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University of Alberta

A Control Theory Model for Cancer Treatment by Radiotherapy

by

Gregory Belostotski

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in

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Signature

18287 93 Av Edmonton, AB
T5T 1V2, Canada

Abstract

A control theory model for radiotherapy treatment of cancer, based on the Lotka-Voltera competition system, is created to analyze the dynamics of interaction of cancer and healthy tissues. Using standard stability analysis, the stability of the system is described and qualified as "treatment" or "cure". The key feature of the model is the use of a harvesting-type control term to represent radiotherapy, where radiation-induced harvesting is equivalent to the reduction of cancer cell concentration. Furthermore, four different methods of radiation delivery are modelled with four different control mechanisms. Perturbation analysis is used to model the side-effects and accidental harvesting of healthy cells by radiation. Finally, the model is validated with numerical examples with the use of a Matlab differential equation solver.

I would like to acknowledge my parents for all the big and little things that they do.

I would like mention my supervisor Dr. Freedman in appreciation for all his help with this thesis. Big thanks to my brother Leonid for his frequent help and advice. Also special thanks to Michelle Grinman for her medical expertise and advice.

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Chapter 1

Introduction

This thesis is an attempt to model the dynamics of cancer reduction through treatment by radiotherapy. The goal is to create a mathematical model that successfully describes the following features of a treatment strategy:

1. an early detection leads to a successful treatment,
2. different types of disease require different treatment plans,
3. the outcome of the treatment depends on the initial conditions (conditions at the time of diagnosis) as well as on the characteristics of the disease,
4. very small side-effects and treatment inaccuracies do not affect the outcome.

To lay the foundation for the work, in Chapter 2 we present medical and mathematical background, along with definitions, theorems, and the outline of mathematical theory. In Chapter 3, we introduce the control theory competition model. The model is a dynamical system of ordinary differential equations with control. The control is used to represent the reduction of cell concentration due to radiation. Standard stability analysis [19] is used to derive conditions leading to a stable, positive internal

equilibrium; a stable, positive internal periodic solution; or a complete eradication of cancer. These results, in practical terms, may be described as "cure", "treatment", or "death" as follows:

1. a "cure" is the case where cancer concentration tends to zero (cancer eradication),
2. a "treatment" is a stable positive equilibrium or a stable positive periodic solution,
3. a "death" is caused by the solutions case where the healthy tissue concentration tends to zero (healthy tissue extinction).

This project features four different mechanisms of radiation delivery. They include continuous, constant radiation, continuous radiation that is proportional to the instantaneous cancer concentration, continuous radiation that is proportional to the ratio of cancer to healthy cell concentration, and periodic administration of radiation. These mechanisms reflect some current practices and practicality of radiation administration. Perturbation analysis is used in Chapter 4 to model the side-effects of radiation. We use perturbation analysis to reflect the realities of radiotherapy such as careful administration of radiation and some little expected side-effects. Finally, Chapters 5 and 6 provide numerical examples and conclusions respectively. To solve the system numerically, we select parameter values that meet the stability conditions as well as generalize some of the available data. Unfortunately, to the best knowledge of the author, not all parameters may be generated from experimental data. This need to collect more information and data is outlined in the conclusion in Chapter 6. Furthermore, we provide a discussion on the implications of this work, directions for future research, selection of treatment plans, and testing of this theory.

Chapter 2

Motivation and Project Outline

Cancer is becoming a crucial field of research given its increased incidence in North America in recent decades. In fact, the 2004 press release from the Canadian Cancer Society estimates that there will be close to 150 thousand new cases and 68 thousand deaths in Canada in that year. This represents an increase from predictions in 2003 of 140 thousand new cases and 67 thousand new deaths [6]. However, the emergence of new technologies has the potential for significant morbidity and mortality reduction [15, 21].

The term "cancer" encompasses diseases with enormous diversity [15, 21]. For example, cancers may vary in terms of the organ system they affect, their interactions with healthy tissue, and their ability to differentiate, replicate, and metastasize [1, 15, 21].

All cancers requiring treatment have high differentiation and proliferation rates. To support this rapid growth, cancer cells often compete with the surrounding tissue for various resources to support their cell function. Such resources may include oxygen, space, and nutrients such as phosphorous [14]. Cancer, if left to run its course without treatment, may also interfere with the normal functioning of the organism ei-

ther by mass effects, or by the release of substances that induce biochemical changes in the organism [15, 21]. However, medical research and practice have developed procedures and treatments that can be successful in limiting or even curing a variety of cancers. Included in these developments are surgery, chemotherapy, radiation therapy, immunotherapy, and other primary or adjuvant interventions [7, 15, 21, 22].

In this work, we concentrate on radiotherapy as the primary treatment strategy as it has been proven to be an effective tool in combating cancer [18, 21]. Radiation therapy is a treatment procedure that uses radiation to kill malignant cells. This treatment targets rapidly reproducing cells such as those in cancer [22]. Therefore, when cancer cells are irradiated, there is a lesser effect on more slowly reproducing surrounding healthy cells. As such, the intent of this project is to model the dynamics and interactions of healthy and cancer cells under these conditions.

There have been numerous mathematical models developed recently that mainly focus on the natural history of cancer and do not analyze the effects of treatment. The American Institute of Mathematical Sciences, publisher of the Discrete and Continuous Dynamical Systems Journal, has devoted an entire issue of their publication to this topic [12]. It includes 21 papers on the subject of mathematical models in cancer. Of these models, most deal with the modeling of cancer without treatment. However, the paper by Burden, Ernstberger, and Fister [5] from that issue deserves a special mention. Their paper deals with the topic of optimal control. The authors apply similar assumptions to the ones in this work. However, unlike this project, Burden et al describe optimal control conditions of cancer treatment by immunotherapy. This project joins research in [5, 8, 20, 23] and others to model cancer responses to particular treatment strategies.

Unlike many other publications on the topic of mathematical modeling of cancer, here control theory is applied to model radiotherapy as the means to influence the competitive dynamical system by cell harvesting. The control theory application to

model harvesting in a dynamical system has been previously used in [4]. There, however, the model represents a predator-prey type of dynamics.

To simplify the model, we assume that the concentrations of cancer and healthy cells exist in the same region of the organism. We do not take into account the spacial distribution of cancer. Rather, we model the continuous change in the total concentrations of cancer and healthy cells when influenced by radiation. We consider the radiation of a cluster of cancer cells with the surrounding healthy tissue. We expect some radiation to "miss" the cluster and affect healthy cells in the vicinity thus changing the dynamics of the system. We also assume that radiation does not have a long lasting effect on the rates of proliferation or the nature of competition. To simplify the model, such recovery times are assumed to be negligible. Further work, perhaps considering the mathematical delay theory, is needed to address the recovery issue. With the above assumptions, the dynamics of the competitive system is affected by simple removal of cancer and healthy tissue by radiation.

2.1 System Introduction and Definitions

As previously stated, to simplify the development of the model, we assume that the nature of interaction of cancer and healthy cells is a competition for resources, and that cancer cells will presumably win without treatment.

We assume that there is a maximum concentration of healthy tissue and a maximum concentration of cancer cells supported by the organism. These maximum values are each called the carrying capacity or K. Furthermore, we assume that the optimal rate of net growth of healthy tissue and of cancer, their proliferation, is directly proportional to the current concentration of each population. The constant of proportionality in this instance, α, is referred to as the proliferation coefficient. One more assumption is required to account for the interaction between healthy and can-

cer tissue. It is often assumed that the rate of decrease in a population concentration due to competition is directly proportional to the product of the two populations concentrations. The product is justified by noting that the probability of interaction changes as the population size of each changes. The proportionality constant in the competition term, β, is referred to as the competition coefficient.

Traditionally, the following Lotka-Voltera system is used to model competition [10]:

$$\begin{aligned} \dot{x_1} &= \alpha_1 x_1(1 - \tfrac{x_1}{K_1}) - \beta_1 x_1 x_2 \\ \dot{x_2} &= \alpha_2 x_2(1 - \tfrac{x_2}{K_2}) - \beta_2 x_1 x_2, \end{aligned} \tag{2.1}$$

where

$\dot{} = \frac{d}{dt}$

x_1 represents the concentration of the competitor that loses (healthy cells),

x_2 represents the concentration of the competitor that wins (cancer cells),

$\alpha_i > 0$ are the respective proliferation coefficients,

$K_i > 0$ are the respective carrying capacities,

$\beta_i > 0$ are the respective competition coefficients,

$i = 1, 2.$

In the absence of radiation, cancer (i.e. x_2) wins resulting in the following conditions [10]:

$$K_1 < \frac{\alpha_2}{\beta_2} \quad \text{and} \quad K_2 > \frac{\alpha_1}{\beta_1}. \tag{2.2}$$

This produces one globally stable equilibrium at $(x_1, x_2) = (0, K_2)$ for positive initial values [10].

We assume that the administration of radiation removes a large amount of cancer cells and a small amount of healthy cells from the system. Here, the terms "large" and "small" are used as a relation to the appropriate cell population at a particular location in the organism. Radiotherapy is in fact a control mechanism on the rates of change of x_i by harvesting them. System (2.1) is modified to account for this:

$$\begin{aligned} \dot{x_1} &= \alpha_1 x_1(1 - \tfrac{x_1}{K_1}) - \beta_1 x_1 x_2 - \eta_1(t, x_1, x_2) \\ \dot{x_2} &= \alpha_2 x_2(1 - \tfrac{x_2}{K_2}) - \beta_2 x_1 x_2 - \eta_2(t, x_1, x_2) \\ \eta_1(t, x_1, x_2) &\leq \eta_2(t, x_1, x_2). \end{aligned} \tag{2.3}$$

Here, $\eta_i(t, x_1, x_2) > 0$, $i = 1, 2$, are the controls due to radiation, and α_1, α_2, β_1, β_2, K_1, and K_2 satisfy condition (2.2).

2.2 Project Outline

In practice, different types of cancers require different modes of delivery of radiation and different amounts of radiation [1, 7, 15, 21]. That and the fact that the effect of radiation on healthy cells (i.e "harvesting" of healthy cells) should ideally be zero leads us to consider the following four possible control mechanisms:

Case 1: $\eta_1(t, x_1, x_2) \equiv 0$, $\eta_2(t, x_1, x_2) = \gamma$,

Case 2: $\eta_1(t, x_1, x_2) \equiv 0$, $\eta_2(t, x_1, x_2) = \gamma x_2$,

Case 3: $\eta_1(t, x_1, x_2) \equiv 0$, $\eta_2(t, x_1, x_2) = \gamma \frac{x_2}{x_1}$,

Case 4: $\eta_1(t, x_1, x_2) \equiv 0$, $\eta_2(t, x_1, x_2) = \begin{cases} \gamma & nkT \leq t < (nk+1)T \\ 0 & (nk+1)T \leq t < (n+1)kT, \end{cases}$

where $n \in \mathbb{N}$, T is the length of time of radiation exposure, $k - 1$ is the rest time between radiation exposures, and kT is the total time between the any two treatments

(the period of the function).

Case 1 represents a general irradiation of a cancer by a steady and constant amount of radiation. Case 2 assumes that the amount of radiation is directly proportional to the concentration of cancer cells. Case 3 assumes the dosage is set proportional to the ratio of concentrations of cancer cells to healthy cells. Case 4 considers a periodic administration of radiation. In Chapter 3, several necessary conditions and theorems will be developed to discuss the flow of the solutions and the stability of various equilibria in Cases 1, and 3. The following Dulac [19] criteria is applied to set conditions for the absence of periodic solutions.

Theorem 1 (Dulac's Criteria). *Let Ω be a simply connected region in $\Re^2$. Let* $\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{bmatrix}$ *where $f_1(x_1, x_2), f_2(x_1, x_2) \in C^1(\Omega)$. If there exists a function $B \in C^1(\Omega)$ such that $\frac{\partial}{\partial x_1}(Bf_1(x_1, x_2)) + \frac{\partial}{\partial x_2}(Bf_2(x_1, x_2))$ is not identically zero and does not change sign in Ω. Then the system has no closed orbit entirely in Ω.*

In case number two, Lyapunov Theory will be used to derive global stability conditions of the internal equilibrium. To prove the existence of periodic solutions in Case 4, we will use the following theorem by Massera [17]:

Theorem 2 (Massera's Theorem). *If a system of ODE's is of second order and if all its solutions exist in the future, and if one of them is bounded in the future, then a periodic solution exists.*

A more plausible model should account for healthy tissue damage due to radiation. Perturbation analysis [3, 13, 19] of system (2.3) will be used in Chapter 4 to model such effects.

Chapter 3

Control Mechanisms

3.1 Introduction to Control

The term "control" is typically used to describe external modifications to the dynamics of the system [16]. We will devote the next four sections to study system of equations (2.3) under the following different external interventions:

Case 1: constant control,

Case 2: control proportional to the concentration of cancer cells,

Case 3: control proportional to the ratio of concentrations of cancer to healthy tissue,

Case 4: periodic control.

3.2 Case 1

3.2.1 Existence of Equilibria

Consider the following system:

$$\begin{aligned} \dot{x_1} &= \alpha_1 x_1(1 - \tfrac{x_1}{K_1}) - \beta_1 x_1 x_2 \\ \dot{x_2} &= \alpha_2 x_2(1 - \tfrac{x_2}{K_2}) - \beta_2 x_1 x_2 - \gamma. \end{aligned} \tag{3.1}$$

Let $a = \alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2$. In the absence of radiation, i.e. $\gamma = 0$, the system (2.1) generates the following isoclines:

$$\begin{aligned} \Gamma_1 &: x_1 = K_1 - \tfrac{\beta_1 K_1}{\alpha_1} x_2 \\ \Gamma_2 &: x_1 = \tfrac{\alpha_2}{\beta_2} - \tfrac{\alpha_2}{\beta_2 K_2} x_2. \end{aligned} \tag{3.2}$$

The sign of a describes the nature of the interaction between healthy and cancer cells. Consider the slopes of Γ_1 and Γ_2 in (3.2). If

$$\begin{aligned} &\text{(i)} \quad -\tfrac{\alpha_2}{\beta_2 K_2} > -\tfrac{\beta_1 K_1}{\alpha_1} \Rightarrow a < 0, \\ &\text{(ii)} \quad -\tfrac{\alpha_2}{\beta_2 K_2} = -\tfrac{\beta_1 K_1}{\alpha_1} \Rightarrow a = 0, \\ &\text{(iii)} \quad -\tfrac{\alpha_2}{\beta_2 K_2} < -\tfrac{\beta_1 K_1}{\alpha_1} \Rightarrow a > 0. \end{aligned} \tag{3.3}$$

When $a > 0$ (respectively $a < 0$) the isoclines (3.2) produce graphs as shown in Figure 3.1 (respectively Figure 3.2). The two isoclines do not intersect since we restrict our analysis to the case when cancer wins the competition (conditions (2.2)). When radiation is introduced, the equations of isoclines (3.2) will change to:

$$\begin{aligned} \Gamma_1 &: x_1 = K_1 - \tfrac{\beta_1 K_1}{\alpha_1} x_2 \\ \Gamma_3 &: x_1 = \tfrac{\alpha_2}{\beta_2} - \tfrac{\alpha_2}{\beta_2 K_2} x_2 - \tfrac{\gamma}{\beta_2 x_2}. \end{aligned} \tag{3.4}$$

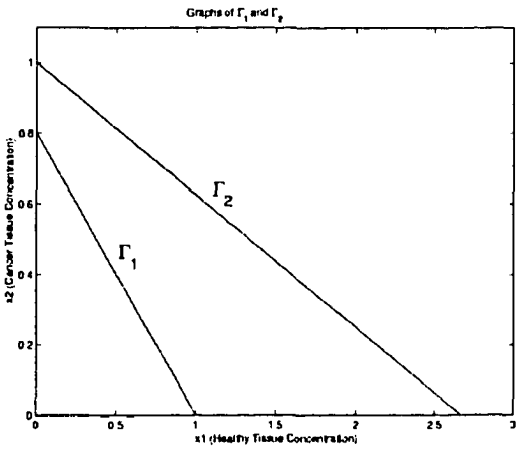

Figure 3.1: Isoclines of (2.1): $a > 0$

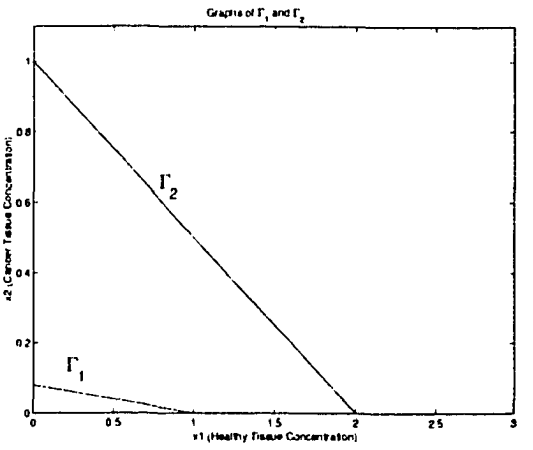

Figure 3.2: Isoclines of (2.1): $a < 0$

Notice that on Γ_3 the limit $\lim_{x_2 \to 0+} x_1 = -\infty$.

In addition, on Γ_3, $\frac{dx_1}{dx_2} = -\frac{\alpha_2}{\beta_2 K_2} + \frac{\gamma}{\beta_2 x_2^2}$ and $\frac{d^2x_1}{dx_2^2} = -\frac{2\gamma}{\beta_2 x_2^3}$. Thus, Γ_3 will have the shape as depicted in Figures 3.3 and 3.4 with the vertex (maximum value of x_1) at:

$$(x_1, x_2) = \left(\frac{\alpha_2}{\beta_2} - \frac{2}{\beta_2}\sqrt{\frac{\alpha_2 \gamma}{K_2}}, \sqrt{\frac{K_2 \gamma}{\alpha_2}} \right).$$

In the positive x_1 x_2 plane these isoclines may intersect twice, once, or zero times as in Figures 3.3 and 3.4. The number of intersections depends on the size of γ and the dynamics of cancer-healthy tissue interaction represented by a.

