Some Systems of Ordinary Differential Equations from Cancer Modeling: Qualitative Analysis and Optimal Treatment

by

Xiang Wan

A thesis submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Master of Science

Auburn, Alabama
Aug 6, 2011

Keywords: cancer model, immunotherapy, radiotherapy, chemotherapy, bang-bang

Approved by

Georg Hetzer, Chair, Professor of Mathematics
Wenxian Shen, Professor of Mathematics
Xiaoying Han, Assistant Professor of Mathematics

Abstract

In this thesis, we study four systems of ordinary differential equations, which model the interrelationships between different cell populations while tumor cells exist, and treatments, such as immunotherapy, chemotherapy, and radiotherapy, are applied.

For the first two models, we only consider the case with radiation treatment. For the first model, we consider a single general cell population with its corresponding radiated cell population. Meanwhile, two different kinds of radiation are studies separately: constant and decay; for the second model, we consider the host and tumor cell populations together with their corresponding radiated cell populations, which behave in the same way as that in the first model.

For the third and fourth models, we consider both the immunotherapy and chemotherapy. The third model includes three cell populations: host cells, tumor cells, and immune cells, as well as the drug concentration. We study the properties of its null-surfaces, equilibria, and the stability of them; in the fourth model, we not only extend the previous model into one with six populations, with the immune cells in the third model being specified into three different ones: $CD8^{+}T$ cells, circulating lymphocytes, and IL-2. but also focus on the situation when controls are added in a linear manner. We investigate the existence of controls and find the characterization of optimal bang-bang control.

Acknowledgments

This thesis would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study.

First and foremost, my greatest thanks extend to Dr. Georg Hetzer for his patience and guidance throughout this endeavor at Auburn University. I got lots of advisable suggestions from him back to the time when I applied to this department, and Dr. Hetzer took considerable time and energy to further the progress in my studies of Mathematics. I will never forget the sincerity and encouragement that he showed to me.

I would also like to thank Dr. Wenxian Shen on the committee, who is such a great teacher of mine for many courses. I have been learning so much from her. I am also thankful for the excellent example she has provided as a successful professor and a good person. My sincere thanks also go to Dr. Xiaoying Han for serving as the committee members.

I wish to express my greatest appreciation for my parents, my sister, and her lovely daughter, who have given their love and constant support throughout my life. Thanks for always being with me.

I offer my regards and blessings to all other people who supported me in any respect during the completion of the project.

Table of Contents

Chapter 1

Introduction

Cancer has been known as a deadly disease of mankind from prehistoric time, and research into cancer tumor treatment began only recently from a historic point of view [15]. The growth of cancerous tumor is a complicated process involving multiple biological interactions. Also, the response of tumors to active treatments such as chemotherapy and radiotherapy is complex, but important to understand. A tumor's response to treatment depends on many factors, including the severity of the disease, the application of the treatment, and the strength of patient's own immune response. Mathematical modeling of this process is viewed as a potentially powerful tool in the development of improved treatment regimens. The mathematical modeling of tumor growth and treatment has been approached by a number of researchers using a variety of models over the past decades [33].

The main types of cancer treatments involve surgery, chemotherapy, radiotherapy, and immunotherapy, either in isolation, or in combination of two or more of these. A given specific type of cancer will have a preferred treatment depending on, among other things, where the cancer is located and its stage of development. We introduce three therapies that are widely used in practice in the following context: Radiotherapy, Chemotherapy, and Immunotherapy.

- **Radiotherapy**

  Radiotherapy is a treatment procedure that uses radiation to kill malignant tumor cells. This treatment targets rapidly growing and dividing cells such as those in cancer[1]. Radiation destroys cells by causing one or more chromosomes to break. When this happens, the cells cannot reproduce and eventually die off [2] [3] [4]. Hence the question of

persistence or extinction of a community of cells exposed to radiation is of paramount interest. Moreover, it is sometimes possible for the broken chromosomes to recombine. This may lead to the original configuration of the chromosomes, it may lead to mutation, or the recombination may be completely ineffective [4] [5]. Here we view the first of these possibilities as a probability of broken cells becoming whole again. Finally, the radiation protocol may be one of two modes: constant dosage, which is similar to the case of long term radiation after a nuclear accident; decaying radiation, such as radioactive material implanted to fight lung cancer [6].

- **Chemotherapy**

  Another of the most common and fundamental forms of treatment is chemotherapy, which involves injecting into the body a type of drug designed to attack the cancer cells. This type of drug also attacks normal (host) cells causing common side effects such as hair loss (Radiotherapy has the same side effects sometimes). Much research into chemotherapy is involved with designing the drug so as to maximize the effect on cancer and minimize the side effects [7]. Therefore, when developing effective treatment strategies, understanding the effects of chemotherapeutic drugs on tumors is of primary importance. Several approaches to modeling chemotherapeutic induced cell-kill (killing of tumor cells) have been developed. One of the early approaches was by citeskipper1964experimental, which propose that cell-kill due to a chemotherapeutic drug was proportional to the tumor population. This hypothesis is based on in vitro studies in the murine leukemia cell-line L1210. It states that for a fixed dose, the reduction of large tumors occurred more rapidly than for smaller tumors. The concept in [8] is referred to as the log-kill mechanism. [9] [10] find this model to be inconsistent with clinical observations of Hodgkin's disease and acute lymphoblastic leukemia which showed that, in some cases, reduction in large tumors was slower than in histologically similar smaller tumors. Therefore, [9] [10] hypothesize that the cell-kill is proportional

to the growth rate (e.g., exponential, logistic, or Gompertz) of the tumor. A third hypothesis notes that some chemotherapeutic drugs must be metabolized by an enzyme before being activated. This reaction is saturable due to the fixed amount of enzyme. Thus, [11] develops the Emax model which describes cell-kill in terms of a saturable function of Michaelis-Menton form.

- **Immunotherapy**

  Meanwhile, immunotherapy refers to the use of natural and synthetic substances to stimulate the immune response. This involves stimulating the immune system to work harder or using an outside source of cells, such as synthesized immune system proteins. Immunological therapies include the use of antigen and non-antigen specific agents such as cytokines. Cytokines are hormones produced in the immune system that regulate the growth and activity of other immune system cells and blood cells. Cytokines alone can give the immune system a boost or given with other immunotherapies they can be used as adjuvants [12]. Cytokines have been used to treat melanoma, leukemia, lymphoma, neuroblastoma, Kaposis sarcoma, mesothelioma, brain cancer, cancer of the kidney, and cancer of the cervix. It is therefore important that we begin to develop mathematical models of tumor growth that include an immune system response, and ultimately a response to immunotherapy.

  Interleukin-2 (IL-2) is a cytokine that was approved by the FDA in 1992 for treatment of metastatic renal cell (kidney) cancer. IL-2 became the first cytokine approved for use alone in treating advanced cancer [21]. Since that time, it has also been approved to treat people with metastatic melanoma. IL-2 can be used as a single-drug treatment for these cancers, or it may be combined with other forms of immunotherapy, such as vaccines. IL-2 helps immune system cells reproduce more rapidly once they are in the patient. The use of IL-2 together with chemotherapy or with other cytokines (such as

interferon-alpha) may increase their effectiveness against some cancers, but the side effects of the combined treatment are also increased [34].

- **Optimal Control**

  Once an adequate model of interacting cell populations is constructed, we focus on the design of an improved treatment protocol. To this end, we employ the tools of optimal control theory. This theory originated in economics, where it was used to optimize cost or profit. It was subsequently applied to engineering problems and finally to biological models [21]. The goal of different therapies is to destroy the tumor cells, while maintaining adequate amounts of healthy tissue. From a mathematical point of view, adequate destruction of tumor cells might mean forcing the system out of the basin of an unhealthy spiral node, or out of a limit cycle, and into the basin of attraction of a stable, tumor-free equilibrium. Alternatively, if the therapy pushes the system into a limit cycle in which the size of the tumor is small for a long period of time (as long as the life of the patient, for example), this could also be considered as 'cure' [20].

  Optimality in treatment might be defined in a variety of ways. The general goal is to keep the patient healthy while killing the tumor. In this thesis, we choose to minimize the tumor population, while constraining the normal cells to stay above some minimal level. Therefore, the development of therapies protocol can be phrased as an optimal control problem with constraints: for a fixed time interval, find the points within that interval at which the drug should be administered so that the number of tumor cells has been minimized, while the number of healthy cells has been kept above a prescribed threshold [20].

There have been many models, which tried to focus on simulating single or multiple important elements of the multifaceted process of tumor growth and response to therapy, with or without considering the optimal control. Based on these studies, people are trying

to design or improve treatment protocol by employing the tools of optimal control theory. See [13], [14], [15], [1] [16] [17].

This thesis is based on the models developed in [18] [19] [20] [21]. We build four different systems by stating the biological behaviors of each population, specifying most of the functional terms of them, and summarizing the mathematical form of these systems. We analyze the qualitative properties of them, especially for the fourth one, to which we consider the existence and characterization of the optimal bang-bang control.

The main mathematical tools that we employ here are from Ordinary Differential Equations (ODE) and Optimal Control Theory. The organization of this thesis is as follows: We first give a wide range of background, including some fundamental definitions and important theorems from ODE. Afterward, we formulate the four systems of ordinary differential equations. Next, we investigate the qualitative details of these systems one by one, where we frequently use the theorems we stated before. In the end, we give two appendices, one of which gives the definitions and theorems concerning the One-point Compactification, the other of which contains a brief summary of the optimal control theory, including the problem, formulation, hypothesis, and solution outline.

Chapter 2

Background and Preliminary Knowledge

Definition 2.1. *(Hyperspace topology [22]) Suppose that X is a topological space. Then the hyperspace of X, denoted by 2^X, is the space of compact subsets of X. Suppose that $U_1, \cdots, U_n$ is a finite collection of open subset of X, then*

$$R(U_1, \cdots, U_n) = \{K \in 2^X | K \subset \cup_{i=1}^n U_i \text{ and for all } 1 \leq i \leq n, k \cap U_i \neq \emptyset\}$$

is a basic open set for the hyperspace topology.

Theorem 2.2. *[22] If X is compact, so is 2^X.*

Theorem 2.3. *[22] If X is a metric space with the bounded metric d, then the associated Hausdorff metric generated the topology of 2^X.*

Definition 2.4. *(Asymptotically autonomous process with limit semiflow [23]) Assume (X, d) is a metric space, $t_0 \in \mathbb{R}$, and $\Delta = \{(t, s) | t_0 \leq s \leq t < \infty\}$. A continuous mapping $\Phi : \Delta \times X \to X$ is called a nonautonomous process if it satisfies:*

(i) $\Phi(s, s, x) = x, s \geq t_0$.

(ii) $\Phi(t, s, \Phi(s, r, x)) = \Phi(t, r, x), t \geq s \geq r \geq t_0$.

The process is called autonomous if, additionally,

(iii) $\Phi(t + r, s + r, x) = \Phi(t, s, r), t \geq s \geq t_0, r > 0$.

In this case, we set $\Theta(t, x) = \Phi(t + t_0, t_0, x)$, and call Θ an autonomous semiflow.

Moreover, the nonautonomous process Φ is called asymptotically autonomous with limit semiflow Θ, if Θ is an autonomous semiflow on X, and

$$\Phi(t_i + s_i, s_i, x_i) \to \Theta(t, x) \text{ as } i \to \infty \text{ in the metric space } X$$

for any sequences $t_i \to t, s_i \to \infty, x_i \to x$.

Definition 2.5. *(Chain Recurrent [23]) Let X and Θ be as in definition 2.4, $A \subseteq X$ be a nonempty positively invariant set under Θ, and $x, y \in A$. For $\varepsilon > 0, t > 0$, an (ε, t)-chain from x to y (in A) is a sequence $\{x = x_1, x_2, \ldots, x_{n+1} = y; t_1, t_2, \ldots, t_n\}$ of points x_i in A and time $t_i > t$ such that dist$(\Theta(t_i, x_i), x_{i+1}) < \varepsilon, i = 1, 2, \ldots, n$. A point $x \in A$ is called chain recurrent in A if for every $\varepsilon > 0, t > 0$, there exists an (ε, t)-chain from x to x in A. The set A is said to be chain recurrent if every point in A is chain recurrent in A.*

Remark 2.6. *We are interested in the case that A is compact, connected, and invariant.*

Definition 2.7. *(ω-limit set [23] [24]) If Phi is a nonautonomous semiflow on X and $(s, x) \in [t_0, \infty) \times X$, then the forward orbit of Φ through (s, x) is defined to be*

$$\mathcal{O}_\Phi(s, x) = \{\Phi(t, s, x) : t \geq s\} \subset X.$$

If $\mathcal{O}_\Phi(s, x)$ has compact closure in X, then the ω-limit set of (s, x) (or of $\mathcal{O}_\Phi(s, x)$) is defined by

$$\omega_\Phi(s, x) = \bigcap_{\tau \geq s} \overline{\{\Phi(t, s, x) : t \geq \tau\}},$$

where, for a subset A of X, $\overline{A}$ denotes the closure of A in X. In other words, $y \in \omega_\Phi(s, x)$ if there is a sequence $t_j \to \infty, t_j > s$, such that $\Phi(t_j, s, x) \to y, j \to \infty$.

In the case of an autonomous semiflow Θ, the ω-limit set is independent of s and hence we denote it by $\omega_\Theta(x)$:

$$\omega_\Theta(x) = \bigcap_{\tau \geq 0} \overline{\{\Theta(t, x) : t \geq \tau\}}.$$

An equivalent definition for ω-limit set for an autonomous semiflow is as follows: suppose that ϕ_t is a autonomous semiflow on $\mathbb{R}^n$ and $p \in \mathbb{R}^n$. A point x in $\mathbb{R}^n$ is called an ω-limit point of the orbit through p if there is a sequence of numbers $t_1 \leq t_2 \leq t_3 \leq \cdots$ such that $t_i \to \infty$ and $\lim_{i\to\infty} \phi_{t_i}(p) = x$. The collection of all such ω-limit points is called the ω-limit set of p.

Lemma 2.8. *[25] Suppose $\{f_n\}, n = 1, 2, \ldots,$ is a sequence of functions defined and continuous on an open set $D \subset \mathbb{R}^{n+1}$ with $\lim_{n\to\infty} f_n = f_0$ uniformly on compact subsets of D. Suppose (t_n, x_n) is a sequence of points in D convergent to $(t_0, x_0) \in D$ as $n \to \infty$, and let $\phi_n(t), n = 0, 1, \ldots,$ be a solution of the equation $\dot{x} = f_n(t, x)$ passing through the point (t_n, x_n). If $\phi_0(t)$ is defined on $[a, b]$ and is unique, then there is an integer n_0 such that each $\phi_n(t), n \geq n_0$ can be defined on $[a, b]$ and converges to $\phi_0(t)$ uniformly on $[a, b]$.*

Proof. Please refer to [25] for the detailed proof. □

Definition 2.9. *Again, (X, d) is a metric space, and $t_0 \in \mathbb{R}$. Consider the following systems*

$$\dot{x} = f(t, x) \tag{2.1}$$

$$\dot{y} = g(y) \tag{2.2}$$

where $x, y \in \mathbb{R}^n, f : \mathbb{R}^+ \times \mathbb{R}^n \to \mathbb{R}^n$ and $g : \mathbb{R}^n \to \mathbb{R}^n$ are continuous vector functions. Assume the initial value problems for each system have unique solutions defined for all future time after the initial time.

