Optimal Control of Antigen Specific Antibody Interactions for Cancer Immunotherapy

by

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Abstract

In the history of cancer treatment, the immunotherapy is considered to be the most promising treatment approach. The idea behind this breakthrough is to stimulate the patient's own immune system to recognize the cancer cells and destroy them. In this therapy, the antibodies are known to be powerful medications to activate the immune system in different ways. They circulate throughout the body until they discover a substance that body recognize as alien i.e. antigen and bind to them. Similarly, cancer cells often have molecules on their surface known as tumor-associated antigens. The researchers can design many clones of the antibody that only target a certain antigen type such as one found on tumors or cancer cells. Then, these are used as an effective drug for treating cancer. Thus, the antigen specific antibody interactions play a vital role in cancer immunotherapy.

In this study, we propose a dynamic model to represent the population of antigens and antibodies in cancer patients; in particular we focus on the antigen-specific-antibody interactions to elicit an immune response that leads to the death of cancer cells. We formulate a terminal control problem where the schedule and doses of these antibodies are considered as control variables. The objective functional has been formulated as a measure of antigen population at the end of the treatment period. Pontryagin minimum principle (PMP) has been used to obtain the optimal control policies. For illustration, a series of numerical results is presented showing the effectiveness of immune therapy for cancer treatment corresponding to the different scenarios, choices of parameters and treatment periods. The results indicate that the control doses are followed by the emergence of antigen population. This approach would be potentially applicable to determine and prescribe the optimal doses and schedules for cancer patients.

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Dedication

”To my beloved family who shaped my life and honorable supervisors for their extraordinary encouragements and supports.”

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Nomenclature

Abbreviations

Ab	Antibody
Ag	Antigen
DCV	Dendritic Cell Vaccine
DP	Dynamic Programming
HER2	Human Epidermal Growth Factor Receptor 2
IL-2	Interleukin 2
mAb	Monoclonal Antibody
pAb	Polyclonal Antibody
PD-1	Programmed Cell Death-1 inhibitor
PD-L1	Programmed Death Ligand 1 inhibitor
PMP	Pontryagin's Minimum (Maximum) Principle

Mathematical Symbols

B_i	population of antibody class of i
G_i	population of antigen class of i
α_i	intrinsic growth rate of antibody class of i
δ_i	intrinsic growth rate of antigen class of i
β_{ij}	impact of j-th class of antigen on i-th class of antibody
η_{ij}	impact of j-th class of antibody on i-th class of antigen
u_k	control drug of group k

γ_{ik}	effect of k-th drug (or control) on i-th class of antibody and antigen
ω_i	weighting value in cost functional for antigen class of i

Subscripts

i	specific class of antigen or antibody
j	other classes of antigens or antibodies
κ	number of classes of antibodies and antigens
k	group of control drug
m	number of control drugs

Chapter 1

Introduction

This thesis report studies the optimal control of antigen specific antibody interactions for cancer immunotherapy. For this purpose, a dynamic model has been proposed to analyze the temporal behavior of antigen-antibody dynamics in cancer affected patients including a methodology to obtain an optimal treatment policies for them.

1.1 Motivation

Mathematical modelling of bio-chemical processes has been widely used to analyze the dynamic behavior of biological phenomena. This analysis can also be applied in both clinical and experimental settings [35]. In the era of intense and rapid development of cancer immunotherapy, such efforts can prove to be significant in developing effective and efficient drug administration regimes [25]. Currently, immunotherapy is a very active area of cancer research where a certain portion of a patient's immune system is used to fight cancer. Therefore, if the interactions of the immune system with cancer cells or tumor cells are described by a dynamic model and the objective function is formulated so as to reflect the population level of cancer cells in the body, it is possible to determine when and to what extent one must activate the immune system to kill the cancer cell population [13].

Furthermore, unlike chemotherapy which targets directly on the tumor, the immunotherapy acts on the immune system, then the immune system attacks the tumor cells. Such process takes time and varies from patient to patient depending upon their immunity. Besides, if the treatment is not effective, the administration of immunotherapy may result in wasted time during which the stage of cancer might have become much serious [46].

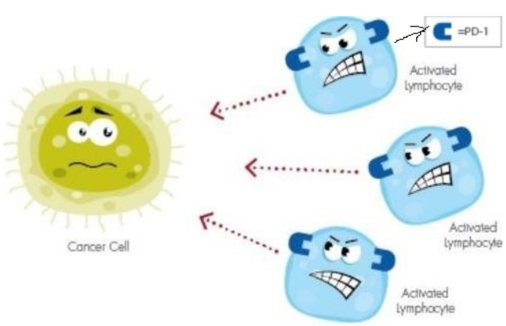
Therefore, during the diagnosis or early stage of treatment, it would be advantageous if a predictive model could be used to predict the efficacy of immunotherapy.

1.2 Cancer Immunotherapy

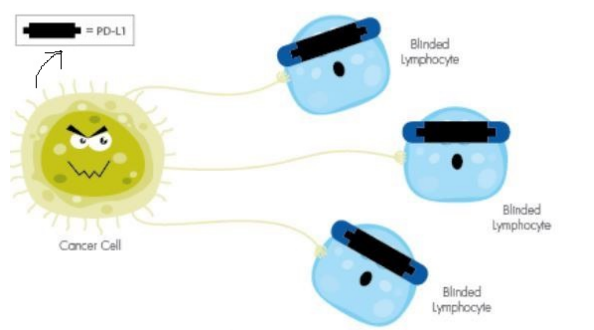
Cancer immunotherapy was first introduced by William B. Coley in 1890 [39]. It is based on the idea that the immune system of human body, which can be described as a network of cells, tissues, and organs, naturally works to defend the body against the attacks by "foreign" invaders (pathogens) [29]. The immune system cells that circulate in the bloodstream are typically known as white blood cells. They are of different types and have different roles of attacking foreign substances in different ways. *Lymphocytes* are one of the main cells in immune system, particularly important in fighting cancer. There are mainly two categories of lymphocytes: T cells and B cells [30]. The *T cell* has a specialized structure on their surface that can recognize body's own cells as infected or cancerous and destroy them whereas the *B cells* generate antibodies that attack invading viruses, bacteria, and toxins [42] etc. *Antibodies* are the large Y-shaped blood proteins produced in response to the counteracting proteins called antigen. On the other hand, the *antigens* are defined as the toxin or other foreign particles such as chemicals, bacteria, viruses, and pollens that induce an immune response [36]. Thus, antigen-antibody reaction is the fundamental chemical reaction that takes place in human body in order to protect it from harmful toxic chemicals or particles, pathogens etc. In this reaction, they interact with each other through a high affinity binding much like lock and key [12]. Once attached, they can recruit other elements of the immune system to kill the cancer cells [45]. Moreover, depending upon the particular class and subtype, antibodies may interact with other serums, proteins or different antigens in the body [43].

The idea for treating cancer is based on this antigen-antibody reaction. The antibodies can be produced in laboratories and designed to target specific antigen type, which is found in cancer affected cells [20]. First, one has to identify the right antigen to target and then create many clones of the required antibodies in laboratories. These are called monoclonal (mAbs) or polyclonal antibodies (pAbs) [43]. Each of these has a distinct mechanism of action. They are designed to boost or restore the immune function resulting to limit the cancer cell growth or destroying them in some manner [42].

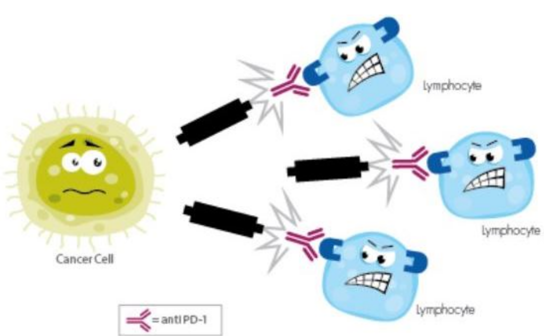
For example, one way is to help immune system to distinguish between normal cells and tumor cells. *PD-1* is a checkpoint protein on immune cells (lymphocytes). The main task of this checkpoint protein is to prevent immune system from attacking normal cells, tissues and organs. Cancer cells take this advantage. They secret another protein called *PD-L1*, which bind onto *PD-1* protein that turns immune cells (lymphocytes) to be inactive. Figures 1.1a and 1.1b show that the lymphocytes have successfully recognized the abnormal cancer cells but due to the reaction of *PD-1* and *PD-L1* (Figure 1.1b) they become inactive to destroy them. Several antibodies have been designed to act as a checkpoint inhibitor to re-activate the immune system. *IpilimuAb*, *NivolumAb* and *PembrolizumAb* are such type of antibodies [31]. They work by binding to the *PD-1* on lymphocytes so that they are no longer available to bind with *PD-L1* on cancerous cells (Figure 1.1c). Another antibody *AtezolizumAb* works by binding to *PD-L1* (Figure 1.1d). In both cases, the result is the same: *PD-L1* and *PD-1* can no longer bind to each other. Thus the immune system (lymphocytes) become active to recognize the tumor cells and destroy them effectively [42]. Oncologists have also approved a combination immunotherapies of ipilimumab, nivolumab and pembrolizumab to treat patients with skin cancer Melanoma [31].



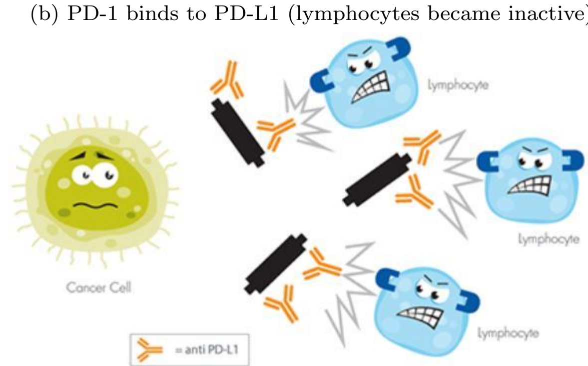
(a) Lymphocytes recognise cancer cells.



(b) PD-1 binds to PD-L1 (lymphocytes became inactive).



(c) Anti PD-1 reactivate lymphocytes.



(d) Anti PD-L1 reactivate lymphocytes.

Figure 1.1: Basic idea of antigen-antibody interaction for cancer immunotherapy. [42]

Another example is *trastuzumAb*, which is an antibody against the antigen class of *HER2* [43]. Breast and stomach cancer cells sometimes have large amounts of this *HER2* protein on their surface. When *HER2* is activated, it helps the cancer cells to spread rapidly. *TrastuzumAb* binds to these proteins and stops them from becoming active. Thus it inhibits the growth of cancer cells. Over the past couple of decades, the US Food and Drug Administration (FDA) have approved more than a dozen mAbs or pAbs to treat some particular types of cancers. As researchers discover more antigens linked to cancer, they would be able to design more antibodies to fight them. Clinical trials of newer Abs are now being done on many types of cancer [43]. Besides, these antigen-antibody therapies, immunotherapy encompasses some other treatment approaches for treating cancer[45].

• **Monoclonal Antibodies:** In this approach, the tumor-specific monoclonal or polyclonal antibodies are used to elicit a direct or indirect immune response that leads to cancer cell death [43].

• **Checkpoint Modulator:** Here, the idea is to block the ability of immune checkpoint proteins from limiting the strength of tumor and activate the natural immune response quickly [43].

• **Immune System Modulators - Cytokines:** Cytokines is another type of immune cell that stimulate T-cells of the immune system to fight cancer. Two types of cytokines are used to treat patients with cancer: interleukins and interferons.

• **Immune Cell Therapy:** This is also called adoptive cell transfer (ACT) therapy. Here T-cells are collected from the patient's tumor and the most powerful ones (in the sense of ability to recognise tumors) are cultured in the laboratory in large quantity and then activated by treatment with cytokines and infused in the patient's body to destroy the tumor [2].

• **Therapeutic Cancer Vaccines:** Vaccines are not yet a major type of treatment for cancer. Dendritic cell vaccines (DCV), autologous tumor cell vaccines, vector-based vaccines are successfully tested in different types of cancer.

All the treatment approaches mentioned above are based on the idea of activating immune response against cancer cells with the help of some kind of reaction among the proteins, enzymes and cells. In our thesis, although we particularly focus on antigen specific antibody treatment therapy, the model we propose here is sufficiently general to be adopted in all the above mentioned techniques.

1.3 Optimal Control Theory

The theory of optimal control has been well developed for over sixty years [34]. Many systems: physical, chemical, biological, or ecological, can be modeled by mathematical relations in many ways [26]. These are called dynamic systems where the elements of the systems change over time or any other independent variable according to the dynamical relations. It is possible to apply some type of external inputs (controls) to steer these systems from one state to another state. Here, the input applied to the system corresponding to the best situation is called "optimal" control. Therefore, the optimal control problem is to determine this input to the system that satisfy some physical constraints while at the same time maximize or minimize a chosen objective functional. Following the optimal control theory, this study includes modeling of antigen specific antibody interaction from system engineering point of view and finding an optimal input (doses of antibodies) to stimulate the immune system response of cancer patients.

There are two well-known techniques for solving optimal control and decision problems: one is the Pontryagin's maximum (or minimum) principle (PMP) [11] and the other is the Bellman's dynamic programming (DP) [9]. Here, we adopt Pontryagin's minimum principle which has been a powerful tool for solving the problems with constrained optimal control inputs.

The basic control problem can be described as follows:

Consider the system:

$$\dot{x} = f(t, x(t), u(t)); \quad t \in [t_1, t_2] \equiv I. \tag{1.1}$$

with initial state $x(t_1) = x_1 \in R^n$, final state $x(t_2) = x_2 \in R^n$, x_2 is free and the control set U is a closed bounded subset of R^m and $u \in \mathcal{U}$, where $\mathcal{U}$ denotes the admissible class of control set.

Consider a general cost functional as mentioned below:

$$J(u) = \int_{t_1}^{t_2} l(t, x(t), u(t))dt + \mathbf{\Phi}(x(t_2)). \tag{1.2}$$

The problem is to find a control law $u \in \mathcal{U}$ that minimizes the cost functional as defined in 1.2 subject to the dynamic constraint of the system 1.1 while transferring from the state x_1 at time t_1 to the state x_2 at time t_2 [1].

The cost function consists of two main parts namely, the running cost ($\int_{t_1}^{t_2} l(t, x(t), u(t))dt$) and the terminal cost ($\mathbf{\Phi}(x(t_2))$). The running cost is responsible for optimizing the costs during the plan period while the terminal cost part has the responsibility of minimizing the gap between the desired state of the system and the obtained states from the system model at the end of the plan period [27]. Different types of costs may be considered according to the main concern of the problem. If the cost functional contains the terminal cost function only, it is called the *Mayer* problem, if the cost functional has only the running cost term, it is called the *Lagrange* problem. The problem is of the *Bolza* type if the cost functional includes both [26].

Pontryagin introduced a function called Hamiltonian that plays an important role in the Pontryagin Maximum principle and described as follows:

$$H(t, x, \psi, u) \equiv < f(t, x, u), \psi > + l(t, x, u) \tag{1.3}$$

Here

$$< f(t, x, u), \psi >= \psi' f(t, x, u)$$

The Pontryagin minimum principle (PMP) theorem can be stated to derive the necessary conditions of optimality as below:

Theorem 1.1(Pontryagin's minimum principle). Suppose $f(t, x, u)$ is measurable in t, C^1 in x and continuous and convex in u. In order for the pair (x, u) to be optimal, it is necessary that there exists a multiplier $\psi \in AC(I, R^n)$, $I = [t_1, t_2]$, such that the following inequality and equations hold:

(a) $H(t, x(t), \psi(t), u(t)) \leqslant H(t, x(t), \psi(t), v(t));$ for $\forall v \in \mathcal{U}_{ad},$ a.e. on I,

(b) $\dot{x} = H_\psi = f(t, x, u), \quad x(t_1) = x_1;,$

(c) $\dot{\psi} = -H_x = -f'(t, x, u)\psi - l_x(t, x, u), \quad \psi(t_2) = \mathbf{\Phi}_x(x(t_2))$

Proof: [1], Corollary 6.2.6. •

1.4 Computation of Optimal Controls

With the advances of computer technologies, the theory of optimal control is now widely used in multi-disciplinary research area and applications such as telecommunication and network, rocket engineering, industrial production, biological systems, socio-economic systems etc [34]. In most cases the solution of these two point boundary value problem is an extremely difficult task [1]. In practice, it is relatively easy to compute the optimal solution through iterative techniques using the necessary conditions of optimality. Some of the commonly used methods are the gradient descent method, second variation, quasilinearization method, and primal-dual method [1].

In this research, we apply gradient method as given in [1] to solve the optimal control problem. It is a first-order iterative optimization algorithm for finding the local minimum of a function [41]. For optimal control problem, it works on the idea of updating the controls using the gradient vector, in such a way that successive iterations produce maximum reduction of the cost.

To illustrate it, first consider the following control problem:

$$\text{minimize}\ \left\{J(u) = \int_0^T l(t,x(t),u(t))dt + \mathbf{\Phi}(x(T))\right\} \tag{1.4}$$

Subject to the dynamic constraint:

$$\begin{cases} \dot{x} = f(t,x(t),u(t)); \quad u \in \mathcal{U} \\ x(0) = x_1 \end{cases} \tag{1.5}$$

Define the Hamiltonian $H(t,x,\psi,u)$ by

$$H(t,x,\psi,u) = l(t,x(t),u(t)) + < f(t,x(t),u(t)), \psi > \tag{1.6}$$

Then it follows from the **Theorem 1.1** that the optimal control u^o and the corresponding pair (x^o,ψ^o) satisfy the system equation 1.5, and the adjoint equation,

$$\begin{cases} \dot{\psi} = -H_x = -f'(t,x(t),u(t))\psi - l_x(t,x(t),u(t)), \\ \psi(T) = \mathbf{\Phi}_x(x(T)) \end{cases} \tag{1.7}$$

and the inequality

$$H(x^o(t),u^o(t),\psi^o(t)) \leqslant H(x^o(t),u(t),\psi^o(t));\ \text{for } \forall u \in \mathcal{U}_{ad},\ \text{a.e. on } [0T] \tag{1.8}$$

where, $x^o \equiv x(u^o)$ and $\psi^o \equiv \psi(u^o)$

First of all, an initial control is guessed to determine the solution to a problem in which one or more of the necessary conditions of optimality are satisfied as mentioned in Theorem 1.1. This solution is then used to adjust the initial guess to obtain the next solution that comes closer to satisfy all the necessary conditions. Thus if the steps are repeated until the iterative procedure converges, all the necessary conditions will eventually be satisfied [18]. The iterative procedure is presented in the following steps:

Step 1 Guess $u_1 \in \mathcal{U}$ and set iteration index $n = 1$

Step 2 Solve the initial-value problem (1.5) with $u(t) = u_n(t)$ to get $x_n(t)$.

Step 3 Using the data x_n and u_n, solve the adjoint system (1.7) to obtain ψ_n

Step 4 Compute the gradient vector

$$g_n(t) = H_u(t, x_n(t), \psi_n(t), u_n(t)).$$

Step 5

(a) if $g_n(t) \neq 0$, then modify $u_n(t)$ to $u_{n+1}(t) = u_n(t) - \varepsilon g_n(t)$ by choosing step size $\varepsilon > 0$ sufficiently small so that $u_{n+1}(t) \in \mathcal{U}_{ad}$ and $J(u_{n+1}) \leq J(u_n)$. A stopping criterion has been used at this stage.

If $|J(u_{n+1}) - J(u_n)| \leq \delta$ for some small $\delta > 0$, then stop, otherwise set $u_n = u_{n+1}$, $n = n + 1$ and go for **step 2**.

(b) If $g_n(t) = 0$ at the nth stage, then u_n is the local minimizing element of $J(u)$.

1.5 Objective

Based on the above philosophies, the main objective of this thesis is to propose a mathematical model based on population dynamics of the two competing species: antigens and antibodies and apply the theory of optimal control to obtain the most effective and efficient treatment policy to minimize and eventually destroy the antigen population. The following list of objectives will be the focus of this thesis:

1. Propose a dynamic model that describes the temporal evolution of antibodies and antigens in cancer patients including the control terms where the schedule and doses of the antibodies are considered as control variables.

2. Define an objective functional that minimizes the antigen population at the end of treatment period.

3. Formulate the optimal control problem and apply Pontryagin minimum principle to determine the optimal treatment policies.

4. Implement an algorithm based on gradient descent technique for numerical simulation of the system.

5. Demonstrate the system behavior corresponding to different scenarios and choices of parameters.

1.6 Contributions

The main purpose of mathematical modeling is to translate the real world problem into a mathematical one as well as investigate the important questions that arise from it. However, in mathematical modeling it is challenging to develop the simplest possible model that considers the main features of the phenomenon of interest [6]. We find the models in previous studies are more descriptive, comprehensive and complex [19], [16], [13], [14], [15], [6] (detailed explanations are discussed in literature review chapter). In this thesis, we present a simple phenomenological approach to describe the antigen-antibody dynamics and formulate an optimal control problem for minimizing the antigen population.

More specifically, the study provides the following contributions:

1. In this study and for the first time to the best of our knowledge, the antigen specific antibody dynamics are proposed by using the Lotka-Volterra [33] prey-predator model. The original model is simply modified [1] by including the control terms that represents the dose of antibody therapeutics to reinforce their production rate to attack the antigens. Another new aspect is, the model is simple but effective enough to include the multiple classes of antigens and antibodies interaction as well as multiple types of drug administration for targeting one or more than one class of antigen.

