates each solution in the population using a fitness function

to measure its quality, is the fundamental component of this methodology. Then, using genetic operators like crossover and mutation, which introduce variations and produce new offspring, the best solutions are chosen to "reproduce" and pass on their qualities to the following generation. This iterative process of selection, reproduction, and replacement continues until a satisfactory solution is found, mimicking the natural evolutionary process where the most suitable individuals thrive and pass on their genetic material to future generations. The newly generated offspring solutions replace the less fit individuals in the population.

To address multi-objective optimization problems in optimal control theory, a common approach is to use a weighting scheme. This involves converting the multiple, often conflicting, objectives into a single objective function by assigning weights to each objective. The weighted sum of the objectives is then optimized, allowing the multi-objective problem to be treated as a single-objective optimization problem. This weighting scheme provides a way to balance the trade-offs between the different objectives and find a compromise solution that satisfies the decision-maker's preferences. By transforming the multi-objective problem into a single-objective formulation, the problem can be more readily solved using established optimal control techniques, such as the Pontryagin's minimum principle or dynamic programming. The choice of the weighting factors is crucial in this process, as it directly influences the final solution and the balance between the competing objectives.

$$\min K = w_1 \int T\, dt + w_2 \int M\, dt$$

$$\dot{K} = w_1 T + w_2 M$$

Where,

$$w_1 + w_2 = 1$$

A well-known multi-objective evolutionary method called NSGA-II finds a well-distributed set of Pareto-optimal solutions by utilizing elitist selection, crowding distance, and non-dominated sorting. In order to preserve diversity, it divides the population into non-domination levels, favors solutions with greater crowding distances, and chooses the best solutions from both the parent and progeny populations to create the next generation. Standard genetic operators like crossover and mutation are used by NSGA-II to generate new solutions, which enables it to efficiently search the search space and find the best trade-offs between several objectives. Figure 3.1 shows the splitting front and selection of solution based on crowding distance.

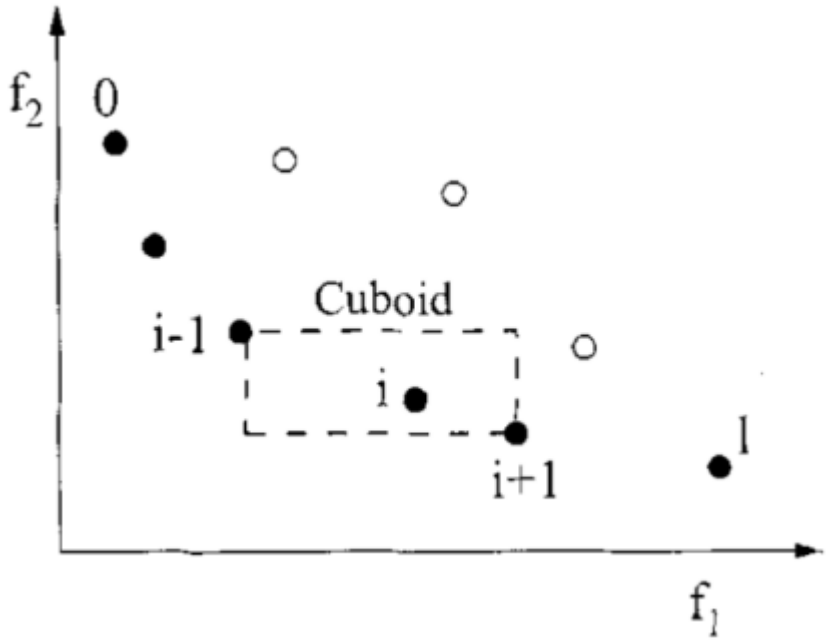

Figure 3.1: Selection of solution based on crowding distance in the splitting front.

3.6 Simulation Software.

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. All of the results can be plot and represent using matplotlib libraries and pandas.

For the Evolutionary Algorithm, Non-dominated Sorting Genetic Algorithm (NSGA-II) is applied to optimize the multiple-objective problem. NSGA-II the compliment with Eucledian distance and Hypervolume (HV) to obtain the best solution. Both Euclidean and HV can be obtain from pymoo libraries.

3.7 Simulation workflow

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. For Multi-Objective Optimization Problem, pymoo libraries can be utilize to run the NSGA-II algorithm. Euclidean distance and Hypervolume can be employed to get the best solution. The platform offers a Jupyter Notebook interface that enables users to generate and execute Python code cells, compose explanatory text, and present data visually. Simulation workflow can be presented as the Figure 3.2.