Define $\Phi = \Phi(t, s, x_0)$ to be the solution of system (2.1) with the initial value being $x(s) = x_0$, and $\Theta = \Theta(t, x_0)$ to be the solution of system (2.2) with the initial value being $y(0) = x_0$.

Proposition 2.10. *We use the same assumptions and notations as in the definition 2.9. Then Φ is asymptotically autonomous with limit semiflow Θ if one of the two following conditions is satisfied:*

$(A) : f(t,x) \to g(x)$ *as* $t \to \infty$ *uniformly on compact subsets of* $\mathbb{R}^n$.

(B) : g *is locally Lipschitz, and, for each compact subset* $K \subset \mathbb{R}^n$, *there is a function* $\mu_K : [0,\infty) \to [0,\infty)$ *satisfying* $\mu_K(t) \to 0$ *as* $t \to \infty$ *and*

$$\left| \int_t^{t+\sigma} [f(s,x) - g(x)] ds \right| \leq \mu_K(t)$$

for every $(x,\sigma) \in K \times [0,1]$ *and* $t > 0$.

Proof. By definition, we want to show $\Phi(t_j + s_j, s_j, x_j) \to \Theta(t,x)$ as $j \to \infty$ for any three sequences $t_j \to t, s_j \to \infty, x_j \to x$ as $j \to \infty$.

(A) : Let $T > 0$ be such that $t_j < T, j \geq 0$. Then observe that $\Phi(t + s_j, s_j, x_j)$ is the solution of $\dot{x} = f(t + s_j, x)$ with $x(0) = x_j$. Also, since $f(t,x) \to g(x)$ as $t \to \infty$ uniformly on compact subsets of $\mathbb{R}^{n+1}$, by lemma 2.8, $\Phi(t + s_j, s_j, x_j) \to \Theta(t,x)$ as $j \to \infty$ uniformly on $[0,T]$. Therefore,

$$\Phi(t_j + s_j, s_j, x_j) \to \Theta(t,x) \text{ as } j \to \infty.$$

(B) : Since $\Theta(t, x_j) \to \Theta(t,x)$ as $j \to \infty$ uniformly on $[0,T]$ (since $[0,T]$ is compact), there exists a $K \subset \mathbb{R}^n$ and $\varepsilon > 0$ such that K is compact and

$$\bigcup_{\substack{t \in [0,T] \\ j \geq 0}} \{y : |y - \Theta(t, x_j)| < \varepsilon\} \subset K.$$

Since g is locally Lipschitz on K, let L be the associated Lipschitz constant, and choose $\delta > 0$ such that $\delta e^{LT} < \varepsilon$. Then by our assumption, there exists a function $\mu_K(T)$ on $[0,\infty)$ satisfying $\mu_K(t) \to 0$ as $t \to \infty$ and

$$\left| \int_t^{t+\sigma} [f(s,x) - g(x)] ds \right| \leq \mu_K(t)$$

for $x \in K$ and $\sigma \in [0,T]$. Since $\mu_K(t) \to 0$, choose $S > 0$ such that $\mu_K(s) < \delta$ for $s > S$. Denote $u_j = \Phi(t + s_j, s_j, x_j), v_j(t) = \Theta(t, x_j)$. Then

$$\begin{aligned} |u_j(t) - v_j(t)| &= \left| \left[\int_0^t f(\tau + s_j, u_j(\tau))\, d\tau + x_j \right] - \left[\int_0^t g(v_j(\tau))\, d\tau + x_j \right] \right| \\ &\leq \left| \int_{s_j}^{s_j+t} [f(\tau, u_j(\tau - s_j)) - g(v_j(\tau - s_j))]\, d\tau \right| \\ &\quad + \int_0^t |g(u_j(\tau)) - g(v_j(\tau))|\, d\tau \\ &\leq \mu_K(s_j) + L \int_0^t |u_j(\tau) - v_j(\tau)|\, d\tau. \end{aligned}$$

By the Gronwall's inequality,

$$|u_j(t) - v_j(t)| \leq \mu_k(s_j) e^{Lt} \leq \delta e^{LT} \leq \varepsilon$$

for $0 \leq t \leq T$. By the definition of K, it follows that $u_j(t) \in K$ for all $T \in [0,T]$ if $s_j > S$ and $u_j \to u, j \to \infty$ uniformly. As in part (A), we finish the proof. □

Lemma 2.11. *We use the same assumptions and notations as in the definition 2.5. Assume A is connected and chain recurrent with Θ representing the associated autonomous semiflow. Then for any $x, y \in A, \varepsilon > 0, T > 0$, there exists a (ε, T)-chain from x to y.*

Proof. Let $\delta = \dfrac{\varepsilon}{3}$. Since A is connected, there exists $a_1, \cdots, a_n \in A$ with $x = a_1, y = a_n$, and

$$d(a_i, a_{i+1}) < \delta, \quad , i = 1, \cdots, n-1.$$

Now, since A is chain recurrent, for each $1 \leq i \leq n$, there exist a (δ, T)-chain from a_i to a_i:

$$\{a_i = b_{i_1}, \cdots, b_{i_n} = a_i; t_{i_1}, \cdots, t_{i_{n-1}}\}, b_j \in A, t_j \geq T.$$

To get a chain from x to y, we can 'connect' these chains together, namely, we get a new sequence

$$\{x = a_1 = b_{1_1}, \cdots, b_{1_n}, b_{2_1}, \cdots, b_{n_n} = a_n = y; t_{1_1}, \cdots, t_{n_n-1}\}, b_{i_j} \in A, t_{i_j} \geq T.$$

To verify that this is a (ε, T)-chain, it suffices to check whether or not those points where the chain is connected in the above way satisfy the definition of (ε, T)-chain. For $1 \leq i \leq n-1$,

$$\begin{aligned} d(\Theta(t_{i_n}, b_{i_n}), b_{i+1_1}) &= d(\Theta(t_{i_n}, a_i), a_{i+1}) \\ &\leq d(\Theta(t_{i_n}, a_i), a_i) + d(a_i, a_{i+1}) \\ &< \delta + \delta \\ &< \varepsilon. \end{aligned}$$

□

Lemma 2.12. *We use the same assumptions and notations as in the definition 2.4, where Θ is an autonomous semiflow. Let $T > 0$ and $\mathcal{O}_\Theta^T(x) = \{\Theta(t, x) : t \geq T\}$. Given $y \in \omega_\Theta(x)$ and $\varepsilon > 0, t_0 > 0$. There exists a (ε, t_0)-chain*

$$\{y = y_1, \cdots, y_l, y_{l+1} = y; t_1, \cdots, t_l\}$$

such that $y_i \in \mathcal{O}_\Theta^T(x)$ for $i = 1, 2, \cdots, l$, $t_i = t_0$ for $i = 1, 2, \ldots, l-1$ and $t_0 \leq t_l < 2t_0$.

Proof. Since $y \in \omega_\Theta(x)$, there exists $\tau_n \to \infty$ such that $\Theta(\tau_n, x) \to y$ as $n \to \infty$. Choose $N > 0$ such that

$$d(\Theta(\tau_N + t, x), \Theta(t, y)) < \varepsilon \quad \text{for } t \in [0, t_0].$$

Similarly, we can choose $M > N > 0$ such that $\tau_M > \tau_N + 2t_0$ and $d(\Theta(\tau_M, x), y) < \epsilon$. Let l be such that $\tau_M - \tau_N = lt_0 + r$ for some $r \in [0, t_0)$.

Now let $y_1 = y, y_i = \Theta(\tau_N + (i-1)t_0, x)$ for $i = 2, \ldots, l$, $y_{l+1} = y$, $t_i = t_0$ for $i = 1, \ldots, l-1$, $t_l = t_0 + r$. We can check that $d(\Theta(t_1, y_1), y_2) = d(\Theta(\tau_N + t_0, x), \Theta(t_0, y)) < \varepsilon$, $d(\Theta(t_i, y_i), y_{i+1}) = 0$ for $i = 2, \ldots, l-1$, and

$$d(\Theta(t_l, y_l), y_{l+1}) = d(\Theta(\tau_N + lt_0 + r, x), y) = d(\Theta(\tau_M, x), t) < \varepsilon.$$

□

Proposition 2.13. *We use the same assumptions and notations as in the definition 2.5, where Θ is an autonomous semiflow, and suppose that $\mathcal{O}_\Theta(x) = \{\Theta(t, x) : t > 0\}$ has compact closure in X. Then $\omega_\Theta(x)$ has the following properties:*

(a) $\omega_\Theta(x)$ is nonempty, compact, and connected.

(b) $\omega_\Theta(x)$ is invariant.

(c) $\omega_\Theta(x)$ attracts $\Theta(t, x)$:

$$d_X(\Theta(t, x), \omega_\Theta(x)) \to 0, t \to \infty.$$

(d) $\omega_\Theta(x)$ is is chain recurrent.

Proof. (a), (b), and (c) are classical results. Check [24]

To prove (d), we need to show that for any $y \in \omega_\Theta(x)$, $\varepsilon > 0$, and $t_0 > 0$, there exists an (ε, t_0)-chain lying in $\omega_\Theta(x)$ which connects y to itself.

From lemma 2.12, for each $n \in \mathbb{N}$, there exists a $(\frac{1}{n}, t_0)$-chain:

$$\{y = y_1^n, \ldots, y_{l_n+1}^n = y; t_1^n, \ldots, t_{l_n}^n\}$$

with $y_i \in \mathcal{O}_\Theta^T(x)$ for $i = 1, \ldots, l_n + 1$. Furthermore, We denote the sets $\{y_i^n\}_{i=1}^{l_n+1}$ by Y^n.

First we notice that Y^n are all finite therefore compact and $Y^n \subset \overline{\mathcal{O}_\Theta^T(x)}$ which is also compact. Apple Theorem 2.2 and consider $\overline{\mathcal{O}_\Theta^T(x)}$ as the whole space, then, W.L.O.G.,

$Y^n \to \widetilde{Y}$ in the hyperspace topology with some $\widetilde{Y} \subset \overline{\mathcal{O}^T_\Theta(x)}$ being compact. (Otherwise we take a subsequence of Y^n.) Since $y \in Y^n$ for all n, then $y \in \widetilde{Y} \subset \omega_\Theta(x)$. Next, we will construct our chain by points from $\widetilde{Y}$.

Since $\widetilde{Y}$ is compact, there exists a $\delta > 0$ such that if $\widetilde{y_1}, \widetilde{y_2} \in \widetilde{Y}$ and $d(\widetilde{y_1}, \widetilde{y_2}) < \delta$, then

$$d(\Theta(t, \widetilde{y_1}), \Theta(t, \widetilde{y_1})) < \frac{\varepsilon}{3} \text{ for } t \in [0, 2t_0].$$

Furthermore, let $N > 0$ be such that $\frac{1}{N} < \frac{\varepsilon}{3}$ and $D(Y^N, \widetilde{Y}) < \frac{\varepsilon}{3}$, where D is the Hausdorff metric. We finish the proof by carrying out the following steps.

1. Let $\widetilde{y_1} = y$, pick up $\widetilde{y_2} \in \widetilde{Y}$ such that $d(\widetilde{y_2}, y_2^N) < \delta$, and $t_1 = t_0$. Then

$$\begin{aligned} d(\Theta(t_0, \widetilde{y_1}), \widetilde{y_2}) &= d(\Theta(t_0, y_1^N), \widetilde{y_2}) \\ &< d(\Theta(t_0, y_1^N), y_2^N) + d(y_2^N, \widetilde{y_2}) \\ &< \frac{1}{N} + \delta < \varepsilon. \end{aligned}$$

   Also, since $d(\widetilde{y_2}, y_2^N) < \delta$, by how we chose δ, $d(\Theta(t_0, \widetilde{y_2}), \Theta(t_0, y_2^N)) < \frac{\varepsilon}{3}$.

2. Pick up $\widetilde{y_3} \in \widetilde{Y}$ such that $d(\widetilde{y_3}, y_3^N) < \delta$, and $t_2 = t_0$. Then

$$\begin{aligned} d(\Theta(t_0, \widetilde{y_2}), \widetilde{y_3}) &< d(\Theta(t_0, \widetilde{y_2}), \Theta(t_0, y_2^N)) + d(\Theta(t_0, y_2^N), y_3^N) + d(y_3^N, \widetilde{y_3}) \\ &< \frac{\varepsilon}{3} + \frac{1}{N} + \delta < \varepsilon. \end{aligned}$$

   Also, $d(\widetilde{y_3}, y_3^N) < \delta$ induces $d(\Theta(t_0, \widetilde{y_3}), \Theta(t_0, y_3^N)) < \frac{\varepsilon}{3}$.

$\vdots$

(l^N). Set $\widetilde{y}_{l^N+1} = y$ and $t_{l^N} \in [t_0, 2t_0)$, we have

$$\begin{aligned} d(\Theta(t_{l^N}, \widetilde{y_{l^N}}), \widetilde{y}_{l^N+1}) &< d(\Theta(t_{l^N}, \widetilde{y_{l^N}}), \Theta(t_{l^N}, y_{l^N}^N)) + d(\Theta(t_{l^N}, y_{l^N}^N), y_{l^N+1}^N) \\ &< \frac{\varepsilon}{3} + \frac{1}{N} < \varepsilon. \end{aligned}$$

Therefore, $\{y = \widetilde{y}_1, \ldots, \widetilde{y}_{l^N+1}; t_1, \ldots, t_{l^N}\}$ is the desired chain.

□

Remark 2.14. *If Φ is a nonautonomous process but asymptotically autonomous with limit semiflow Θ, then Φ and Θ can be embedded in a single autonomous semiflow Ψ on a larger metric space $Z = [t_0, \infty] \times X$, where $[t_0, \infty]$ is the one-point compactification of $[t_0, \infty)$ in the usual sense (see Appendix A.), and a metric ρ on Z is defined by $\rho((s,x),(t,y)) = |h(s) - h(t)| + d(x,y)$, where $h : [t_0, \infty] \to [0,1]$ is the map defined as follows:*

$$h(t) = \begin{cases} \dfrac{t - t_0}{1 + t - t_0}, & t < \infty, \\ 1, & t = \infty. \end{cases}$$

The embedding is: $\Psi : [0, \infty) \times Z \to Z$,

$$\Psi(t, (s,x)) = \begin{cases} (t + s, \Phi(t + s, s, x)), & t_0 \le s < \infty \\ (\infty, \Theta(t, x)), & s = \infty \end{cases} \tag{2.3}$$

Clearly, Ψ is continuous and a semiflow on Z.

Lemma 2.15. *We use the same assumptions and notations as in the definition 2.4, where Φ is an asymptotically autonomous process with limit semiflow Θ, and assume $\mathcal{O}_\Theta(s,x)$ has compact closure in X. Then $\mathcal{O}_\Psi(s,x)$ has compact closure in Z and*

$$\{\infty\} \times \omega_\Phi(s,x) = \omega_\Psi(s,x). \tag{2.4}$$

Proof. Since Θ is the limit semiflow, by the definition, $s_j \to \infty$, therefore we take the second embedding of (2.3). (2.4) follows.

