A Numerical Study of a Delay Differential Equation Model for Breast Cancer

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(ABSTRACT)

In this thesis we construct a new model of the immune response to the growth of breast cancer cells and investigate the impact of certain drug therapies on the cancer. We use delay differential equations to model the interaction of breast cancer cells with the immune system. The new model is constructed by combining two previous models. The first model accounts for different cell cycles and includes terms to evaluate drug treatments, but ignores quiescent tumor cells. The second model includes quiescent cells, but ignores the immune response and drug treatments. The new model is obtained by combining and modifying these two models to account for quiescent cells, immune cells and includes drug intervention terms. This new model is used to evaluate the effects of pulsed applications of the drug Paclitaxel for models with and without quiescent cells. We use sensitivity equation methods to analyze the sensitivity of the model with respect to the initial number of immune cytotoxic T-cells. Numerical experiments are conducted to compare the model predictions to observed behavior.

This thesis is dedicated to my parents and Robab.

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Chapter 1

Introduction

In this Chapter we provide a short overview of what is known about breast cancer. In addition, we provide some statistical data about cancer and then describe how cancer behaves on a cellular level. This basic background is essential in order to understand how one constructs the phenomenological models governed by delay differential equations. This background material also helps place the mathematical model in a biological context. Since the models are described by delay differential equations and numerical methods are employed to simulate these equations, we also provide a brief background on delay systems in Section 1.2.

1.1 An Overview of Breast Cancer

Every year in the United States, approximately $1,399,790$ people are diagnosed with cancer leading to $564,830$ deaths. In a study done by the National Cancer Institute, there is a about a 40% chance for the average person to develop cancer in their lifetime. This figure includes males and females of all races [1].

Among women in the United States, skin cancer is the most common cancer, followed by breast cancer. Nearly one in three US women have been diagnosed with breast cancer. There are two levels of cancer: in situ and invasive. In situ cancer is one that has not yet spread to other parts of the body, whereas invasive cancer has moved to some other part of the body. In situ breast cancer is usually curable, however invasive breast cancer is more difficult to treat. In 2005 the American Cancer Society's Surveillance Research group estimated that during the period $2005 - 2006$ there would be approximately $56,890$ new cases of in situ breast cancer and $201,730$ new cases of invasive breast cancer among women over 40. The same study estimated that in 2005 more than $39,300$ women over 40, would die of breast cancer. Between 1987 and 2002 the rate of incidence of breast cancer was increasing by 0.3% a year. It has been suggested that some reasons for the increase since the mid 1970's include hormone replacement therapy and obesity. Other factors that increase the relative risk of breast cancer include relatives with breast cancer, oral contraceptive use and Jewish heritage [1].

In general, it is believed that cancer cells are mutated cells. It has been speculated

that some viral infections, exposure to chemicals and radiation may drive cells to become mutated. It was once believed that these mutated cells go on to reproduce quickly producing many more daughter cells than normal cells that are capable of reproducing. A more modern perspective explains that it is not that cancer cells simply reproduce faster, but that they lose the ability to control their cell cycle. A normal, non-cancerous cell has many checkpoints along its cell cycle. During these checkpoints a normal cell will stop the cycle if it detects an abnormality [20]. With this type of unmanageable proliferation, more and more genetic material gets lost, making newer cancer cells even more mutated than the original cancer cells. Eventually there will be billions of mutated cells and a tumor will be formed. This explains why it is imperative to catch cancer early in the cell cycle.

The interaction between the body's immune system, drugs and a tumor is very complex. In order to obtain a manageable model, we quickly review some key details about this system. Like all eukaryotic cells, tumor cells have four distinct parts to their cell cycle: G_1 (pre-synthetic) phase, S (synthetic) phase, G_2 (post-synthetic) phase and mitosis. The phases G_1, S and G_2 are collectively known as the interphase stage. This is the stage where the cell prepares for division or mitosis.

