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Optimal and Model Free Control of Tumor Immune Interaction Dynamic to Schedule Cancer Treatments

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To the Graduate Council:

I am submitting herewith a thesis written by Mohamed Alsager entitled "Optimal and Model Free Control of Tumor Immune Interaction Dynamic to Schedule Cancer Treatments." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Electrical Engineering.

Seddik Djouadi, Major Professor

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Optimal and Model Free Control of Tumor Immune Interaction Dynamic to Schedule Cancer Treatments

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Abstract

Cancer is an intricate disease that can attack different parts of the human body. In the most common types of cancer, abnormal cells divide uncontrollably and impair body tissue. Cross disciplinary research has long aided expansion of our knowledge and ability to approach problems with a different perspective. Engineers and clinicians can collaborate to solve mysteries surrounding cancer cells function and responses. Engineers have contributed to cancer treatment, by studying new ways to diagnose and treat cancer. According to a study by John Hopkins university [6] engineered nano-particles can induce immune reaction and kill cancer cells. In addition, new ways of delivering cancer therapy to actuate the immune system to kill cancerous cells were found through engineering research.

The goal behind modeling biological systems is to drive the states to a desirable outcome using control elements in the dynamic system. In this thesis, we explore the effects of an Intelligent Proportional Integral Derivative (iPID) controllers; using optimal and model free control to improve the state of a cancer patient using recommended safe dosages. A non-linear mathematical model of Ordinary Differential Equations (ODE) is used to simulate a virtual cancer patient using realistic valued parameters. It is important to bear in mind that the human body is complex and variable. In particular, the immune response can vary from one patient to another. The parameters used to model the cancer have been deduced by clinicians and engineers to represent the tumor immune interaction using mathematical equations.

The dissertation will begin by exploring the cancer therapy's mathematical model, the controllability and observability to assure that the model is controllable, and explore different control methods and compare the results.

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

The objective of this thesis is to control a nonlinear set of ODEs that represents a virtual cancer patient. Control theory has long been used in different applications such as economics, engineering, biological systems, etc. to control outside elements to produce the best possible outcome [36]. The aim of this thesis is to explore control techniques that cure the malignant tumor through chemo and immunotherapy and bring the virtual patient to a healthy state. It is worth mentioning that the nonlinear cancer model does not apply to all cancer patients because the biology of humans is different: immune response, genetics, varying underlying health conditions, and type of cancer. Therefore, the biological reaction will also differ. In addition, due to the lack of information in biological processes, it is difficult to accurately model and parameterize a paradigm that is general to all cancer patients.

1.1 Motivation

Cancer is a disease in which a cluster of cells (tumor) form and divide uncontrollably. A tumor can be benign (non cancerous) or malignant (cancerous) [7]. Benign tumors tend to grow slowly and do not spread or invade other body parts on the other hand, a malignant tumor can attack healthy cells and tissues and grow rapidly from the initial place where it formed . Early diagnosis often leads to a more effective treatment because the spread of the cancerous cells will not have reached dangerous levels. Cancer is treated differently based on the type of cancer and how far it has expanded. Cancer severely impacts people all over the

world. According to the National Cancer Institute (NCI), cancer is one of the most causes leading to death. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide [1]. The number is projected to increase yearly.

In recent decades, much research toward modeling the dynamics of immune system and cancer therapy has been conducted. As a result of modeling biological systems, using computational tools, and applying different control methodologies researches have obtained desirable outcomes in treating illnesses as seen for example in [19, 13, 39]. The motivation behind the thesis is to explore control methods than can assist medical professionals in cancer treatment scheduling. The various control methods can be analyzed in order to select the most effective drug delivery therapy. The therapy should be balanced, meaning safe amount of dosage for quickest possible recovery time. In the next section we present a review of cancer modeling in recent decades, the different cancer dynamics presented, and the clinical tests carried out to attain the system parameters.

1.2 Cancer Dynamic Model

Due to the overwhelming effect of cancer on the lives of millions of people, much research has been devoted to treatments, therapy scheduling, and diagnosis. Modeling systems in various fields of study has been a powerful tool, allowing researchers to better understand the behavior of systems. In addition, it allows in identifying potential outcomes due to a change, or making adjustments to enforce a a certain outcome. Certainly, through control theory and simulation tools, we are able to manipulate the behavior of the system and achieve desired results. The cancer model dynamic being investigated in this thesis is composed of states and input variables. The states are: tumor cells, lymphocyte cells, and pharmacokinetics. The input variables include chemo and immunotherapy injections.

1.2.1 Modeling Tumor growth

Tumors occur because of accumulated **epigenetic alterations** within single cells which is the change of organisms due to change in gene expression rather the genetic code itself. That cell then divides and expands uncontrollably. The abnormal **proliferation** (rapid increase

and expansion) of tumor cells puts a strain on the human body in the sense that, these cells feed on nutrients and oxygen to cause the tumor to grow even larger. They compete against the healthy cells for these resources. Once the tumor starts growing in size, the cells in the center of tumor begin to die due to lack of resources. As a results the growth of the tumor slows down. The necrotic (dead) cells **Vascular endothelial growth factor** (VEGF) is activated. It is a protein signal that stimulates **angiogenesis** which is the formation of new blood vessels by sprouting from existing blood vessels to restore oxygen; since there is a lack of blood flow. Once the new blood vessels have formed the tumor then begins to expand again. The process is described in figure 1.1. The Tumor cells are always the first to arrive on the scene meaning, they deplete the resources and unlike the healthy cells they can expand and break out to other parts of the body to continue feeding and growing to form new tumors. This process is called **metastasis**, where the word malignant is derived from. According to [5], some of the key differences between tumor and normal cells are as follows:

- The cancer cells have abnormal shapes and nucleus size.
- Cancer cells are less specialized than normal cell. When normal cells form, they mature to be distinct and have special functions and tasks.
- Tumor cells can evade signals that tell cells to stop dividing. The process is known as programmed cell death, or **apoptosis**. The body uses this function to discard unnecessary cells.

The differences between normal and cancerous cells can be seen in figure 1.2. It is evident that the underlying process of the tumor growth is complex. So how did researchers formulate the mathematical model of tumor growth?

In the literature one will find a variation of mathematical formulations of tumor growth and cancer treatments. The mathematical formulations resorted to expressing the model by Partial (PDE) or Ordinary Differential Equations (ODE) as in [31, 19] respectively. The model parameters may also differ based on the treatment used, for example the model used in [39] the author presents chemo and immunotherapy as control inputs while in [20] only

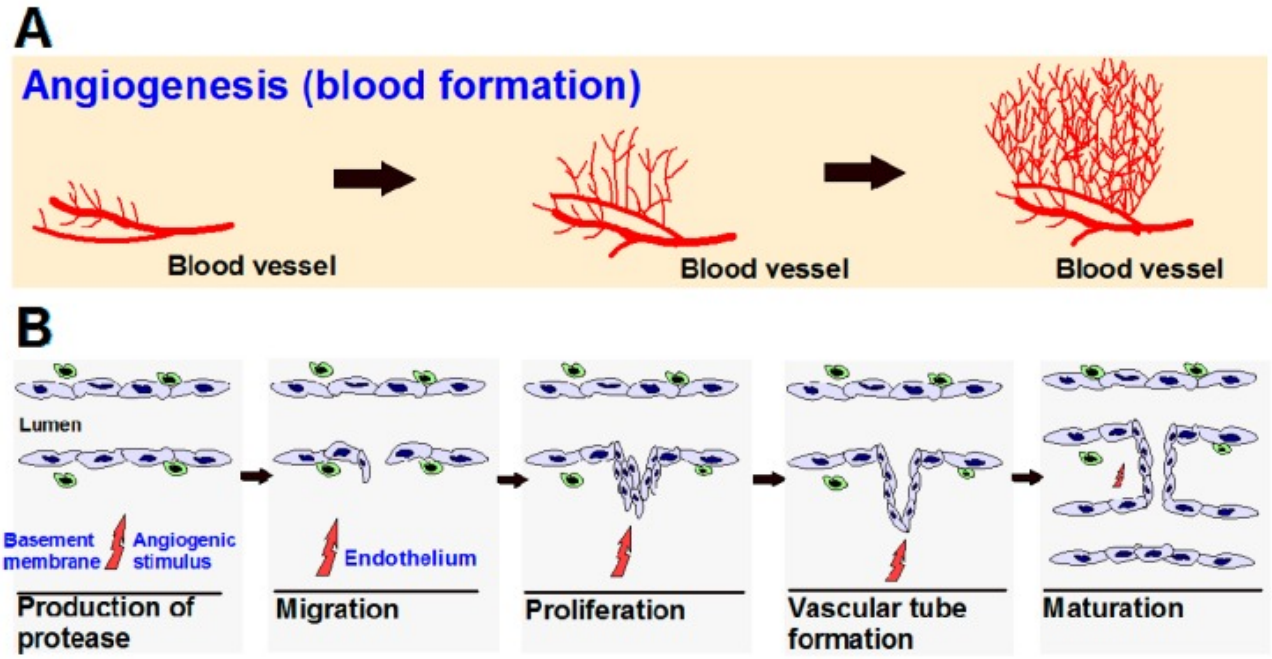


Figure 1.1: (A) Angiogenesis is the process of the development of new blood vessels from pre-existing vessels, which allows for tumor progression; (B) Steps in angiogenesis [42]

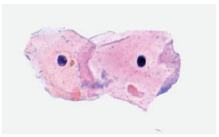
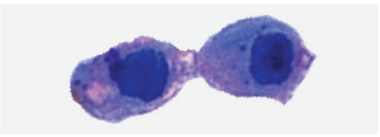
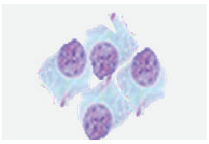
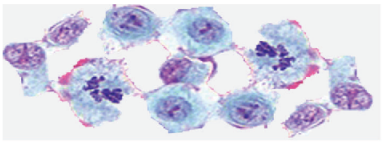
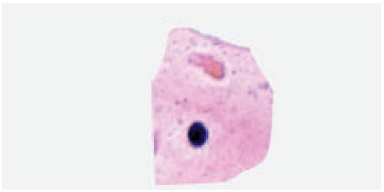
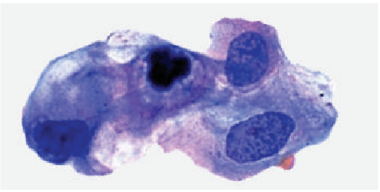
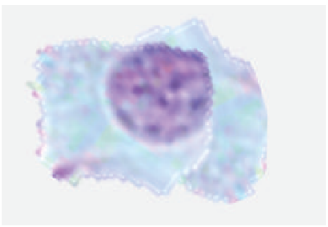
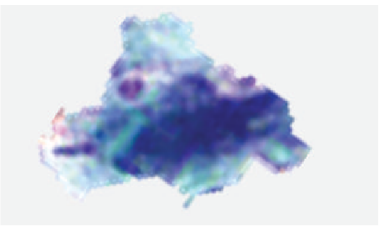
Normal cells	Cancerous cells	Description of cancerous cells
		Large and variably shaped nuclei
		Many dividing cells and disorganized arrangements
		Variation in size and shape of nuclei
		Loss of normal feature (shape and morphology)

Figure 1.2: Differences between normal and cancerous cells [43]

a chemotherapy inhibitor is used.

The general form of Tumor growth is represented by:

$$\dot{x_1} = \mu_C \cdot x_1, \quad x_1(0) = x_1^0. \tag{1.1}$$

where $x_1(t)$ represents the tumor cells at time t and μ_C is the growth rate. Most models have expanded on equation (1.1) by incorporating proliferation rate, the affect of necrotic cells, the therapy agent inhibitors, angiogenesis, etc.

In order to limit the carrying capacity of tumor cells other terms have been proposed in the literature [34, 38]:

$$\dot{x_1} = \mu_C x_1 (1 - \frac{x_1}{x_\infty}), \quad x_1(0) = x_1^0. \tag{1.2}$$

$$\dot{x_1} = -\mu_C x_1 \ln(\frac{x_1}{x_\infty}), \quad x_1(0) = x_1^0. \tag{1.3}$$

which is mainly logistic growth and Gompertizian growth as seen in equations (1.2) and (1.3) respectively. Both consider a limited cancer carrying capacity represented by x_∞. In the thesis we focus on the logistic growth.

1.2.2 Modeling Lymphocyte Cells

In this section we present facts pertaining to the immune system summarized from [3, 8]. A Lymphocyte is a type of immune cell that is made in the bone marrow and found in the lymph tissues. It is a type of white blood cell that combats antigens and foreign bodies. It is part of the adaptive immune system. There are two types of immune responses: innate and adaptive immunity. The innate immune system is the first line of defence; soon after the appearance of antigens or a foreign substance the nonspecific defense mechanisms is activated within hours of an antigen's appearance in the body. The innate immune system reacts the same way to different antigen's every time and it does not have immune memory which is the reason the mechanism is referred to as nonspecific. These mechanisms include

physical barriers such as skin, chemicals in the blood, and immune system cells that attack foreign cells in the body.

Adaptive immunity refers to antigen-specific immune response. The mechanism of the adaptive immunity is far more intricate than the innate response. The adaptive immunity combats antigens as follows:

1. The antigen must be first processed and recognized
2. The adaptive immune system sends an array of immune cells to kill the antigen. It tries using distinct types of cells and methods to get rid of the antigen.
3. If the immune system is successful in defeating the antigen, the treatment type along with the specific antigen type are saved to the immune memory in case of future breach of the same antigen, the immune system will be more efficient.

