Nonlinear Controller Design for the Chemotherapy Treatment of Brain Tumor

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Approval

It is certified that the contents and form of the thesis entitled "**Nonlinear Controller Design for the Chemotherapy Treatment of Brain Tumor**" submitted by **Muhammad Zubair** have been found satisfactory for the requirement of the degree.

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Abstract

There are various methods for the treatment of Brain Tumor few of these are Surgery, Chemotherapy, Radiation Therapy etc. Treatment methods of Brain Tumors not only depend on the type of tumor but also on other factors like age of patient, duration of tumor, size of tumor etc. For less severe tumors i.e. Benign, sometimes applying surgery is suitable because these tumors are small in size and have definite edges. While in case of a severe tumors i.e. Malignant suggesting surgery won't be a good option as these tumors don't have definite boundaries and are attached very closely with other sensitive tissues of brain. Also, when the patient is a child it is suggested to go with an option other than surgery. In this research Non Linear Techniques have been applied by using Chemotherapy Treatment method on a Brain Tumor model.

The main objective of the thesis is to design a controller for the therapeutic agent in order to minimize the tumor cells, maintain a safe amount of healthy cells and ensure suitable amount of drug during the therapy process. Three nonlinear controllers have been designed for this purpose; 1) Synergetic Controller 2) Backstepping Controller 3) Lyapunov Redeisgn. The nonlinear controllers use Lyapunov based stability theory to analyze the system's asymptotic stability and convergence of the tumor cells to their desired reference. The simulations have been performed in Matlab/Simulink and the results show that this therapy is effective enough to reduce the tumor cells to zero while a safe amount of healthy cells has been retained using minimum amount of therapeutic agent.

Dedication

I dedicate this thesis to my parents, my brother, my sister, my Supervisor and all the teachers of SEECS who have taught and supported me.

Certificate of Originality

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any degree or diploma at NUST SEECS or at any other educational institute, except where due acknowledgement has been made in the thesis. Any contribution made to the research by others, with whom I have worked at NUST SEECS or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except for the assistance from others in the project's design and conception or in style, presentation and linguistics which has been acknowledged.

Author Name: **Muhammad Zubair**
Signature: _____

Acknowledgment

I would like to thank Allah Almighty for HIS countless blessings in my life and to give me the opportunity to thank HIM. I would like to thank my parents for their love, care and their financial and moral support. I would like to thank my brother for being a great mentor and for guiding me at every step of my life. I would like to thank all my teachers who have taught me from school till university for their contribution in building my life and for making me the person I am. I am especially grateful to my supervisor; Dr. Iftikhar Ahmad Rana for his guidance, support, faith and for giving me an opportunity to prove my skills. In the end, I would like to thank SEECS (School of Electrical Engineering and Computer Sciences) for helping me along the way and for giving me an opportunity to attend the best engineering institute in Pakistan.

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Chapter 1

Introduction

Severe form of Brain Tumor is Malignant which is a Cancer. Cancer means abnormal production of cells due to some changes in the DNA of a cell in human body. Researchers are looking for the changes in the DNA of a cell which initiate unwanted growth of cells which lead to tumor. Malignant tumors are broadly classified on the basis of where they initiate i.e. tumors which initiate inside the skull and tumors which start from outside of skull. First category is considered as Primary Brain Tumors while the tumors initiated outside skull are termed as metastasis tumors or Secondary Brain Tumor. Around the globe, hundreds and thousands of people are diagnosed with Brain Tumor every year. Only in United States, some 78,980 people diagnosed with Brain Tumors in 2018. This includes an estimated 23,830 primary malignant brain tumors, and 55,150 non-malignant brain tumors [1]. While In Pakistan, well known cancer hospital Shoukat Khanum, registered a total of 6207 patients in 2017 diagnosed with Brain Tumor. Among these 6207, majority 5941 patients were of Malignant Tumor while 391 were of Benign Tumor (less severe form of tumor) [2].

1.1 What is a Brain Tumor ?

An ordinary tumor is defined as an unwanted growth of cells due to some changes in the DNA inside the cell. The definition of Brain Tumor is not different from this in any sense, when this tumor occurs inside the skull is termed as brain tumor. Sometimes brain tumor initiates from other organ and spread towards the brain this is considered as Secondary Brain Tumor.

1.2 What are the symptoms?

The Symptoms of Brain Tumor vary depending on the severity of tumor. Generally, these symptoms base on location, size and duration of tumor. Following are some major symptoms

- Fatigue
- Headaches (more in the morning)
- Nausea or Vomiting
- Seizures
- Speech Problems (hard to find proper words)
- Sleep Problems
- Memory Problems
- Vision Problems [3]

1.3 What causes Brain Tumor?

Researchers are still looking for what causes Primary Brain Tumors and how to prevent tumors that start in the brain. Risk of Brain Tumor increases if someone has

- a family member having brain tumor
- having cancer cells somewhere in the body
- having exposure of pesticides
- inherited family diseases (like neurofibromatosis) [4]

1.4 Major Types of Brain Tumors

Brain Tumor is a contagious disease. There are more than 120 types of Brain tumors. [5] Broadly speaking the brain tumors can be categorized on the basis of location as 1) primary brain tumors and 2) secondary brain tumors. [6]The brain tumor that starts in the skull is termed as primary while in case of a secondary brain tumor, cancer cells spread to brain from other organ for example lung or breast, this is also known as a metastatic brain tumor. By

severity these can be divided into Benign and Malignant [4]. In the following comparison, MRI scans of a benign and malignant brain tumor are given. Left side of the figure is showing Benign Tumors while right side is showing Malignant. We can see in the figure Benign tumors have well defined edges so they can be removed surgically. While Malignant tumors have an irregular border that invades normal tissue with finger-like projections making surgical removal difficult. [7]

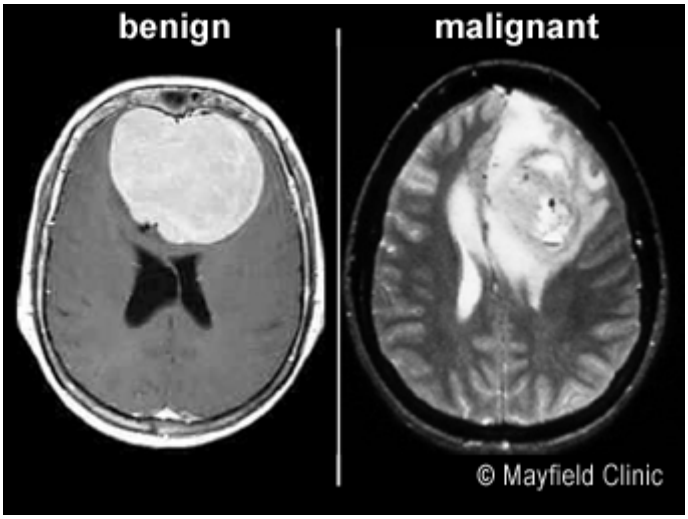

Figure 1.1: Comparison between Malignant and Benign
[4]

1.5 Brain Tumor Treatment Methods

The treatment of Brain Tumor depends on following important factors

- Age of patient, overall health, and medical history
- The size, location and type of tumor
- Rate at which tumor is spreading and chance of its re occurrence [1]
- How a patient can tolerate certain medications, procedures, or therapies

By utilizing above mentioned details, tumors are first categorized in low grade and high grade tumors. The low grade tumors are further classified in grade I and grade II tumors. Low grade grade I tumors, which are not aggressive, can be treated by surgery, radiation therapy and chemotherapy. Often, low grade grade I tumors are treated with surgery alone. On the other hand,

low-grade grade II tumors, are treated via chemotherapy, or a clinical trial if one is available.

For High Grade Tumors following treatment techniques are in practice

1.5.1 Chemotherapy

In this therapy, drugs are used to kill rapidly growing cells. As tumor cells increase in a rapid manner, so the tumor cells are effectively destroyed through this process.It can either taken orally or intravenously. [1].