The topology on Z is the product topology on $\{\infty\} \times X$. Since $\mathcal{O}_\Theta(s,x)$ has compact closure in X, by the definition of compactness, it has a finite open cover, say C, in X. Then

we can construct an open cover C' of $\mathcal{O}_\Psi(s,x)$ by setting

$$C' = \{[t_0, \infty] \times E | E \in C\}.$$

It follows immediately that $\mathcal{O}_\Psi(s,x)$ has compact closure in Z. □

Theorem 2.16. *We use the same assumptions and notations as in the definition 2.4, where* Φ *is an asymptotically autonomous process with limit semiflow* Θ*, and assume the forward orbit* $\mathcal{O}_\Phi^+(s,x)$ *has compact closure in* X*. The* ω*-limit set* $\omega_\Phi(s,x)$ *has the following properties:*

(a) $\omega_\Phi(s,x)$ *is nonempty, compact, and connected.*

(b) $\omega_\Phi(s,x)$ *is invariant under the semiflow* Θ*:*

$$\Theta(t, \omega_\Phi(s,x)) = \omega_\Phi(s,x) \text{ for each } t \geq 0.$$

(c) $\omega_\Phi(s,x)$ *attracts* $\Phi(t,s,x)$*:*

$$d_X(\Phi(t,s,x), \omega) \to 0, t \to \infty.$$

(d) $\omega_\Phi(s,x)$ *is is chain recurrent for* Θ*.*

Proof. By lemma 2.15, $\mathcal{O}_\Psi(s,x)$ has compact closure in Z, then by proposition 2.13, $\omega_\Psi(s,x)$ is nonempty, compact, and connected. (a) then follows. Similarly, $\omega_\Psi(s,x)$ is invariant under Ψ, therefore we proved (b). For (c), we observe that

$$d_Z(\Psi(t,(s,x)), \omega_\Psi(s,x)) = \left| \frac{t+s-t_0}{1+t+s-t_0} - 1 \right| + d_X(\Phi(t,s,x), \omega_\Phi(s,x)) \to 0 \text{ as } t \to \infty.$$

This induces $d_X(\Phi(t,s,x), \omega_\Phi(s,x)) \to 0$ as $t \to \infty$. Finally, $\{\infty\} \times \omega_\Phi(s,x)$ being chain recurrent in Z implied that $\omega_\Phi(s,x)$ is also chain recurrent in X. □

Theorem 2.17. *(Poincaré-Bendixson Theorem in $\mathbb{R}^2$ [26]) Suppose $f \in C^1(E)$ where E is an open subset of $\mathbb{R}^2$, and ϕ is the solution flow of the system $\dot{x} = f(x)$. If Ω is a nonempty compact ω-limit set of ϕ, and Ω does not contain a rest point, then Ω is a periodic orbit.*

Corollary 2.18. *[26] We use the same notations and assumptions as in the Theorem 2.17. If E contains a periodic orbit Γ of the system $\dot{x} = f(x)$ and its interior U, then U contains at least one rest point of the system.*

Theorem 2.19. *(Dulac's Criterion [24]) Consider a smooth differential equation system*

$$\dot{x} = f(x, y), \dot{y} = g(x, y).$$

If there is a smooth function $B(x, y)$ defined on a simply connected region $\Omega \subset \mathbb{R}^n$ such that $\frac{\partial}{\partial x}(B \cdot f) + \frac{\partial}{\partial y}(B \cdot g)$ is not identically zero and of a fixed sign on Ω, then the system has no periodic solution on Ω.

Theorem 2.20. *(Lyapunov's Stability Theorem [24]) Consider autonomous system*

$$\dot{x} = f(x), x \in \mathbb{R}^n.$$

Let x_0 be a rest point of this system and $U \subset \mathbb{R}^n$ be an open set containing x_0. A continuous function $h : U \to \mathbb{R}$ is called a Lyapunov Function of the above system at x_0 if it satisfies:

1. *$h(x_0) = 0$.*
2. *$h(x) > 0$ for $x \in U \backslash \{x_0\}$.*
3. *h is continuously differentiable on the set $U \backslash \{x_0\}$, and, on this set,*

$$\dot{h}(x) = \mathrm{grad}h(x) \cdot f(x) \leq 0.$$

$h(x)$ is called a strict Lyapunov Function if, additionally,

(4) $\dot{h}(x) < 0$ *on* $U \backslash \{x_0\}$.

For the above system, if there exists a Lyapunov Function defined on an open neighborhood of a rest point of the system, then this rest point is stable. Moreover, if the Lyapunov Function is a strict Lyapunov Function, then this rest point is asymptotically stable.

Definition 2.21. *(Subsolution and Supersolution [27]) Let* $f(t,x)$ *be defined in* $D \subset \mathbb{R}^2$. *Consider the following system with initial value*

$$\dot{y} = f(t,x) \quad \text{for } t \in J = [t_0, t_0 + a], \quad y(t_0) = K, \tag{2.5}$$

where K *is a constant, and* $a > 0$. *Suppose* $y(t)$ *is a solution of the system.* y_-/y^+ *is called a subsolution/supersolution of the above system if it is differentiable on* J *and satisfies*

$$\dot{y_-} \leq f(t,x) \quad \text{on } J, \quad y_-(t_0) \leq K. \qquad \textit{subsolution}$$
$$\dot{y^+} \geq f(t,x) \quad \text{on } J, \quad y^+(t_0) \geq K. \qquad \textit{supersolution}$$

Theorem 2.22. *(Kamke's Comparison Theorem, version of unique solution [27]) Under the previous definition, where* f *is a continuous function, and* D *is an open subset of* $\mathbb{R}^2$, *if the initial value problem* (2.5) *has a unique solution on* J, *then*

$$y_-(t) \leq y(t) \leq y^+(t) \quad \text{on } J.$$

Theorem 2.23. *(Carathéodory's Existence Theorem [28]) Consider the initial value problem*

$$\begin{aligned} \dot{x} &= f(t, x(t)), \\ x(\tau) &= \xi, \end{aligned}$$

where $(\tau, \xi) \in D$, *with* D *a nonempty open subset of* $\mathbb{R} \times \mathbb{R}^n$, *and* $f : D \to \mathbb{R}^n$. *It has a solution if for some open set* $R_{a,b} \subset D$ *centered at* τ, ξ, *the restriction of* f *to* $R_{a,b}$ *is*

continuous in x for fixed t, measurable in t for fixed x, and satisfies

$$|f(t,x)| \leq m(t), \quad (t,x) \in R_{a,b},$$

for some m integrable over the interval $[\tau - a, \tau + a]$.

Next we will introduce several definitions and theorems from optimal control theory. Please refer to Appendix B for the fundamental background, such as basic terminologies and general problem formulation, and an outline of solving optimal (bang-bang) control problem.

Definition 2.24. *(Optimal control [29]) Consider the following optimal control problem:*

$$\min \quad J = \int_0^T F(x(t), u(t), t)\, dt + S(x(T), T) \tag{2.6}$$

$$\dot{x}(t) = f(x(t), u(t), t), \quad x(0) = x_0 \tag{2.7}$$

$$g(x(t), u(t), t) \geq 0 \tag{2.8}$$

$$h(x(t), t) \geq 0 \tag{2.9}$$

$$a(x(T), T) \geq 0 \tag{2.10}$$

$$b(x(T), T) = 0 \tag{2.11}$$

where T is free on $[0, t_f]$, $F : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R} \to \mathbb{R}$, $S : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}$, $f : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R} \to \mathbb{R}^n$, $g : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R} \to \mathbb{R}^s$, $h : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^q$, $a : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^l$, and $b : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^{l'}$. Assume that F, S, f, g, h, a, and b are continuous over their domain, respectively.

Define the (state-dependent) set of admissible values

$$\Omega(x,t) = \{u \in \mathbb{R}^m | g(x,u,t) \geq 0\} \subset \mathbb{R}^m$$

and the set

$$N(x,t) = \{(F(x,u,t) + \gamma, f(x,u,t)) | \gamma \leq 0, u \in \Omega(x,t)\} \subset \mathbb{R}^{n+1}$$

where m and n are the number of control and state variables, respectively.

We are looking for a measurable function $u(\cdot)$ mapping from $[0,T]$ into $\mathbb{R}^m$ and a corresponding function $x(\cdot)$ mapping from $[0,T]$ into $\mathbb{R}^n$ which is absolutely continuous, such that the constraint (2.7) — (2.11) are satisfied and the objective functional (2.6) takes its minimum value.

Theorem 2.25. *(Filippov-Cesari Theorem [29]) Under the previous definition, we assume that F, S, f, g, h, a, and b are continuous in all their arguments at all points (x,u,t). Furthermore, suppose that the following conditions hold:*

1. *There exists an admissible solution pair.*
2. *$N(x,t)$ is convex for all $(x,t) \in \mathbb{R}^n \times [0,t_f]$.*
3. *There exists $\delta > 0$ such that*

$$\|x(t)\| < \delta$$

   for all admissible $\{x(t), u(t)\}$ and t.

4. *There exists $\delta_1 > 0$ such that $\|u\| < \delta_1$ for all $u \in \Omega(x,t)$ with $\|x\| < \delta$.*

Then there exists an optimal triple $\{T^*, x^*, u^*\}$ with $u^*(\cdot)$ measurable.

Theorem 2.26. *(Pontryagin's Maximum/Minimum Principle, or PMP [21], [30])*

Use the same notations and assumptions as in the definition 2.24, where we assume $\mathbf{u}(t) = (u_1(t), \ldots, u_m(t))$ is a piecewise continuous control function and $\mathbf{x}(t) = (x_1(t), \ldots, x_n(t))$ be the corresponding continuous and piecewise differentiable state function defined on the fixed interval $[t_0, t_1]$ that minimizes

$$\int_{t_0}^{t_1} f(t, \mathbf{x}(t), \mathbf{u}(t))\ dt$$

subject to the differential equations

$$\dot{x}_i(t) = g_i(t, \mathbf{x}(t), \mathbf{u}(t)), \quad i = 1, \ldots, n,$$

initial conditions

$$x_i(t_0) = x_{i0}, \quad x_{i0} \textit{ fixed}, \quad i = 1, \ldots, n,$$

terminal conditions

$$x_i(t_1) = x_{i1}, \quad x_{i0} \textit{ fixed}, \quad i = 1, \ldots, p,$$

$$x_i(t_1) \geq x_{it}, \quad x_{i0} \textit{ fixed}, \quad i = p+1, \ldots, q$$

$$x_i(t_1) \textit{ is free}, \quad i = q+1, \ldots, n,$$

and control variable restriction

$$\mathbf{u}(t) \in U, \quad U \textit{ is a given set in } \mathbb{R}^m.$$

We assume that $f, g, \partial f/\partial x_j$, and $\partial g_i/\partial x_j$ are continuous functions of all their arguments for all $i = 1, \ldots, n$ and $j = 1, \ldots, n$. Then there exist continuous functions (adjoint functions) $\lambda(t) = (\lambda_1(t), \ldots, \lambda_n(t)) : \mathbb{R} \to \mathbb{R}^n$, where for all $t_0 \leq t \leq t_1$ we have $\lambda(t) \neq \mathbf{0}$ such that for every $t_0 \leq t \leq t_1$,,

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

where the Hamiltonian function H is defined by

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = f(t, \mathbf{x}, \mathbf{u}) + \sum_{i=1}^{n} \lambda_i g_i(t, \mathbf{x}, \mathbf{u}).$$

Moreover, except at points of discontinuity of $\mathbf{u}^*(t)$,

$$\dot{\lambda}(t) = -\partial H(t, \mathbf{x}^*(t), \mathbf{u}^*(t), \lambda(t))/\partial x_i, \quad i = 1, \ldots, n.$$

Finally, the following transversality conditions are satisfied:

$$\lambda_i(t_1) \quad \textit{no conditions}, \quad i = 1. \ldots, p, \tag{2.12}$$

$$\lambda_i(t_1) \geq 0, \ \textit{the equality holds if } x_i^*(t_1) > x_{i1}, \quad , i = p+1, \ldots, q, \tag{2.13}$$

$$\lambda_i(t_1) = 0, \quad , i = q+1, \ldots, n. \tag{2.14}$$

Chapter 3

Model Description

3.1 General assumptions

We will study three types of therapies in this thesis: Immunotherapy, Chemotherapy, and Radiotherapy. What we list below are several assumptions about these therapies that some models in this thesis share, each of which represents a certain well-accepted behavior of a population or between populations.

Immune response: The intrinsic growth rates of tumor and immune cell populations are assumed to obey logistic laws. Also, the immune cells will kill the tumor cells at some rate, which results in the death of both populations. Furthermore, in the absence of any tumor cell, the immune cells will die off at a constant rate.

Chemotherapy: Medicines will kill not only tumor cells, but also host and immune cells, of which the rate is modeled by the term $-k(1 - e^{-\sigma M})$ with k denoting the response coefficient. The parameters k and σ can be adjusted according to clinical data.

Radiation: The radiation affects all types of cell. Furthermore, it is sometimes possible for broken chromosomes to recombine, so that 'broken' tumor or host cells can become viable cells again. This is here modeled to occur at a constant rate.

3.2 Model I: Single population with Radiotherapy only

We start with the case with radiotherapy only. More specifically, we deal with one cell population (either host or tumor cells) and establish some general mathematical properties and dynamics of the system. We will study the double-population case in the next model.

$A(t)$ and $A_r(t)$ denote the population densities at time t of the cell populations under consideration and the associated radiated cell populations, respectively.

- We assume logistic growth for the cell population with r and K denoting the intrinsic growth rate and carrying capacity, respectively.
- Radiated cells with broken chromosomes are represented by $D(t)u$, where $D(t)$ is the rate of radiation protocol, a nonnegative function. It's reasonable to ask furthermore that $D(t) \not\equiv 0$. We consider two cases for $D(t)$ in this model:
  1. $D(t) = D_0 > 0$, constant.
  2. $D(t) = D_0 e^{-\alpha t}$, decay.
- p is the rate at which the radiated cells recombine into normal cells, and δ is the washout rate of radiated cells.

After the discussion above, the system turns out to be of the following form:

$$\begin{cases} \dot{A} = rA(1 - \dfrac{A}{K}) - D(t)A + pA_r \\ \dot{A}_r = D(t)A - pA_r - \delta A_r \\ A(0) \geq 0; A_r(0) \geq 0 \end{cases} \tag{3.1}$$

3.3 Model II: Double populations with Radiotherapy only

In this model, we inherit the same assumptions as in Model I and consider the case with both host and tumor cells, which includes additional competition between these two populations.

- $H(t)$ and $T(t)$ denote the population densities at time t of the host and tumor cell populations, respectively, with $H_r(t)$ and $T_r(t)$ for radiated host and tumor cell populations, respectively; r_i and K_i denote the intrinsic growth rates and carrying capacities, respectively.

- The radiotherapy is designed in such a way that full radiation concentration affects the cancer cells, and a small proportion of the radiation affects the host cells.

- We only consider the case with constant radiation rate here, i.e., $D(t) = D$, where D is a constant.

- We assume the same washout rate, δ, but different recombining rates for these two populations, which are denoted by p_1 and p_2 for the radiated host and tumor cells, respectively.