In Oncology modeling, the lymphocyte cells is a good indicator of the immune system and the healthy cells. An oversimplified expression pertaining Lymphocyte cell growth is given in (1.4):

$$\dot{x_2} = \mu_I x_2, \quad x_2(0) = x_2^0. \tag{1.4}$$

where $x_2(t)$ represents the lymphocyte cells at time t and μ_I denotes the tumor stimulated proliferation rate of the lymphocyte cells. The author in [10] proposed a model that takes into account the effects of tumor cells on lymphocyte cell growth, as can be seen in equation (1.5)

$$\dot{x_2} = \mu_I \mathcal{J}(x_1, x_2), \quad x_2(0) = x_2^0. \tag{1.5}$$

where $\mathcal{J}(x_1, x_2)$ denotes the growth rate function of Lymphocyte cells.

1.2.3 Modeling Chemotherapy

Chemotherapy is a drug treatment that uses powerful chemical agents such as Alkylating, Antimetabolites, Antitumor antibiotics, etc [4]. The different types of chemotherapy agents differ in compound and in which phase the agent interacts with the body, but it is mainly used to kill fast growing tumor cells. Much work has been done to examine the effects of chemotherapy interactions, in [37] the author introduced the function $\mathcal{M}$ in equation (1.6):

$$\dot{x_1} = \mu_C x_1(1 - \frac{x_1}{x_\infty}) - \mathcal{M}(x_1, u_1), \quad x_1(0) = x_1^0. \tag{1.6}$$

The concentration at time t of the chemotherapy drug is $u_1(t)$ and $\mathcal{M}$ denotes the decrease in tumor cells due to the chemotherapy agent. The assumption made is that the net change in the tumor cell population is the difference between the increase in cells due to cell proliferation, and decrease in cells due to the chemotherapy drug injection $\mathcal{M}(\cdot)$. The chemotherapy drug used in equation (1.6 is assumed to be nonspecific phase Alkylating agents so that, differences in growth fraction are insignificant thus, the proportion of cells killed depends on the tumor growth rate. The drug effect term is usually considered proportional to the tumor cell population, so $\mathcal{M}(x, u_1) = \sigma x_1 u_1$. According to [35], the Pharmacokinetics is not taken into account, because the drug dosage is equal to the concentration of the chemotherapy drug in the body however, that is an inaccurate depiction. The authors suggest evaluating the concentration by adding another state x_3 to represent the chemotherapeutic concentration:

$$\dot{x_3} = -ax_3 + bu_1, \quad x_3(0) = 0. \tag{1.7}$$

Equation (1.7) allows us to model the drug concentration growth or decay. The chemotherapy also has an effect on the lymphocyte cells. The authors in [41] proposed a model that takes account the effects of chemotherapy agents on the lymphocyte cells:

$$\dot{x_2} = \mu_I \mathcal{J}(x_1, x_2) - \mathcal{L}(x_2, u_1) -, \quad x_2(0) = x_2^0. \tag{1.8}$$

where $\mathcal{L}(x_2, u_1)$ is the effect of chemotherapy agent on lymphocyte cells. It will have an adverse effect on both the tumor and lymphocyte cell populations.

1.2.4 Modeling Immunotherapy

In section 1.2.4, we summarize facts about immunotherapy from [2] and introduce the notion of modeling immunotherapy on the tumor-immune interaction dynamic. The immune system instinctively combats infections and diseases. It is made up of white blood cells, organs, and lymph tissues. One of the tasks of the immune system, is to detect and destroy abnormal cells and prevents the growth of cancer tumors. Ordinarily immune cells can be found in and around tumors. These cells referred to as **tumor-infiltrating lymphocytes** or TILs are a sign that the immune system is responding to the tumor. It has been found that patients whose tumors have TILs often have a better chance in fighting cancer.

Although the immune system can halt or minimize cancer growth, cancer cells have ways to evade the immune system. Cancer cell's defence mechanism includes:

- Changing their genetic structures to imperceptible to the immune cells.
- They have proteins on their surface of that can disengage immune cells.
- Interfering with the response of the immune cells by changing the formation of the cells on the surface of the tumor.

It is evident that in some cases the immune system is successful in combating the tumor however, if the tumor growth expands, immunotherapy can help the immune system fight cancer. There are various types of immunotherapies used to treat cancer, these include [2]:

- **Immune checkpoint inhibitors**, They block proteins that are called immune checkpoints. These checkpoints keep the immune response from being too strong.

When the check points are blocked they allows immune cells to be more severe and kill cancer cells.

- **T-cell transfer therapy**, The most active T-cells (immune cells) in a patient's body combating against the tumor are extracted. In the lab they reproduce and modify those T-cells to better kill the cancer cells. Then they are injected back into the patient's blood stream.

- **Monoclonal antibodies**, which are immune proteins created in the lab to mark the cancer cells so that the immune system can easily spot and target the cancer cells.

- **Treatment vaccines**, which are used to boost the immune system. They are different from normal vaccines that prevent viruses or disease.

Immunotherapy is not as widely used as other therapies such as chemotherapy, radiation, and surgery. In addition, not all patients respond to immunotherapy. There's ongoing clinical research to find better combinations of immunotherapies to treat cancer.
Constructing a mathematical model to capture the mechanism of the immunotherapy is very complex and there are unknown parts of the system. According to [21], although there have been large strides in biological modeling, there are still some open questions in immune system modeling. The dynamic of the innate and immune response need to be examined at the molecular tissue and cellular level to better grasp the dynamics of the immune system. Researchers have focused on the immune system parts that have significant effect on tumor growth [17]. A general model that is accepted among oncology researchers presented in [19] formulates the tumor-immune interaction as follows:

$$\begin{aligned} \dot{x_1} &= \mu_C x_1(1 - \frac{x_1}{x_\infty}) - \gamma x_1 x_2 - \sigma x_1 u_1, \\ \dot{x_2} &= \mu_I x_1 x_2 - \mu_I \beta x_1^2 x_2 - \chi x_2 + \alpha + \lambda x_2 u_2. \end{aligned} \tag{1.9}$$

We will use the model represented by the system in (1.9) in the thesis with a modification introduced in equation (1.7).

1.3 Background and Overview

The dynamic tumor growth model in [40] is used in this thesis. The model is concerned with tumor-immune interaction with the presence of outside control to achieve the necessary outcome. Two control methods are used to attain a healthy state: Model Free Control (MFC) and Optimal Control (OC). OC introduces an objective function which is the goal that the control tries to reach, while the MFC technique steers the controls toward the healthy state and injects it back into the dynamical model in iterative fashion. In the following subsections we provide a brief introduction of the control techniques used.

1.3.1 Optimal Control

Optimal Control theory is a mathematical optimization method that obtains a control to produce the best outcome possible based on a predetermined goal. It is also referred to as dynamic optimization [36]. Optimal Control strategies have long been used in dynamic models. In [22], optimal control was used for harvesting in a predator-prey parabolic system, while in [16] it was used for maximizing final yield when growth is limited by time or resources. For more examples of optimal control strategies see [13, 15, 18, 17].
In this research, the OC method is used to control the dynamical tumor model for a specified time interval. We use varying objective functions and impose different constraints on the states and control inputs. We analyze the different OC objective functions to capture the optimum solution. In the case of the tumor growth model the desired outcome is to treat the virtual patient and reach a healthy equilibrium using minimal chemotherapy injections. Although chemotherapy has shown successful outcome in treating cancer, it can causes serious side effects, and high dosages can be toxic.

1.3.2 Model Free Control

Through research and derivation of mathematical equations different control methods have been developed. The formulation of control methods differ, but the ultimate objective is to control the system. Model Free Control is an intelligent Proportional Integration Derivative controller (iPID), which uses an online approach to estimate parameters [24]. Although

MFC was only introduced in 2008-2009 [23] it was applied to numerous control problems in different areas and displayed favorable results. For example implementing MFC to study immune response in [13], MFC was also used for controlling intelligent transportation systems in [9]. For more examples on MFC applications see [14, 11, 45].

Using functional analysis and elementary differential algebra, MFC can be applied to complex models to deduce control inputs capable of acquiring desirable outcomes. The MFC methodology includes a set of parameters that need to be tuned by trial and error, and are dependent on the dynamics of model. A detailed interpretation of the theoretical formulation of MFC control will be presented later in chapter **??**.

1.4 Summary of Contributions

The contribution of the thesis is summarized as follows:

1. The thesis proves the nonlinear cancer model is locally controllable. The controllability matrix is found and the rank is calculated. It is important to establish that the system is indeed controllable in order to reach the goal of treating the patient. If the system is uncontrollable then the therapies used are deemed insufficient and will not help the patient get to a healthy state.

2. The thesis proves the nonlinear cancer model is locally observable. The observability matrix is found and the rank is calculated. It is important to establish that the system is indeed observable in order to have a clear understanding of the behavior of the dynamic cancer model.

3. Using OC methods, the cancer patient is cured and recovers within a 60-day treatment regimen. The OC strategy proves to be successful when tested under different constraints and initial conditions.

4. The model-free control method was also explored. The online intelligent controller showed positive results and was able to provide a successful treatment regimen within the 60-day treatment period. Some of the MFC parameters displayed better results and so they were selected by means of trial and error.

1.5 Organization of Thesis

The Thesis is organized as follows:-

- Chapter 2 introduces the dynamical model of the tumor-immune interaction. The parameters of the model will be defined. Based on the dynamical model the healthy equilibrium and unhealthy equilibrium are derived.
- In Chapter 3 the concept of controllability and observabilty for the nonlinear dynamical model consisting of ODE is explained. The Controllability and Observability rank is calculated.
- Chapter 4 gives an in-depth examination of two distinct control methods: OC and MFC. The control methods are applied to the virtual patient to derive suitable controls to treat the patient and the results are presented.
- Chapter 5 concludes the work that has been done in this research thesis and suggests future work to be explored.

Chapter 2

The Cancer Mathematical Model

tumor-immune biological models were first introduced in 1980 by Stepenova [44]. In Chapter 2 we introduce the mathematical cancer model for the tumor-immune interaction. The model explored throughout the thesis was previously introduced in [40]. The author in [35], deduced that the dosage of the therapy is not equal to the amount of drug concentrated in the patient's body, so the initial model used in [19] and [39] has been expanded by adding a state representing pharmacokinetics (PK) which captures the amount of chemotherapy concentrated in the patient's body.

2.1 Virtual Patient

The mathematical model is composed of nonlinear ODEs, which represents the tumor-immune interaction given by equations (2.1) - (2.3).

$$\dot{x_1} = \mu_C x_1 - \frac{\mu_C}{x_\infty} x_1^2 - \gamma x_1 x_2 - \sigma x_1 x_3, \tag{2.1}$$

$$\dot{x_2} = \mu_I x_1 x_2 - \mu_I \beta x_1^2 x_2 - \chi x_2 + \alpha + \lambda x_2 u_2 - \varrho x_3 x_2, \tag{2.2}$$

$$\dot{x_3} = -a x_3 + b u_1. \tag{2.3}$$

The biological model referenced above is attentive to the progression of Tumor Cells (TC) population, the Lymphocyte Cells (LC) population, and the chemotherapy drug concentration. A tumor can either be malignant (cancerous) or benign (non-cancerous). The

tumor forms as a result of abnormal cells dividing in the body. The cells in the human body continuously divide for repair and growth. However, the tumor formation is an irregularity that can lead to cancer. The TC count is observed by equation (2.1).

LCs are a type of white blood cells composed mainly of B lymphocytes and T lymphocytes. B lymphocytes make antibodies, while T lymphocytes help kill tumor cells and help control immune responses [3]. LC count can be an indication of the body's immune response. LC count is observed by equation (2.2).

Monitoring levels of chemotherapy concentration in the body is extremely important in cancer treatment. Using high quantities of chemotherapy can be toxic and lead to death. As mentioned previously, the concentration of chemotherapy existent in the body of the patient is not equal to the chemotherapy dosage. The model monitors the chemotherapy concentration in equation (2.3).

The dynamic cancer model is represented by the tumor-immune system interactions in the presence of input variables: cytotoxic agents and immuno-stimulator to treat the virtual patient. The aim is to move the initial conditions of the states from the malignant to the benign region.

The tumor-immune system interaction is composed of three states:

- x_1 : Tumor cell population;
- x_2 : Lymphocyte cell population; and
- x_3 : Chemotherapy drug concentration in patient.

The model comprises two time varying control inputs denoted as follows:

- $u_1(t)$: dosage of a cytotoxic agent; and
- $u_2(t)$: cytokines which is a generic immuno-stimulator.

The treatment duration of the model examined is 60-days. Given initial conditions of the states and after performing the distinct control techniques, the condition of the virtual patient is examined and the following outcomes can be expected:

1. benign outcome: The treatment is considered successful in reducing the tumor size to the benign equilibrium and preventing further spread of the cancer.

2. Malignant outcome: The treatment has failed in containing the spread of the cancer leading the states to travel to the malignant equilibrium due to tumor growth and immunity suppression.

When the dynamic model is uncontrolled: meaning that the time varying control inputs are not injected in the system (u_1,u_2=0) the outcome of differing initial conditions is given in the phase portrait in figure 2.1. The phase portrait is the state space trajectory of the system. It reveals invaluable information of the behavior of the system and determines the equilibrium points. It can be seen from the phase portrait that the behavior of the dynamic relies heavily on the initial conditions which is logical. It has been established that the results of combating cancer in early stages is far more optimistic than the late-stage of cancer when the spread has overwhelmingly reached lymph nodes and other parts of the body. The macroscopic malignant equilibrium point is $x_m = (766.4, .018, 0)$, and the benign one is $x_b = (41.45, .954, 0)$.