1.5.2 Radiation Therapy

: In this therapy, different forms of radiations (X-rays etc.) are used. These powerful rays can destroy tumor cells or delay tumor growth. [1].

1.5.3 Targeted Therapy

As the name suggests, this therapy targets a specific area. A target is set on a specific element of a cell, such as molecules or pathways required for cell growth and X-rays are bombarded to kill tumor cells. [1].

1.5.4 Tumor Treating Fields

In this technique, A wearable device is used. This device produces electric fields to destroy the rapid cell division exhibited by cancer cells. [1].

1.6 Pros and Cons of Chemotherapy

All treatments mentioned above are intended to prolong and improve life of a patient as long as possible. Chemotherapy treatment has comparatively more advantages than disadvantages. Further, If a Patient is uncertain about initial diagnosis or recurrence it is more beneficial to consider a Chemotherapy option. In Chemotherapy treatment of Brain Tumor patients are administered by drugs which are designed to kill tumor cells. Although chemotherapy may improve overall survival in patients with the most malignant primary brain tumors but it does so in only about 30 percent of patients. Chemotherapy is often preferable in young children because using radiation may have negative effects on the developing brain. Finally, to decide chemotherapy treatment of Brain tumor is based on a patient's overall health, type of tumor, and extent of the cancer. [3].

1.7 Basic Brain Tumor Models

Brain Tumor mathematical models do not give quite enough information and that is why it is difficult to understand the human immune system response behaviour against infected tumor cells. Due to its nonlinear behavior, Brain Tumor chemotherapy treatment is a non-linear control problem.When state of tumor cells is perturbed with the induction of drug observation of brain system is important. These models are not very well defined like many other systems due to which it is difficult to design a perfect control for drug given. It has been seen that a control method which is good for one individual is a total failure for another one. [8].

1.8 Motivation

Brain Tumor is one of the worst diseases in the world and a lot effort has been made to find the inside reasons of this disease. From most of the literature, it is evident that major reason of primary brain tumor is not clearly known to researchers. But research is been going on this and it is considered as a hot potato in the field of medical science. Up till now, we know due to some changes in the DNA of cells some unwanted cells are produce which form a layer of tumor. [9] If the produced unwanted cells are cancerous then multiple layers of Brain Tumors are obtained otherwise if the unwanted cells are not cancerous then a limited layer of Brain Tumor is obtained. [10] In 2018, United States of America registered some 78,980 cases of Brain Tumor (having malignant brain tumor only). While in Pakistan some 80,000 patients annually diagnosed having same disease. Number of patients having Malignant Brain Tumor are more in Pakistan while in USA case is different.

1.9 Problem Statement

- In treatment of tumors, the rate of drug prescription is vital for the patient. [11]
- A too-much-amount of drug will kill the tumor cells but will also destroy the healthy ones.
- On the other hand, a small amount of that drug will not be able to treat or kill the tumor cells.

- Tumor cells growth rate is high as compared to the normal cells. So, reduction of tumor cells is an important problem in this regard. The tumor cells are killed with a proper application of chemotherapeutic drug with constant administration as it can also destroy the normal cells.

- Maintenance of healthy cells above safe levels is very important. Many researches have defined the safe amount of normal cells that are necessary to be maintained in order to survive. The limit may vary according to the condition of the disease. So, normal cells amount should be administered during the therapy process.

- Third and the most important objective of this research is to administer the quantity of chemotherapeutic drug. Different papers define the safe amount of therapeutic drug to be used during a specific period of therapy. It is important to regulate the amount of chemotherapeutic drug in order to reduce the tumor cells as well as save as many normal cells as possible.

1.10 Proposed Approach

A balanced amount of drug that not only kills the tumor cells but also prevents damage to the healthy cells is crucial. This amount of drug prescribed can be suggested by Lyapunov based Control. Different mathematical models have been proposed to address the issue. [11] These models mainly have four basic states i.e. tumor cells, healthy cells, immune cells and amount of drug.The Non Linear based algorithms using Lyapunov Redesign, Synergetic Control and Backstepping are used to suggest a control input u which controls the required amount of drug. The problem is to design a controller through a control technique that can achieve following objectives:

- Reduction and tracking of tumor cells to their desired reference value.

- Sustenance of as many healthy cells as possible after the therapy. The normal cells in the Synergetic controller design are also tracked to a safe limit.

- Application of minimum amount of therapeutic agent being administered in the therapy process

The performance of the proposed controllers have been tested using Matlab/Simulink.

1.11 Thesis Layout

Chapter 2 reviews tumor cells, immune system and chemotherapy therapies while literature is done in chapter 3. Synergetic based control is designed in chapter 4. While backstepping control is designed in chapter 5. Lyapunov Redesign control is proposed in chapter 6. Comparison of proposed controllers, conclusion and future work is proposed in chapter 7.

Chapter 2

Literature Review

2.1 Mathematical Models

From the past research it is evident that there is lot can be done in this field. Researchers has so far mentioned and analyzed few outcomes related to treatment of brain tumors, among them few key can be listed as: 1. State Space Modelling of Brain Tumor 2. Optimal Control Technique on Brain Tumor Model State space model of brain tumor was first introduced by Al Gohary in [12]. It is a four state single input model. The four states were tumor cells, immune cells, healthy cells and amount of drug. The control input u is in the drug state with amount of drug. A mathematical model without drug has been suggested in [6]. A three state mathematical model for immunotherapy treatment of brain tumor is suggested in [12] A mathematical model under the attack of chemotherapeutic agents has been suggested in [11]. By Linearization stability of tumor state is observed in [11]. Nonlinear control problem is solved by using PMP [11]. Optimal values of tumor cells were obtained by applying optimal dosage of drug in the tumor system [11]. It considered that the values of healthy and immune cells were not decrease during treatment in [11] far mentioned and analyzed few outcomes related to treatment of brain tumors, among them few key can be listed as: 1. State Space Modelling of Brain Tumor 2. Optimal Control Technique on Brain Tumor Model State space model of brain tumor was first introduced in [6]. It was a four state single input model. The four states were tumor cells, immune cells, healthy cells and amount of drug. The control input u was in the drug state with amount of drug.

- A mathematical model without drug has been suggested in [6]
- A three state mathematical model for immunotherapy treatment of brain tumor is suggested in [6]

- A mathematical model under the attack of chemotherapeutic agents has been suggested in [12]
- By Linearization stability of tumor state is observed in [11]
- Nonlinear control problem is solved by using PMP [11]
- Optimal values of tumor cells were obtained by applying optimal dosage of drug in the tumor system [11]
- It considered that the values of healthy and immune cells were not decrease during treatment in [11]

2.2 Review of Control Techniques

From above literature review, we can observe following control techniques have been applied so far.

2.2.1 Linear Control

By using linearization, at first all states have been put in the Jacobian Matrix and stability of states has been observed.

2.2.2 Optimal Control

By using PontrayginâĂŹs Maximum Principle, initial optimal values of tumor cells, immune cells, healthy cells and drug has been obtained. Then graphs of these are plotted to observe the behavior of these states [13]. Most of the research in the past deals with the design of optimal control for different types of Brain Tumors. Optimal control technique has been applied to design the control law in [11]

Chapter 3

Mathematical Model of Brain Tumor

The mathematical model of Brain Tumor has been proposed in [11]. This model has been considered in this research. It is a four state nonlinear model with a control input u. The states in the model represent tumor cells, healthy cells, immune cells and amount of chemotherapeutic agent.