During the resting phase G_1, the parent cells grow larger, cytoplasm is added and organelles are reproduced. This phase is the longest of all phases; it can take up to to 48 hours. The next phase is the S phase, which can take anywhere from 8 to 20 hours to complete. Once the S phase is complete, each chromosome consists of two sister chromatids connected at the centromere. Replication of deoxyribosenucleicacid (DNA) occurs at this stage. Throughout the G_2 phase the cells keep growing, making the final preparations for mitosis (or cell division). This stage can last up to 4 hours [21]. During mitosis, the cellular components and the replicated chromosomes are divided to ensure that each daughter cell receives equal distribution. Mitosis is a short phase, lasting about 30 minutes. Some cells have an additional stage known as the G_0, or quiescent phase. At this stage the cell refrains from dividing for a long period of time. A quiescent cell will need some stimuli to enter the cell cycle (see [19]). Some cells may never enter the quiescent phase, while others like many nerve cells, may stay in it for their entire life cycle.

Cytokines are proteinous hormones secreted by one cell for the purpose of changing the behavior or properties of itself or another cell. The immune system uses cytokines extensively (see [11] and [19]). Cytokines are used by B-lymphocytes to activate T-lymphocytes. The T-lymphocytes cells "attack" and eliminate the tumor cells. There are different types of T cells. We will only be considering the cytotoxic T-cells. The tumor cells also have the capacity to deactivate the lymphocytes. As the tumor grows it induces a deactivation of the lymphocytes that enter into the cell. This process is called immunodepression [17].

Chemotherapy is one of several ways of combatting cancer cells. There are two main types of chemotherapy drugs. The first type interfere with the cellular activity of the tumor cells and the second type attacks the tumor cells during a specific cell cycle. In this thesis we will be studying the latter. The drug Paclitaxel is an example of a cycle specific drug. Paclitaxel is a drug used to treat breast, ovarian, head and neck cancer. Sometimes Paclitaxel is used with other drugs such as 5-FU or Doxorubicin for attacking a variety of other cancers [20].

In recent years, several papers have been devoted to the problems of modeling and analysis of the interaction between cycle specific drugs, the immune system and tumor cells. Our study begins with two of these papers: *Heuristic Design of Cancer Chemotherapies* by M. Villasana and G. Ochoa [21] and *Dynamics Analysis and Limit Cycle in a Delayed Model*

for Tumor Growth with Quiescence by R. Yafia [22]. After we discuss the above papers we will introduce a new model which combines parts from each model.

1.2 A Short Review of Delay Differential and Sensitivity Equations

Differential equations have long been used to model various cell populations. In many cases ordinary differential equations (ODEs) are the starting point in the modeling process. When time delays (due to feedback, cells division time lags, etc.) become important, then delay differential equations become a natural tool for modeling in the life sciences. For example, the classic predator-prey ODE model suggested by Lotka and Volterra in the 1920's has the form

$$\frac{dx(t)}{dt} = a_1 x(t) - b_1 x(t) y(t) \tag{1.1}$$

$$\frac{dy(t)}{dt} = -a_2 y(t) + b_2 x(t) y(t), \tag{1.2}$$

with initial conditions

$$x(0) = x_0, \qquad y(0) = y_0, \tag{1.3}$$

where $x(t)$ represents the population of prey and $y(t)$ the population of predators at time t and a_1, a_2, b_1, b_2 are positive constants. If one considers the fact that a change in the population of the prey will not immediately affect the population of the predators and conversely, then the system (1.1)- (1.2) becomes a delay differential equation (DDE) of the form

$$\frac{dx(t)}{dt} = a_1 x(t) - b_1 x(t) y(t - r_1) \tag{1.4}$$

$$\frac{dy(t)}{dt} = -a_2 y(t) + b_2 x(t - r_2) y(t), \tag{1.5}$$

with initial conditions

$$x(0) = x_0, \quad x(s) = \phi(s), \qquad y(0) = y_0 \quad y(s) = \varphi(s), \ -\tau < s < 0 \tag{1.6}$$

where $r_1 > 0$ and $r_2 > 0$ are time delays and the functions $\phi(\cdot)$ and $\varphi(\cdot)$ are the initial past history functions.