The boundary equilibria on the x_2 axis will exist if $0 = \frac{\alpha_2}{\beta_2} - \frac{\alpha_2}{\beta_2 K_2} x_2 - \frac{\gamma}{\beta_2 x_2}$ or, equivalently, $0 = \alpha_2 x_2^2 - K_2 \alpha_2 x_2 + \gamma K_2$ has positive solutions. Therefore,

$$\begin{aligned} &\gamma < \frac{\alpha_2 K_2}{4} \Rightarrow \text{ two positive real solutions } 0 < x_2 < \frac{K_2}{2}, \ \frac{K_2}{2} < x_2 < K_2 \\ &\gamma = \frac{\alpha_2 K_2}{4} \Rightarrow \text{ one positive real solution } x_2 = \frac{K_2}{2} \\ &\gamma > \frac{\alpha_2 K_2}{4} \Rightarrow \text{ no positive real solutions.} \end{aligned} \tag{3.5}$$

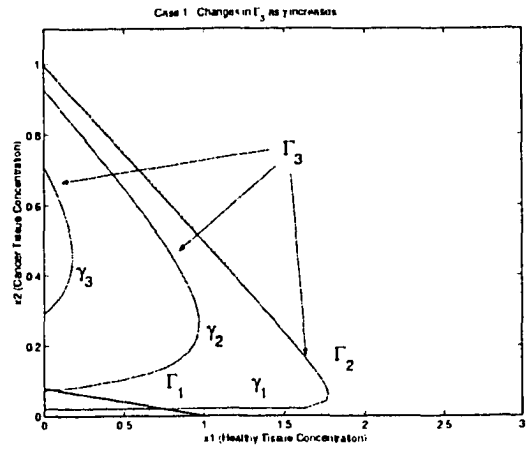

Figure 3.3: Isoclines of (3.4): $a < 0$. Changes in shape of Γ_3 for different values of γ: $\gamma_1 < \gamma_2 < \gamma_3$.

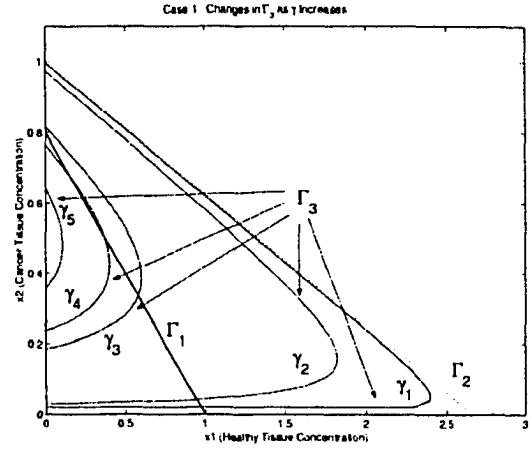

Figure 3.4: Isoclines of (3.4): $a > 0$. Changes in shape of Γ_3 for different values of γ: $\gamma_1 < \gamma_2 < \gamma_3 < \gamma_4 < \gamma_5$.

To develop conditions necessary for an internal equilibrium first we solve the system (3.4):

$$ax_2^2 - bx_2 + \alpha_1 K_2 \gamma = 0, \tag{3.6}$$

where $a = \alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2$ and $b = K_2\alpha_1(\alpha_2 - K_1\beta_2)$. The solutions of this quadratic equation (3.6) are

$$x_2 = \frac{b \pm \sqrt{b^2 - 4a\alpha_1 K_2 \gamma}}{2a}.$$

This x_2 defines the location of an internal equilibrium. The equilibrium from now on is labeled as $E^* = (x_1^*, x_2^*)$.

Conditions (2.2) $\Rightarrow b > 0$ since $\beta_2 K_1 < \alpha_2$. Variable a, however, may be positive,

negative, or zero. Therefore, by conditions (3.3), the solutions to (3.6) are:

$$
\begin{aligned}
&a<0 \Rightarrow \quad x_2{}^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a} && \text{is the only potential solution,}\\
&a=0 \Rightarrow \quad x_2{}^* = \frac{\gamma}{\alpha_2-\beta_2 K_1} && \text{is the only possible solution,}\\
&a>0 \Rightarrow \quad x_2{}^* = \frac{b\pm\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a} && \text{gives two potential solutions.}
\end{aligned}
\tag{3.7}
$$

There may also be a single solution when Γ_3 is tangent to Γ_1. In this case, $x_2{}^* = \frac{b}{2a}$ and $\gamma = \frac{b^2}{4a\alpha_1 K_2} = \frac{\alpha_1 K_2}{4a}(\alpha_2-\beta_2 K_1)^2$ or $\gamma = \frac{a(x_2{}^*)^2}{K_2\alpha_1}$. In order to have a solution in the first quadrant, $x_1{}^*$ should also satisfy: $0 < x_1{}^* < K_1$. Thus (3.4) $\Rightarrow 0 < x_2{}^* < \frac{\alpha_1}{\beta_1}$. We obtain the following further restrictions on γ:

$$
\begin{aligned}
&a<0 \Rightarrow 0<\gamma<\frac{\alpha_1\alpha_2}{\beta_1 K_2}\left(K_2-\frac{\alpha_1}{\beta_1}\right),\\
&a=0 \Rightarrow 0<\gamma<\frac{\alpha_1\alpha_2-\alpha_1\beta_2 K_1}{\beta_1},\\
&a>0 \Rightarrow \begin{cases} 0<\gamma<\frac{\alpha_1\alpha_2}{\beta_1 K_2}\left(K_2-\frac{\alpha_1}{\beta_1}\right), & \text{(one solution.)}\\ \frac{\alpha_1\alpha_2}{\beta_1 K_2}\left(K_2-\frac{\alpha_1}{\beta_1}\right)<\gamma<\frac{\alpha_1 K_2}{4a}(\alpha_2-\beta_2 K_1)^2, & \text{(two solutions.)}\end{cases}
\end{aligned}
\tag{3.8}
$$

Note that (3.8) must be satisfied concurrently with (2.2), (3.5), and (3.3) since the existence of internal solutions must guarantee the existence of solutions on the axis. In Chapter 5, numerical examples of when all of these conditions are satisfied concurrently will be provided.

3.2.2 Local Stability of Internal Equilibria

The local stability of the internal equilibria in Case 1 (system (3.1)) may be determined by considering the variational matrix of system (3.1). Let M represent the

variational matrix. Then

$$M = \begin{bmatrix} \frac{\partial \dot{x_1}}{\partial x_1} & \frac{\partial \dot{x_1}}{\partial x_2} \\ \frac{\partial \dot{x_2}}{\partial x_1} & \frac{\partial \dot{x_2}}{\partial x_2} \end{bmatrix}$$

$$= \begin{bmatrix} \alpha_1(1 - 2\frac{x_1}{K_1}) - \beta_1 x_2 & -\beta_1 x_1 \\ -\beta_2 x_2 & \alpha_2(1 - 2\frac{x_2}{K_2}) - \beta_2 x_1 \end{bmatrix}. \tag{3.9}$$

We would like to study the stability of the internal equilibrium, $E^* = (x_1{}^*, x_2{}^*)$. This equilibrium is found at the intersection of isoclines Γ_1 and Γ_3 ($\dot{x_1} = 0$ and $\dot{x_2} = 0$ respectively). The conditions for the existence of such an equilibrium are derived in section 3.2.1. Notice that when $\dot{x_1} = 0$, $\beta_1 x_2 = \alpha_1(1 - \frac{x_1}{K_1})$; and when $\dot{x_2} = 0$, $\beta_2 x_1 + \frac{\gamma}{x_2} = \alpha_2(1 - \frac{x_2}{K_2})$. Therefore, matrix (3.9) evaluated at $E^* = (x_1{}^*, x_2{}^*)$ is simplified to:

$$M^* = \begin{bmatrix} -\alpha_1 \frac{x_1{}^*}{K_1} & -\beta_1 x_1{}^* \\ -\beta_2 x_2{}^* & \frac{\gamma}{x_2{}^*} - \alpha_2 \frac{x_2{}^*}{K_2} \end{bmatrix}. \tag{3.10}$$

The eigenvalues (λ) are the solutions of the equation:

$$0 = \det(\lambda I - M^*) =$$

$$= \lambda^2 + \lambda\left(\alpha_1 \frac{x_1{}^*}{K_1} + \alpha_2 \frac{x_2{}^*}{K_2} - \frac{\gamma}{x_2{}^*}\right) + \alpha_1 \frac{x_1{}^*}{K_1}\left(\alpha_2 \frac{x_2{}^*}{K_2} - \frac{\gamma}{x_2{}^*}\right) - \beta_1\beta_2 x_1{}^* x_2{}^*. \tag{3.11}$$

If $\alpha_2 \frac{x_2{}^*}{K_2} - \frac{\gamma}{x_2{}^*} < 0$, then the eigenvalues are of opposite signs and the equilibrium is a saddle point. However if $\alpha_2 \frac{x_2{}^*}{K_2} - \frac{\gamma}{x_2{}^*} > 0$, then $\alpha_1 \frac{x_1{}^*}{K_1}(\alpha_2 \frac{x_2{}^*}{K_2} - \frac{\gamma}{x_2{}^*}) - \beta_1\beta_2 x_1{}^* x_2{}^*$ may

be negative (a saddle point equilibrium), or positive. We simplify the expression:

$$\alpha_1 \frac{x_1^*}{K_1}\left(\alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}\right) - \beta_1\beta_2 x_1^* x_2^* =$$
$$\frac{x_1^*}{x_2^* K_1 K_2}[x_2^{*2}(\alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2) - \alpha_1 K_2\gamma] =$$
$$\frac{x_1^*}{x_2^* K_1 K_2}[x_2^{*2} a - \alpha_1 K_2\gamma].$$

Since the equilibrium is located at x_2^* given by (3.6), we obtain the following:

$$\frac{x_1^*}{x_2^* K_1 K_2}\left[\left(\frac{b \pm \sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a}\right)^2 a - \alpha_1 K_2\gamma\right] =$$
$$\frac{x_1^*}{x_2^* K_1 K_2}\left[\frac{2b^2 \pm 2b\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - 4a\alpha_1 K_2\gamma}{4a} - \alpha_1 K_2\gamma\right] =$$
$$\frac{x_1^*}{2a x_2^* K_1 K_2}[b^2 \pm b\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - 4a\alpha_1 K_2\gamma] =$$
$$\frac{x_1^*}{2a x_2^* K_1 K_2}[\left(\sqrt{b^2 - 4a\alpha_1 K_2\gamma}\right)^2 \pm b\sqrt{b^2 - 4a\alpha_1 K_2\gamma}] =$$
$$\frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} \pm b).$$

In the case where $a > 0$,

$$\frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} + b) > 0,$$
$$\frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - b) < 0.$$

These expressions correspond to $x_2^* = \frac{b+\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ and to $x_2^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ respectively. In the case where $a < 0$,

$$\frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - b) < 0.$$

This expression corresponds to the only possible internal equilibrium when $a < 0$ located at $x_2^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$.

Therefore, the equilibrium at $x_2^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ is a saddle point for both $a < 0$ and $a > 0$.

The equilibrium at $x_2^* = \frac{b+\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ corresponds to positive $\alpha_2\frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}$. Here

$$\alpha_1\frac{x_1^*}{K_1} + \alpha_2\frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*} > 0 \Rightarrow Re(\lambda_{1,2}) < 0.$$

Therefore, the equilibrium at $x_2^* = \frac{b+\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ is stable.

3.2.3 Stability of the Equilibria of System (3.1)

To study the stability of different equilibria, we determine the flow in various regions defined by isoclines Γ_1 and Γ_3.

First we calculate $\frac{dx_2}{dx_1}$:

$$\frac{dx_2}{dx_1} = \frac{\dot{x_2}}{\dot{x_1}} = \frac{x_2\left(\alpha_2 - \frac{\alpha_2 x_2}{K_2} - \beta_2 x_1 - \frac{\gamma}{x_2}\right)}{x_1\left(\alpha_1 - \frac{\alpha_1 x_1}{K_1} - \beta_1 x_2\right)}. \tag{3.12}$$

The sign of this derivative together with the separate signs of $\dot{x_1}$ and $\dot{x_2}$ describes the flow of the solutions to system (3.1).

Consider two points (K_1, K_2) and $(\frac{1}{2}K_1, 0)$. At point (K_1, K_2), the denominator in (3.12) is equal to $-K_1K_2\beta_1 < 0$. From the equation of Γ_1 in (3.2), the right side of Γ_1 at $(x_1, x_2) = (K_1, K_2)$ is $K_1 - \frac{\beta_1 K_2}{\alpha_1}K_1$. This is negative since $\frac{\beta_1}{\alpha_1}K_2 > 1$ by conditions (2.2) given in section 2.1. Therefore the point (K_1, K_2) is above Γ_1. At the second point, $(x_1, x_2) = (\frac{1}{2}K_1, 0)$, the denominator of (3.12) is equal to $\frac{1}{4}K_1\alpha_1$ and it is positive. The right side of the equation of Γ_1 is equal to K_1 since $x_2 = 0$. Therefore the point $(\frac{1}{2}K_1, 0)$ is below Γ_1 and to the right of $x_1 = 0$. Since along Γ_1

and for all $x_1 = 0$, the derivative $\dot{x_1} \equiv 0$, the denominator of $\frac{dx_2}{dx_1}$ changes its sign only along Γ_1 and along the x_2 axis. Thus, we make the following generalization:

> Generalization 1: For any point $(\hat{x_1}, \hat{x_2})$ above (respectively below) Γ_1 and to the right of the x_2 axis, the denominator of (3.12) and $\dot{x_1}$ are negative (respectively positive).

Similarly, $\dot{x_2} \equiv 0$ along Γ_3. Therefore, the numerator of $\frac{dx_2}{dx_1}$ changes its sign along Γ_3. In section 3.2.1, we showed that Γ_3 has the vertex at

$$(x_1, x_2) = \left(\frac{\alpha_2}{\beta_2} - \frac{2}{\beta_2}\sqrt{\frac{\alpha_2\gamma}{K_2}}, \sqrt{\frac{K_2\gamma}{\alpha_2}} \right).$$

This vertex is in the positive quadrant if $\gamma < \frac{\alpha_2 K_2}{4}$ (see conditions (3.5)). Then the point $\left(0, \sqrt{\frac{K_2\gamma}{\alpha_2}}\right)$ is to the left of the vertex, and the point $\left(\frac{\alpha_2}{\beta_2}, \sqrt{\frac{K_2\gamma}{\alpha_2}}\right)$ is to the right. At point $\left(0, \sqrt{\frac{K_2\gamma}{\alpha_2}}\right)$ the numerator of (3.12) is as follows:

$$\begin{aligned} \dot{x_2} &= \sqrt{\frac{K_2\gamma}{\alpha_2}} \left(\alpha_2 - \frac{\alpha_2}{K_2}\sqrt{\frac{K_2\gamma}{\alpha_2}} - \gamma\sqrt{\frac{\alpha_2}{K_2\gamma}} \right) \\ &= \sqrt{\frac{K_2\gamma}{\alpha_2}} \left(\alpha_2 - 2\sqrt{\frac{\alpha_2\gamma}{K_2}} \right). \end{aligned}$$

Since $\gamma < \frac{\alpha_2 K_2}{4}$, we get $\alpha_2 - 2\sqrt{\frac{\alpha_2\gamma}{K_2}} > 0$. Therefore, the numerator (and $\dot{x_2}$) is positive. At point $\left(\frac{\alpha_2}{\beta_2}, \sqrt{\frac{K_2\gamma}{\alpha_2}}\right)$, the numerator of (3.12) is as follows:

$$\begin{aligned} \dot{x_2} &= \sqrt{\frac{K_2\gamma}{\alpha_2}} \left(\alpha_2 - \frac{\alpha_2}{K_2}\sqrt{\frac{K_2\gamma}{\alpha_2}} - \beta_2\frac{\alpha_2}{\beta_2} - \gamma\sqrt{\frac{\alpha_2}{K_2\gamma}} \right) \\ &= \sqrt{\frac{K_2\gamma}{\alpha_2}} \left(-2\sqrt{\frac{\alpha_2\gamma}{K_2}} \right). \end{aligned}$$

Therefore, the numerator (and $\dot{x_2}$) at this point is negative. We generalize these

results below:

> Generalization 2: If $(\hat{x_1}, \hat{x_2})$ is any point on Γ_3 in the positive quadrant, then at any point $(x_1, \hat{x_2})$ such that $x_1 < \hat{x_1}$ (respectively $x_1 > \hat{x_1}$), the numerator of (3.12) and $\dot{x_2}$ are positive (respectively negative).

We combine the above results into the following theorems describing the stability of various equilibria. Consider the existence of a single internal equilibrium ($\hat{E}$) and two boundary equilibria $E_l(0, x_{2_l})$, $E_h(0, x_{2_h})$ on the x_2 axis (see Figure 3.5). Also, consider four different regions (labeled 1 through 4 in Figure 3.5). By Generalization 1, $\dot{x_1}$ is positive in regions 1 and 2 and $\dot{x_1}$ is negative in regions 3 and 4. By Generalization 2, $\dot{x_2}$ is positive at all points in regions 2 and 3, and negative at all points in regions 1 and 4. Therefore (as illustrated by Figure 3.6) the following hold:

Region 1: $\dot{x_1} > 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the right,

Region 2: $\dot{x_1} > 0$ and $\dot{x_2} > 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is up and to the right,

Region 3: $\dot{x_1} < 0$ and $\dot{x_2} > 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is up and to the left,

Region 4: $\dot{x_1} < 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is down and to the left.

The following theorem describes the stability of the equilibria.

Theorem 3. *The internal equilibrium $\hat{E}$ is a saddle point, the boundary equilibrium E_l is unstable, and the boundary equilibrium E_h is locally stable.*

Proof. Since the flow in regions 1 through 4 is as described above, $\hat{E}$ is a saddle point equilibrium, E_l is an unstable equilibrium, and E_h is a stable equilibrium. □

Let $\hat{E}$ and $\tilde{E}$ represent two equilibria in the interior (possible only if $a > 0$), and $E_l(0, x_{2_l})$ and $E_h(0, x_{2_h})$ represent equilibria on the x_2 axis (see Figure 3.7). Consider the 5 regions (labeled 1 through 5 in Figure 3.7). Generalizations 1 and 2 imply the following:

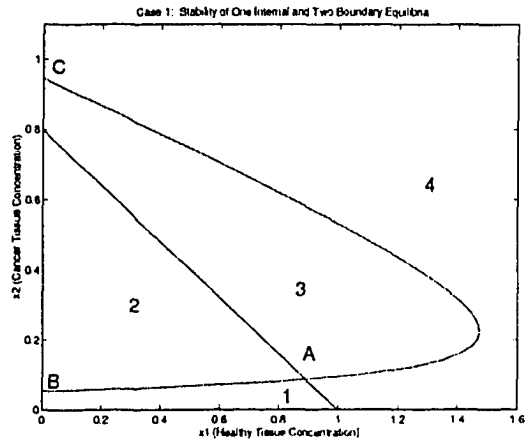

Figure 3.5: $A = \hat{E}$, $B = E_l(0, x_{2_l})$, $C = E_h(0, x_{2_h})$. Numbers 1 through 4 indicate regions between the isoclines.