Although the state of the virtual patient can only be benign or malignant, the interplay of interaction is not confined to tumor suppression or tumor expansion. On the contrary, studies have shown that tumors may survive in microscopic levels having a dormant state, and can be reactivated due to sudden events affecting the immune system [32]. If the immune system experiences impairments due to disease or in some cases drugs such as immuno-suppressing agents that are used to prohibit the immune system from causing damage to the body preceding an organ transplant, then the tumor may restart developing [19].

Figure 2.2 illustrates the interconnections of the mathematical model in equations (2.1) - (2.3) of tumor and immune interaction in the presence of other parameters and time varying inputs. The larger shapes symbolize the states of the system which are the TCs, LCs, and PKs. The two smaller shapes symbolize the time varying inputs consisting of chemotherapy drug and immunotherapy stimulators. The lines connecting the states and inputs are the parameters of the system which will be defined in table 2.1.

The dynamic equations describe the interactions of the three states: x_1,x_2, and x_3 are governed by various parameters and two time varying control inputs: $u_1(t)$ and $u_2(t)$. The reference set of parameters are given in [40], and shown in Table 2.1 along with their definitions and numerical values.

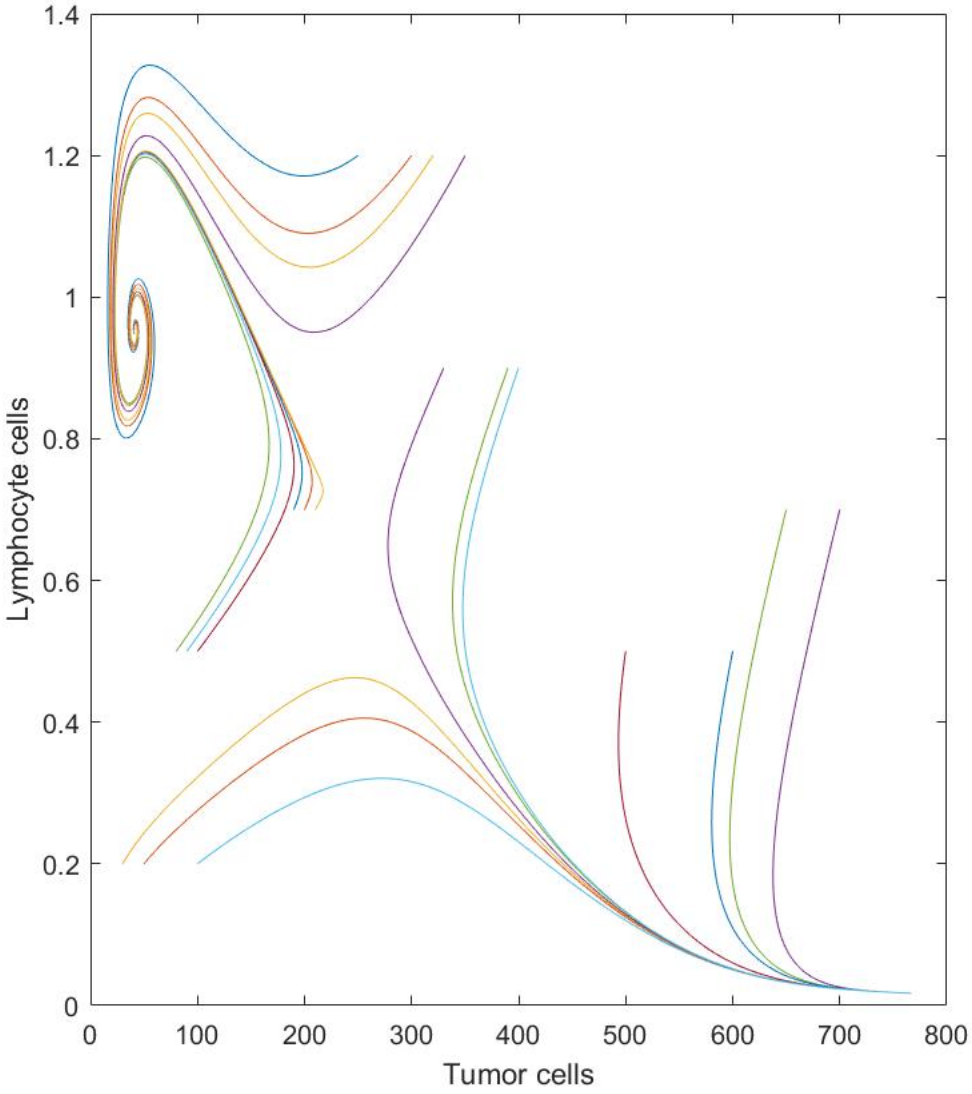


Figure 2.1: Phase portrait of tumor-immune interaction model

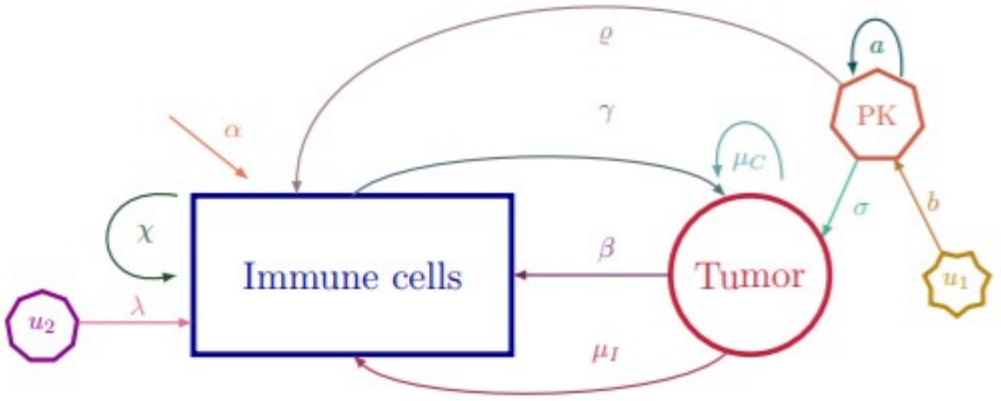


Figure 2.2: Diagram of tumor-immune system interaction in response to time varying input controls consisting of u_1 and u_2 which denote chemotherapy and immunotherapy respectively [40].

Table 2.1: Numerical values and definitions of the parameters in the cancer model [40].

Parameter	Definition	Numerical Value
μ_C	tumor growth rate	$1.0078 \cdot 10^7$ cells/day
μ_I	tumor stimulated proliferation rate	.0029 day^{-1}
α	rate of immune cells influx	.0827 day^{-1}
β	inverse threshold	.0040
γ	interaction rate	$1 \cdot 10^7$ cells/day
χ	death rate	.1873 day^{-1}
σ	chemotherapeutic killing parameter	$1 \cdot 10^7$ cells/day
λ	immunotherapy injection parameter	$1 \cdot 10^7$ cells/day
x_∞	fixed carrying capacity	$780 \cdot 10^6$ cells
ϱ	chemo-induced loss of immune cells	1
a	chemotherapy concentration decay	0.5
b	drug rate effect on chemotherapy concentration	1

Chapter 3

Nonlinear Controllability and Observability

3.1 Introduction

Before designing a controller for any system, a control engineer must examine a system and determine that it is controllable: the inputs injected into the system will achieve the desired outputs. Systems deemed to be uncontrollable will behave at random and may never achieve the required outputs. Controllability relates to our model in the sense that; the chemotherapy and immunotherapy injections will indeed reduce the tumor size to the benign region without compromising the health of lymphocyte cell count. Observability is also another important concept which conveys how well the state variables are estimated based on the output or the external states. In linear systems the controllability and observability are easily checked based on the rank of the controllability and observability matrices, the system can be verified as being controllable and or observable. However, the dynamic of the tumor-immune interaction model is nonlinear and requires more rigorous computation. The local controllability and local observability of the system can be checked using linear algebraic manipulation of the system equations. Chapter 3 presents the concept of local controllability and local observability of nonlinear systems alongside the computation to ascertain that the system is locally controllable and locally observable. The theorems, definitions, and equations used in chapter 3 are summarized from the work presented in [29, 27, 26, 30, 25].

3.2 Nonlinear Controllability

The dynamical system is said to be locally controllable if there exists an external input u that is able to move the internal state of a system from any initial state x^0 to any other final state x^1 in a finite time interval. Otherwise, the system is said to be uncontrollable. Note that controllability does not mean that the final state can be maintained, merely that any state can be reached. Lie Brackets are used in calculating controllability matrix rank in nonlinear system. The Lie Bracket and nonlinear controllability is defined below.

Definition 3.1. *Consider two vector fields $f(x)$ and $g(x)$ in $\Re^n$ space. Then the Lie bracket operation generates a new vector field [25]:*

$$[f,g] \equiv \frac{dg}{dx}f - \frac{df}{dx}g \tag{3.1}$$

Higher order Lie brackets can be defined as follows:

$$\begin{aligned} &(ad_f^1) \equiv [f,g], \\ &(ad_f^2) \equiv [f,[f,g]], \\ &\quad ... \\ &(ad_f^k) \equiv [f,(ad_f^{k-1})] \quad for \quad k = [1,2,...]. \end{aligned} \tag{3.2}$$

Note: the "ad" stands for adjoint.

Consider an affine control system $\sum$, described in local coordinates by [29]:

$$\sum : \begin{cases} \dot{x}(t) = f(x(t),u(t)) = & f(x(t)) + \sum_{i=1}^{m} g_i(x(t))u_i(t), \\ y(t) = h(x(t)), & x(0) = x^0. \end{cases} \tag{3.3}$$

where $t \mapsto u_i(t)$ is a control function with values in a convex set $\Omega \subset \mathbb{R}$, $t \mapsto x(t)$ is the state trajectory with $x(t) \in \mathbb{R}^n$, and $t \mapsto y(t)$ is the output curve with $y(t) \in \mathbb{R}^p$. Given

the system in equation (3.3) initialized at x^0, the map:

$$S_{x^0} : \{t \mapsto u(t), t \in [0,T]\} \longrightarrow \{t \mapsto y(t), t \in [0,T]\} \tag{3.4}$$

is called the input-output map.

Suppose we are given a system $\sum$ and an initial state x^0. Let x^1 be another state. Is it possible to choose a control input $t \mapsto u(t)$ to steer $\sum$ from x^0 to x^1? Is x^1 accessible from x^0? $\sum$ is said to be **controllable** if every state is accessible from every other state [29].

Theorem 3.2. *The system is said to be locally* ***accessible*** *about a point x^0 if and only if the* ***controllability matrix*** *C spans $\mathbb{R}^n$: rank (C)=n and C is defined by [25]:*

$$C = [g_1, ..., g_m, [f, g_1], ..., [f, g_m], [f, (ad_f^1)], ..., [f, (ad_f^k)]] \tag{3.5}$$

3.2.1 The Controllability Rank

In this section, the concept of nonlinear controllability is applied to the tumor-immune interaction model to calculate the controllability matrix C defined in equation (1). The tumor-immune interaction model given by equations (2.1) - (2.3) can be rewritten as:

$$\sum : \begin{cases} \dot{x}(t) = f(x(t)) + g_1(x)u_1 + g_2(x)u_2, \\ y(t) = h(x(t)), \quad x(0) = x^0. \end{cases} \tag{3.6}$$

where $f(x)$ is a function such that: $\mathbb{R}^3 \to \mathbb{R}^3$, $x(t) \in \mathbb{R}^3$, y: $\mathbb{R}^3 \to \mathbb{R}^2$. $g_1(x)$,$g_2(x)$, and $f(x)$ of system (3.6) are defined as follows:

$$g_1 = \begin{bmatrix} 0 & 0 & b \end{bmatrix}^T, \tag{3.7}$$

$$g_2 = \begin{bmatrix} 0 & \lambda x_2 & 0 \end{bmatrix}^T, \tag{3.8}$$

$$f(x) = \begin{bmatrix} \mu_C x_1 - \frac{\mu_C}{x_\infty} x_1^2 - \gamma x_1 x_2 - \sigma x_1 x_3 \\ \mu_I x_1 x_2 - \mu_I \beta x_1^2 x_2 - \chi x_2 + \alpha - \varrho x_3 x_2 \\ -a x_3 \end{bmatrix}. \tag{3.9}$$

From theorem 3.2 and the defined functions of the dynamical system in (3.7)-(3.9) the controllability matrix becomes:

$$C = \begin{bmatrix} g_1, & g_2, & [f, g_1], & [f, g_2], & [f, [f, g_1]], & [f, [f, g_2]] \end{bmatrix}. \tag{3.10}$$

The controllability matrix is calculated using the **Matlab** function "liebracket" which results in:

$$C = \begin{bmatrix} 0 & 0 & 3 & x_1 & x_1 x_2 & .. & .. \\ 0 & x_2 & const & x_2 & .08 & .. & .. \\ 1 & 0 & 3 & 1/2 & 0 & .. & .. \end{bmatrix} \tag{3.11}$$

The rank of $C = 3$ which means the system is deemed locally controllable. Note that columns five and six of C are not calculated because the current matrix C has a rank of three and cannot go any higher, so there is no need for further calculations.

System $\sum$ defined in equation (3.6) is locally controllable; which means that every state is accessible from every other state. In other words, the virtual patient can be treated by using chemo and immunotherapy u_1 and u_2, respectively, to compress the TC (x_1) while maintaining a healthy level of lymphocytes (x_2) in the patient's body.