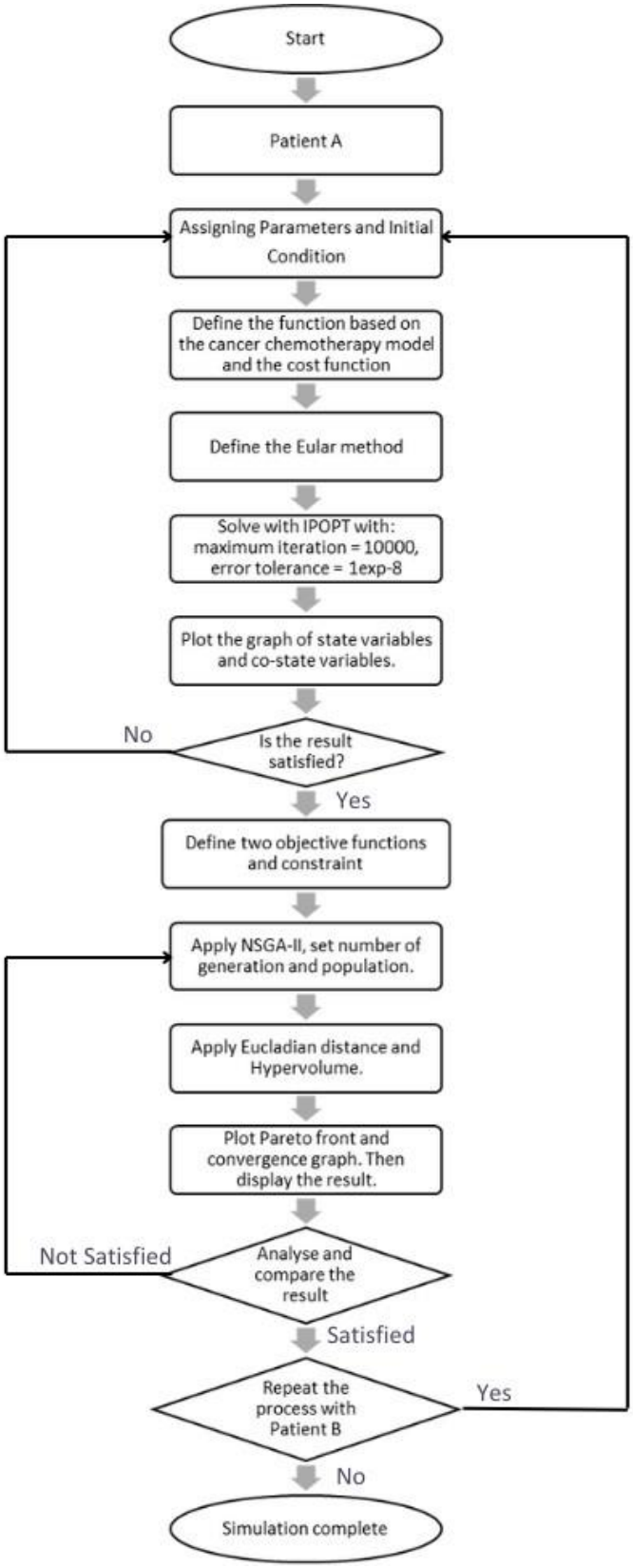

Figure 3.2: Workflow of simulation for patient A and B for optimal control with Evolutionary Algorithm.

CHAPTER 4: RESULT AND DISCUSSION

4.1 Results

The discretization techniques were implemented. A Mathematical 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.

The cancer chemotherapy model has a constraint that must be respected to minimize T and M. This means the optimization problem is a Constrained Multi-Objective Optimization Problem (CMOOP). To solve this type of problem, we can apply the necessary and sufficient optimality conditions. This allows us to find the optimal solution while taking the constraint into account. In other words, the cancer chemotherapy model has certain requirements or limits that need to be met. Because of this, the optimization process is more complex than a standard multi-objective optimization. We have to use specialized techniques, like applying optimality conditions, to find the best solution that satisfies the constraint. Non-dominated Sorting Genetic Algorithm (NSGA-II), one of Evolutionary Algorithm, is applied to both optimal-control to get the best solution for each patient. In the algorithm, w1, which is the weight, can be achieved for the best solution. The iteration has been done with 10 generation and 50 population for each generation. A Pareto Optimal Front can be obtained and the best solution can be decided with the influence of w1 and w2. In the optimal Pareto front graph, x-axis (F1) represents objective function 1, T, and y-axis(F2) represent objective function 2, M. A convergence graph can be plot to represents the progress of the optimization algorithm towards the true

Pareto optimal front over the course of the iterations or generations. The Hypervolume (HV) measures the volume of the region bounded by the Pareto front and a dominated reference point in the n-dimensional objective space, where n is the number of objectives. A higher HV value indicates a better set of non-dominated solutions, as it suggests the Pareto front has better diversity (spread of solutions) and better convergence (closeness to the true optimal Pareto front), which are desirable properties when optimizing the trade-offs in the cancer chemotherapy problem.

4.1.1 Result of Patient A

The results for the personalized chemotherapy for reference patient can be shown at Figure 4.1. Figure 4.1 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 4.1 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.

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 4.1, 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 patient A 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.

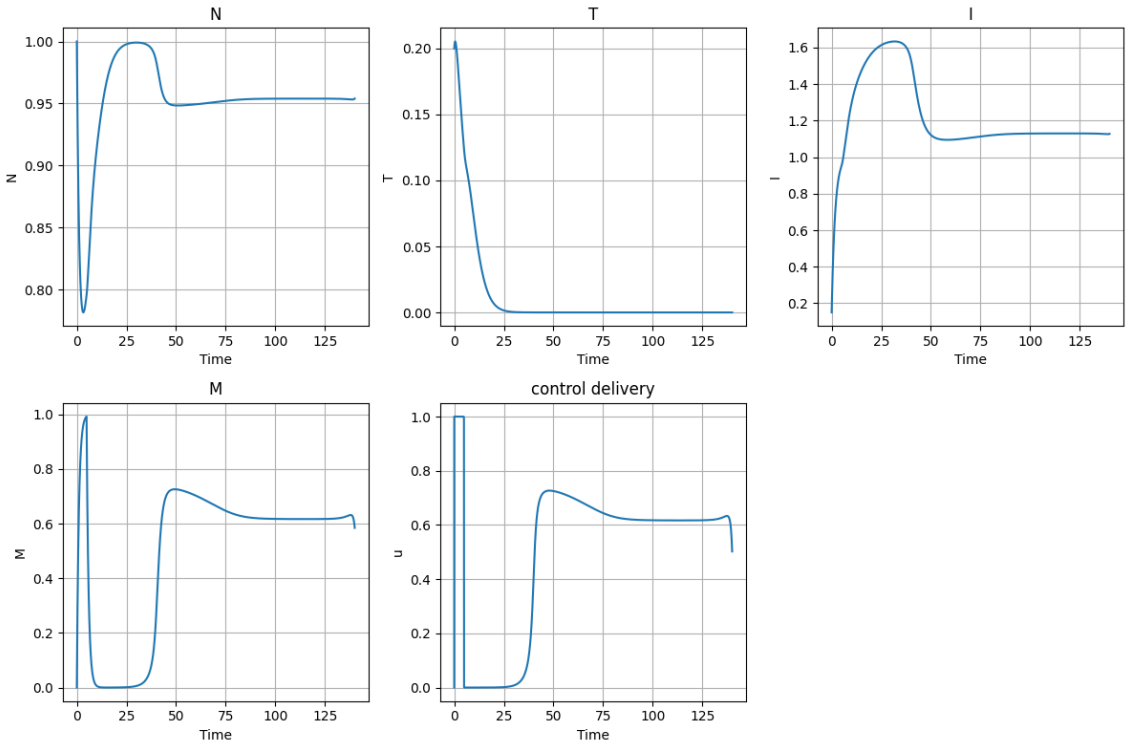

Figure 4.1: Optimal result for N, T, I, M and control variable, u, for patient A.