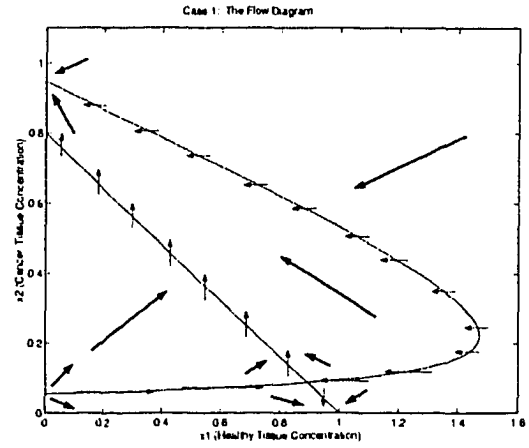

Figure 3.6: The flow diagram in the regions 1,2,3 and 4. Small arrows show the direction in which the solutions will cross the isoclines.

Region 1: $\dot{x_1} > 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the right,

Region 2: $\dot{x_1} > 0$ and $\dot{x_2} > 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is up and to the right,

Region 3: $\dot{x_1} < 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the left,

Region 4: $\dot{x_1} < 0$ and $\dot{x_2} > 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is up and to the left,

Region 5: $\dot{x_1} > 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is down and to the right.

Figure 3.8 illustrates the flow in each of the regions. The above leads to the following theorem.

Theorem 4. *The internal equilibrium $\hat{E}$ is a saddle point. The internal equilibrium $\tilde{E}$ is locally stable. The boundary equilibrium E_l is unstable. Finally, the boundary equilibrium E_h is a saddle point.*

Proof. Since the flow in regions 1 through 5 is as described above, $\hat{E}$ is a saddle point equilibrium, $\tilde{E}$ is a stable equilibrium, E_l is an unstable equilibrium, and E_h is a saddle point equilibrium. □

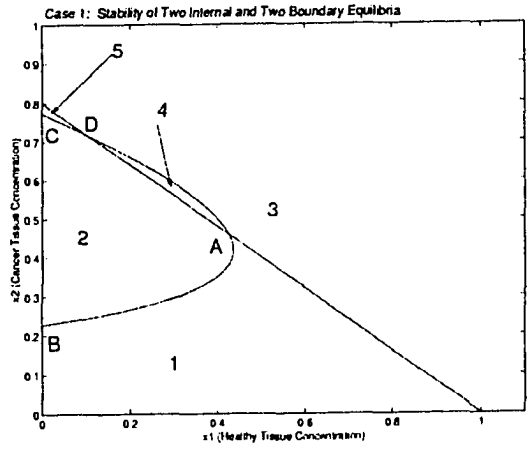

Figure 3.7: $A = \hat{E}$, $B = E_l(0, x_{2_l})$, $C = E_h(0, x_{2_h})$, and $D = \tilde{E}$. Numbers 1 through 5 indicate regions between the isoclines.

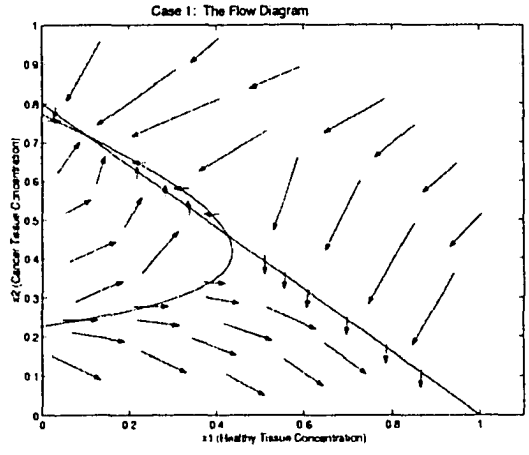

Figure 3.8: The flow diagram in the regions 1,2,3,4, and 5. Small arrows show the direction in which the solutions will cross the isoclines.

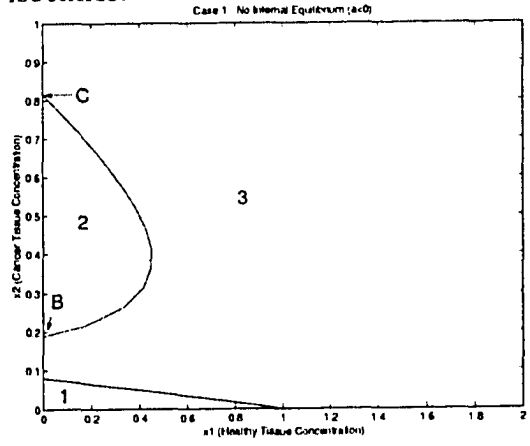

Figure 3.9: $B = E_l$, $C = E_h$. Numbers 1,2, and 3 indicate regions between isoclines.

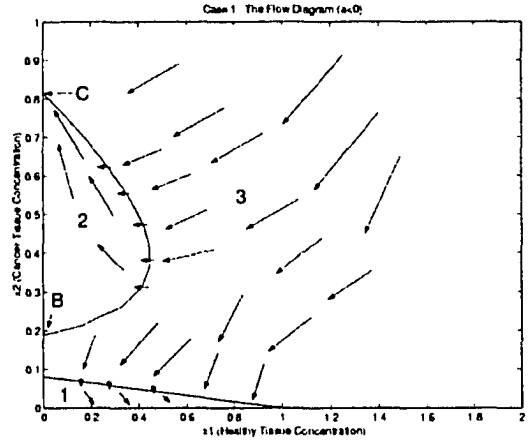

Figure 3.10: The flow in the regions 1,2, and 3.

When $a < 0$ and γ is large enough, there may be two boundary equilibria ($E_l(0, x_{2_l})$ and $E_h(0, x_{2_h})$) and no internal equilibria (see Figure 3.9). In this case, the isoclines define three regions (labeled 1,2,and 3 in Figure 3.9). We use the Generalizations 1 and 2 to describe the flow across these regions (see Figure 3.10 for illustration):

Region 1: $\dot{x_1} > 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the right,

Region 2: $\dot{x_1} < 0$ and $\dot{x_2} > 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is up and to the left,

Region 3: $\dot{x_1} < 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the left.

We use the following theorem to prove the stability of the boundary equilibria.

Theorem 5. *The boundary equilibrium E_l is an unstable equilibrium. The boundary equilibrium E_h is a saddle point equilibrium.*

Proof. Since the flow in regions 1 through 3 is as described above, E_l is a saddle point equilibrium, and E_h is a stable equilibrium. □

The most desirable case in terms of treatment of cancer is when γ is large enough to produce the flow towards the x_1-axis (cancer extinction). Here, we have two equilibria at $E_l(0, x_{2_l})$ and at $E_h(0, x_{2_h})$ (see Figure 3.11). We use the Generalizations 1 and 2 again to describe the flow through regions 1, 2, and 3 (see Figure 3.11):

Region 1: $\dot{x_1} > 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the right,

Region 2: $\dot{x_1} > 0$ and $\dot{x_2} > 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is up and to the right,

Region 3: $\dot{x_1} < 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the left.

The flow in these regions is illustrated in Figure 3.12. The following theorem describes the stability of the equilibria.

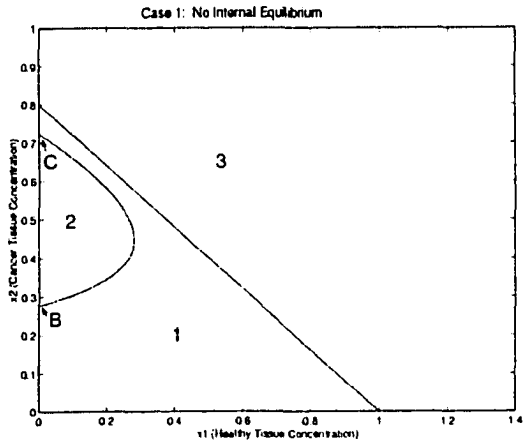

Figure 3.11: $B = E_l$, $C = E_h$. Numbers 1,2, and 3 indicate regions between isoclines.

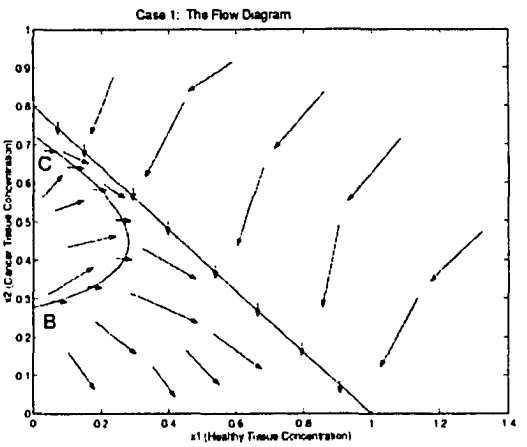

Figure 3.12: The flow in the regions 1,2, and 3.

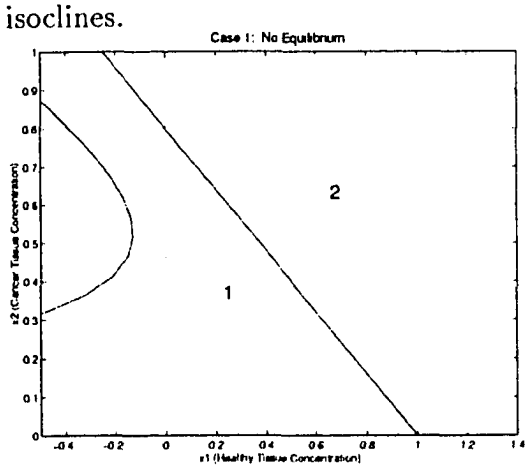

Figure 3.13: No equilibrium. Numbers 1 and 2 indicate regions between isoclines. The dashed line represents x_2 axis. All points on isocline Γ_3 have $x_1 < 0$.

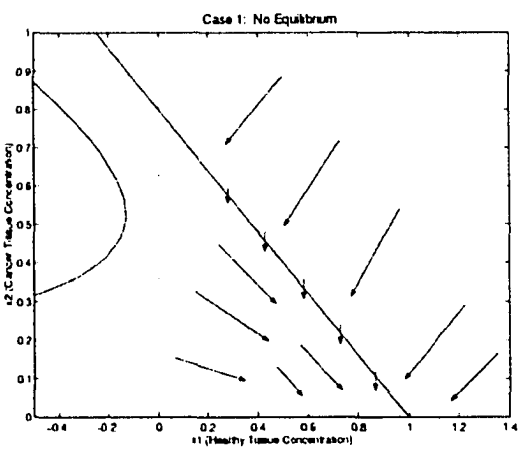

Figure 3.14: The flow in the region 1 is down and to the right. The flow in region 2 is down and to the left.

Theorem 6. *The boundary equilibrium E_l is unstable. The boundary equilibrium E_h is a saddle point.*

Proof. Since the flow in regions 1 through 3 is as described above, E_l is unstable equilibrium, and E_h is a stable equilibrium. □

Finally, it is possible to increase γ so that no equilibria exist. This is illustrated in Figure 3.13.

In this case, the flow in regions 1 and 2 (see Figure 3.14) can be determined from the generalizations 1 and 2:

Region 1: $\dot{x_1} > 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} < 0$ and the flow is down and to the right,

Region 2: $\dot{x_1} < 0$ and $\dot{x_2} < 0 \Rightarrow \frac{dx_2}{dx_1} > 0$ and the flow is down and to the left.

Since the flow in both regions is down, the solution of any system originating in the interior will result in complete extinction of x_2.

3.2.4 Existence of Periodic Solutions

In this section, we check the possibility of a periodic solution in Case 1 (System (3.1)). We use the Dulac criteria [19] to establish a condition on γ such that no periodic solutions exist. For any $x_1 > K_1$, $\dot{x_1} < 0$, and for any $x_2 > K_1$, $\dot{x_2} < 0$. Consider the region $\Omega : \delta < x_1 < K_1, \delta < x_2 < K_2$, where $\delta > 0$ is very small. Since outside of this region both $\dot{x_1} < 0$ and $\dot{x_2} < 0$, all solutions originating outside of Ω will enter and stay in Ω. Let function $B(x_1, x_2) = (x_1 x_2)^{-1} \in C^1(\Omega)$. Then

$$\frac{\partial}{\partial x_1}(B\dot{x_1}) + \frac{\partial}{\partial x_2}(B\dot{x_2}) = -\frac{\alpha_1}{x_2 K_1} - \frac{\alpha_2}{x_1 K_2} + \frac{\gamma}{x_1 {x_2}^2}. \tag{3.13}$$

This expression is not identically zero. We want to show that expression (3.13) changes its sign outside of Ω. Let expression (3.13) equal 0:

$$\begin{aligned} 0 &= -\frac{\alpha_1}{x_2 K_1} - \frac{\alpha_2}{x_1 K_2} + \frac{\gamma}{x_1 {x_2}^2} \\ &= \frac{-1}{K_1 K_2 x_1 {x_2}^2}(\alpha_2 K_1 {x_2}^2 + \alpha_1 K_2 x_1 x_2 - K_1 K_2 \gamma). \end{aligned}$$

This is true for $\alpha_2 K_1 {x_2}^2 + \alpha_1 K_1 x_1 x_2 - K_1 K_2 \gamma = 0$, or, equivalently, along the curve

$$\Phi: \quad x_1 = \tfrac{-\alpha_2 K_1}{\alpha_1 K_2} x_2 + \tfrac{K_1 \gamma}{\alpha_1 x_2}.$$

Here along Φ

$$\left.\frac{dx_1}{dx_2}\right|_{\Phi} = \frac{-\alpha_2 K_1}{\alpha_1 K_2} - \frac{K_1 \gamma}{\alpha_1 {x_2}^2} < 0.$$

When $x_1 = 0$, $x_2 = \pm\sqrt{\frac{\gamma K_2}{\alpha_2}}$. Since the derivative is negative, both branches of Φ are decreasing from their x_2 intercepts. We, therefore, ignore the branch of Φ that is below x_1 axis. The limit of x_1 as x_2 tends to 0 along Φ:

$$\left.\lim_{x_2 \to 0} x_1\right|_{\Phi} = \lim_{x_2 \to 0}\left(\frac{-\alpha_2 K_1}{\alpha_1 K_2} x_2 + \frac{K_1 \gamma}{\alpha_1 x_2}\right) = \infty.$$

We now see that Φ is a strictly decreasing curve that lies entirely in the first quadrant for $0 \leq x_2 < \sqrt{\frac{\gamma K_2}{\alpha_2}}$. We want to establish the conditions such that Φ does not enter region Ω. In particular, we want to establish the conditions such that when $x_2 = K_2$, along Φ $x_1 \geq K_1$. Let $x_2 = K_2$, then

$$\begin{aligned} K_1 &\leq \frac{-\alpha_2 K_1}{\alpha_1 K_2} K_2 + \frac{K_1 \gamma}{\alpha_1 K_2} \quad \Rightarrow \\ 1 &\leq \frac{-\alpha_2}{\alpha_1} + \frac{\gamma}{\alpha_1 K_2} \quad \Rightarrow \\ \gamma &\geq (\alpha_1 + \alpha_2) K_2 \end{aligned}$$

Therefore, for $\gamma \geq (\alpha_1+\alpha_2)K_2$ curve Φ never enters region Ω and no periodic solutions in Ω may exist. Since all solutions enter region Ω and no solutions leave that region, no periodic solutions exist for $\gamma \geq (\alpha_1 + \alpha_2)K_2$.

3.3 Case 2

In this section system (2.3) takes on the form:

$$\begin{aligned} \dot{x_1} &= x_1(\alpha_1 - \gamma_1 - \tfrac{\alpha_1 x_1}{K_1}) - \beta_1 x_1 x_2, \\ \dot{x_2} &= x_2(\alpha_2 - \gamma_2 - \tfrac{\alpha_2 x_2}{K_2}) - \beta_2 x_1 x_2. \end{aligned} \tag{3.14}$$

In order for this system to have practical meaning, $\alpha_1 > \gamma_1$ and $\alpha_2 > \gamma_2$. Otherwise, the radiation dosage is too high and both populations tend towards extinction: $\dot{x_1}, \dot{x_2} < 0$. In the case where $\alpha_2 < \gamma_2$, $\dot{x_2} < 0$, and no further analysis is required as the concentration of cancer cells is decreasing.

3.3.1 Existence of Equilibria of System (3.14)

First, observe that $\dot{x_1}(0, x_2) = \dot{x_2}(x_1, 0) = 0$. Therefore, we will have boundary equilibria at

$$(0,0), \quad (K_1(1 - \tfrac{\gamma_1}{\alpha_1}), 0), \quad (0, K_2(1 - \tfrac{\gamma_2}{\alpha_2})).$$

The isoclines for this system are (see Figures 3.15 and 3.16):

$$\begin{aligned} \Gamma_4 &: x_2 = \tfrac{\alpha_1 - \gamma_1}{\beta_1} - \tfrac{\alpha_1}{\beta_1 K_1} x_1 \\ \Gamma_5 &: x_2 = \tfrac{\alpha_2 - \gamma_2}{\alpha_2} K_2 - \tfrac{\beta_2 K_2}{\alpha_2} x_1. \end{aligned} \tag{3.15}$$

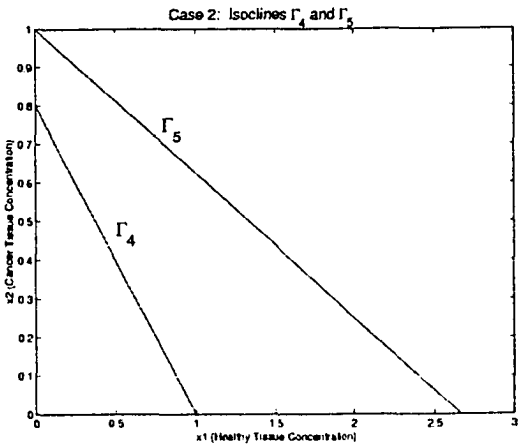

Figure 3.15: Graphs of the isoclines in Case 2 ($a > 0$) without radiation.