The system, in this way, becomes

$$\begin{cases} \dot{H} = r_1 H(1 - \dfrac{H}{K_1}) - \varepsilon DH + p_1 H_r - c_1 HT \\ \dot{H}_r = \varepsilon DH - p_1 H_r - \delta H_r \\ \dot{T} = r_2 T(1 - \dfrac{T}{K_2}) - DT + p_2 T_r - c_2 HT \\ \dot{T}_r = DT - p_2 T_r - \delta T_r \\ H(0) \geq 0; H_r(0) \geq 0; T(0) \geq 0; T_r(0) \geq 0 \end{cases} \tag{3.2}$$

3.4 Model III: Tumor model with Immune Resistance and Chemotherapy

Next, we will look at some more detailed cells population behaviors. In this model, we will introduce three populations: tumor cells, immune cells, and normal (host) cells, of which the population densities at time t are denoted by $T(t), I(t)$, and $H(t)$, respectively.

- We assume that the immune cells have a source with a constant influx rate s. Moreover, in the absence of any tumor, they will die off at a per capita rate d, so that the immune cells population won't blow up, but has an upper bound $\dfrac{s}{d}$.

- The presence of tumor cells stimulate the immune response, represented by the Michaelis-Menten form $\dfrac{\rho I(t)T(t)}{\alpha + T(t)}$, which is wildly used in enzyme kinetics modeling (the same as

the terms used in [31],[32]). It's easy to see that this term is positive and monotonically increasing with respect to T. We will use similar terms again in the next model.

- The reaction between immune and tumor cells would result in the death for both, which leads to two competition terms:

$$-c_1 I(t)T(t) \quad \text{and} \quad -c_2 I(t)T(t).$$

- Both the tumor and normal cell populations obey logistic growth laws, with r_i and K_i representing the intrinsic growth rates and carrying capacities for these two types of cells, respectively. Thus, we have the following growth terms:

$$r_2 T(1 - \frac{T}{K_2}) \quad \text{and} \quad r_3 H(1 - \frac{H}{K_3}).$$

- In addition, there are two terms representing the competition between tumor and host cells:

$$-c_2' T(t)H(t) \quad \text{and} \quad -c_3 T(t)H(t).$$

- We add the effect of drugs into the system. $M(t)$ denote the amount of drugs at time t. By section 3.1, the response rates for all three types of cells are given by the terms:

$$-k_i(1 - e^{-\sigma_i M}), \quad i = 1, 2, 3$$

where for mathematical convenience and unknown of details of pharmacokinetics, we let $\sigma_i = 1, i = 1, 2, 3$ in the preliminary studies.

- The amount of drug is determined by the given dose, $v(t)$, and a per capita decay rate of the drug once it's injected, at the rate d_4.

Thus, we model this system as

$$\begin{cases} \dot{I} = s - d_1 I + \dfrac{\rho IT}{\alpha + T} - c_1 IT - k_1(1 - e^{-M})I \\ \dot{T} = r_2 T(1 - \dfrac{T}{K_2}) - c_2 IT - c_2' TH - k_2(1 - e^{-M})T \\ \dot{H} = r_3 H(1 - \dfrac{H}{K_3}) - c_3 TH - k_3(1 - e^{-M})H \\ \dot{M} = v(t) - d_4 M \end{cases} \tag{3.3}$$

3.5 Model IV: Immuno-Chemotherapy with controls

In this model, we introduce a mixed-therapy method to treat cancer. More specifically, we combine two biological therapies, Tumor Specific T Cell ($CD8^+$T CTL) and cytokine IL-2, together with a type of chemotherapy. We also consider controls of these therapies in the system.

There are six populations in this model. The population densities at time t are denoted by:

$T(t)$**:** Tumor cells

$N(t)$**:** Natural Killer cells

$C(t)$**:** Number of circulating lymphocytes

$S(t)$**:** Tumor Specific T cells ($CD8^+$T cells)

$I(t)$**:** Immunotherapy (cytokine IL-2) concentration

$M(t)$**:** Chemotherapy medicine concentration

We assume the similar functional terms to the ones in [14]. The functions of action/reaction between these populations can be categorized into several types.

Growth and death terms: The growth of tumor cells are assumed to obey logistic laws. Both Natural Killer cells and $CD8^+$T cells have constant death rates, while the growth

of the former comes partially from circulating lymphocytes. The circulating lymphocytes have a constant production rate and a constant death rate. Both chemotherapy and immunotherapy are assumed to decay proportionally to their concentrations.

Killing terms: The tumor cells will be killed by both the Natural Killer cells and the $CD8^+T$ cells. Also, the chemotherapy medicine will affect all types of cells. The form of inhibition is the same as in the system (3.1).

Stimulation and recruitment: The IL-2 stimulates the recruitment of both the Natural Killer cells and the $CD8^+T$ cells. The latter will also be stimulated by the debris of tumor cells. On the other hand, the $CD8^+T$ cells will also stimulate the production of IL-2. These stimulations shall be modeled by the Michaelis-Menten form [33]. The Natural Killer cells killing the tumor cells may enhance the production of the $CD8^+T$ cells. The same effect will be produced by the encounters between circulating lymphocytes and tumor cells.

Control terms: We can control the population concentration of CTLs, IL-2, and medicine.

Before building the whole model, let's discuss the detailed mathematical terms first in the following text.

$\mathbf{T(t)}$: The same as before, simple logistic growth term of the tumor cell population, $rT(1-\frac{T}{K})$, is assumed in the absence of medicine and immune interactions. Death of tumor cells due to the Natural Killer cells and $CD8^+T$ cells is modeled by a mass action term, $-cNT$, and a ratio dependent term, $-D(S,T)T = -d\frac{(S/T)^l}{s/n^l+(S/T)^l}T$ [33], respectively. Death due to chemotherapy medicine is given in the form that we used to assume, $-k_T(1-e^{-\sigma_T M})T$.

$\mathbf{N(t)}$: The constant rate source term of Natural Killer cells due to circulating lymphocytes is eC, while the linear natural death term is $-fN$. By killing the tumor cells, there

is an extra death term, $-pNT$. Stimulation due to IL-2 is modeled in the Michaelis-Menten form, $\frac{p_N NI}{g_N + I}$. The same as before, death due to chemotherapy medicine is given by $-k_N(1 - e^{-\sigma_N M})N$.

$\mathbf{C(t)}$: The circulating lymphocytes has a constant source term, α, and a linear death term, $-\beta C$, together with the death due to medicine, $-k_C(1 - e^{-\sigma_C M})C$.

$\mathbf{S(t)}$: For the CD8$^+$T cells, we assume there exists a modified (in the presence of IL-2) linear death term, $-\frac{\theta m S}{\theta + I}$, as well as a modified quadratic death term, $-\frac{u_0 S^2 CI}{\kappa + I}$, due to the inhibition by circulating lymphocytes. CTLs will also die through interaction with tumor cells, modeled by $-qST$. Also, the stimulations on the CD8$^+$T cells by Natural Killer cells and circulating lymphocytes interacting with tumor cells are represented by $a_1 NT$ and $a_2 CT$, respectively. The stimulatory effect on the CD8$^+$T cells by the debris of tumor cells and the IL-2 are represented by $\frac{p_T ST}{g_T + T}$ and $\frac{p_I SI}{g_I + I}$, respectively. Similarly, death due to medicine is modeled by $-k_S(1 - e^{-\sigma_S M})S$.

$\mathbf{I(t)}$: The IL-2 is assumed to be with a linear death rate, $-\mu_I I$, and a constant source from Circulating Lymphocytes, ρC. We use $\frac{p_S SI}{g_S + I}$ to represent the stimulatory production from the CD8$^+$T cells.

$\mathbf{M(t)}$: Once injected, medicine (chemotherapy) is assumed to have a linear decay rate, $-\gamma M$.

All of the controls are in the term of $\eta_X v_X(t)$, where X denotes corresponding populations.

After the discussion above, we can summarize the system as

$$
\begin{cases}
\dot{T} = rT(1-\dfrac{T}{K}) - cNT - D(S,T)T - k_T(1-e^{-\sigma_T M})T \\
\dot{N} = eC - fN - pNT + \dfrac{p_N NI}{g_N + I} - k_N(1-e^{-\sigma_N M})N \\
\dot{C} = \alpha - \beta C - k_C(1-e^{-\sigma_C M})C \\
\dot{S} = -\dfrac{\theta m S}{\theta + I} - \dfrac{u_0 S^2 CI}{\kappa + I} - qST + a_1 NT + a_2 CT \\
\qquad + \dfrac{p_I SI}{g_I + I} + \dfrac{p_T ST}{g_T + T} - k_S(1-e^{-\sigma_S M})S + \eta_S v_S(t) \\
\dot{I} = -\mu_I I + \rho C + \dfrac{p_S SI}{g_S + I} + \eta_I v_I(t) \\
\dot{M} = -\gamma M + \eta_M v_M(t)
\end{cases}
\tag{3.4}
$$

where $D(S,T) = d\dfrac{(S/T)^l}{s/n^l + (S/T)^l}$.
Also, $T(0) \geq 0; N(0) \geq 0; C(0) \geq 0; S(0) \geq 0; I(0) \geq 0; M(0) \geq 0$.

Chapter 4

Analytic Results

4.1 Model I

Before starting to analyze the three cases individually, we first take a look at some preliminary properties of the system (3.1).

Proposition 4.1. *Assume that* $(A(t), A_r(t))$ *is the solution of the initial value problem* (3.1)*, and* $D(t)$ *is continuous, then* $A(t) \geq 0$*,* $A_r(t) \geq 0$*.*

Proof. $(0, 0)$ is an equilibrium. It suffices to prove that $A(t)$ and $A_r(t)$ cannot cross the A-axis and A_r-axis.

By the continuity of $D(t)$, $A(t)$ and $A_r(t)$ are at least continuous over a small time interval $[0, \epsilon]$ since they are the solutions of the initial value problem (3.1). Assume $A(0) = 0, A_r(0) > 0$, then $\dot{A}(0) = pA_r(0) > 0$, hence there exists a $0 < \varepsilon < \epsilon$ such that $\dot{A}(t) > 0, A_r(t) > 0$ for $t \in [0, \varepsilon]$. Thus,

$$A(t) = \int_0^t \dot{A}(t)\, dt > 0 \quad \text{for } t \in (0, \varepsilon],$$

Similar argument can imply the same conclusion for $A(0) > 0, A_r(0) = 0$, as $\dot{A}_r(0) = D(0)A_r(0) > 0$.

For the case that $A(0) > 0, A_r(0) > 0$, if the solution orbit intersects either A-axis or A_r-axis at some time point, for instance, $t_1 > \varepsilon$, we use the same arguments above to show that the orbit will stay in the first quadrant, with $A(0)$ and $A_r(0)$ being substituted by $A(t_1)$ and $A_r(t_1)$, respectively. □

Proposition 4.2. *IVP System* (3.1) *is dissipative within the set*

$$\mathcal{R} = \mathbb{R}^2_+ \cap \left\{ (A, A_r) | A + A_r \leq \max \left\{ A(0) + A_r(0), \frac{K(r+\delta)^2}{4r\delta} \right\} \right\}.$$

where $\mathbb{R}^2_+ = \{(A, A_r) | A \geq 0, A_r \geq 0\}$.

Proof. Let $X = A + A_r$, then we combine the two equations in the initial value problem (3.1) together:

$$\begin{aligned} \dot{X} &= rA(1 - \frac{A}{K}) - \delta A_r \\ &= -\delta X - \frac{r}{K}A^2 + (r+\delta)A \\ &= -\delta X + \frac{K(r+\delta)^2}{4r} - \frac{r}{K}(A - \frac{K(r+\delta)}{2r})^2 \\ &\leq -\delta X + \frac{K(r+\delta)^2}{4r} \end{aligned}$$

Solving the corresponding equality, we get

$$\widetilde{X}(t) = \left(X(0) - \frac{K(r+\delta)^2}{4r\delta} \right) e^{-\delta t} + \frac{K(r+\delta)^2}{4r\delta}.$$

Therefore, by the Kamke comparison theorem (Theorem 2.22) ,

$$X \leq \max \left\{ X(0), \frac{K(r+\delta)^2}{4r\delta} \right\}$$

where $X(0) = A(0) + A_r(0)$. □

Next, we will discuss cases with different types of $D(t)$ and see some analytical properties for each of them.

4.1.1 Constant radiation

In this case, $D(t) = D_0 > 0$, where D_0 is a constant. The system (3.1) becomes

$$\begin{aligned} \dot{A} &= rA(1-\frac{A}{K}) - D_0 A + pA_r \\ \dot{A}_r &= D_0 A - pA_r - \delta A_r \\ A(0) &\geq 0; A_r(0) \geq 0 \end{aligned} \tag{4.1}$$

Then, by solving the corresponding equations

$$\begin{cases} rA(1-\frac{A}{K}) - D_0 A + pA_r = 0 \\ D_0 A - pA_r - \delta A_r = 0 \end{cases}$$

we can get at most two reasonable distinct equilibria of the initial value problem (4.1):

$$\begin{aligned} & E_0 &=& (0,0) \\ \text{and} \qquad & E_1 &=& \left(K\frac{r(p+\delta)-\delta D_0}{r(p+\delta)}, KD_0\frac{r(p+\delta)-\delta D_0}{r(p+\delta)^2} \right) \\ & &=& (u_1, v_1) \neq E_0, \quad u_1 \geq 0, v_1 \geq 0. \end{aligned}$$

Theorem 4.3. *E_1 exists if and only if E_0 is unstable.*

Proof. For one direction, E_1 existing means that $u \geq 0, v \geq 0$, and the equalities cannot hold at the same time. Since $D_0 \neq 0$, and all other parameters are positive in this model, it is also equivalent to say that $r(p+\delta) - \delta D_0 > 0$, which is

$$0 < D_0 < \frac{r(p+\delta)}{\delta} \tag{4.2}$$

.

Now consider the linearized system

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} r - \frac{2rA}{K} - D_0 & p \\ D_0 & -p-\delta \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} \tag{4.3}$$

of the IVP system (4.1). Then for E_0, the eigenvalues of its corresponding Jacobean matrix are

$$\lambda_{\pm} = \frac{-(p+\delta+D_0-r) \pm \sqrt{(p+\delta+D_0-r)^2 + 4[D_0 p + (r-D_0)(p+\delta)]}}{2}.$$

It is clear that at least λ_- has negative real part. Now (4.2) induces that

$$4[D_0 p + (r-D_0)(p+\delta)] > 0,$$

which indicates λ_+ has positive real part. Therefore, E_0 is unstable.

Similarly arguments yield the other direction. □

Theorem 4.4. *If E_1 does not exist, then E_0 is asymptotically stable.*

Proof. If E_1 does not exist, then E_0 is the only equilibrium. By the dissipativity (proposition 4.2), it suffices to prove that there is no periodic solution.

If there is a periodic orbit, then by the corollary 2.18, it must surround an equilibrium, which is E_0 in this case. Use the dissipativity again, it's clear that this type of periodic orbit does not exist, because if it does, then part of the orbit must lie in the dissipative region in proposition 4.2, therefore cannot keep being periodic but approaches E_0. Hence, E_0 is globally asymptotically stable. □

Theorem 4.5. *If E_1 exists, then it is globally asymptotically stable on $\mathbb{R}^2 \backslash E_0$.*

Proof. From proposition 4.3, E_0 is unstable. Since the system is dissipative, we only need to show that there is no periodic solution.