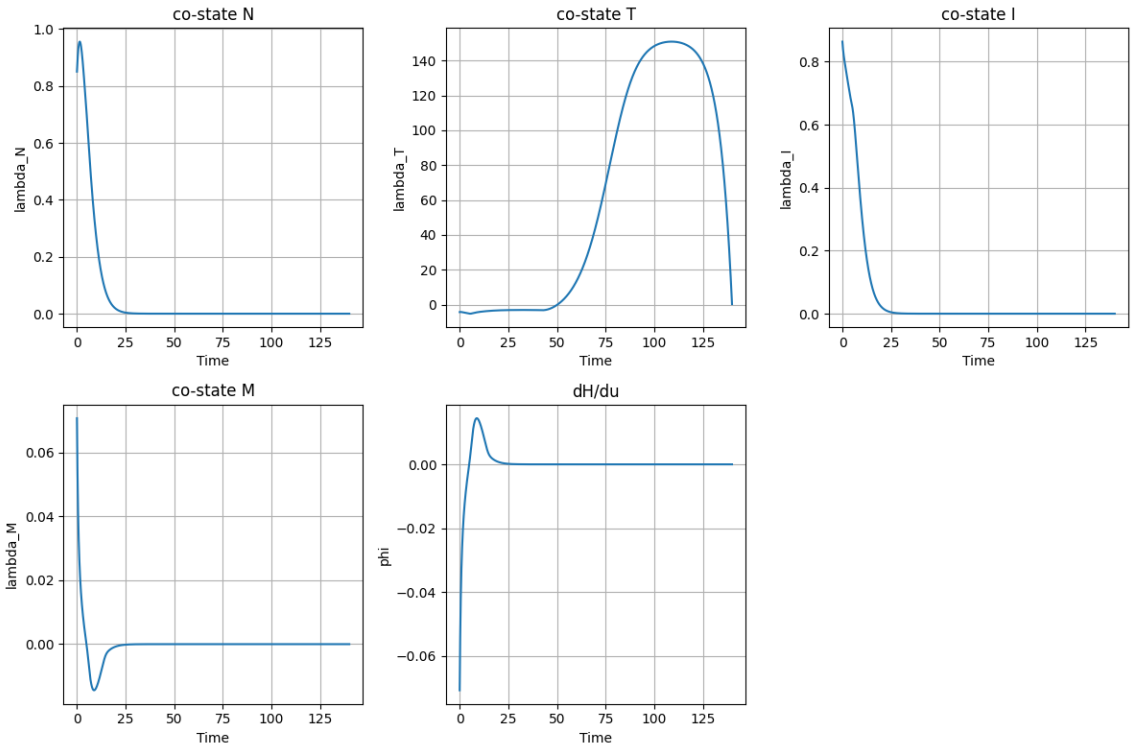

Figure 4.2: Co-state variables result with switching function $\frac{\partial H}{\partial u}$, for patient A.

In Figure 4.2, 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.

After applying NSGA-II algorithm with the parameters, Pareto Optimal Front is obtained as shown in figure 4.3. the Pareto front represents the set of non-dominated solutions. It defines the best trade-off between competing objectives. After applying Euclidean distance in to the Pareto front, the w1 is 0.9694580320684465 and w2 is 0.030541967931553504, to get the best solution at point (169.75999549, 108.08784255). The constraint violation values, -0.06197415, implies the violation of constraint in the solution but in a minor degree. The hypervolume of 17.736919219306643 provides a quantitative measure of the size and diversity of the Pareto front. This value tells us that the optimization algorithm was able to generate a relatively well-distributed set of Pareto optimal solutions that cover a substantial portion of the objective space.

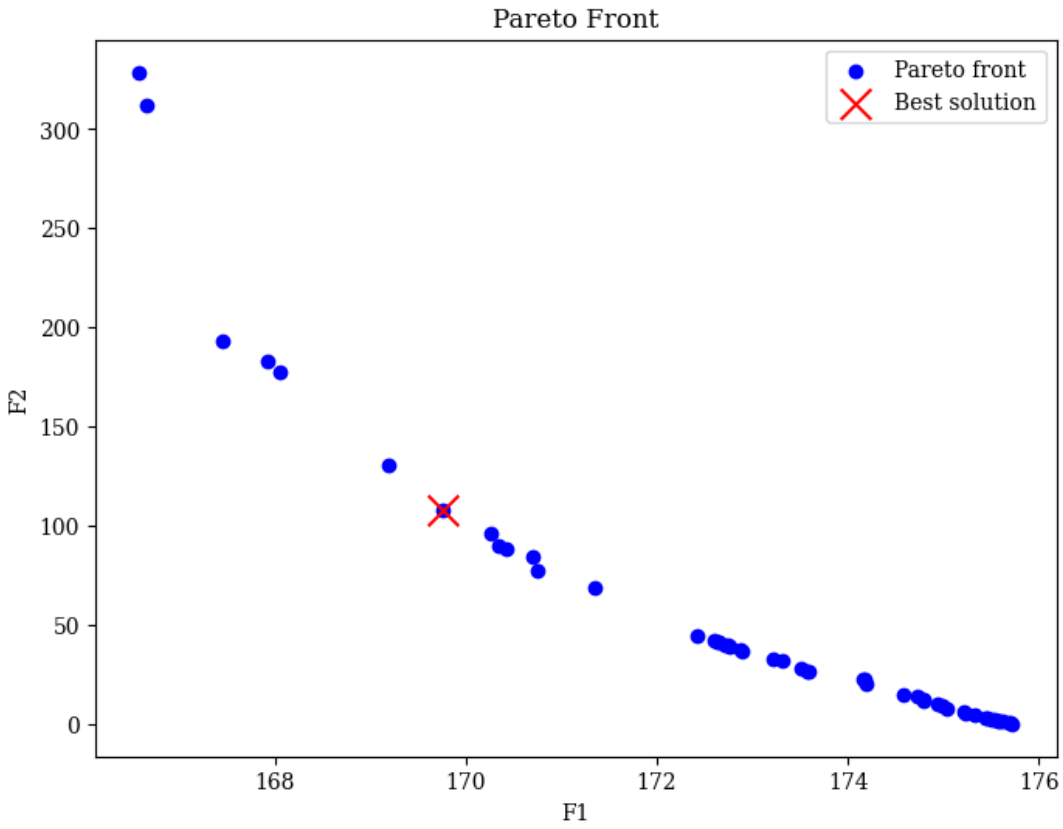

Figure 4.3: Optimal Pareto front with the best solution for patient A.

A convergence graph can be obtained which represent the progress of optimization algorithm as shown in figure 4.4. It shows that at the initial constant portion slightly above 0.007150, the optimization algorithm is not making any progress in improving the objective function value at start. The algorithm is struggling to find good initial solutions that can be refined. Start from 4th generation, it starts decreasing indicates the objective function value is improving as the algorithm progresses. The optimization is now moving in the right direction towards the optimal Pareto front. After 5th generation, the final constant region suggests the algorithm has converge to a steady state. This indicates the algorithm has likely reached the best solution.