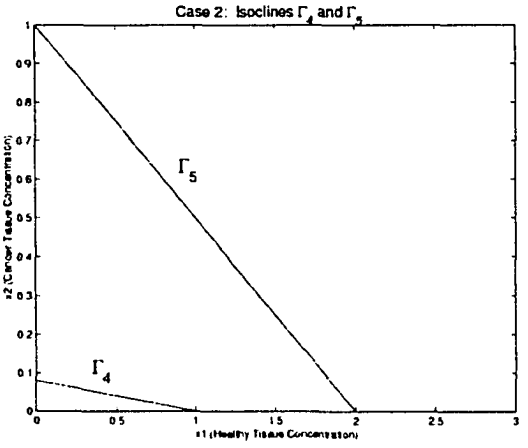

Figure 3.16: Graphs of the isoclines in Case 2 ($a < 0$) without radiation.

The internal equilibrium is then:

$$
\begin{aligned}
x_1^* &= \frac{(\alpha_1 - \gamma_1)\alpha_2 K_1 - (\alpha_2 - \gamma_2)K_1 K_2 \beta_1}{a} \\
x_2^* &= \frac{\alpha_1 - \gamma_1}{\beta_1} - \frac{\alpha_1}{\beta_1}\left(\frac{\alpha_2(\alpha_1 - \gamma_1) - K_2\beta_1(\alpha_2 - \gamma_2)}{a}\right).
\end{aligned} \tag{3.16}
$$

Note that in the case of this internal equilibrium $E^* = (x_1^*, x_2^*)$:

$$
\begin{aligned}
\alpha_1 - \gamma_1 &= \frac{\alpha_1}{K_1} x_1^* + \beta_1 x_2^* \\
\alpha_2 - \gamma_2 &= \frac{\alpha_2}{K_2} x_2^* + \beta_2 x_1^*.
\end{aligned} \tag{3.17}
$$

This equilibrium is possible for parameter values below.

1. $a > 0 \Rightarrow \frac{K_2\beta_1}{\alpha_2}(\alpha_2 - \gamma_2) < \alpha_1 - \gamma_1 < \frac{\alpha_1}{K_1\beta_2}(\alpha_2 - \gamma_2)$.

2. $a < 0 \Rightarrow \frac{\alpha_1}{K_1\beta_2}(\alpha_2 - \gamma_2) < \alpha_1 - \gamma_1 < \frac{K_2\beta_1}{\alpha_2}(\alpha_2 - \gamma_2)$.

Alternatively, there will be no internal equilibrium if the above parameter values are not satisfied.

3.3.2 Stability Analysis of System (3.14)

To determine the stability of internal equilibria we will use Lyapunov theory. Let

$$V(x_1, x_2) = x_1 - x_1^* - x_1^* \ln \frac{x_1}{x_1^*} + x_2 - x_2^* - x_2^* \ln \frac{x_2}{x_2^*}. \tag{3.18}$$

Then $V(x_1^*, x_2^*) = 0$ and $V(x_1, x_2) > 0$ for $(x_1, x_2) \neq (x_1^*, x_2^*)$. Therefore $V(x_1, x_2)$ is positive definite. Computing $\dot{V}$ we get

$$\dot{V} = \dot{x_1}(\frac{x_1 - x_1^*}{x_1}) + \dot{x_2}(\frac{x_2 - x_2^*}{x_2}). \tag{3.19}$$

Then, we substitute (3.14) into (3.19):

$$\dot{V} = (\alpha_1 - \gamma_1 - \frac{\alpha_1}{K_1}x_1 - \beta_1 x_2)(x_1 - x_1^*) + \dots$$
$$\cdots + (\alpha_2 - \gamma_2 - \frac{\alpha_2}{K_2}x_2 - \beta_2 x_1)(x_2 - x_2^*).$$

Use conditions (3.17) to get

$$\dot{V} = \left(-\frac{\alpha_1}{K_1}x_1 - \beta_1 x_2 + \frac{\alpha_1}{K_1}x_1^* + \beta_1 x_2^*\right)(x_1 - x_1^*) + \dots$$
$$\cdots + \left(-\frac{\alpha_2}{K_2}x_2 - \beta_2 x_1 + \frac{\alpha_2}{K_2}x_2^* + \beta_2 x_1^*\right)(x_2 - x_2^*) =$$
$$= \left(-\frac{\alpha_1}{K_1}(x_1 - x_1^*) - \beta_1(x_2 - x_2^*)\right)(x_1 - x_1^*) + \dots$$
$$\cdots + \left(-\frac{\alpha_2}{K_2}(x_2 - x_2^*) - \beta_2(x_1 - x_1^*)\right)(x_2 - x_2^*) =$$
$$= -\frac{\alpha_1}{K_1}(x_1 - x_1^*)^2 - (\beta_1 + \beta_2)(x_1 - x_1^*)(x_2 - x_2^*) - \frac{\alpha_2}{K_2}(x_2 - x_2^*)^2.$$

Therefore, $\dot{V} = 0$ at (x_1^*, x_2^*). We want to determine the values of the parameters that guarantee $\dot{V} < 0$ for all x_1 and x_2. Since the above equation is a quadratic opening down, we want to select the parameters such that

$$(\beta_1 + \beta_2)^2 - 4\frac{\alpha_1\alpha_2}{K_1K_2} \leq 0.$$

If $a > 0$, then $\beta_1\beta_2 < \frac{\alpha_1\alpha_2}{K_1K_2}$ and

$$(\beta_1 + \beta_2)^2 - 4\frac{\alpha_1\alpha_2}{K_1K_2} < (\beta_1 + \beta_2)^2 - 4\beta_1\beta_2 = (\beta_1 - \beta_2)^2.$$

Therefore, it is possible for $(\beta_1 + \beta_2)^2 - 4\frac{\alpha_1\alpha_2}{K_1K_2}$ to be negative. However if $a < 0$, then $\beta_1\beta_2 > \frac{\alpha_1\alpha_2}{K_1K_2}$ and

$$(\beta_1 + \beta_2)^2 - 4\frac{\alpha_1\alpha_2}{K_1K_2} > (\beta_1 + \beta_2)^2 - 4\beta_1\beta_2 = (\beta_1 - \beta_2)^2 \geq 0.$$

Therefore, when parameters are such that $a < 0$ it is not possible for $(\beta_1+\beta_2)^2-4\frac{\alpha_1\alpha_2}{K_1K_2}$ to be negative.

The internal equilibrium in Case 2 is a globally stable equilibrium if $a > 0$ and the parameters are such that

$$(\beta_1 + \beta_2)^2 \leq 4\frac{\alpha_1\alpha_2}{K_1K_2}. \tag{3.20}$$

Condition (3.20) is the precise condition for global stability of the interior equilibrium. When the condition is not met, the equilibrium is not stable. In fact, it is a saddle point since this system reduces to a two-species Lotka-Voltera predator-prey system [10].

The local stability of boundary equilibria may be determined by linearizing the

system (3.14) about the equilibria. First we compute the variational matrix.

$$M = \begin{bmatrix} \alpha_1 - \gamma_1 - 2\alpha_1 \frac{x_1}{K_1} - \beta_1 x_2 & -\beta_1 x_1 \\ -\beta_2 x_2 & \alpha_2 - \gamma_2 - 2\alpha_2 \frac{x_2}{K_2} - \beta_2 x_1 \end{bmatrix}. \tag{3.21}$$

For $(\bar{x_1}, \bar{x_2}) = (0,0)$ the matrix (3.21) is

$$\bar{M} = \begin{bmatrix} \alpha_1 - \gamma_1 & 0 \\ 0 & \alpha_2 - \gamma_2 \end{bmatrix}.$$

Since $\alpha_1 > \gamma_1$ and $\alpha_2 > \gamma_2$, this matrix has two positive eigenvalues and $(0,0)$ is globally unstable [13, 19].

For $(\bar{x_1}, \bar{x_2}) = (K_1(1 - \frac{\gamma_1}{\alpha_1}), 0)$ matrix (3.21) is

$$\bar{M} = \begin{bmatrix} \gamma_1 - \alpha_1 & -\beta_1 K_1 \left(1 - \frac{\gamma_1}{\alpha_1}\right) \\ 0 & \alpha_2 - \gamma_2 - \beta_2 K_1 \left(1 - \frac{\gamma_1}{\alpha_1}\right) \end{bmatrix}.$$

Then the determinant and the trace of $\bar{M}$ are:

$$\begin{aligned} det\bar{M} &= \frac{\beta_2 K_1}{\alpha_1}(\alpha_1 - \gamma_1)^2 + (\alpha_1 - \gamma_1)(\gamma_2 - \alpha_2), \\ tr\bar{M} &= \left(\frac{\beta_2 K_1}{\alpha_1} + 1\right)(\gamma_1 - \alpha_1) + (\alpha_2 - \gamma_2). \end{aligned} \tag{3.22}$$

The equilibrium is a saddle point if

$$det\bar{M} < 0 \Rightarrow 0 < \alpha_1 - \gamma_1 < \frac{\alpha_1}{\beta_2 K_1}(\alpha_2 - \gamma_2). \tag{3.23}$$

The equilibrium is stable if

$$
\begin{aligned}
&det\bar{M} > 0 \Rightarrow \alpha_1 - \gamma_1 > \frac{\alpha_1}{\beta_2 K_1}(\alpha_2 - \gamma_2), \\
&tr\bar{M} < 0 \Rightarrow \alpha_1 - \gamma_1 > (\alpha_2 - \gamma_2)\frac{\alpha_1}{\alpha_1 + \beta_2 K_1}.
\end{aligned} \tag{3.24}
$$

Finally, the equilibrium is unstable if

$$
\begin{aligned}
&det\bar{M} > 0 \Rightarrow \alpha_1 - \gamma_1 > \frac{\alpha_1}{\beta_2 K_1}(\alpha_2 - \gamma_2), \\
&tr\bar{M} < 0 \Rightarrow \alpha_1 - \gamma_1 < (\alpha_2 - \gamma_2)\frac{\alpha_1}{\alpha_1 + \beta_2 K_1}.
\end{aligned} \tag{3.25}
$$

For $(\bar{x}_1, \bar{x}_2) = (0, K_2(1 - \frac{\gamma_2}{\alpha_2}))$ matrix (3.21) is

$$
\bar{M} = \begin{bmatrix} \alpha_1 - \gamma_1 - \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma_2) & 0 \\ -\frac{\beta_2 K_2}{\alpha_2}(\alpha_2 - \gamma_2) & \gamma_2 - \alpha_2 \end{bmatrix}.
$$

Then the determinant and the trace of $\bar{M}$ are:

$$
\begin{aligned}
det\bar{M} &= \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma_2)^2 + (\alpha_2 - \gamma_2)(\gamma_1 - \alpha_1), \\
tr\bar{M} &= \left(\frac{\beta_1 K_2}{\alpha_2} + 1\right)(\gamma_2 - \alpha_2) + (\alpha_1 - \gamma_1).
\end{aligned} \tag{3.26}
$$

The equilibrium is a saddle point if

$$
det\bar{M} < 0 \Rightarrow \alpha_1 - \gamma_1 > \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma_2). \tag{3.27}
$$

The equilibrium is stable if

$$
\begin{aligned}
&det\bar{M} > 0 \Rightarrow 0 < \alpha_1 - \gamma_1 < \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma_2), \\
&tr\bar{M} < 0 \Rightarrow \alpha_1 - \gamma_1 < \left(\frac{\beta_1 K_2}{\alpha_2} + 1\right)(\alpha_2 - \gamma_2).
\end{aligned} \tag{3.28}
$$

Finally, the equilibrium is unstable if

$$
\begin{aligned}
&det\bar{M} > 0 \Rightarrow 0 < \alpha_1 - \gamma_1 < \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma_2), \\
&tr\bar{M} < 0 \Rightarrow \alpha_1 - \gamma_1 > \left(\frac{\beta_1 K_2}{\alpha_2} + 1\right)(\alpha_2 - \gamma_2).
\end{aligned} \tag{3.29}
$$

3.4 Case 3

In Case 3, the control in system (2.3) is proportional to the ratio $\frac{x_2}{x_1}$ as follows

$$
\begin{aligned}
\dot{x_1} &= \alpha_1 x_1(1 - \tfrac{x_1}{K_1}) - \beta_1 x_1 x_2, \\
\dot{x_2} &= \alpha_2 x_2(1 - \tfrac{x_2}{K_2}) - \beta_2 x_1 x_2 - \gamma\tfrac{x_2}{x_1}.
\end{aligned} \tag{3.30}
$$

The following sections describe the stability of the system (3.30).

3.4.1 Existence of Equilibria of System (3.30)

We will have equilibria at $(x_1, x_2) = (K_1, 0)$ or at the intersection of the isoclines Γ_6 and Γ_7 given below:

$$
\begin{aligned}
\dot{x_1} = 0 \quad \Gamma_6 : &\qquad x_2 = \tfrac{\alpha_1}{\beta_1} - \tfrac{\alpha_1}{\beta_1 K_1} x_1, \\
\dot{x_2} = 0 \quad \Gamma_7 : &\quad x_2 = K_2 - \tfrac{\beta_2 K_2}{\alpha_2} x_1 - \gamma\tfrac{K_2}{\alpha_2 x_1}.
\end{aligned} \tag{3.31}
$$

Let $(x_1{}^*, x_2{}^*)$ represent the point of intersection of the isoclines (i.e. interior equilibrium). Then, $\dot{x_1}(x_1{}^*, x_2{}^*) = 0$ and $\dot{x_2}(x_1{}^*, x_2{}^*) = 0$. If we substitute $(x_1{}^*, x_2{}^*)$ into the system (3.30), we get the following conditions:

$$
\begin{aligned}
\beta_1 x_2{}^* &= \alpha_1(1 - \frac{x_1{}^*}{K_1}) \\
\beta_2 x_1{}^* + \frac{\gamma}{x_1{}^*} &= \alpha_2(1 - \frac{x_2{}^*}{K_2}).
\end{aligned} \tag{3.32}
$$

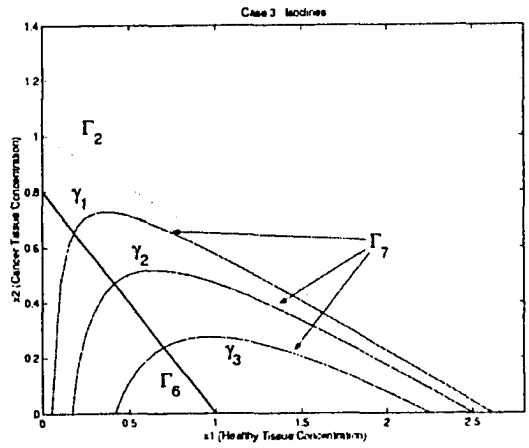

Figure 3.17: Intersection of the isoclines in Case 3 for $a > 0$. Three isoclines of Γ_7 show the effect of increasing γ: $\gamma_1 < \gamma_2 < \gamma_3$. Only one internal equilibrium is possible.

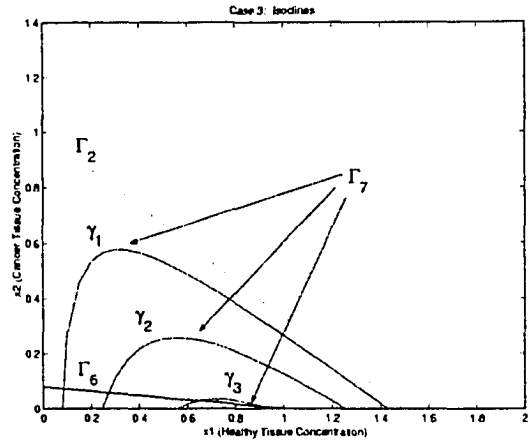

Figure 3.18: Intersection of the isoclines in Case 3 for $a < 0$. Three isoclines of Γ_7 show the effect of increasing γ: $\gamma_1 < \gamma_2 < \gamma_3$. Two internal equilibria are possible (see the curve labeled γ_3).

The system of isoclines (3.31) has the solution given by

$$ax_1^2 + bx_1 - \gamma K_1 K_2 \beta_1 = 0, \tag{3.33}$$

where a is as before and $b = K_1\alpha_2(K_2\beta_1 - \alpha_1)$. Conditions (2.2) imply $b > 0$, while a may be positive, zero, or negative depending on the inherent dynamics of cancer and healthy cells as was observed in Cases 1 and 2. Therefore,

$$x_1^* = \frac{-b \pm \sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}}{2a}. \tag{3.34}$$

For $a > 0$, equation (3.34) will have solutions for all γ. The values of γ that will

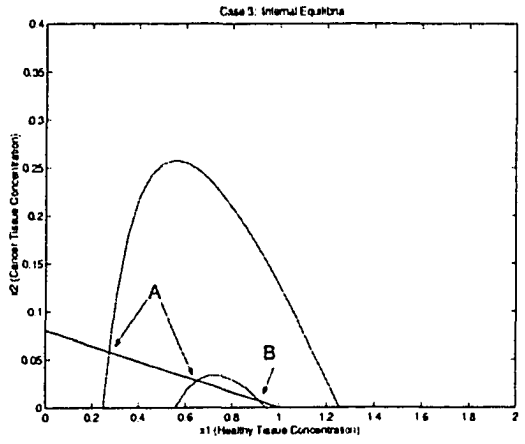

Figure 3.19: Case 3: Internal equilibria when $a < 0$. Letter A represents equilibrium at $x_1{}^* = \frac{-b+\sqrt{b^2+(4aK_1K_2\beta_1)\gamma}}{2a}$. Letter B represents the internal equilibrium at $x_1{}^* = \frac{-b-\sqrt{b^2+(4aK_1K_2\beta_1)\gamma}}{2a}$.

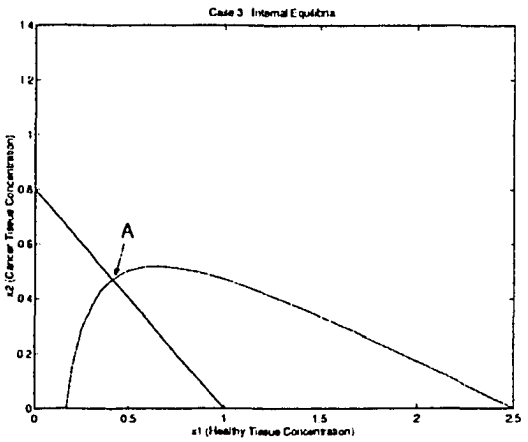

Figure 3.20: Case 3: Internal equilibria when $a > 0$. Only one internal equilibrium is possible in this case. Letter A represents the equilibrium at $x_1{}^* = \frac{-b+\sqrt{b^2+(4aK_1K_2\beta_1)\gamma}}{2a}$.

give a solution in the domain $0 < x_1 \leq K_1$ are

$$\gamma \leq \tilde{\gamma} = \frac{K_1 a + b}{K_2 \beta_1}.$$

In this instance, there can only be one solution (see Figure 3.17).