We use the Dulac's Criterion (Theorem 2.19) to prove this. Choose $B(A, A_r) = \dfrac{1}{A \cdot A_r}$ in the Dulac's Criterion and apply it to the initial value problem (4.1):

$$\begin{aligned} & \frac{\partial}{\partial A}\left\{\frac{1}{A\cdot A_r}\left[rA\left(1-\frac{A}{K}\right) - D_0 A + pA_r\right]\right\} + \frac{\partial}{\partial A_r}\left[\frac{1}{A\cdot A_r}(D_0 A - pA_r - \delta A_r)\right] \\ = \; & -\frac{r}{K\cdot A_r} - \frac{p}{A^2} - \frac{D_0}{A_r^2} \\ < \; & 0 \end{aligned}$$

This holds for any $(A, A_r) \in \mathbb{R}^2_+$. Then by the Dulac's Criterion, the initial value problem does not have any periodic solution in $\mathbb{R}^2_+$. □

Theorem 4.6. *The IVP system* (4.1) *persists if and only if* $0 < D_0 < \dfrac{r(p+\delta)}{\delta}$*, otherwise both populations die off.*

Proof. Combine the above 3 theorems. The system persists if and only if E_1 exists, which by Theorem 4.3 is equivalent with $0 < D_0 < \dfrac{r(p+\delta)}{\delta}$. Furthermore, Theorem 4.5 guarantees it is asymptotically stable.

If not, then by Theorem 4.4, any orbit will approach the equilibrium E_1, the extinction.

□

4.1.2 Decay radiation

In this case, we assume $D(t) = D_0 e^{-\alpha t}$. The system (3.1) becomes

$$\begin{aligned} \dot{A} &= rA(1 - \frac{A}{K}) - D_0 e^{-\alpha t} A + pA_r \\ \dot{A}_r &= D_0 e^{-\alpha t} A - pA_r - \delta A_r \\ A(0) &\geq 0; A_r(0) \geq 0 \end{aligned} \tag{4.4}$$

Theorem 4.7. *Let* $(A(t), A_r(t))$ *be the solution of the initial value problem* (4.4)*, then*

$$\begin{aligned} & \lim_{t\to\infty} (A(t), A_r(t)) = (0, 0) \\ \textit{or} \qquad & \lim_{t\to\infty} (A(t), A_r(t)) = (K, 0). \end{aligned}$$

Proof. We consider the asymptotic system by taking the limit of t to ∞.

$$\begin{aligned} \dot{A} &= rA(1 - \frac{A}{K}) + pA_r \\ \dot{A}_r &= -pA_r - \delta A_r \end{aligned} \tag{4.5}$$

By Theorem 2.16, the ω-limit sets of system (4.4) are contained within the chain recurrent sets of system (4.5). But the only chain recurrent sets of (4.5) are $(0,0)$ and $(K,0)$. This follows from two observations:

(1) For any orbit starting from a point of which the A_r-coordinate is not 0, by the second equation of the initial value problem (4.5), it will approach some point on the A-axis. Therefore, for any of these points, there would not be any chain connecting it to itself.

(2) For any orbit starting from a point lying on the A-axis other than $(0,0)$ and $(K,0)$, the A_r-coordinate will remain the same; but by the first equation of the initial value problem (4.5), the evolution of A obeys the logistic law, which will approach K. Therefore, as the same reason as last case, there would not be any chain connecting any of these points to itself.

□

4.2 Model II

Similarly as proposition 4.2, we get the following corollary:

Corollary 4.8. *The initial value problem* (3.2) *is dissipative within the set*

$$\mathcal{R} = \mathbb{R}^4_+ \bigcap \left\{ (H, H_r, T, T_r) | X \leq \max \left\{ X(0), \frac{K_1(r_1+\delta)^2}{4r_1\delta} + \frac{K_2(r_2+\delta)^2}{4r_2\delta} \right\} \right\}.$$

where $\mathbb{R}^4_+ = \{(H, H_r, T, T_r) | H \geq 0, H_r \geq 0, T \geq 0, T_r \geq 0\}$ *and* $X = H + H_r + T + T_r$.

Proof. The proof is similar as in the Theorem 4.2. Let $X = H + H_r + T + T_r$, then by (3.2),

$$\begin{aligned}
\dot{X} &= r_1 H(1 - \frac{H}{K_1}) - \delta H_r - c_1 HT + r_2 T(1 - \frac{T}{K_2}) - \delta T_r - c_2 HT \\
&\leq -\delta X + (r_1 H + \delta H - \frac{r_1 H^2}{K_1}) - c_1 HT + (r_2 T + \delta T - \frac{r_2 T^2}{K_2}) - c_2 HT \\
&\leq -\delta X - \frac{r_1}{K_1}[H - \frac{K_1}{2r_1}(r_1 + \delta)]^2 + \frac{K_1(r_1+\delta)^2}{4r_1} - c_1 HT \\
&\quad -\frac{r_2}{K_2}[T - \frac{K_2}{2r_2}(r_2 + \delta)]^2 + \frac{K_2(r_2+\delta)^2}{4r_2} - c_2 HT \\
&\leq -\delta X + \frac{K_1(r_1+\delta)^2}{4r_1} + \frac{K_2(r_2+\delta)^2}{4r_2}
\end{aligned}$$

Solving the corresponding equality, we can get

$$\widetilde{X} = \left[X(0) - \left(\frac{K_1(r_1+\delta)^2}{4r_1\delta} + \frac{K_2(r_2+\delta)^2}{4r_2\delta}\right)\right] e^{-\delta t} + \frac{K_1(r_1+\delta)^2}{4r_1\delta} + \frac{K_2(r_2+\delta)^2}{4r_2\delta}.$$

By using the Kamke comparison theorem (Theorem 2.22), we can get the desired result. □

Also, in absence of radiation, the system (3.2) reduces to a competition system

$$\begin{cases} \dot{H} = r_1 H(1 - \frac{H}{K_1}) - c_1 HT \\ \dot{T} = r_2 T(1 - \frac{T}{K_2}) - c_2 HT \\ H(0) \geq 0; T(0) \geq 0. \end{cases} \tag{4.6}$$

A well-known result shows that cancer cells will win in the competition under the hypothesis

$$c_2 K_1 < r_2 \quad \text{and} \quad r_1 < c_1 K_2. \tag{4.7}$$

Remark 4.9. *We will call* (4.7) *the 'cancer hypothesis' and we assume this throughout the remainder of this section for Model II.*

4.2.1 Equilibria

There are four types of equilibria:

- **Null state** $E_0 = (0, 0, 0, 0)$ always exists.

- **Tumor free** $E_1 = (a, b, 0, 0) \neq E_0, a \geq 0, b \geq 0$. This state exists if the initial value problem

$$\begin{cases} r_1 H(1 - \dfrac{H}{K_1}) - \varepsilon DH + p_1 H_r - c_1 HT = 0 \\ \varepsilon DH - p_1 H_r - \delta H_r = 0 \\ H(0) \geq 0; T(0) \geq 0. \end{cases}$$

has a nonnegative solution.

Since $T = 0$, by (4.2), we get the conditions

$$0 < D < \frac{r_1(p_1 + \delta)}{\varepsilon\delta} \tag{4.8}$$

and

$$(a, b) = \left(K_1 \frac{r_1(p_1 + \delta) - \varepsilon\delta D}{r_1(p_1 + \delta)}, K_1 \varepsilon D \frac{r_1(p_1 + \delta) - \varepsilon\delta D}{r_1(p_1 + \delta)^2} \right) \tag{4.9}$$

Remark 4.10. *Notice that, theoretically, we can always make ε sufficiently small to guarantee the existence of this tumor free equilibrium. However, in reality, ϵ measures the relative efficiency of the radiation, and this ratio is not easy to modify!*

- **Dead** $E_2 = (0, 0, c, d) \neq E_0, c > 0, d > 0$, in which the host cells die off. Similarly as above, the condition for the existence of this type of equilibrium is

$$0 < D < \frac{r_2(p_2 + \delta)}{\delta} \tag{4.10}$$

and

$$(c, d) = \left(K_2 \frac{r_2(p_2 + \delta) - \delta D}{r_2(p_2 + \delta)}, K_2 D \frac{r_2(p_2 + \delta) - \delta D}{r_2(p_2 + \delta)^2} \right) \tag{4.11}$$

- **Coexisting** $E_3 = (a^*, b^*, c^*, d^*)$. To decide the conditions for the existence of this equilibrium, let's consider the IVP system (3.2) and solve

$$\begin{pmatrix} r_1 H(1 - \frac{H}{K_1}) - \varepsilon DH + p_1 H_r - c_1 HT \\ \varepsilon DH - p_1 H_r - \delta H_r \\ r_2 T(1 - \frac{T}{K_2}) - DT + p_2 T_r - c_2 HT \\ DT - p_2 T_r - \delta T_r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

After calculation and considering $a^* \neq 0, b^* \neq 0, c^* \neq 0, d^* \neq 0$, we have

$$\begin{cases} \begin{bmatrix} \frac{r_1}{K_1} & c_1 \\ c_2 & \frac{r_2}{K_2} \end{bmatrix} \cdot \begin{bmatrix} H \\ T \end{bmatrix} = \begin{bmatrix} A \\ B \end{bmatrix} \\ H_r = \dfrac{\varepsilon D}{p_1 + \delta} H \\ T_r = \dfrac{D}{p_2 + \delta} T \end{cases} \tag{4.12}$$

where $A = r_1 - \varepsilon D + \dfrac{p_1 \varepsilon D}{p_1 + \delta}, B = r_2 - D + \dfrac{p_2 D}{p_2 + \delta}$. Therefore, E_3 exists if and only if the matrix $\begin{bmatrix} \frac{r_1}{K_1} & c_1 \\ c_2 & \frac{r_2}{K_2} \end{bmatrix}$ is invertible, namely,

$$r_1 r_2 \neq c_1 c_2 K_1 K_2.$$

and

$$\begin{pmatrix} H \\ H_r \\ T \\ T_r \end{pmatrix} = \begin{pmatrix} \dfrac{r_2 K_1 A - c_1 K_1 K_2 B}{r_1 r_2 - c_1 c_2 K_1 K_2} \\ \dfrac{\varepsilon D(r_2 K_1 A - c_1 K_1 K_2 B)}{(p_1 + \delta)(r_1 r_2 - c_1 c_2 K_1 K_2)} \\ \dfrac{c_2 K_1 K_2 A - r_1 K_2 B}{c_1 c_2 K_1 K_2 - r_1 r_2} \\ \dfrac{D(c_2 K_1 K_2 A - r_1 K_2 B)}{(p_2 + \delta)(c_1 c_2 K_1 K_2 - r_1 r_2)} \end{pmatrix}$$

4.2.2 Stability

From (4.3), we calculate the variational matrix being

$$\begin{bmatrix} r_1 - \dfrac{2r_1H}{K_1} - \varepsilon D - c_1T & p_1 & -c_1H & 0 \\ \varepsilon D & -p_1 - \delta & 0 & 0 \\ -c_2T & 0 & r_2 - \dfrac{2r_2T}{K_2} - D - c_2H & p_2 \\ 0 & 0 & D & -p_2 - \delta \end{bmatrix} = \begin{bmatrix} M_1 & M_2 \\ M_3 & M_4 \end{bmatrix} \tag{4.13}$$

where $M_i s$ are 2×2 matrices.

If $(\hat{a}, \hat{b}, \hat{c}, \hat{d})$ is a general equilibrium, by solving the characteristic equation, the eigenvalues are given as follows. For mathematical convenience, denote $\Gamma = r_1 - \dfrac{2r_1H}{K_1} - \varepsilon D - c_1T$, $\Upsilon = r_2 - \dfrac{2r_2T}{K_2} - D - c_2H$.

Since $\det(M_2) = 0$, $\det(M_3) = 0$, it's easy to get

$$\begin{aligned} \lambda_{1\pm} &= \frac{1}{2}\left[(\Gamma - p_1 - \delta) \pm \sqrt{(\Gamma + p_1 + \delta)^2 + 4\varepsilon D p_1}\ \right] \\ \lambda_{2\pm} &= \frac{1}{2}\left[(\Upsilon - p_2 - \delta) \pm \sqrt{(\Upsilon + p_2 + \delta)^2 + 4D p_2}\ \right] \end{aligned} \tag{4.14}$$

Notice all of the eigenvalues are real.

- Null state. For E_0,

$$\begin{aligned} \lambda^0_{1\pm} &= \frac{1}{2}\left[(r_1 - \varepsilon D - p_1 - \delta) \pm \sqrt{(r_1 - \varepsilon D + p_1 + \delta)^2 + 4\varepsilon D p_1}\ \right] \\ \lambda^0_{2\pm} &= \frac{1}{2}\left[(r_2 - D - p_2 - \delta) \pm \sqrt{(r_2 - D + p_2 + \delta)^2 + 4D p_2}\ \right] \end{aligned}$$

By Theorem 4.3, E_0 is unstable if and only if (4.8) and (4.10) are satisfied, i.e. E_0 is stable if and only if $D > \max\left\{\dfrac{r_1(p_1+\delta)}{\varepsilon\delta}, \dfrac{r_2(p_2+\delta)}{\delta}\right\}$.

- Tumor free. For E_1,

$$\begin{aligned}\lambda^1_{1\pm} &= \frac{1}{2}\Big[(r_1 - \frac{2r_1a}{K-1} - \varepsilon D - p_1 - \delta) \\ &\quad \pm \sqrt{(r_1 - \frac{2r_1a}{K-1} - \varepsilon D + p_1 + \delta)^2 + 4\varepsilon D p_1}\ \Big] \qquad (4.15)\\ \lambda^1_{2\pm} &= \frac{1}{2}\Big[(r_2 - D - c_2a - p_2 - \delta) \pm \sqrt{(r_2 - D - c_2a + p_2 + \delta)^2 + 4Dp_2}\ \Big] \qquad (4.16)\end{aligned}$$

Theorem 4.11. *E_1 is stable if and only if*

$$D > \max\left\{\frac{r_1(p_1+\delta)(r_2 - c_2K_1 - p_2 - \delta)}{r_1(p_1+\delta) - \varepsilon\delta c_2K_1}, \frac{r_1(p_1+\delta)(p_2+\delta)(r_2 - c_2K_1)}{\delta[r_1(p_1+\delta) - \varepsilon c_2K_1(p_2+\delta)]}\right\}$$

Proof. Here, by (4.8), we assume sufficiently small ε to guarantee E_1 exists. By Theorem 4.5, it suffices to make $\lambda^1_{2\pm} < 0$.