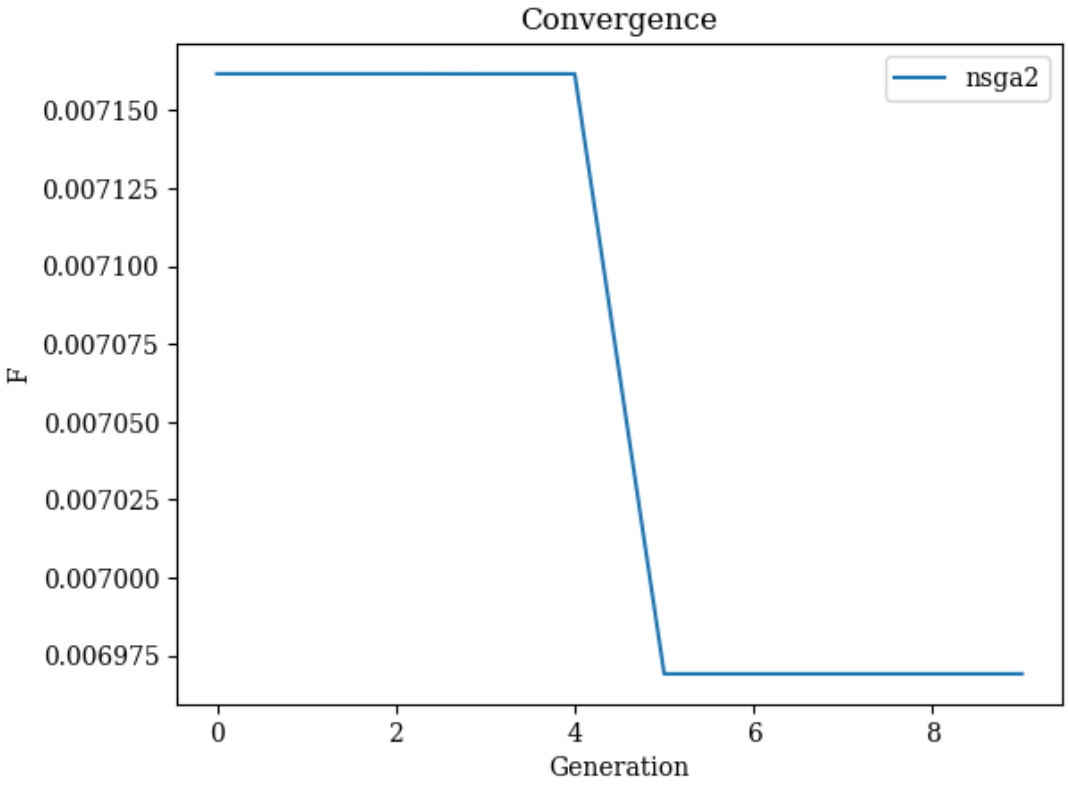

Figure 4.4: Convergence of algorithm for patient A.

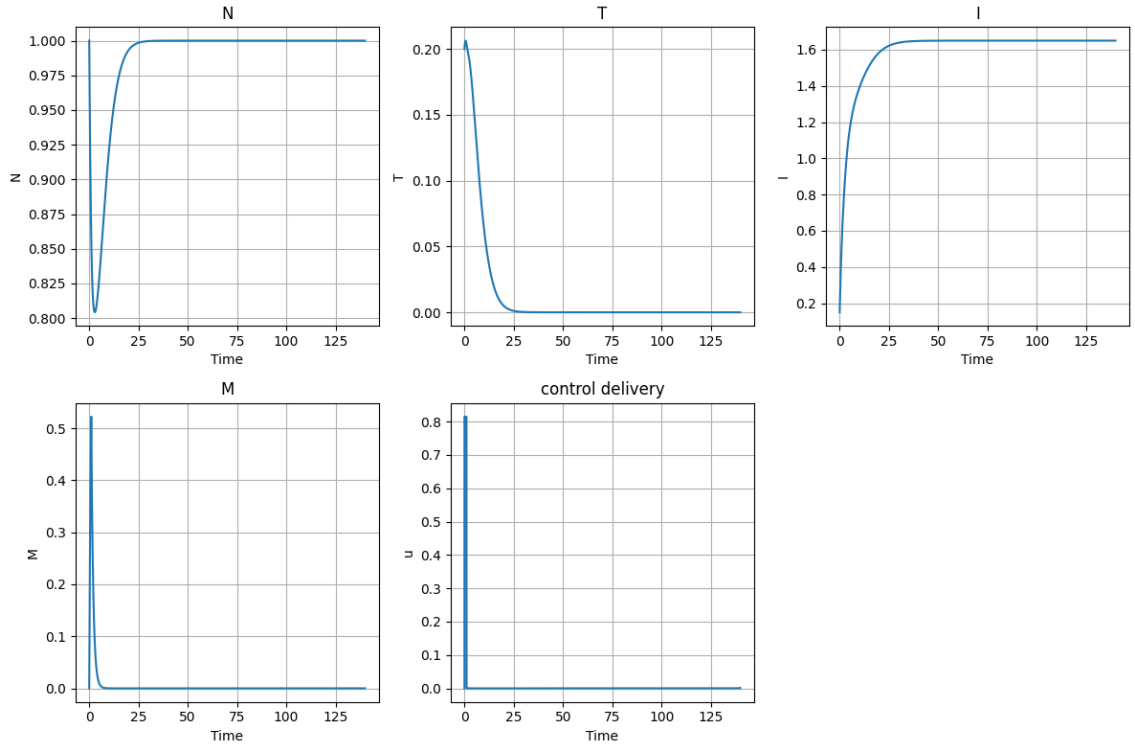

Figure 4.5: Optimal result for N, T, I, M and control variable, u, for patient A, after applying NSGA-II