For $a < 0$, in order to have any solutions, $b^2 + (4aK_1K_2\beta_1)\gamma \geq 0 \Rightarrow$

$$\gamma \leq \bar{\gamma} = \frac{-b^2}{4aK_1K_2\beta_1}.$$

To find the values of γ that give solutions in the domain $0 < x_1 \leq K_1$ we need to solve

$$\frac{-b \pm \sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}}{2a} < K_1.$$

Recall that $a < 0$. Suppose $-b \pm \sqrt{b^2 + (4aK_1K_2\beta_1)\gamma} > 2aK_1$ and $b + 2aK_1 > 0 \Rightarrow$ $a > K_2\beta_1(K_1\beta_2 - \alpha_2)$. Then we can only have one solution for $\gamma < \tilde{\gamma}$ where $\tilde{\gamma}$ is as

above. Otherwise, if $b+2aK_1 < 0 \Rightarrow a > K_2\beta_1(K_1\beta_2 - \alpha_2)$, we will have two solutions when

$$\gamma < \bar{\gamma} \leq \tilde{\gamma},$$

and we will have one solution $x_1 = -b + \sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}$ when

$$\gamma \leq \tilde{\gamma} < \bar{\gamma}.$$

Figure 3.18 illustrates the possible internal equilibria in this case.

3.4.2 Stability Analysis of System (3.30)

Let M represent the variational matrix of system (3.30). Then

$$\begin{aligned} M &= \begin{bmatrix} \frac{\partial \dot{x_1}}{\partial x_1} & \frac{\partial \dot{x_1}}{\partial x_2} \\ \frac{\partial \dot{x_2}}{\partial x_1} & \frac{\partial \dot{x_2}}{\partial x_2} \end{bmatrix} = \\ &= \begin{bmatrix} \alpha_1 - 2\alpha_1\frac{x_1}{K_1} - \beta_1 x_2 & -\beta_1 x_1 \\ \gamma\frac{x_2}{x_1^2} - \beta_2 x_2 & \alpha_2 - 2\alpha_2\frac{x_2}{K_2} - \beta_2 x_1 - \frac{\gamma}{x_1} \end{bmatrix}. \end{aligned} \tag{3.35}$$

To discuss the stability of $(\bar{x_1}, \bar{x_2}) = (K_1, 0)$, consider matrix (3.35) evaluated at that point:

$$\bar{M} = \begin{bmatrix} -\alpha_1 & -\beta_1 K_1 \\ 0 & \alpha_2 - \beta_2 K_1 - \frac{\gamma}{K_1} \end{bmatrix}.$$

The eigenvalues are the solutions of the following expression:

$$\begin{aligned} 0 &= \det(\lambda I - \bar{M}) = \\ &= \lambda^2 + \lambda\left[\alpha_1 + \left(\beta_2 K_1 - \alpha_2 + \frac{\gamma}{K_1}\right)\right] + \alpha_1\left(\beta_2 K_1 - \alpha_2 + \frac{\gamma}{K_1}\right). \end{aligned} \tag{3.36}$$

We know that $\beta_2 K_1 - \alpha_2 < 0$ by conditions (2.2). Therefore, $\beta_2 K_1 - \alpha_2 + \frac{\gamma}{K_1}$ may be:

1: positive when $\gamma > K_1\alpha_2 - \beta_2 {K_1}^2$,

2: zero when $\gamma = K_1\alpha_2 - \beta_2 {K_1}^2$,

3: negative when $\gamma < K_1\alpha_2 - \beta_2 {K_1}^2$.

The stability of the boundary equilibrium would then be a locally stable node, a locally stable focus, or a saddle point respectively.

Let $({x_1}^*, {x_2}^*)$ represent an equilibrium in the interior. We use the conditions (3.32) to simplify matrix (3.35).

$$M^* = \begin{bmatrix} -\frac{\alpha_1 {x_1}^*}{K_1} & -\beta_1 {x_1}^* \\ \frac{\gamma {x_2}^*}{({x_1}^*)^2} - \beta_2 {x_2}^* & -\frac{\alpha_2 {x_2}^*}{K_2} \end{bmatrix}. \tag{3.37}$$

The eigenvalues are the solutions of the following expression:

$$\begin{aligned} 0 &= \det(\lambda I - M^*) = \\ &= \lambda^2 + \lambda\left(\alpha_1 \frac{{x_1}^*}{K_1} + \alpha_2 \frac{{x_2}^*}{K_2}\right) + \frac{\alpha_1\alpha_2 {x_1}^* {x_2}^*}{K_1 K_2} + \frac{\beta_1 \gamma {x_2}^*}{{x_1}^*} - \beta_1\beta_2 {x_1}^* {x_2}^* = \\ &= \lambda^2 + \lambda\left(\alpha_1 \frac{{x_1}^*}{K_1} + \alpha_2 \frac{{x_2}^*}{K_2}\right) + \frac{{x_2}^*}{K_1 K_2 {x_1}^*}\left[\beta_1 K_1 K_2 \gamma + a({x_1}^*)^2\right]. \end{aligned} \tag{3.38}$$

Here, $\alpha_1 \frac{{x_1}^*}{K_1} + \alpha_2 \frac{{x_2}^*}{K_2} > 0$. If $a > 0$, then

$$\frac{{x_2}^*}{K_1 K_2 {x_1}^*}\left[\beta_1 K_1 K_2 \gamma + a({x_1}^*)^2\right] > 0,$$

and the eigenvalues are both negative. Therefore, the internal equilibrium is a stable node (Figure 3.20). If $a < 0$, then the expression $\frac{{x_2}^*}{K_1 K_2 {x_1}^*}\left[\beta_1 K_1 K_2 \gamma + a({x_1}^*)^2\right]$ may

be positive, zero, or negative. When we substitute equation (3.34) into (3.38) we get:

$$0 = \lambda^2 + \lambda\left(\alpha_1\frac{{x_1}^*}{K_1} + \alpha_2\frac{{x_2}^*}{K_2}\right) + \cdots$$
$$+ \frac{{x_2}^*}{K_1K_2{x_1}^*}\left[\beta_1K_1K_2\gamma + a\left(\frac{-b \pm \sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}}{2a}\right)^2\right] =$$
$$= \lambda^2 + \lambda\left(\alpha_1\frac{{x_1}^*}{K_1} + \alpha_2\frac{{x_2}^*}{K_2}\right) + \cdots$$
$$+ \frac{{x_2}^*\sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}}{2aK_1K_2{x_1}^*}\left[\sqrt{b^2 + (4aK_1K_2\beta_1)\gamma} \pm b\right].$$

Recall that $b = K_1\alpha_2(K_2\beta_1 - \alpha_1) > 0$. Since $a < 0$,

$$\frac{{x_2}^*\sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}}{2aK_1K_2{x_1}^*}\left[\sqrt{b^2 + (4aK_1K_2\beta_1)\gamma} - b\right] > 0,$$
$$\frac{{x_2}^*\sqrt{b^2 + (4aK_1K_2\beta_1)\gamma}}{2aK_1K_2{x_1}^*}\left[\sqrt{b^2 + (4aK_1K_2\beta_1)\gamma} + b\right] < 0.$$

Therefore, the real part of the eigenvalues are both negative (respectively one negative and one positive). The internal equilibrium $({x_1}^*, {x_2}^*)$ is locally stable when ${x_1}^* = \frac{-b+\sqrt{b^2+(4aK_1K_2\beta_1)\gamma}}{2a}$. Respectively, the internal equilibrium $({x_1}^*, {x_2}^*)$ at ${x_1}^* = \frac{-b-\sqrt{b^2+(4aK_1K_2\beta_1)\gamma}}{2a}$ is a saddle point equilibrium (Figure 3.19).

3.5 Case 4

Periodic control takes into account the practical aspects of administration of radiation to treat cancer. The original system here is modified to include a periodic control term:

$$\begin{aligned} \dot{x_1} &= \alpha_1x_1(1 - \frac{x_1}{K_1}) - \beta_1x_1x_2, \\ \dot{x_2} &= \alpha_2x_2(1 - \frac{x_2}{K_2}) - \beta_2x_1x_2 - \eta_2(t, x_1, x_2), \end{aligned} \tag{3.39}$$

where $\eta_2(t, x_1, x_2) = \begin{cases} \gamma & nkT \leq t < (nk+1)T \\ 0 & (nk+1)T \leq t < (n+1)kT, \end{cases}$ as described in the introduction.

Here, γ may be chosen from the considerations of Case 1. Since $\eta_2(t, x_1, x_2)$ is not equivalent to zero, there are no (x_1, x_2) values such that $\dot{x_1} = 0$ and $\dot{x_2} = 0$ concurrently for all t. Therefore, there are no trivial periodic solutions. The existence of a periodic solution is now guaranteed by a theorem of Massera (J. Massera) that requires:

- the existence of solutions in the future
- the existence of at least one bounded solution in the future.

Both of these conditions are satisfied since $\dot{x_1} < 0$ whenever x_1 exceeds K_1, and $\dot{x_2} < 0$ whenever x_2 exceeds K_2. We demonstrate such periodic solutions in Chapter 5.

Chapter 4

Perturbation Analysis

In this section we will allow the positive stable equilibrium solutions to be perturbed by unspecified external agents. These agents represent accidental direct or indirect damage of healthy tissue. Such damage may be termed as side-effects. We consider the perturbations of Case 1 and Case 3. It is sensible to consider the perturbation only of the situations with positive internal stable equilibrium. The analysis of the perturbed system is presented below while the numerical results are provided in Chapter 5.

Consider the following equations:

(4.1a)
$$\begin{cases} \dot{x_1} - \alpha_1 x_1 + \frac{x_1^2 \alpha_1}{K_1} + \beta_1 x_1 x_2 + \epsilon g = 0 \\ \dot{x_2} - \alpha_2 x_2 + \frac{x_2^2 \alpha_2}{K_2} + \beta_2 x_1 x_2 + \gamma = 0 \end{cases}$$

(4.1b)
$$\begin{cases} \dot{x_1} - \alpha_1 x_1 + \frac{x_1^2 \alpha_1}{K_1} + \beta_1 x_1 x_2 + \epsilon g \frac{x_2}{x_1} = 0 \\ \dot{x_2} - \alpha_2 x_2 + \frac{x_2^2 \alpha_2}{K_2} + \beta_2 x_1 x_2 + \gamma \frac{x_2}{x_1} = 0 \end{cases}.$$

The parameter ϵ may be viewed here as the percentage of healthy cells that are

affected by radiation. Let the solution to (4.1) be

$$\text{(4.2)} \qquad \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \varphi_1(t) \\ \varphi_2(t) \end{pmatrix} + \epsilon \begin{pmatrix} x_1^{(1)} \\ x_2^{(1)} \end{pmatrix} + \epsilon^2 \begin{pmatrix} x_1^{(2)} \\ x_2^{(2)} \end{pmatrix} \ldots,$$

where $\begin{pmatrix} \varphi_1(t) \\ \varphi_2(t) \end{pmatrix}$ is the solution to systems (3.1) and (3.30) such that either a stable equilibrium exists. Let the initial conditions satisfy

$$\text{(4.3)} \qquad \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}(0) = \begin{pmatrix} \varphi_1(0) \\ \varphi_2(0) \end{pmatrix}, \text{ and, for all } n > 0, \begin{pmatrix} x_1^{(n)} \\ x_2^{(n)} \end{pmatrix}(0) \equiv \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

Then from system (4.1) we calculate the resulting differential equations for different powers of ϵ. The result is similar in both cases:

$$\text{(4.4a)} \qquad \text{for } \epsilon^1 \qquad \begin{pmatrix} \dot{x}_1^{(1)} \\ \dot{x}_2^{(1)} \end{pmatrix} = A^{(1)} \begin{pmatrix} x_1^{(1)} \\ x_2^{(1)} \end{pmatrix} + B^{(1)},$$

$$\text{(4.4b)} \qquad \text{for } \epsilon^2 \qquad \begin{pmatrix} \dot{x}_1^{(2)} \\ \dot{x}_2^{(2)} \end{pmatrix} = A^{(2)} \begin{pmatrix} x_1^{(2)} \\ x_2^{(2)} \end{pmatrix} + B^{(2)}.$$

In Case 1

$$A^{(1)} = A^{(2)} = \begin{pmatrix} \alpha_1 - 2\frac{\alpha_1}{K_1}\varphi_1(t) - \beta_1\varphi_2(t) & -\beta_1\varphi_1(t) \\ -\beta_2\varphi_2(t) & \alpha_2 - 2\frac{\alpha_2}{K_2}\varphi_2(t) - \beta_2\varphi_1(t) \end{pmatrix}$$

$$B^{(1)} = \begin{pmatrix} -g \\ 0 \end{pmatrix}$$

$$B^{(2)} = -\begin{pmatrix} \beta_1 x_1^{(1)} x_2^{(1)} + \frac{\alpha_1 (x_1^{(1)})^2}{K_1} \\ \beta_2 x_1^{(1)} x_2^{(1)} + \frac{\alpha_2 (x_2^{(1)})^2}{K_2} \end{pmatrix},$$

and in Case 3

$$A^{(1)} = A^{(2)} = \begin{pmatrix} \alpha_1 - 2\frac{\alpha_1}{K_1}\varphi_1(t) - \beta_1\varphi_2(t) & -\beta_1\varphi_1(t) \\ \gamma\frac{\varphi_2(t)}{(\varphi_1(t))^2} - \beta_2\varphi_2(t) & \alpha_2 - 2\frac{\alpha_2}{K_2}\varphi_2(t) - \beta_2\varphi_1(t) - \gamma\frac{1}{\varphi_1(t)} \end{pmatrix}$$

$$B^{(1)} = \begin{pmatrix} -g\frac{\varphi_2(t)}{\varphi_1(t)} \\ 0 \end{pmatrix}$$

$$B^{(2)} = -\begin{pmatrix} -g\frac{\varphi_2(t)x_1^{(1)}}{(\varphi_1(t))^2} + g\frac{x_2^{(1)}}{\varphi_1(t)} + \beta_1 x_1^{(1)}x_2^{(1)} + \frac{\alpha_1(x_1^{(1)})^2}{K_1} \\ \gamma\frac{\varphi_2(t)(x_1^{(1)})^2}{(\varphi_1(t))^3} - \gamma\frac{x_1^{(1)}x_2^{(1)}}{(\varphi_1(t))^2} + \beta_2 x_1^{(1)}x_2^{(1)} + \frac{\alpha_2(x_2^{(1)})^2}{K_2} \end{pmatrix}$$

In Case 3, $\frac{x_2}{x_1}$ is expanded as follows:

$$\begin{aligned} \frac{x_2}{x_1} &= \frac{\varphi_2(t) + \epsilon x_2^{(1)} + \epsilon^2 x_2^{(2)} + \dots}{\varphi_1(t) + \epsilon x_1^{(1)} + \epsilon^2 x_1^{(2)} + \dots} \\ &= \frac{\varphi_2 t + \epsilon x_2^{(1)} + \epsilon^2 x_2^{(2)} + \dots}{\varphi_1(t)(1 + \epsilon(\frac{x_1^{(1)}}{\varphi_1(t)} + \epsilon\frac{x_1^{(2)}}{\varphi_1(t)} + \dots)} \\ &= \frac{\varphi_2(t) + \epsilon x_2^{(1)} + \epsilon^2 x_2^{(2)} + \dots}{\varphi_1(t)} \times \frac{1}{1 + \epsilon(\frac{x_1^{(1)}}{\varphi_1(t)} + \epsilon\frac{x_1^{(2)}}{\varphi_1(t)} + \dots)}. \end{aligned}$$

Since $x_1^{(n)}(0) = x_2^{(n)}(0) = 0$, for $n > 0$, use the Taylor expansion of $\frac{1}{1+x}$ about 0 to get:

$$\begin{aligned} \frac{x_2}{x_1} = &\left(\frac{\varphi_2(t)}{\varphi_1(t)} + \epsilon\frac{x_2^{(1)}}{\varphi_1(t)} + \epsilon^2\frac{x_2^{(2)}}{\varphi_1(t)} + \dots\right) \times \\ &\left(1 - \epsilon(\frac{x_1^{(1)}}{\varphi_1(t)} + \epsilon\frac{x_1^{(2)}}{\varphi_1(t)} + \dots) + \epsilon^2(\frac{x_1^{(1)}}{\varphi_1(t)} + \epsilon\frac{x_1^{(2)}}{\varphi_1(t)} + \dots)^2 - \dots\right). \end{aligned}$$

Notice that both (4.4a) and (4.4b) are nonhomogeneous, linear equations with initial

conditions (4.3). Thus, the solution to (4.4) is

$$\text{(4.5a)} \qquad \begin{pmatrix} x_1^{(1)} \\ x_2^{(1)} \end{pmatrix} = \Phi_1(t) \int_0^t \Phi_1^{-1}(s) B^{(1)}(s) ds, \qquad \text{where } \Phi_1' = A^{(1)} \Phi_1,$$

$$\text{(4.5b)} \qquad \begin{pmatrix} x_1^{(2)} \\ x_2^{(2)} \end{pmatrix} = \Phi_2(t) \int_0^t \Phi_2^{-1}(s) B^{(2)}(s) ds, \qquad \text{where } \Phi_2' = A^{(2)} \Phi_2.$$

Therefore, the solution to (4.1) is

$$\text{(4.6)} \qquad \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \varphi_1(t) \\ \varphi_2(t) \end{pmatrix} + \epsilon \left(\Phi_1(t) \int_0^t \Phi_1^{-1}(s) B^{(1)}(s) ds \right) + \ldots$$
$$\ldots + \epsilon^2 \left(\Phi_2(t) \int_0^t \Phi_2^{-1}(s) B^{(2)}(s) ds \right) + O(\epsilon^3).$$

Since ϵ is taken to be small, the stability of this solution will be the same as the stability of the solutions to (3.1) and (3.30). No change in stability, in practical terms, means that if the initial conditions and parameter values of the unperturbed system are favourable to achieving a cure or a treatment, then the cure or a treatment will be the result for the perturbed system. In other words, very small side-effects will not affect the outcome of the treatment.

