COLLEGE OF SCIENCE AND TECHNOLOGY
SCHOOL OF SCIENCE
DEPARTMENT OF MATHEMATICS

APPLIED OPTIMAL CONTROL IN CANCER CHEMOTHERAPY

Janvier Nshimyumukiza

Student number: 217090044

Bachelor of Science

in

Mathematics

Supervisor: Dr. Japhet Niyobuhungiro

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By
Janvier Nshimyumukiza
Registration number: 217090044

Thesis Submitted in Partial Fulfillment of the Academic Degree of
Bachelor of Science
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Supervisor: Dr. Japhet Niyobuhungiro

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Declaration

I, Janvier NSHIMYUMUKIZA student at University of Rwanda, Nyarugenge Campus, College of Science and Technology, School of Science, Department of Mathematics. Hereby declare that, work presented in this Bachelor thesis titled "*Applied of Optimal Control in Cancer Chemotherapy*", except where otherwise indicated, this document is entirely my own work and has not been submitted in whole or in part to any other university or any other higher learning institution. This was done under supervision of Dr. Japhet Niyobuhungiro. [1].

September, 2020

Janvier NSHIMYUMUKIZA

[1]University of Rwanda-College of Science and Technology, Rwanda

Certificate

This is to certify that project work entitled **Applied Optimal Control in Cancer Chemotherapy** is a record of the original work done by Janvier NSHIMYUMUKIZA(Registration number: 217090044) in Partial Fulfillment of the Academic Degree of Bachelor of Science in Mathematics. Done in Department of Mathematics, School of Science, University of Rwanda during 2019-2020 academic year.

Supervisor	**Head of Department**
Dr. Japhet NIYOBUHUNGIRO	Dr. Marcel NDENGO
Date.....	Date.....
Signature.....	Signature.....

Dedication

I humbly dedicate this thesis to everyone who played a great role by supporting me to make it at this far, and in my overall personal growth. I wholeheartedly dedicate this thesis to my loving family, who always keep motivating me to never give up, and who provide me the endless various kind of support.

I humbly would like to dedicate this work to my friends, colleagues and classmates who have shared me with their wisdom, motivation, and support.

At a glance, I dedicate this thesis to the Almighty God, thank you for guidance, strength, power of mind, protection and skills and for giving me a healthy life.

Abstract

By applying the Pontryagins Minimum Principle of Optimal Control Theory to an ordinary differential equation modeling a cancer-cells growth, we presented the effective optimal strategies for cancer chemotherapy. The main tools used in this thesis are Pontryagin's minimum principle, Optimal control theory, and numerical methods for simulations. This work presents the general background about cancer in first section; preliminaries and literature review on optimal control, gompertz growth, and cancer in the second section. The mathematical modeling for cancer chemotherapy is found in its own third section where the objective functional to be minimized are presented and the model governing the cell growth and cell-kill is found there and it is based on Gompertz growth and Skipper's log kill hypothesis where the main goal is to pull the tumor volume to the desired level with minimized treatment costs and side effects. In the end, model formulated into the optimal control problem is analyzed and later numerical simulations is done there to present graphically the outcome. Within numerical simulations, different scenario were simulated and it gave an understanding of chemotherapy outcomes for different cases. This numerical simulations approve our strategies as effective and optimal for treating malignant/cancerous tumor.

Acknowledgment

I would first like to thank my thesis supervisor Dr.Japhet Niyobuhungiro. Despising the challenging conditions due to existing global pandemic; COVID-19, He has always been there whenever I needed him and helped me to keep focused on what to do. He consistently allowed this thesis to be my own work,but steered in the right direction whenever he thought I needed it.

I would like to thank all Lecturers of Department of Mathematics, you really made this four years period enjoyable as well as productive.

Finally, I deeply express gratitude to each of my family member, friends and to all my classmates for providing me with various kinds of support and keeping me aspired and stick to my career. you'll have been a reason to keep steered in right way. Thank you.

Contents

Chapter 1

Introduction

In this thesis, we start introducing the topic in chapter 1, Preliminaries are presented in Chapter 2, Mathematical model is described in Chapter 3, Analysis and numerical simulations are given in Chapter 4 while concluding remarks are given in Chapter 5.

1.1 Background

According to World Health Organization WHO's researches, cancer is ranked as the second leading cause of death across the globe, and is responsible for an estimated 9.6 million deaths in 2018. Globally, 1 in 6 deaths is due to cancer and approximately, 70% of deaths from cancer occur in low- and middle- income countries. Cancer is not only about taking people's lives but also their wealth; it was seen that the economic impact of cancer is significant and is increasing. The total annual economic cost of cancer in 2010 was estimated at approximately US $1.16 trillion [1]. The expensiveness and high cancer mortality rates in low- and middle- income countries, could be the proof that the significant portion of deaths from cancer are mainly due to inconsistent treatment techniques, insufficient finance to treat cancer or combination of both. IARC says that only 20% of low- and middle- income countries have the required and necessary data to control cancer policy [2]. By today, some of the most-killing cancer types, such as breast cancer, cervical cancer, oral cancer, and colorectal cancer have high cure rates when detected and diagnosed early. The WHO recommends Effective Treatment and Early Detection as the essence to pace away the cancer mortality [3]. Early Detection involves early diagnosis and screening. When cancer is identified early, it is more likely to respond to effective treatment and can result in a greater probability of surviving, less unhealthfulness, and it saves victim's money as s/he doesn't need to undergo the expensive treatment. Screening aims to identify people with abnormalities suggestive of a specific cancer or pre-cancer who possesses any symptoms and prompt them for diagnosis and treatment. A perfect diagnosis is essential for appropriate and effective treatment for every cancer type. Different techniques of treatments for cancer are used alone or in combination depending on

cancer type. Most cancers are treated with chemotherapy, surgery and/or radiotherapy. The cancer treatment modalities reported are surgery, radiation therapy, and systemic treatment, including: chemotherapy, targeted therapy, hormonal therapy, and immunotherapy. The treatment techniques are selected based on various aspects including: location of the tumor, size of the tumor, patient's age and the existing health conditions. Many common targeted therapies are classified as chemotherapy in the National Cancer Database NCDB [4]. Today, chemotherapy is often recommended by doctors as the best and systematic way of treating the both low-grade and high-grade brain tumor cancer [5]. It uses drugs that kill dividing cancerous cells and prevent tumor from growing. the drugs are called cytotoxic which means toxic to cells (cyto). The drugs damage cells as they go through cell division processes to make the drugs more effective to cancer cells which divide more rapidly than the normal cells. Chemotherapy can be used for various purpose [6] including:

- **To achieve remission or cure** - This is when chemotherapy is used to stimulate and accelerate the disappearance of cancer symptoms.
- **To help other treatments** – when the patient has taken the others treatment which cannot stand alone to kill cancerous cells, chemotherapy also is taken to help previous treatments. If chemotherapy is given after main treatment (adjuvant treatment), its goal is to get rid of any remaining cancer cell.
- **To control the cancer** – even if the treatment fails, the chemotherapy can be used to prevent tumor from growing to further location.
- **To relieve symptoms** - chemotherapy is used to shrink the tumor size and reduce pain to improve health and wellbeing of the patient.
- **To stop cancer from coming back** - months or years after success remission by initial cancer chemotherapy, patient may need to undergo chemotherapy to prevent cancer from re-invading. This is called maintenance chemotherapy.