3.1 State Space Representation of Brain Tumor

The first model introduced was without interaction of amount of drug. Later, amount of drug was introduced in the model and it is modified as following: [11]

$$\frac{dT(t)}{dt} = T(t)[r_1(1 - b_1T(t)) - c_2I(t) - c_3H(t) - a_1(1 - e^{-D(t)})] \tag{3.1a}$$

$$\frac{dH(t)}{dt} = H(t)[r_2(1 - b_2H(t)) - c_4T(t) - a_2(1 - e^{-D(t)})] \tag{3.1b}$$

$$\frac{dI(t)}{dt} = s + I(t)[\frac{r_3T(t)}{\alpha + T(t)} - c_1T(t) - d_1 - a_3(1 - e^{-D(t)})] \tag{3.1c}$$

$$\frac{dD(t)}{dt} = v(t) - d_2D(t) \tag{3.1d}$$

where

- T: Number of Tumor cells
- H: Number of Healthy cells

- I: Number of Immune cells
- D: Amount of drug
- s: influx rate of immune cells
- d_1: death rate of cells in the absence of tumor
- d_2: death rate of the drug
- r_1: per capita growth rate of tumor cells
- r_2: per capita growth rate of healthy cells
- b_1: Reciprocal carrying capacity of tumor cells
- b_2: Reciprocal carrying capacity of tumor cells
- c_1, c_2, c_3, c_4: system respose coefficients
- a_1, a_2, a_3: system respose coefficients
- $v(t)$: given dose of the drug

The above mention model has twelve parameters. Later, Al Gohary simplied this model to eight parameters [11] Al Alavi and Norabadi simplified this model as follows: [11]

$$\dot{y_1} = y_1[k_1(1 - y_1) - n_2 y_3 - n_3 y_2 - m_1(1 - e^{-y_4})] \tag{3.2a}$$
$$\dot{y_2} = x_2[k_2(1 - y_2) - n_4 y_1 - m_2(1 - e^{-y_4})] \tag{3.2b}$$
$$\dot{y_3} = 1 + y_3[\frac{k_3 y_1}{v_1 + y_1} - n_1 y_1 - v_2 - m_3(1 - e^{-y_4})] \tag{3.2c}$$
$$\dot{y_4} = u - y_4 \tag{3.2d}$$

where

- y_1: Number of Tumor cells
- y_2: Number of Healthy cells
- y_3: Number of Immune cells
- y_4: Amount of drug
- u: control variable

- n_1, n_2, n_3, n_4: positive real constants
- m_1, m_2, m_3: system response coefficients of respective cells
- k_1, k_2, k_3: per capita growth of respective cells

In this research above mentioned model has been used. In above system first equation y_1 contains information regarding change in tumor cells with respect to time while second equation y_2 explains behaviour of healthy cells. Third equation describe relationship of immune cells with other parameters. All these equations contain a term $1-e^{-D}$ which represents amount of drug to be injected. In the fourth equation u is introduced which is control variable for amount of drug.

Chapter 4

Synergetic Controller Design

There are several Non Linear Control Techniques, among these techniques, one of the simplest technique is synergetic control. This technique is an approximation of Sliding Mode Control. In this technique a macro variable is designed. This macro variable includes errors of all states or the states with known reference in order to track them. The macro varible is then put into a dynamic equation mentioned in eq (4.2) to design the controller. The dynamc equation needs to be zero. At the end a Lyapunov Function is selected to achieve asymptotic stability.

The advantage of Synergetic control is that it guarantees the convergence of states to their in finite time and it is chattering free. The Synergetic controller is not effected by the system uncertainties and all kind of internal and external disturbances

The Synergetic control technique has been used in [8] to control HIV virus.

4.1 Control Design Methodology

In chapter 04, we have seen the Brain Tumor model with the interaction of drug. Now by using Synergetic control method on that model, we will introduce only one variable that contains the tracking error for all states, which is defined as follows:

$$\sigma = C_1(y_1 - y_{1ref}) + C_2(y_2 - y_{2ref}) + C_3(y_3 - y_{3ref}) + C_4(y_4 - y_{4ref}) \quad (4.1)$$

To track all the states to their desired reference values , we use a dynamic equation as follows:

$$T\dot{\sigma} + \sigma = 0 \quad (4.2)$$

where T defines the convergence rate of states to $\sigma = 0$.
Taking derivative of σ from eq.(4.1) w.r.t time, we obtain:

$$\dot{\sigma} = C_1(\dot{y_1} - \dot{y_{1ref}}) + C_2(\dot{y_2} - \dot{y_{2ref}}) + C_3(\dot{y_3} - \dot{y_{3ref}}) + C_4(\dot{y_4} - \dot{y_{4ref}}) \quad (4.3)$$

Since y_{1ref}, y_{2ref}, y_{3ref} and y_{4ref} are constants so, their derivatives will be zero. By putting the value of $\dot{y_1}$, $\dot{y_2}$, $\dot{y_3}$ and $\dot{y_4}$ from eq., , and in eq.(4.3), we obtain:

$$\begin{aligned}\dot{\sigma} = C_1[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4})]] \\ + C_2[y_2[k_2(1-y_2) - n_4y_1 - m_2(1-e^{-y_4})]] \\ + C_3[1 + y_3[\frac{k_3y_1}{v_1+y_1} - n_1y_1 - v_2 - m_3(1-e^{-y_4})]] + \\ C_4[u - y_4] \quad (4.4)\end{aligned}$$

By putting the value of $\dot{\sigma}$ and σ from equation (4.1) and (4.2) respectively in equation (4.3) we get:

$$\begin{aligned}T[C_1[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4})]] \\ + C_2[y_2[k_2(1-y_2) - n_4y_1 - m_2(1-e^{-y_4})]] \\ + C_3[1 + y_3[\frac{k_3y_1}{v_1+y_1} - n_1x_1 - v_2 - m_3(1-e^{-y_4})]] \\ + C_4[u - y_4]] + [k_1(y_1 - y_{1ref}) + k_2(y_2 - y_{2ref}) \\ + k_3(y_3 - y_{3ref}) + k_4(y_4 - y_{4ref})] = 0 \quad (4.5)\end{aligned}$$

Now, rearranging it to find u(t), we obtain:

$$u(t) = y_4 - \frac{1}{C_4}(C_1\dot{y_1} + C_2\dot{y_2} + C_3\dot{y_3}) - \frac{C_1y_1}{C_4*T} - \frac{C_2y_2}{C_4*T} - \frac{C_1y_3}{C_4*T} - (1/T)*y_4 \quad (4.6)$$

Putting values of $\dot{y_1}$,$\dot{y_2}$ and $\dot{y_3}$, we get:

$$\begin{aligned}u(t) = y_4 - \frac{1}{C_4}[C_1[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4})]] + C_2[y_2[k_2(1-y_2) - n_4y_1 - \\ m_2(1-e^{-y_4})]] + C_3[1 + y_3[\frac{k_3y_1}{v_1+y_1} - n_1y_1 - v_2 - m_3(1-e^{-y_4})]] \\ - \frac{C_1y_1}{C_4*T} - \frac{C_2y_2}{C_4*T} - \frac{C_1y_3}{C_4*T} - (1/T)*y_4\end{aligned}$$

which is the desired control law for chemotherapy of brain tumor using Synergetic control technique.

4.2 Checking Stability of the System

Now proving the asymptotic stability of the controller. We consider a Lyapunov function as follows:

$$V = \frac{1}{2}\sigma^2 \tag{4.7}$$

Taking derivative of V from eq.(4.7) w.r.t time

$$\dot{V} = \dot{\sigma}\sigma \tag{4.8}$$

Now putting value of $\dot{\sigma}$ from eq.(4.2) in eq.(4.8, we obtain:

$$\dot{V} = -\frac{\sigma^2}{T} \tag{4.9}$$

Hence the system is asymptotically stable.