2. An optimal control problem is formulated where the dose and drug administration schedule of the antibody therapeutics are considered as control variables. The objective functional is defined to minimizes the antigen population at the end of treatment plan. Pontryagin minimum principle (PMP) is applied to derive the necessary conditions of the optimality.

3. An algorithm has been developed for the computation of optimal controls based on gradient descent technique. Using the algorithm we conduct numerical simulation of the model and analyse the effect of different system parameters which also represents different case studies. We propose a simple but effective method whereby, after diagnosis, the oncologist will be able to determine and prescribe an optimal drug regimen for the cancer patients. It is also applicable in different clinical models for example, the model of influenza infection [8], drug distribution in body [32], epidemic model [10] etc.

4. A paper has been written on the basis of this thesis and accepted in the *Journal of Dynamics of Continuous, Discrete and Impulsive Systems Series B: Applications & Algorithms*, vol 26(1), 2019 [4].

5. A detail spatiotemporal model related to this thesis has already been published in the *Journal of Abstract Differential Equations and Applications*, vol 8(1):48–70, 2017 [2] which helps to investigate a variety of biomedical systems with respect to both time and space.

6. Another paper based on this study is in progress to be submitted to Journal of Biostatistics and Biometric Applications (JBBA; ISSN: 2455-765X).

1.7 Organization

The report presented in this thesis is organized in five chapters. These five chapters are structured as follows:

1. Chapter 1 is entitled "Introduction". This chapter describes the idea of cancer immunotherapy, theory of optimal control, the computation of optimal control problem, objectives and contribution of the research area.

2. Chapter 2 is entitled "Literature Review". It introduces the related researches by other research groups.

3. Chapter 3 is entitled "Mathematical Model and Problem Formulation". It proposes the dynamic model to represent the antigen-antibody interaction and defines the objective functional. It also includes the formulation of optimal control problem and states the Pontryagin minimum principle to solve it.

4. Chapter 4 is entitled "Numerical Computation and Discussion of Results". This chapter describes the computational algorithm and discuss the simulation result in detail.

5. Chapter 5 is entitled "Conclusion". The study has been concluded and the future plans are drawn here.

Chapter 2

Literature Review

2.1 Related Works

The dynamics between the cancer cells and the different components of the immune system are continuously changing and vary complex. Hence, understanding these dynamics to derive a cancer-immune model has been proved to be a very challenging task [6]. In recent decades considerable progress has been made in this area.

Authors in [19] and [16] propose a detail mathematical model to investigate the dynamics between tumor cells, immune-effector cells (T-cell), and the cytokines (interleukin-2 or IL-2). IL-2 is a protein that occurs naturally in the body. IL-2 does not kill tumor cells directly. Instead, IL-2 works by stimulating T-cells of the immune system to fight cancer [40]. The model includes the growth rate and the decay rate of tumor and immune system cells as well as the chemical reaction rate [44] among them. They consider the reaction rate formula of enzyme and substrate that consists of the concentration of substrates, maximum rate achieved by the system in saturation of the substrate, and the reaction constant. Later on, authors in [13] adopt the same model and formulate an optimal control problem to determine under what circumstances the tumor can be eliminated. The external source of effector cells are considered as control variables. They introduce an objective functional to maximize the effector cells and interleukin-2 concentration and to minimize the tumor cells. They simulate the system numerically (using gradient method) by varying three factors: antigenicity (ability to prevent the immune response) of tumor cells, the strength of the dosage of the given drug and the weight associated with the drug component. The time frame is selected as 350 days. The results state that the optimal control is bang-bang in nature which means it switches between the lower and the upper admissible boundary along the whole treatment period. While the tumor population level goes higher, the control is to admit the highest dose and while it is low, the control is zero (no medication).

Based on the above mentioned model, authors in [14], [15] develop a new population dynamic model to represent the competition among immune system cells and the tumor cells where the control is defined by the schedule of injections of Dendritic cells vaccines (DCV). Dendritic cells vaccine is a very effective cancer vaccine that breaks down cancer cells into smaller pieces so that the immune cells (T-cell) can see them and start an immune reaction against them [47]. They present a five dimensional system including two types of T-cells population, cancer cell population, matured dendritic cell population along with the vaccine (DCV) and interleukin (IL-2) population rate. This model includes also the similar terms as in previous model [13] i.e. the growth rate, decay rate and chemical reaction rate. They formulate their cost functional as a measure of final value of tumor mass at the end of 6 months of treatment period. They simulate the system with steepest decent method. The result of this paper shows that at the beginning of the treatment period the first vaccine is to apply the highest admissible dose to reduce the tumor promptly. The rest of the vaccines are smaller than the first one.

Another research group in [6] has proposed a spatiotemporal model to represent the proliferation of the B-cells and plasma cells, formulation of antibodies from them and their interactions with the antigens. B cells differentiate into short-lived plasma cells that produce antibodies [21]. All of them are heterogeneously distributed in the human physiological system. Taking into account the diffusivity of B-cells, plasma cells, antibodies and antigens, they propose a system of partial differential equations. The system equations include their proliferation rate, natural death rates, rate of differentiate into plasma cells, antibodies and antigens and a diffusion term to denote the spread of these molecules across the body. They solve the system numerically with respect to time and space which shows that for some particular choice of parameters, the model is able to represent the clinical conditions that has been observed in colon cancer, breast cancer and in several types of lymphomas. They keep the formulation of optimal control problem or optimization approach as a future work.

Authors in [28], propose a mathematical model to describe the dynamics of tumour-immune interactions in the presence of chemotherapy. They also adopt a predator prey formulation between the immune cells and tumour cells. They formulate an optimal control problem where the control variables include the population of effector cells, tumor cells and the doses of chemotherapy drugs. Therefore, the control problem is to determine the optimal drug dose that will maximize the amount of effector cells and minimize the number of tumour cells to keep the patient healthy. They simulate the system for 30 days treatment period and found that the optimal treatment strategy reduces the load of tumour cells within 10 days and increases the effector cells after 5 days of starting therapy.

2.2 Comparison of Proposed Approach with Related Works

As mentioned earlier in first chapter, that immunotherapy encompasses five different approaches. The model proposed in [13] is based on the treatment approach of **immune system modulators - cytokines**. On the other hand, Authors in [15] modified their model according to the **cancer vaccine (DCV) treatment**. Only the third research group [6] has proposed a model to investigate antigen-antibody dynamics. But they do not consider any optimal control or optimization approach in their model. The model we propose here represents both of the treatment approach of **Monoclonal Antibodies** and **Checkpoint Modulator**. It is also more general and simple to be adapted in other approaches by adding the state equations of other parts of immune system.

On the other hand, the models discussed in the previous section are based on the biochemical enzyme reaction among the Tumor cells, T-Cells, B-Cells and other cells of the immune system. Typically, the biological systems include a large number of uncertain parameters to describe the underlying biochemical reaction. When such models are first developed, these parameters are often sourced from the available literature. But in practise, it requires as much high quality data as possible. Measuring protein concentrations inside the living cells, tissues and organisms is quite challenging as the measurements can be noisy or sometimes the continuous movement of the living cells may lead to sparse data collection [17]. This indicates a clear need to represent some or all of the interaction parameters in a precise and collective way to ensure that the model can fit into the available experimental data. Therefore, an ideal biological model should be detail enough to convey the information of the biological phenomena adequately while at the same time should be simple enough that enables it to predict the system behavior under the practical settings [37].

In this study, we present such simple phenomenological model to represent the antigens and antibodies' dynamics [23] whereby one simply attempts to describe the interaction dynamics according to the observed relationship without any attempt to explain why the variables interact the way they do. Our model only includes the growth rate and the interaction coefficient parameters. From the successful case histories, it is possible to determine the intrinsic growth rates and the admitted drug doses through which a system identification process can be carried out to obtain the optimal interaction parameters for the established classes of antibodies and antigens. Once this is done, the identified model can be used for future case studies.

Another major feature is, unlike the previous models, it allows both antigen specific and antigen non-specific antibody interactions. This feature provides a way to investigate the case when a specific class of antibodies interact with different classes of antigens, proteins or serum and causes negative side effects or collateral damage. Lastly, it offers multiple controls i.e. multiple drugs administration for targeting different classes of antigens. Thus, the proposed dynamic system of equations are not only a simple and new approach in modelling of cancer immunotherapy but also effective enough to investigate different scenarios (e.g. interaction with different proteins, combination of immunotherapies, side effects of drug applications etc.).

Chapter 3

Mathematical Model and Problem Formulation

3.1 Modelling of Antigen-Antibody Interaction

The interaction between antibodies and antigens can be mathematically modeled by use of the well known population dynamics which has become a vital tool in the field of demography, ecology, micro-biology, medicine (immunology) etc [1]. Italian biologist Alfred Lotka and mathematician Vito Volterra first introduced the basic model in the early 20th century [33]. It was developed to analyze the dynamics of two competing species, prey-predator systems. The antigen-antibody interaction is also of similar type of phenomena. It is known that for each antigen there is a specific antibody that can bind onto it and chemically interact to destroy it. So there may be many different antibodies as there are antigens.

Let, B stand for antibody and G for antigen and denote their population densities by $\{B_i, G_i, i = 1, 2, ..., \kappa\}$. It may be assumed that there are κ different antigens and correspondingly κ different antibodies. The population dynamics is given by the following system of equations:

$$\dot{B}_i = \left(\alpha_i + \sum_{j=1}^{\kappa} \beta_{ij} G_j + \sum_{k=1}^{m} \gamma_{ik} u_k\right) B_i; \quad B_i(0) = B_{0_i}, \quad i = 1, 2, \cdots \kappa. \tag{3.1}$$

$$\dot{G}_i = \left(\delta_i + \sum_{j=1}^{\kappa} \eta_{ij} B_j\right) G_i; \quad G_i(0) = G_{0_i}, \quad i = 1, 2, \cdots \kappa, \tag{3.2}$$

Where,

1. α_i denotes the production rate of antibodies by the natural immune system.
2. $\{\beta_{ij},\ j = 1, 2, ..., \kappa\}$ are the interaction coefficients of the j-th antigen with the i-th antibody, i.e. the impact of antigen G_j on the antibody B_i.
3. δ_i denotes the intrinsic growth rate of antigens (for example cancer cells).
4. $\{\eta_{ij},\ j = 1, 2, ..., \kappa\}$ represent similar conjoint interaction of the population of j th antibodies with the i th antigen i.e. the impact of the j-th antibody B_j on the i-th antigen G_i.
5. $\{u_k, k = 1, 2, ..., m\}$ are the controls(drugs) to boost immune system,
6. γ_{ik} is the effect of k-th drug (or control) on the i-th antibody. If positive, it will enhance the immune system response, if zero no effect(neutral), if negative it is harmful to the antibodies formulation.

If $\gamma_{ik} = 0$, the k-th drug has no contribution towards the production of antibody B_i. In the language of non-specialists, these are drugs (and foods) capable of promoting the production of antibodies thereby reinforcing the immune system.

Instead of the linear growth $\alpha_i B_i$ of antibody population, a logistic growth rate such as $\alpha_i\left(1 - \frac{B_i}{K_i}\right)B_i$ can be considered. Here, the parameter K_i denotes the carrying capacity of antibody B_i. In nature, the populations may grow exponentially for some period, but they will ultimately be limited by the resource availability. Moreover, researches for antibody growths and formulation suggest [5] (page 1), [22] (page 795) that the antibodies are proteins, and proteins are encoded by genes. The diversity of antibodies proves a fact that an animal is not able to produce more antibodies than there are genes available in its genome. The mammalian (human) immune system has a fixed genetic mechanism that enables it to support a maximum level of antibodies. Therefore, the growth of antibody population should not exceed this limit to maintain the sustainability of the immune system. This limit is termed as carrying capacity [7] (page 2) which can be determined by the oncologists during the identification and design phase of antibody therapeutics.

It is important to mention the clinical significance of the interaction coefficients $\{\beta_{ij},\ \eta_{ij}\}$. In general there are three possibilities:

1. $\beta_{ij} > 0$, the presence of specie G_j (antigens) promotes the growth of specie B_i (antibodies). Here in the case of antigen-antibody population this does not occur.

2. $\beta_{ij} < 0$, the existence of specie G_j inhibits the growth of the specie B_i. This is the situation here; antibodies are spent in combatting the antigens.

3. $\beta_{ij} = 0$, the species B_i, G_j are neutral (no interaction). In other words these two classes of antibodies and antigens do not bind to each other.

The family of interaction coefficients $\{\eta_{ij}\}$ have similar interpretation. In the case of immune system dynamics, again η_{ij} are either negative (active) or zero (neutral). It is known that there are many different antigens and correspondingly many different antibodies. The antibodies are antigen specific in the sense that each type of antigen requires a specific type of antibody for interaction. The values of these interaction coefficients are generally negative. Some of them may be zero (ineffective) and some others are large negative (highly effective) and some are small negative or even small positive (mildly effective/harmful). The diagonal elements $\{\beta_{ii}, \eta_{ii}, i = 1, 2, ...\kappa\}$ are generally predominant, representing the antigen-specific-antibody interaction while the off diagonal elements can represent side effects. In order to understand the effect of the off-diagonal terms, let us consider only the specific terms $\beta_{ij}G_jB_i$ and $\eta_{ji}B_iG_j$. If $\eta_{ji} < \beta_{ij} \leq 0$, it is clear that more antigens are killed by fewer antibodies while the reverse situation holds in case $0 \geq \eta_{ji} > \beta_{ij}$ where more antibodies are spent to kill fewer antigens. Thus, the model presented here is adequately general to allow both antigen-specific-antibody interaction as well as nonspecific interactions which may include collateral damage or side effects.

Typically, the biological systems consist of uncertain parameters to describe the underlying biochemical reaction. Particularly for this antigen-antibody interaction, it is quite challenging to measure the protein growth rates, concentrations and their reaction rates specially inside the living cells, tissues and organisms and the measurements can be noisy or sometimes the continuous movement of the living cells may lead to sparse data collection [17] (page 2). Taking into account this, the proposed model can be further extended to a nonlinear uncertain system as developed by Ahmed et al. in [3] (page 150-151) that allows to observe the dynamics of the system in a noisy environment.

3.2 Formulation of Objective Functional

T1‘r4 qAhe objective of the physician is to prescribe optimal doses of drugs to promote the natural growth of antibody and inhibit the growth of antigen population i.e. bring it down to a harmless or clinically acceptable level in a given period of time, say $I \equiv [0, T]$.

Hence, the objective functional can be chosen as follows:

$$J(u) = \sum_{i=1}^{\kappa} \int_0^T \upsilon_i [G_i(t) - {G_i}^d(t)]^2 dt + \sum_{i=1}^{\kappa} \int_0^T q_i {u_i}^2 dt + \sum_{i=1}^{\kappa} \omega_i [G_i(T) - G_{d_i}]^2 \tag{3.3}$$

This functional $J(\cdot)$ is given by the sum of three terms. The weights assigned to each of the specific terms are represented by the parameters $\{\upsilon_i, q_i, \omega_i\}$. The first term is said to be the integral or running cost. It represents the discrepancy between the actual antigen population and the level of desired population at any time t during the treatment plan. The functions $\{{G_i}^d(t),\ i = 1, 2, \cdots, \kappa\}$ appearing in the integral cost denotes the desired levels of population at time t. This level can be determined only by the doctors or oncologists. The parameters, υ_i, represents the relative importance of the difference between the desired and actual antigen population level at any time t.

The second term represents the cost associated with control efforts which is associated with treatment cost for each of the control drugs $\{u_i,\ i = 1, 2, \cdots, \kappa\}$. The weights, q_i represents the relative cost of control drugs u_i.

Lastly the third term is known to be the terminal cost, denotes the mismatch between the targeted population at the end of the treatment period and the actual population level reached. Here, $\{G_i(T),\ i = 1, 2, \cdots, \kappa\}$ denotes the population of antigens at the end of the treatment period and $\{G_{d_i},\ i = 1, 2, \cdots, \kappa\}$ is desired target of population level of antigen at the end of the treatment period. This may be taken as zero as the target is to eliminate the antigens completely. The parameters ω_i represents the relative importance given to the difference between the desired population level and the level which is originally obtained in the end of the treatment period.

In this study, the desired levels of population $\{{G_i}^d(t)$ at time t are not available to investigate. Moreover, the treatment of cancer is quite expensive and the patients prefer to be cure at any cost. Following this, the running cost for this problem has not been considered here. Then the objective is to bring down the antigens population into a desired level in the end of treatment scheme. The objective functional can now be written as:

$$J(u) = \Phi(G(T)) \equiv \{\sum_{i=1}^{\kappa} \omega_i [G_i(T) - G_{d_i}]^2\} \tag{3.4}$$

3.3 Optimal Control of Antigen-Antibody Interaction

After defining the objective functional J in 3.4, the problem is to determine an optimal control $u^o \in \mathcal{U}_{ad}$ that minimizes this functional, subject to the dynamic constraint (3.1)-(3.2). Now, we introduce a version of Pontryagin minimum principle (PMP) [1] to solve this optimal control problem.

Consider the 2κ-dimensional system given by the following system of differential equations,

$$\dot{x_i} = \left(\alpha_i + \sum_{j=1}^{\kappa} \beta_{ij} x_j + \sum_{k=1}^{m} \gamma_{ik} u_k\right) x_i; \text{ for } i = 1,\, 2\, ,\, ,\, ,\, \kappa \tag{3.5}$$

$$\dot{x_i} = \left(\delta_i + \sum_{j=1}^{\kappa} \eta_{ij} x_j\right) x_i; \text{ for } i = \kappa + 1,\, \kappa + 2, ..., 2\kappa. \tag{3.6}$$

Where $\{x_i(t) \equiv \{B_i(t), G_i(t), i = 1, 2 \cdots \kappa, t \geq 0\}\}$ denotes the state of the system at time t, and $\{u(t) \equiv \{u_k(t), k = 1, 2, \cdots, m\}\}$ represents the control. Let U be any closed bounded subset of R_+^m represents the control constraint set which means the controls are allowed to take values only from the set U. We represent the class of admissible control set by $\mathcal{U}_{ad}$. Therefore, the target is to obtain an optimal control policy $u^o(t)$, $t \in I$ from the class of admissible set $\mathcal{U}_{ad}$ that minimizes the functional J as given by the expression (3.4) subject to the dynamic constraint (3.5)-(3.6) i.e. $\{J(u^o) \leq J(u);\ \forall\ u \in \mathcal{U}_{ad}\}$. Let's introduce the Pontryagin Hamiltonian function H by the following expression,

$$H(t, x_i, \psi_i, u) = \sum_{i=1}^{\kappa} f_i(x, u)\psi_i + \sum_{i=\kappa+1}^{2\kappa} f_i(x, u)\psi_i = \sum_{i=1}^{2\kappa} f_i(x, u)\psi_i. \tag{3.7}$$

Next, on the basis of the Pontryagin Minimum Principle (PMP) as stated in **Theorem 1.1**, the necessary conditions of optimality for this problem are mentioned as below:

(a) $H(x^o(t), u^o(t), \psi^o(t)) \leqslant H(x^o(t), u(t), \psi^o(t))$; for $\forall u \in \mathcal{U}_{ad}$, a.e. on $I = [0, T]$,

(b) $\frac{dx_i}{dt} = H_{\psi_i} = f_i(x^o(t), u^o(t))$, a.e. on $I = [0, T]$; for $i = 1, 2, ..., 2\kappa$,

(c) $\frac{d\psi_i}{dt} = -H_{x_i} = -\sum_{i=1}^{2\kappa} \frac{\partial f_i(x^o(t), u^o(t))}{\partial x_i} \psi_i$, a.e. on $I = [0, T]$; for $i = 1, 2, ..., 2\kappa$,

$\psi_i(T) = \Phi_{x_i} = 0$; for $i = 1, 2, ..., \kappa$

$\psi_i(T) = \Phi_{x_i} = 2\omega_i[x_i(T) - x_{di}]$; for $i = \kappa + 1, \kappa + 2, ..., 2\kappa$.

Chapter 4

Numerical Computation and Discussion of Results

4.1 Computational Algorithm

In this section, we introduce an algorithm for numerical simulation of the optimal control problem based on the minimum principle. The computation is based on the basic gradient descent method as presented in Algorithm 1 and implemented on MATLAB [34], [24], [38], [18]. The model consists of two systems of differential equations, the first one is the state equations (x) including the controls (u) and the other one is the adjoint equations (ψ). An initial guess is chosen for the ($x(0)$) and for the control ($u(0)$). From here the state equations are solved via fourth-order Runge-Kutta integrator. The adjoint equations take the updated state variables to obtain the new solutions for the adjoint variables as they are coupled with state equations.

Then the gradient vector (g_n) is computed to obtain the new control for next iteration. Here, the main task in steepest descent method is to determine the descent direction (search direction) and choose a step size (ε) at each iteration that successive iterations produce maximum reduction of the cost functional. It is also necessary to check the feasibility of the new controls at each iteration. To ensure a monotonically decreasing sequence of cost functional, each trial control is required to provide a smaller cost functional than the preceding one [18]. Thus, the target is to move in the steepest descent direction until there is no further decrease in cost functional ($J(u)$). Generally, the step size is determined by some ad hoc strategy. Authors in [18] showed one possible way by using a single variable

Algorithm 1 Computational Algorithm

Initialization:

Choose an array of initial states (x_0) and control (u_0)

Set system parameter $\alpha, \beta, \gamma, \delta, \eta, \omega$

Set $T \in \mathbb{R}^+$ and $N \in \mathbb{R}^+$

Set stopping criteria (τ), maximum iteration (n_{max});

Output:

Optimal control u^o

Optimal cost $J(u^o)$.