Chapter 5

Numerical Solutions

In this chapter, we demonstrate numerical solutions of system (2.3) or, more specifically, the systems (3.1),(3.14),(3.30), and (3.39) that represent Cases 1 through 4 respectively. We use a MATLAB ODE solver (ode23s) to solve and graph the solutions to each system with randomly chosen initial values. The discussion and interpretation of the results will follow in Chapter 6.

The stability analysis shows different outcomes for different parameters α_i, β_i, and K_i where $i = 1, 2$; as well as for different values of the control parameter γ. In particular, we demonstrate how the stability of the solutions when the parameters are such that $a < 0$ is different from the stability when the parameters are such that $a > 0$ (where $a = \alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2$).

5.1 Parameter Selection

To carry out numerical analysis of all four cases we need to choose parameter values such that they reflect the available data as well as satisfy all of the conditions outlined in Chapter 3. Unfortunately, cancer allows for a wide range of parameters in

terms of the proliferation rate and carrying capacity. Another difficulty in parameter selection is the fact that there is no readily available data for the competition coefficient. Finally, some parameters may continuously change throughout treatment by radiotherapy and as cancer progresses. The last two issues are left for future research. In our initial setup, we assume that the parameter values remain constant with time (i.e. the parameter values are independent of time or cancer and healthy tissue concentrations).

Since the carrying capacity ($K_i, i = 1, 2$) for both neoplastic and non-neoplastic tissues is different for different organs, and varies greatly for different ages of the host, we use the non-dimensional number 1 to represent the carrying capacity of each population. The capacity concentration of healthy and cancer tissues are both equal to one not as a suggestion that there should be an equal amount of each of the type of cells. In fact, such suggestion is generally incorrect. We use 1 to allow us to represent the instantaneous concentrations of both populations (x_1 and x_2) as a fraction of their carrying capacity. Therefore, the initial conditions should satisfy ${x_1}^o, {x_2}^o \leq 1$. However, we do provide numerical examples where this inequality is not satisfied to illustrate the mathematical notions of locally or globally "stable", locally or globally "unstable", and "saddle point". The data for the fraction (or the percent) of the population remaining at different dosages of radiation does exist in the medical literature. One example of this data is given by G.G. Steel in [22].

The range of the proliferation constants, α_1 and α_2, may be chosen by considering current data that commonly uses the terms "doubling time", "cell cycle time", and "growth fraction" to reflect the speed of cancer and healthy tissue growth [2, 22]. Doubling time represents the amount of time required for a culture or a population to double. The term "double" may be applied to both the physical size (diameter of a tumor or its volume), and the number of cells present.

For tumors, available data mentions doubling times as fast as a few hours to as

slow as a few weeks or months. Doubling time represents exponential growth of the entire population such as a tumor. Since most tumors have a very high degree of differentiation within, doubling time can be best thought of as the average rate of growth. The growth fraction takes into account the fact that not all cells continue to divide and assist tissue proliferation. The assumption that a normally dividing cell produces two daughter cells is not always valid. For instance, some offspring may mutate (a very common occurrence, particularly in cancer) and not divide. Instead, we allow for there to be a fraction of daughter cells that do not contribute to the future growth. Thus, the growth fraction is equal to $GF = \frac{ln(2-f)}{ln2}$, where f is the fraction of cells that are non-dividing [2]. We use the data obtained by Steel [22] and mentioned by Begg in [2] on doubling time and growth fraction to provide numerical examples of the proliferation coefficient. The derivation of the proliferation coefficient is as follows. Let GF be the growth fraction for a particular tumor. Then, the population $P(t)$ at time t is

$$\begin{aligned} P(t) &= P(0)e^{\frac{t}{ln(2-f)}} \\ &= P(0)e^{\frac{t}{GFln2}}. \end{aligned}$$

Therefore,

$$\dot{P(t)} = GFln2P(t).$$

Thus, we can use the available data for the growth fraction to represent the parameter α:

$$\alpha = GFln2.$$

The mean GF is approximately 0.32 in leukaemias and 0.49 in cancers [2, 22]. Therefore, we calculate the corresponding mean values for α_2 to be 0.22 and 0.34 respectively. In this work, we select α_2 to be in the range between 0.2 and 0.4.

For healthy tissue, proliferation is often limited to cell regeneration to compen-

sate for cell loss due to apoptosis. Therefore, in adults, cell proliferation may be a very small value as no tissue is assumed to have a net cell gain. However, cell regeneration in healthy tissue after damage caused by cancer and radiation should not be negligible. For the purposes of obtaining numerical examples, we select the range for α_1 to be between 10^{-3} and 10^{-2}. These values correspond to a growth fraction of approximately 1.4×10^{-3} and 1.4×10^{-2}.

The estimate of the competition coefficient is a task that is much more complicated. To the best knowledge of the author, no comparison of the tumor size–healthy tissue size at different stages of cancer is readily available. Therefore, we make the case in the concluding paragraphs of this work for future investigation into obtaining such data. In the mean time, we use a general estimate for both parameters. We select both β_1 and β_2 such that competition conditions (2.2) are satisfied. Therefore,

$$\tfrac{\alpha_1}{\beta_1} < K_2 \Rightarrow \beta_1 > \tfrac{\alpha_1}{K_2} \quad \text{and} \quad \tfrac{\alpha_2}{\beta_2} > K_1 \Rightarrow \beta_2 < \tfrac{\alpha_2}{K_1}.$$

Thus, we use the range of $0 < \beta_2 < 0.22$ and $0.01 < \beta_1 < 10$. We select and manipulate values of β_1 and β_2 in such a way as to provide examples for the theory developed in Chapters 2 and 3.

Next, we need to select a reasonable range for the rate of change of cell concentration due to radiation (parameter γ). Results obtained by Steel [22], also listed in Oxford Oncology [21], relate radiation dosage to cell survival. These results suggest that at a low dose radiation rate of approximately 0.2Gy/min more than 10% (in some instances as high as 90%) of cancer tissue survives. As the amount of radiation is increased to what is considered a high dose radiation rate of approximately 14Gy/min, less than 0.1% of the radiated cancer cells survive. Therefore, in the numerical examples provided below, we use the values for γ in the range between 0.001 and 0.3 in all four cases. Since the effect of radiation on healthy tissue is much smaller

$a > 0$	$\alpha_1 = 8 \times 10^{-3}$	$\alpha_2 = 0.4$	$\beta_1 = 0.01$	$\beta_2 = 0.15$	$K_1 = 1$	$K_2 = 1$
$a < 0$	$\alpha_1 = 8 \times 10^{-3}$	$\alpha_2 = 0.3$	$\beta_1 = 0.1$	$\beta_2 = 0.15$	$K_1 = 1$	$K_2 = 1$

Table 5.1: Case 1: Parameter Values

than the effect on cancer tissue concentration, in Case 2 we estimate that $\gamma_1 \leq \frac{1}{10}\gamma_2$.

Finally, the perturbation value ϵ is selected to represent the fraction of healthy tissue accidentally affected by radiation. Since the estimate of the threshold value of ϵ is a very complicated matter, we select $\epsilon < 0.1\%$ or less than 0.001 of healthy tissue concentration. We leave the derivation of the estimate of ϵ for future research.

5.2 Numerical Analysis of Case 1

In this section, we present graphical illustration of all the possible situations in Case 1. The stability analysis of Case 1 shows the emergence of two types of cancer-healthy tissue dynamics. These are:

1. $\alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2 = a > 0$,

2. $\alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2 = a < 0$.

We summarize the different parameter values used in this section in Table 5.1. We first note that these parameter values satisfy inequalities (2.2) and (3.3):

$$\frac{\alpha_1}{\beta_1} < K_2 \Rightarrow \begin{cases} \frac{8\times10^{-3}}{0.01} < 1 \\ \frac{8\times10^{-3}}{0.1} < 1 \end{cases} \qquad \frac{\alpha_2}{\beta_2} > K_1 \Rightarrow \begin{cases} \frac{0.4}{0.15} > 1 \\ \frac{0.3}{0.1} > 1 \end{cases}$$

$$a > 0 \Rightarrow 8 \times 10^{-3} \cdot 0.4 - 0.01 \cdot 0.15 \cdot 1 \cdot 1 = 0.0017 > 0$$

$$a < 0 \Rightarrow 8 \times 10^{-3} \cdot 0.3 - 0.1 \cdot 0.15 \cdot 1 \cdot 1 = -0.0126 < 0$$

In addition, we use inequalities (3.5) and (3.8) to select γ. According to (3.5), $\gamma < \frac{\alpha_2 K_2}{4}$ will guarantee boundary and internal equilibria. So, we need to select γ to be

Equilibria Types	$a > 0$	$a < 0$
No equilibria	$\gamma = 0.15$	$\gamma = 0.08$
Two boundary equilibria	$\gamma = 0.09$	$\gamma = 0.045$
Two boundary and two internal equilibria	$\gamma = 0.07$	None
One internal equilibrium	$\gamma = 0.05$	$\gamma = 0.01$

Table 5.2: γ Values.

less than 0.1 when $a > 0$ and less than 0.075 when $a < 0$. Also, from inequality (3.8):

$$a < 0 \Rightarrow 0 < \gamma < \frac{8 \times 10^{-3} \cdot 0.3}{0.1 \cdot 1}\left(1 - \frac{8 \times 10^{-3}}{0.3}\right),$$

$$a > 0 \Rightarrow \begin{cases} 0 < \gamma < \frac{8\times10^{-3}\cdot0.4}{0.01\cdot1}\left(1 - \frac{8\times10^{-3}}{0.01}\right) \\ \frac{8\times10^{-3}\cdot0.4}{0.01\cdot1}\left(1 - \frac{8\times10^{-3}}{0.01}\right) < \gamma < \frac{8\times10^{-3}\cdot}{4\cdot0.0017}(0.4 - 0.15\cdot1)^2 \end{cases}$$

Therefore, for parameters in Table 5.1 when $a < 0$, we require the γ to be in the range of $0 < \gamma < 0.02208$ to have one positive internal equilibrium and be in the range $0 < \gamma < 0.075$ to have two positive boundary equilibria. These conditions are satisfied concurrently. When parameters are selected such that $a > 0$ (see Table 5.1), the restrictions on γ are as follows. In order to have two positive internal equilibria γ should satisfy $0.064 < \gamma < 0.0735$. In order to have one positive internal equilibrium, γ should be $0 < \gamma \leq 0.064$. Finally, in order to have boundary equilibria and no positive internal equilibria, γ should satisfy $0.0735 < \gamma < 0.1$. Once again, all of these inequalities are satisfied concurrently. To demonstrate each of these situations, we select γ as shown in Table 5.2. We use the values in Table 5.1 and in Table 5.2 to numerically analyze Case 1.

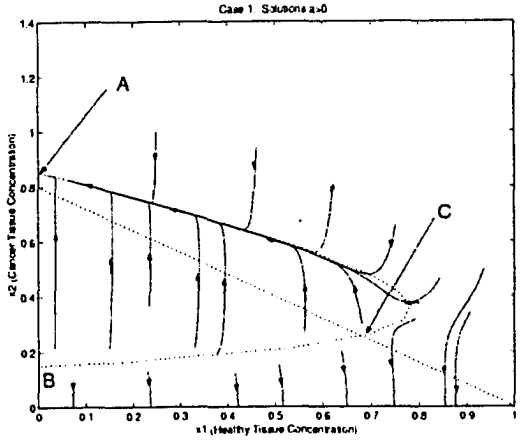

Figure 5.1: Solutions to system in Case 1, $a > 0$, $\gamma = 0.05$, and randomly selected initial values. Point A represents a stable boundary equilibrium E_h, point B represents the unstable boundary equilibrium E_l, and point C is the internal saddle point equilibrium E^*_1.

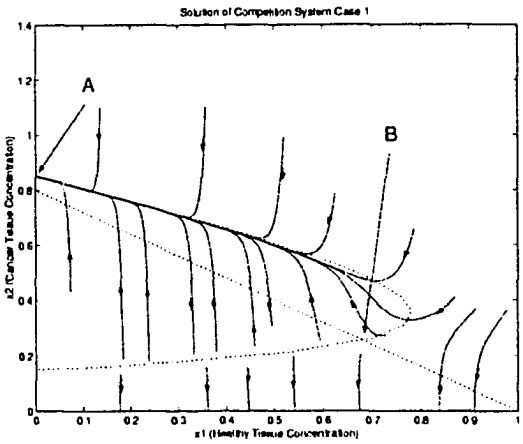

Figure 5.2: Solutions to system in Case 1, $a > 0$, $\gamma = 0.05$, randomly selected initial values, and $\epsilon = 0.001$. Point A represents a stable boundary equilibrium E_h, and point B is the internal saddle point equilibrium E^*_1.

5.2.1 Case 1: $a > 0$

Figure 5.1 (respectively Figure 5.2) illustrates the stability of the system (respectively the perturbed system with $\epsilon = 0.001$) where $\gamma = 0.05$ is such that there is only one positive internal equilibrium E^*_1, and there are two boundary equilibria (E_h and E_l). The numerical solutions confirm the analysis in Chapter 3 that:

1. the internal equilibrium E^*_1 is a saddle point,

2. the boundary equilibrium E_l is an unstable equilibrium,

3. the boundary equilibrium E_h is a stable equilibrium.

The stability of this situation under a small perturbation does not change.

Figure 5.3 (respectively Figure 5.4) illustrates the stability of the system (respectively the perturbed system with $\epsilon = 0.00001$) where $\gamma = 0.07$ is such that there are

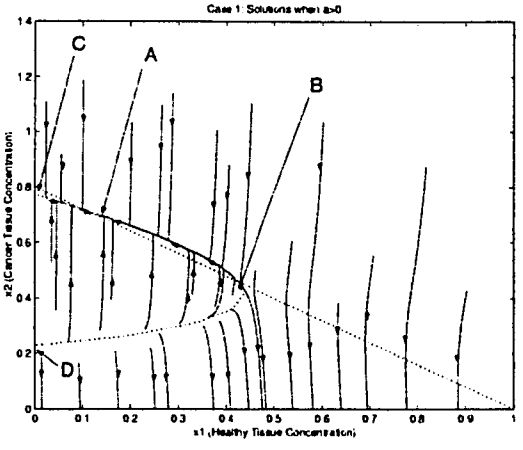

Figure 5.3: Solutions to system in Case 1, $a > 0$, $\gamma = 0.07$, and randomly selected initial values. Point A represents a stable internal equilibrium E^*_2, point B represents an internal saddle point equilibrium E^*_1, point C represents a boundary saddle point equilibrium E_h, and point D represents the unstable boundary equilibrium E_l.

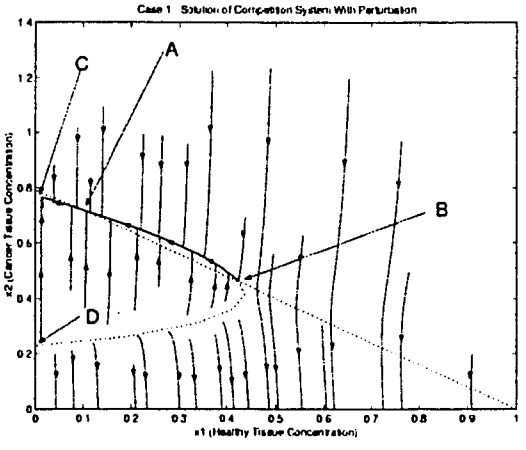

Figure 5.4: Solutions to system in Case 1, $a > 0$, $\gamma = 0.07$, randomly selected initial values, and $\epsilon = 0.00001$. Point A represents a stable internal equilibrium E^*_2, point B represents an internal saddle point equilibrium E^*_1, point C represents a boundary saddle point equilibrium E_h, and point D represents the unstable boundary equilibrium E_l.

two positive internal equilibria (E^*_1 and E^*_2), and there are two boundary equilibria ($E_h(0, x_{2h})$ and $E_l(0, x_{2l})$). The numerical solutions confirm the analysis in Chapter 3 that:

1. the internal equilibrium E^*_1 is a saddle point,

2. the internal equilibrium E^*_2 is a stable equilibrium,

3. the boundary equilibrium E_l is an unstable equilibrium,

4. the boundary equilibrium E_h is a saddle point equilibrium.

The stability of this situation under a small perturbation does not change.

Figure 5.5 (respectively Figure 5.6) illustrates the stability of the system (respectively the perturbed system with $\epsilon = 0.001$) where $\gamma = 0.09$ is such that there is no

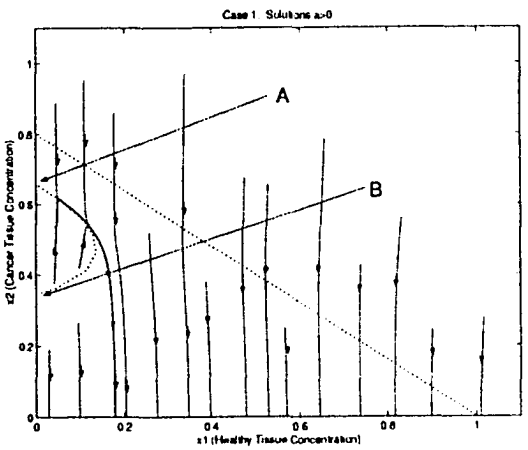

Figure 5.5: Solutions to system in Case 1, $a > 0$, $\gamma = 0.09$, and randomly selected initial values. Point A represents a saddle point boundary equilibrium E_h, and point B represents a boundary unstable equilibrium E_l. The solutions tend towards the x_1 axis and cancer cell concentration of zero.

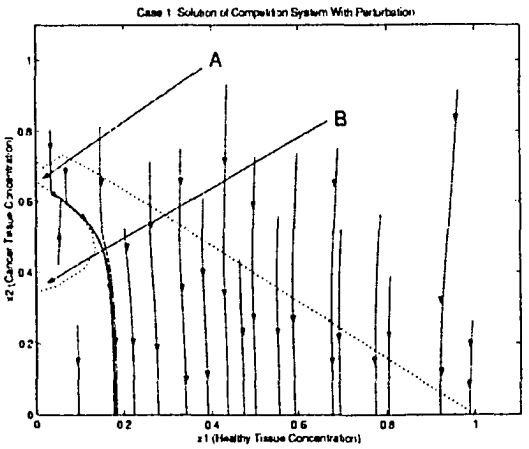

Figure 5.6: Solutions to system in Case 1, $a > 0$, $\gamma = 0.09$; randomly selected initial values, and $\epsilon = 0.00001$. Point A represents a saddle point boundary equilibrium E_h, and point B represents a boundary unstable equilibrium E_l. The solutions tend towards the x_1 axis and cancer cell concentration of zero.

positive internal equilibrium and there are two boundary equilibria (E_h and E_l). The numerical solutions confirm the analysis in Chapter 3 that:

1. the boundary equilibrium E_l is an unstable equilibrium,

2. the boundary equilibrium E_h is a saddle point equilibrium.