Chemotherapy is a time dependent treatment. Therefore, understanding tumor growth over time and cell-kill strategies are essentials of treating cancer with chemotherapy. Several tumor growth models including linear growth, cubic root growth, exponential growth, were proposed with different fitness. The author ANNA KANE LAIRD [7], described the dynamics of tumor growth following the Gompertzian growth. It is a sigmoid growth function which describes growth as being slowest at the start and fastest at the end of a given time period. The main cell-kill hypotheses are Emax model, Skipper's log-kill hypothesis, and Norton-Simon hypothesis with each possessing different pharmacokinetics and pharmacodynamics effects of the drug on tumor size. In 2003, Renee Fister and John Carl have placed two objective functionals where each functional has considered its own criterion. One considers "minimal tumor burden at the end of the treatment and toxicity in terms of area under the

drug concentration curve" and the second, which is very interesting; considers the closeness of the tumor mass to the desired level [8].

1.2 Problem statement

In this thesis, we consider the time-dependent optimal control strategies for optimal chemotherapy. By putting costs and side effects into considerations, it is imperative to minimize the closeness of the tumor size to the desired level. The model below assumes Gompertz growth and uses Skipper's log kill hypothesis. In fact, we reduce the squared-distance between the real tumor size and the desired level; $N(t) - N_d$ relative to control drug $u(t)$. Since our primary goal is to pull the tumor mass to the desired level, the best fit functional (previously used by Renee Fister and John Carl [8]) is:

$$J(u) = \int_0^T [a(N(t) - N_d)^2 + bu^2(t)]dt$$

Subject to

$$\begin{cases} \dot{N}(t) = r.N(t).\log(\frac{1}{N(t)}) - u(t).\delta.N(t) \\ N(0) = N_0; u(t)0; (T) = 0 \end{cases} \tag{1.1}$$

The control functions, $u(t)$, is bounded to be non negative. The optimal control drug has to be found in this thesis.

1.3 Motivation

Understanding that the cancer is the second leading cause of death globally, and that it mostly kills the people in low- and middle- income country, have sparked my interests in working on effective cancer chemotherapy. It has come to my attention that probably; many deaths from cancer are results of ineffective treatment. Therefore, I have thought that my contribution of working on optimal chemotherapy strategies would play a great role by developing the cheapest and effective techniques to treat cancer. My work is prioritizing low costs by optimizing quantity of control drugs and minimizing side effects that would severely harm the good health of the patients. Moreover, optimal control has became center of my interests in all undergraduate studies. Therefore, combining my passion to solve real world problems with my interests have motivated me to do this work.

1.4 Research objectives

The main research objective is to apply the optimal control to study and develop optimal strategies for chemotherapy. The objective is achieved by formulating and solving the Optimal Control Problem OCP where the goal is to find the control $u(t)$ that will drive the tumor density to a desired level N_d and minimizes the side effects of the drug.

1.5 Methodology

In this thesis, the main tool used is Pontryagin's Minimum Principle. We assume Gompertzian growth and use Skipper's log-kill hypothesis

- Derivation and theoretical analysis of necessary conditions for optimality.
- Writing Matlab codes for implementation
- Analysis of different scenarios including input parameters, controls, and sensitivity analysis.
- Adding the final payoff to the objective functional with only running cost.
- Discussing the impact of adding this terminal cost to the objective functional.

Chapter 2

Preliminaries

This chapter covers the general notions about cancer and its treatment. Since, the data concerning cancer and its treatment are rare in low- and middle- income countries, chapter may span the data and information from high-income countries. However, it doesn't limit the contents to be relevant for every country.

2.1 CANCER

Cancer is the diseases of the cells growing abnormally, out of control and in wrong place. Cancer describes a range of diseases that can affect different organs, tissue, and parts of human body. Our body is made up of billions of cells like a building blocks make a house. Our body constantly makes new cells for several purposes like: growing, replacing the worn-out tissue and healing injuries. New cells are made through cell division process; a cell grows and split into two. Generally, when the cells are dead, they shrink to leave place for new cells which are made through cell division. When the cells don't grow, divide and die in the usual way, it may cause the abnormality of blood or lymph fluid in the body, or form a lump called a tumor. A tumor may be benign or malignant. A benign or unharmful tumor is made up of abnormal cells confined at one area and are not able to spread to further parts of the body; this is not cancer. On the other hand, the malignant tumor which is harmful; is made up of cancerous cells which have the ability to spread to the other parts of the body. Their mobility is done through bloodstream or lymphatic system. The malignant tumor is usually named after the organ or type of cell affected. The malignant tumor that has not spread to the other parts of the body is called localized cancer. A tumor may invade deeper into surrounding tissue and grow its own blood vessels, a process known as angiogenesis. If cancerous cells grow and spread to form a tumor to a new part of the body, it is called a secondary cancer or metastatic cancer. A metastasis keeps the name of the original cancer. For example, lung cancer that spread to the liver is called metastatic breast cancer, even though the person may be experiencing symptoms caused by problems in the liver.

2.1.1 Cancer status in Rwanda

By today, Rwanda has an operational cancer policies, strategies, and action plan to control the epidemy. Rwanda has a population of approximately 12.5 million of people. In 2012, GLOBOCAN data [9] says that there were 8263 new cancer cases with 3520 in men and 4743 in women. In 2018, (6 years later), the number of active cases were raised to 10,704 with 4,520 in men and 6,184 in women. In 2018, all the recorded deaths from cancer were 7,662 making a 5-year cancer prevalence in Rwanda to be 17,997. The main cancer types are Cervix uteri, breast, Colorectum, Stomach and Liver. According to IARC [9], the risk of dying from cancer before the age of 75 years is 10.1% in men, 11.1% in women and 10.6% in both sexes.

2.1.2 Cancer chemotherapy

Today, chemotherapy is often recommended by doctors as the best and systematic way of treating the both low-grade and high-grade brain tumor cancer [5]. It uses drugs that kill dividing cancerous cells and prevent tumor from growing. the drugs are called cytotoxic which means toxic to cells (cyto). The drugs damage cells as they go through cell division processes to make the drugs more effective to cancer cells which divide more rapidly than the normal cells. Chemotherapy can be used for various purpose [6] including:

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2.2 GOMPERTZIAN GROWTH

The Gompertzian growth is the growth model where the growth rate is small at the beginning, big in the middle after some time, and afterwards, small as the growth reaches its exhaustion value. In the 1960s A.K. Laird [7] for the first time successfully used the Gompertzian curve to fit data of growth of tumors. In fact, tumors are cellular populations growing in a confined space where the availability of nutrients is limited. Denoting the tumor size as $N(t)$ it is useful to write the Gompertzian Curve as follows:

$$N(t) = K.e^{ln(\frac{N(0)}{K}).e^{-\alpha.t}}$$

Where:

- $N(0)$ is the size of tumor at the starting observation time,
- K is the carrying capacity, i.e. the maximum size that can be reached with the available nutrients. In fact, $\lim_{t\to+\infty} N(t) = K$. Note that, in absence of therapies etc. Usually it is $N(0) < K$, whereas, in presence of therapies, it may be $N(0) > K$;
- α is a constant related to the proliferative ability of the cells.