1: Subdivide the interval $[t_0, t_f] \equiv [0, T]$ into N equal subintervals and assume the control is piecewise-constant control $u^{(n)}(t) = u^{(n)}(t_i),\ t \in [t_i, t_{i+1}],\ i = 0, 1, 2, .., N-1$, where the iteration index $n = 0$.

2: Integrate the state equations from 0 to T with initial guesses $x(t_0) = (x_0)$ and $u(t_0) = (u_0)$.

3: Store the resulting state trajectory ($x^{(n)}$) and control variables ($u^{(n)}$).

4: Use $u^{(n)}$ and $x^{(n)}$ to integrate the costate equations backward in time starting from the costate $\psi^{(n)}(T)$ at the terminal time T. The terminal costate is given by $\psi^{(n)}(T) = \phi_x(x^{(n)}(T))$ where $\phi(\cdot)$ defines the terminal cost.

5: Using the triple $\{u^{(n)},\ x^{(n)},\ \psi^{(n)}\}$ compute the gradient $g_n(t) = H_u(t, x^{(n)}(t), \psi^{(n)}(t), u^{(n)}(t)) = \sum_{i=1}^{\kappa} \gamma_{ik} x_i \psi_i$ and store this vector.

6: Compute the cost function $J(u^{(n)})$ using Eq. 3.4 and store.

7: **if** $\|g_n\| = 0$ **or** $\|g_n\| < \tau$ **or** $|J(u^{(n)}) - J(u^{(n-1)})| < \tau$ **then**

$u^o \leftarrow u^{(n)}$

$J(u^o) \leftarrow J(u^{(n)})$

return

Otherwise

Continue

8: Determine the step size ε^n sufficiently small such that $J(u^{(n)}) \leq J(u^{(n-1)})$.

9: Construct the control for the next iteration $u^{(n+1)} = u^{(n)} - \varepsilon^n g_n(t),\ t \in I$ such that $u^{(n+1)} \in \mathcal{U}_{ad}$.

10: **if** $n < n_{max}$ **then**

Set $n = n + 1$ and **goto** *Step 2*.

Otherwise

Issue message “ALGORITHM didn’t converge within n_{max} iteration”.

search for selecting the step size (ε). For this algorithm, we adopt the same idea. First we choose an arbitrary starting value of step size (ε) for the first iteration and use it to compute the next control $u^{(n+1)}$. Then a search among values of $\varepsilon > 0$ is carried out until smaller value of the cost functional is obtained than that of the preceding iteration. This is accomplished by reducing the step size by a few percent of the initial choice at each iteration and comparing the current value of cost functional with the previous one. For a smooth iteration it requires to start with a very small initial choice (ε^1). Also the larger step size may results severe oscillations in the cost functionals [18]. On the contrary, a very small initial choice may not reduce the cost functional significantly and requires a lot of iterations to converge. Therefore, it is necessary to perform a number of trials and computations for selecting an initial choice of step size for each particular set of parameters. The iterative process continues until the difference in the current and previous values of the cost functional $|J(u^{(n)}) - J(u^{(n-1)})|$ or the norm of the gradient vector $\|g_n\|$ is within an acceptable tolerance τ. The value used for the termination tolerance (τ) also depends on the problem and the level of desired accuracy. It requires several trials to run the problem before τ is selected. Here, for quick convergence, we select the range of τ is ($1 \times 10^{-6} - 1 \times 10^{-8}$). However, if necessary, the algorithm can be run for a longer period for lower tolerance levels.

4.2 Parameter Selection

In order to use the proposed system model (3.1)-(3.2) for immunotherapy, it is essential to select appropriate values for the parameters. For this purpose, a system identification process (an inverse problem) can be carried out on the basis of laboratory data. Thus, it is possible to determine the optimal set of interaction parameters to get the best fit for the established classes of antibodies and antigens. Once this is done, the identified model can be used to study the temporal evolution of antigen-antibody interaction in cancer patients and determine the optimal treatment protocols.

In this model, the i-th class of antibodies interact with the i-th class of antigens (antigen specific antibody). The physicians want to ensure minimum side effects. However, in any large biochemical process it is not always possible to eliminate intra-species interaction and hence side effects. Our model includes all such interactions. If there are intra-species interactions, the effect can be positive, inhibitory or neutral.

Table 4.1: Range of Parameter Values

Antibody		Antigen	
Parameter	Range of Values	Parameter	Range of Values
α_i	$0.0001 \sim 0.2\ day^{-1}$	δ_i	$0.18 \sim 0.431\ day^{-1}$
β_{ij}	$-\ 1.5 \sim 0.0\ AG^{-1}day^{-1}$	η_{ij}	$-\ 2.0 \sim 0.0\ AB^{-1}day^{-1}$
γ_{ij}	$0.001 \sim 1.5$ dose		

In this work, for illustration only, we select the intrinsic growth rates proposed in the following references [14] (page 725) and [6] (page 138). We choose arbitrarily larger values for antigen specific antibody interaction coefficients (i.e. diagonal terms β_{ii}, η_{ii}) and the strength of doses (control) γ_{ii}). Similarly, we keep smaller values for the non-specific interactions i.e. the off-diagonal terms (β_{ij}, η_{ij}), and side effects of other drugs (γ_{ik}). The diagonal elements (β_{ii}, η_{ii} and γ_{ii}) are generally predominant and the choices of larger values make them highly effective in the growth of $i-$th antibody population whereas the choices of lower values of off-diagonal elements β_{ij}, η_{ij} and γ_{ik} make them lower effective or neutral (when it is zero).

4.3 Numerical Results

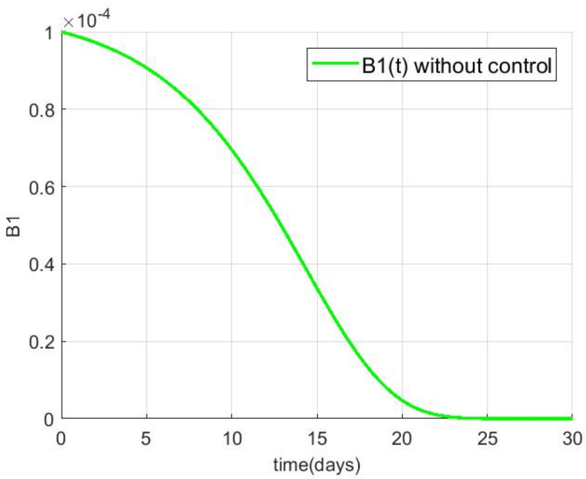
In this section, we conduct numerical simulation of the model using the algorithm introduced in the preceding section to demonstrate the effects of various parameters. In the following, six sets of results are presented for three different treatment periods. For simplicity and better computational performance, we have not taken into account large medication period. In example 1, we observe one class of antigen-antibody (B_1, G_1) interaction. In example 2 and 3 we analyze the same case study including logistic growth rate of antibodies with different carrying capacity. Next, example 4 and 5 represent two classes of antigen-antibody interactions (B_1, G_1) and (B_2, G_2). Example 4 demonstrates only the effect of antigen-specific-antibody interaction (i.e. diagonal parameters only β_{ii}, η_{ii}) correspond to the two different choice of interaction coefficients. Similarly, the example 5 illustrates the same case study with the additional non-specific interaction between the i-th class of antibody B_i and the j-th class of antigen G_j (i.e. off-diagonal parameters β_{ij} & η_{ji}). Finally, in example 6, we select three classes of antigen-antibody pair (B_1, G_1), (B_2, G_2), and (B_3, G_3) to determine the effect of j-th class of control drugs on i-th class of antigen-antibody interaction. We also examine the effect of stronger dose of drugs on the growth of the i-th class of pair by selecting a larger value of γ_{ii} than the other classes.

4.3.1 One Class of Antigen and Antibody Interaction

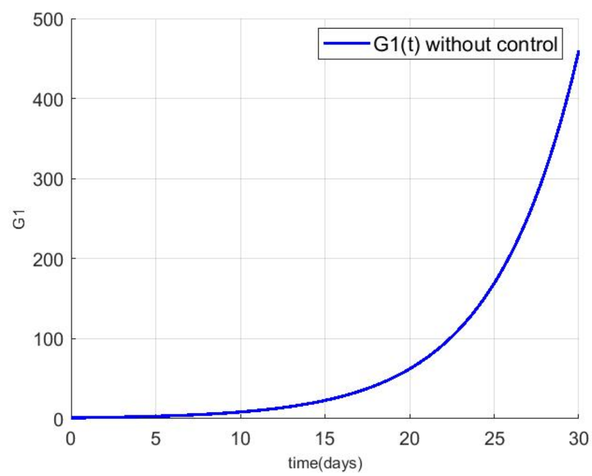
Table 4.2: Parameter Values of Example 1

Antibody		Antigen	
$B_1(0)$	0.0001	$G_1(0)$	1.14
α_1	0.2	δ_1	0.431
β_{11}	$-$ 0.01	η_{11}	$-$ 0.07
γ_{11}	1.00	ω_1	1000

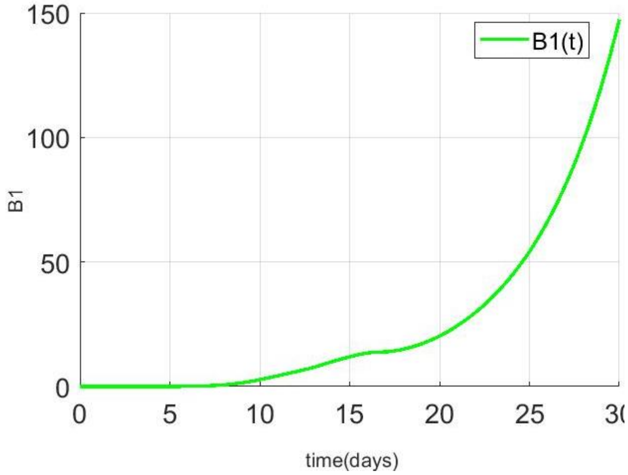
Example 1: As mentioned earlier that each class of antibody is designed to target one specific class of antigen. First we consider such interaction between one particular class of antigen and antibody (B_1, G_1). The non-specific interaction with other classes is not taken into account here. In this example, we assume a specified period of time for treatment such as $[0, T]$ where $T = 30$ days. The time period is partitioned into 10 segments. Naturally, the phenomena describes that antibodies are produced when there are already existing antigens. Therefore, the initial value of the antigen population level is chosen as 1.14 and that of antibody as 0.0001. This indicates that the patient has severe immune deficiency. If the maximum admissible dose is 1000 units, it is scaled down to 1. Following this, we select the control constraint set as $U = \{u : 0 \leq u \leq 1\}$. The initial guess of control $u(t), t \in I$, is chosen identically zero. The parameter values for this case have been enlisted in Table 4.2. Then we run the optimization algorithm. The result for this scenario is shown in Figure 4.1.



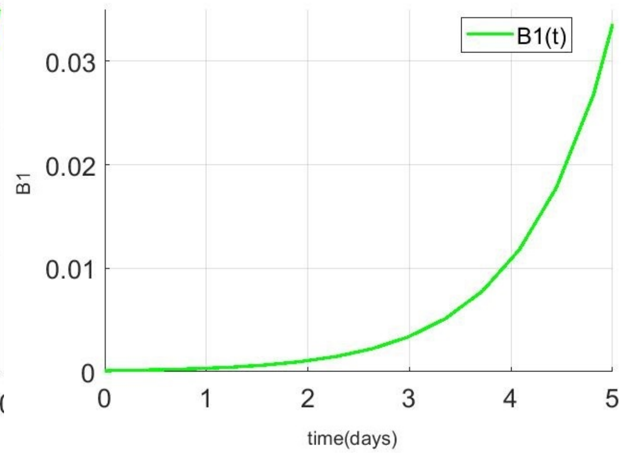
(a) B_1 without control.



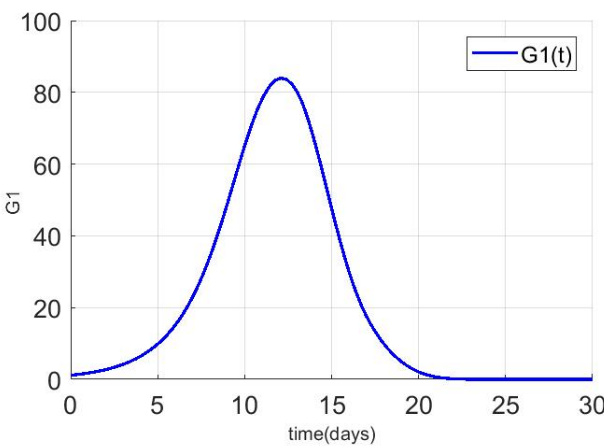
(b) G_1 without control.



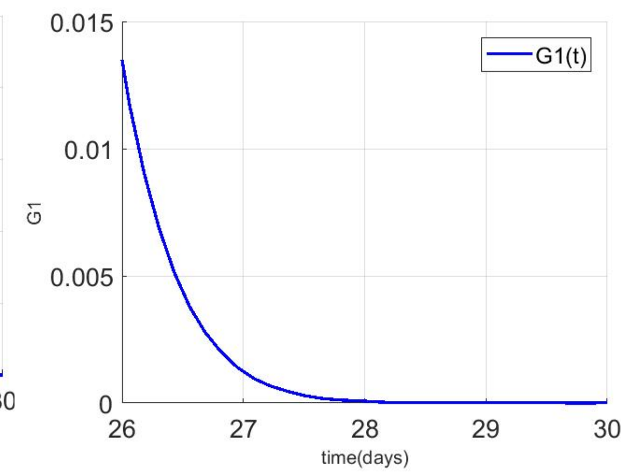
(c) State trajectory of B_1



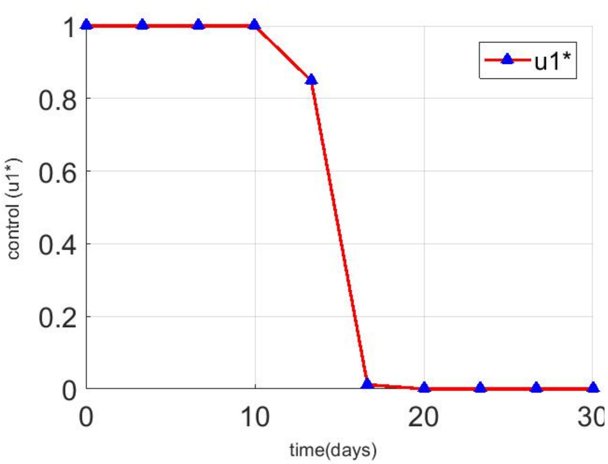
(d) B_1 from 0 to 5 days.



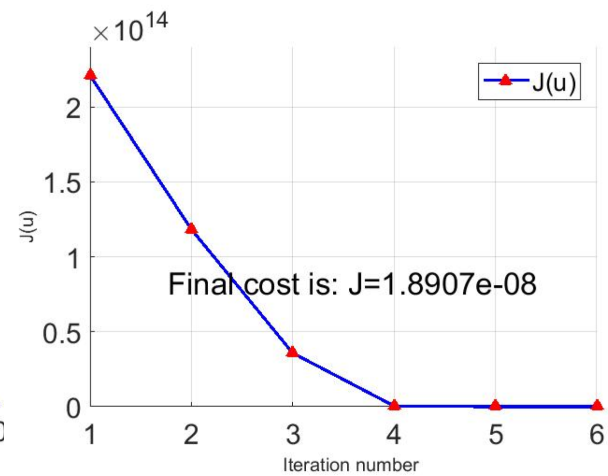
(e) State trajectory of G_1.



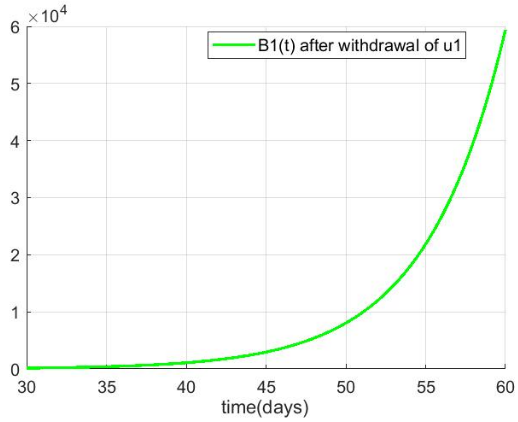
(f) G_1 from 26 to 30 days.



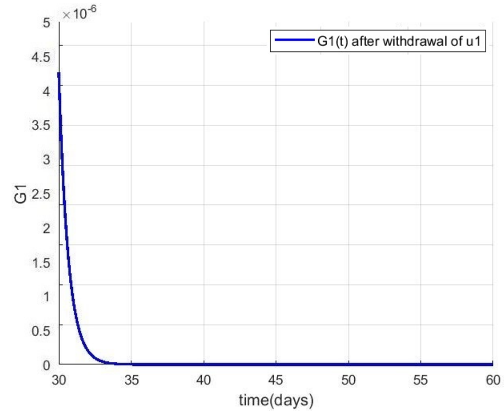
(g) Optimal control u^0



(h) Cost function $J(u^0)$.



(i) B_1 beyond 30 days



(j) G_1 beyond 30 days

Figure 4.1: Example 1 (one class of antigen-antibody interaction).

Parameters: [$B_{1_0} = 0.0001$ and $G_{1_0} = 1.14$, $\alpha_1 = 0.2$, $\delta_1 = 0.431$, $\beta_{11} = -0.01$, $\eta_{11} = -.07$;, $\gamma_{11} = 1.0$, $\omega_1 = 1000$.]

In Figure 4.1a and 4.1b, the states trajectories are shown without the control (drugs) input. We notice that, the population of antibody (B_1) declines nearly to zero whereas the population of antigen (G_1) grows massively during the entire period. Thus, it is clear that, without drug administration (control), the growth of antibodies is not sufficiently strong to fight the growing antigens. It also proves the immune deficiency of the patient.

Next, in Figure 4.1c and 4.1e, the states trajectories are shown corresponding to the optimal control (u_1) input (Figure 4.1g). Figure 4.1c illustrates that during the initial 15 days of treatment period, the population of antibody (B_1) is very low. It appears to be zero over the initial 5 days. For clear illustration, the gradual growth of antibodies during this stage is shown in an expanded segments in Figure 4.1d.

In contrast, Figure 4.1e depicts that the antigen (G_1) population grows continuously upto the 12th day of treatment period arriving at a peak 83.9 and then declines to a satisfactory level of 0.74 by the day of 20th. At the end of treatment period the population successfully ends up on 4.34×10^{-6}. Another expanded segment of antigen population for last four days (26th-30th) is shown in Figure 4.1f which illustrates the decline of antigen population clearly. Since, there is a competitive interaction, it is evident that during the initial stage of treatment period, the antibodies are spent out in fighting antigens. Once the population level of antigens goes down, apparently the antibody population starts to grow faster.

The corresponding optimal treatment policy as observed in Figure 4.1g, is to apply the largest admissible dose up to 10 days and then reduce the strength as the antigen population keeps declining. The objective functional converges after 6 iterations and reaches to the level of 1.89×10^{-8} as shown in Figure 4.1h.

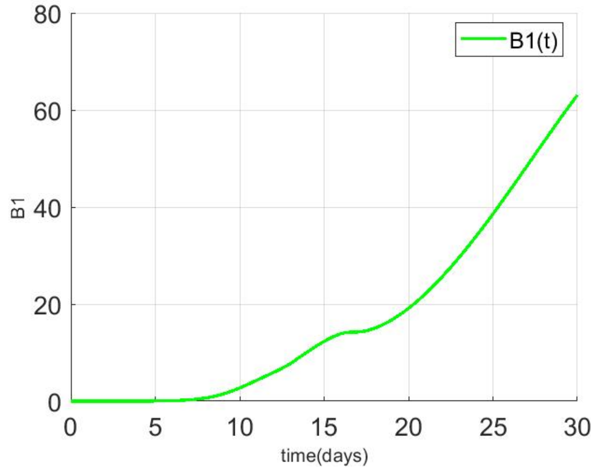
The system is run beyond 30 days to observe the after-effects (after the withdrawal of medications) on antigen-antibody population in Figure 4.1i and 4.1j. It is seen that in the next 30 days the population of antigen has not grown further and it declines to 2.2×10^{-27}. On the other hand, due to the presence of exponential growth rate, the population of antibody keeps growing. As discussed in Chapter 3 that the population of antibody should be kept within a clinically specified level by using the logistic growth rate term. In the following examples, the proposed model is simulated including the logistic growth rate term with two different capacities to demonstrate the system behavior.