3.3 Nonlinear Observability

Intuitively, a system is said to be observable if in a finite system the previous states can be obtained by observing sensor measurements. For controllability in nonlinear systems the concept of accessibility is studied, similarly for observability in nonlinear systems it is expressed by the notion of distinguishability.

Definition 3.3. *Two states x^0 and x^1 are **distinguishable** if there exists an input function $u^*(t)$ such that: $f(x^0) \neq f(x^1)$ [25].*

To obtain the local observability matrix the "Lie derivative" is used.

Definition 3.4. *Given a system $\dot{x} = Ax$ [25],*

$$z_i = M_i x \quad i \in [1,p], \quad M_i \text{ is } 1\times n \text{ vector}$$
$$\implies z_i = h_i(x) = L_f^0(h_i)$$
$$\dot{z}_i = L_f^1(h_i)$$
$$z_i^{(k)} = L_f^k(h_i)$$

$$\text{Define } G = \begin{bmatrix} L_f^0(h_1) & \dots & L_f^0(h_p) \\ \dots & \dots & \dots \\ L_f^{n-1}(h_1) & \dots & L_f^{n-1}(h_p) \end{bmatrix} = \begin{bmatrix} M_1 x & \dots & M_p x \\ \dots & \dots & \dots \\ M_1 A^{n-1} x & \dots & M_p A^{n-1} x \end{bmatrix}$$

Note that the term $L_f^0(h) = h$ and the Lie derivative looks like :

$$L_f(h) = \left[\frac{dh}{dx_1}, \dots, \frac{dh}{dx_2}\right] \begin{bmatrix} f_1(x) \\ \dots \\ f_n(x) \end{bmatrix} \implies L_f(h) \text{ is a scalar.}$$

Now, a gradient operator is defined:

$$dG = \begin{bmatrix} dL_f^0(h_1) & \dots & dL_f^0(h_p) \\ \dots & \dots & \dots \\ dL_f^{n-1}(h_1) & \dots & dL_f^{n-1}(h_p) \end{bmatrix} = O$$

*O is the **local observability** matrix.*

For control u^*, and initial state x^0, the local observability matrix is defined as follows:

$$O(x^0, u^*) = \begin{bmatrix} dL_f^0(h_1) \\ \dots \\ dL_f^0(h_p) \\ dL_f^{n-1}(h_1) \\ \dots \\ dL_f^{n-1}(h_p) \end{bmatrix} \tag{3.12}$$

Theorem 3.5. *Let G denote the set of all finite linear combinations of the Lie derivative of h_1,...,h_p with respect to f for various values of u(t) (constant value). Let dG denote the set of all their gradients. If n linearly independent vectors are found within dG, then the system is* ***locally observable*** *[25].*

The system is ***locally observable****, that is distinguishable at point x^0 if there exists a neighborhood of x_0 such that in this neighborhood,*

$$x_0 \neq x_1 \implies z(x_0) \neq z(x_1)$$

"if the sensor reading are different, then the states are different"

3.3.1 The Observability Rank

Applying the definitions and theorems of section 3.3; the local observability matrix of the tumor-immune interaction model is defined as follows:

$$O = \begin{bmatrix} dh_1 \\ dh_2 \\ dh_3 \\ dL_f^1(h_1) \\ dL_f^1(h_2) \\ dL_f^1(h_3) \end{bmatrix} \tag{3.13}$$

where h_1, h_2, h_3 are equal to x_1, x_2, and x_3, respectively, and $L_f^1(h_1)$, $L_f^1(h_2)$ and $L_f^1(h_3)$ are equal to f_1, f_2 and f_3, respectively. It is easily determined that the observability matrix dh_1, dh_2, and dh_3 forms a 3x3 identity matrix which will have a rank of 3. This means that the system is locally observable.

3.4 Controllability and Observability Summary

Controllability addresses the issue of actuation and the ability of the actuators to control the states of the system. On the other hand, observability addresses the issue of sensing and the ability of the sensors to capture the dynamical behavior of the system.
Observability is the dual notion of controllability. It deals with determining the states of the system from the knowledge of the input $u(t)$ and output $y(t)$. More precisely:

1. Observability refers to determining the initial state x^0 from future inputs and outputs $u(t)$ and $y(t)$, respectively, for duration time T.

2. Controllability refers to determining the final state x^1 from past inputs and outputs $u(t)$ and $y(t)$, respectively, for duration time T.

From the theorems and definitions referenced in chapter 3, it was determined that the system is locally controllable and locally observable.

Chapter 4

Applying Distinct Control Techniques on tumor-immune Interaction Model

4.1 Control of Nonlinear Systems

Nonlinear control theory is concerned with nonlinear analysis of dynamic systems. The systems can be Time Invariant (TI) or Time Varying (TV). In TI systems the dynamical model is not time dependant while a TV system is. The tumor-immune model does not depend on time so it is considered to be TI. Nonlinear systems do not adhere to the superposition principle. Nonlinear control deals with applying mathematical techniques for stability analysis and designing nonlinear feedback control [30, 28]. Chapter 4 will cover the use of two different control techniques: optimal control and model free control. After formulating the control techniques to design a controller to drive the tumor to the safe region, we run simulations and preview results.

4.2 Optimal Control

Optimal Control theory is concerned with finding an adequate control input for a system, such that the optimality criterion is achieved. The optimal control problem has an objective function composed of state and input variables. For e.g. a sufficient objective function in the cancer immune system would be to minimize the tumor size. An objective function is chosen

by the practitioner to achieve a certain objective. What follows was summarized from the work presented in [36, 39]. In section 4.2, we introduce the mathematical definitions and formulation of the OC.

Definition 4.1. *Consider a system with n state variables, m control inputs, and a payoff function* Γ *[36],*

$$J = \inf_{u_1,...,u_m} \int_{t_0}^{t_1} f(t, x_1(t), ..., x_n(t), u_1(t), ..., u_m(t))dt + \Gamma(x_1(t_1), ..., x_n(t_1))$$

subject to

$$\begin{aligned} \dot{x_i}(t) &= g_i(t, x_1(t), ..., x_n(t), u_1(t), ..., u_m(t)), \\ x_i(t_0) &= x_{i0} \ for \ i = 1, 2, ..., n, \end{aligned} \tag{4.1}$$

where f *and* g_i *are continuously differentiable in all variables. There are no requirements on m,n. The system at hand has three states and two inputs (*$m = 2$*,* $n = 3$*). where* $x \in \mathbb{R}^n$ *is the state,* $u \in \mathbb{R}^m$ *is the control input, functions* f*:* $\mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^m \mapsto \mathbb{R}$*,* $g : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^m \mapsto \mathbb{R}$*, and* Γ*:* $\mathbb{R}^n \mapsto \mathbb{R}$ *are polynomials.*

Remark 1. *The Objective function also known as the cost function "J" is selected based on the desired goal. It can have numerous terms, such as setting the end bounds for the final states or integrals of inputs to satisfy different control objectives.*

Formulating the nominal Optimal Control problem using definition 4.1 yields

$$J = \min_{u_1,u_2} \int_0^{60} f(t, x_1, x_2, x_3, u_1, u_2)dt$$

subject to

$$\begin{aligned} \dot{x_1} &= \mu_C x_1 - \frac{\mu_C}{x_\infty} x_1^2 - \gamma x_1 x_2 - \sigma x_1 x_3, \\ \dot{x_2} &= \mu_I x_1 x_2 - \mu_I \beta x_1^2 x_2 - \chi x_2 + \alpha + \lambda x_2 u_2 - \varrho x_3 x_2, \\ \dot{x_3} &= -a x_3 + b u_1. \end{aligned}$$

$$
\begin{aligned}
x(0) &= x^{t_0} = \{500, 0.5, 0\}, \\
x(60) &= x^{t_1} = \{41.45, 0.954, 0\}, \\
0 \leq u_1 \leq 1,\ & 0 \leq u_2 \leq 1, \\
0 \leq x_1 \leq 780, & \\
0 \leq x_2 \leq 5, & \\
t \in [0, 60]. &
\end{aligned} \tag{4.2}
$$

Remark 2. *The states have fixed end points defined by x^{t_1} which ensures that the states will reach the benign region by the end of the time interval at $t_1 = 60$.*

Remark 3. *The control inputs u_1 and u_2 are bounded between [0,1] in the normalized system dynamic where the maximum dosage injection is 1.*

Remark 4. *Constraints are added to the states to ensure practical limits and compactness of the state set.*

Remark 5. *The different objective functions used are as follows:*

$$f_1 = (x_1 + x_2)\ dt, \tag{4.3}$$

$$f_2 = (x_1^2 + x_2^2)\ dt,\ \textit{and} \tag{4.4}$$

$$f_3 = (u_1^2 + u_2^2)\ dt. \tag{4.5}$$

Optimal Control allows formulation of control problems as mathematical optimization problems. **OpenOCL** provides a modeling language that helps to implement a direct collocations method, and interfaces **CasADi** and **ipopt** to solve nonlinear system dynamics [33, 12]. The toolboxes are used in conjunction with **Matlab** to solve the optimal control problem and simulates the state trajectories after solving for the optimal inputs u_1^* and u_2^*. Note that the objective function must be formulated in a manner to achieve the objective. In the tumor-immune interaction model, we minimize the controls to drive the state to the benign region. The reason for minimizing the chemotherapy and immunotherapy injections is due to their toxicity. Over dosage of the injections is life threatening and may lead to a

death outcome. For example overusing the cytotoxic agent u_1 may rid the patient of the tumor cells but also lead to death; although the tumor was treated the patient is dead which defeats the purpose of the treatment. In the addition, the immunotherapy injection u_2 is also toxic if used in large amounts and so it must be constrained accordingly. The constraints of the optimal control problem in equation (4.2) will keep the system in the safe region, thus the treatment is safe and the patient will not be subject to poisoning due to overdose of the chemical agents used for treatment.

4.2.1 Simulations

In section 4.2.1 the OC method is applied to the cancer dynamical model and the system (4.2) was used to formulate the OC problem and the results from the simulations are presented. As can be seen the OC method successfully treated the virtual patient within the treatment duration, but only after choosing the correct objective function given by equation (4.5). The OC method converged to the benign equilibrium in approximately forty days in most cases. The OC technique also reserved the use of chemotherapeutic agent; large doses were used in cases with an initially high tumor cell count and only for approximately the first 10-days of the treatment regimen. The results are presented in figures 4.1 - 4.7. Equations (4.3), (4.4), and (4.5) were used to produce the state trajectories in figures 4.1, 4.2, and 4.3 - 4.7, respectively.

4.3 Model Free Control

The MFC technique and procedure in section 4.3 was summarized from the work presented in [13, 23, 24]. Model Free Control is based on a continuously updated local model using the knowledge of the input-output behavior of the system. The framework behind MFC was derived using differential algebra. The advantage of using MFC, is that unknown or finite dimensional complex models can be replaced with an ultra local model [24]. It is an online controller because it continuously examines the current and previous states of the system to derive the inputs for the next iteration. MFC is applied to the cancer model and the results

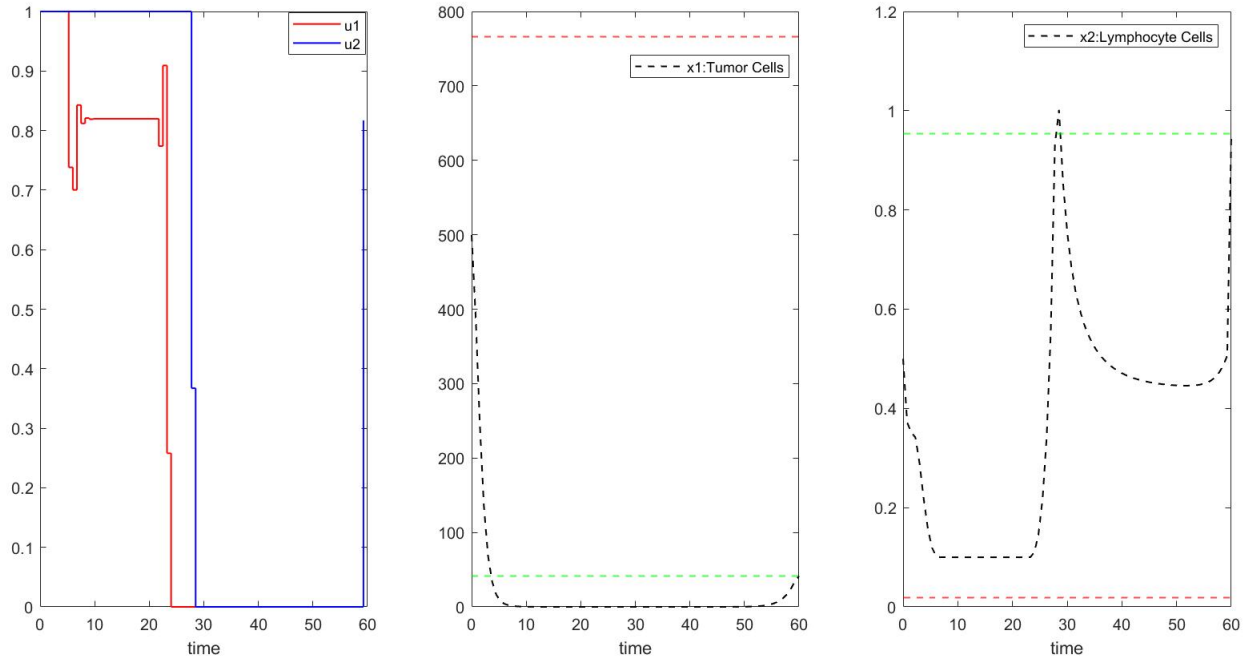


Figure 4.1: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). Initial condition is $x^0 = (500, 0.5)$ and the integrand in the cost function is $f = x_1 + x_2$.