During the past thirty years we have seen the development of a fairly complete theory for existence, uniqueness, continuous dependence, stability and numerical approximation of such systems. The references see [9] and [10] provide the basic background needed in this thesis and hence we shall not attempt to review all this material. We shall also be interested in sensitivity and variational equations (sensitivity equations for the initial data) for DDE systems. Although sensitivity with respect to general initial data requires the use of Fréchet derivatives, we will focus on the special case where the initial functions are constant (e.g., in the previous equations $\phi(\cdot) \equiv x_0$ and $\varphi(\cdot) \equiv y_0$). In this case the sensitivity equations are easier to derive and to simulate. Thus, we consider a system of n delay differential equations with one delay $r > 0$ and constant initial data of the form

$$\dot{x}(t) = f(t, x(t), x(t - r), q), \quad x(s) \equiv x_0, \ -\tau < s < 0, \tag{1.7}$$

where q is a vector of parameters and x_0 is a vector of initial values. Here $f : R \times R^n \times R^n \times R^m \to R^n$ has the form

$$f(t, x, z, q) = [f_1(t, x, z, q), \quad f_2(t, x, z, q), ldots, \quad f_n(t, x, z, q)]^T,$$

where $f_i : R \times R^n \times R^n \times R^m \to R$ are real-valued.

In order to define the sensitivity with respect to an initial condition, we let $x(t, x_0)$ denote the solution to equation (1.7) on $0 \leq t < T$. Assume that the initial vector is given by

$$x_0 = \theta = [\theta_1, \theta_2, \ldots, \theta_n]^T$$

and one is interested in the sensitivity defined by

$$\frac{\partial x(t, x_0)}{\partial \theta_j} \triangleq s_j(t, \theta). \tag{1.8}$$

It is straight forward to show that (with appropriate assumptions on $f(t, x, z, q)$ that the sensitivity $s_j(t, \theta)$ satisfies the linear delay differential equation

$$\begin{aligned} \dot{s}_i(t, \theta) = &[f_x(t, x(t), x(t - r), q)]s_j(t, \theta) \\ &+ [f_z(t, x(t), x(t - r), q)]s_j(t - r, \theta), \end{aligned} \tag{1.9}$$

with initial condition

$$s_j(s, \theta) \equiv e_j, \ -\tau < s < 0, \tag{1.10}$$

where e_j is the standard unit vector $[0, 0, \ldots, 1, \ldots, 0]^T$ with a 1 in the j^{th} slot and 0 elsewhere. Here, $[f_x(t, x(t), x(t-r), q)]$ and $[f_z(t, x(t), x(t-r), q)]$ are the Jacobian matrices of partial derivatives evaluated at $(t, x(t), x(t - r), q)$.

We shall use the MATLAB^{TM} package DDE23 to simulate the delay and sensitivity equations. Details of DDE23 may be found in the article *Solving DDEs in MATLAB* by L. F. Shampine, S. Thompson that appeared in Applied Numerical Mathematics, **37** (2001), 441–458 (see [18]). We note that in some cases this software can produce negative cancer cell counts due to numerical errors. This problem also occurs in ordinary differential equation solvers and should be considered when using off-the-shelf packages. We will discuss this issue again in the conclusion section. However, all the numerical results presented here stayed well within expected values for the initial conditions considered in this paper.

Chapter 2

Cancer Models

In this chapter we provide three models for breast cancer. The first model comes from a series of papers by M. Villasana, G. Ochoa and A. Radunskaya. Their model focuses on the effect of a cycle specific drug on proliferating tumor cells and cytotoxic T-cells (see [19], [20] and [21]). However, the quiescent cells are ignored in these papers. The second model comes from the paper [22] by Yafia and considers the interconnected growth patterns of both proliferating and quiescent cells. Based on a combination and modification of these two models, we form a new model and then use this new model to analyze the effect of Paclitaxel on proliferating, quiescent and immune cells. This analysis is one of the main contributations of this thesis.