4.3.2 One Class of Antigen-Antibody Interaction Including Logistic Growth Rate

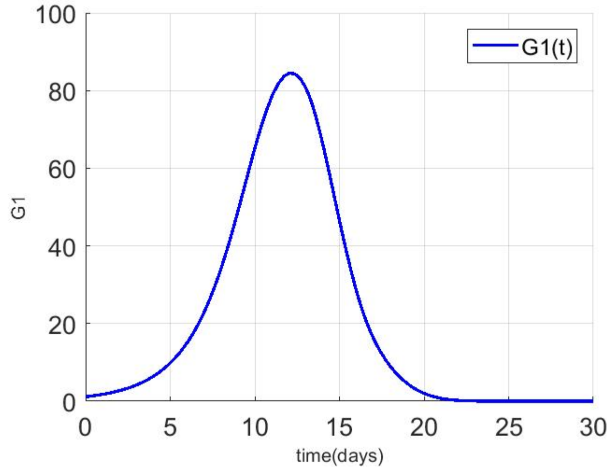
Example 2: In this example, the case of previous study has been simulated including the logistic growth rate term. First of all, the carrying capacity for antibody B_1 is selected as $K_1 = 100$. Since all the parameters (Table 4.3) are kept same as previous example and we limit the growth of antibody population by adding the logistic term, it is clear that without the control drugs the presence of the antibodies should not be strong enough to prevent the growth of antigens as before. For limited space these plots are not repeated again. The result for this scenario is shown in Figure 4.2.

Table 4.3: Parameter Values of Example 2 & 3

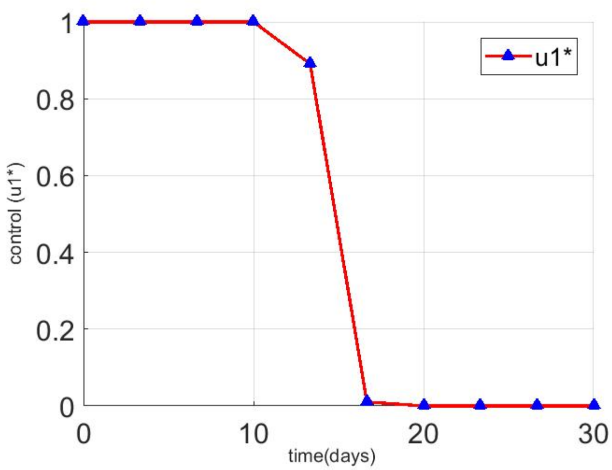
Parameter		Values	
$B_1(0)$	0.0001	$G_1(0)$	1.14
α_1	0.2	δ_1	0.431
K_1		100 / 10	
β_{11}	$-$ 0.01	η_{11}	$-$ 0.07
γ_{11}	1.00	ω_1	1000



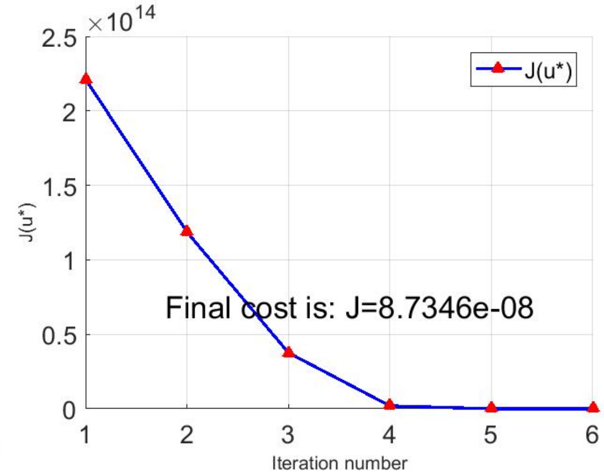
(a) State trajectory of B_1



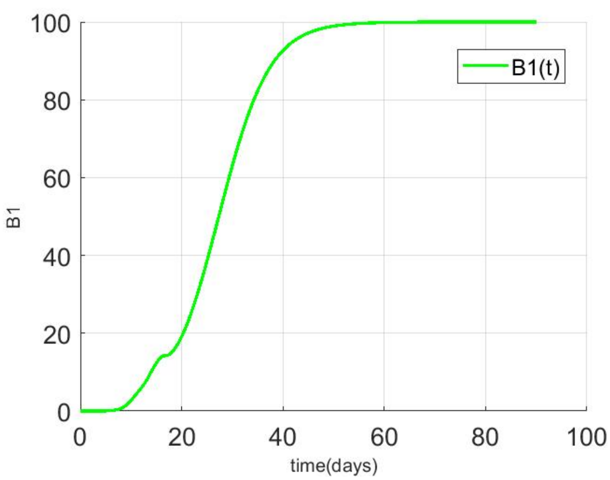
(b) State trajectory of G_1.



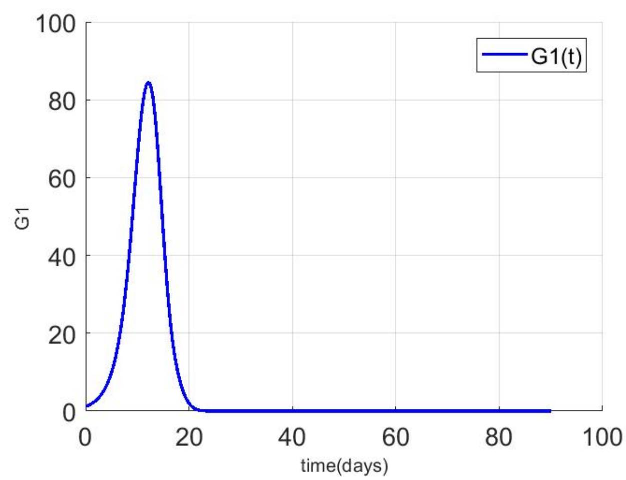
(c) Optimal control u^0



(d) Cost function $J(u^0)$.



(e) B_1 in treatment and post treatment period.



(f) G_1 in treatment and post treatment period

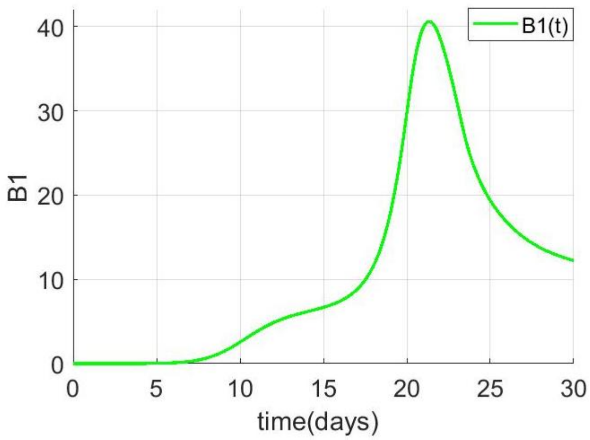
Figure 4.2: Example 2 (one class of antigen-antibody interaction with carrying capacity $K_1 = 100$).

Parameters: [$B_{1_0} = 0.0001$ and $G_{1_0} = 1.14$, $\alpha_1 = 0.2$, $K_1 = 100$, $\delta_1 = 0.431$, $\beta_{11} = -0.01$, $\eta_{11} = -.07$;, $\gamma_{11} = 1.0$, $\omega_1 = 1000$.]

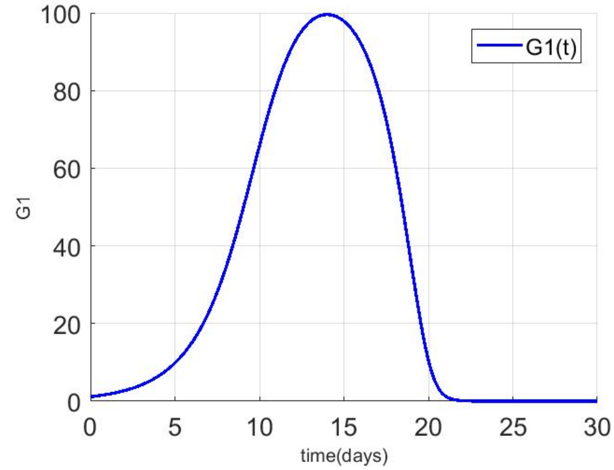
Figure 4.2a shows that, at the beginning of treatment period (upto 9 days), the population of antibody (B_1) shows a gradual rise. However, in the following 21 days it has not grown as faster as in the previous result (4.1a). This is due to the presence of logistic term $\alpha_1\left(1 - \frac{B_1}{K_1}\right)$. In logistic growth, the species's growth gets smaller and smaller as the population size approaches to it's carrying capacity. Moreover, the exponential growth produces a J-shaped curve, while the logistic growth produces a S-shaped curve. In order to demonstrate the logistic growth of antibodies (B_1), the system has been simulated for next 60 days after withdrawal of medication. The population curve throughout the treatment and post-treatment period is plotted together in Figure 4.2e which clearly indicates that the exponential growth happens for around 55 days, then the growth of antibodies slows down and once it reaches at the level of carrying capacity (100) it levels off on the day of 60th. Thus the logistic term produces a S-shaped curve and maintains the B_1 population within a specified level ($K_i = 100$).

On the other hand, Figure 4.2b illustrates that the population of antigens (G_1) follows the similar trajectory of the previous scenario (4.1b). From first day onward, it continues to grow rapidly till 13th arriving at a peak 80, then starts to decline ending up on 9.34×10^{-6}. In the post treatment period the G_1 population also remain at low level as shown in Figure 4.2f. Figure 4.2c states that the optimal control policies almost remain same which is to allow 4 highest admissible dose upto 10th day and then reduce it as per of the decline of antigen's population. The objective functional takes 6 iterations to reach to the level 8.73×10^{-8} as shown in Figure 4.2d.

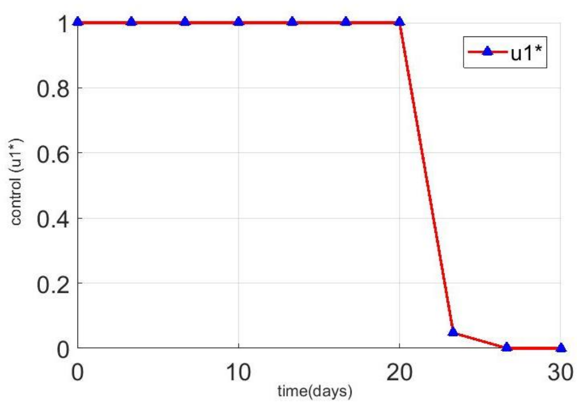
Example 3: Next, we decrease the carrying capacity to $K_1 = 10$ and evaluate the response of the system. The simulation results for this case are shown in Figure 4.3. In Figure 4.3a, the population of antibody (B_1) continues to grow upto 23rd day exceeding the level of carrying capacity. It happens because of the state equation of B_1 includes not only the growth rate but also the other additional terms (controls and interaction with antigens). By comparing with the previous scenarios, the size of the population of G_1 (Figure 4.3b) gets apparently bigger than it was in the previous cases (Figure 4.2b). It indicates that we limit the growth of antibody population by selecting a small carrying capacity which causes higher growth of antigens population. The state trajectory of G_1 starts from 1.14, rising to a peak around 100 on the day of 14th and then declines sharply to a satisfactory level of 0.93 on 23rd day. Figure 4.3c states that the corresponding control policy is to admit 7 largest admissible doses (full dose of medication) upto the same period and then reduce as the antigen population starts to decline.



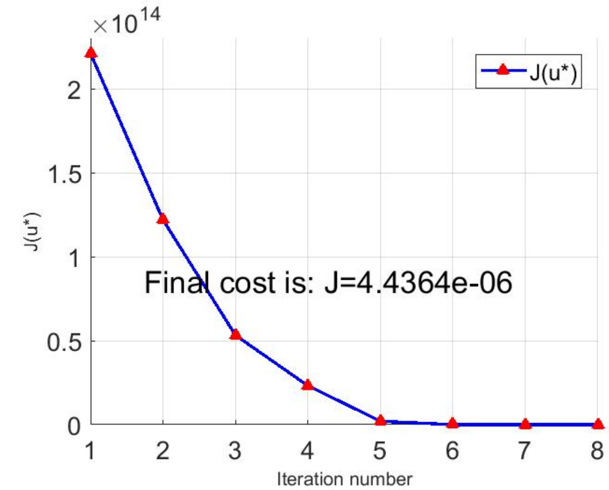
(a) State trajectory of B_1



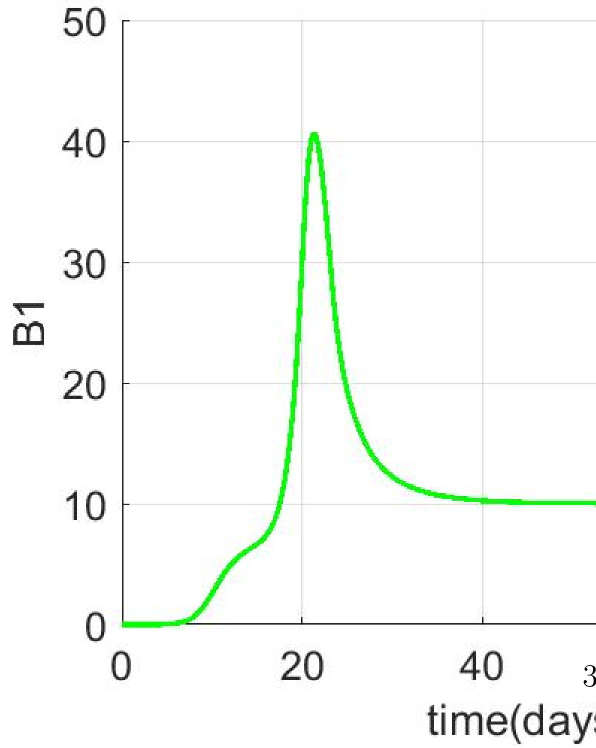
(b) State trajectory of G_1.



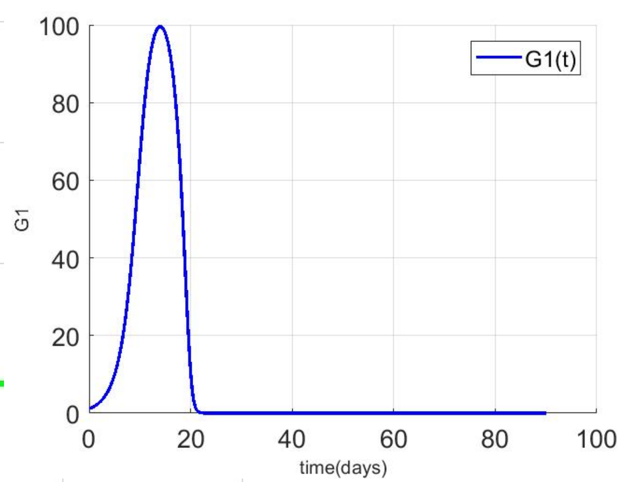
(c) Optimal control u^0



(d) Cost function $J(u^0)$.



(e) B_1 in treatment and post treatment period



(f) G_1 in treatment and post treatment period

Therefore, it is evident that due to the application of large amount of control dose (antibody therapeutics), the B_1 population grows continuously upto 23rd day, exceeding it's carrying capacity to fight the antigens. Once the antigen (G_1) population goes down after 23rd day, the antibody (B_1) population also stops growing further and starts to decline sharply.

In order to observe the growth of B_1 and G_1 population in the following days we run the system upto the day of 90th. Figures 4.2e and 4.2f yields the entire growth of B_1 and G_1 during the treatment (0th-30th) and post treatment period (30th-90th). It is noticed that the population of B_1 ends up on 10 (carrying capacity) on the day of 40th and continues to stay at this level for the rest of the period. In contrast, the population of antigen (G_1) remains small during these period. These two analyses indicate that the antibodies successfully attack the antigens with different level of carrying capacity. Higher control doses are required for the antibodies with lower carrying capacity to fight the antigens.

4.3.3 Two Classes of Antigen-Antibody Interactions Excluding Non-Specific Interaction

Example 4: Next, we consider two distinct classes of antigens-antibodies (B_1, G_1) (B_2, G_2) interaction and assume the treatment period to be $T = 25$ days. Here, two different types of control drugs (u_1 and u_2) are used to produce the growth of B_1 and B_2 to attack G_1

Table 4.4: Parameter Values of Example 4

Parameters		Values		Parameters		Values	
$B_1(0)$		0.014		$G_1(0)$		1.1	
$B_2(0)$		0.014		$G_2(0)$		1.1	
α_1		0.0001		δ_1		0.2	
α_2		0.0001		δ_2		0.2	
K_1		10		K_2		10	
β_{11}	-0.15	β_{12}	0	η_{11}	-0.2	η_{12}	0
β_{21}	0	β_{22}	-0.2	η_{21}	0	η_{22}	-0.15
γ_{11}	1.00	γ_{12}	0	ω_1		100	
γ_{21}	0	γ_{22}	1.00	ω_2		100	

and G_2 respectively. First, we determine the effect of antigen specific antibody interaction coefficients (i.e. diagonal interaction parameters β_{ii} and η_{ii}). As mentioned in chapter 3 that, for successive competitive interaction between particularly i-th class of antigen and i-th class of antibody, the interaction coefficients β_{ii} and η_{ii} both should be negative. The value of $\beta_{ii} < 0$ illustrates that the existence of antigen G_i inhibits the growth of the antibody B_i. In other words, antibodies are spent out in fighting (or chemically combining with) antigens. Similarly, the value of $\eta_{ii} < 0$ depicts same, the presence of B_i inhibits the growth of G_i. In this case, as both of the classes are distinct from each other, the interaction rate between B_1 and G_1 is also different from the rate between B_2 and G_2. We choose β_{11} greater than η_{11} for first class of antigen-antibody (B_1, G_1) interaction and η_{22} greater than β_{22} for the second class of (B_2, G_2) pair. To evaluate the effect of this coefficients, we keep all other parameters (growth rate, initial values and control coefficients) same. Here, we do not consider the non-specific interaction which means the interaction between i-th class of antibody (e.g. B_1) and j-th class of antigen (e.g. G_2) or vice versa. For this purpose, the off-diagonal interaction parameters β_{ij} and η_{ij} are also set to zero. The control constraint set is selected as in the previous case. The parameter values for this case are enlisted in Table 4.4. Results for this scenario are presented in Figure 4.4.

At first, the system responses are shown without the control drugs in Figure 4.4a, 4.4b, 4.4c and 4.4d which clearly indicate that the presence of antibodies is not strong enough to inhibit the growth of antigens.

Next, Figure 4.4e and 4.4g illustrate the state of B_1 and G_1 population growth corresponding to the optimal control input u_1 (Figure 4.4i) for the following diagonal interaction parameters:

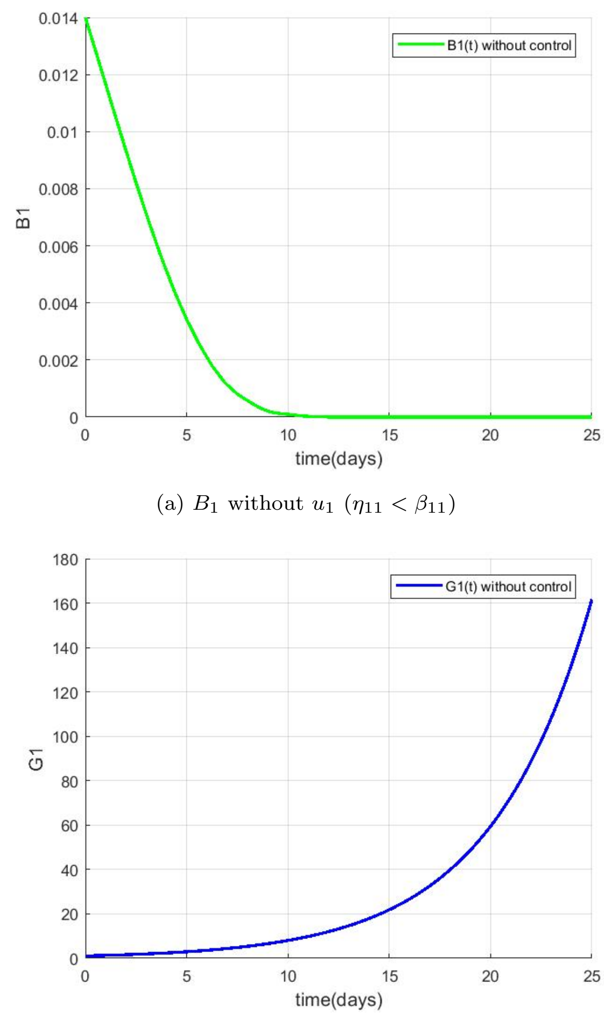
$$\eta_{11} = -0.2 < \beta_{11} = -0.15 < 0.$$

It is noticed that, the G_1 population has experienced a continuous growth upto 8th day of treatment period arriving at a peak of 2.69. After that it declines to a satisfactory level 0.001 by 12th day and finally ends up on 7.11×10^{-11}. To fight with low amount of antigens the corresponding control policy is to admit 3 largest admissible doses upto 6th day of medication period, then reduces to 0.82 on the day of 9th, 0.02 on 11th and finally ends to zero in the rest of the period. The antibody B_1 has also experienced a low growth due to the lower dose of drug administration. Once the antigens population declines, the B_1 is still growing steadily as shown in the after effects in Figure 4.4l. This is because, it is expected to reach and stay on it's level of carrying capacity $K_1 = 10$ in the following period. As we are not concerned here to observe the growth of antibody (B_1) population, we do not run the system for large period of time to observe it's further growth. On the other hand, Figure 4.4m shows that the population of antigen (G_1) has not grown anymore and continues to decline.

In converse, the Figure 4.4f and 4.4h depicts the system responses corresponding to the control drug u_2 (Figure 4.4j) for the following diagonal interaction parameters:

$$\beta_{22} = -0.2 < \eta_{22} = -0.15 < 0.$$

It is interesting to notice that the population of class of G_2 (Figure 4.4h) has become almost twice in size compare to G_1 (Figure 4.4g) and takes 17 days to decline to a satisfactory level of 0.001. The final G_2 population is 1.20×10^{-5}.