4.3 Simulation and Results

Following values of parameters have been used for the simulation.
$y_1(0) = 14$, $y_2(0) = 0.25$, $y_3(0) = 1.55$, $y_4(0) = 1.35$

Parameter	Value of Parameter
k_1	30
k_2	48
k_3	29
n_l	2
n_2	1.3
n_3	0.47
n_4	8
m_1	9
m_2	15
m_3	4
v_1	0.25
v_2	10
u_{max}	20

The values of the references and gains used for monotonic therapy are as follows. $y_{1ref} = 0$, $y_{2ref} = 0.9$, $y_{3ref} = 10$, $y_{4ref} = 0$

Parameter	Value of Parameter
C_1	350
C_2	20
C_3	30
C_4	35
T	1

Table 4.1: Values of Gains for Synergetic Control

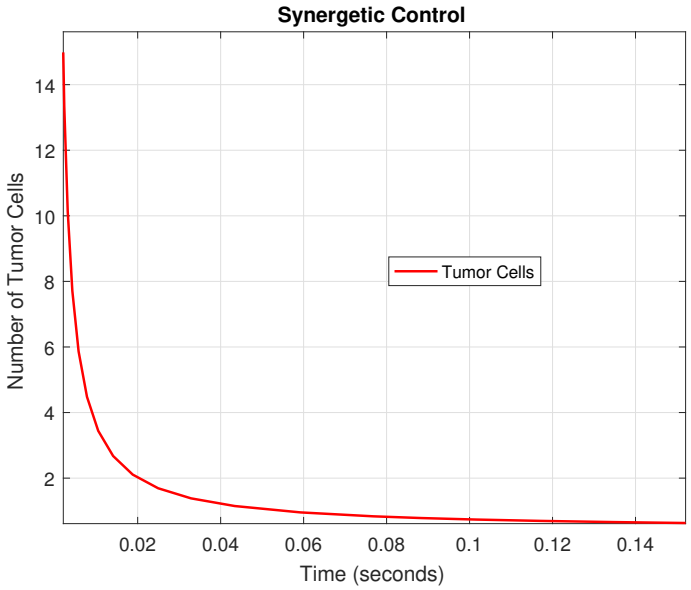

Figure 4.1: Behavior of Tumor Cells

Fig.**??** shows the behavior of tumor cells under chemotherapy. The cells are tracked to zero with some steady state error.
The healthy cells as shown in fig.4.3 shows that the healthy cells are within the safe limits.
The total quantity of therapeutic agent consumed during the process is calculated to be 46.3 that is less than the maximum limit mentioned for the therapeutic agent. The graph of control input is shown in fig.4.5.

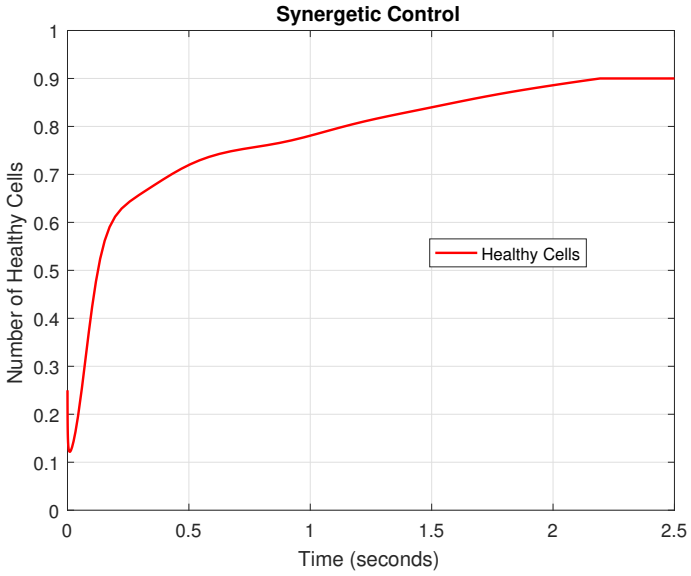

Figure 4.2: Behavior of Healthy Cells

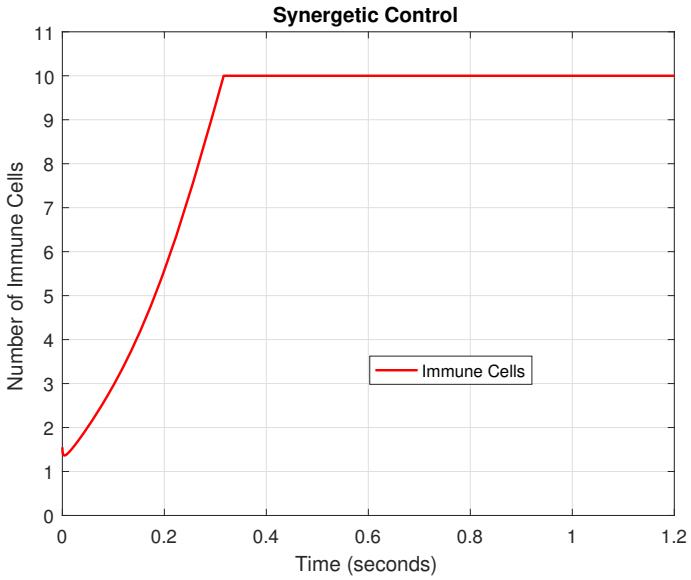

Figure 4.3: Behavior of Immune Cells

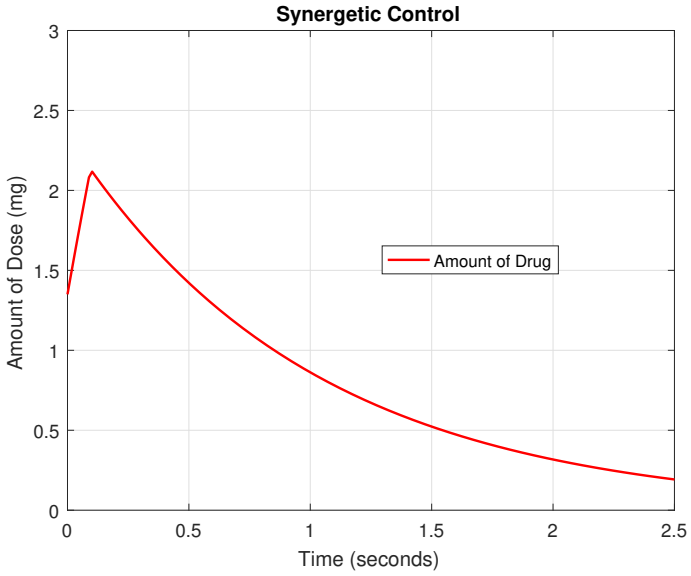

Figure 4.4: Quantity of Chemotherapeutic Agent

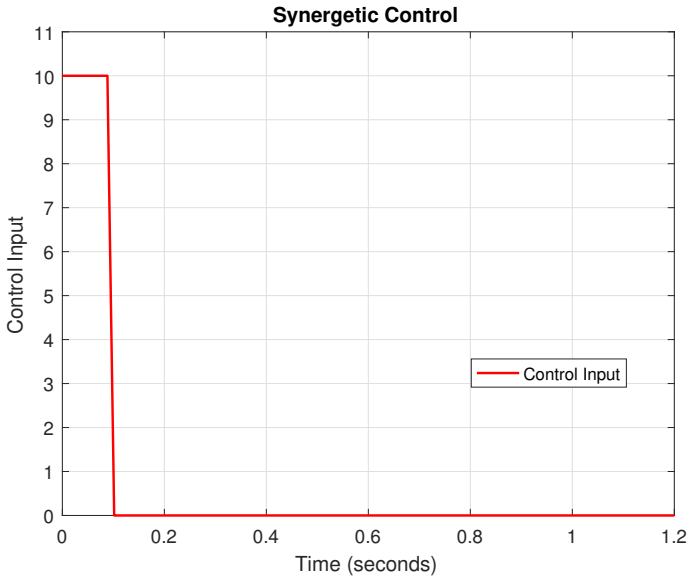

Figure 4.5: Control Input

Chapter 5

Backstepping Controller Design

Backstepping is a nonlinear recursive control technique that involves Lyapunov based stability theory to design the control law. The Backstepping technique involves the tracking of any known state in the system and then backs out to the other states by deriving their control laws, eventually reaching the state with the control input. The technique uses Lyapunov function to analyze the system stability at each step ultimately calculating the desired control law ensuring the system asymptotic stability.
The advantage of the technique is that it does not require the cancellation of non-linearities for its application [8]. It may need a strict feedback form to apply the recursive technique. The main disadvantage of Backstepping is the complexity due to the recursive technique and feedback of other states of the system. The backstepping control has been used in [8]