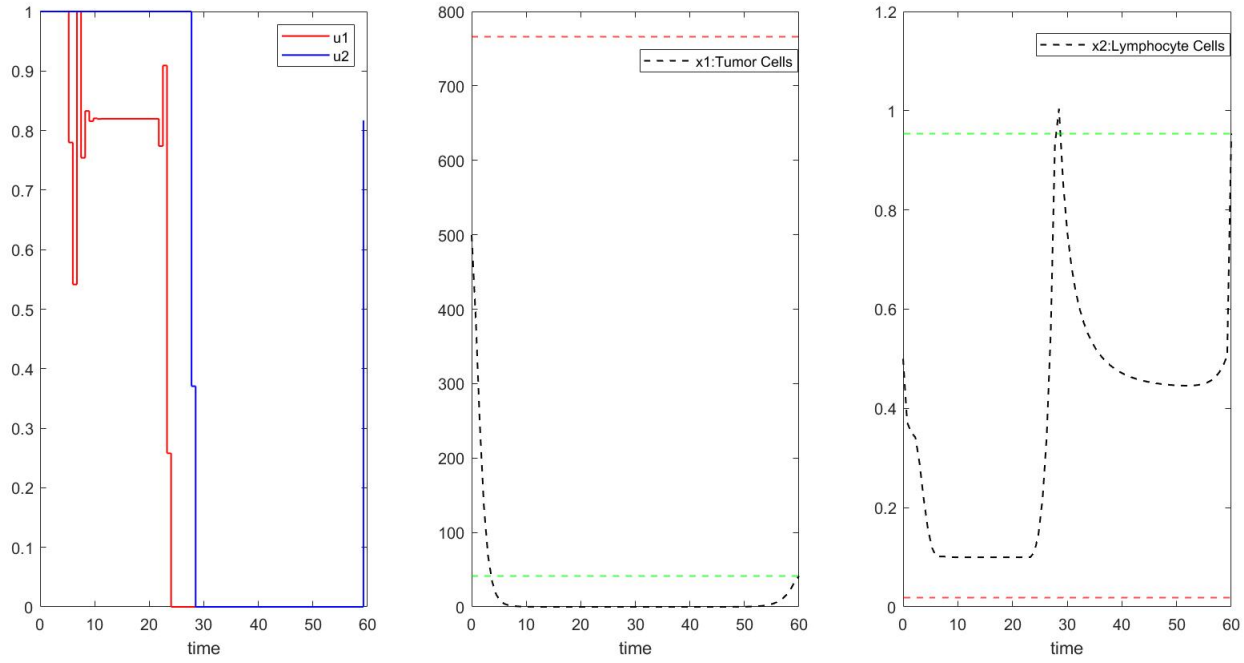


Figure 4.2: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). Initial condition is $x^0 = (500, 0.5)$ and the integrand in the cost function is $f = x_1^2 + x_2^2$.

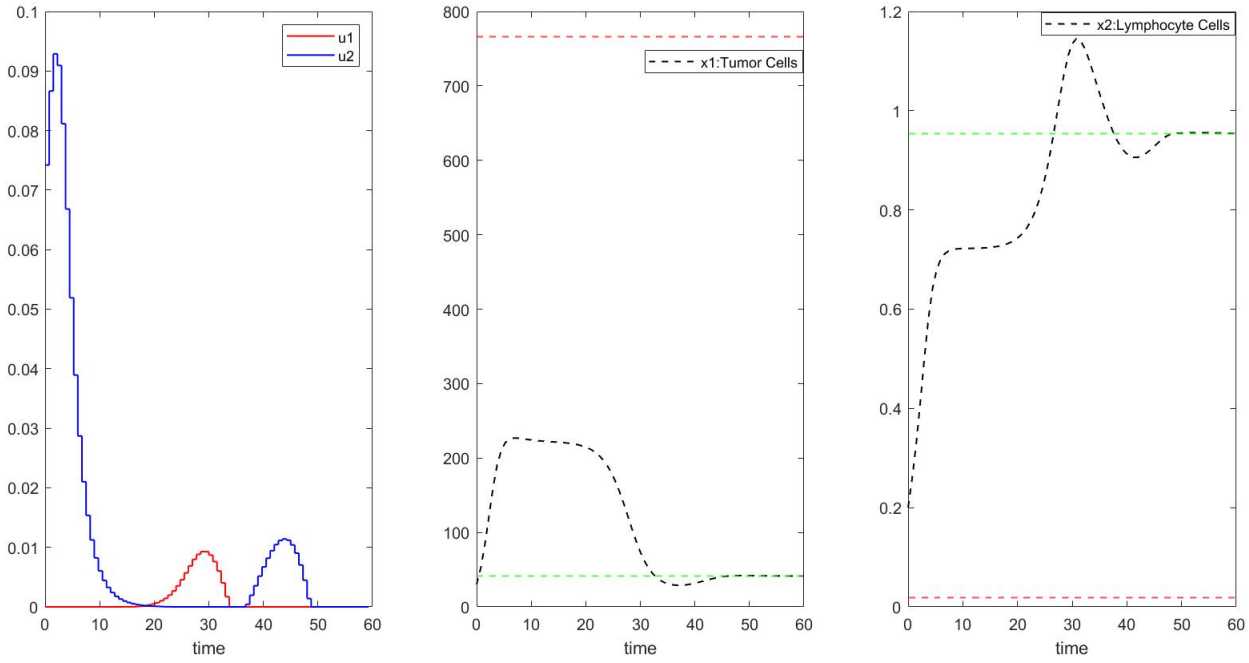


Figure 4.3: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). Initial condition is $x^0 = (30, 0.2)$ and the integrand in the cost function is $f = u_1^2 + u_2^2$.

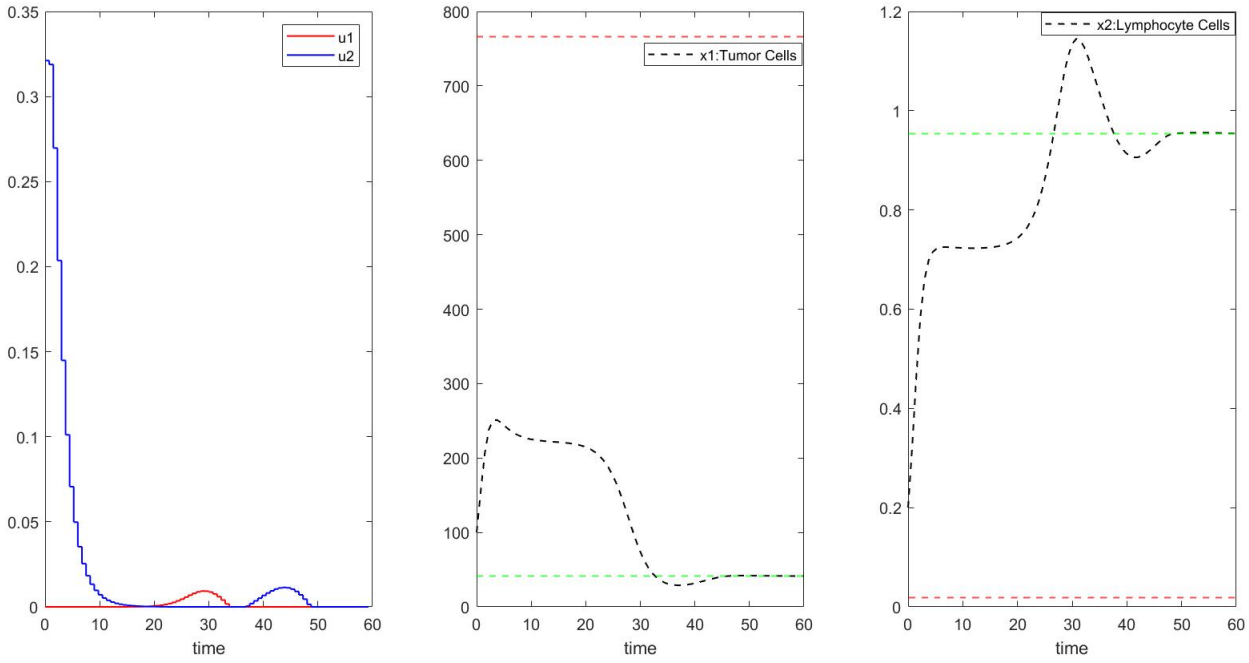


Figure 4.4: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). Initial condition is $x^0 = (100, 0.2)$ and the integrand in the cost function is $f = u_1^2 + u_2^2$.

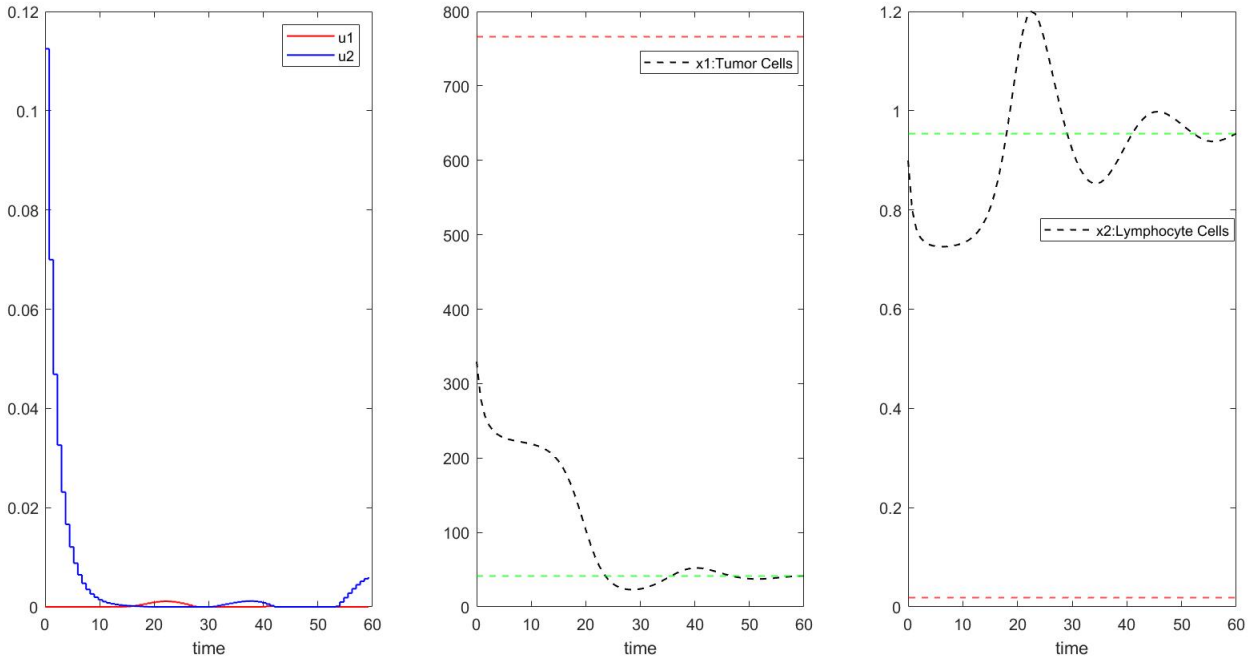


Figure 4.5: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (330, 0.9)$ and the integrand in the cost function is $f = u_1^2 + u_2^2$.

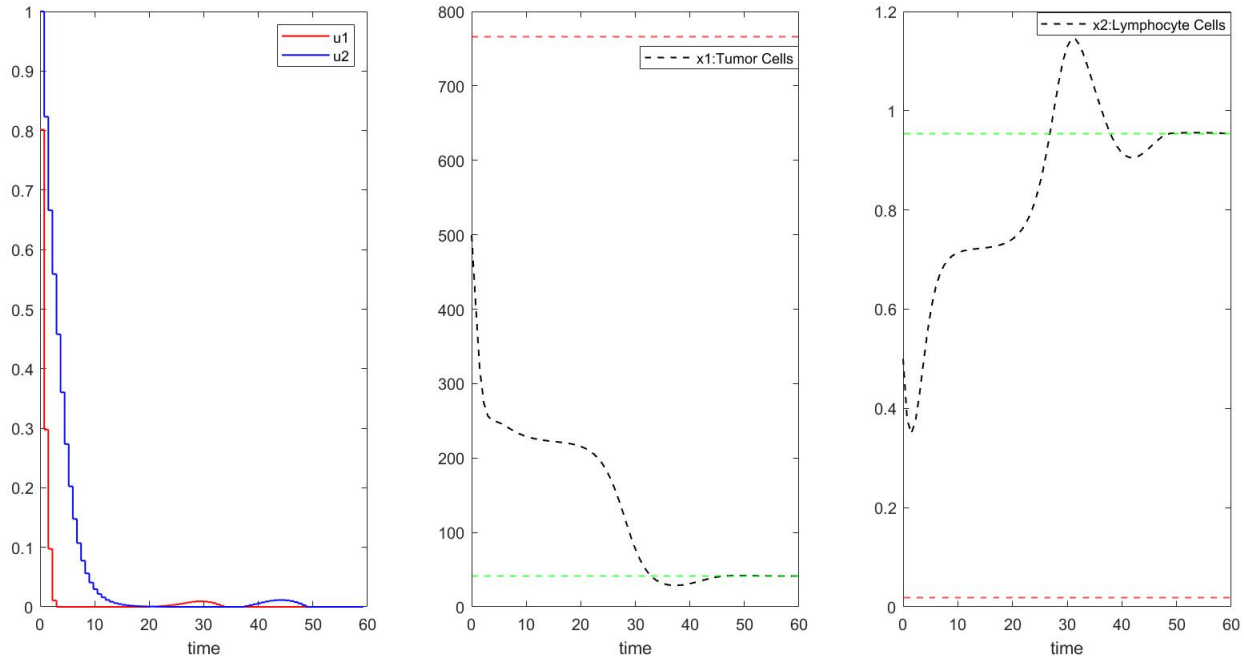


Figure 4.6: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (500, 0.5)$ and the integrand in the cost function is $f = u_1^2 + u_2^2$.