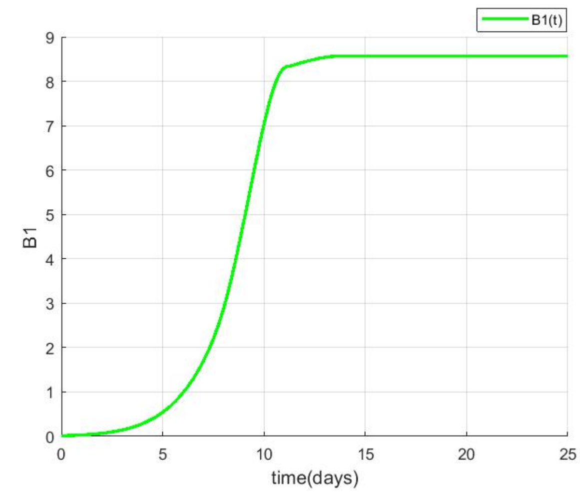


(a) B_1 without u_1 ($\eta_{11} < \beta_{11}$)

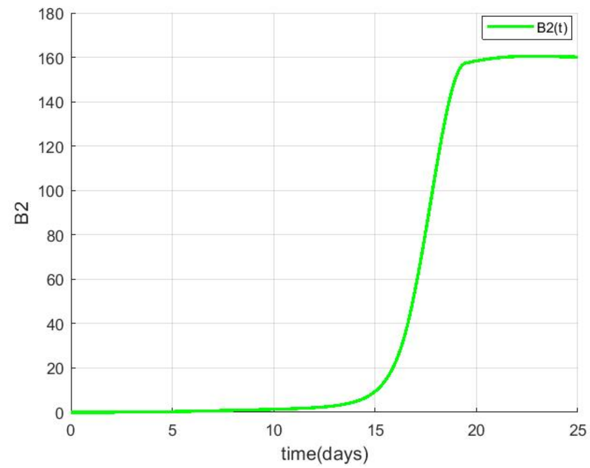
(b) B_2 without u_2 ($\beta_{22} < \eta_{22}$)

(c) G_1 without u_1 ($\eta_{11} < \beta_{11}$)

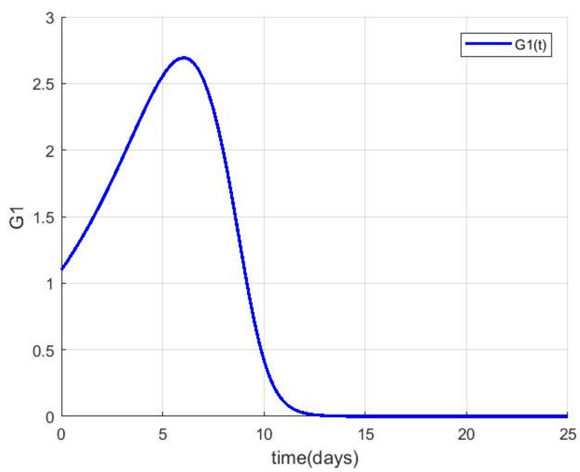
(d) G_2 without u_2 ($\beta_{22} < \eta_{22}$)



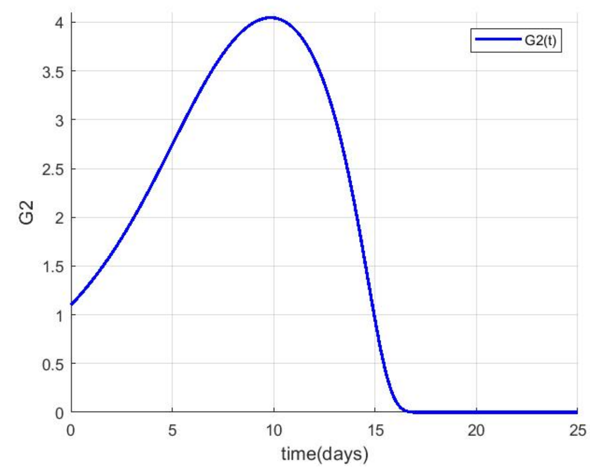
(e) B_1 ($\eta_{11} < \beta_{11}$)



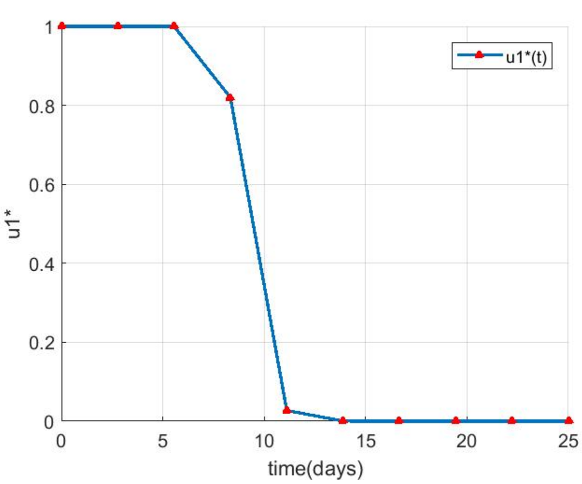
(f) B_2 ($\beta_{22} < \eta_{22}$)



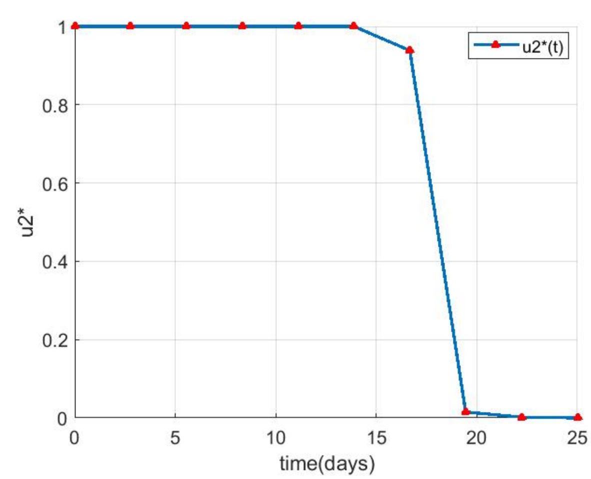
(g) G_1 ($\eta_{11} < \beta_{11}$)



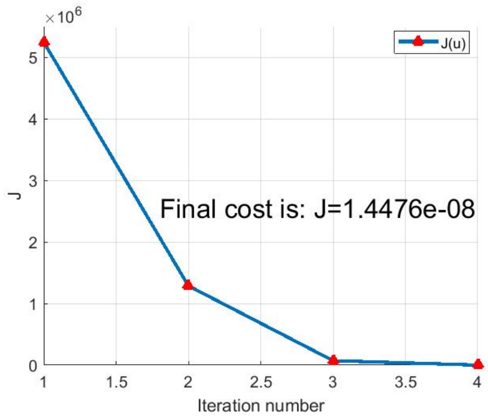
(h) G_2 ($\beta_{22} < \eta_{22}$)



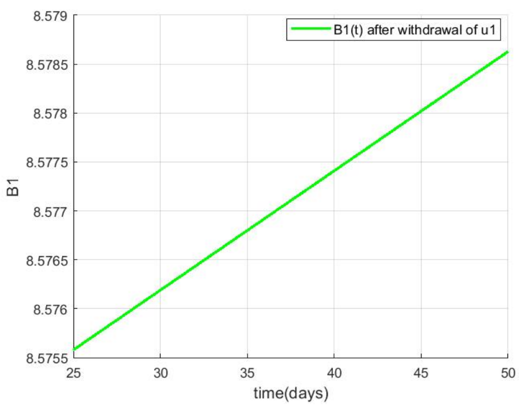
(i) Control u_1 ($\eta_{11} < \beta_{11}$)



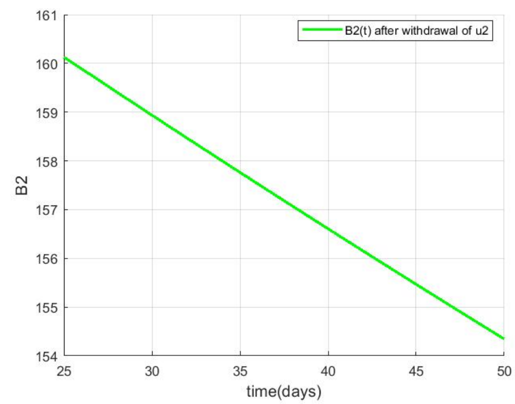
(j) Control u_2 ($\beta_{22} < \eta_{22}$)



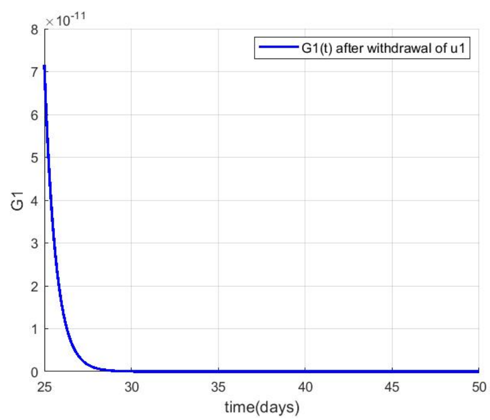
(k) Cost functional.



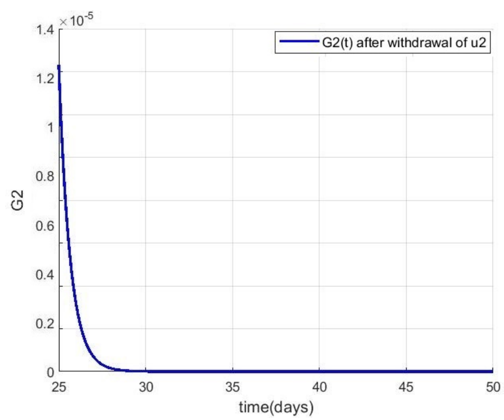
(l) B_1 beyond 25 days ($\eta_{11} < \beta_{11}$)



(m) B_2 beyond 25 days ($\beta_{22} < \eta_{22}$)



(n) G_1 beyond 25 days ($\eta_{11} < \beta_{11}$)



(o) G_2 beyond 25 days ($\beta_{22} < \eta_{22}$)

Figure 4.4: Example 4 (Two classes of antigen-antibody interaction).

Parameters: [$B_1(0) = 0.014$, $B_2(0) = 0.014$ and $G_1(0) = 1.055$, $G_2(0) = 1.055$, $\alpha_1 = 0.0001$, $\alpha_2 = 0.0001$, $\delta_1 = 0.2$, $\delta_2 = 0.2$, $\beta_{11} = -1.5$, $\beta_{12} = -0.001$ *or* -0.007, $\beta_{21} = 0.0$, $\beta_{22} = -2.0$, $\eta_{11} = -2.0$, $\eta_{12} = 0.0$, $\eta_{21} = -0.007$ *or* -0.001, $\eta_{22} = -1.5$, $\gamma_{11} = 1.0$, $\gamma_{12} = 0.0$, $\gamma_{12} = 0.0$, $\gamma_{21} = 0.0$, $\gamma_{22} = 1.0$, $\omega_1 = 100$, $\omega_2 = 100$].

Figure 4.4j illustrates that the optimal treatment policy (u_2) to inhibit the large population of G_2, is to apply 7 highest admissible doses upto 14th day, then reduce to 0.9 on the day of 16th, 0.01 on 19th and finally ends up zero in rest of the period. Due to the application of large amount of control dose (u_2), the antibody B_2 (Figure 4.4f) population is also much higher than B_1 (Figure 4.4e). It is seen that B_2 already exceeds the carrying capacity $K_2 = 10$ and reaches to a very high level 160. Once the antigen level goes down to the satisfactory level, it starts to fall, although it is not visible in the graph. Figure 4.4m shows the further growth of B_2 after withdrawal of medication (u_2) where we notice that it sharply declines to keep the population level within the carrying capacity ($K_2 = 10$). The antigen population of G_2 has not grown further as observed in Figure 4.4o. Finally, the objective function converges after 4 iterations and reaches to the level of 1.44×10^{-8} as shown in Figure 4.4k.

Here, we observe that both of the scenarios fulfill the target of inhibiting the growth of antigens' population. The explanation of these results is that in our proposed model the state equation of G_i includes the intrinsic growth rate and interaction terms whereas the equation of B_i includes the additional control terms along with the growth rate and interaction terms. Therefore, during the case of $\eta_{ii} < \beta_{ii} < 0$, the value of η_{ii} is more negative that makes it highly effective in state equation of G_i and thus it results small population of antigens. Similarly, when the value of β_{ii} is less negative that turns it to be lower effective in state equation of B_i. It causes higher population of B_i compare to G_i and makes a favorable environment where higher growth of antibodies requires less amount of drug and time to kill the lower amount of antigens.

The situation for the opposite scenario ($\beta_{ii} < \eta_{ii} < 0$) can be considered as less favorable where large amount of time and drugs are required to minimize the antigen population. Therefore, the significance of this analysis is, after identification of the model parameters it would be easier to interpret the treatment period or schedule by observing the coefficients parameters (β_{ii} and η_{ii}).

4.3.4 Two Classes of Antigen-Antibody Interactions Including Non-Specific Interaction

Example 5: Next, we consider the non-specific interactions between the i-th class of antibodies B_i and the j-th class of antigens G_j. We assume that the antibody B_1, which is primarily designed to fight antigen G_1, is also mildly interacting with antigen G_2. As explained in Chapter 3, when the interaction coefficient η_{21} is chosen smaller than β_{12}, the antibody B_1 is stronger (more effective) than the antigen G_2. The reverse situation holds for β_{12} smaller than η_{21}. Keeping all other parameters same for both classes, we conduct simulation experiment to determine the effect of the interaction between different classes (i.e. B_1 and G_2). Numerical results for these two specific scenarios are shown in Figure 4.5.

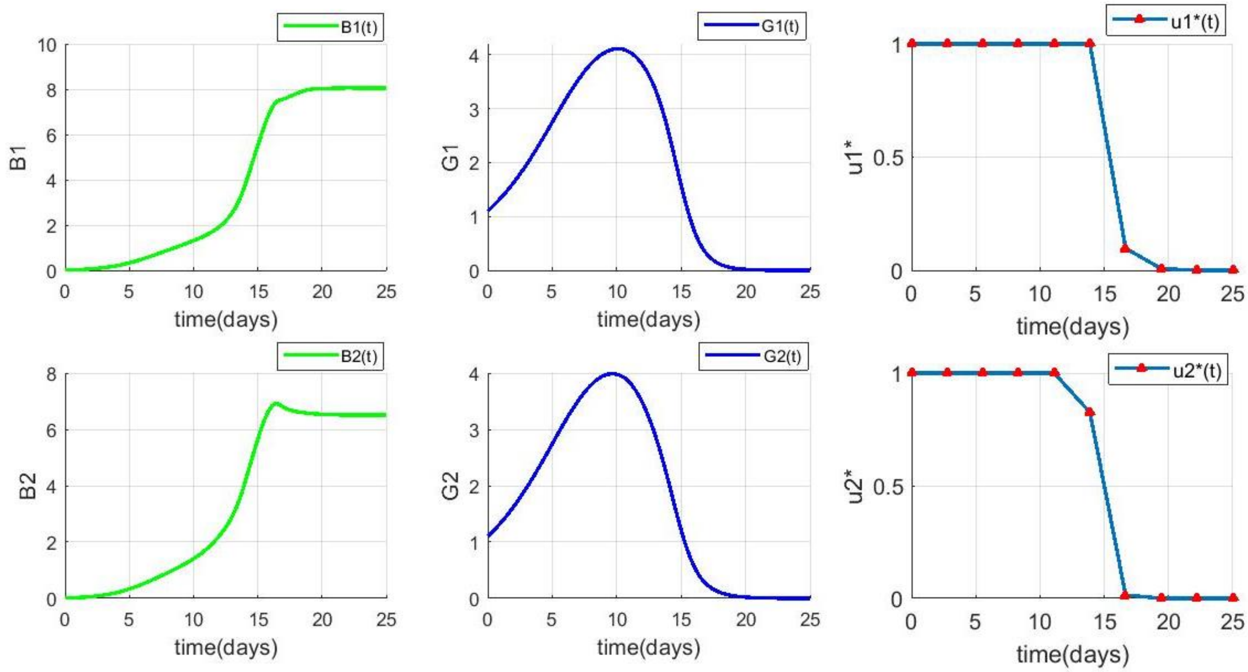
Table 4.5: Parameter Values of Example 5

<table>
<tr><th colspan="2">Parameters</th><th colspan="2">Values</th><th colspan="2">Parameters</th><th colspan="2">Values</th></tr>
<tr><td colspan="2">$B_1(0)$</td><td colspan="2">0.014</td><td colspan="2">$G_1(0)$</td><td colspan="2">1.1</td></tr>
<tr><td colspan="2">$B_2(0)$</td><td colspan="2">0.014</td><td colspan="2">$G_2(0)$</td><td colspan="2">1.1</td></tr>
<tr><td colspan="2">α_1</td><td colspan="2">0.0001</td><td colspan="2">δ_1</td><td colspan="2">0.2</td></tr>
<tr><td colspan="2">α_2</td><td colspan="2">0.0001</td><td colspan="2">δ_2</td><td colspan="2">0.2</td></tr>
<tr><td colspan="2">K_1</td><td colspan="2">10</td><td colspan="2">K_2</td><td colspan="2">10</td></tr>
<tr><td>β_{11}</td><td>-0.2</td><td>β_{12}</td><td>-0.001 / -0.0021</td><td>η_{11}</td><td>-0.15</td><td>η_{12}</td><td>0</td></tr>
<tr><td>β_{21}</td><td>0</td><td>β_{22}</td><td>-0.2</td><td>η_{21}</td><td>-0.0021 / -0.001</td><td>η_{22}</td><td>-0.15</td></tr>
<tr><td>γ_{11}</td><td>1.00</td><td>γ_{12}</td><td>0</td><td colspan="2">ω_1</td><td colspan="2">100</td></tr>
<tr><td>γ_{21}</td><td>0</td><td>γ_{22}</td><td>1.00</td><td colspan="2">ω_2</td><td colspan="2">100</td></tr>
</table>

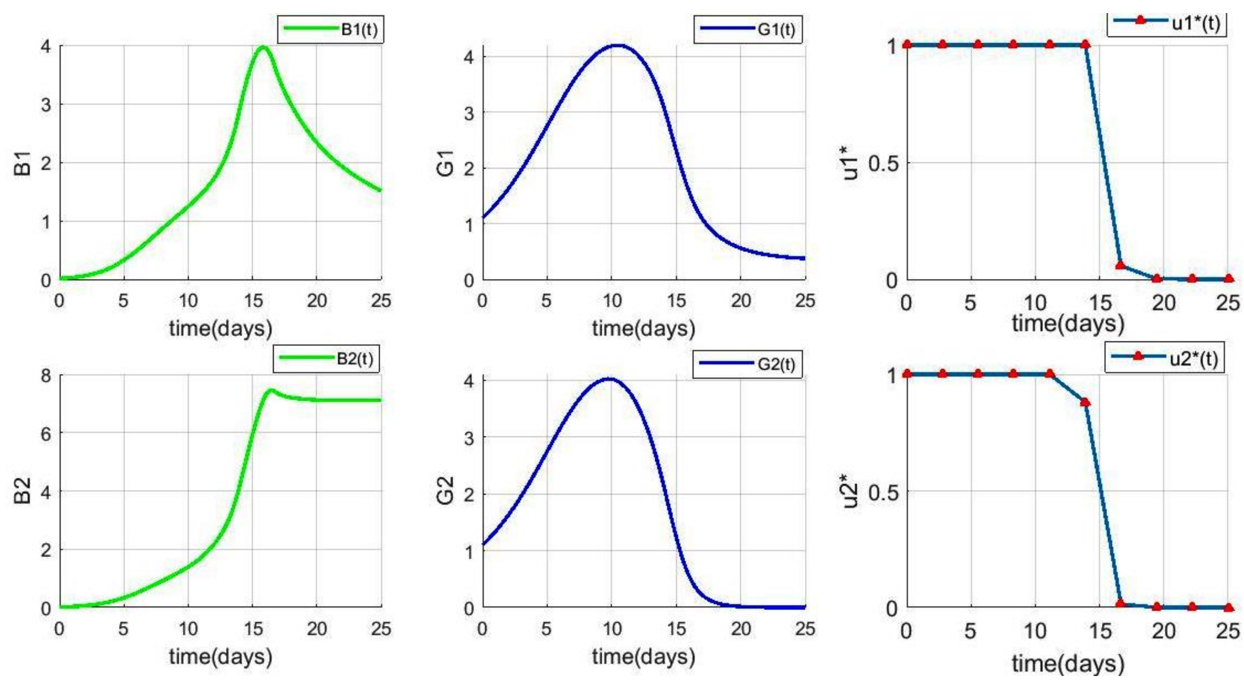
Since all the parameters are kept as previous example, the system responses without control input also remain same. For limited space these are not repeated again. Figure 4.5a and 4.5c illustrate the system responses correspond to the following off-diagonal interaction parameters:

$$\eta_{21} = -0.0021 < \beta_{12} = -0.001 < 0.$$

In Figure 4.5a, there are three major points to notice: first the population of antigen G_2 declines faster than antigen G_1, secondly, the population of antibody B_1 is lower than the population of B_2 and thirdly the corresponding control policy u_1 is found to admit larger doses than that of u_2. Here, B_1 attacks the antigen G_1 leading to its population decline within first 22 days to a satisfactory level of 0.001. The population of G_1 finally ends up on 8.44×10^{-5} in the end of treatment coarse. The optimal treatment doses (u_1) for this class is to admit the largest dose admissible up to 13th day and then reduce it to 0.1 on the day of 16th, 0.01 on 19th, 0.008 on 22nd and finally 0 (i.e. no dose) on the last day of treatment period.