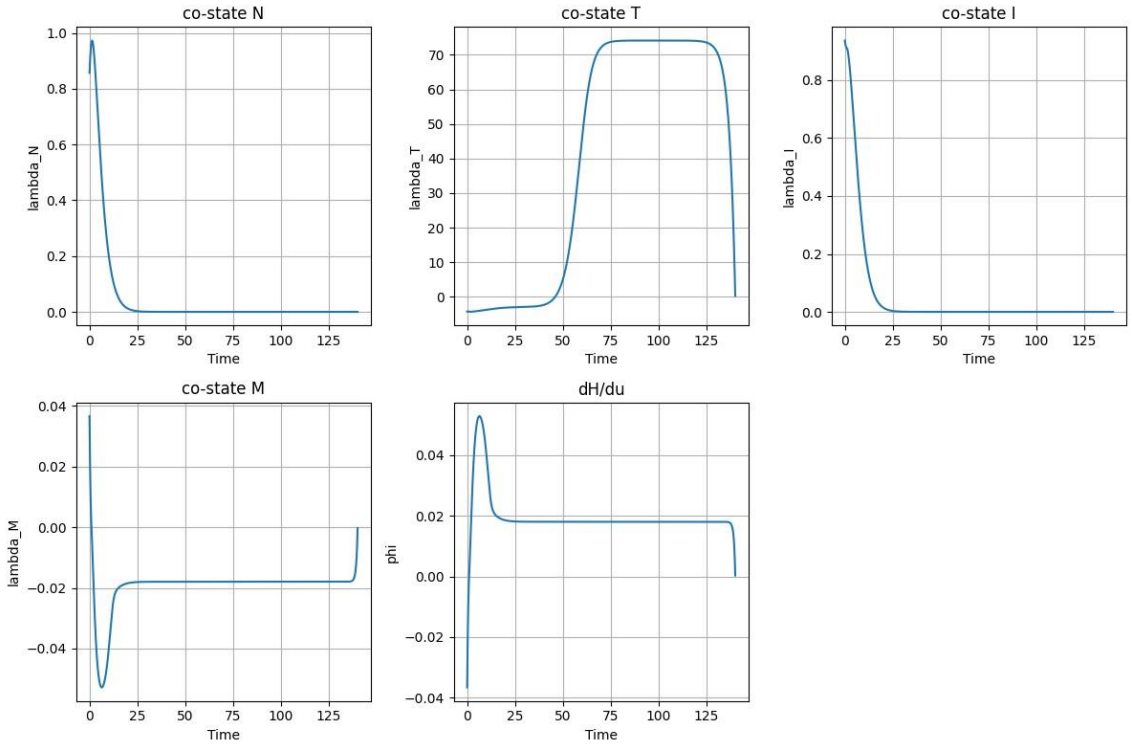

Figure 4.6: Co-state variables result with switching function ∂H/∂u, for patient A, after applying NSGA-II.

The result after apply NSGA-II can be shown in figure 4.5 and figure 4.6. In figure 4.5, it can be seen that normal cell, N is increasing from 0 to 1.0 in a very short time, from start to day 25th. Immune cell, I, is more than 1.6 after day 25th. Both N and I shows more consistent and faster result compare to previous result. Drug concentration in blood stream, M and control delivery, u shown different result compare to the previous result. M is slightly above 0.5 and u is above 0.8 at the start. Both M and u rapidly drop and become zero before day 25th. As for co-state variable result, it shows very small different compare to the previous result. Co-state M is dropping from start with the value of almost 0.04, to lower than -0.04 then increase to -0.02 at day 25th. It became constant until 140, which it became zero. The opposite reaction can be seen for switching function, $\frac{\partial H}{\partial u}$. The switching function becomes zero because the boundary of the drug concentration constraint is satisfied.

4.1.2 Result of Patient B

The results for the personalised chemotherapy for patient B can be shown at Figure 4.7. Figure 4.7 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 4.7 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 4.7 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 4.7, 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 patient B 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 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 chemotherapy treatment in preventing the development and survivability of cancer cells.

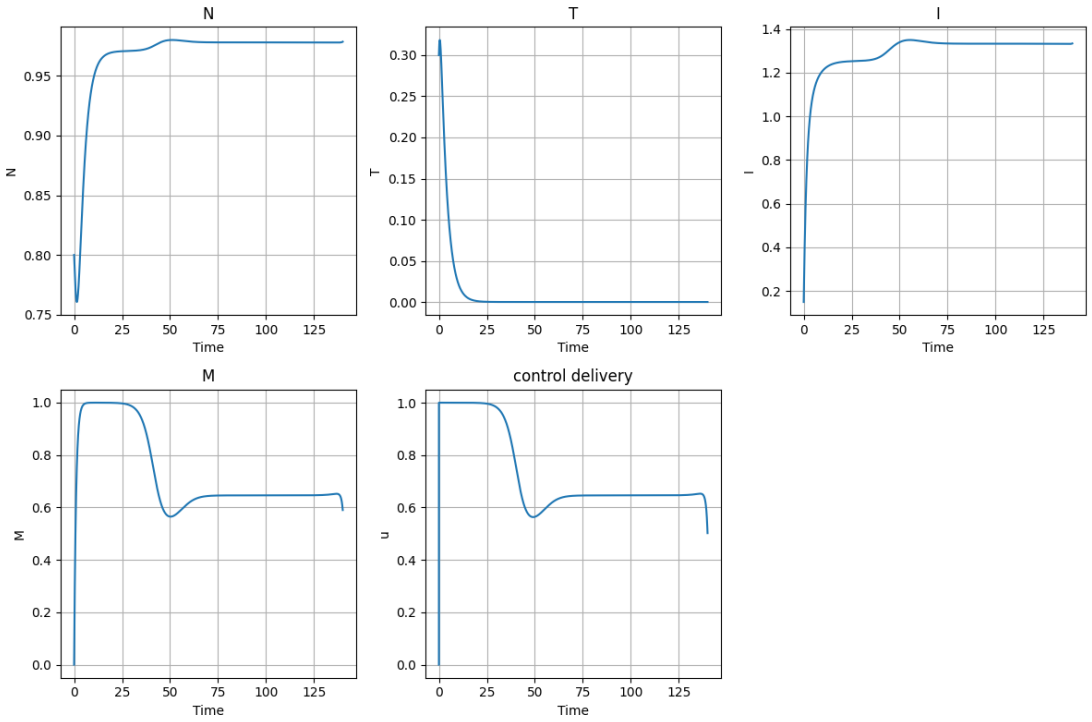

Figure 4.7: Optimal result for N, T, I, M and control variable, u, for patient B.