By (4.16), $\lambda^1_{2\pm}$ are real, and

$$\begin{aligned}&\lambda^1_{2\pm} < 0 \\ \Rightarrow\ &\begin{cases} r_2 - D - c_2a - p_2 - \delta < 0 \\ \sqrt{(r_2 - D - c_2a + p_2 + \delta)^2 + 4Dp_2} < |r_2 - D - c_2a - p_2 - \delta| \end{cases} \\ \Rightarrow\ &\begin{cases} [r_1(p_1+\delta) - \varepsilon\delta c_2K_1]D > r_1(p_1+\delta)(r_2 - c_2K_1 - p_2 - \delta) \\ \delta[r_1(p_1+\delta) - \varepsilon c_2K_1(p_2+\delta)]D > r_1(p_1+\delta)(p_2+\delta)(r_2 - c_2K_1) \end{cases} \\ \Rightarrow\ &\begin{cases} D > \dfrac{r_1(p_1+\delta)(r_2 - c_2K_1 - p_2 - \delta)}{r_1(p_1+\delta) - \varepsilon\delta c_2K_1} \\ D > \dfrac{r_1(p_1+\delta)(p_2+\delta)(r_2 - c_2K_1)}{\delta[r_1(p_1+\delta) - \varepsilon c_2K_1(p_2+\delta)]} \end{cases}\end{aligned}$$

The third step deduction is guaranteed by ε being sufficiently small. □

Theorem 4.12. (Global stability of the tumor free equilibrium)

Recall from (4.9) *that $E_1 = (a, b, 0, 0)$. Then E_1 is globally asymptotically stable if*

1. $\dfrac{\gamma^2}{\alpha^2} - 2\beta < 0$

2. $\dfrac{(c_1+c_2)^2}{\alpha} - \dfrac{2c_2}{K_2} < 0$

3. $r_2 - c_2 a < 0$

Proof. We prove this by constructing a Lyapunov function. Let

$$V(H, H_r, T, T_r) = H - a - a\ln\frac{H}{a} + H_r - b - b\ln\frac{H_r}{b} + T + T_r \tag{4.17}$$

This function satisfies the first two conditions in Theorem 2.20. Now compute

$$\begin{aligned}
\dot{V} &= (H-a)\left[r_1(1-\frac{H}{K_1}) - \varepsilon D + p_1\frac{H_r}{H} - c_1 T\right] \\
&\quad +(H_r - b)\left[\varepsilon D\frac{H}{H_r} - p_1 - \delta\right] + r_2 T(1-\frac{T}{K_2}) - c_2 HT - \delta T_r \\
&\quad \left(\text{Since } \varepsilon D = r_1(1-\frac{a}{K_1}) + \frac{p_1 b}{a} \quad \text{and} \quad \frac{a}{b} = \frac{p_1+\delta}{\varepsilon D}\right) \\
&= (H-a)\left[r_1(1-\frac{H}{K_1}) - r_1(1-\frac{a}{K_1}) - \frac{p_1 b}{a} + \frac{p_1 H_r}{H}\right] \\
&\quad +(H_r - b)\left[\varepsilon D\frac{H}{H_r} - \varepsilon D\frac{a}{b}\right] + r_2 T(1-\frac{T}{K_2}) - c_1 T(H-a) - c_2 HT - \delta T_r \\
&= (H-a)\left[-\frac{r_1}{K_1}(H-a) - \frac{p_1 b}{aH}(H-a) + \frac{p_1}{H}(H_r - b)\right] \\
&\quad +(H_r - b)\left[\frac{-\varepsilon D a}{bH_r}(H_r - b) + \frac{\varepsilon D}{H_r}(H-a)\right] - \frac{c_2}{K_2}T^2 \\
&\quad -c_1 T(H-a) - c_2 T(H-a) + r_2 T - c_2 aT - \delta T_r \\
&= -(\frac{r_1}{K_1} + \frac{p_1 b}{aH})(H-a)^2 - \frac{\varepsilon D a}{bH_r}(H_r - b)^2 + (\frac{p-1}{H} + \frac{\varepsilon D}{H_r})(H-a)(H_r - b) \\
&\quad -\frac{c_2}{K_2}T^2 - (c_1+c_2)(H-a)T + (r_2 - c_2 a)T - \delta T_r \\
&\quad \left(\text{let } \alpha = \frac{r_1}{K_1} + \frac{p_1 b}{aH}, \beta = \frac{\varepsilon D a}{bH_r}, \gamma = \frac{p-1}{H} + \frac{\varepsilon D}{H_r}\right) \\
&= -\alpha(H-a)^2 - \beta(H_r - b)^2 + \gamma(H-a)(H_r - b) \\
&\quad -\frac{c_2}{K_2}T^2 - (c_1+c_2)(H-a)T + (r_2 - c_2 a)T - \delta T_r
\end{aligned}$$

For mathematical convenience, we consider

$$\begin{aligned} 2\dot{V} &= -\alpha[(H-a)-\frac{\gamma}{\alpha}(H_r-b)]^2+(\frac{\gamma^2}{\alpha^2}-2\beta)(H_r-b)^2 \\ &\quad -\alpha[(H-a)-\frac{c_1+c_2}{\alpha}T]^2+\left[\frac{(c_1+c_2)^2}{\alpha}-\frac{2c_2}{K_2}\right]T^2 \\ &\quad +2(r_2-c_2a)T-2\delta T_r \end{aligned}$$

Consequently, if

$$\frac{\gamma^2}{\alpha^2}-2\beta<0, \frac{(c_1+c_2)^2}{\alpha}-\frac{2c_2}{K_2}<0, \text{and } r_2-c_2a<0$$

then $\dot{V}<0$, which makes V satisfy the third condition of Theorem 2.20, therefore E_1 is globally asymptotically stable. □

- Dead.

Corollary 4.13. *The dead equilibrium E_2 is stable if and only if*

$$D>\max\left\{\frac{r_2(p_2+\delta)(r_1-c_1K_2-p_1-\delta)}{\varepsilon r_2(p_2+\delta)-\delta c_1K_2}, \frac{r_2(p_1+\delta)(p_2+\delta)(r_1-c_1K_2)}{\delta[\varepsilon r_2(p_2+\delta)-c_1K_2(p_1+\delta)]}\right\}$$

4.3 Model III

To understand the dynamics of this system, we analyze the null-surfaces and equilibria of the drug-free system which is the simplification of system (3.3) without any term involving the medicine $M(t)$.

$$\begin{cases} \dot{I} = s - d_1 I + \dfrac{\rho IT}{\alpha + T} - c_1 IT \\ \dot{T} = r_2 T(1 - \dfrac{T}{K_2}) - c_2 IT - c_2' TH \\ \dot{H} = r_3 H(1 - \dfrac{H}{K_3}) - c_3 TH \end{cases} \tag{4.18}$$

4.3.1 Null-surfaces

The three sets of null-surfaces of the system (4.18) are as follows:

- N_1:

$$s - d_1 I + \frac{\rho IT}{\alpha + T} - c_1 IT = 0$$
$$\Rightarrow I = \frac{s(\alpha + T)}{(d_1 + c_1 T)(\alpha + T) + \rho T} = f(T).$$

If $(d_1 + c_1 T)(\alpha + T) + \rho T \neq 0$. This is a curved surface parallel to the N-axis in the I-T-N surface.

- N_2:

$$r_2 T(1 - \frac{T}{K_2}) - c_2 IT - c_2' TH = 0$$
$$\Rightarrow T = 0 \quad \text{or} \quad T = K_2 + \frac{c_2 K_2}{r_2} I + \frac{c_2'}{r_2} H = g(I, H).$$

N_2 is a plane.

- N_3:

$$r_3 H(1 - \frac{H}{K_3}) - c_3 TH = 0$$
$$\Rightarrow H = 0 \quad \text{or} \quad H = K_3 + \frac{c_3 K_3}{r_3} T = h(T).$$

N_3 is a plane which parallel to I-axis.

4.3.2 Equilibria

There are three types of equilibria:

- **Tumor free** In this category, we consider the tumor population to be zero and the host cells population to be nonzero. The equilibrium is of the form $(\frac{s}{d_1}, 0, K_3)$.

- **Dead** We classify an equilibrium as "dead" if the host cells population is zero. There are two types of this category of equilibria.
  - $(\frac{s}{d_1}, 0, 0)$ in which both tumor and normal cells die off.
  - $(a, b, 0)$ in which a, b satisfy $f(b) = 0, g(a) = 0$. The solution, if it exists, is unique upon fixed parameters. In this case, only the normal cells died off and the tumor cells survived.

- **Coexisting** (a, b, c) in which a, b, c satisfying

$$a = f(b), b = g(a, c), c = h(b), \tag{4.19}$$

which induces

$$\begin{aligned} a &= \frac{s(\alpha + b)}{(d_1 + c_1 b)(\alpha + b) + \rho b} \\ b &= K_2 + \frac{c_2 K_2}{r_2} a + \frac{c_2'}{r_2} c \\ c &= \frac{c_3 K_3}{r_3} b \end{aligned}$$

By solving the second and third linear equations and then plugging into the first one, we can get a cubic equation of a, which means, depending on the parameters, there could be zero, one, two, or three different coexisting equilibria, which may not necessarily locate in the first quadrant, but the whole $\mathbb{R}^3$, theoretically.

4.3.3 Stability

- We use linearization around the equilibria to analyze the stability. The linearized system is as follows

$$\begin{bmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \end{bmatrix} = \begin{bmatrix} -d_1 - c_1 T & \frac{\rho I \alpha}{(\alpha + T)^2} - c_1 I & 0 \\ -c_2 T & r_2 - \frac{2 r_2 T}{K_2} - c_2 I - c_2' H & -c_2' T \\ 0 & -c_3 H & r_3 - \frac{2 r_3 H}{K_3} - c_3 T \end{bmatrix} \begin{bmatrix} u \\ v \\ w \end{bmatrix} \tag{4.20}$$

- Tumor free equilibrium. In principle, we want the tumor free equilibrium to be stable so that the system will move toward the tumor free state starting at least locally. By linearization around this equilibrium, we can get the system

$$\begin{bmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \end{bmatrix} = \begin{bmatrix} -d_1 & \frac{\rho s}{d_1 \alpha} - \frac{c_1 s}{d_1} & 0 \\ 0 & r_2 - \frac{c_2 s}{d_1} - c_2' K_3 & 0 \\ 0 & -c_3 K_3 & -r_3 \end{bmatrix} \begin{bmatrix} u \\ v \\ w \end{bmatrix} \tag{4.21}$$

with eigenvalues

$$\begin{aligned} \lambda_1 &= -d_1 < 0 \\ \lambda_2 &= r_2 - \frac{c_2 s}{d_1} - c_2' K_3 \\ \lambda_3 &= -r_3 < 0 \end{aligned}$$

So the equilibrium is stable when $\lambda_2 < 0$, i.e.

$$r_2 < \frac{c_2 s}{d_1} + c_2' K_3. \tag{4.22}$$

As r_2 is the growth rate of the tumor cells, which is normally large compared with c_2 and c_2', (4.22) tells us there is a big chance that the tumor free equilibrium is unstable. This indicates the importance or the therapies, for example chemotherapy.

- Dead equilibria. Similarly, we use (4.20) to analyze the stability of them.

  * Of the first type of dead equilibrium $(\frac{s}{d_1}, 0, 0)$, the eigenvalues are

$$\begin{aligned} \lambda_1 &= -d_1 < 0 \\ \lambda_2 &= r_2 - \frac{c_2 s}{d_1} \\ \lambda_3 &= r_3 > 0 \end{aligned}$$

    which indicates this equilibrium is always unstable.

  * Of the second type of dead equilibrium $(a, b, 0)$, λ_1 and λ_2 are the solutions of the equation

$$\lambda^2 - (d_1 - r_2 + \frac{2r_2 b}{K_2} + c_2 a)\lambda - d_1 r_2 + \frac{2r_2 b d_1}{K_2} + c_2 a d_1 + \frac{c_2 b \rho a \alpha}{(\alpha + b)^2} + c_1 c_2 a b = 0,$$

    and $\lambda_3 = r_3 - c_3 b$. So this equilibrium could be either stable or unstable, depending on the parameters.

4.4 Model IV

For this model, we focus on investigating the qualitative properties of bang-bang controls in the system, therefore determining the optimal therapies treatments schedule for patients. To achieve this goal, we need to look at the existence and characterization of the optimal bang-bang control. For the background, please, refer to Appendix B.

4.4.1 Objective Functional

In particular, we wish to minimize the objective functional

$$J(v_S, v_I, v_M) = \int_{t_0}^{t_f} T(t) + \varepsilon_S v_S + \varepsilon_I v_I + \varepsilon_M v_M \; dt \tag{4.23}$$

where $\varepsilon_S, \varepsilon_I$ and ε_M are weight factors, $t_0 = 0$, and t_f is the terminal time which is fixed. This control problem is under two constraints. The first one requires the tumor cell population to be bounded throughout the time interval $[0, t_f]$. It is formulated by

$$T(t_f) \leq \Delta, \quad \Delta \text{ is a constant.} \tag{4.24}$$

The other constraint confines the total amount of Chemotherapy medicine used through the therapy. It is given in a integration form.

$$\int_{t_0}^{t_f} v_m(t)dt \leq \Gamma, \quad \Gamma \text{ is a constant.} \tag{4.25}$$

4.4.2 Existence of Optimal Control

We establish the existence of an optimal control by the Filippov-Cesari existence theorem (Theorem 2.25).

Theorem 4.14. *(Existence of Optimal Control) Given the IVP system* (3.4) *under the constraints* (4.24) *and* (4.25)*, with the set of all admissible controls being*

$$U = \{u = (v_s(t), v_I(t), v_M(t)) | v_S(t), v_I(t), v_M(t) \in [0,1] \textit{piecewise continuous}\},$$

then there exists an optimal control $\widehat{u} = (\widehat{v_S}, \widehat{v_I}, \widehat{v_M})$ *for the objective functional* (4.23)*, namely,*

$$J(\widehat{u}) = \min_{u \in [0,1]^3} J(u).$$

Proof. To apply the Filippov-Cesari existence theorem (Theorem 2.25), we need to verify its four conditions.

Use the notation of Theorem 2.25 for our system, then

$$x = \begin{pmatrix} T \\ N \\ C \\ S \\ I \\ M \end{pmatrix}$$

where $x \in \mathbb{R}^6$, and

$$N(x,t) : \mathbb{R}^6 \times \mathbb{R}^+ \to \mathbb{R}^7.$$

$N(x,t) =$

$$\begin{pmatrix} T(t) + \varepsilon_S v_S + \varepsilon_I v_I + \varepsilon_M v_M + \gamma \\ rT(1 - \frac{T}{K}) - cNT - D(S,T)T - k_T(1 - e^{-\sigma_T M})T \\ eC - fN - pNT + \frac{p_N NI}{g_N + I} - k_N(1 - e^{-\sigma_N M})N \\ \alpha - \beta C - k_C(1 - e^{-\sigma_C M})C \\ -\frac{\theta m S}{\theta + I} - \frac{u_0 S^2 C I}{\kappa + I} - qST + a_1 NT + a_2 CT + \frac{p_I SI}{g_I + I} + \frac{p_T ST}{g_T + T} - k_S(1 - e^{-\sigma_S M})S + \eta_S v_S(t) \\ -\mu_I I + \rho C + \frac{p_S SI}{g_S + I} + \eta_I v_I(t) \\ -\gamma M + \eta_M v_M(t) \end{pmatrix}$$

where $\gamma \leq 0$. The first one asks the existence of an admissible solution pair for the state and controls, which was showed in [34] and [35].

For the second condition, notice all of the control terms and γ are linear, therefore for any $A_1, A_2 \in N(x,t)$, $\zeta A_1 + (1-\zeta)A_2 \in N(x,t)$ for $\zeta \in [0,1]$. This shows $N(x,t)$ is convex.