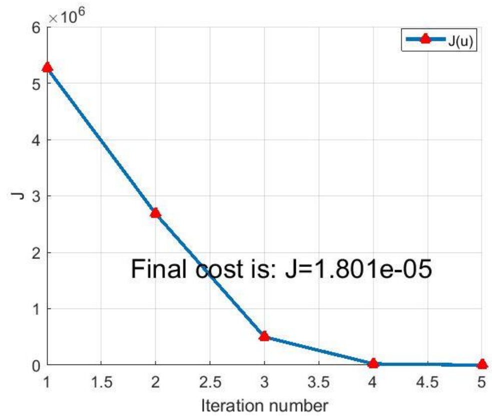


(a) States and control ($\eta_{21} = -0.0021 < \beta_{12} = -0.001$)

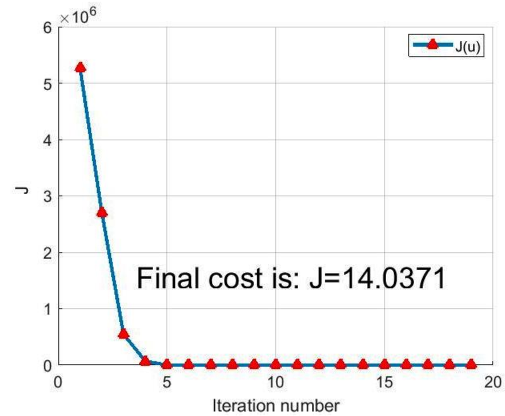


(b) States and control ($\beta_{12} = -0.0021 < \eta_{21} = -0.001$)

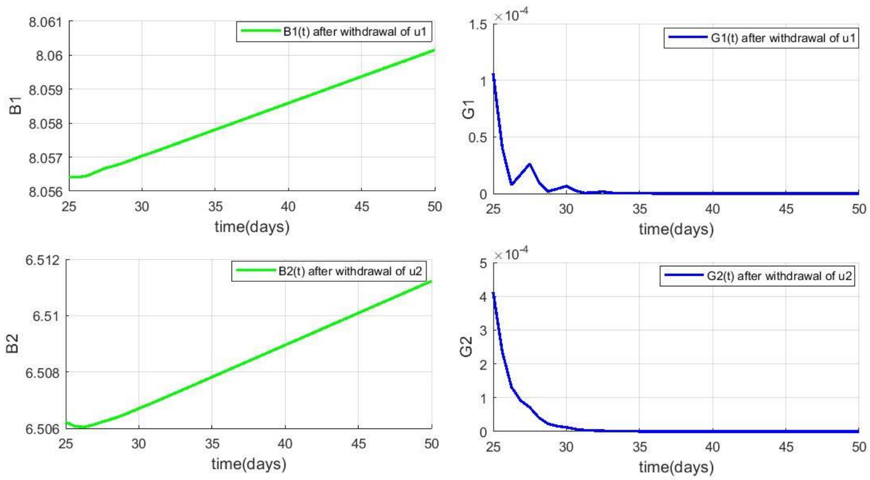
Parameters: [$B_1(0) = 0.014$, $B_2(0) = 0.014$ and $G_1(0) = 1.1$, $G_2(0) = 1.1$, $\alpha_1 = 0.0001$, $\alpha_2 = 0.0001$, $K_1 = 10$, $K_2 = 10$, $\delta_1 = 0.2$, $\delta_2 = 0.2$, $\beta_{11} = -0.2$, $\beta_{12} = -0.001$ *or* -0.0021, $\beta_{21} = 0.0$, $\beta_{22} = -0.2$, $\eta_{11} = -0.15$, $\eta_{12} = 0.0$, $\eta_{21} = -0.0021$ *or* -0.001, $\eta_{22} = -0.15$, $\gamma_{11} = 1.0$, $\gamma_{12} = 0.0$, $\gamma_{12} = 0.0$, $\gamma_{21} = 0.0$, $\gamma_{22} = 1.0$, $\omega_1 = 100$, $\omega_2 = 100$].



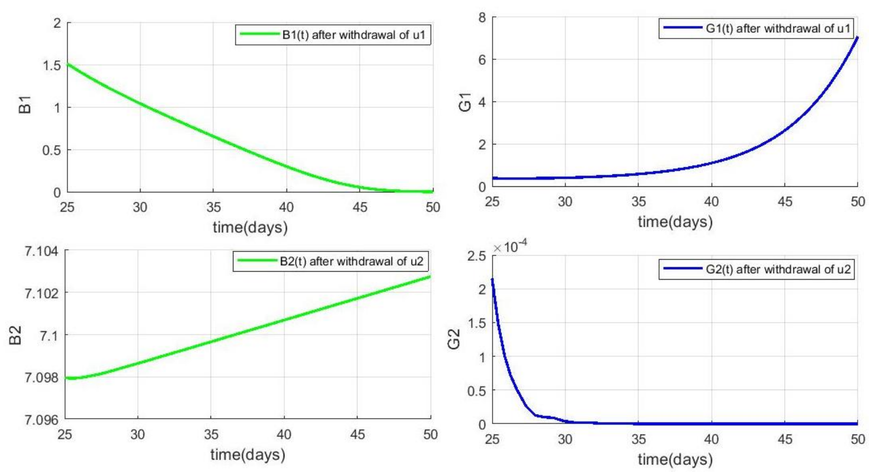
(c) J for ($\eta_{21} = -0.0021 < \beta_{12} = -0.001$)



(d) J for ($\beta_{12} = -0.0021 < \eta_{21} = -0.001$)



(e) State beyond 25 days ($\eta_{21} = -0.0021 < \beta_{12} = -0.001$)



(f) State beyond 25 days ($\beta_{12} = -0.0021 < \eta_{21} = -0.001$)

Figure 4.5: Example 5 (Two classes of antigen-antibody interaction with non-specific interaction).

On the other hand, for the second class of pair (B_2, G_2), it takes 18 days for population of G_2 to be declined to the same satisfactory level of 0.001. Final population of class of G_2 is 8.91×10^{-7}. The treatment policy (u_2) is to inject highest admissible dose upto 11th day, then reduce as per of the declination of G_2. Thus it proves that the choice of coefficient $\eta_{21} < \beta_{12}$ successfully engages some of the antibodies B_1 to combine and fight with antigen G_2. That's why, the population of G_2 dies out earlier and lower amount of control doses (u_2) are required to kill them. It also results lower population B_1 than the population of B_2.

The cost functional converges after 5 iterations and reaches at 7.12×10^{-7} as shown in Figure 4.5c. The system has been run beyond 25 days in Figure 4.5e. We can notice that the population of B_1 which are spent much on fighting both of antigens classes of G_1 and G_2, does not exceed the level of carrying capacity $(K_1 = 10)$. Similarly, the population of antibody class of B_2 also does not exceed it's carrying capacity $K_2 = 10$. From 25th day and onward, both of them start to grow faster to reach to the level of 10. The population of antigen class of G_1 and G_2 has not grown further.

In converse, the Figure 4.5b and 4.5d, illustrate the system responses correspond to the following off-diagonal interaction parameters:

$$\beta_{12} = -0.0021 < \eta_{21} = -0.001 < 0.$$

Here, the states and control trajectories follow the same rule of the previous scenario $(\eta_{21} < \beta_{12})$. That is, the class of antigen G_2 declines faster than G_1, the population of antibody B_1 is much lower than B_2 and the treatment dose u_1 is found to be larger than u_2.

But in comparison with the previous scenario $(\eta_{21} < \beta_{12} < 0)$, it is clearly visible that the choice of coefficients $\beta_{12} < \eta_{21} < 0$ makes antigen class of G_2 more aggressive, therefore the antibody class of B_1 gets weaker. As a result, the population of G_1 does not decline much with the control drugs u_1. By the end of treatment period, the antigen (G_1) population level is 0.37 which is much higher than that of the all previous scenarios. Most important thing is to notice the growth of antibody (B_1) population. It is evident, that the antibodies (B_1) are spent out in fighting with both classes of antigens (G_1 and aggressive G_2) resulting low population. B_1 starts to grow from it's initial value of 0.014 (Figure 4.5b), rising to a peak of 4.0 which is almost half of the previous case (Figure 4.5a), then sharply starts to decline again. Here, the carrying capacity of class of B_1 is chosen as $K_1 = 10$ which is far ahead of it's current level of population. Since the population of antigens (G_1)

starts to decline after 17th day, the population of B_1 should try to reach to the level of 10 rather than spending out massively. This is somewhat a new state trajectory that we observe here. In all the previous case studies we have noticed that, while the population of antigens declines to a satisfactory level, sooner or later the population of antibodies starts to reach to the carrying capacity. Here the opposition of this characteristic indicates that, although the population of G_1 starts to fall, it has not reached yet to a harmless level and it may starts to grow again.

Similarly, the population of antigen G_2 takes longer period (22 days) than that of the first scenario (i.e 18 days) to reach to a satisfactory level of 0.0012. Thus it also proves the aggressiveness of class of G_2. At the same time, the population of antibody (B_2) starts to grow from 0.014 arriving at a peak of 7.8 on the days of 21st and then starts to fall steadily. Due to the application of control drugs (u_2) and the interaction of antibody (B_2), the population of G_2 successfully declines to an optimized level of 2.14×10^{-4} by the end of treatment period.

Figure 4.5d yields that the cost functional takes 19 iterations to converge and reaches to a level of 14.03 which is much higher than all the previous results. This is because of the higher population of antigen G_1 at the end of treatment period. As explained in the algorithm section that in the optimization problem the cost functional converges when there is no further improvement. Here, we choose the stopping criteria $\tau = 1 \times 10^{-8}$. The process of iteration continues until the difference in the current and previous values of the cost functional goes below to this value.

Finally, the system is run beyond 25 days in Figure 4.5f where it is more interesting to observe the after-effects (after the withdrawal of medications) on the system. In the post treatment period (from 25th - 50th day) the population of antigen class of G_1 again starts to grow. Thus it proves that the antibodies (B_1) are spent out in fighting the regenerated population of G_1. This is a significant finding where it implies that the medication for these particular case study should not be withdrawn right after the first course of treatment. On the other hand, the second class of antigen G_2 has not grown like G_1 and remains within a low satisfactory level. The population of antibody B_2 grows slowly to reach to the carrying capacity level ($K_2 = 10$).

Thus, the proposed model is beneficial to detect the treatment strategies for the case where the antibodies react with other antigens or harmful particles.

4.3.5 Three Classes of Antigen-Antibody Interactions Including the Effect of Multiple Drugs and Larger Dose Treatment

Example 6: Following the similar strategies, we consider the interaction between 3 classes of antibodies (B_1, B_2, B_3) and the corresponding three classes of antigens (G_1, G_2, G_3). As this is a high dimensional system, we select small treatment period $T = 15$ days for better computational performance. Furthermore, for quick remedy (within 15 days) from the cancer, we increase the upper limit of the control constraint set to be $U = \{u : 0 \leq u \leq 2.5\}$ which implies aggressive treatment. In this example, we assume that there are three distinct classes of drugs (3 distinct controls) to boost the growth of the three distinct classes of antigen-specific-antibodies.

Table 4.6: Parameter Values of Example 6

<table>
<tr><th colspan="3">Parameters</th><th colspan="3">Values</th><th colspan="3">Parameters</th><th colspan="3">Values</th></tr>
<tr><td colspan="3">$B_1(0)$</td><td colspan="3">0.014</td><td colspan="3">$G_1(0)$</td><td colspan="3">1.015</td></tr>
<tr><td colspan="3">$B_2(0)$</td><td colspan="3">0.014</td><td colspan="3">$G_2(0)$</td><td colspan="3">1.015</td></tr>
<tr><td colspan="3">$B_3(0)$</td><td colspan="3">0.014</td><td colspan="3">$G_3(0)$</td><td colspan="3">1.015</td></tr>
<tr><td colspan="3">α_1</td><td colspan="3">0.001</td><td colspan="3">δ_1</td><td colspan="3">0.22</td></tr>
<tr><td colspan="3">α_2</td><td colspan="3">0.001</td><td colspan="3">δ_2</td><td colspan="3">0.22</td></tr>
<tr><td colspan="3">α_3</td><td colspan="3">0.001</td><td colspan="3">δ_3</td><td colspan="3">0.22</td></tr>
<tr><td colspan="2">K_1</td><td colspan="2">50</td><td colspan="2">K_2</td><td colspan="2">50</td><td colspan="2">K_3</td><td colspan="2">50</td></tr>
<tr><td>β_{11}</td><td>-1.5</td><td>β_{12}</td><td>0.0</td><td>β_{13}</td><td>0.0</td><td>η_{11}</td><td>-2.0</td><td>η_{12}</td><td>0</td><td>η_{13}</td><td>0</td></tr>
<tr><td>β_{21}</td><td>0.0</td><td>β_{22}</td><td>-1.5</td><td>β_{23}</td><td>0.0</td><td>η_{21}</td><td>0.0</td><td>η_{22}</td><td>-2.0</td><td>η_{23}</td><td>0</td></tr>
<tr><td>β_{31}</td><td>0.0</td><td>β_{32}</td><td>0.0</td><td>β_{33}</td><td>-1.5</td><td>η_{31}</td><td>0.0</td><td>η_{32}</td><td>0.0</td><td>η_{33}</td><td>-2.0</td></tr>
<tr><td>γ_{11}</td><td>1.00</td><td>γ_{12}</td><td>0.01</td><td>γ_{13}</td><td>0.001</td><td colspan="3">ω_1</td><td colspan="3">100</td></tr>
<tr><td>γ_{21}</td><td>0.0</td><td>γ_{22}</td><td>1.00</td><td>γ_{23}</td><td>0.0</td><td colspan="3">ω_2</td><td colspan="3">100</td></tr>
<tr><td>γ_{31}</td><td>0.0</td><td>γ_{32}</td><td>0.0</td><td>γ_{33}</td><td>1.5</td><td colspan="3">ω_3</td><td colspan="3">100</td></tr>
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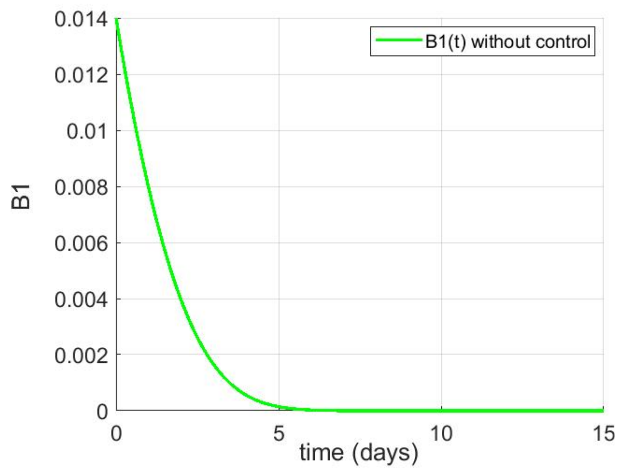
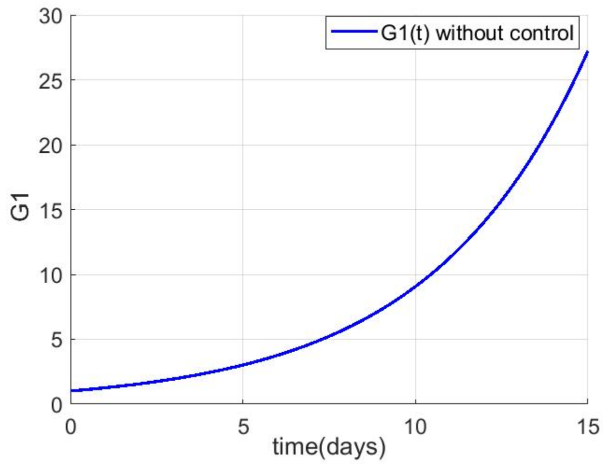
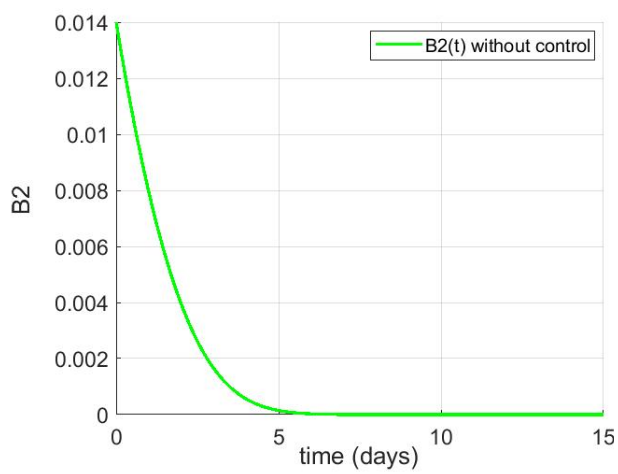


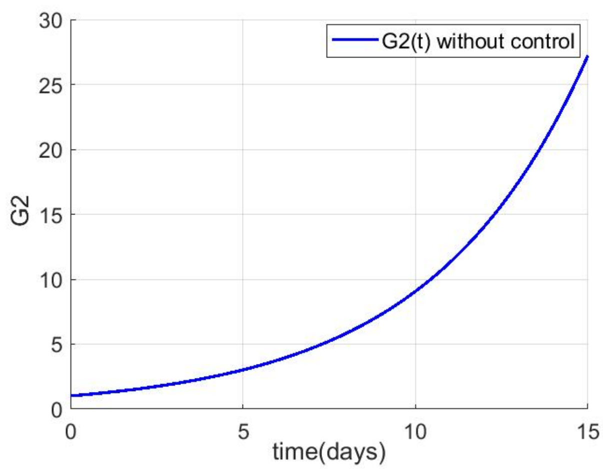
(a) B_1 without control



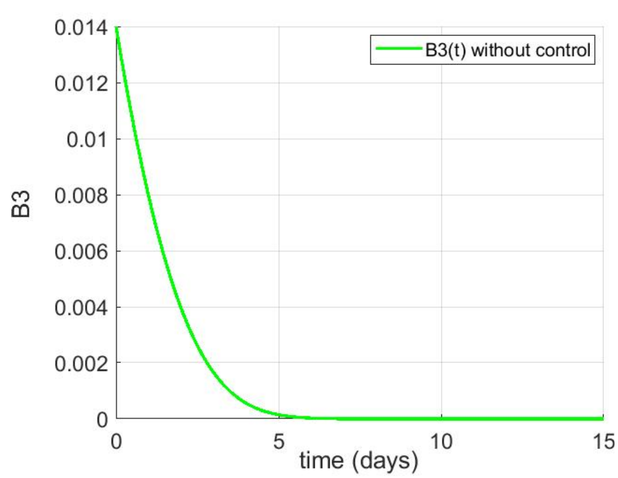
(b) G_1 without control



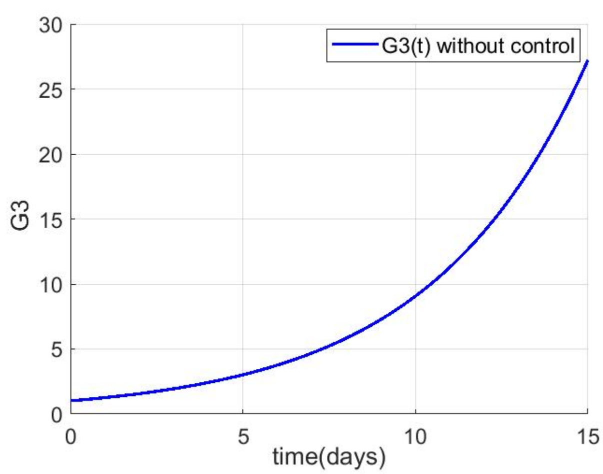
(c) B_2 without control



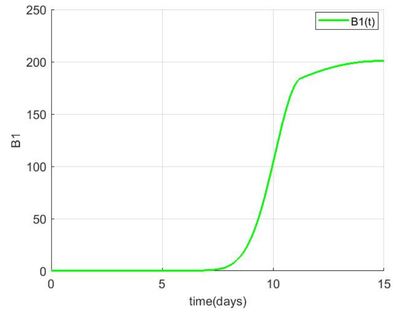
(d) G_2 without control



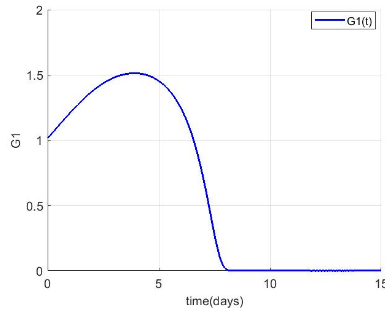
(e) B_3 without control



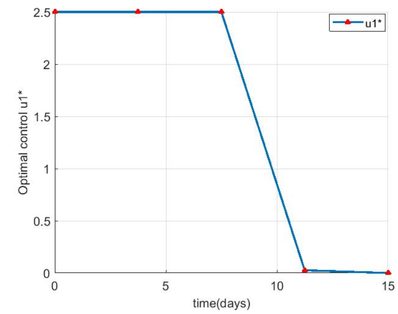
(f) G_3 without control



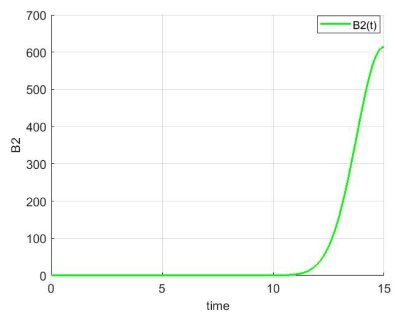
(g) B_1 ($\gamma_{11} = 1, \gamma_{12} = 0.01, \gamma_{13} = 0.001$)