2.1 Model 1: Model of Tumor Cells During Mitosis and Interphase

Cell growth of various types of cells, whether they be immune cells or yeast cells have certain features in common. Therefore, a mathematical model of a particular cell growth may be used to model other types of cell growth, provided some basic changes can be made. In general, many of these models lead to ordinary differential equations (ODEs) which assume large populations of cells. This is a reasonable assumption for the cancer models considered here. Although differential equations assume continuous (in time) functions and cellular division is a discrete process, ODEs often capture many of the important features of cell division in large cell populations. For example, the following model is a system of ordinary differential equations that are often used to describes lymphocyte division. For $j = 1, 2, \ldots, J$, let $N_j(t)$ be the population of lymphocytes at time t, after j divisions. If α_j denotes the rate of cell proliferation and β_j denotes the rate of cell death, then one is lead to the system

$$\frac{dN_0(t)}{dt} = -(\alpha_0 + \beta_0)N_0(t) \tag{2.1}$$

$$\frac{dN_j(t)}{dt} = 2\alpha_{j-1}N_{j-1}(t) - (\alpha_j + \beta_j)N_j(t), \quad j = 1, 2, ..., J. \tag{2.2}$$

By adjusting the parameters, this model can be used for many types of cell growth. The terms involving $2\alpha_{j-1}$ in equations (2.2) occur because during mitosis a cell will split into two new cells. However, since cell division is a discrete process, there is a discrete time delay

between the time a cell is born and when it divides. As we mentioned above, it might take days for a cell to start dividing. This time delay has been incorporated in many models which again leads to models governed by delay differential equations. A nice comparison of cell growth models based on ordinary differential equations and delay differential equations (DDEs) can be found in [2].

In 2001 M. Villasana [19] developed a model of the interactions between proliferating tumor cells, drugs and the immune system. This model was also used to develop optimal drug treatment strategies. In 2003, Villasana and Radunskaya [20] used a similar DDE to model to analyze the stability of such systems. In 2004 Villasana and Ochoa [21] extended and improved these initial models and provided parameter estimates needed to construct drug treatment strategies. All of these results are based on models that ignore the quiescent cells and lead to "optimal bang-bang" types of controls. These models are relatively simple but they produce results that are indicative of realistic cancer growth. Also, these models incorporate the deactivation of immune cells by tumor cells, a concept first introduced by Kuznetsov and Taylor in 1994 [12]. As noted in these papers, excluding the quiescent stage may be too much of a simplification. Nevertheless, much can be learned from studying Villasana and Ochoa's model [21]. We use this model as a starting point in the development of the new model below.

For high risk women, there are a number of anti-estrogen drugs that cut down the incidence of breast cancer. One of these drugs, Tamoxifen, has been shown to reduce the number of breast cancer cases in high risk women by nearly half. Another drug, Raloxifene, is effective in reducing the risk of breast cancer in postmenopausal women because the risk of breast cancer increases dramatically as women get older. Currently, there are many drugs that are being tested in hopes of having greater efficacy but producing less side effects for the patient [1]. A better understanding of cancer should aid this progress.

Paclitaxel is a cycle specific drug that targets the S-phase. However, the drug produces no visible effect until mitosis. Cycle specific drugs are commonly used and usually interfere with mitosis by inhibiting the cell from proliferating. This model takes into account the fact that drugs not only kill the tumor cells but will also kill some of the immune system's cells. The model also assumes that the drug will arrest the tumor cells that are in mitosis. The resident time of cells in interphase is denoted by τ and is in days. Also, while the tumor cells are in interphase they are attacked by Paclitaxel but they does not die until they are in mitosis τ days later. Note that mitosis is a very short stage compared to interphase and so a time delay in the mitosis stage is not included in the model in [21]. The model introduced in [21] divides the population of tumor cells into interphase cells and mitosis cells which are represented by $T_I(t)$ and $T_M(t)$, respectively. The term, $I(t)$ represents the population of immune cells which are the population of cytotoxic T-cells.