From the above equation of the Gompertz curve, it is easy to verify that the dynamics of the tumor volume $N(t)$ is governed by the Gompertz differential equation:

$$\dot{N}(t) = \alpha ln(\frac{K}{N(t)}).N(t)$$

Which can be broken down into the form:

$\dot{N}(t) = F(N(t)).N(t)$; with $\dot{F}(N)$ is negative definite.

$F(N)$ is the instantaneous proliferation rate of the cellular population, whose decreasing nature is due to the competition for the nutrients due to the increase of the cellular population, similarly to the logistic growth rate. However, there is a fundamental difference: in the logistic case the proliferation rate for small cellular population is finite:

$$F(N) = \alpha(1 - (\tfrac{N}{K})^v) \Longleftarrow F(0) = \alpha \prec +\infty$$

Whereas in the Gompertz case the proliferation rate is unbound:

$$\lim_{x \leftarrow 0^+} F(N) = \alpha \ln(\tfrac{K}{N}) = +\infty$$

The Gompertz model is well known and widely used in many aspects of biology. It has been frequently used to describe the growth of animals and plants, as well as the number or volume of bacteria and cancer cells. In my case study, I have assumed the tumor growth to follow the Gompertz model.

2.3 OPTIMAL CONTROL

Definition 2.1 *Optimal control is the process of finding the control and state law for a dynamic system over a period of time so that the performance of the system is optimal with respect to some criterion, such as control effort, tracking error, energy consumption, or amount of time taken to reach a target.*

Generally, Optimal control is the process of determining control and state trajectories for a dynamic system over a period of time to minimize a performance index. Optimal control is closely related in its origins to the theory of calculus of variations. Some important contributors to the early theory of optimal control and calculus of variations include Johann Bernoulli $(1667-1748)$, Isaac Newton $(1642-1727)$, Leonhard Euler $(1707-1793)$, Ludovico Lagrange $(1736-1813)$, Andrien Legendre $(1752-1833)$, Carl Jacobi $(1804-1851)$, William Hamilton $(1805-1865)$, Karl Weierstrass $(1815-1897)$, Adolph Mayer $(1839-1907)$, and Oskar Bolza $(1857-1942)$. Some important milestones in the development of optimal control in the 20th century include the formulation dynamic programming by Richard Bellman $(1920-1984)$ in the 1950s, the development of the minimum principle by Lev Pontryagin $(1908-1988)$ and co-workers also in the 1950s, and the formulation of the linear quadratic regulator and the Kalman filter by Rudolf Kalman $(b.1930)$ in the 1960s [10].

Optimal control and its ramifications have found applications in many different fields, including aerospace, process control, robotics, bioengineering, economics, finance, and management science, and it continues to be an active research area within control theory. Before the arrival of the digital computer in the 1950s, only fairly simple optimal control problems could be solved. The arrival of the digital computer has enabled the application of optimal control theory and methods to many complex problems.

Formulation of optimal control problems

There are various types of optimal control problems, depending on the performance index, the type of time domain (continuous, discrete), the presence of different types of constraints, and what variables are free to be chosen. The formulation of an optimal control problem requires the following:

- A mathematical model of the system to be controlled,
- A specification of the performance index,
- A specification of all boundary conditions on states, and constraints to be satisfied by states and controls,
- A statement of what variables are free.

General case with fixed final time and no terminal or path constraints

If there are no path constraints on the states or the control variables, and if the initial and final times are fixed, a fairly general continuous time optimal control problem can be defined as follows:

Problem 1. Find the control vector trajectory $\mathbf{u} : [t_0, t_f] \subset \mathbb{R} \mapsto \mathbb{R}^{n_u}$ to minimize the performance index:

$$J = \varphi(\mathbf{x}(t_f)) + \int_{t_0}^{t_f} L(\mathbf{x}(t), \mathbf{u}(t), t)dt \tag{1}$$

subject to:

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), t),\ \mathbf{x}(t_0) = \mathbf{x}_0 \tag{2}$$

where $[t_0, t_f]$ is the time interval of interest, $\mathbf{x} : [t_0, t_f] \mapsto \mathbb{R}^{n_x}$ is the state vector, $\varphi : \mathbb{R}^{n_x} \mapsto \mathbb{R}$ is a terminal cost function, $L : \mathbb{R}^{n_x} \times \mathbb{R}^{n_u} \times \mathbb{R} \mapsto \mathbb{R}$ is an intermediate cost function, and $\mathbf{f} : \mathbb{R}^{n_x} \times \mathbb{R}^{n_u} \times \mathbb{R} \mapsto \mathbb{R}^{n_x}$ is a vector field. Note that equation (2) represents the dynamics of the system and its initial state condition. Problem 1 as defined above is known as the Bolza problem. If $L(\mathbf{x}, \mathbf{u}, t) = 0$, then the problem is known as the Mayer problem, if $\varphi(\mathbf{x}(t_f)) = 0$, it is known as the Lagrange problem. Note that the performance index $J = J(\mathbf{u})$ is a functional, this is a rule of correspondence that assigns a real value to each function u in a class. Calculus of variations [11] is concerned with the optimisation of functionals, and it is the tool that is used in this section to derive necessary optimality conditions for the minimization of $J(u)$.

Adjoin the constraints to the performance index with a time-varying Lagrange multiplier vector function $\lambda : [t_0, t_f] \mapsto \mathbb{R}^{n_x}$ (also known as the co-state), to define an augmented performance index $\bar{J}$:

$$\bar{J} = \varphi(\mathbf{x}(t_f)) + \int_{t_o}^{t_f} \left\{ L(\mathbf{x}, \mathbf{u}, t) + \lambda^T(t) \left[\mathbf{f}(\mathbf{x}, \mathbf{u}, t) - \dot{\mathbf{x}} \right] \right\} dt \tag{3}$$

Define the Hamiltonian function H as follows:

$$H(\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t) = L(\mathbf{x}(t), \mathbf{u}(t), t) + \lambda(t)^T \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), t), \tag{4}$$

such that $\bar{J}$ can be written as:

$$\bar{J} = \varphi(\mathbf{x}(t_f)) + \int_{t_o}^{t_f} \left\{ H(\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t) - \lambda^T(t)\dot{\mathbf{x}} \right\} dt$$

Assume that t_0 and t_f are fixed. Now consider an infinitesimal variation in $\mathbf{u}(t)$, that is denoted as $\delta\mathbf{u}(t)$. Such a variation will produce variations in the state history $\delta\mathbf{x}(t)$, and a variation in the performance index $\delta\bar{J}$:

$$\delta\bar{J} = \left[\left(\frac{\partial\varphi}{\partial\mathbf{x}} - \lambda^T \right) \delta\mathbf{x} \right]_{t=t_f} + \left[\lambda^T \delta\mathbf{x} \right]_{t=t_O} + \int_{t_o}^{t_f} \left\{ \left(\frac{\partial H}{\partial\mathbf{x}} + \dot{\lambda}^T \right) \delta\mathbf{x} + \left(\frac{\partial H}{\partial\mathbf{u}} \right) \delta\mathbf{u} \right\} dt$$