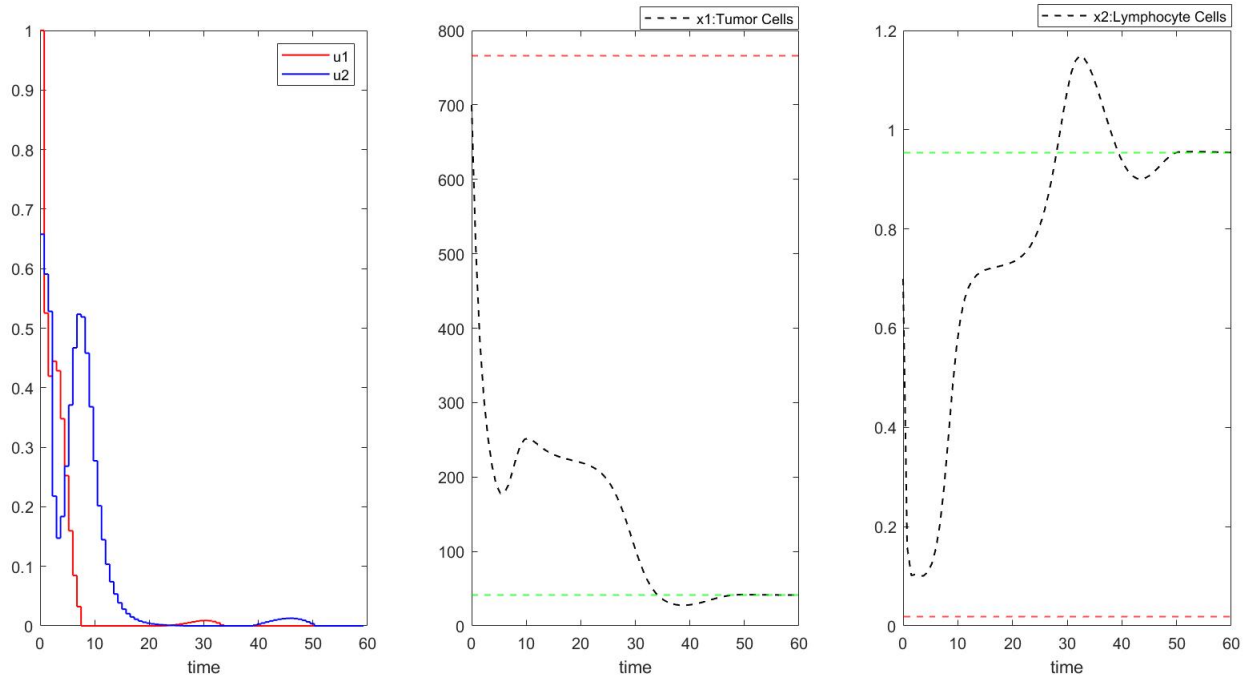


Figure 4.7: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). Initial condition is $x^0 = (700, 0.7)$ and the integrand in the cost function is $f = u_1^2 + u_2^2$.

are presented. The next set of equations define the methodology behind model free control [23].

$$y^{(v)} = F_{est} + \alpha u \tag{4.6}$$

$$F_{est} = \frac{-6}{L^3} \int_t^{t-L} (L - 2\sigma)y(\sigma) + \alpha\sigma(L - \sigma)u(\sigma)d\sigma \tag{4.7}$$

$$e = y - y^* \tag{4.8}$$

$$u = \frac{F_{est} - \dot{y^*} + K_p e}{\alpha} \tag{4.9}$$

where

- $y^{(v)}$ is the derivative of order $v >= 1$ of y.
- u and y are the control input and output variables.
- F_{est} represents the plant estimate in its entirety including the poorly known parts, and the disturbances.
- α is a constant parameter that is selected such that $y^{(v)}$ and αu are of the same magnitude.
- y^* is the reference trajectory.
- e is the tracking error.

Implementing the MFC procedure is done in the following order [13]:

1. Set $u_1 = 0$, define reference trajectory y_1^*, and initialize K_{p1} and α_1
2. Obtain measurement of states x_1 and inputs u_1
3. Estimate F_{est1} by using equation (4.7)
4. calculate u_1 according to equation (4.9) and return to step 2.

Remark 6. *Since the cancer model used contains two inputs and three outputs we will treat them as a decoupled system and find* u_1 *and* u_2 *accordingly.*

Remark 7. *To avoid any confusion* α *is a parameter in the cancer model, while* $\alpha_{1,2}$ *is a parameter used in the Model Free Control method.*

The MFC parameters are shown in table 4.1.

- Selecting $\alpha_{1,2}$ is done through trial and error to obtain desired results of the output states x_1 ,x_2. The states will vary widely depending on the numerical values chosen for $\alpha_{1,2}$. This shows that MFC parameters chosen are specific to the model they are intended for. As stated in [24] $\alpha_{1,2}$ is not a priori defined parameter, but it is chosen by the practitioner.
- L represents the number of the most recent measurements considered for each iteration of the MFC.
- $y^*_{1,2}$ is the reference trajectory which is the benign equilibrium which is where we want the states x_1, x_2 to settle.
- The sample time $tsamp_{1,2}$ is .1 so for 60 days there is 601 samples.
- $Kp_{1,2}$ represents the tuning parameters for MFC. In the same fashion of finding $\alpha_{1,2}$, the tuning parameters are determined by trial and error.

4.3.1 MFC Simulations

In section 4.3.1 the MFC method is applied to the cancer dynamical model using parameters in table 4.1 and the results from the simulations are shown. As can be seen, the MFC method successfully treated the virtual patient by reducing the tumor size through chemotherapy and immunotherapy injections over the period of the treatment while maintaining safe levels of Lymphocyte cell population. It is evident from the figures 4.8 - 4.17 that the model free control method converges within approximately twenty days, half the time it takes when using the optimal control method. However, the MFC method uses the chemotherapeutic agent u_1 immoderately even in cases where there is a low number of tumor cells in the initial condition.

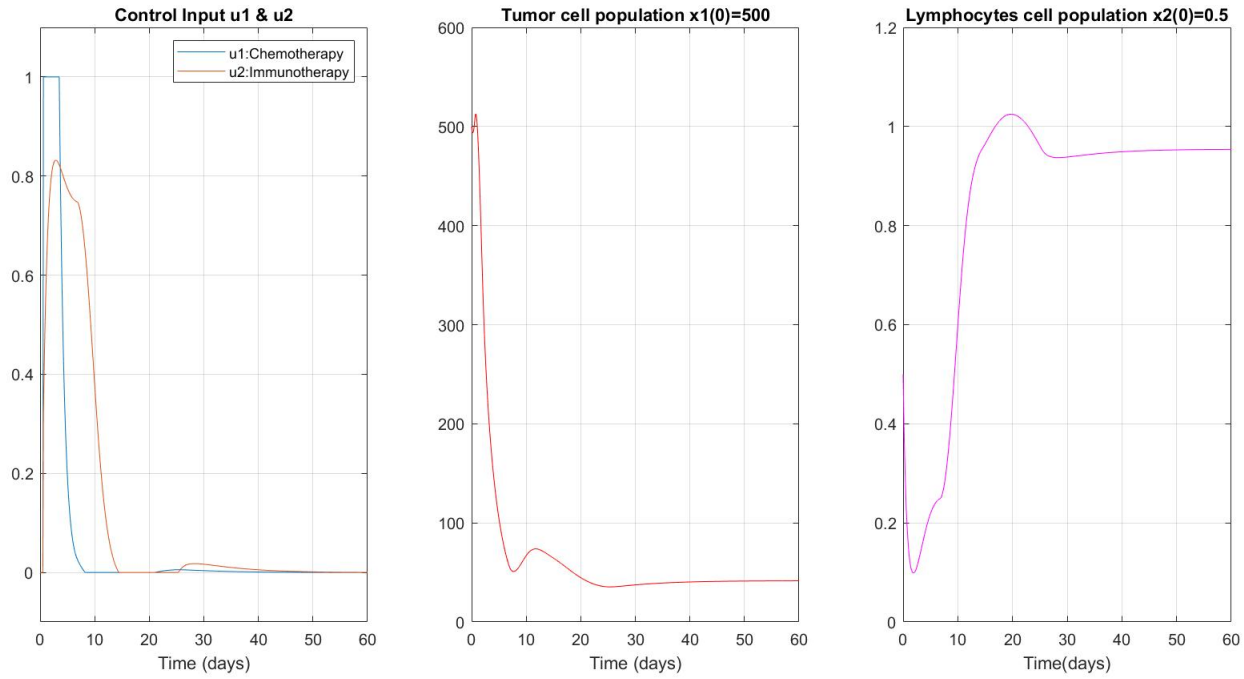


Figure 4.8: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (500, 0.5)$.

Table 4.1: Numerical values and definitions of the Model Free Control parameters

MFC Parameter	Definition	Numerical Value
$\alpha_{1,2}$	magnitude adjuster	1000, 5000
$L_{1,2}$	past measurements taken	3, 3
$y^*_{1,2}$	Reference Trajectories	41.45, 0.954
$tsamp_{1,2}$	time lapse	0.1, 0.1
$Kp_{1,2}$	Tuning parameters	0.001, 6

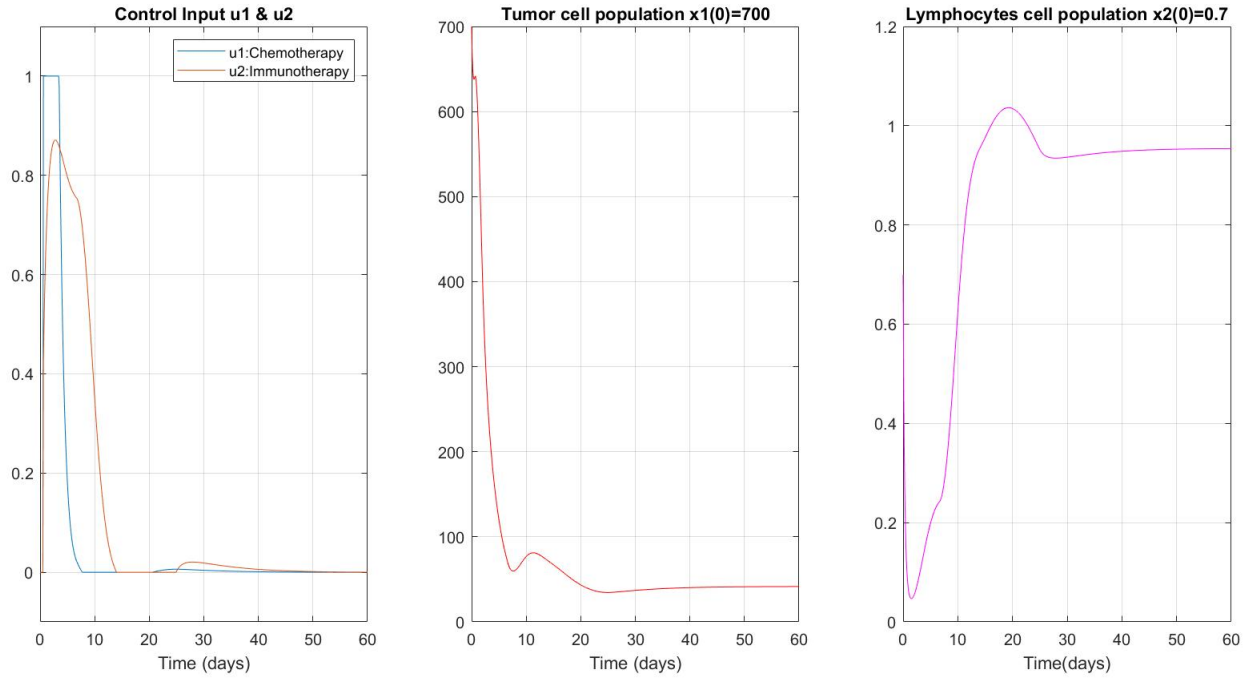


Figure 4.9: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (700, 0.7)$.