The stability of this situation under a small perturbation does not change.

5.2.2 Case 1: $a < 0$

Figure 5.7 (respectively Figure 5.8) illustrates the stability of the system (respectively the perturbed system with $\epsilon = 0.001$) where $\gamma = 0.01$ is such that there is only one positive internal equilibrium $E^*{}_1$, and there are two boundary equilibria (E_h and E_l). The numerical solutions confirm the analysis in Chapter 3 that:

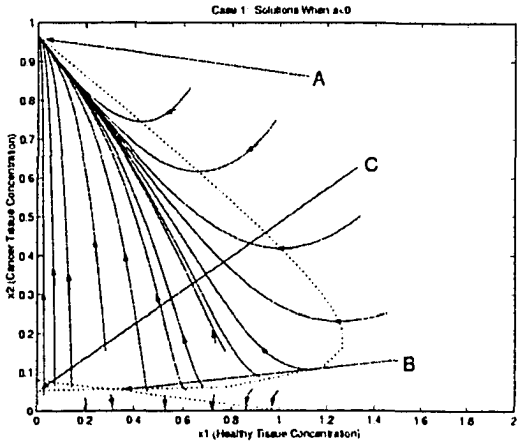

Figure 5.7: Solutions to system in Case 1, $a < 0$, $\gamma = 0.01$, and randomly selected initial values. Point A is a stable boundary equilibrium E_h, point B is the internal saddle point equilibrium E^*_1, and point C is the unstable boundary equilibrium E_l.

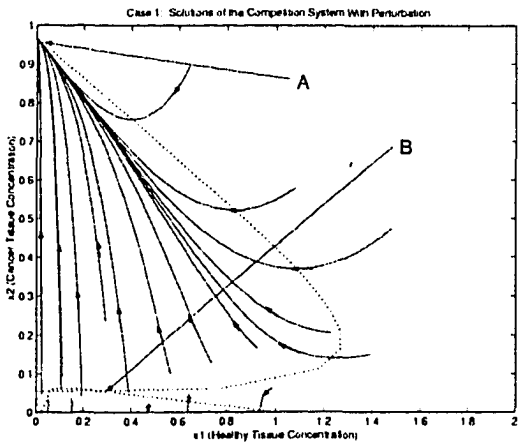

Figure 5.8: Solutions to system in Case 1 under perturbation, $a < 0$, $\gamma = 0.01$, randomly selected initial values, and $\epsilon = 0.001$. Point A represents a stable boundary equilibrium E_h, and point B is the internal saddle point equilibrium E^*_1.

1. the internal equilibrium $E^*_1$is a saddle point,

2. the boundary equilibrium E_l is an unstable equilibrium,

3. the boundary equilibrium E_h is a stable equilibrium.

The stabilities of the equilibria are not affected by small perturbations.

Figure 5.9 (respectively Figure 5.10) illustrates the stability of the system (respectively the perturbed system with $\epsilon = 0.001$) where $\gamma = 0.045$ is such that there is no positive internal equilibrium and there are two boundary equilibria (E_h and E_l). The numerical solutions confirm the analysis in Chapter 3 that:

1. the boundary equilibrium E_l is a saddle point equilibrium,

2. the boundary equilibrium E_h is a stable equilibrium.

The stability of either case under a small perturbation does not change.

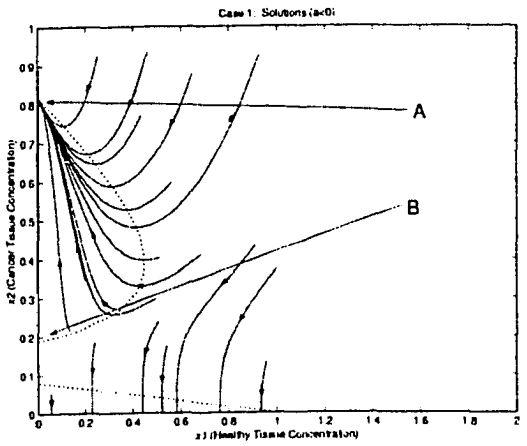

Figure 5.9: Solutions to system in Case 1 under perturbation, $a < 0$, $\gamma = 0.045$, and randomly selected initial values. Point A is a stable boundary equilibrium E_h, point B is the boundary saddle point equilibrium E_l.

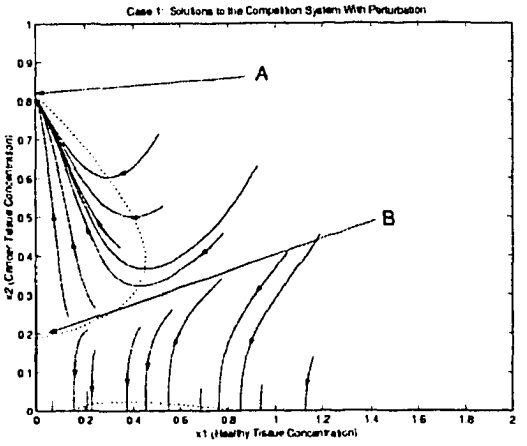

Figure 5.10: Solutions to system in Case 1 under perturbation, $a < 0$, $\gamma = 0.045$, randomly selected initial values, and $\epsilon = 0.001$. Point A represents a stable boundary equilibrium E_h and point B is the boundary saddle point equilibrium E_l.

5.3 Numerical Analysis of Case 2

In this section, we present graphical illustration of all the possible situations in Case 2. We expect the internal equilibrium (if such an equilibrium exists) to be globally stable if the inequality (3.20) is satisfied. The existence of the internal equilibrium is guaranteed when the following inequalities are satisfied:

1. $a > 0 \Rightarrow \frac{K_2\beta_1}{\alpha_2}(\alpha_2 - \gamma_2) < \alpha_1 - \gamma_1 < \frac{\alpha_1}{K_1\beta_2}(\alpha_2 - \gamma_2)$.

2. $a < 0 \Rightarrow \frac{\alpha_1}{K_1\beta_2}(\alpha_2 - \gamma_2) < \alpha_1 - \gamma_1 < \frac{K_2\beta_1}{\alpha_2}(\alpha_2 - \gamma_2)$.

In both cases, since $K_2 > \frac{\alpha_1}{\beta_1}$ and $K_1 < \frac{\alpha_2}{\beta_2}$, not all positive γ_1 and γ_2 will satisfy the above inequalities. Consider the parameter values in Table 5.3.

These four possible results of the solutions to the system in Case 2 are depicted in Figures 5.11, 5.12, 5.13, and 5.14. We first verify if the parameter values satisfy all the different stability conditions.

	α_1	α_2	β_1	β_2	K_1	K_2	γ_1	γ_2
Stable Boundary Equilibrium $(0, \tilde{x}_2)$	8×10^{-3}	0.4	0.01	0.15	1	1	0.006	0.05
One Globally Stable Internal Equilibrium	8×10^{-3}	0.4	0.01	0.15	1	1	10^{-3}	0.15
One Saddle Point Internal Equilibrium	8×10^{-3}	0.3	0.1	0.15	1	1	10^{-3}	0.2
Stable Boundary Equilibrium $(\tilde{x}_1, 0)$	8×10^{-3}	0.4	0.01	0.15	1	1	2×10^{-4}	0.27

Table 5.3: Case 2: Parameter Values

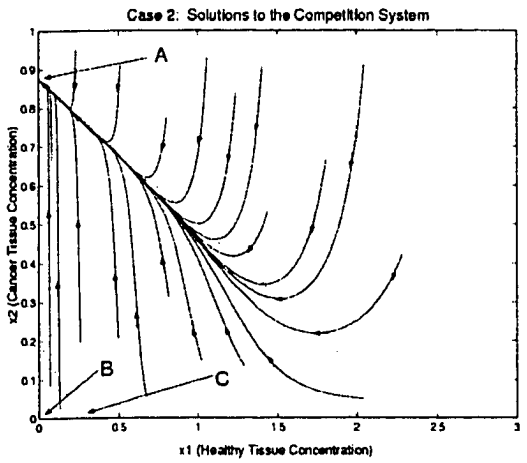

Figure 5.11: Solutions to the system in Case 2 for several randomly selected initial values and $\alpha_1 = 8 \times 10^{-3}$, $\alpha_2 = 0.4$, $\beta_1 = 0.01$, $\beta_2 = 0.15$, $K_1 = K_2 = 1$, $\gamma_1 = 0.006$, and $\gamma_2 = 0.05$. Point A is the stable boundary equilibrium $(0, K_2(1 - \frac{\gamma_2}{\alpha_2})$, point B represents the unstable equilibrium $(0, 0)$, and point C represents the saddle point equilibrium $(K_1(1 - \frac{\gamma_1}{\alpha_1}), 0)$

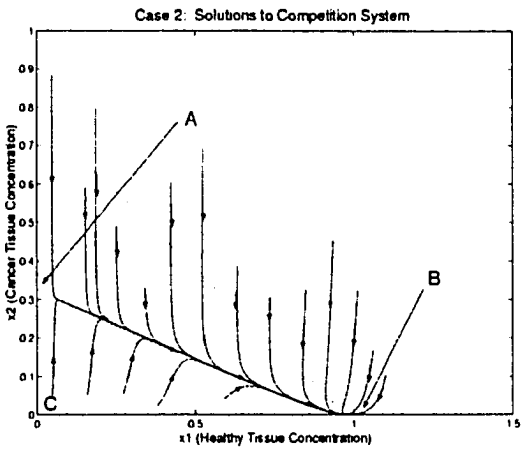

Figure 5.12: Solutions to the system in Case 2 for several randomly selected initial values and $\alpha_1 = 8 \times 10^{-3}$, $\alpha_2 = 0.4$, $\beta_1 = 0.01$, $\beta_2 = 0.15$, $K_1 = K_2 = 1$, $\gamma_1 = 2 \times 10^{-4}$, and $\gamma_2 = 0.27$. Point A represents the saddle point boundary equilibrium $(0, K_2(1 - \frac{\gamma_2}{\alpha_2})$, point B represents the stable boundary equilibrium $(K_1(1 - \frac{\gamma_1}{\alpha_1}), 0)$, and point C represents the unstable equilibrium $(0, 0)$.

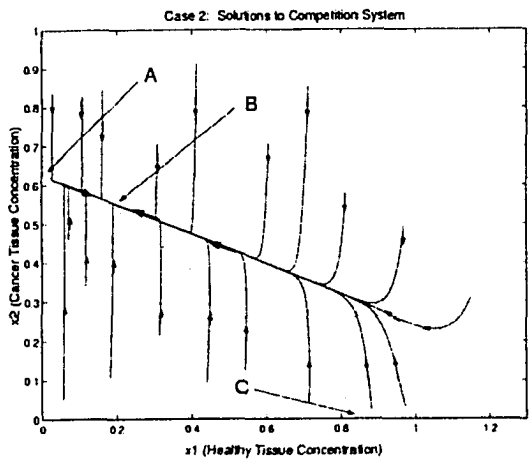

Figure 5.13: Solutions to the system in Case 2 for several randomly selected initial values and $\alpha_1 = 8 \times 10^{-3}$, $\alpha_2 = 0.4$, $\beta_1 = 0.01$, $\beta_2 = 0.15$, $K_1 = K_2 = 1$, $\gamma_1 = 10^{-3}$, and $\gamma_2 = 0.15$. Point A represents the saddle point boundary equilibrium $(0, K_2(1 - \frac{\gamma_2}{\alpha_2})$, point B is the stable boundary equilibrium E^*, and point C is the saddle point boundary equilibrium $(K_1(1 - \frac{\gamma_1}{\alpha_1}), 0)$. Point $(0,0)$ is an unstable equilibrium.

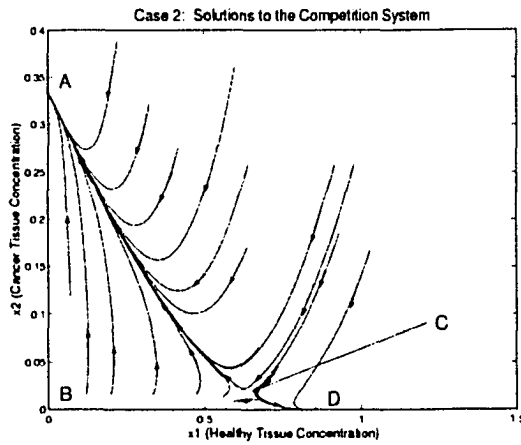

Figure 5.14: Solutions to the system in Case 2 for several randomly selected initial values and $\alpha_1 = 8 \times 10^{-3}$, $\alpha_2 = 0.3$, $\beta_1 = 0.1$, $\beta_2 = 0.15$, $K_1 = K_2 = 1$, $\gamma_1 = 10^{-3}$, and $\gamma_2 = 0.2$. Point A represents the stable boundary equilibrium $(0, K_2(1 - \frac{\gamma_2}{\alpha_2})$, point B is the unstable equilibrium $(0,0)$, point C is the saddle point internal equilibrium E^*, and point D is the stable boundary equilibrium $(K_1(1 - \frac{\gamma_1}{\alpha_1}), 0)$. Point $(0,0)$ is an unstable equilibrium.

$a > 0$	$\alpha_1 = 8 \times 10^{-3}$	$\alpha_2 = 0.4$	$\beta_1 = 0.01$	$\beta_2 = 0.15$	$K_1 = 1$	$K_2 = 1$
$a < 0$	$\alpha_1 = 8 \times 10^{-3}$	$\alpha_2 = 0.3$	$\beta_1 = 0.1$	$\beta_2 = 0.2$	$K_1 = 1$	$K_2 = 1$

Table 5.4: Case 1: Parameter Values

Figure 5.11 depicts the solutions to the system in Case 2 when parameters are selected such that only the boundary equilibrium $(0, \tilde{x_2}) = (0, K_2(1 - \frac{\gamma_2}{\alpha_2}))$ is stable and no internal equilibrium exists.

Figure 5.12 depicts the solutions to the system in Case 2 when parameters are selected such that only the boundary equilibrium $(\tilde{x_1}, 0) = (K_1(1 - \frac{\gamma_1}{\alpha_1}), 0)$ is stable and no internal equilibrium exists.

Figures 5.13 and 5.14 show two possible situations with an internal equilibrium. Figure 5.13 shows a globally stable equilibrium when parameters are such that $a > 0$. Figure 5.14 shows a saddle point equilibrium when parameters are such that $a < 0$.

5.4 Numerical Analysis of Case 3

This section is devoted to providing the numerical examples to illustrate all the different solutions to the system in Case 3. Much like Cases 1 and 2, the stability analysis of Case 3 shows the emergence of two types of cancer-healthy tissue dynamics. These are:

1. $\alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2 = a > 0$,

2. $\alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2 = a < 0$.

We summarize the different parameter values used in this section in Table 5.4.

Figure 5.15 shows the stability of the internal equilibrium when $a > 0$ and $\gamma = 0.08$. As we can see from the figure, the equilibrium in the interior is stable, while the

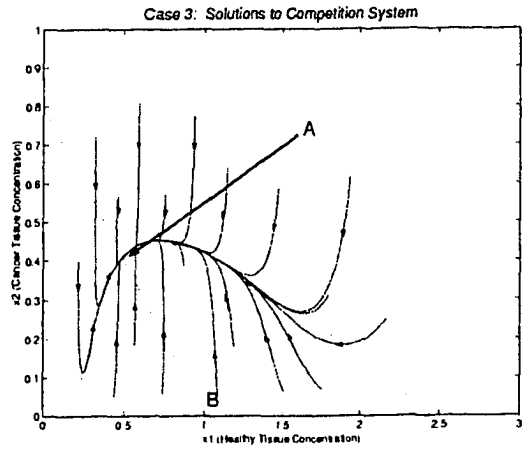

Figure 5.15: Solutions to system in Case 3, $a > 0$, $\gamma = 0.08$, and randomly selected initial values. Point A represents a stable internal equilibrium E^*, and point B is the boundary saddle point equilibrium.

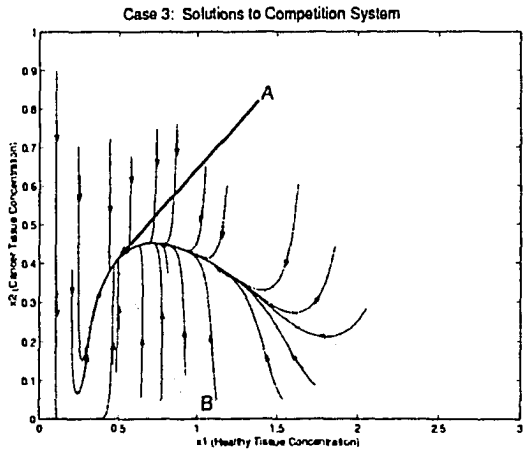

Figure 5.16: Solutions to system in Case 3, $a > 0$, $\gamma = 0.08$, randomly selected initial values, and the perturbation parameter $\epsilon = 0.0001$. Point A represents a stable internal equilibrium E^*, and point B is the boundary saddle point equilibrium.

boundary equilibrium is unstable. When system is perturbed, perturbation parameter is $\epsilon = 0.0001$, the stability does not change as we can see from Figure 5.16.

Figure 5.17 shows the stability of the internal equilibrium when $a < 0$ and $\gamma = 0.08$. The internal equilibrium is stable (a stable focus to be exact), and the boundary equilibrium is a saddle point. Under small perturbations, the system, perturbation parameter is $\epsilon = 0.0001$, the stability does not change as we can see from Figure 5.18.

In Figure 5.19, we see the stability of the system when $a < 0$ and $\gamma = 0.105$. There are two internal equilibria–one is a stable focus and the other is a saddle point equilibrium. The boundary equilibrium is a stable equilibrium as well. Under small perturbations, the system, perturbation parameter is $\epsilon = 0.0001$, the stability does not change as we can see from Figure 5.20.