5.1 Control Design Methodology

The controller design method using the Backstepping controller has been explained below for chemotherapy treatment of Brain Tumor. Error equation for Tumor Cells can be given as:

To track the tumor cells to a reference value y_{1ref}, we define an error e_1 as follows:

$$e_1 = y_1 - y_{1ref} \tag{5.1}$$

where e_1 is the difference between the tumor cells and their desired reference value $y_{_1ref}$. Now taking derivative of eq.(5.1) w.r.t time:

$$\dot{e_1} = \dot{y_1} - \dot{y}_{1ref} \tag{5.2}$$

By putting value of $\dot{y_1}$ from eq.(4.1) in equation(5.2), we obtain:

$$\dot{e_1} = y_1[k_1(1 - y_1) - n_2y_3 - n_3y_2 - m_1(1 - e^{-y_4})] - \dot{y}_{1ref} \tag{5.3}$$

5.1.1 Lyapunov Candidate Function

The error defined by equation (5.2) must approach to zero. For this purpose, we take a Lyapunov candidate function as follows:

$$V_1 = \frac{1}{2}e_1^2 \tag{5.4}$$

where V_1 is positive definite.
Now taking derivative of V_1 from equation (5.4) w.r.t time, we obtain:

$$\dot{V_1} = e_1\dot{e_1} \tag{5.5}$$

By putting value of e_1 from eq.(5.3) in eq.(5.5), we obtain:

$$\dot{V_1} = e_1[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4}] - \dot{y}_{1ref}] \tag{5.6}$$

To make $\dot{V_1}$ negative definite, let

$$[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4})] - \dot{y}_{1ref}] = -c_1e_1 \tag{5.7}$$

where c_1 is a design parameter. So, equation (**??**) becomes:

$$\dot{V_1} = -c_1e_1^2 \tag{5.8}$$

Now obtaining virtual control α for quantity of chemotherapeutic agent by using eq.(5.7)

$$\alpha = -ln[\frac{1}{m_1y_1}[-c_1e_1 - y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4})]] \tag{5.9}$$

Now using the virtual control α as a reference for the quantity of chemotherapeutic agent; the error for tracking is defined as:

$$e_2 = y_4 - \alpha \tag{5.10}$$

Putting value of y_4 from eq.(5.10) in eq.(5.3) will give us the updated value of $\dot{e_1}$ as:

$$\dot{e_1} = y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-(\alpha+e_2)}))] - \dot{y}_{1ref} \tag{5.11}$$

By putting value of α from eq.(5.9) in eq.(5.11), we obtain:

$$\dot{e_1} = y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-(-ln(A)+e_2)}))] - \dot{y}_{1ref} \tag{5.12}$$

where $A = \frac{1}{m_1y_1}[-c_1e_1 - y_1k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1(1-e^{-y_4})]$

By putting the value of $\dot{e_1}$ from eq.(5.12) in eq.(5.6), we obtain:

$$\dot{V_1} = e_1[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1 1 - e^{-(-ln(A)+e_2)}]] \tag{5.13}$$

Now taking the derivative of e_2 w.r.t time from eq.(5.10) gives:

$$\dot{e_2} = \dot{y_4} - \dot{\alpha} \tag{5.14}$$

Taking derivative of α from eq.(5.9) w.r.t time to find $\dot{\alpha}$ as follows:

$$\dot{\alpha} = [\frac{-1}{c_1e_1/m_1y_1 - k_1(1-y_1)/m_1 + n_2y_3/m_1 + n_3y_2/m_1 + 1}] \\ [\frac{(m_1y_1)(-c_1\dot{e_1}) - (-c_1e_1)(m_1\dot{y_1})}{(m_1y_1)^2} * \frac{k_1\dot{y_1} + n_3\dot{y_2} + n_2\dot{y_3}}{m_1}] \tag{5.15}$$

for simplicity, rearranging values of $\dot{\alpha}$

$$\dot{\alpha} = [\frac{(c_1m_1y_1\dot{e_1} - c_1m_1\dot{y_1}e_1)/(m_1y_1)^2}{-c_1e_1/m_1y_1 - k_1(1-y_1)/m_1 + n_2y_3/m_1 + n_3y_2/m_1 + m_1}]*[\frac{k_1\dot{y_1} + n_3\dot{y_2} + n_2\dot{y_3}}{m_1}] \tag{5.16}$$

$$\dot{\alpha} = [\frac{(c_1m_1y_1\dot{e_1} - c_1m_1\dot{y_1}e_1)/(m_1y_1)^2}{-c_1e_1/y_1 - k_1(1-y_1) + n_2y_3 + n_3y_2 + m_1}]*[k_1\dot{y_1} + n_3\dot{y_2} + n_2\dot{y_3}] \tag{5.17}$$

Now, by putting the value of $\dot{y_4}$ from eq.(5.1) in eq.(5.14), we obtain:

$$\dot{e_2} = u(t) - y_4 - \dot{\alpha} \tag{5.18}$$

5.1.2 Combined Lyapunov Candidate

Now, defining a Lyapunov candidate function to ensure convergence of both e_1 and e_2 to zero. The function is defined as follows:

$$V = V_1 + \frac{1}{2}e_2^2 \tag{5.19}$$

Taking derivative of V from eq.(5.19) w.r.t time, we obtain:

$$\dot{V} = \dot{V_1} + e_2\dot{e_2} \tag{5.20}$$

By putting value of $\dot{V_1}$ from eq.(5.8) and value of $\dot{e_2}$ from eq.(5.18) in eq.(5.20), we obtain:

$$\dot{V} = e_1[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1 1 - e^{-(-ln(A)+e_2)}]] + e_2\dot{e_2} \tag{5.21}$$

By rearranging eq.(5.23), we obtain:

$$\dot{V} = e_1^2[y_1[k_1(1-y_1) - n_2y_3 - n_3y_2 - m_1 1 - e^{ln(A)}]] - m_1e_1y_1e^{-e_2} + e_2\dot{e_2} \tag{5.22}$$

$$\dot{V} = e_1[e_1[y_1[k_1(1-y_1) - n_2x_3 - n_3x_2 - m_1 1 - e^{ln(A)}]]] - e_2[\frac{m_1e_1y_1e^{-e_2}}{e_2} - \dot{e_2}] \tag{5.23}$$

To make $\dot{V}$ negative definite, we take:

$$c_2e_2 = \frac{m_1e_1y_1e^{-e_2}}{e_2} - \dot{e_2} \tag{5.24}$$

so:

$$\dot{e_2} = \frac{m_1e_1y_1e^{-e_2}}{e_2} - c_2e_2 \tag{5.25}$$

So, eq.(5.22) becomes:

$$\dot{V} = -c_1e_1^2 - c_2e_2^2 \tag{5.26}$$

which shows that system is asymptotically stable.