Since the Lagrange multipliers are arbitrary, they can be selected to make the coefficients of $\delta\mathbf{x}(t)$ and $\delta\mathbf{x}(t_f)$ equal to zero, as follows:

$$\dot{\lambda}(t)^T = -\frac{\partial H}{\partial\mathbf{x}}, \tag{5}$$

$$\lambda(t_f)^T = \left. \frac{\partial\varphi}{\partial\mathbf{x}} \right|_{t=t_f} . \tag{6}$$

This choice of $\lambda(t)$ results in the following expression for $\bar{J}$, assuming that the initial state is fixed, so that $\delta\mathbf{x}(t_0) = 0$:

$$\delta\bar{J} = \int_{t_o}^{t_f} \left\{ \left(\frac{\partial H}{\partial\mathbf{u}} \right) \delta\mathbf{u} \right\} dt$$

For a minimum, it is necessary that $\delta\bar{J} = 0$. This gives the stationarity condition:

$$\frac{\partial H^T}{\partial\mathbf{u}} = \mathbf{0} . \tag{7}$$

Equations (2), (5), (6), and (7) are the first-order necessary conditions for a minimum of J. Equation (5) is known as the co-state (or adjoint) equation. Equation (6) and the initial state condition represent the boundary (or transversality) conditions. These necessary optimality conditions, which define a two point boundary value problem, are very useful as they allow to find analytical solutions to special types of optimal control problems, and to define numerical algorithms to search for solutions in general cases. Moreover, they are useful to check the extremality of solutions found by computational methods. Sufficient conditions for general nonlinear problems have also been established. Distinctions are made between sufficient conditions for weak local, strong local, and strong global minima. Sufficient conditions are useful to check if an extremal solution satisfying the necessary optimality conditions actually yields a minimum, and the type of minimum that is achieved [11].

The theory presented above does not deal with the existence of an optimal control that minimizes the performance index,J. Moreover, a key point in the mathematical theory of optimal control is the existence of the Lagrange multiplier function [12] $\lambda(t)$.

It was shown by Pontryagin and co-workers (Pontryagin, 1987) that in this case, the necessary conditions (2), (5) and (6) still hold, but the stationarity condition (7), has to be replaced by:

$$H(\mathbf{x}^*(t), \mathbf{u}^*(t), \lambda^*(t), t) \leq H(\mathbf{x}^*(t), \mathbf{u}(t), \lambda^*(t), t)$$

for all admissible u, where * denotes optimal variables. This condition is known as Pontryagin's minimum principle. According to this principle, the Hamiltonian must be minimised over all admissible u for optimal values of the state and co-state variables.

One special class of optimal control problem involves finding the optimal input $u(t)$ to reach a terminal constraint in minimum time.

General formulation of Pontriagin Minimum Principle

The main tool that will be used is the Pontriagin Minimum Principle, which is used in optimal control theory to find the best possible control for taking a dynamical system from one state to another, especially in the presence of constraints for the state or input controls.

Theorem 2.1 *Let (x^*, u^*) be a controlled trajectory defined over the interval $[0, T]$. If (x^*, u^*) is optimal, then there exist a constant $\lambda_0 \geq 0$ and a co-vector $\lambda : [0, T] \to (\mathbb{R}^n)^*$, the so-called adjoint variable, such that the following conditions are satisfied [13]:*

1. *Non-triviality of the multipliers: $(\lambda_0, \lambda(t)) \neq 0$ for all $t \in [0, T]$.*

2. *Adjoint equation: the adjoint variable λ is a solution to the time-varying linear differential equation*

$$\dot{\lambda}(t) = -\lambda_0 \frac{\partial L}{\partial x}(x^*(t), u^*(t)) - \lambda(t) \frac{\partial f}{\partial x}(x^*(t), u^*(t)).$$

3. *Minimum condition: almost everywhere in $[0, T]$ we have that the Hamiltonian:*

$$H(\lambda_0, \lambda(t), x^*(t), u^*(t)) = \min_{v \in U} H(\lambda_0, \lambda(t), x^*(t), v) = constant.$$

4. *Transversality condition: at the endpoint of the controlled trajectory, the co-vector*

$$(H + \lambda_0 \frac{d\varphi}{dt}, -\lambda + \lambda_0 \frac{d\varphi}{dx}) \in (\mathbb{R}^{n+1})^*$$

is orthogonal to the terminal manifold N, with $\varphi(x(t))$ a continuously differentiable function.

This is equivalent to the existence of a multiplier $v \in (\mathbb{R}^{n+1-k})^*$ *such that*

$$H + \lambda_0 \frac{d\varphi}{dt} + v\frac{d\Psi}{dt} = 0, \lambda = \lambda_0 \frac{d\varphi}{dx} + v\frac{d\Psi}{dx}$$

at $(T, x^*(T))$. *Where* $\Psi(x(t))$ *is a continuously differentiable function.*

Derivation of the Necessary Condition

Proposition 2.1 *Let have the optimal control problem:*

Minimize

$$J = \int_0^T f(\boldsymbol{x}(t), \boldsymbol{u}(t), t)dt \tag{8a}$$

subject to:

$$\dot{\boldsymbol{x}}(t) = g(\boldsymbol{x}(t), \boldsymbol{u}(t), t), \ \boldsymbol{x}(0) = \boldsymbol{x}_0 \tag{9a}$$

If u^* *is an optimal control and* x^* *corresponding state, then*

$\frac{\partial H}{\partial \boldsymbol{u}} = \boldsymbol{0}$ - *Optimal equation ,* $\dot{\lambda} = -\frac{\partial H}{\partial \boldsymbol{x}}$ - *Adjoint equation and* $\lambda(T) = \boldsymbol{0}$ - *transversality condition.*

Where Hamiltonian, $H = f(\boldsymbol{x}(t), \boldsymbol{u}(t), t) + \lambda g(\boldsymbol{x}(t), \boldsymbol{u}(t), t)$

Proof 2.1 *Taking* $\boldsymbol{u}^* + ah(t)$ *with* $h(t)$ *a variation function and* $a \in \mathbb{R}$. *Let* $\boldsymbol{y}(t, a)$ *be a state corresponding to* $\boldsymbol{u}^* + ah(t)$

From (8a) and (9a) we have:

$$\frac{d\boldsymbol{y}}{dt}(t, a) = g(\boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t), t), \ \boldsymbol{y}(0, a) = \boldsymbol{x}_0, \ \boldsymbol{y}(t, 0) = \boldsymbol{x}^*(t)$$

and

$$J(a) = \int_0^T f(\boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t), t)dt$$

when

$$\left.\frac{dJ}{da}\right|_{a=0} = \boldsymbol{0}$$

Since:

$$\int_0^T \frac{d}{dt}(\lambda(t)\boldsymbol{y}(t, a))dt = \lambda(T)\boldsymbol{y}(T, a) - \lambda(0)\boldsymbol{y}(0, a)$$

$$\int_0^T \frac{d}{dt}(\lambda(t)\boldsymbol{y}(t, a))dt + \lambda(0)\boldsymbol{y}(0, a) - \lambda(T)\boldsymbol{y}(T, a) = \boldsymbol{0}$$

adding the above to $J(a)$, we get:

$$J(a) = \int_0^T [f(\boldsymbol{y}(t,a), \boldsymbol{u}^* + ah(t), t) + \frac{d}{dt}(\lambda(t), \boldsymbol{y}(t,a))]dt + \lambda(0)\boldsymbol{y}(0,a) - \lambda(T)\boldsymbol{y}(T,a)$$

$$J(a) = \int_0^T [f(\boldsymbol{y}(t,a), \boldsymbol{u}^* + ah(t), t) + \dot{\lambda}(t)\boldsymbol{y}(t,a) + \lambda(t)g(\boldsymbol{y}(t,a), \boldsymbol{u}^* + ah(t), t)]dt + \lambda(0)\boldsymbol{y}(0,a)$$
$$-\lambda(T)\boldsymbol{y}(T,a)$$