For the third condition, consider the first equation of the IVP system (3.4):

$$\begin{aligned}\dot{T} &= rT(1-\frac{T}{K}) - cNT - D(S,T)T - k_T(1-e^{-\sigma_T M})T \\ &\leq rT.\end{aligned}$$

Solve the corresponding equality, we get $\widetilde{T} = T_0 e^{rt}$. By the Kamke Comparison Theorem, $T(t) \leq T_0 e^{rt}$. Therefore, $T_0 e^{rt_f}$ is an upper bound of $T(t)$. We denote it as T^*. Now, consider the system of $x^+ = \begin{bmatrix} T^+ & N^+ & C^+ & S^+ & I^+ & M^+ \end{bmatrix}^T$:

$$(T^+)' = rT^+ \tag{4.26}$$

$$(N^+)' = eC^+ + p_N N^+ \tag{4.27}$$

$$(C^+)' = \alpha \tag{4.28}$$

$$(S^+)' = a_1 N^+ T^* + a_2 C^+ T^* + (p_I + p_T)S^+ + \eta_S v_S(t) \tag{4.29}$$

$$(I^+)' = \rho C^+ + p_S S^+ + \eta_I v_I(t) \tag{4.30}$$

$$(M^+)' = \eta_M v_M(t) \tag{4.31}$$

Compare with the system (3.4), it's easy to see that $(x^+)' \geq x'$. Therefore, x^+ is a supersolution of the system (3.4). We only need to prove it is bounded, which can be shown by the following steps. Notice that the time interval is $[t_0, t_f]$, which is finite.

1. By (4.28), C^+ is bounded above. Say an upper bound is C^*. Also, T^+ is bounded above by T^*. M^+ is also bounded above because of (4.25). Let M^* denote an upper bound of it.

2. Combine the above results with (4.27), we get $(N^+)' \leq Constant + p_n N^+$, therefore N^+ is bounded above by, say, N^*.

3. Combine the results from above two steps with (4.29), together with the fact that $v_S(t)$ is finite, we get $(S^+)' \leq Constant + (p_I + p_T)S^+$. Then S^+ could be bounded by, say, S^*. Similarly, I^+ could be bounded by I^*.

Thus, we find a constant $\delta > 0$ such that $\|x\| < \|x^+\| < \delta$.

Since v_s, v_I, v_M are all finite, there must be an upper bound for $\|u\| = \|(v_s, v_I, v_M)\|$ over $[t_0, t_f]$. □

4.4.3 Characterization of the Optimal Bang-bang Control

We now develop the representations of the optimal control by using PMP (Theorem 2.26).

The first constraint is a terminal inequality, but the second one is given in the integral form. Therefore, we need to deal with it before we start to discuss the characterization. The method is similar as the one being used in [36].

We introduce a new variable Y for this purpose. Assume

$$\dot{Y} = v_M(t), \tag{4.32}$$

then by (4.25),

$$Y(0) = 0 \quad \text{and} \quad Y(t_f) \leq \Gamma. \tag{4.33}$$

We add (4.32) to the system (3.4) as we add a extra variable. Also, (4.33) is viewed as a new constraint to replace the previous second constraint. We then consider the adjoint functions.

Theorem 4.15. *(Characterization of the Optimal Bang-bang Control). Given an optimal control triple, $\widehat{u} = (\widehat{v_S}, \widehat{v_I}, \widehat{v_M})$, there exists adjoint variables $\boldsymbol{\lambda} = (\lambda_1, \ldots, \lambda_7)$ satisfying: (To*

simplify the expressions, define $\Pi = dl \cdot \dfrac{(s/n^l)(S/T)^{l-1}}{[s/n^l + (S/T)^l]^2}$.*)*

$$
\begin{aligned}
\dot{\lambda_1} &= -1 - \lambda_1 \left[r - \frac{2rT}{K} - cN - D + \Pi(S/T) - k_T(1 - e^{-\sigma_T M}) \right] \\
&\quad -\lambda_2 pN - \lambda_4 \left[-qS + a_1 N + a_2 C + \frac{p_T g_T S}{(g_T + T)^2} \right] \\
\dot{\lambda_2} &= \lambda_1 cT - \lambda_2 \left[-f - pT + \frac{p_N I}{g_N + I} k_N (1 - e^{-\sigma_N M}) \right] - \lambda_4 a_1 T \\
\dot{\lambda_3} &= -\lambda_2 e + \lambda_3 \left[\beta + k_C (1 - e^{-\sigma_C M}) \right] + \lambda_4 (\frac{u_0 S^2 I}{\kappa + I} - a_2 T) - \lambda_5 \rho \\
\dot{\lambda_4} &= \lambda_1 \Pi + \lambda_4 \left[\frac{\theta m}{\theta + I} + \frac{2u_0 SCI}{\kappa + I} + qT - \frac{p_I I}{g_I + I} - \frac{p_T T}{g_T + T} + k_S (1 - e^{-\sigma_S M}) \right] - \lambda_5 \frac{p_S I}{g_S + I} \\
\dot{\lambda_5} &= -\lambda_2 \frac{p_N g_N N}{(g_N + I)^2} - \lambda_4 \left[\frac{\theta m S}{(\theta + I)^2} - \frac{u_0 \kappa S^2 C}{(\kappa - I)^2} + \frac{p_I g_I S}{(g_I + I)^2} \right] + \lambda_5 \left[\mu_I - \frac{p_S g_S S}{(g_S + I)^2} \right] \\
\dot{\lambda_6} &= \lambda_1 k_T \delta_T T e^{-\delta_T M} + \lambda_2 k_N \delta_N N e^{-\delta_T N} + \lambda_3 k_C \delta_C C e^{-\delta_T C} + \lambda_4 k_S \delta_S S e^{-\delta_S M} + \lambda_6 \gamma \\
\dot{\lambda_7} &= 0
\end{aligned}
$$

Moreover, the transversality conditions are

$$\lambda_i(t_f) = 0, i = 2, \ldots, 6, \lambda_1(t_f) \geq 0, \lambda_7(t_f) \geq 0.$$

In addition, of the optimal controls, the switching functions are:

$$\psi_S = \varepsilon_S + \lambda_4 \eta_S \tag{4.34}$$

$$\psi_I = \varepsilon_I + \lambda_5 \eta_I \tag{4.35}$$

$$\psi_M = \varepsilon_M + \lambda_6 \eta_M \tag{4.36}$$

and the characterizations are given by:

$$v_S(t) = \begin{cases} 0 & if \quad \psi_S > 0 \\ 1 & if \quad \psi_S < 0 \\ singular & if \quad \psi_S = 0 \end{cases}$$

$$v_I(t) = \begin{cases} 0 & if \quad \psi_I > 0 \\ 1 & if \quad \psi_I < 0 \\ singular & if \quad \psi_I = 0 \end{cases}$$

$$v_M(t) = \begin{cases} 0 & if \quad \psi_M > 0 \\ 1 & if \quad \psi_M < 0 \\ singular & if \quad \psi_M = 0 \end{cases}$$

Proof. We follow the regular outline of solving optimal control problem stated in Appendix B. First of all, let's construct the Hamiltonian of the modified system.

$$\begin{aligned} H &= T(t) + \varepsilon_S v_S + \varepsilon_I v_I + \varepsilon_M v_M \\ &\quad + \lambda_1 \left[rT(1 - \frac{T}{K}) - cNT - D(S,T)T - k_T(1 - e^{-\sigma_T M})T \right] \\ &\quad + \lambda_2 \left[eC - fN - pNT + \frac{p_N NI}{g_N + I} - k_N(1 - e^{-\sigma_N M})N \right] \\ &\quad + \lambda_3 \left[\alpha - \beta C - k_C(1 - e^{-\sigma_C M})C \right] \\ &\quad + \lambda_4 \left[-\frac{\theta m S}{\theta + I} - \frac{u_0 S^2 CI}{\kappa + I} - qST + a_1 NT + a_2 CT + \frac{p_I SI}{g_I + I} \right. \\ &\qquad \left. + \frac{p_T ST}{g_T + T} - k_S(1 - e^{-\sigma_S M})S + \eta_S v_S(t) \right] \\ &\quad + \lambda_5 \left[-\mu_I I + \rho C + \frac{p_S SI}{g_S + I} + \eta_I v_I(t) \right] \\ &\quad + \lambda_6 \left[-\gamma M + \eta_M v_M(t) \right] \\ &\quad + \lambda_7 v_M(t). \end{aligned}$$

Then, the adjoint state equations can be formulated as

$$\begin{aligned}\dot{\lambda_1} = -\frac{\partial H}{\partial T} &= -1 - \lambda_1 \left[r - \frac{2rT}{K} - cN - D + \Pi(S/T) - k_T(1 - e^{-\sigma_T M}) \right] \\ &\quad -\lambda_2 pN - \lambda_4 \left[-qS + a_1 N + a_2 C + \frac{p_T g_T S}{(g_T + T)^2} \right] \end{aligned} \tag{4.37}$$

$$\dot{\lambda_2} = -\frac{\partial H}{\partial N} = \lambda_1 cT - \lambda_2 \left[-f - pT + \frac{p_N I}{g_N + I} k_N (1 - e^{-\sigma_N M}) \right] - \lambda_4 a_1 T \tag{4.38}$$

$$\dot{\lambda_3} = -\frac{\partial H}{\partial C} = -\lambda_2 e + \lambda_3 \left[\beta + k_C (1 - e^{-\sigma_C M}) \right] + \lambda_4 (\frac{u_0 S^2 I}{\kappa + I} - a_2 T) - \lambda_5 \rho \tag{4.39}$$

$$\begin{aligned}\dot{\lambda_4} &= -\frac{\partial H}{\partial S} \\ &= \lambda_1 \Pi + \lambda_4 \left[\frac{\theta m}{\theta + I} + \frac{2u_0 SCI}{\kappa + I} + qT - \frac{p_I I}{g_I + I} - \frac{p_T T}{g_T + T} + k_S (1 - e^{-\sigma_S M}) \right] \\ &\quad -\lambda_5 \frac{p_S I}{g_S + I} \end{aligned} \tag{4.40}$$

$$\begin{aligned}\dot{\lambda_5} &= -\frac{\partial H}{\partial I} \\ &= -\lambda_2 \frac{p_N g_N N}{(g_N + I)^2} - \lambda_4 \left[\frac{\theta m S}{(\theta + I)^2} - \frac{u_0 \kappa S^2 C}{(\kappa - I)^2} + \frac{p_I g_I S}{(g_I + I)^2} \right] + \lambda_5 \left[\mu_I - \frac{p_S g_S S}{(g_S + I)^2} \right] \end{aligned} \tag{4.41}$$

$$\begin{aligned}\dot{\lambda_6} &= -\frac{\partial H}{\partial M} \\ &= \lambda_1 k_T \delta_T T e^{-\delta_T M} + \lambda_2 k_N \delta_N N e^{-\delta_T N} + \lambda_3 k_C \delta_C C e^{-\delta_T C} + \lambda_4 k_S \delta_S S e^{-\delta_S M} \\ &\quad +\lambda_6 \gamma \end{aligned} \tag{4.42}$$

$$\begin{aligned}\dot{\lambda_7} &= -\frac{\partial H}{\partial Y} \\ &= 0 \end{aligned} \tag{4.43}$$

We first prove that the above system has a solution. Since the right-hand side functions are linear combination of λ_is, hence continuous with respect to $\boldsymbol{\lambda}$. From the previous theorem, we know all of the supersolutions are bounded on $[0, t_f]$. Therefore, by Theorem 2.23, we get the existence of $\lambda_i, i = 1, \ldots, 7$.

Next, we want to find the transversality conditions. For the original system, no variable except $T(t)$ and $Y(t)$ has restriction. In another word, all variables except $T(t)$ and $Y(t)$ are free. Hence, by (2.12) – (2.14) in Theorem 2.26,

$$\lambda_i(t_f) = 0, \quad i = 2, \ldots, 6.$$

From the proof of theorem 4.14, we know $T(t)$ has an upper bound $T_0 e^{rt_f}$, Thus, $\lambda_1(t_f) \geq 0$. Similarly, by (4.33), $Y(t)$ has an upper bound Γ, which indicates $\lambda_7(t_f) \geq 0$.

Finally, we can find the switching functions and the characterizations of the optimal bang-bang control according to Appendix B. By (B.3),

$$(f_2, g_2) = \begin{cases} (\varepsilon_S, \eta_S), & \text{for } v_S(t), \\ (\varepsilon_I, \eta_I), & \text{for } v_I(t), \\ (\varepsilon_M, \eta_M), & \text{for } v_M(t). \end{cases}$$

Thus, we get (4.34)–(4.36). The characterizations are given by the definition. □

Chapter 5

Conclusion and Discussion

We have studied four different ODE systems about cancer therapies. For the first three models, we focus on the qualitative analysis of their dynamical properties; for the last one, we investigate the optimal control for the whole system for the purpose of improving the treatment protocol.

There are several further subjects that we can look at in the future:

1. For the optimal control, we can further look at higher order representation of the control. Also, the competition between different populations may need some further, more detailed assumptions, so as to deal with different kinds of tumor cells.

2. All these four systems are built by ODEs. To study and understand the interrelationship more specifically, we can employ the tool of partial differential equations (PDE). A summary of some work that has been done in this area can be found in [37].

Bibliography

[1] G. Belostotski and H.I. Freedman. A control theory model for cancer treatment by radiotherapy. *Int. J. Pure Appl. Math*, 25:447–480, 2005.

[2] L.G. Hanin, L.V. Pavlova, and A.Y. Yakovlev. *Biomathematical problems in optimization of cancer radiotherapy*. CRC, 1993.

[3] R.K. Sachs, P.L. Chen, P.J. Hahnfeldt, and L.R. Hlatky. Dna damage caused by ionizing radiation. *Mathematical biosciences*, 112(2):271–303, 1992.

[4] H. Schollnberger. Adaptive response and dose-response plateaus for initiation in a state-vector model of carcinogenesis. *International journal of radiation biology*, 75(3):351–364, 1999.

[5] J.A. Nickoloff and M.F. Hoekstra. *DNA Damage and Repair: Advances from phage to humans*. Contemporary cancer research. Humana Press, 2001.

[6] H.D. Thames and J.H. Hendry. *Fractionation in radiotherapy*. Taylor & Francis, 1987.

[7] R.T. Skeel. *Handbook of Cancer Chemotherapy*. Number v. 236 in Handbook of Cancer Chemotherapy. Lippincott Williams & Wilkins, 2007.

[8] H.E. Skipper, F.M. Schabel Jr, and W.S. Wilcox. Experimental evaluation of potential anticancer agents. xiii. on the criteria and kinetics associated with" curability" of experimental leukemia. *Cancer chemotherapy reports. Part 1*, 35:1, 1964.

[9] L. Norton and R. Simon. Tumor size, sensitivity to therapy, and design of treatment schedules. *Cancer treatment reports*, 61(7):1307, 1977.

[10] L. Norton and R. Simon. The norton-simon hypothesis revisited. *Cancer treatment reports*, 70(1):163, 1986.

[11] N.H. Holford and L.B. Sheiner. Pharmacokinetic and pharmacodynamic modeling in vivo. *Critical reviews in bioengineering*, 5(4):273, 1981.

[12] K.R. Fister and J.H. Donnelly. Immunotherapy: an optimal control theory approach. *Mathematical biosciences and engineering: MBE*, 2(3):499, 2005.

[13] C. Chan, A.J.T. George, and J. Stark. T cell sensitivity and specificity-kinetic proofreading revisited. *Discrete and Continuous Dynamical Systems Series B*, 3(3):343–360, 2003.

[14] L.G. de Pillis, W. Gu, and A. Radunskaya. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. *Journal of theoretical biology*, 238(4):841–862, 2006.

[15] S. T. R. Pinho, H. I. Freedman, and F. Nani. A chemotherapy model for the treatment of cancer with metastasis. *Mathematical and Computer Modelling*, 36(7-8):773 – 803, 2002.