Now, putting value of $\dot{\alpha}$ and $\dot{e_2}$ in equation 5.20 we get:

$$\dot{e_2} = u(t) - y_4 + \dot{\alpha} \tag{5.27}$$

$$\frac{m_1e_1y_1e^{-e_2}}{e_2} - c_2e_2 = u(t) - y_4 + [\frac{(c_1m_1y_1\dot{e_1} - c_1m_1\dot{y_1}e_1)/(m_1y_1)^2}{-c_1e_1/y_1 - k_1(1-y_1) + n_2y_3 + n_3y_2 + m_1}] * [k_1\dot{y_1} + n_3\dot{y_2} + n_2\dot{y_3}] \tag{5.28}$$

Hence, The required input u(t) can be given as:

$$u(t) = y_4 + \frac{m_1e_1y_1e^{-e_2}}{e_2} - c_2e_2 - [\frac{(c_1m_1y_1\dot{e_1} - c_1m_1\dot{y_1}e_1)/(m_1y_1)^2}{-c_1e_1/y_1 - k_1(1-y_1) + n_2y_3 + n_3y_2 + m_1}] * [k_1\dot{y_1} + n_3\dot{y_2} + n_2\dot{y_3}] \tag{5.29}$$

5.2 Simulation and Results

Following values of parameters have been used for the simulation.
$y_1(0) = 0$, $y_2(0) = 0$, $y_3(0) = 0$, $y_4(0) = 0$

Parameter	Value of Parameter
k_1	30
k_2	48
k_3	29
n_l	2
n_2	1.3
n_3	0.47
n_4	8
m_1	9
m_2	15
m_3	4
v_1	0.25
v_2	10
u_{max}	20

Table 5.1: Values of parameters

5.3 Gains and Reference Parameters

The values of the reference and gains used for chemotherapy treatment of Brain Tumor are as follows.
$y_{1ref} = 0$, $y_{2ref} = 0.75$

Parameter	Value of Parameter
c_1	10
c_2	20

Table 5.2: Values of Gains for Backstepping Control

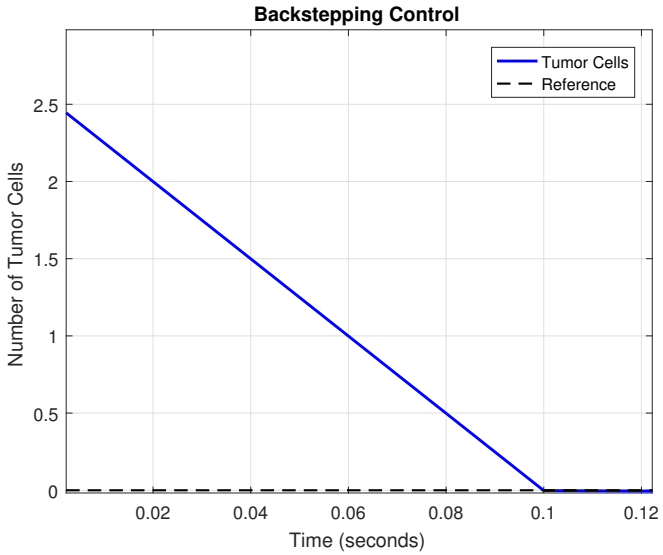

Figure 5.1: Behavior and Tracking of Tumor Cells

The reference for the tumor cells is set to zero. As shown in fig.5.1, the steady state error in case of Backstepping is present.
The normal cells as shown in fig.5.2 are maintained above the minimum prescribed value mentioned by the parameter x_{2min}.
The total quantity of therapeutic agent being used in the therapy process is calculated by calculating the area under the curve (fig.5.3). The value is 55.2 and is less than the maximum bound on therapeutic agent $\boldsymbol{D}$.

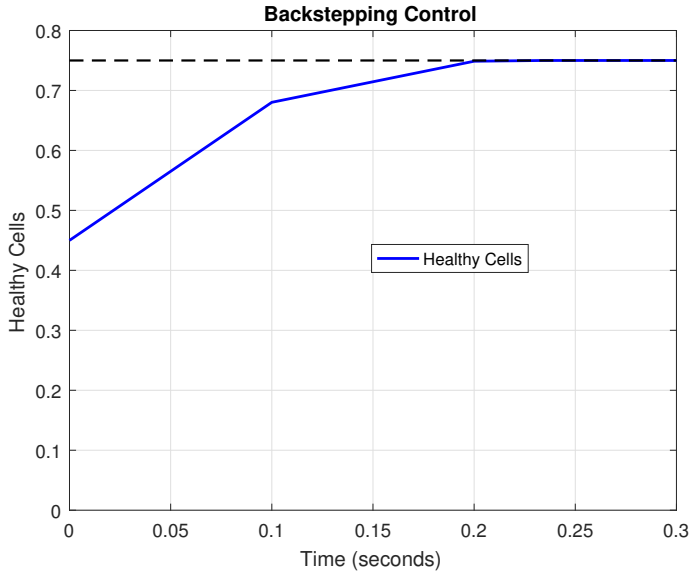

Figure 5.2: Behavior of Healthy Cells

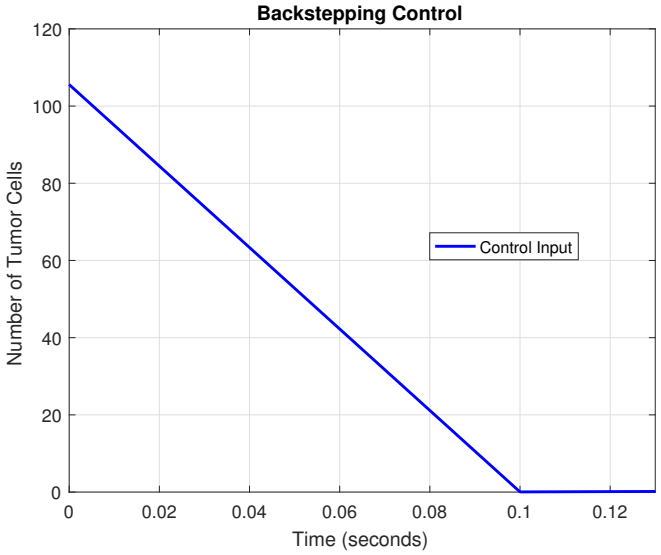

Figure 5.3: Control Input

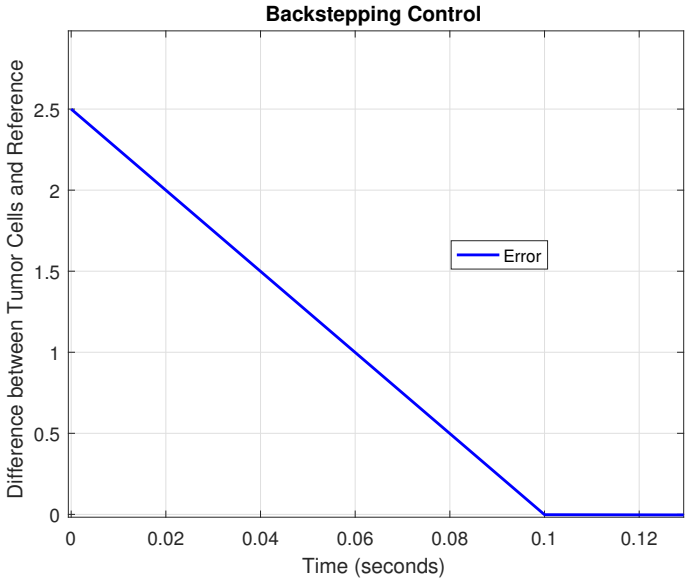

Figure 5.4: Error

Chapter 6

Lyapunov Redesign

Lyapunov Rdesign control technique is similar to the generic Backstepping control technique with a main difference of addition of an integral term in order to account for the sum of the error during the simulation time.
The main advantage of Lyapunov Redesign is the removal of steady state error due to the integral term and also improves the convergence rate of states to their desired reference [7].
The Lyapunov Redesign technique has been applied in [7] to control HIV and winding system respectively.