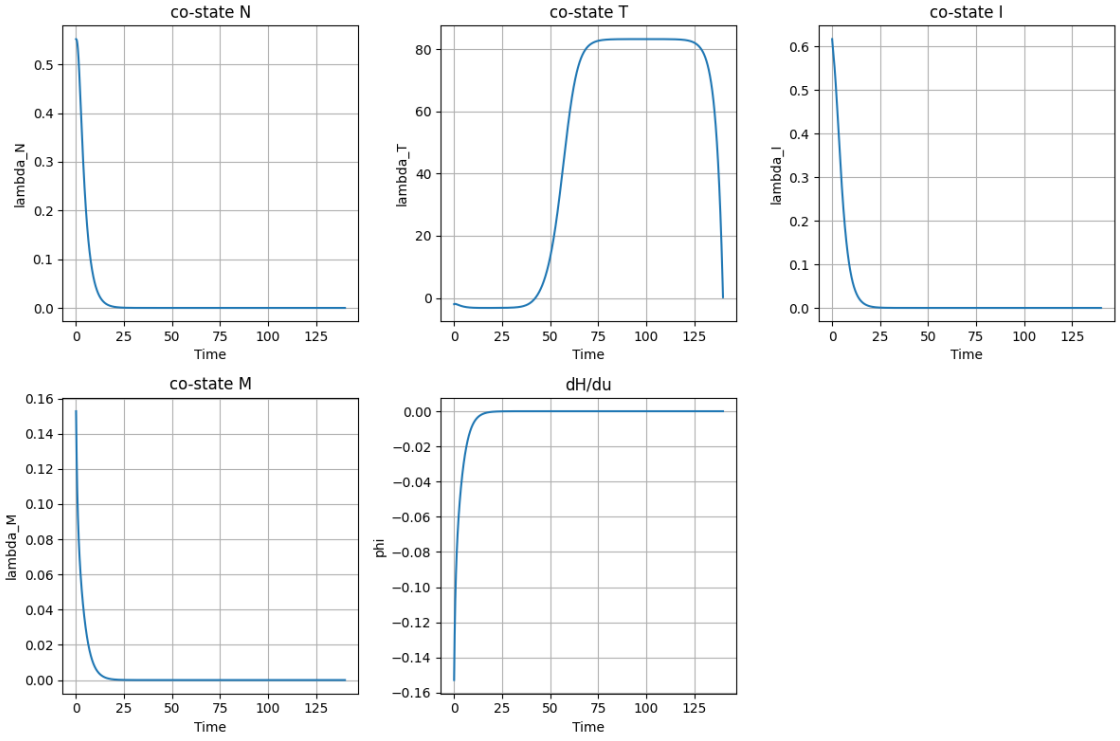

Figure 4.8: Co-state variables result with switching function ∂H/∂u, for patient B.

In Figure 4.8, 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.

After applying NSGA-II algorithm with the parameters, Pareto Optimal Front is obtained as shown in figure 4.9. the Pareto front represents the set of non-dominated solutions. It defines the best trade-off between competing objectives. After applying Euclidean distance in to the Pareto front, the w1 is 0.9694580320684465 and w2 is 0.030541967931553504, to get the best solution at point (169.75999549, 108.08784255). The constraint violation values, -0.06197415, implies the violation of constraint in the solution but in a minor degree. The hypervolume of 17.736919219306643 provides a quantitative measure of the size and diversity of the Pareto front. This value tells us that the optimization algorithm was able to generate a relatively well-distributed set of Pareto optimal solutions that cover a substantial portion of the objective space.

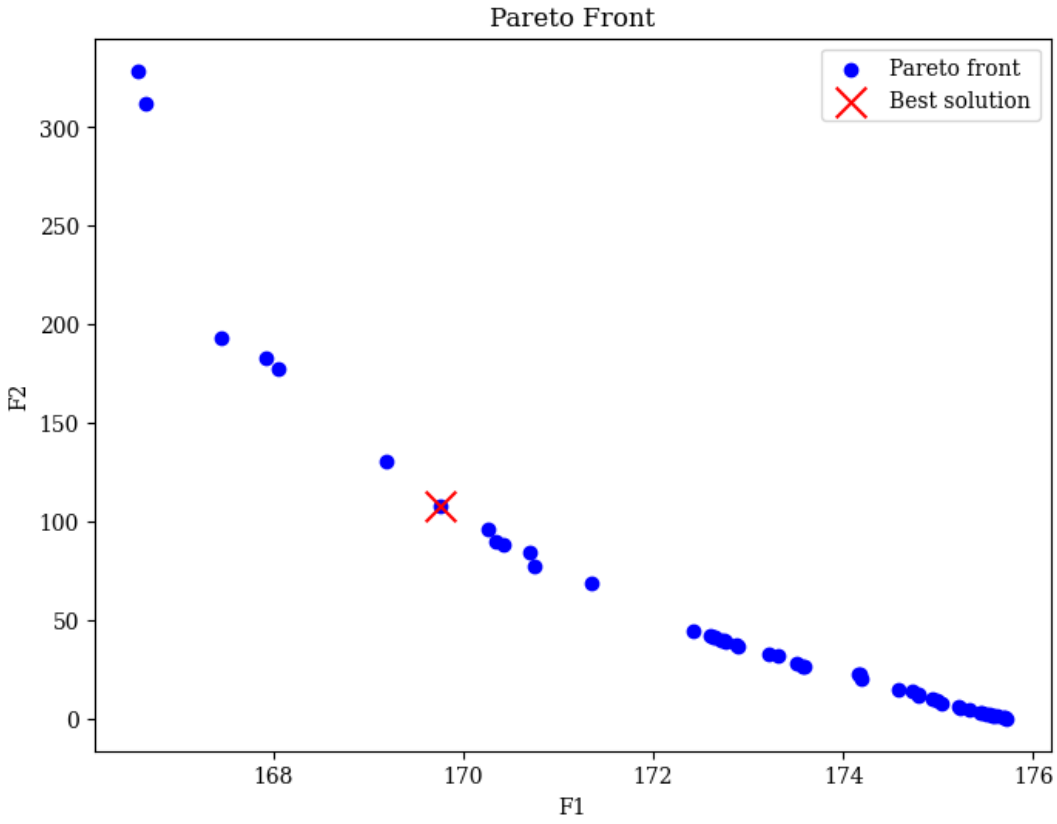

Figure 4.9: Optimal Pareto front with the best solution for patient B.

A convergence graph can be obtained which represent the progress of optimization algorithm as shown in figure 4.10. It shows that at the initial constant portion slightly above 0.00254, the optimization algorithm is not making any progress in improving the objective function value at start. The algorithm is struggling to find good initial solutions that can be refined. Start from 2nd generation, it starts decreasing indicates the objective function value is improving as the algorithm progresses. The optimization is now moving in the right direction towards the optimal Pareto front. It became constant at 3rd generation. From 4th generation to 6th generation it continue decrease. At 6th generation, the final constant region suggests the algorithm has converge to a steady state. This indicates the algorithm has likely reached the best solution.