In Figure 5.19, we see the stability of the system when $a < 0$ and $\gamma = 0.105$. There are two internal equilibria–one is a stable focus and the other is a saddle point

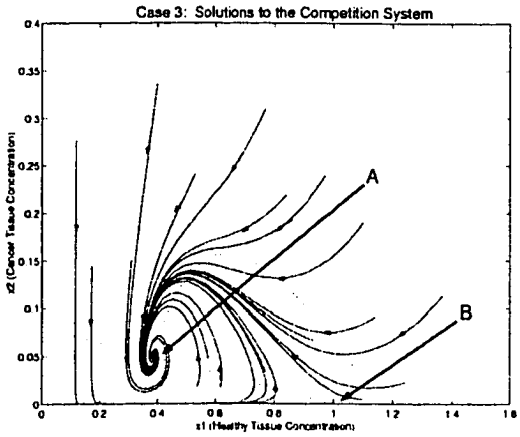

Figure 5.17: Solutions to system in Case 3, $a < 0$, $\gamma = 0.08$, and randomly selected initial values. Point A represents a stable internal equilibrium E^*, and point B is the boundary saddle point equilibrium.

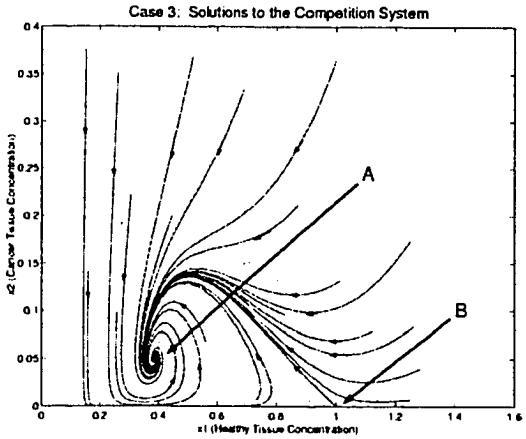

Figure 5.18: Solutions to system in Case 3, $a < 0$, $\gamma = 0.08$, randomly selected initial values, and a perturbation parameter $\epsilon = 0.0001$. Point A represents a stable internal equilibrium E^*, and point B is the boundary saddle point equilibrium.

equilibrium. The boundary equilibrium is a stable equilibrium as well. Under small perturbations, the system, perturbation parameter is $\epsilon = 0.0001$, the stability does not change as we can see from Figure 5.20.

Figure 5.21 (respectively Figure 5.22) shows the stability of the system (respectively the perturbed system with $\epsilon = 0.0001$) when $a < 0$ and $\gamma = 0.11$. There are no internal equilibria since γ no longer satisfies conditions that are derived in section 3.4. In this case, there is only one stable boundary equilibrium. The stability of this equilibrium is not affected by small perturbations.

5.5 Numerical Analysis of Case 4

In this periodic administration of radiation section, we are interested in whether or not a stable, positive limit cycle exists. We use values and analysis of Case 1 for parameter

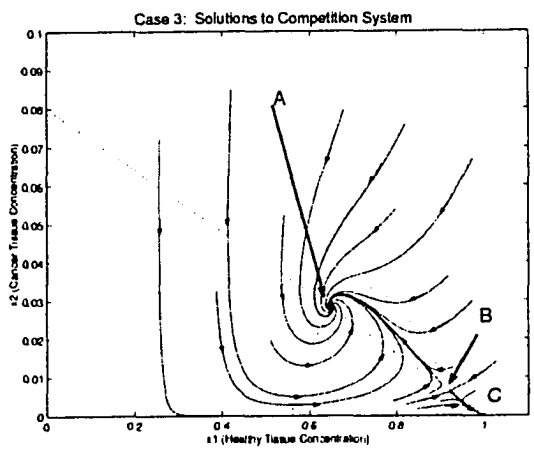

Figure 5.19: Solutions to system in Case 3, $a < 0$, $\gamma = 0.105$, and randomly selected initial values. Point A represents a stable internal equilibrium, and point B is the internal saddle point equilibrium, and point C is the stable boundary equilibrium.

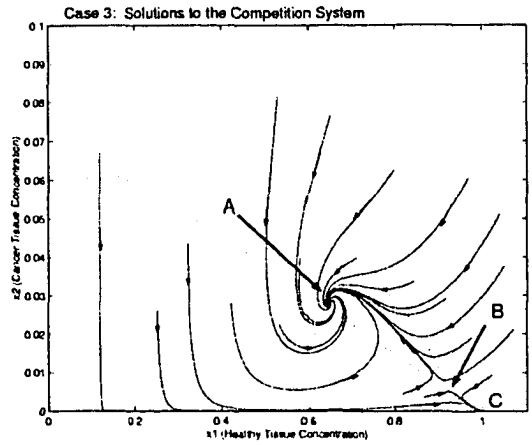

Figure 5.20: Solutions to system in Case 3, $a < 0$, $\gamma = 0.105$, randomly selected initial values, and a perturbation parameter $\epsilon = 0.0001$. Point A represents a stable internal equilibrium, and point B is the internal saddle point equilibrium, and point C is the stable boundary equilibrium.

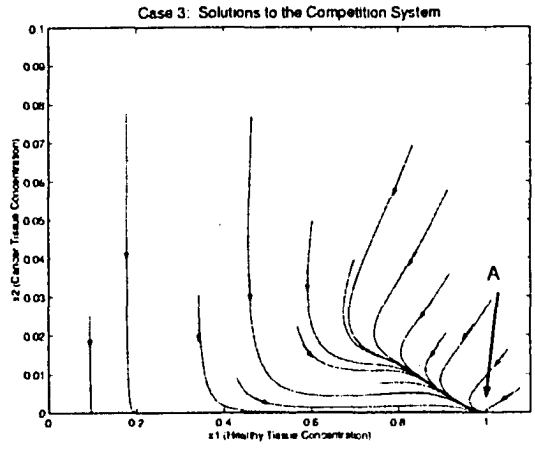

Figure 5.21: Solutions to system in Case 3, $a < 0$, $\gamma = 0.11$, and randomly selected initial values. Point A represents a stable boundary equilibrium.

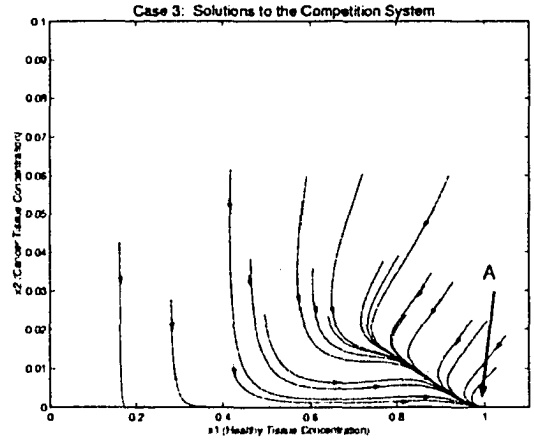

Figure 5.22: Solutions to system in Case 3, $a < 0$, $\gamma = 0.11$, randomly selected initial values, and a perturbation parameter $\epsilon = 0.0001$. Point A represents a stable boundary equilibrium.

selection. When radiation is absent, the solutions to the system tend towards a stable, boundary equilibrium $(0, K_2)$ and cancer win (or the death of the healthy tissue). Radiation is turned on and off to periodically drive the system towards x_1 axis and to provide the organism time to recuperate. Considering the analysis in Case 1, when parameters are selected so that $a > 0$ and γ is such that the solutions to the competition system tend towards x_1 axis (complete cancer extinction), periodic solutions may form as radiation is turned on and off. However, when $a < 0$, even for large values of γ, the flow is often towards a stable equilibrium on the x_2 axis (Figure 5.9). Therefore, the dynamics of the competition system when $a < 0$ are not favorable to a successful treatment with a periodic solution. Figure 5.23 shows the existence of a positive periodic solution when $a > 0$ and $\gamma = 0.07$. The length of one radiation exposure is equal to the length of one rest period between exposures. In this solution, we do not discuss the units of time or particular treatment plans. The length of treatment or rest my be in hours, days or other time frames. When radiation is administered with different length of exposure and at different frequencies, the numerical analysis shows periodic, successful and unsuccessful treatment outcomes. These outcomes are shown in Figures 5.24, 5.25, and 5.26 respectively when $a > 0$. Figures 5.27 and 5.28 show the possibility of a successful and unsuccessful result of treatment when $a < 0$. We leave the discussion of controllability and the success of other periodic solutions for future research.

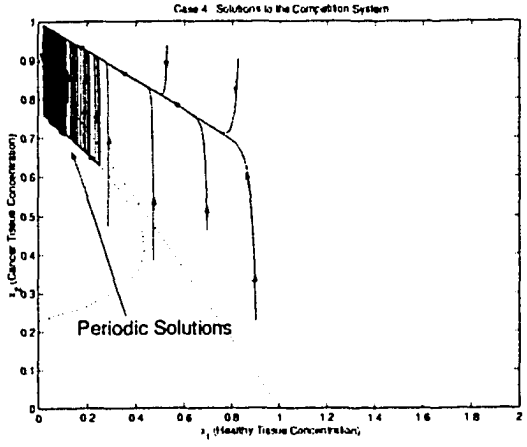

Figure 5.23: Periodic solutions to the system in Case 4, $a > 0$, $\gamma = 0.07$, and randomly selected initial values. The length of radiation exposure is equal to the length of the rest time between exposures.

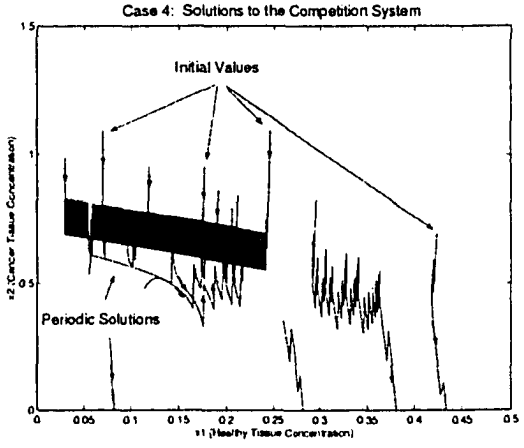

Figure 5.24: Periodic solutions to the system in Case 4, $a > 0$, $\gamma = 0.09$, and randomly selected initial values. The length of radiation exposure is four times longer than the length of the rest time between exposures.

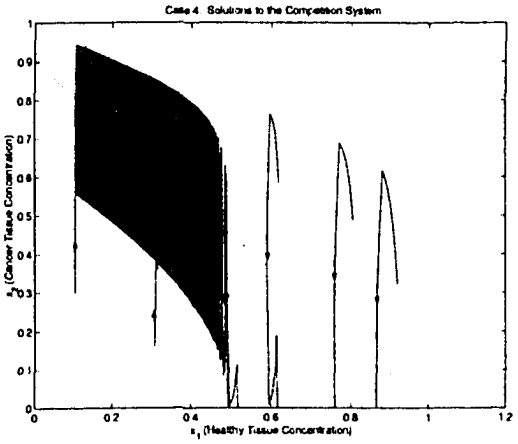

Figure 5.25: Solutions to the system in Case 4, $a > 0$, $\gamma = 0.1$, and randomly selected initial values. The length of radiation exposure is equal to the length of the rest time between exposures. The dark region represents oscillating solutions that eventually tend towards x_1 axis. This represents a complete cure.

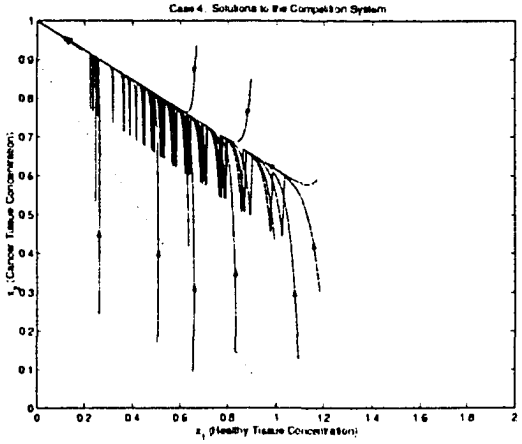

Figure 5.26: Solutions to the system in Case 4, $a > 0$, $\gamma = 0.1$, and randomly selected initial values. The length of radiation exposure is $\frac{1}{5}$ of the length of the rest time between exposures. Solutions tend towards x_2 axis. This represents an unsuccessful treatment plan.

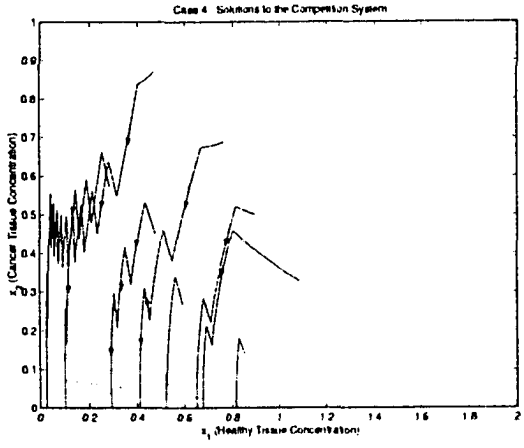

Figure 5.27: Periodic solutions to the system in Case 4, $a < 0$, $\gamma = 0.1$, and randomly selected initial values. The length of radiation exposure is twice the length of the rest time between exposures. The solutions tend towards x_1 axis an a complete cure.

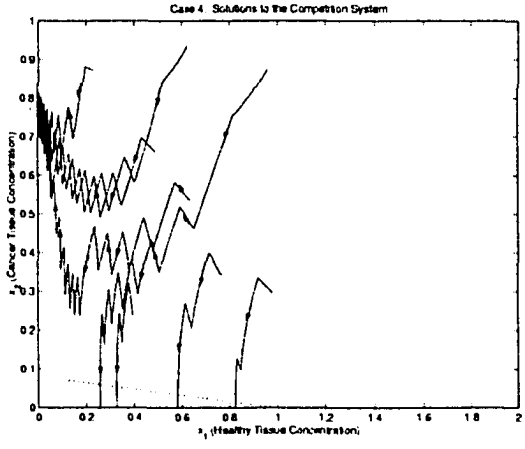

Figure 5.28: Periodic solutions to the system in Case 4, $a < 0$, $\gamma = 0.08$, and randomly selected initial values. The length of radiation exposure is twice the length of the rest time between exposures. Some solutions tend towards x_1 axis and a complete cure, while others tend to x_2 axis and a cancer win.

Chapter 6

Conclusion

6.1 Discussion

To relate the model and its stability analysis to the treatment of cancer by radiotherapy, we need to interpret equilibria and the flow of the system in biological terms. First of all, any positive, internal stable equilibrium or any positive, stable periodic solution means that the treatment was successful in terminating the overall cancer growth. However, this state can be maintained only with continuous application of radiation. We observe such internal equilibria in Case 1, Case 2, and Case 3; while Case number 4 achieves a positive, periodic solution. At certain large radiation doses, we observe the solutions flow towards the x_1 axis (and the cancer concentration of zero). These solutions are preferred as this results in the complete cure without the continuous radiation administration. However, such treatments may not be plausible or safe.

Case number 1, continuous and constant administration of radiation, is a successful treatment plan for cancer at early stages of detection. Even at low radiation dosage, it is possible to drive the cancer concentration to zero. However, intermediate

and advanced stages of cancer may not be treatable. Through mathematical analysis, two types of cancer have emerged. The first type is "aggressive" (fast-spreading and difficult to treat), while the second type is "passive". Mathematically, these two types are classified according to the sign of parameter a ($a = \alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2$) as:

$a < 0$: "Aggressive" cancer.

$a > 0$: "Passive" cancer.

Through the analysis, Case 1 treatment strategy of "aggressive" cancers is successful only at early detection stages or at very large radiation doses. In both instances, cancer concentration is driven to zero. However, the very large radiation dose may pose other risks to the entire organism; and so the risks associated with this treatment plan may outweigh the benefits.

"Passive" cancers may be treated with medium doses of radiation. Mathematically, this outcome is equivalent to the positive, stable internal equilibrium we observe in Case 1 when $a > 0$. Early detection or increase in radiation dosage may also result in the complete cure as with the "aggressive" cancers. However, by the very nature of "passive" cancers, radiation amounts to achieve this result may be lower and so the risk factors may not be as high.

Case number two assumes that the radiation dosage is set to be directly proportional to the instantaneous cancer concentration. Radiation is administered continuously throughout the course of treatment. This is the only case out of the four where we include the direct effects of the radiation on healthy cells. Again, the dynamics of the solution (and the medical implications) of the system were affected by the sign of parameter a. The analysis of"aggressive" cancers (i.e. when $a < 0$) shows the emergence of a saddle point equilibrium at medium radiation doses. In this case, cancer may be completely cured when detected early. However, when $a > 0$ and the cancer is "passive", we show that when there is an internal equilibrium, it is a global internal

equilibrium. Therefore, this treatment plan is successful in controlling cancers at any stage of advancement. Finally, for both types of cancer ("aggressive" and "passive"), large radiation doses lead to the complete removal of cancer cells from the organism. As it was argued in Case 1, this treatment may not be practical since large amounts of radiation pose other health risks.

Case 3 allows for the radiation dose to be proportional to the current ratio of cancer cell concentration to healthy cell concentration. As healthy cell concentration is decreasing, the rate of radiation delivery will increase. We observe the emergence of both a stable and the unstable internal equilibria at various levels of radiation. When cancer is "passive", the internal equilibrium is stable and we have a successful treatment strategy. When the parameters are selected to represent an "aggressive" cancer, there may be two internal equilibria–one is stable and the other one is not. What is interesting about Case 3 is that even the most advanced cancers may be driven to an internal and positive stable equilibrium (i.e. a successful treatment).

Case number 4 achieves an internal, positive periodic solutions for carefully selected parameters to represent the effect of radiation, and wait and rest times. It is also possible to apply the radiation periodically such that cancer concentration is driven to zero. This method for applying radiation seems to be more practical than the other two in terms of delivering of radiation as well as providing the opportunity for the organism to recover from the effects of the radiation.

6.2 Research Direction

The analysis and the proposed treatment plans create some exciting possibilities for treating cancer with radiation. However, many aspects of this work need to be further explored.

First of all, we see different results in various courses of treatment. Some treat-

ments are very successful when treating the advanced stages of cancer (Cases 2 and 3). Others (Cases 1 and 4) are usually more successful whenever cancer concentration is low. Therefore, by combining some of these methods, an interesting problem to consider in the future is the complete curability of cancer through control.

In addition, the effects of the radiation on healthy tissue needs to be modelled with greater precision. This may be accomplished by considering the parameters α, β, and K to be functions of treatment time and radiation. The practicality of radiation treatment (cost-benefit analysis) requires a more precise estimate of the perturbation parameter ϵ.

Further analysis of controllability of the system, particularly in Case 4, is required to set optimal treatment times and radiation amounts. Finally, more data needs to be collected to verify this model. Continuous data of healthy tissue and cancer tissue concentration at different stages of the disease with and without treatment is required to verify the model and to estimate the value of parameter β.

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