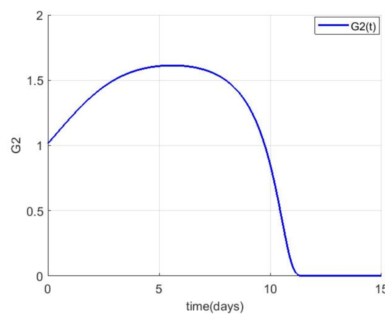
(h) G_1 ($\gamma_{11} = 1, \gamma_{12} = 0.01, \gamma_{13} = 0.001$)



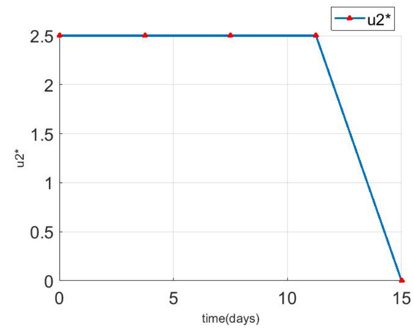
(i) Control (u_1)



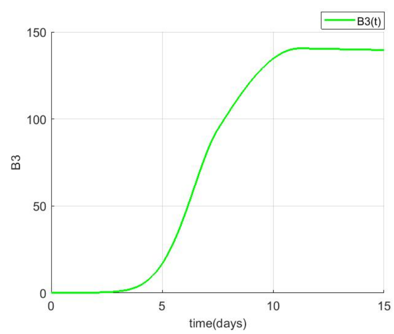
(j) B_2 ($\gamma_{21} = 0, \gamma_{22} = 1, \gamma_{23} = 0$)



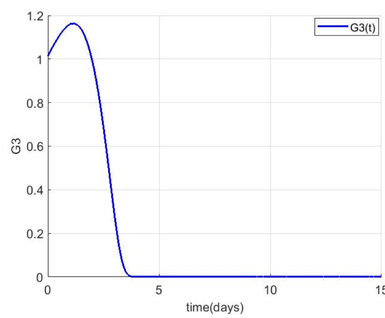
(k) G_2 ($\gamma_{21} = 0, \gamma_{22} = 1, \gamma_{23} = 0$)



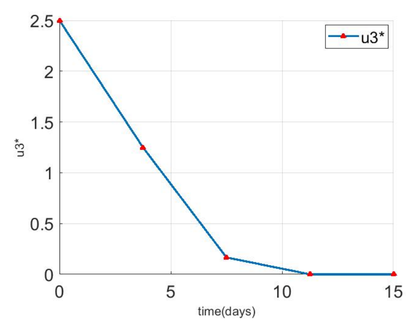
(l) Control (u_2)



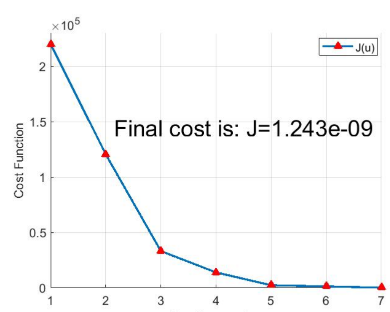
(m) B_3 ($\gamma_{31} = 0, \gamma_{32} = 0, \gamma_{33} = 1.5$)



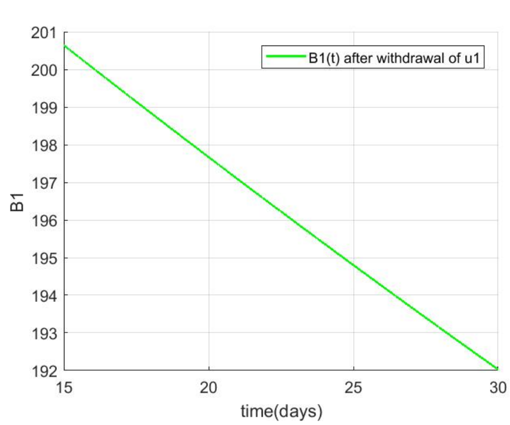
(n) G_3 ($\gamma_{31} = 0, \gamma_{32} = 0, \gamma_{33} = 1.5$)



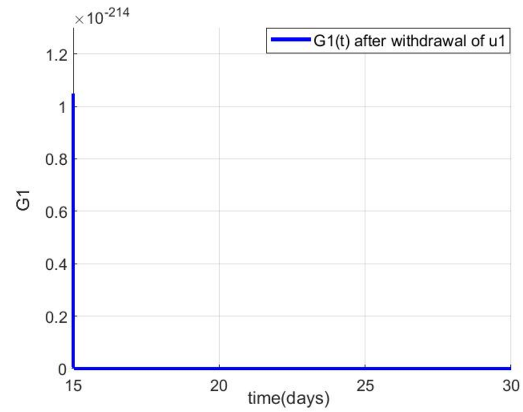
(o) Control (u_3)



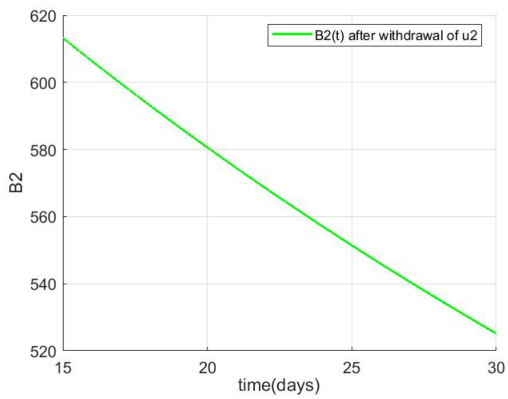
(p) Cost functional



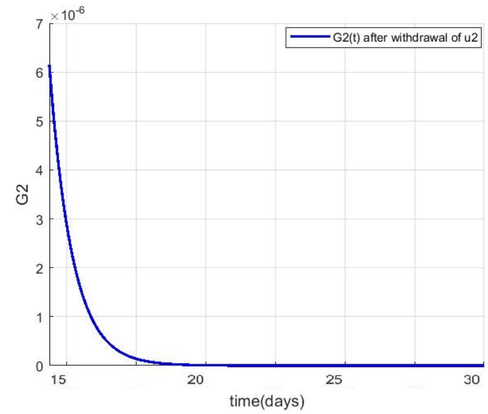
(q) B_1 beyond 15 days



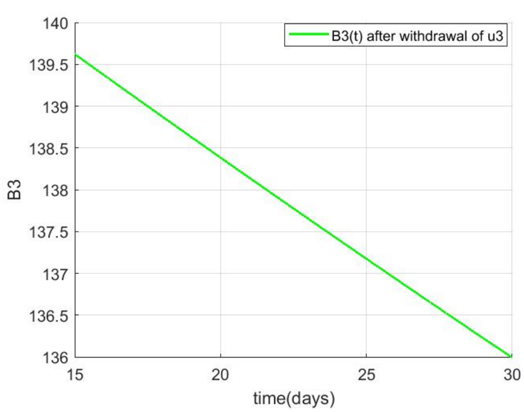
(r) G_1 beyond 15 days



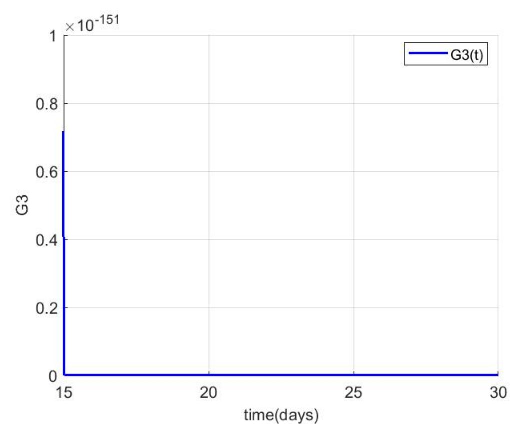
(s) B_2 beyond 15 days



(t) G_2 beyond 15 days



(u) B_3 beyond 15 days



(v) G_3 beyond 15 days

Figure 4.6: Example 6 (Three classes of antigen-antibody interaction).

Parameters: [$B_1(0) = 0.014$, $B_2(0) = 0.014$ and $G_1(0) = 1.055$, $G_2(0) = 1.055$, $\alpha_1 = 0.0001$, $\alpha_2 = 0.0001$,$K_1 = 50$, $K_2 = 50$, $K_3 = 50$ $\delta_1 = 0.2$, $\delta_2 = 0.2$, $\beta_{11} = -1.5$, $\beta_{12} = -0.001$ *or* -0.007, $\beta_{21} = 0.0$, $\beta_{22} = -1.5$, $\eta_{11} = -2.0$, $\eta_{12} = 0.0$, $\eta_{21} = -0.007$ *or* -0.001, $\eta_{22} = -2.0$, $\gamma_{11} = 1.0$, $\gamma_{12} = 0.0$, $\gamma_{12} = 0.0$, $\gamma_{21} = 0.0$, $\gamma_{22} = 1.0$, $\omega_1 = 100$, $\omega_2 = 100$].

As mentioned earlier, that the coefficient ($\gamma_{ik},\ i = 1, 2, 3, ..\ \kappa$ and $k = 1, 2, 3, ..\ m$) is the effect of k-th drug (or control) on the i-th antibody production. If $\gamma_{ik} = 0$, the k-th drug has no contribution towards the production of antibody B_i. If positive, it will enhance the immune system response and if negative it is harmful to the antibodies formulation. Here, the diagonal terms (γ_{ii}) contribute the primary antigen-specific-antibody production rate while the off diagonal terms (γ_{ik}) represent positive, neutral or negative contribution towards their growth. Keeping all other parameters fixed for the three classes, we run the system to evaluate the effect of both diagonal and off-diagonal control coefficients.

Firstly, for $(B_1 - G_1)$ interaction, we select the dose strength of primary drug (control) u_1 to be $\gamma_{11} = 1.0$ and the off diagonal coefficients $\gamma_{12} = 0.01$, $\gamma_{13} = 0.001$. The later may represent two perspective of treatment: either the side effects of other drugs or the supplementary drugs administration. In our assumption, we consider the first one. Here, the drug u_2 and u_3, which is primarily designed to kill respectively G_2 and G_3, is also helping to kill G_1.

Moreover, the method of checkpoint protein inhibitor is discussed in chapter 1, where a combination of three antibodies *IpilimuAb*, *NivolumAb* and *PembrolizumAb* are used as therapeutic to bind on *PD-1* checkpoint protein. The choice of off-diagonal coefficients $\gamma_{12},\ \gamma_{13} > 0$ may also provide such supplementary contribution towards the growth of antibody B_1 to attack the antigen G_1. In that case, the values of these coefficients $(\gamma_{12},\ \gamma_{13})$ represent the percentage of the different drugs therapeutics and should be comparatively larger than the chosen values. Although we do not consider this here, our model provides a way to allow such multiple drug (control) applications for inhibiting the growth of the checkpoint proteins.

Secondly, for $(B_2 - G_2)$ class, the diagonal coefficient is chosen as $\gamma_{22} = 1.0$ while the off diagonal coefficients are chosen as $\gamma_{21} = \gamma_{23} = 0$.

Thirdly, for $(B_3 - G_3)$ pair, the effectiveness of drug u_3 has been boosted up by choosing $\gamma_{33} = 1.5$. In order to evaluate the effect of larger doses, the off diagonal coefficients are fixed at zero. The parameter values for this example are enlisted in Table 4.6. The simulation results are shown in Figure 4.6.

Figures 4.6(a)-(f) yield the state trajectories without the control drugs which indicate that the presence of antibodies are not strong enough to inhibit the growth of antigens. Next the system responses are shown corresponding to the optimal control input in Figures 4.6(g)-(p).

It is clear from the state trajectories in Figure 4.6h and 4.6k that, due to the side effect of both of the drugs u_2 and u_3, the population of G_1 declines faster than G_2. The population of G_1 declines to a satisfactory level of 0.0001 within the 9th day of treatment period while the of population of G_2 takes around 12 days to reach to same level. Also the Figure 4.6i shows that the corresponding optimal policy u_1 for this class is found to be the maximum dose admissible up to 8 days which is smaller than that of u_2 (up to 12 days) in Figure 4.6l.

Furthermore, because of the larger treatment dose (1.5 times more than that of other two classes), the population of G_3 dies out faster than (within 4 days) any of the other two classes as shown in Figure 4.6n. The corresponding control policy u_3 (Figure 4.6o) also decreases monotonically unlike any of the other two.

On the other hand, Figures 4.6g, 4.6j, 4.6m illustrates that the population of antibodies (B_1, B_2, B_3) grow gradually until the antigens' population (G_1, G_2, G_3) goes below to the level of 0.0001. For limited space we do not repeat the expanded segments of their gradual growth. After that, B_1, B_2 and B_3 start to grow faster and reach at very high level of 200, 600 and 120 respectively. As explained earlier that the highest level of antibodies' population actually vary according to the application of control doses u_1, u_2 and u_3. Also in this example, the highest value of admissible control constraint set is chosen as 2.5 which is much higher than that of the previous cases. Thus it results higher growth of antibodies' population after the elimination of antigens. However, the further growth of antibodies' population are shown in Figure 4.6q, 4.6s and 4.6u for the next 15 days which illustrate that the antibodies (B_1, B_2, B_3) decline sharply to reach their level of (50) carrying capacity. The antigens' population (G_1, G_2 and G_3) also continue to decline and have not grown anymore as shown in Figure 4.6r, 4.6t and 4.6v. Finally, the objective functional, converges after 7 iterations and reaches to the level of 1.24×10^{-9} as shown in Figure 4.6p.

Thus, the model is useful to identify the effects of multiple drugs or larger dose strength while using the antibody therapeutics to treat cancer.

Chapter 5

Conclusion

5.1 Summary of Thesis

In this thesis, we propose a dynamic model to represent the temporal evolution of the population of antigens and antibodies in human patients suffering from cancer. We also present a methodology to determine the optimal treatment policies for cancer immunotherapy. The model is based on minor modification of the well-known Lotka–Volterra population model. The original model is extended by including controls which represent the drugs and their doses used to fight cancer. We have formulated an optimal control problem with the objective of minimizing and possibly eliminating the antigen population. We have used Pontryagin minimum principle to determine the optimal strategies. Using the minimum principle, we obtain the optimal doses of drugs in terms of their strength and scheduled applications.

We solve the optimal control problem numerically by using the gradient descent method and presented six different examples corresponding to different scenarios and choice of parameters. First of all, we determine the optimal treatment policy of one class of antibody formulation that targets one specific class of antigen. We observe that with the help control drugs, the growth of antibody is strong enough to inhibit the growth of antigens. But after elimination of antigen population, the antibody keeps growing.

Next, in order to keep the antibody population within a specified level, we modify the model including the logistic growth rate term. In the following two examples we simulate the system with two different carrying capacities. We find that higher control drugs are required to reinforce the formulation of antibody with lower carrying capacity.

In the fourth example, we analyze the effect of antigen-specific-antibody interaction coefficient parameters and determine the condition that requires the less amount of time and drug application to kill the antigens.

The fifth example includes the antigen-nonspecific-antibody interaction coefficient parameters. We have found that while interacting with other classes of antigens, the antibody may become weak and not be able to eliminate its targeting antigen completely.

Finally, in the sixth example we have shown that our model successfully determines the effects of multiple drugs supplementation. Furthermore, if the effect of any drug is negative or prevents the growth of antibodies instead of antigens, our model is also able to investigate that.

In all the case studies, given the constraints as described, the control variables always start with the largest admissible dose and then reduce as per of the decline of antigen population level. Thus it suffices the optimality of the control input (i.e. drugs administration). By using this model the physician may predict the treatment course beforehand and modify it. For example: increasing the treatment period or boosting up the drug strength by selecting a higher control constraints etc. This optimal treatment policy approach is potentially applicable in a variety of clinical problems where the relation of the drug and its impact on the pathological conditions are possible to describe by a dynamic system.

5.2 Future Work

This research can be further improved from different point of views. First of all, the real-world modeling depends on many variables simultaneously. As a result, modelling some phenomena from the real world with the help of ordinary differential equations (ODE) restricts the analysis to one independent variable (e.g. time) only. Because of this restriction, ODE models may fail to reflect the dynamics as shown by the original phenomena. Instead of using an ODE model here, it would be appropriate to use a partial differential equation (PDE) model where the state variables depend on both time and space. For this thesis we do not take into account the partial differential model of antigen-antibody dynamics. As a future prospect, we hope to extend this research by considering a spatio-temporal model to analyse the effect of movement of the antigens and the antibodies while circulating throughout the body.

Another future aspect is the model can be successfully established by turning it into a parameter optimization problem with the help of some sample data along with the admitted drug doses for treating cancer patients.

Finally, from the perspective of optimization and optimal control theory, one possible improvement is, to solve the problem with other optimization techniques, optimizer tools and compare the results. Thus it may help to develop the most effective algorithm and establish a methodology for determining the optimal treatment policies for cancer immunotherapy. In future, we hope to establish this model for cancer immunotherapy and propose a better methodology for successful application.

Appendices

Appendix A

Source Code of Optimal Controls (treatment policies)

A.1 Main Script

Using the algorithm presented in the "Computational Algorithm" of Chapter 4, we developed MATLAB codes for different dimension of the proposed system. Because of the length limitation of thesis, only the code for 3 classes of antigen-antibody interaction has been included here. If requested, all the codes can be provided.

Each of the code consists of five main functions.