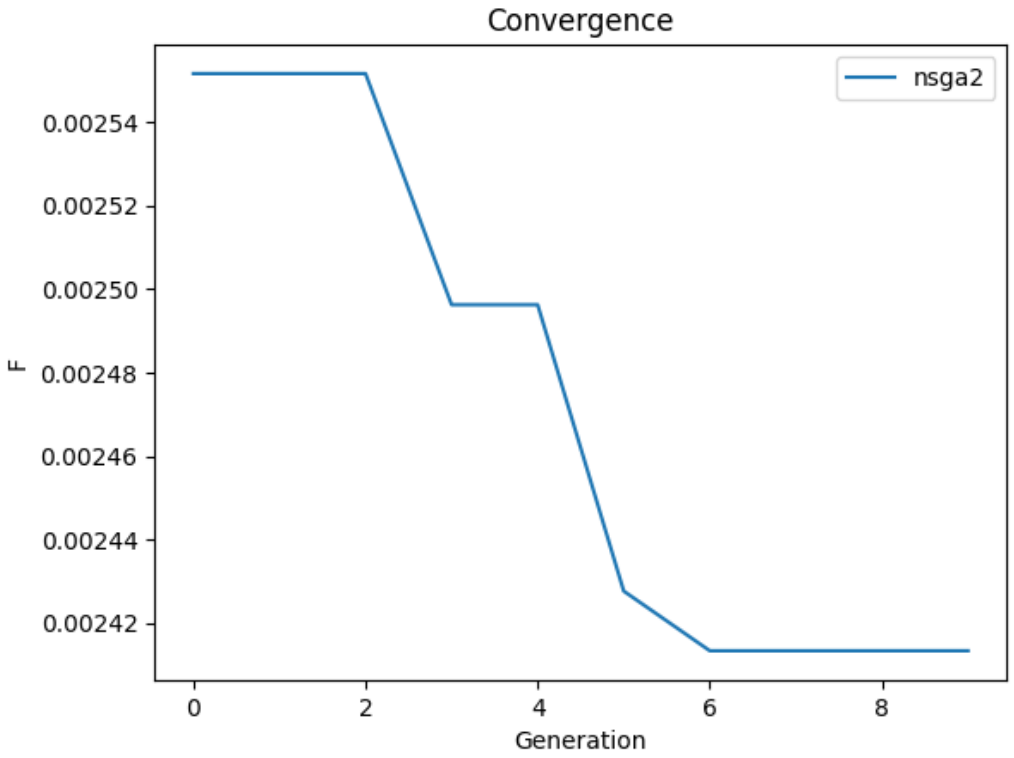

Figure 4.10: Optimal Pareto front with the best solution for patient B.

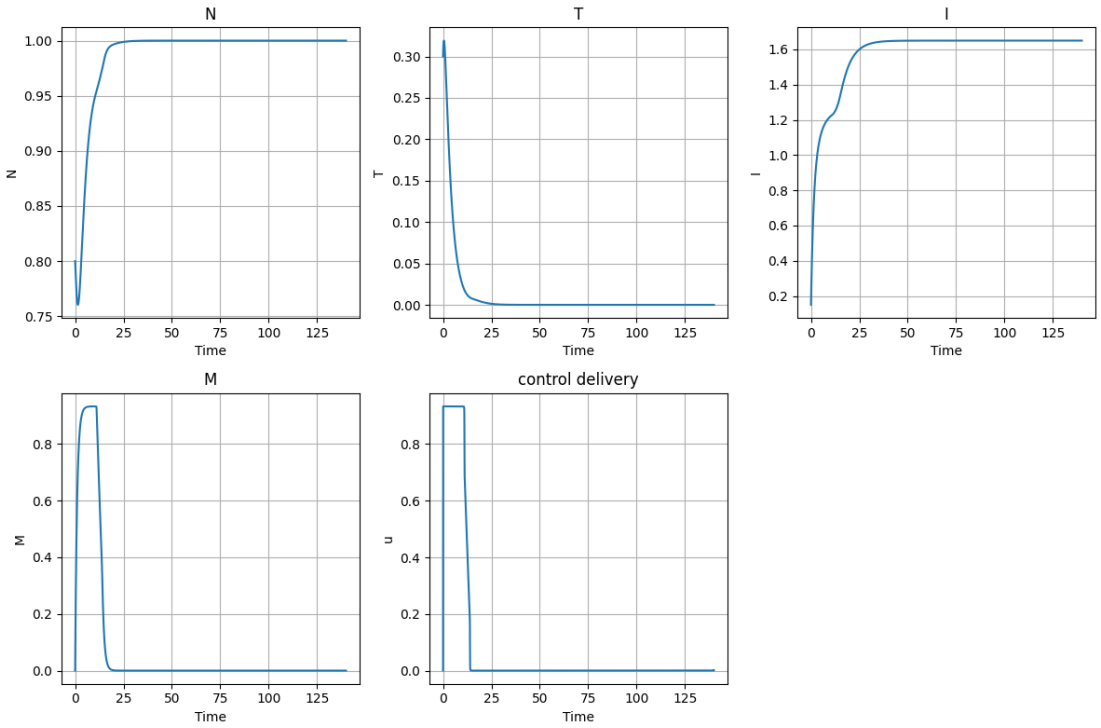

Figure 4.11: Optimal result for N, T, I, M and control variable, u, for patient B, after applying NSGA-II.

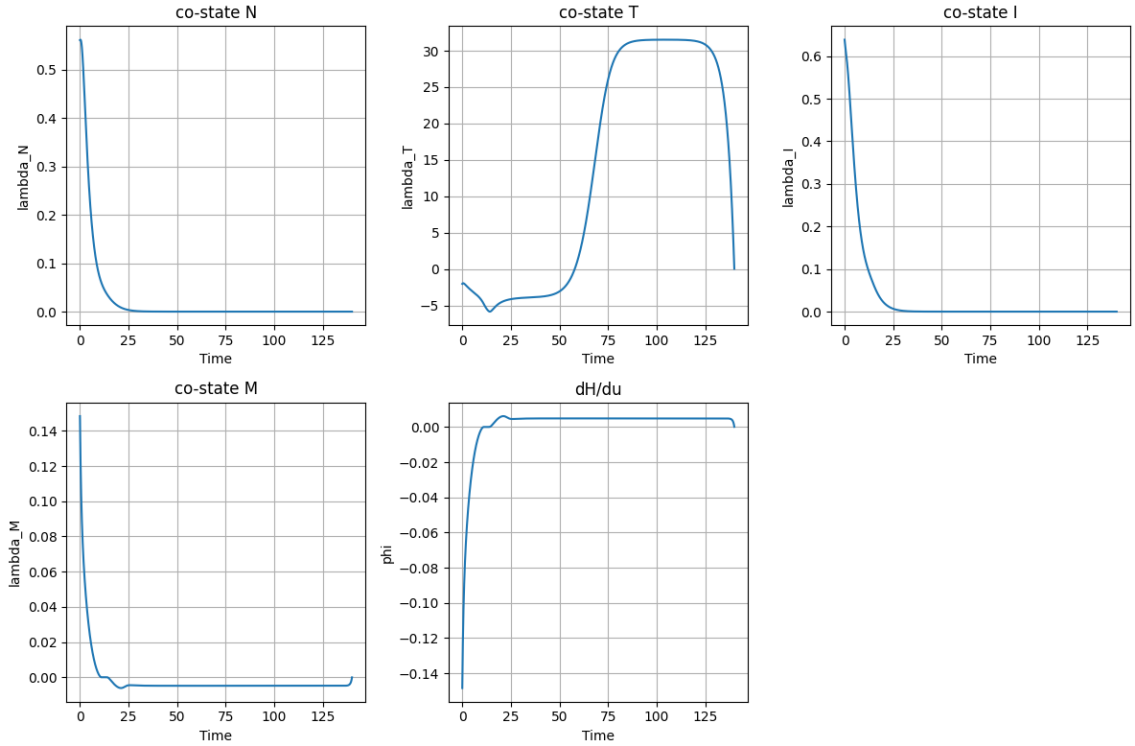

Figure 4.12: Co-state variables result with switching function ∂H/∂u, for patient B, after applying NSGA-II.