6.1 Control Design Methodology

We will again recall from chapter 04 the Brain Tumor model, Now to apply Lyapunov Redesign we select a simple Lyapunov Function candidate as follows:

$$V(y) = 1/2(c_1 y_1)^2 + 1/2(c_2 y_2)^2 + 1/2(c_3 y_3)^2 + 1/2(c_4 y_4)^2 \tag{6.1}$$

Taking derivative of V(y) w.r.t time:

$$\dot{V(y)} = y_1\dot{y_1} + y_2\dot{y_2} + y_3\dot{y_3} + y_4\dot{y_4} \tag{6.2}$$

Now, putting values of $\dot{y_1}$, $\dot{y_2}$, $\dot{y_3}$ and $\dot{y_4}$ in $\dot{V}$

$$\begin{aligned}\dot{V}(y) = c_1 y_1[y_1 k_1(1-y_1) - n_2 y_3 - n_3 y_2 - m_1(1-e^{y_4})] \\ + c_2 y_2[y_2 k_2(1-y_2) - n_4 y_1 - m_2(1-e^{y_4})] \\ + c_3 x_3[1 + y_3\frac{k_3 y_1}{v_1 + y_1} - n_1 y_1 - v_2 - m_3(1-e^{y_4})] + c_4 x_4(u - y_4)\end{aligned} \tag{6.3}$$

Now, simplifying to obtain suitable $u(t)$

$$\dot{V}(y) = c_1k_1y_1^2 - c_1y_1^3 - c_1n_2(y_1)^2x_3 - c_1n_3y_1^2y_2 - c_1m_1y_1^2(1-e^{-y_4}) + c_2k_2y_2^2 - c_2y_2^3 - c_2n_4y_1y_2^2 - c_2m_2y_2^2(1-e^{y_4}) + c_3y_3 + c_3[\frac{k_3y_1y_3^2}{v_1+y_1} - n_1y_1y_3^2 - v_2y_3^2 - m_3y_3^2(1-e^{y_4})] + c_4y_4u - c_4y_4^2 \tag{6.4}$$

Now, The required u(t) can be given as :

$$u(t) = 1/y_4[-c_1k_1y_1^2 + c_1y_1^3 + c_1n_2y_1^2y_3 - c_1n_3y_1^2y_2 - c_2k_2y_2^2 + c_2y_2^3 + c_2n_4y_1y_2^2 - c_3y_3 - \frac{c_3k_3y_1y_3^2}{v_1+y_1} - c_3n_1y_1y_3^2] \tag{6.5}$$

6.1.1 Stability of the System

By putting value of above u(t) in $\dot{V}$, we will get:

$$V = -(m_1y_1^2 + m_1y_2^2 + m_1\dot{y}_3^2)(1 - e^{-y_4}) - y_4^2 - v_2y_3^2 \tag{6.6}$$

Now, from above equation it is clear that for the system to be asymptotically stable following condition must be satified:

$$(1 - e^{-y_4}) > 0$$

As we know that y_4 is the amount of drug, so this will always remain positive. This will make $\dot{V}(y)$ always strictly negative so the system will be Asymptotically Stable.

6.2 Simulation and Results

Following values of parameters have been used for the simulation.
$y_1(0) = 2.5$, $y_2(0) = 0.25$, $y_3(0) = 1.5$, $y_4(0) = 0$

Parameter	Value of Parameter
k_1	30
k_2	48
k_3	29
n_l	2
n_2	1.3
n_3	0.47
n_4	8
m_1	9
m_2	15
m_3	4
v_1	0.25
v_2	10
u_{max}	20

Table 6.1: Values of parameters

The values of the references and gains used for monotonic therapy are as follows.
$x_{1ref} = 0$, $x_{2ref} = 0.75$

Parameter	Value of Parameter
c_1	2
c_2	5
c_3	13
c_3	8

Table 6.2: Values of Gains for Lyapunov Redesign

The behavior of tumor cells for the chemotherapy treatment under the Lyapunov Redesign controller is shown in fig.6.1. The tumor cells in this case show very close to zero.
The healthy cells in this case are also retained above the minimum prescribed value (fig.6.3).
The total quantity of chemotherapeutic agent consumed in this process is calculated to be 56.2 that is less than the maximum bound on the quantity of therapeutic agent (fig.6.4).
The graph of control input is shown in fig.6.5.