Differentiating with respect to a, we get:

$$\frac{dJ(a)}{da} = \int_0^T [f_{\boldsymbol{x}}\frac{\partial \boldsymbol{y}}{\partial a} + f_{\boldsymbol{u}}\frac{\partial}{\partial a}(\boldsymbol{u}^* + ah(t)) + \dot{\lambda}(t)\frac{\partial \boldsymbol{y}}{\partial a} + \lambda(t)(g_{\boldsymbol{x}}\frac{\partial \boldsymbol{y}}{\partial a} + g_{\boldsymbol{u}}\frac{\partial}{\partial a}(\boldsymbol{u}^* + ah(t)))]dt$$
$$-\lambda(T)\tfrac{\partial \boldsymbol{y}}{\partial a}(T,a)$$

$$\left.\frac{dJ}{da}\right|_{a=0} = \boldsymbol{0}$$

implies

$$\int_0^T [(f_{\boldsymbol{x}} + \lambda(t)g_{\boldsymbol{x}} + \dot{\lambda}(t))\frac{d\boldsymbol{y}}{da}(t,0) + (f_{\boldsymbol{u}} + \lambda(t)g_{\boldsymbol{u}})h(t)]dt - \lambda(T)\frac{\partial \boldsymbol{y}}{\partial a}(T,0)$$

choosing $\lambda(t)$ such that
$\dot{\lambda} = -[f_{\boldsymbol{x}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t) + \lambda(t)g_{\boldsymbol{x}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t)]$, *adjoint equation*
and $\lambda(T) = \boldsymbol{0}$, Transversality condition

$$\int_0^T (f_{\boldsymbol{u}} + \lambda g_{\boldsymbol{u}})h(t)dt = \boldsymbol{0},$$

where $h(t)$ is an arbitrary function.

$f_{\boldsymbol{u}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t) + \lambda(t)g_{\boldsymbol{u}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t) = \boldsymbol{0}$ *-Optimal equation*

for all $0 \le t \le T$

Changing the objective functional from $J = \int_0^T f(\mathbf{x}(t), \mathbf{u}(t), t)dt$ to $J = \varphi(\mathbf{x}(T)) + \int_0^T f(\mathbf{x}(t), \mathbf{u}(t), t)dt$

Proposition 2.2 *Let have the optimal control problem with the terminal cost function:*

Minimize

$$J = \varphi(\mathbf{x}(T)) + \int_0^T f(\boldsymbol{x}(t), \boldsymbol{u}(t), t)dt \tag{8b}$$

subject to:

$$\dot{\boldsymbol{x}}(t) = g(\boldsymbol{x}(t), \boldsymbol{u}(t), t),\ \ \boldsymbol{x}(0) = \boldsymbol{x}_0 \tag{9b}$$

If u^* is an optimal control and x^* corresponding state, then

$\frac{\partial H}{\partial \boldsymbol{u}} = \mathbf{0}$ *- Optimal equation ,* $\lambda' = -\frac{\partial H}{\partial \boldsymbol{x}}$ *- Adjoint equation and*
$\lambda(T) = \varphi'(\mathbf{x}(T))$ *- transversality condition*
*where Hamiltonian, H= f(**x**(t),**u**(t),t)+* $\lambda g(\boldsymbol{x}(t), \boldsymbol{u}(t), t)$

Proof 2.2 *Taking* $\boldsymbol{u}^* + ah(t)$ *with* $h(t)$ *a variation function and* $a \in \mathbb{R}$.
Let $\boldsymbol{y}(t, a)$ *be a state corresponding to* $\boldsymbol{u}^* + ah(t)$.

From (8b) and (9b) we have that:

$$\frac{d\boldsymbol{y}}{dt}(t, a) = g(\boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t), t),\ \ \boldsymbol{y}(0, a) = \boldsymbol{x}_0,\ \ \boldsymbol{y}(t, 0) = \boldsymbol{x}^*(t)$$

and $J(a) = \varphi(\mathbf{y}(T, a)) + \int_0^T f(\boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t), t)dt$

when $\left.\frac{dJ}{da}\right|_{a=0} = \varphi'(\mathbf{x}(T))\frac{\partial \boldsymbol{y}}{\partial a}(T, 0)$

Since:

$$\int_0^T \frac{d}{dt}(\lambda(t)\boldsymbol{y}(t, a))dt = \lambda(T)\boldsymbol{y}(T, a) - \lambda(0)\boldsymbol{y}(0, a)$$

$$\int_0^T \frac{d}{dt}(\lambda(t)\boldsymbol{y}(t, a))dt + \lambda(0)\boldsymbol{y}(0, a) - \lambda(T)\boldsymbol{y}(T, a) = \boldsymbol{0}$$

adding the above to $J(a)$, we get:

$$J(a) = \varphi(\mathbf{x}(T)) + \int_0^T [f(\boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t), t) + \tfrac{d}{dt}(\lambda(t), \boldsymbol{y}(t, a))]dt + \lambda(0)\boldsymbol{y}(0, a) - \lambda(T)\boldsymbol{y}(T, a)$$

$$J(a) = \int_0^T [f(\boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t), t) + \dot{\lambda}(t)\boldsymbol{y}(t, a) + \lambda(t)g(t, \boldsymbol{y}(t, a), \boldsymbol{u}^* + ah(t))]dt + \lambda(0)\boldsymbol{y}(0, a)$$
$$-\lambda(T)\boldsymbol{y}(T, a) + \varphi(\mathbf{x}(T))$$

Differentiating with respect to a, we get:

$$\frac{dJ(a)}{da} = \int_0^T [f_{\boldsymbol{x}}\frac{\partial \boldsymbol{y}}{\partial a} + f_{\boldsymbol{u}}\frac{\partial}{\partial a}(\boldsymbol{u}^* + ah(t)) + \dot{\lambda}(t)\frac{\partial \boldsymbol{y}}{\partial a} + \lambda(t)(g_{\boldsymbol{x}}\frac{\partial \boldsymbol{y}}{\partial a} + g_{\boldsymbol{u}}\frac{\partial}{\partial a}(\boldsymbol{u}^* + ah(t)))]dt$$
$$-\lambda(T)\tfrac{\partial \boldsymbol{y}}{\partial a}(T, a) + \varphi'(\mathbf{x}(T))\tfrac{\partial \boldsymbol{y}}{\partial a}(T, a)$$

$$\left.\frac{dJ}{da}\right|_{a=0} = \varphi'(\mathbf{x}(T))\frac{\partial \boldsymbol{y}}{\partial a}(T,0)$$

implies

$$\int_0^T [(f_{\boldsymbol{x}} + \lambda(t)g_{\boldsymbol{x}} + \dot{\lambda})\frac{d\boldsymbol{y}}{da}(t,0) + (f_{\boldsymbol{u}} + \lambda(t)g_{\boldsymbol{u}})h(t)]dt - (\lambda(T) + \varphi'(\mathbf{x}(T)))\frac{\partial \boldsymbol{y}}{\partial a}(T,0)$$