The result after apply NSGA-II can be shown in figure 4.11 and figure 4.12. In figure 4.11, it can be seen that normal cell, N is 1.0 and immune cell, I is 1.6 after day 25th. Both N and I shows increment compare to previous result. Drug concentration in blood stream, M and control delivery, u shown different result compare to the previous result. M and u are slightly above 0.8 after day one and become zero constantly start from day 25th. As for co-state variable result, in Figure 4.12, it shows very small different compare to the previous result. With the value of above 0.14 at the start then drop until below zero. Then it increase to zero on the final day. The opposite reaction can be seen for switching function, $\frac{\partial H}{\partial u}$. The switching function becomes zero because the boundary of the drug concentration constraint is satisfied.

4.2 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 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 3.2 and Table 3.3, 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 simulation results from applying the NSGA-II algorithm to the multi-objective optimization problem provide useful information on the algorithm's performance and efficacy. First, the Pareto optimum front provided by NSGA-II is a well-distributed set of non-dominated solutions that identify the best trade-offs between competing objectives. The Euclidean distance analysis for both patients found the ideal solution at the position (169.75999549, 108.08784255), with weights w1 = 0.9694580320684465 and w2 = 0.030541967931553504. This solution has a slight constraint violation of -0.06197415, which is the same for both patients, demonstrating that the method was successful in finding a near-optimal solution that meets the requirements to a great extent.

The hypervolume values of 17.736919219306643 for patients A and B, respectively, indicate that the NSGA-II algorithm was able to develop a diverse and evenly distributed set of Pareto optimum solutions that covered a considerable percentage of the objective space. This is a desirable quality because it enables decision-makers to consider a variety of different solutions and make informed trade-offs between competing objectives.

The convergence graph displays the effectiveness of the NSGA-II algorithm. The first constant area of the graph shows that the algorithm failed to discover excellent initial solutions, but after it got going, the objective function value began to improve significantly. The subsequent reduction in the objective function value and the last

constant region indicate that the algorithm has converged to a steady-state solution, which is most likely the best answer possible under the given restrictions.

Overall, the simulation results show that the NSGA-II algorithm is effective at solving the multi-objective optimization problem, providing a well-distributed set of Pareto optimal solutions, and converges to the best solution that meets the stated constraints. The findings of this analysis can be utilized to inform decision-making and drive future research and development in this area.

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.

CHAPTER 5: CONCLUSION

5.1 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.

5.2 Impact of Work to Environment and Society

This research has a substantial impact in various aspects. First and foremost, it possesses the capacity to significantly enhance cancer therapy outcomes and elevate the quality of life for patients. The study seeks to minimize medication and tumor concentrations while ensuring acceptable levels of normal cell concentrations in cancer treatment by combining optimum control approaches with evolutionary algorithms and applying them to drug administration. This optimized strategy has the capacity to diminish the adverse consequences of chemotherapy, enhance treatment effectiveness, and offer a more patient-focused approach to cancer care.

Furthermore, the research makes a valuable contribution to the efficient utilization of resources and the promotion of sustainability. Through the optimization of drug concentrations and the minimization of tumor growth, it is possible to decrease the total amount of medication required for effective therapy. This optimization results in a more efficient allocation of resources, including chemotherapeutic medications, leading to decreased waste and a diminished environmental impact linked to their manufacturing and disposal. This is consistent with the ideals of sustainable healthcare practices.

Moreover, the research holds the capacity to diminish healthcare expenditures. Through the optimization of drug administration, it is possible to reduce the total amount of medication and the length of therapy while still ensuring effectiveness. This decrease in treatment demands might result in financial savings for patients, healthcare systems, and insurance companies. Additionally, it has the potential to enhance the availability of medical care and mitigate the economic strain on individuals and healthcare institutions.

The study enhances therapy methods and optimization methodologies. The incorporation of optimal control approaches with evolutionary algorithms broadens the range of treatment optimization solutions. The research showcases the effectiveness of this method in the field of cancer chemotherapy, paving the way for future developments in treatment regimens and optimization tactics. This has the potential to result in more sophisticated and efficient treatments, not only for cancer but also for other intricate medical disorders.

Ultimately, the research promotes further cooperation and investigation. The results of this study establish a basis for further investigation and cooperation in the realm of enhancing cancer therapy. Researchers and practitioners can utilize this study as a foundation to investigate more sophisticated control tactics, verify the results using a wider array of chemotherapeutic models, and employ optimal control techniques in other areas of cancer treatment. The collective endeavor and persistent investigation can result in perpetual innovations in cancer therapy and contribute to the general improvement of the discipline.

To summarize, this research has a broad and significant impact, encompassing enhanced patient outcomes, optimized resource allocation, reduced costs, the progress of treatment regimens, and the opportunity for future research and collaboration. This study proposes a potential approach to improve the efficacy and long-term viability of cancer treatment by optimizing drug administration.

5.3 Future Work

The project will be expanded by incorporating two more Evolutionary Algorithms: Multi-Objective Differential Evolution (MODE) and Non-dominated Sorting Genetic Algorithm-III (NSGA-III). These techniques will be utilized to improve the mathematical model and broaden the solution space.

Based on Differential Evolution (DE) principles, MODE is a potent multi-objective optimization algorithm. By utilizing its capacity to effectively explore the solution space and converge towards the Pareto-optimal front, it will be used to solve the multi-objective optimization problem as stated in the mathematical model. against determine whether MODE is a good fit for tackling the given problem, its performance will be compared against the NSGA-II algorithm that was previously used.

NSGA-III is an enhanced iteration of the NSGA-II algorithm, tailored to address issues involving multiple objectives. To optimize these multi-objective issues, NSGA-III will be utilized, and the mathematical model will be expanded to include more objectives. The improved capacity of NSGA-III to sustain a well-distributed set of solutions along the Pareto-optimal front will be used to offer a thorough comprehension of the trade-offs between the conflicting goals.

By using these two evolutionary algorithms, MODE and NSGA-III, the research will advance through a more thorough exploration of the solution space, a better comprehension of the trade-offs between the various objectives, an assessment of how well these more recent EA techniques perform in comparison to the previously used NSGA-II algorithm, and a refinement of the mathematical model to produce more precise and logical data to meet the project's goals. In order to improve the overall study outcomes and help establish a thorough optimization framework for the problem at hand, the application of MODE and NSGA-III results will be carefully reviewed and compared to the findings from the prior work.

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APPENDIX