- One main function for gradient optimization
- One function for the state equations
- One function for the costate equations
- One function for the gradient vector
- One function for the updating control variables

```
%----------------gradient optimization--------------------
clc
clear all
close all
```

```
diary('6D.txt')

%%
%-----------Enter all parameters------------

%-----------Stopping criterion-------------
eps = 1e-2;
eps_j = 1e-8;

%-----------Initial step size-------------
step = 0.4;

%-----------Fix the treatment period-------------

time_factor=1;
t0 = 0; tf = 15;
t_segment = 5;
Tu = linspace(t0, tf, t_segment);    % discretize time


%-----------The number of iteration index-------------

max_iteration = 1000;                  % Maximum number of iterations

n=input('Enter number of antigens or antibodies: ')

%{
%----------initial guess------------
for i=1:2*n;
    initx(i)=input('enter initial guess: ');
end
    initx=reshape(initx,1,2*n)

%----------alpha------------
```

```
for i=1:n;
    alpha(i)=input('elements alpha: ');
end
    alpha=reshape(alpha,n,1)

%----------Carrying capacity------------

for i=1:n;
    K(i)=input('elements carrying capacity: ');
end
    K=reshape(K,n,1)



%----------beta------------
for i=1:n^2;
    beta(i)=input('elements beta: ');
end
    beta=reshape(beta,n,n)

%----------gamma------------
for i=1:n^2;
    gamma(i)=input('elements gamma: ');
end
    gamma=reshape(gamma,n,n)

%----------delta------------
for i=1:n;
    delta(i)=input('elements delta: ');
    end
    delta=reshape(delta,n,1)


%----------eta------------
for i=1:n^2;
```

```
    eta(i)=input('elements eta: ');
    end
    eta=reshape(eta,n,n)

%}

%------Initial guess of Control --------
u1 = zeros(1,t_segment);
%u1= u1 + 0.001;
u2 = zeros(1,t_segment);
%u2= u2 + 0.002;
u3 = zeros(1,t_segment);
%u3= u3 + 0.003;

%----------Set the control constraint-------
c=input('Set the highest admissible constraint of control ')

u1( u1>c )=c;
u1( u1<0 )=0;
u2( u2>c )=c;
u2( u2<0 )=0;
u3( u3>c )=c;
u3( u3<0 )=0;

%--------Initial value of Cost function----------
J_old=0;

%----------Weight in cost function------------
for i=1:n
 fprintf(' Enter Weighting element Weight(%d) :\n',i);
   if i==1
   Weight(i)= 100;
    elseif i==2
     Weight(i)= 100;
```

```
    else
      Weight(i)= 100;
   end
 end
Weight=reshape(Weight,n,1);


%-------------Tolerance of ode45-------------------------

abs_tol=zeros(1,length(initx));
abstol=abs_tol+1e-4;
options = odeset('RelTol', 1e-4, 'AbsTol',abstol);
%%
%--------State trajectories without control----------
[Tx_p,X_p]=ode45(@(t,x) stateEq_3D_log(n,t,x,u1,u2,u3,Tu,alpha,.........
beta, gamma, delta, eta, Weight, Kb1, Kb2, Kb3, Kg1, Kg2, Kg3,..........
time_factor), [t0 tf], initx, options)

%--------Plot of State trajectories without control----------
figure(1);
%subplot(3,2,1)
grid on
hold on

plot(Tx_p(:,1), X_p(:,1),'g-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B1(t)');
xlabel('time','fontsize',12);
ylabel('B1','fontsize',12);

figure(2);
%subplot(3,2,2)
grid on
```

```
hold on
%plot(Tx(:,1), x4 ,'b-');
plot(Tx_p(:,1), X_p(:,4) ,'b-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G1(t)');
xlabel('time','fontsize',12);
ylabel(' G1','fontsize',12);
hold on;


figure(3);
%subplot(3,2,3)
grid on
hold on
plot(Tx_p(:,1), X_p(:,2) ,'g-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B2(t)');
xlabel('time','fontsize',12);
ylabel(' B2','fontsize',12);

figure(4);
%subplot(3,2,4)
grid on
hold on
%plot(Tx(:,1), x4 ,'b-');
plot(Tx_p(:,1), X_p(:,5) ,'b-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G2(t)');
xlabel('time','fontsize',12);
ylabel(' G2','fontsize',12);
hold on;
```

```
figure(5);
%subplot(3,2,5)
grid on
hold on
plot(Tx_p(:,1), X_p(:,3) ,'g-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B3(t)');
xlabel('time','fontsize',12);
ylabel('B3','fontsize',12);
hold on;

figure(6);
%subplot(3,2,6)
grid on
hold on
plot(Tx_p(:,1), X_p(:,6), 'b-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G3(t)');
xlabel('time','fontsize',12);
ylabel('G3','fontsize',12);
hold on;

%%
%--------------------------State with Optimal Control----------------------


%------------flag numbers------------
flag=-1
true=0
```

```
for i = 1:max_iteration
% 1)------ start with assumed control u and move forward

[Tx,X] = ode45(@(t,x) stateEq_3D_log(n,t,x,u1,u2,u3,Tu,alpha,.........
beta, gamma, delta, eta, Weight, Kb1, Kb2, Kb3, Kg1, Kg2, Kg3,.........
time_factor), [t0 tf], initx, options)


% 2)-------------------- Move backward to get the trajectory of costates
   x1 = X(:,1); x2 = X(:,2);
   x3 = X(:,3); x4 = X(:,4);
   x5 = X(:,5); x6 = X(:,6);

   p4T=2*Weight(1)*(X(end,4)-0);
   p5T=2*Weight(2)*(X(end,5)-0);
   p6T=2*Weight(3)*(X(end,6)-0);

initp = [0 0 0 p4T p5T p6T];

   [Tp,P] = ode45(@(t,p) costateEq_3D_log(n,t,p,u1,u2,u3,Tu,........
   x1,x2,x3,x4,x5,x6,Tx,alpha, beta, gamma, delta, eta, Weight, ....
   Kb1, Kb2, Kb3, time_factor), [tf t0], initp, options)
   p1 = P(:,1);
   p2 = P(:,2);
   p3 = P(:,3);
   p4 = P(:,4);
   % Important: costate is stored in reverse order. The dimension of
   % costates may also different from dimension of states
   % Use interploate to make sure x and p is aligned along the time axis
   p1 = interp1(Tp,p1,Tx);
   p2 = interp1(Tp,p2,Tx);
   p3 = interp1(Tp,p3,Tx);

% 3)---------- Calculate dH/du with x1(t), x2(t), p1(t), p2(t)
```

```
   h=1;
   dH1 = pH_3D(h,x1,x2,x3,p1,p2,p3,Tx,u1,u2,u3,Tu,...........
   alpha, beta, gamma, delta, eta, Weight, time_factor);
   h=2;
   dH2 = pH_3D(h,x1,x2,x3,p1,p2,p3,Tx,u1,u2,u3,Tu,.........
   alpha, beta, gamma, delta, eta, Weight, time_factor);
   h=3;
   dH3 = pH_3D(h,x1,x2,x3,p1,p2,p3,Tx,u1,u2,u3,Tu,alpha,...
   beta, gamma, delta, eta, Weight, time_factor);

   %Calculate the HNorm with each dh/du

   H_Norm1 = dH1'*dH1;
   H_Norm2 = dH2'*dH2;
   H_Norm3 = dH3'*dH3;


% 4)---------- Calculate the cost function
J(i,1) = Weight(1)*((X(end,4)-0)^2)+ Weight(2)*((X(end,5)-0)^2) + ...
         Weight(3)*((X(end,6)-0)^2)

   J_n = J_old - J(i,1);
   J_abs(i+1,1) =  abs(J_n);


%5)---------- Check the stopping criterion----------

   if (H_Norm1 < eps) && (H_Norm2 < eps) && (H_Norm3< eps)
        fprintf('J_abs < HNorm  \n------------\n');J(i,1)
        flag=1;
           break;
   elseif J_abs(i+1,1) < eps_j
       fprintf('J_abs < eps  \n------------\n');J(i,1)
        flag=1;
```

```
        break;
elseif (i~=1) && (J(i,1)> J_old)
    J_old=J(end,1);
    J(i,:)= []
 true=0;
     while (true==1)
            J_old=J(end,1);
            step = step*0.001;
            u_old1 = u1;
            u1 = AdjControl_3D(dH1,Tx,u_old1,Tu,step,c);
            u_old2 = u2;
            u2 = AdjControl_3D(dH2,Tx,u_old2,Tu,step,c);
            u_old3 = u3;
            u3 = AdjControl_3D(dH3,Tx,u_old3,Tu,step,c);
            x1 = X(:,1); x2 = X(:,2); x3 = X(:,3);
            x4 = X(:,4); x5 = X(:,5); x6 = X(:,6);
            p4T=2*Weight(1)*(X(end,4)-0);
            p5T=2*Weight(2)*(X(end,5)-0);
            p6T=2*Weight(3)*(X(end,6)-0);
            initp = [0 0 0 p4T p5T p6T];
            [Tp,P] = ode45(@(t,p) costateEq_3D_log(n,t,p,u1,u2,u3,.......
            Tu,x1,x2,x3,x4,x5,x6,Tx,alpha, beta, gamma, delta, eta,......
            Weight, Kb1, Kb2, Kb3, time_factor), [tf t0], initp, options)
            p1 = P(:,1);
            p2 = P(:,2);
            p3 = P(:,3);
            p4 = P(:,4);
            p1 = interp1(Tp,p1,Tx);
            p2 = interp1(Tp,p2,Tx);
            p3 = interp1(Tp,p3,Tx);
            h=1;
            dH1 = pH_3D(h,x1,x2,x3,p1,p2,p3,Tx,u1,u2,u3,Tu,alpha,
            beta, gamma, delta, eta, Weight, time_factor);
            h=2;
```

```
                dH2 = pH_3D(h,x1,x2,x3,p1,p2,p3,Tx,u1,u2,u3,Tu,alpha,
                beta, gamma, delta, eta, Weight, time_factor);
                h=3;
                dH3 = pH_3D(h,x1,x2,x3,p1,p2,p3,Tx,u1,u2,u3,Tu,alpha,
                beta, gamma, delta, eta, Weight, time_factor);

                J(i,1) = Weight(1)*((X(end,4)-0)^2)+ Weight(2)*((X(end,5)-0)^2)
                + Weight(3)*((X(end,6)-0)^2)
                if J(i,1)< J_old
                     true=1;
                 end
        end
   else
       step=step*0.5;
           u_old1 = u1;
           u1 = AdjControl_3D(dH1,Tx,u_old1,Tu,step,c);
           u_old2 = u2;
           u2 = AdjControl_3D(dH2,Tx,u_old2,Tu,step,c);
           u_old3 = u3;
           u3 = AdjControl_3D(dH3,Tx,u_old3,Tu,step,c);
   end
   J_old=J(end,1);

end

if i == max_iteration
    disp('Stopped before required residual is obtained.');
end
highest_iteration=i;

%%
%-----------plotting the results----------

figure(7)
```

```
%subplot(3,3,1)
grid on
hold on
plot(Tx(:,1), X(:,1) ,'g-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B1(t)');
xlabel('time(days)','fontsize',12);
ylabel('B1','fontsize',12);

figure(8)
%subplot(3,3,2)
grid on
hold on
plot(Tx(:,1), X(:,4) ,'b-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G1(t)');
xlabel('time(days)','fontsize',12);
ylabel('G1','fontsize',12);
hold on;

figure(9)
%subplot(3,3,3)
grid on
hold on
plot(Tu,u1,'-^','MarkerSize',4,'MarkerEdgeColor','red',...
'MarkerFaceColor','red');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('u1*');
xlabel('time(days)','fontsize',12);
ylabel('Optimal control u1*','fontsize',12);
%ylim([-1 11]);
```

```
figure(10)
%subplot(3,3,4)
grid on
hold on
plot(Tx(:,1), X(:,2) ,'g-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B2(t)');
xlabel('time','fontsize',12);
ylabel('B2','fontsize',12);

figure(11)
%subplot(3,3,5)
grid on
hold on
plot(Tx(:,1), X(:,5) ,'b-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G2(t)');
xlabel('time(days)','fontsize',12);
ylabel('G2','fontsize',12);
hold on;

figure(12)
%subplot(3,3,6)
grid on
hold on
plot(Tu,u2,'-^','MarkerSize',4,'MarkerEdgeColor','red',....
'MarkerFaceColor','red');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('u2*');
xlabel('time(days)','fontsize',12);
```

```
ylabel('Optimal control u2*','fontsize',12);


figure(13)
%subplot(3,3,7)
grid on
hold on
plot(Tx(:,1), X(:,3) ,'g-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B3(t)');
xlabel('time(days)','fontsize',12);
ylabel('B3','fontsize',12);

figure(14)
%subplot(3,3,8)
grid on
hold on
plot(Tx(:,1), X(:,6) ,'b-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G3(t)');
xlabel('time(days)','fontsize',12);
ylabel('G3','fontsize',12);
hold on;

figure(15)
%subplot(3,3,9)
grid on
hold on
plot(Tu,u3,'-^','MarkerSize',4,'MarkerEdgeColor','red',...
'MarkerFaceColor','red');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
```

```
legend('u3*');
xlabel('time(days)','fontsize',12);
ylabel('Optimal control u2*','fontsize',12);


figure(16);
grid on
hold on
iteration=[1:1:highest_iteration]
plot(iteration,J, '-^','MarkerSize',6,'MarkerEdgeColor','red',...
'MarkerFaceColor','red');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
xlabel('Iteration number','fontsize',12);
ylabel('J(u)= Sum of [Weight(i)*(Gi(T)-Gid)^2]','fontsize',12);
legend('J(u)= Sum of [Weight(i)*(Gi(T)-Gid)^2]');
f=J(1,1);
st=(f/1.1);
s = strcat('Final cost is: J=',num2str(J(end,1)));
text(1,f,s,'fontsize',22);

%%
%-----------------------------State at post treatment period---------
if flag == 1
 initx_later= [X(end,1) X(end,2) X(end,3) X(end,4) X(end,5) X(end,6)];
 U1=zeros(1,t_segment);
 U2=zeros(1,t_segment);
 U3=zeros(1,t_segment);
 T0=tf;
 Tf=tf+tf;
 %Tl = linspace(T0, Tf, 10)    % discretize time
 Tl = linspace(T0, Tf, t_segment)    % discretize time
[Tx1,X1] = ode45(@(t,x) stateEq_3D_log(n,t,x,U1,U2,U3,Tl,alpha,....
 beta, gamma, delta, eta, Weight, Kb1, Kb2, Kb3, Kg1, Kg2, Kg3,....
```

```
 time_factor), [T0 Tf], initx_later, options)
end

figure(17);
%subplot(3,2,1)
grid on
hold on
TXW=[Tx; Tx1];
XW=[X; X1];
plot(TXW(:,1), XW(:,1),'g-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
%%plot(TXW(:,1), XW(:,1) ,'.','MarkerSize',0.5,'MarkerEdgeColor',...
'red','MarkerFaceColor','red');
legend('B1(t)');
xlabel('time(days)','fontsize',12);
ylabel('B1','fontsize',12);

figure(18);
%subplot(3,2,2)
grid on
hold on
%plot(Tx(:,1), x4 ,'b-');
plot(TXW(:,1), XW(:,4) ,'b-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G1(t)');
xlabel('time(days)','fontsize',12);
ylabel(' G1','fontsize',12);
hold on;

figure(19);
%subplot(3,2,3)
grid on
```

```
hold on
%plot(Tx(:,1), x2 ,'g-');
plot(TXW(:,1), XW(:,2),'g-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B2(t)');
xlabel('time(days)','fontsize',12);
ylabel('B2','fontsize',12);

figure(20);
%subplot(3,2,4)
grid on
hold on
%plot(Tx(:,1), x4 ,'b-');
plot(TXW(:,1), XW(:,5) ,'b-');
set(gca,'FontSize',17);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G2(t)');
xlabel('time(days)','fontsize',12);
ylabel(' G2','fontsize',12);
hold on;

figure(21);
%subplot(3,2,5)
grid on
hold on
%plot(Tx(:,1), x3 ,'g-');
plot(TXW(:,1), XW(:,3) ,'g-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('B3(t)');
xlabel('time(days)','fontsize',12);
ylabel('B3','fontsize',12);
hold on;
```

```
figure(22);
%subplot(3,2,6)
grid on
hold on
%plot(Tx(:,1), x4 ,'b-');
plot(TXW(:,1), XW(:,6), 'b-');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
legend('G3(t)');
xlabel('time(days)','fontsize',12);
ylabel('G3','fontsize',12);
hold on;

figure(23);
grid on
hold on
iteration=[1:1:highest_iteration]
plot(iteration,J,'-^','MarkerSize',6,'MarkerEdgeColor','red',...
'MarkerFaceColor','red');
set(gca,'FontSize',12);
set(findall(gca, 'Type', 'Line'),'LineWidth',2);
xlabel('Iteration number','fontsize',12);
ylabel('Cost Function','fontsize',12);
legend('J(u)= Weight1*(G1(T)-Gd1)^2 + Weight2*(G2(T)-Gd2)^2 ');
f=J(1,1);
st=(f/1.1);
s = strcat('Final cost is: J=',num2str(J(end,1)));
text(1,f,s,'fontsize',22);

%----------- function for state equation---------------------
% State equations
function dx = stateEq_3D_log(n,t,x,u1,u2,u3,Tu, alpha, beta, gamma,
delta, eta, Weight, Kb1, Kb2, Kb3, Kg1, Kg2, Kg3, time_factor)
```

```
B1=x(1);
B2=x(2);
B3=x(3);
G1=x(4);
G2=x(5);
G3=x(6);
dx = zeros(2*n,1);

u1 = interp1(Tu,u1,t); % Interploate the control at time t
u2 = interp1(Tu,u2,t); % Interploate the control at time t
u3 = interp1(Tu,u3,t); % Interploate the control at time t

dx(1) = time_factor*(alpha(1,1)*B1 - alpha(1,1)*(B1^2)/Kb1  +
        beta(1,1)*B1*G1 + beta(1,2)*B1*G2 + beta(1,3)*B1*G3 +
        (gamma(1,1)*B1).*u1+ (gamma(1,2)*B1).*u2 + (gamma(1,3)*B1).*u3);

dx(2) = time_factor*(alpha(2,1)*B2 - alpha(2,1)*(B2^2)/Kb2 +
        beta(2,1)*B2*G1 + beta(2,2)*B2*G2 + beta(2,3)*B2*G3 +
        (gamma(2,1)*B2).*u1+ (gamma(2,2)*B2).*u2 + (gamma(2,3)*B2).*u3);

dx(3) = time_factor*(alpha(3,1)*B3 - alpha(3,1)*(B3^2)/Kb3 +
        beta(3,1)*B3*G1 + beta(3,2)*B3*G2 + beta(3,3)*B3*G3 +
        (gamma(3,1)*B3).*u1+ (gamma(3,2)*B3).*u2 + (gamma(3,3)*B3).*u3);

dx(4) = time_factor*(delta(1,1)*G1 + eta(1,1)*B1*G1 +
        eta(1,2)*B2*G1 + eta(1,3)*B3*G1);

dx(5) = time_factor*(delta(2,1)*G2 + eta(2,1)*B1*G2 +
        eta(2,2)*B2*G2 + eta(2,3)*B3*G2);

dx(6) = time_factor*(delta(3,1)*G3 + eta(3,1)*B1*G3 +
        eta(3,2)*B2*G3 + eta(3,3)*B3*G3);

%---------- function for Costate equation--------------------
% Costate equations
```

```
function dp = costateEq_3D_log(n,t,p,u1,u2,u3,Tu,x1,x2,x3,x4,x5,x6,xt,alpha,
              beta, gamma, delta, eta, Weight, Kb1, Kb2, Kb3, time_factor)

dp = zeros(2*n,1);

x1 = interp1(xt,x1,t);   % Interploate the state varialbes
x2 = interp1(xt,x2,t);
x3 = interp1(xt,x3,t);   % Interploate the state varialbes
x4 = interp1(xt,x4,t);
x5 = interp1(xt,x5,t);   % Interploate the state varialbes
x6 = interp1(xt,x6,t);
u1 = interp1(Tu,u1,t);     % Interploate the control
u2 = interp1(Tu,u2,t);     % Interploate the control
u3 = interp1(Tu,u3,t);     % Interploate the control

B1=x1;
B2=x2;
B3=x3;
G1=x4;
G2=x5;
G3=x6;

dp(1)= time_factor*(-( p(1).*(alpha(1,1) - 2*alpha(1,1)*B1/Kb1 +
       beta(1,1)*G1 + beta(1,2)*G2 + beta(1,3)*G3 + gamma(1,1).*u1+
       gamma(1,2).*u2 + gamma(1,3).*u3) + p(4).*(eta(1,1)*G1) +
       p(5).*(eta(2,1)*G2) + p(6).*(eta(3,1)*G3) ));

dp(2)= time_factor*(-( p(2).*(alpha(2,1) - 2*alpha(2,1)*B2/Kb2 +
       beta(2,1)*G1 + beta(2,2)*G2 + beta(2,3)*G3 + gamma(2,1).*u1+
       gamma(2,2).*u2 + gamma(2,3).*u3) + p(4).*(eta(1,2)*G1) +
       p(5).*(eta(2,2)*G2) + p(6).*(eta(3,2)*G3) ));

dp(3)= time_factor*(-( p(3).*(alpha(3,1) - 2*alpha(3,1)*B3/Kb3 +
       beta(3,1)*G1 + beta(3,2)*G2 + beta(3,3)*G3 + gamma(3,1).*u1+
```

```
        gamma(3,2).*u2 + gamma(3,3).*u3) + p(4).*(eta(1,3)*G1) +
        p(5).*(eta(2,3)*G2) + p(6).*(eta(3,3)*G3) ));

dp(4)= time_factor*(-( p(1).*(beta(1,1)*B1) +  p(2).*(beta(2,1)*B2) +
        p(3).*(beta(3,1)*B3) + p(4).*(delta(1,1) + eta(1,1)*B1 +
        eta(1,2)*B2 + eta(1,3)*B3 )));

dp(5)= time_factor*(-( p(1).*(beta(1,2)*B1) +  p(2).*(beta(2,2)*B2) +
        p(3).*(beta(3,2)*B3) + p(5).*(delta(2,1) + eta(2,1)*B1 +
        eta(2,2)*B2 + eta(2,3)*B3 )));

dp(6)= time_factor*(-( p(1).*(beta(1,3)*B1) +  p(2).*(beta(2,3)*B2) +
        p(3).*(beta(3,3)*B3) + p(6).*(delta(3,1) + eta(3,1)*B1 +
        eta(3,2)*B2 + eta(3,3)*B3 )));


%----------- function for gradient value---------------------
% Partial derivative of H with respect to u
 function dH = pH_3D(h,x1,x2,x3,p1,p2,p3,tx,u1,u2,u3,Tu,alpha, beta, gamma,
                delta, eta, Weight, time_factor)
B1=x1;
B2=x2;
B3=x3;

% interploate the control
u1 = interp1(Tu,u1,tx);
u2 = interp1(Tu,u2,tx);
u3 = interp1(Tu,u3,tx);

if h==1
    dH = ( p1.* (gamma(1,1)*B1) + p2.* (gamma(2,1)*B2) +
          p3.* (gamma(3,1)*B3) )*(time_factor);
elseif h==2
    dH = ( p1.* (gamma(1,2)*B1) + p2.* (gamma(2,2)*B2) +
          p3.* (gamma(3,2)*B3) )*(time_factor);
```

```
else
    dH = ( p1.* (gamma(1,3)*B1) + p2.* (gamma(2,3)*B2) +
          p3.* (gamma(3,3)*B3) )*(time_factor);
end

%----------- function for updating control---------------------
function u_new = AdjControl_3D(pH,tx,u,tu,step,c)
pH = interp1(tx,pH,tu);
u_new = u - step*pH;
u_new (u_new >c )=c;
u_new (u_new <0 )=0;
```

In order to develop the code for different dimensional system, one should have to change the size of each vector (parameters, control variables, state and co-state variables, gradient vectors) and modify the functions of state and costate equations according to the system. For successful smooth iteration several trials with different step sizes are necessary while running the algorithm.

A.2 Command Window Script

All the parameters value can also be manipulated from the command line. Here's an example:

```
disp('Enter all the values one by one')

n=input('Enter number of antigens or antibodies: ')

enter initial guess:
initx = [0.014 0.014 0.014 1.015 1.015 1.015]

elements alpha:
alpha=[1e-3; 1e-3; 1e-3]

elements carrying capacity:
```

```
K=[50; 50; 50]

elements beta:
beta=[-1.5 0 0;0 -1.5 0; 0 0 -1.5]

elements gamma:
gamma=[1 0.01 0.0001; 0 1 0; 0 0 1.5]

elements delta:
delta=[0.22; 0.22; 0.22]

elements eta:
eta=[-2 0 0; 0 -2 0; 0 0 -2]
```

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