choosing $\lambda(t)$ *such that*

$\lambda' = -[f_{\boldsymbol{x}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t) + \lambda(t)g_{\boldsymbol{x}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t)]$ - *Adjoint equation*
and $\lambda(T) = \varphi'(\mathbf{x}(T))$, *Transversality condition*

$$\int_0^T (f_{\boldsymbol{u}} + \lambda g_{\boldsymbol{u}})h dt = \boldsymbol{0},$$

where $h(t)$ *is an arbitrary function.*

$f_{\boldsymbol{u}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t) + \lambda(t)g_{\boldsymbol{u}}(\boldsymbol{x}^*, \boldsymbol{u}^*, t) = \boldsymbol{0}$ -*Optimal equation*

for all $0 \leq t \leq T$

Remark: The only difference between the above two Optimal Control Problems is transversality condition. Where in Proposition 2.1 Transversality condition is $\lambda(T) = \mathbf{0}$ while in Proposition 2.2 is $\lambda(T) = \varphi'(\mathbf{x}(T))$ due to the terminal cost.

Chapter 3

Mathematical modeling

This chapter develop and explain the model for cancer chemotherapy. It is within this chapter where we formulate the optimal control problem for outstanding optimal cancer chemotherapy.

3.1 Skipper's cell-kill model (log-kill hypothesis)

Generally, the cell-kill model to study for cancerous cells is represented by an ordinary differential equation which previously used in [8]:
$\frac{dN}{dt} = rNF(N) - G(N,t)$

Where:

- N is the tumor volume; the state variable
- r is the growth rate of the tumor
- $F(N)$ is the generalized growth function
- $G(N,t)$ represents the overtime pharmacokinetic and pharmacodynamic effects of the drug on the tumor.

By assuming the Gompertzian growth, the growth function is equal to:
$F(N) = \ln(\frac{1}{N})$

and by using the Skipper's log-kill (known as percentage kill), the function that represents the pharmacodynamic and pharmacokinetic effects of the drug on the tumor is:

$$G(N,t) = u(t) \tag{3.3}$$

Hence using equations (3.1), (3.2), and (3.3) we get the model under investigation to be:

$\frac{dN}{dt} = rNln(\frac{1}{N}) - u(t)\delta N$ (3.4)

Where:

- ***r*** is the growth rate of the tumor.
- ***N*** is the tumor volume at a time t
- ***u(t)*** is the time-dependent pharmacokinetics of the drug. i.e. ***u(t)=0*** implies that there is no drug effect and ***u(t)>0*** is the strength of the drug effect.
- δ is the magnitude of the dose

3.2 Formulation of Optimal Control problem

The objective functional to be minimized is:

$$J(u) = \int_0^T [a(N(t) - N_d)^2 + bu^2(t)]dt \tag{3.5}$$

By putting drug costs (in terms of quantity used) and side effects into considerations, it is imperative to minimize the closeness of the tumor size to the desired level. The measure of the "closeness" of the tumor mass to the desired tumor density, N_d, and the cost of the control, $u(t)$, are minimized over the class of measurable, nonnegative controls. In fact, we pull the tumor volume $N(t)$ to the wanted level Nd by making the squared-distance $(N(t) - N_d)^2$ and quantity of control drug $u(t)$ minimal as much as possible. So, to achieve optimal control strategies, we have to find, u^* such that

$$J(u^*) = \min_{\Omega} J(u) \tag{3.6}$$

where $\Omega = umeasurable|0 \leq u(t), t \in [0, T]$; is the class of all admissible, measurable, nonnegative controls.

Hence from eq. (3.4) and (3.5), the formulated optimal control problem to study is:

Minimize

$$J(u) = \int_0^T [a(N(t) - N_d)^2 + bu^2(t)]dt$$

Subject to

$$\begin{cases} \dot{N}(t) = rN(t)\ln(\frac{1}{N(t)}) - u(t)\delta N(t) \\ N(0) = N_0; u(t) \geq 0; \lambda(T) = 0 \end{cases} \tag{3.1}$$

Chapter 4

Analysis and numerical simulations

4.1 Analysis of Optimal Control

In this section, we consider the existence of an optimal solution pair, the characterization of the optimal control, and the uniqueness concept in association with problem (3.4) such that the objective functional (3.5) involving the nonlinear control term is minimized over the class of controls, U. The necessary conditions for optimality are given by Pontryagin Minimum Principle. This means that solution pair are given from satisfaction of PMP which combines an objective functional with the model to form the Hamiltonian, H, which must be minimized point-wise with respect to u:

$$H = [a(N(t) - N_d)^2 + bu^2(t)] + \lambda[rN(t)\ln(\frac{1}{N(t)}) - \delta u(t)N(t)] \tag{4.1}$$

By applying Pontryagin Maximum Principle [6] and the existence result for the optimal control pairs from [15] , we obtain

$$\begin{cases} \dot{N} = \frac{\partial H}{\partial \lambda} \\ \dot{\lambda} = -\frac{\partial H}{\partial N} \\ 0 = \frac{\partial H}{\partial u} \end{cases} \tag{4.2}$$

Which yield,

$$\begin{cases} \dot{N} = rN\ln(\frac{1}{N}) - \delta uN \\ \dot{\lambda} = -[2a(N - N_d) + \lambda(r - r\ln(\frac{1}{N}) + \delta u)] \\ 0 = 2bu - \lambda\delta N \end{cases} \tag{4.3}$$

With initial and transversality conditions: $N(0) = N_0; u(t) \geq 0; \lambda(T) = 0$
Hence we can prove the existence of solution as follows:

4.1.1 Existence

To move forward, given an optimal control in the admissible set, U, the existence of the state solution for the problem (3.5) is shown and the existence of optimal control for the state system is analyzed as previously done by K. Renee Fister and John Carl Panetta in [8].

Theorem 4.1: Existence of State Solution *Given $u \in U$, there exists a bounded state solution N(t) solving the problem (4.2).*

Proof 4.1 *Given our problem (4.2)*

$$\frac{dN}{dt} = rN(t)\ln(\frac{1}{N(t)}) - \delta u(t)N(t)$$

Since $\ln(\frac{1}{N}) \leq \frac{1}{N}$ $u(t) \geq 0$ $N(t) \geq 0$ *and* $\delta \geq 0$. *We consider the following differential equation in relation to the problem (4.2). The state variable N(t) represent super (biggest possible) solution for problem (4.2).*

$$\frac{dN}{dt} = r \tag{4.3}$$

Then using $0 \leq t \leq T$, *we have*

$$N(t) \leq rT + N_0 \tag{4.4}$$

Hence we obtain the existence of a state solution to the problem (4.2)

Next, the existence of an optimal control for the state system is analyzed. Using the fact that the solution to state equation is bounded, the existence of an optimal control for the problem can be determined using the theory developed Fleming and Rishel [14]