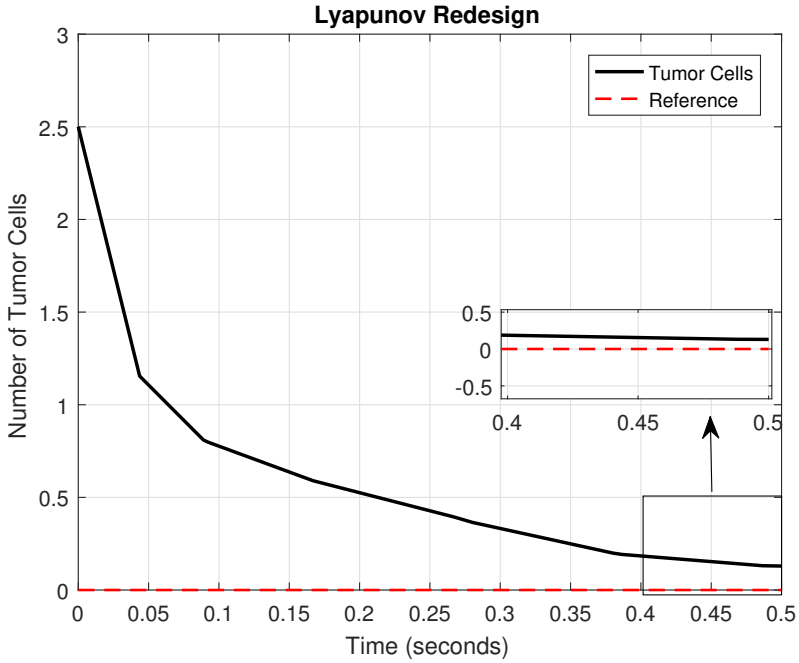

Figure 6.1: Behavior and Tracking of Tumor Cells

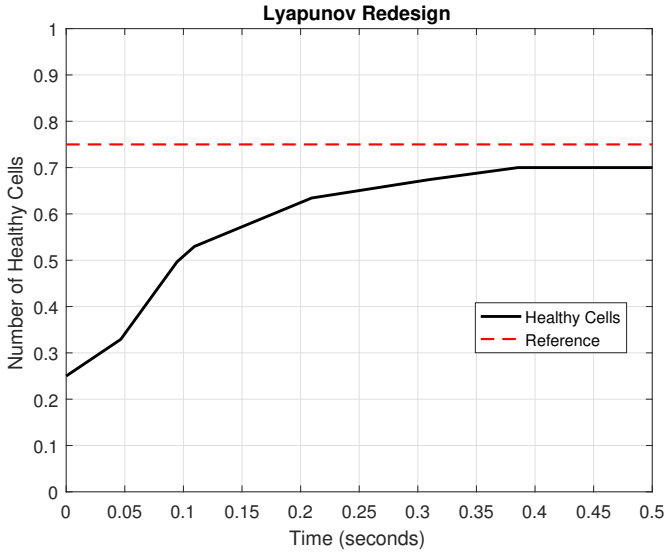

Figure 6.2: Behavior of Healthy Cells

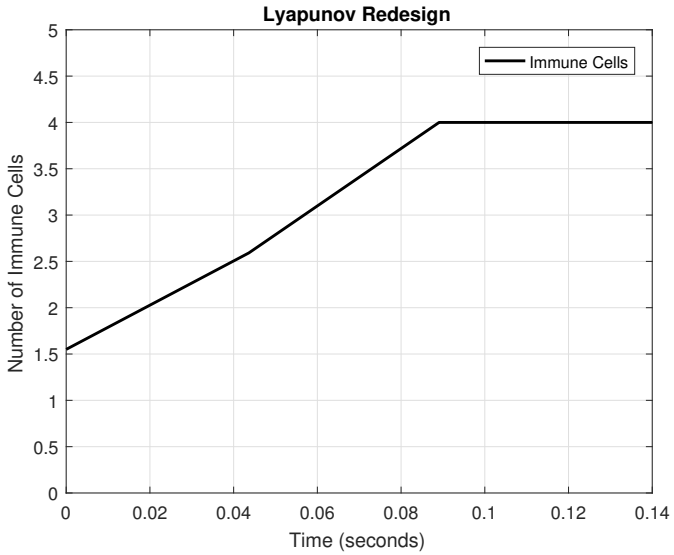

Figure 6.3: Behavior of Immune Cells

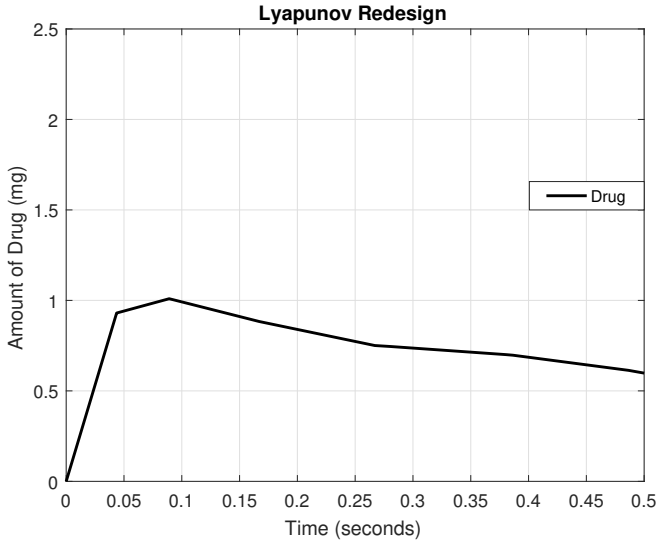

Figure 6.4: Quantity of Chemotherapeutic Agent

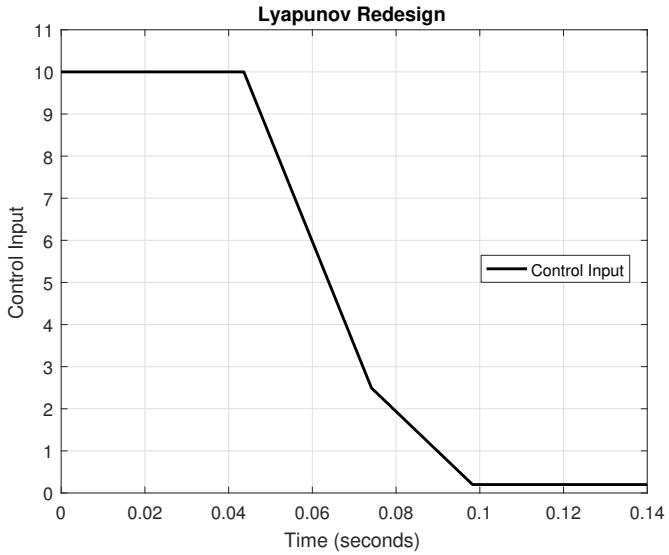

Figure 6.5: Control Input

Chapter 7

Conclusion

In this research, three nonlinear controllers have been proposed in order to control the amount of chemotherapeutic drug for the treatment of Acute Leukemia. The mathematical model of Brain Tumor consists of four states namely tumor cells, healthy cells, immune cells and amount of drug. The control input represents the amount of therapeutic drug that is given to the patient. Chemotherapy treatment is used to describe the efficacy of therapeutic agent on healthy cells, immune cells and tumor cells. Backstepping, Lyapunov Redesign and Synergetic controllers have been designed for the control of tumor cells. The results as shown in the above chapters show that the all controllers are effective enough to track the tumor cells. Whereas in the Synergetic control technique, healthy cells and amount of therapeutic agent are also tracked. The results show that Backstepping is better than Lyapunov Redesign and Synergetic control technique on the basis of convergence of tumor cells to zero and steady state error. The Non Linear control techniques used in this research represents a real approximation of treatment.

7.1 Future Work

To continue above research for the treatment of Brain Tumor following work can be done. A device can be designed to provide chemotherapeutic drug according to patient's requirement. Non Linear Control techniques can be used on immunotherapy model for Brain Tumor. The techniques used for this system can be applied to solve Brain related models in computational neuroscience.

Bibliography

[1] Tom Halkin, "BRAIN TUMOR FACTS & FIGURES, MAY 2018: INCIDENCE, MORTALITY, AND SURVIVAL IN 2018." [Online]. Available: https://blog.braintumor.org/brain-tumor-facts-figures-may-2018-incidence-mortality-and-survival-in-2018/

[2] "Cancer Statistics." [Online]. Available: shaukatkhanum.org.pk/health-care-professionals-researchers/cancer-statistics/

[3] "Most Popular Disease." [Online]. Available: www.kc.bluecircle.in

[4] "Brain Tumors." [Online]. Available: www.mayfieldclinic.com

[5] T. Akman YÄśldÄśz, S. Arshad, and D. Baleanu, "Optimal chemotherapy and immunotherapy schedules for a cancer-obesity model with Caputo time fractional derivative: Optimal chemotherapy and immunotherapy schedules for a cancer-obesity model with Caputo time fractional derivative," *Math Meth Appl Sci*, vol. 41, no. 18, pp. 9390–9407, Dec. 2018. [Online]. Available: http://doi.wiley.com/10.1002/mma.5298

[6] M. Itik, M. U. Salamci, and S. P. Banks, "Optimal control of drug therapy in cancer treatment," *Nonlinear Analysis: Theory, Methods & Applications*, vol. 71, no. 12, pp. e1473–e1486, Dec. 2009. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0362546X09002077

[7] E. Hossain, R. Perez, S. Padmanaban, L. Mihet-Popa, F. Blaabjerg, and V. Ramachandaramurthy, "Sliding Mode Controller and Lyapunov Redesign Controller to Improve Microgrid Stability: A Comparative Analysis with CPL Power Variation," *Energies*, vol. 10, no. 12, p. 1959, Nov. 2017. [Online]. Available: http://www.mdpi.com/1996-1073/10/12/1959

[8] R. S. Butt, I. Ahmad, R. Iftikhar, and M. Arsalan, "Integral Backstepping and Synergetic Control for Tracking of Infected Cells During Early Antiretroviral Therapy," *IEEE Access*, vol. 7, pp. 69 447–69 455, 2019. [Online]. Available: https://ieeexplore.ieee.org/document/8704215/

[9] W. B. Pope, I. Djoukhadar, and A. Jackson, "Neuroimaging," in *Handbook of Clinical Neurology*. Elsevier, 2016, vol. 134, pp. 27–50. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/B9780128029978000037

[10] S. Sharma and G. P. Samanta, "Analysis of the Dynamics of a TumorâĂŞImmune System with Chemotherapy and Immunotherapy and Quadratic Optimal Control," *Differ Equ Dyn Syst*, vol. 24, no. 2, pp. 149–171, Apr. 2016. [Online]. Available: http://link.springer.com/10.1007/s12591-015-0250-1

[11] S. Alavi, J. Norabadi, and M. Arjmand, "Optimal Control Brain Tumor System With Drog And Its Stability," *J. Math. Computer Sci.*, vol. 04, no. 03, pp. 473–486, Apr. 2012. [Online]. Available: http://www.isr-publications.com/jmcs/articles-356-optimal-control-brain-tumor-system-with-drog-and-its-stability

[12] A. El-Gohary, "Chaos and optimal control of equilibrium states of tumor system with drug," *Chaos, Solitons & Fractals*, vol. 41, no. 1, pp. 425–435, Jul. 2009. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0960077908000507

[13] R. Padmanabhan, N. Meskin, and W. M. Haddad, "Reinforcement learning-based control of drug dosing for cancer chemotherapy treatment," *Mathematical Biosciences*, vol. 293, pp. 11–20, Nov. 2017. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0025556417304327