[16] L.G. de Pillis and A. Radunskaya. A mathematical model of immune response to tumor invasion. *Computational Fluid and Solid Mechanics*, 2003.

[17] K.R. Fister and J.C. Panetta. Optimal control applied to competing chemotherapeutic cell-kill strategies. *SIAM Journal on Applied Mathematics*, 63(6):1954–1971, 2003.

[18] H.I. Freedman and S.T.R. Pinho. Persistence and extinction in a mathematical model of cell populations affected by radiation. *Periodica Mathematica Hungarica*, 56(1):25–35, 2008.

[19] H.I. Freedman and S.T.R. Pinho. Stability criteria for the cure state in a cancer model with radiation treatment. *Nonlinear Analysis: Real World Applications*, 10(5):2709–2715, 2009.

[20] L. G. de Pillis and A. Radunskaya. A mathematical tumor model with immune resistance and drug therapy: an optimal control approach. *Journal of Theoretical Medicine*, 3:79–100, 2000.

[21] L.G. de Pillis, K.R. Fister, W. Gu, C. Collins, M. Daub, D. Gross, J. Moore, and B. Preskill. Seeking bang-bang solutions of mixed immuno-chemotherapy of tumors. *Electronic Journal of Differential Equations*, 2007(171):1–24, 2007.

[22] A. Illanes and S.B. Nadler. *Hyperspaces: fundamentals and recent advances*. Monographs and textbooks in pure and applied mathematics. M. Dekker, 1999.

[23] Konstantin Mischaikow, Hal Smith, and Horst R. Thieme. Asymptotically autonomous semiflows: chain recurrence and Lyapunov functions. *Trans. Amer. Math. Soc.*, 347(5):1669–1685, 1995.

[24] C.C. Chicone. *Ordinary differential equations with applications*. Texts in applied mathematics. Springer, 2006.

[25] J.K. Hale. *Ordinary Differential Equations*. Dover Publications, 2009.

[26] L. Perko. *Differential equations and dynamical systems*. Texts in applied mathematics. Springer, 2001.

[27] W. Walter. *Ordinary differential equations*. Graduate texts in mathematics.

[28] D.L. Lukes. *Differential equations: classical to controlled*. Mathematics in science and engineering.

[29] R.F. Hartl, S.P. Sethi, and R.G. Vickson. A survey of the maximum principles for optimal control problems with state constraints. *SIAM review*, 37(2):181–218, 1995.

[30] M.I. Kamien and N.L. Schwartz. *Dynamic optimization: the calculus of variations and optimal control in economics and management*. Advanced textbooks in economics.

[31] Vladimir Kuznetsov, Iliya Makalkin, Mark Taylor, and Alan Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56:295–321, 1994.

[32] Denise Kirschner and John Carl Panetta. Modeling immunotherapy of the tumor immune interaction. *Journal of Mathematical Biology*, 37:235–252, 1998.

[33] L.G. de Pillis and A. Radunskaya. A mathematical model of immune response to tumor invasion. *Computational Fluid and Solid Mechanics*, 2:1661–1668, 2003.

[34] K.R. Fister and J.H. Donnelly. Immunotherapy: an optimal control theory approach. *Mathematical biosciences and engineering: MBE*, 2(3):499, 2005.

[35] T.N. Burden, J. Ernstberger, and K.R. Fister. Optimal control applied to immunotherapy. *Discrete and Continuous Dynamical Systems Series B*, 4(1):135–146, 2004.

[36] D.E. Kirk. *Optimal control theory: an introduction*. Dover books on engineering. Dover Publications, 2004.

[37] P.S. Kim, D. Levy, and P.P. Lee. Modeling and simulation of the immune system as a self-regulating network. *Methods in enzymology*, 467:79–109, 2009.

[38] J.R. Munkres. *Topology*. Prentice Hall, 2000.

[39] L.M. Hocking. *Optimal control: an introduction to the theory with applications*. Oxford applied mathematics and computing science series. Clarendon Press, 1991.

[40] R.V. Gamkrelidze. *Principles of optimal control theory*. Mathematical concepts and methods in science and engineering. Plenum Press, 1978.

[41] G. Leitmann. *The calculus of variations and optimal control: an introduction*. Mathematical concepts and methods in science and engineering. Plenum Press, 1981.

[42] J. Zabczyk. *Mathematical control theory: an introduction*. Modern Birkhauser Classics. Birkhauser, 2007.

[43] S. Lenhart and J.T. Workman. *Optimal control applied to biological models*. Chapman and Hall/CRC mathematical & computational biology series. Chapman & Hall/CRC, 2007.

Appendices

Appendix A

One-point compactification and associated results

Definitions: A topological space X is said to be *locally compact at* x if there is some compact subspace C of X that contains a neighborhood of x. If X is locally compact at each of its points, X is said to be *locally compact*.

Theorem [38]: Let X be a topological space. Then X is locally compact Hausdorff if and only if there exists a space Y satisfying the following conditions:

1. X is a subspace of Y.
2. The set $Y - X$ consists of a single point.
3. Y is compact Hausdorff space.

Definitions: If Y is a compact Hausdorff space and X is a proper subspace of Y whose closure equals Y, then Y is said to be a *compactification* of X. If $Y - X$ equals a single point, then Y is called the *one-point compactification* of X.

Appendix B

Fundamental knowledge of optimal control theory

1. **General formulation [39] [40]**

   We consider the following differential equation in $\mathbb{R}^n$,

   $$\dot{\mathbf{x}} = f(t, \mathbf{x}, \mathbf{u}), \tag{B.1}$$

   The point $\mathbf{x} = (x_1, \cdots, x_n) \in \mathbb{R}^n$ will be called the *state vector (variables)*, and the parameter $\mathbf{u} = (u_1, \cdots, u_r) \in \mathbb{R}^r$ will be called the *control vector (variables)*.

   We call (B.1) the *state equation*, where $f = f(t, \mathbf{x}, \mathbf{u})$ maps from $\mathbb{R}^{1+n+r}$ to $\mathbb{R}^n$. Any absolutely continuous function $\mathbf{x}(t), t \in [t_1, t_2]$ is called a *solution* of this equation on the interval $[t_1, t_2]$ if it satisfies (B.1) for almost all $t \in [t_1, t_2]$.

2. **Hypotheses [39] [40]**

   In order to assure that the state equation possesses a unique solution for a given initial value, we introduce certain hypotheses:

   For the state equation, we assume that f is continuous on its domain and has a continuous derivative with respect to x:

   $$\frac{\partial f}{\partial x} = \left(\frac{\partial f}{\partial x_1}, \cdots, \frac{\partial f}{\partial x_n} \right).$$

   Now we introduce conditions for control vectors. We call a function $\mathbf{x}(t) : [t_0, t_1] \to \mathbb{R}^r$ a *control vector function*, where $t_0, t_1 \in \mathbb{R}^+ \cup \{0\}, t_0 < t_1$. It is *admissible* if it is well defined, measurable, piecewise continuous, integrable with respect to t, and takes its values on a prescribed set $U \subset \mathbb{R}^r$. Here U is called the *set of admissible values* of the control vector.

   We substitute the u in (B.1) by an admissible control $\mathbf{u}(t)$, then we obtain

   $$\dot{\mathbf{x}} = f(t, \mathbf{x}, \mathbf{u}(t)) = F(t, \mathbf{x}),$$

   where $F(t, \mathbf{x})$ is continuously differentiable with respect to $\mathbf{x}$ and measurable with respect to t. By the hypotheses above, we know that given an initial value $\mathbf{x}(t_0) = \mathbf{x}^0$, the state equation (B.1) has a unique piecewise continuous solution. We call $\mathbf{x}(t_0) = \mathbf{x}^0$ and $\mathbf{x}(t_1) = \mathbf{x}^1$ *initial state* and *terminal state*, respectively.

3. **Terminal Time and Feasible Controls**

   We are concerned with problems in which the initial state (value) is assumed and the terminal state belongs to a given subset, T. We called it the *target set*. Notice that the terminal state may be given, or we may only require it to belong to some curve or surface. We call t_1 in the first case is *fixed*, and in the second case is *free*.

   We also restrict consideration to those admissible controls which generate solutions starting from $\mathbf{x}^0$ and terminating at T. A control $\mathbf{u}(t) : [t_0, t_1] \to \mathbb{R}^r$ is *feasible* at $\mathbf{x}^0$ if it is admissible and generates the solution $\mathbf{x}(t) : [t_0, t_1] \to \mathbb{R}^n$ such that $\mathbf{x}(t_0) = \mathbf{x}^0, \mathbf{x}(t_1) \in T$. We let $\mathcal{U}$ denote the set of all feasible controls at $\mathbf{x}^0$.

4. **Objective Functional and Optimal Control Problem [41] [42]**

   Given functions $F(t, \mathbf{x}, \mathbf{u}) : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^r \to \mathbb{R}$ and $S(\mathbf{x}) : \mathbb{R}^n \to \mathbb{R}$, we called

$$J(t, \mathbf{x}, \mathbf{u}, \mathbf{x}^1, t^1) = S(\mathbf{x}^1) + \int_{t_0}^{t_1} F(t, \mathbf{x}(t), \mathbf{u}(t))\ dt \tag{B.2}$$

   the general form of *cost function* or *objective functional*, where $\mathbf{u}(t)$ is an admissible control.

   Therefore, the simplest optimal control problem can be stated as follows:

   Given the state equation (B.1), the set of admissible values U, the terget set T, and the objective functional (B.2), find a control in $\mathcal{U}$ that minimizes (maximizes) J over all controls in $\mathcal{U}$.

   In another word, $\mathbf{u}^*(t) : [t_0, t_1^*] \to \mathbb{R}^r$ is *optimal* at $\mathbf{x}^0$ if and only if it generates the solution $\mathbf{x}^*(t) : [t_0, t_1^*] \to \mathbb{R}^n$ such that $\mathbf{x}^*(t_1^*) \in T$ and

$$J(t, \mathbf{x}^*, \mathbf{u}^*, \mathbf{x}(t_1^*), t_1^*) \leq (\geq) J(t, \mathbf{x}, \mathbf{x}, \mathbf{x}^1, t^1)$$

   for all $\mathbf{u}(t) \in \mathcal{U}$.

   Remark: Sometimes the states variables and control variables may be subject to some extra constraints.

5. **Existence, necessary conditions, and sufficient conditions of optimal controls**

   This four questions, existence,uniqueness, necessary condition, and sufficient condition, have their counterparts in optimal control theory.

   - **Existence:** It is very natural to ask the existence of an optimal control before we start to look for one. Actually there are examples showing that the optimal control may not exist. Also, all of the formulations of the necessary and sufficient conditions, such as PMP, are based on the existence. Actually, it is the most difficult one to answer.
   - **Necessary Condition:** We can derive the optimal control by the Pontryagin's Maximum/Minimum Principle, or PMP. The principle, being stated as Theorem 2.26 in this thesis, introduced the idea of "adjoint" functions to append the

state equation to the objective functional. Adjoint functions have a similar purpose as Lagrange multipliers variables in multiple-variable calculus, which append constraints to the function of several variables to be maximized (or minimized). Thus, we begin by finding appropriate conditions that the adjoint function should satisfy. Then, by differentiating the map from the control to the objective functional, we will derive a characterization of the optimal control variables in terms of the optimal state variables and corresponding adjoint.

After introducing the adjoint and Hamiltonian as in the Theorem 2.26, we have converted the problem of finding a control that maximizes (or minimizes) the objective functional subject to the state equation and initial condition, to maximizing (or minimizing) the Hamiltonian pointwise with respect to the control.

- We don't discuss the sufficient condition and uniqueness of the optimal control in this thesis.

6. **Optimality system [43]**

Now, we outline how the optimal theory can be applied to solve the simplest problems. $(\mathbf{x}^*, \mathbf{u}^*)$ is the pair of optimal variables, and $\boldsymbol{\lambda}(t)$ is the adjoint variable.

(i). Verify the existence of the optimal problem.

(ii). Form the Hamiltonian for the problem.

(iii). Write the adjoint state equation, i.e., a differential equation of $\dot{\boldsymbol{\lambda}}$. Also, we get the corresponding boundary condition $\boldsymbol{\lambda}(t_1)$ from the original initial and terminal conditions. We call the new condition as *transversality condition*.

(iv). Try to eliminate $\mathbf{u}^*$ by using the optimality equation $H_{\mathbf{u}} = 0$, i.e., solve for $\mathbf{u}^*$ in term of $\mathbf{x}^*$ and $\boldsymbol{\lambda}$. We call the result as *optimality condition*.

(v). Solve the two state equations for $\mathbf{x}^*$ and $\boldsymbol{\lambda}$ with two boundary conditions, substituting $\mathbf{u}^*$ in the state equations with the expression for the optimal control from the last step.

(vi). After finding the optimal state and adjoint, solve for the optimal control.

When we are able to solve for the optimal control in terms of $\mathbf{x}^*$ and $\boldsymbol{\lambda}$, we will call that formula for $\mathbf{u}^*$ the *characterization of the optimal control*. The state equations and the adjoint equations together with the characterization of the optimal control and the boundary conditions are called the *optimality system*.

7. **Bang-bang controls**

Since $u(t)$ is bounded, say in $\mathbb{R}^1$, $u(t) \in [a, b]$, we can defined $v(t)$ as

$$u(t) = \frac{1}{2}(a+b) + \frac{1}{2}(a-b)v(t).$$

Therefore, $v(t) \in [-1, 1]$ and is also integrable. Consider a subset of U where the corresponding $v(t)$ only takes the extreme values. Any change in the value of the

control is actually switching from one extreme value to the other. Such controls are called *bang-bang*.

8. **Linear Bang-bang control [43]**

Consider the optimal control problem

$$\begin{aligned} & \min_{\mathbf{u}} \int_{t_0}^{t_1} f_1(t,\mathbf{x}) + \mathbf{u}(t) f_2(t,x)\ dt, \\ \text{subject to} \quad & \dot{\mathbf{x}} = g_1(t,\mathbf{x}) + \mathbf{u}(t) g_2(t,\mathbf{x}), \quad \mathbf{u}(0) = \mathbf{u}_0, \\ & a \le \mathbf{u}(t) \le b. \end{aligned}$$

The integrand function inside the objective functional and the state equation are both linear functions of the control variable u. Thus, the Hamiltonian is also a linear function of u, which can be written as

$$H(\mathbf{x},\mathbf{u},t) = [f_1(t,\mathbf{x}) + \boldsymbol{\lambda}(t) g_1(t,\mathbf{x})] + \mathbf{u}(t)[f_1(t,\mathbf{x}) + \boldsymbol{\lambda}(t) g_2(t,\mathbf{x})].$$

Define

$$\psi(t) = f_2(t,\mathbf{x}) + \boldsymbol{\lambda}(t) g_2(t,\mathbf{x}), \tag{B.3}$$

usually called the *switching function*. Our characterization of $\mathbf{u}^*$ is

$$\mathbf{u}^*(t) = \begin{cases} a & \text{if } \phi(t) < 0, \\ ? & \text{if } \phi(t) = 0, \\ b & \text{if } \phi(t) > 0. \end{cases}$$

If $\psi = 0$ cannot be sustained over a time interval, but occurs only at finitely many points, then the control $\mathbf{u}^*$ is bang-bang.

If $\psi \equiv 0$ on some interval of time, we say $\mathbf{u}^*$ is *singular* on that interval. A characterization of $\mathbf{u}^*$ on this interval must be found using other information.