Theorem 4.2: Existence of Optimal Solution *Given the objective functional,*

$$J(u) = \int_0^T [a(N(t) - N_d)^2 + bu^2(t)]dt$$

Where

$$U=\{u \text{ measurable} \mid 0 \leq u(t),\ t \in [0,T]$$

And for the problem (4.2) we have $N(0) = N_0$, then there exists an optimal control u^* associated with problem (4.2) such that $\min_{u \in U} J(u) = J(u^*)$ if the following conditions, also previously used by Fister and Panetta [8], are met:

1. *The class of all initial conditions with a control u in the admissible control set along with each state equation being satisfied is not empty.*
2. *The admissible control set U is closed and convex.*
3. *The right-hand side of problem (3.4) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of u with coefficients depending on time and the state.*
4. *The integrand of (3.5) is convex on U and is bounded below by $-c_2 + c_1|u|^\eta$ with $c_1 \succ 0$ and $\eta \succ 1$.*

Proof 4.2 *Since the problem has a bounded solution for the initial condition, given an optimal control, by* ***Theorem 4.1****, then the condition (1) is satisfied. By definition, U is closed and convex; the condition (2) is satisfied. To meet the condition (3) we reflect on the right-hand side of eq. (3.4) below:*

$$f(t, N(t), u(t)) = rN \ln(\tfrac{1}{N}) - \delta N u(t),$$

We can see that f is continuous in t, u and N because discontinuity would arise iff $N = 0$ or $N < 0$. In our case we have $N \neq 0$ and it cannot be negative. Hence condition (3) is satisfied. In addition, our problem is written as linear function of the control with coefficients depending on time and state. For the boundedness requirement, we use the bounds in the proof of ***Theorem 4.1*** *to obtain the result. Consequently,*

$$\begin{aligned} |f(t, N(t), u(t))| &\leq \left| rN \ln(\tfrac{1}{N}) \right| + |\delta N u(t)| \\ &\leq r + \delta(N_0 + rT)\,|u(t)| \\ &\leq C_1(1 + |u(t)| + |N(t)|) \end{aligned}$$

Where C_1 depends on r, δ, N_0 and T. Hence, the right-hand side is bounded by a sum of the control and the state. Lastly, the integrand of the objective functional is convex on U. One can consider the second partial of the integrand of the objective functional with respect to the control and find that it is positive. To obtain the necessary lower bound for the integrand, we see that $a(N - N_d)^2 + bu^2 \geq bu^2 \geq -c + bu^2$ for any $c \succ 0$. Therefore, condition (4) is complete and so is the proof.

By applying the optimality condition: $0 = \frac{\partial H}{\partial u} \Leftrightarrow 0 = 2bu - \lambda\delta N$; which gives

$$u^* = \frac{\delta\lambda N}{2b} \geq 0 \tag{4.5}$$

And by substituting in system (4.2) we get new system below which is in two variables:

$$\begin{cases} \dot{N} = rN\ln(\frac{1}{N}) - \delta^2 N(\lambda N)^+ \\ \dot{\lambda} = -[2a(N - N_d) + \lambda(r\ln(\frac{1}{N}) - r - \frac{\delta^2}{2b}(\lambda N)^+)] \\ N(0) = N_0; \lambda(T) = 0 \end{cases} \tag{4.6}$$

Note that $(\lambda N)^+$ to ensure that we kept our optimal control u^* nonnegative.
The uniqueness of the control solution is assured by two facts: (1) the state solution is bounded and (2) the transversality condition on adjoint solution. There is a restriction on the length of the time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction on the length on the time interval is due to the opposite time orientations of (4.1),(4.2), and (13); the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems [16].

4.2 Numerical simulations

In this section, we simulate the result and outcome of this optimal strategies for cancer chemotherapy by using two-point boundary solver in MATLAB. By analyzing the state and the control, we study the relationship of tumor shrinking with different parameters, including growth rate r before the treatment, magnitude δ of the drug and the initial tumor size N_0. The outcome of the simulation will recommend the effective strategies prior to the patient's health status.

First scenario

In this scenario, we simulate the state and control solution by: initial conditions near 97.5% of the carrying capacity with our intent is to pull the state solution to zero. We simulate by setting the average growth rate = 10% or 0.1.

Parameters and their values

Parameters	**values**
Weight paramter a	3
Weight parameter b	1
Growth rate r	0.10
Drug magnitude δ	0.45
Initial conditions N_0	0.975
Desired level N_d	0
Time span T	5.0

By using these conditions, the state solutions drop down faster within the beginning. This means that we get an amazing and fast tumor shrink at the beginning of the treatment. As the drug control tend to exhaust, the tumor volume/the state solution seems to be no longer dropping down. Which means that the patient will need to go through the second round of the treatment at the end of the time period T.

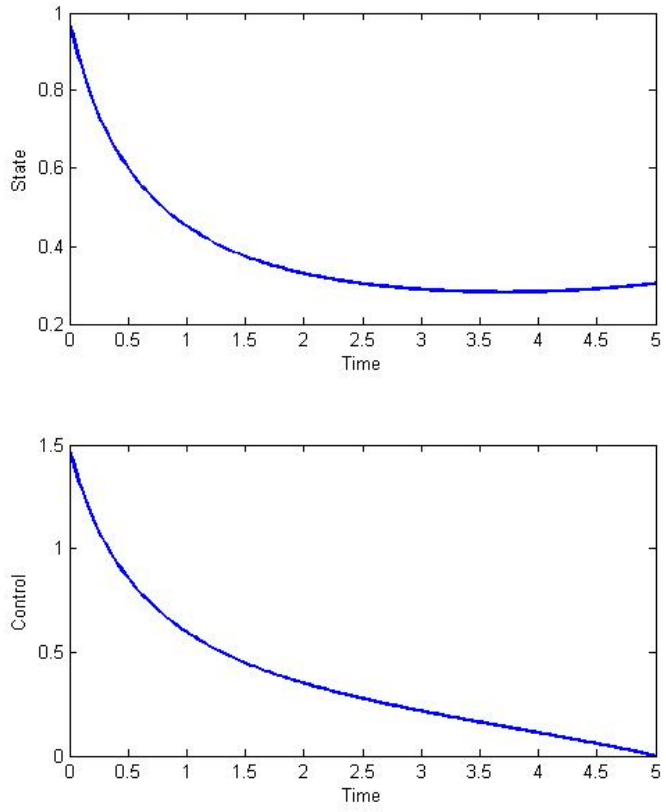

Figure 4.1: *State solution on optimal path and optimal control.*

Second scenario

To understand the drug effects on the tumor volume, it is essential to use the different initial conditions N_0 of the state. This scenario, use the same drug quantity on different tumor volume to learn the interactions between control drug and tumor state. We use N_0 equal to 50%, 75% and 97.5% of carrying capacity.