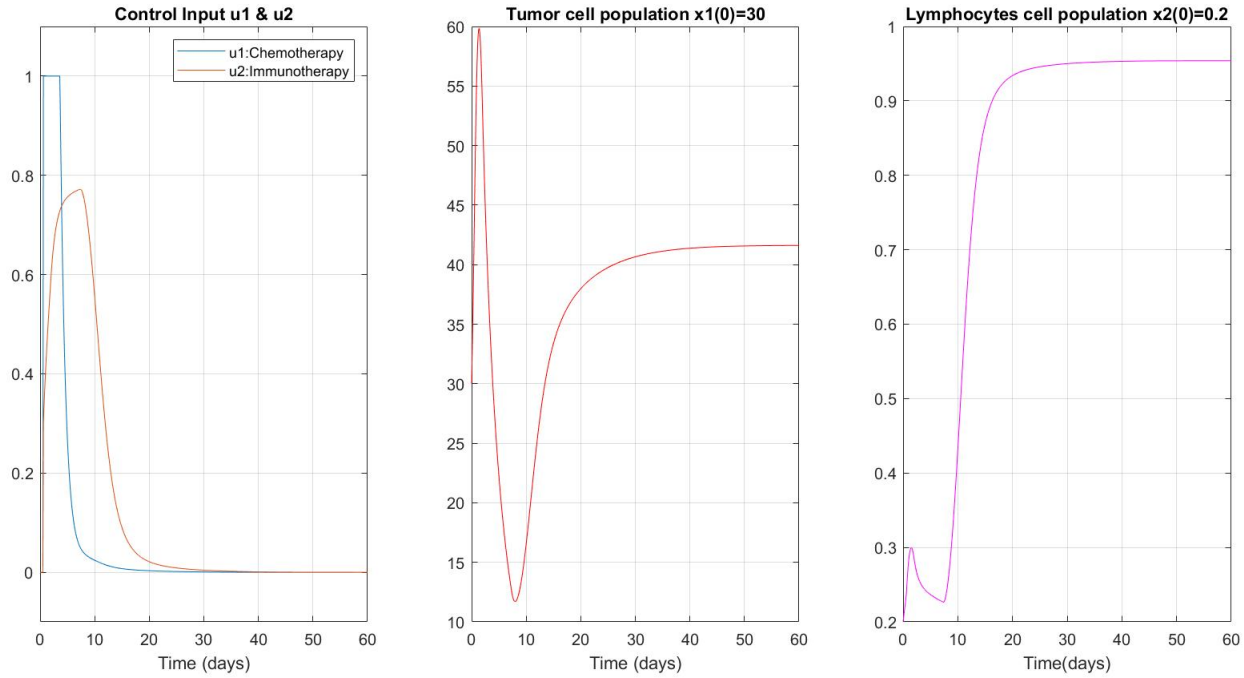


Figure 4.10: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (30, 0.2)$.

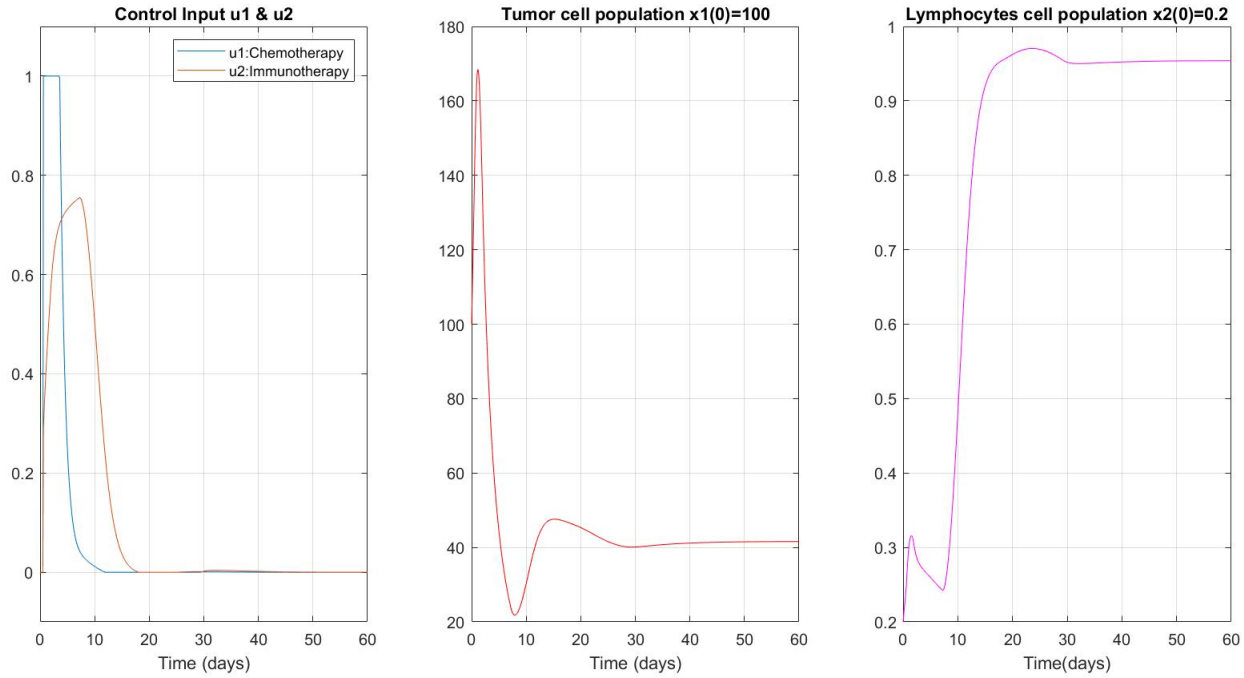


Figure 4.11: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (100, 0.2)$.

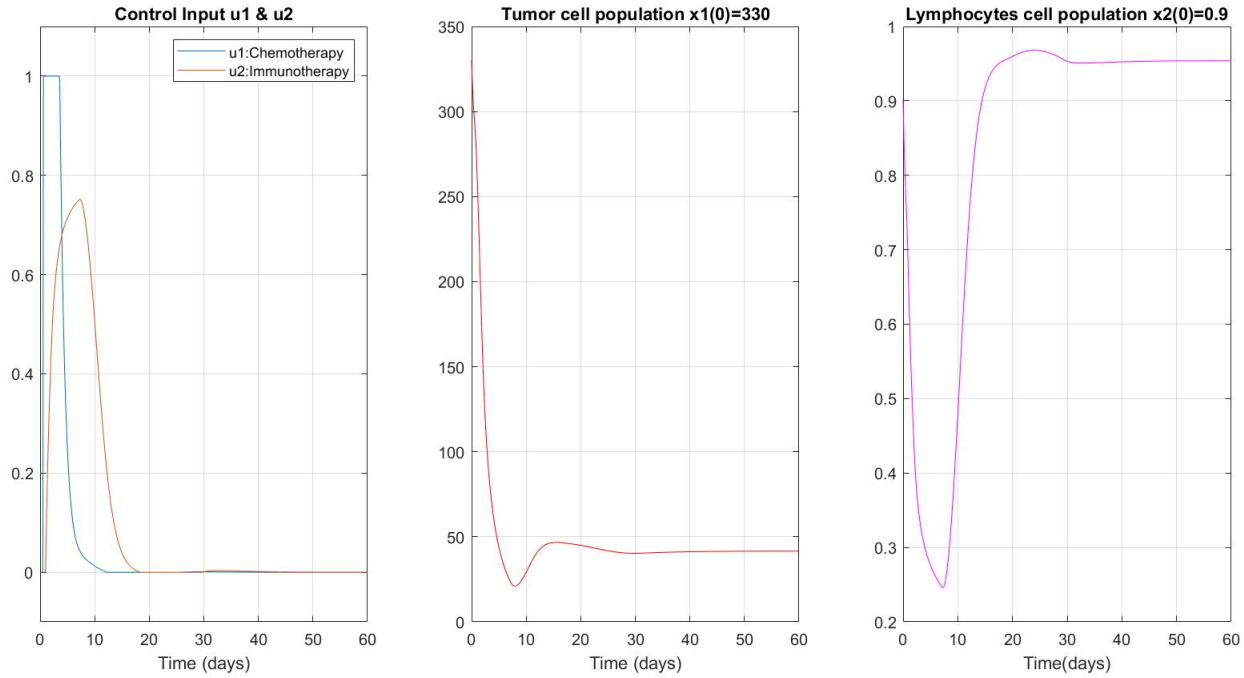


Figure 4.12: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (330, 0.9)$.

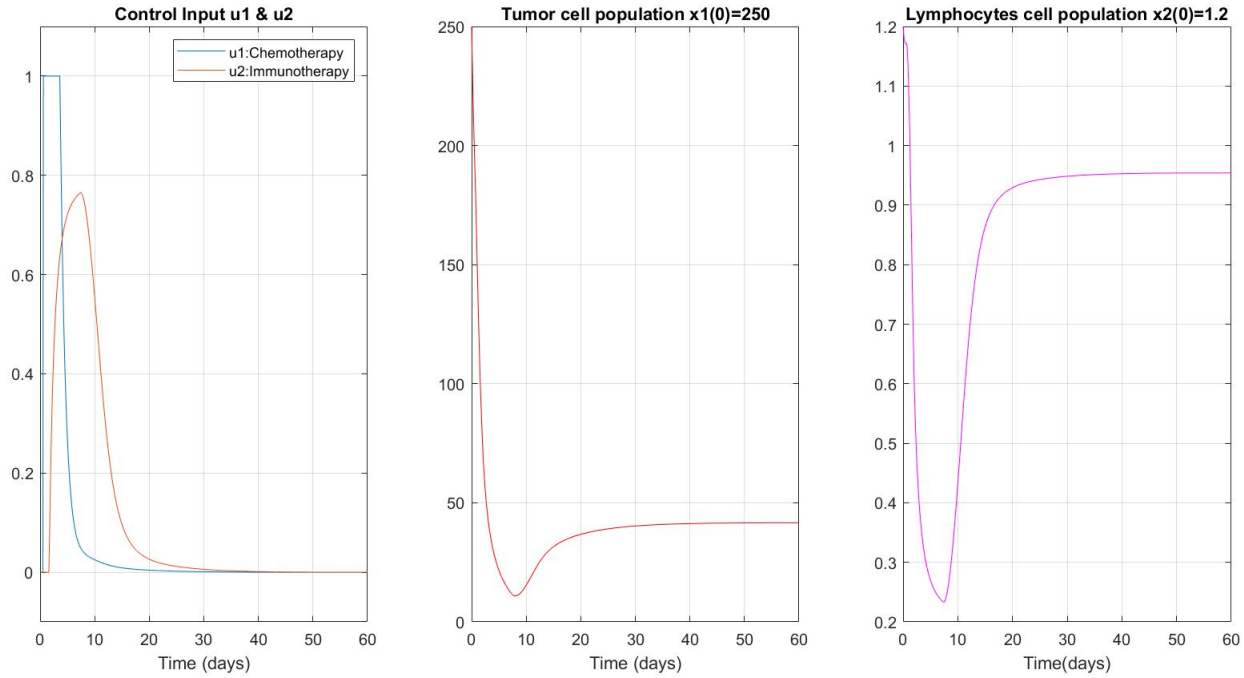


Figure 4.13: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (250, 1.2)$.

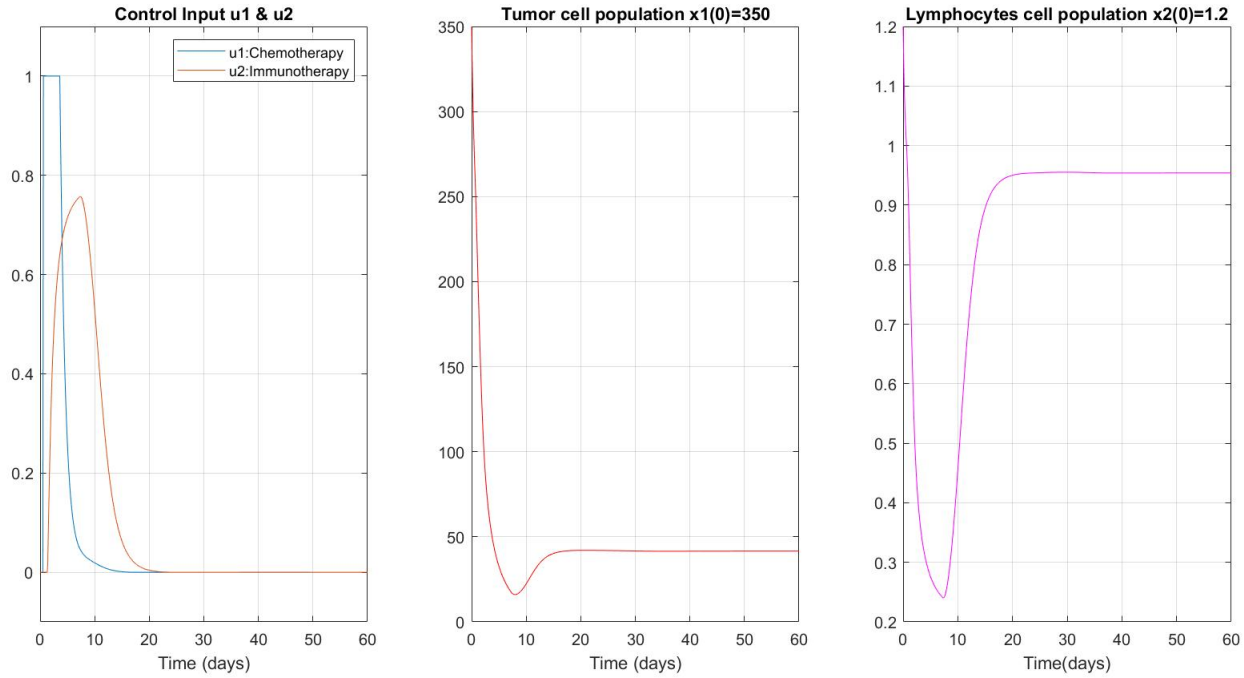


Figure 4.14: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (350, 1.2)$.