Parameters	**values**
Weight paramter a	3
Weight parameter b	1
Growth rate r	0.10
Drug magnitude δ	0.45
Initial conditions N_0	Variable
Desired level N_d	0
Time span T	5.0

Where the values of N_0 are: 0.50; 0.75; 0.975

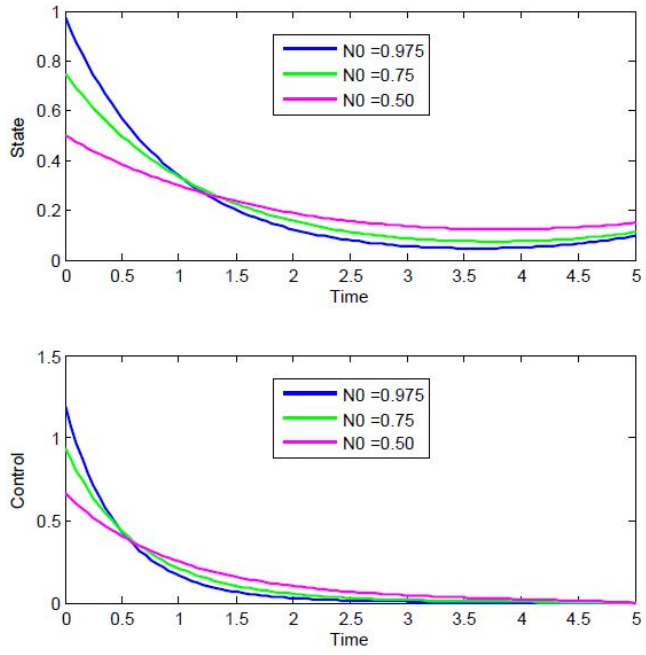

Figure 4.2: *Graphs of optimal State and control solutions with different Initial state conditions*

From the above numerical simulation, important thing to infer from this scenario, is that the quantity of the control drug u^* used must be directly proportional to the initial state solutions N_0. The large tumor volume will react to the drug control more than the small tumor. In addition, the large tumor will be shrunk further and quicker than the small tumor passing the same treatment conditions.

Third scenario

This scenario ought to show the effect of the magnitude δ of the drug on how the tumor shrink. Therefore, it is intended to repeat the first scenario by using the different drug magnitude δ while others parameters are kept fixed.

Parameters	**values**
Weight paramter a	3
Weight parameter b	1
Growth rate r	0.10
Drug magnitude δ	variable
Initial conditions N_0	0.975
Desired level N_d	0
Time span T	5.0

Where the values of δ are: 0.35; 0.45; 0.55; 0.65

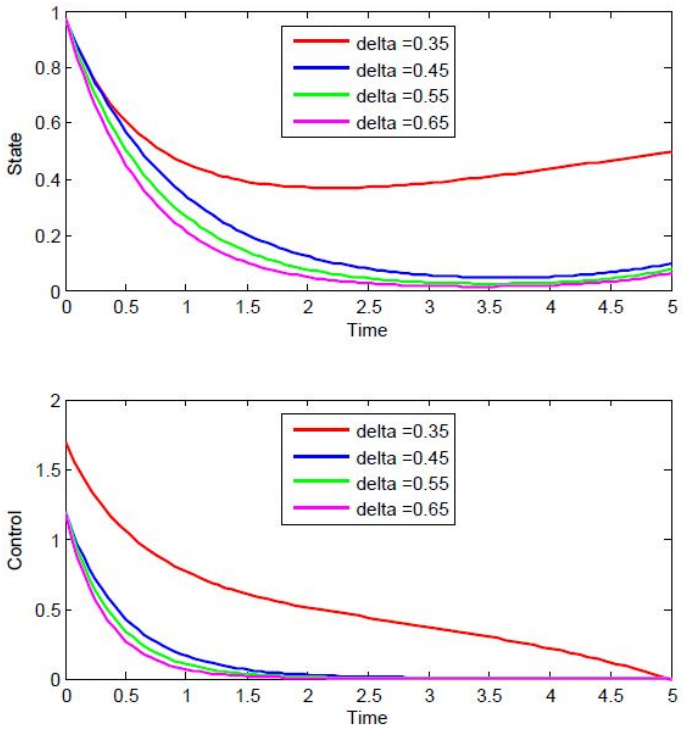

Figure 4.3: *Plot of State on optimal path and Optimal Control solution for different drug magnitude.*

The increase of the magnitude δ of drug results to the faster and bigger descent of state solution N. The more the value of δ the more tendency of the state solution to converge to the desired level N_d . This shows that the quantity of the drug used to treat the patient, has significant meaning on how fast the tumor will shrink. Although the pharmacokinetic and pharmacodynamic effects u^* of the drug possesses only a minor difference for different drug magnitudes, the magnitude matters a lot for the state solution in terms of quantity of the tumor shrunk through the treatment.

Fourth scenario

This scenario aims to study the significance of the tumor growth rate r within the treatment. Thus, we will use the same quantities of parameters used first scenario and vary only the growth rate r of the tumor. Hence, we shall double the growth rate and then observe the difference within the treatment outcome.

Parameters	**values**
Weight paramter a	3
Weight parameter b	1
Growth rate r	variable
Drug magnitude δ	0.45
Initial conditions N_0	0.975
Desired level N_d	0
Time span T	5.0

Where the values of r are: 0.05; 0.10; 0.15; 0.20

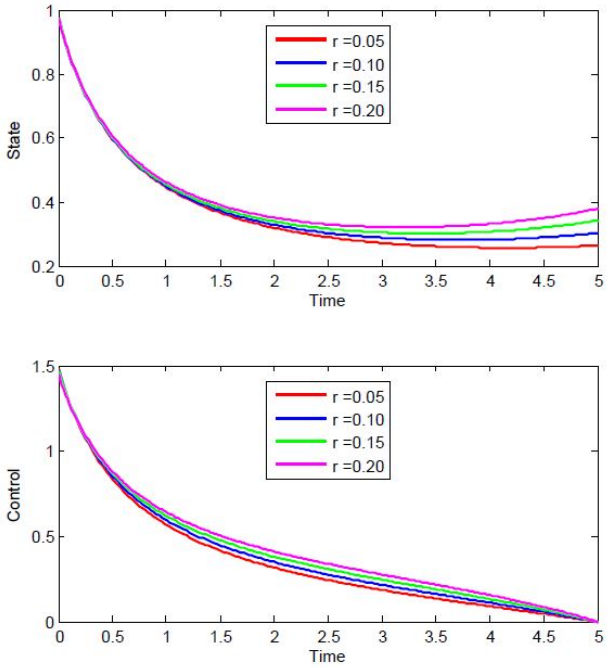

Figure 4.4: *Graph of Optimal State solution and Control over different values of growth rate r.*

From this above figure, as the growth rate r becomes larger, the state solution N^* become less descending. Which means that when growth rate r is large, the state solutions N^* will seem to be more resisting to converge to the desired level N_d. It can be seen that the fast growing tumor will tend to resist the treatment more than that with small r.

Chapter 5

Conclusion and recommendation

In this Thesis, by applying Pontryagin's Minimum Principle, we have used Optimal Control to develop optimal strategies for cancer chemotherapy. This task has been done with the help of Numerical methods to simulate the state and control solutions. General knowledge on cancer and optimal control have been presented. And the model under investigation were analyzed and simulated through different scenarios.

The simulation in scenario 2 shows that the treatment will be more effective to the large tumor and it shows that the cost of the treatment is directly proportional to the tumor volume to be treated. The scenario 3 shows that to increased magnitude of the drug will be more likely to pull the tumor volume to the desired level. Within the late simulation, scenario 4, it is seen that the fast-growing tumor will resist more to approach the desired level as the drug tends to exhaustion. Therefore, it will need the increased drug magnitude.

Our optimal control strategies and model have shown the effectiveness for cancer chemotherapy by pulling the tumor volume to the desired level. And this is achieved at the optimal quantity of the drugs used through the treatment; thus, the cost in minimal as much as possible.

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