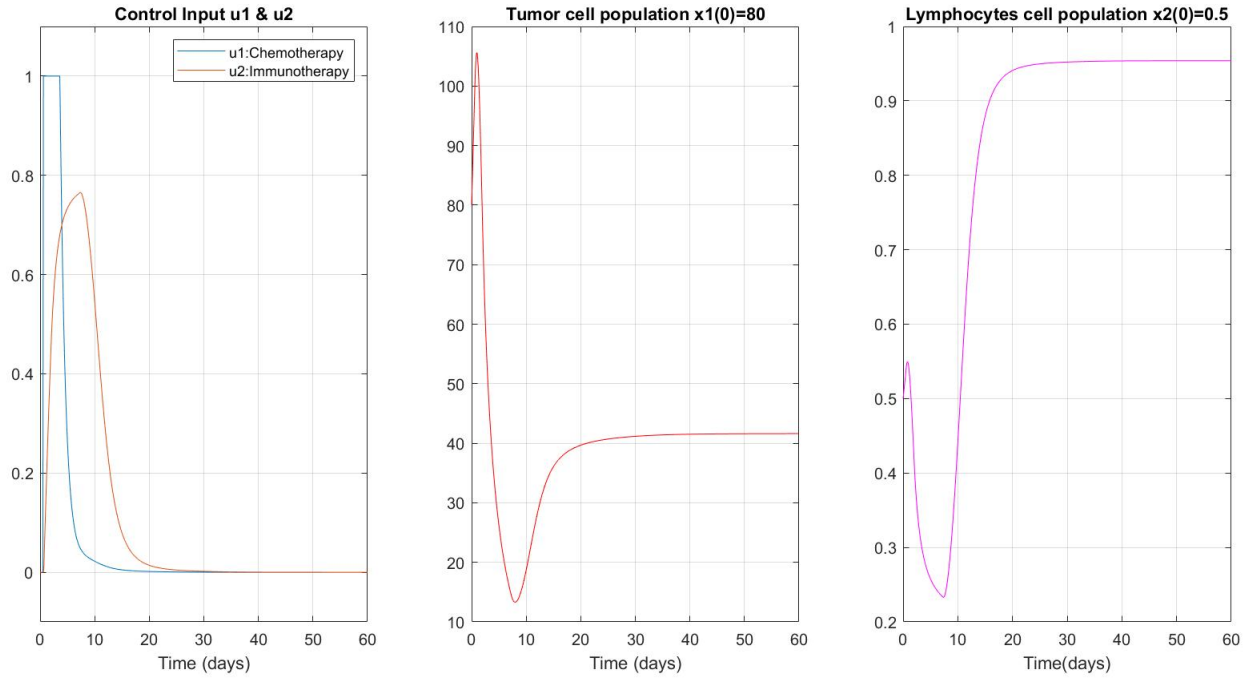


Figure 4.15: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (80, 0.5)$.

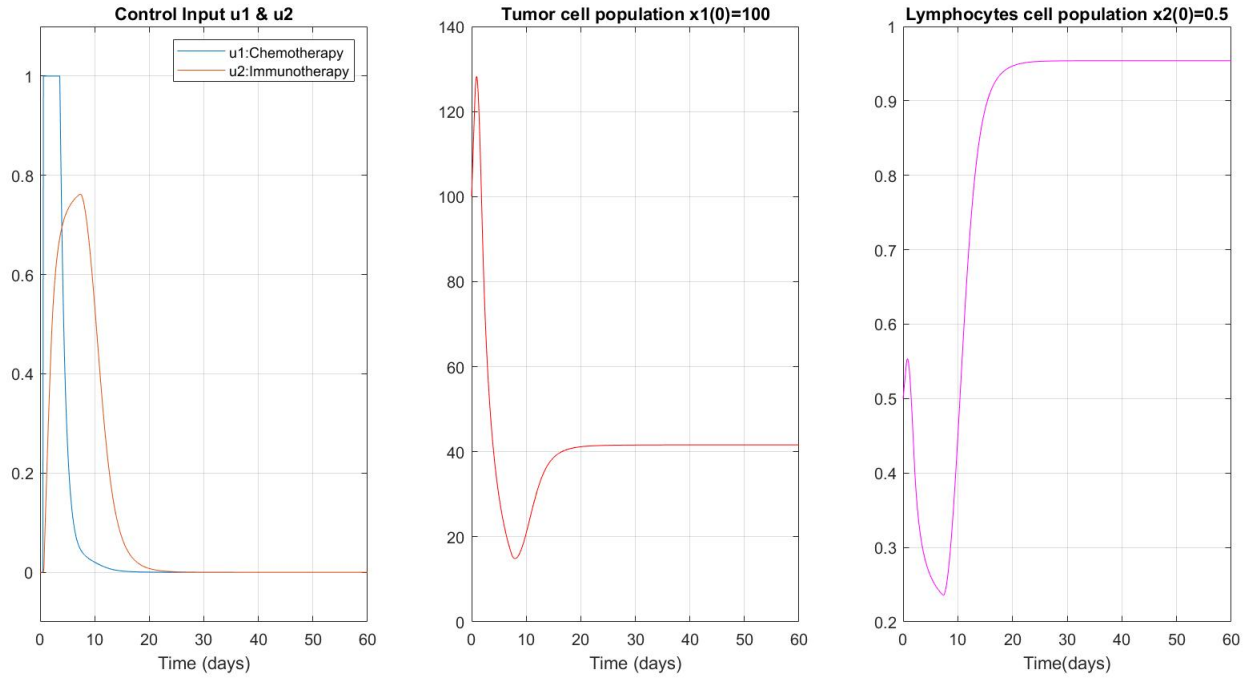


Figure 4.16: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The initial condition is $x^0 = (100, 0.5)$.

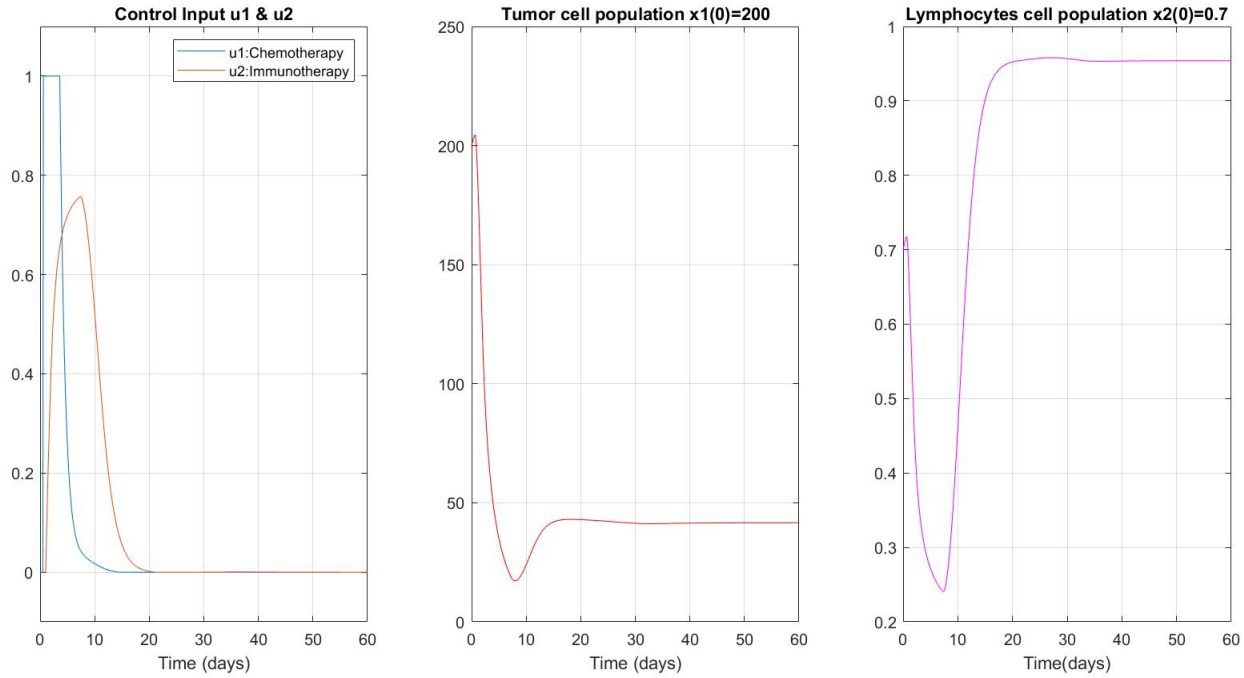


Figure 4.17: Plot of tumor and immune cells x_1 and x_2, respectively, in response to time varying input controls (u_1) and (u_2). The Initial condition is $x^0 = (200, 0.7)$.

Chapter 5

Conclusion and Future Works

In this thesis, we introduced a dynamical model of tumor-immune interaction of a virtual patient. The benign and malignant equilibrium points were calculated to see how the dynamic model will react for different initial conditions with absent controls; chemotherapy and immunotherapy injections. We successfully showed that the mathematical model was locally controllable and observable. Hence, we implemented two distinct control techniques to treat the virtual patient and reduce the tumor size to the benign region. Optimal control and model free control were successful in curing the patient within the treatment period and the results were presented. To obtain the desired results we needed to define the correct objective functions of the OC problem and solve it given the constraints of the system. On the other hand, some of the MFC parameters needed some tuning through trial and error to produce the sought after results. We observed that using the OC resulted in driving the states to the benign region in approximately forty days and the use of chemotherapeutic agents was minimized, especially for low initial tumor cell populations. The MFC consistently used chemotherapy even when the initial condition of the tumor cells was relatively low. This presents a trade-off between treatment time and the use of chemotherapy. It would be interesting to apply the control techniques in a real setting, where the data is measured and the cancer model is simulated to obtain the optimal control injection dosages to treat a patient.

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Appendices

A Summary of Equations

A brief recap of the equations and formulas used throughout the thesis is summarized below.

A.1 Tumor Immune Interaction Model

The mathematical model of nonlinear ODE representing the tumor-immune interaction is given below:

$$\begin{aligned}
\dot{x_1} &= \mu_C x_1 - \frac{\mu_C}{x_\infty} x_1^2 - \gamma x_1 x_2 - \sigma x_1 x_3, \\
\dot{x_2} &= \mu_I x_1 x_2 - \mu_I \beta x_1^2 x_2 - \chi x_2 + \alpha + \lambda x_2 u_2 - \varrho x_3 x_2, \\
\dot{x_3} &= -a x_3 + b u_1.
\end{aligned}$$

The tumor-immune system interaction is composed of three states [40]:

- x_1 : Tumor cell population;
- x_2 : Lymphocyte cell population; and
- x_3 : Chemotherapy drug concentration in patient.

The model comprises two time varying control inputs denoted as follows:

- $u_1(t)$: dosage of a cytotoxic agent; and
- $u_2(t)$: cytokines which is a generic immuno-stimulator.

A.2 Nonlinear Controllability

The system is said to be locally **accessible** about a point x^0 if and only if the **controllability matrix** C spans $\mathbb{R}^n$: rank (C)=n and C is defined by [25]:

$$C = [g_1, ..., g_m, [f, g_1], ..., [f, g_m], [f, (ad_f^1)], ..., [f, (ad_f^k)]] \tag{1}$$

Consider two vector fields $f(x)$ and $g(x)$ in $\Re^n$ space. Then the Lie bracket operation generates a new vector field [25]:

$$[f,g] \equiv \frac{dg}{dx}f - \frac{df}{dx}g \tag{2}$$

Higher order Lie brackets can be defined as follows:

$$\begin{aligned}
&(ad_f^1) \equiv [f,g],\\
&(ad_f^2) \equiv [f,[f,g]],\\
&\quad ...\\
&(ad_f^k) \equiv [f,(ad_f^{k-1})] \quad for \;\; k = [1,2,...].
\end{aligned} \tag{3}$$

Note: the "ad" stands for adjoint.

A.3 Nonlinear Observability

For control u^*, and initial state x^0, the local observability matrix is defined as follows:

$$O(x^0,u^*) = \begin{bmatrix} dL_f^0(h_1) \\ ... \\ dL_f^0(h_p) \\ dL_f^{n-1}(h_1) \\ ... \\ dL_f^{n-1}(h_p) \end{bmatrix}$$

where dL is the Lie derivative.

A.4 Nonlinear Optimal Control

Consider a system with n state variable, m control inputs, and a payoff function Γ,

$$J = \inf_{u_1,...,u_m} \int_{t_0}^{t_1} f(t, x_1(t), ..., x_n(t), u_1(t), ..., u_m(t))dt + \Gamma(x_1(t_1), ..., x_n(t_1))$$

subject to

$$\dot{x_i}(t) = g_i(t, x_1(t), ..., x_n(t), u_1(t), ..., u_m(t)),$$
$$x_i(t_0) = x_{i0} \ for \ i = 1, 2, ..., n,$$

A.5 Model Free Control

$$y^{(v)} = F_{est} + \alpha u$$
$$F_{est} = \frac{-6}{L^3} \int_t^{t-L} (L - 2\sigma)y(\sigma) + \alpha\sigma(L - \sigma)u(\sigma)d\sigma$$
$$e = y - y^*$$
$$u = \frac{F_{est} - \dot{y^*} + K_p e}{\alpha}$$

where

- $y^{(v)}$ is the derivative of order of $v >= 1$ of y.
- u and y are the control input and output variables.
- F_{est} represents the plant in it's entirety including the poorly known parts, and the disturbances.
- α is a constant parameter that is chosen such that $y^{(v)}$ and αu are of the same magnitude.
- y^* is the reference trajectory.
- e is the tracking error.

Vita

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