The Villasana and Ochoa model [21] is given by the five equations

$$\frac{dT_I(t)}{dt} = 2a_4T_M(t) - c_1T_I(t)I(t) - d_2T_I(t) - a_1T_I(t-\tau) \tag{2.3}$$

$$\frac{dT_M(t)}{dt} = a_1T_I(t-\tau) - d_3T_M(t) - a_4T_M(t) - c_3T_M(t)I(t) - k_1(1-e^{-k_2w(t)})T_M(t) \tag{2.4}$$

$$\frac{dI(t)}{dt} = k + \frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha + (T_I(t)+T_M(t))^n} - c_2I(t)T_I(t) - c_4T_M(t)I(t) - d_1I(t) - k_3(1-e^{-k_4w(t)})I(t) \tag{2.5}$$

$$\tag{2.6}$$

$$\frac{dw_1(t)}{dt} = -\lambda_1w_1(t) + c(t) \tag{2.7}$$

$$\frac{dw_2(t)}{dt} = -\lambda_2w_2(t) + c(t) \tag{2.8}$$

with initial conditions

$$T_I(s) = \phi_1(s) \equiv TI_0, \quad -\tau < s \leq 0 \tag{2.9}$$

$$T_M(s) = \phi_2(s) \equiv TM_0, \quad -\tau < s \leq 0 \tag{2.10}$$

$$I(s) = \phi_3(s) \equiv I_0, \quad -\tau < s \leq 0 \tag{2.11}$$

and

$$w_1(0) = 0 \tag{2.12}$$

$$w_2(0) = 0. \tag{2.13}$$

Here,

$$w(t) = r_1w_1(t) + r_2w_2(t) \tag{2.14}$$

is a linear combination of the "states" $w_1(t)$ and $w_2(t)$ and $c(t)$ denotes the concentration of Paclitaxel that is injected into the system at time t. The "kill" terms $k_1(1-e^{-k_2w(t)})T_M(t)$ and $k_3(1-e^{-k_4w(t)})I(t)$ represent the impact of the drug on mitosis and the immune T-cells, respectively. Paclitaxel has a decay that can be modeled with two separate elimination rates. The decay function is chosen so that there is one decay rate in the bloodstream and immediate tissue and a second decay rate that describes the drugs slower decay in the peripheral tissues. There is an upper bound on the kill effect of a drug, so an increased drug dose does not imply more deaths of tumor nor T-cells. This accounts for the choice of the exponential form of these terms used in the paper [21].

The loss of tumor cells due to immune cells is expressed by the terms $T_M(t)I(t)$ and $T_I(t)I(t)$. The term

$$\frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha + (T_I(t)+T_M(t))^n}$$

in equation (2.5) represents the nonlinear growth of the immune cell population due to the presence of a tumor. It is assumed that the immune system in the bone marrow produces

a small fraction of the immune cells. Thus, the constant k, being the birth rate of immune cells without the presence of a tumor, should be small. Parameters ρ, α and n depend on the type of tumor and the health of the patient's immune system; more specifically their ability to produce certain kinds of cytokines. The term ρ represents the increase of immune cells due to a stimulus and should be approximately equal to 0.2. The parameter α represents the half value for the immune response. When the tumor level is equal to α the immune response is half way to its maximum value ρ. Larger values of n mean that it takes the immune system a longer time to recognize the tumor.

The time delay τ represents the number of days the tumor cells reside in the interphase stage and is set to 2 days. Later, we will non-dimensionalize all of the parameters and so this value will change. As we already stated, mitosis is a very short stage and so we do not include a delay for the time it takes the cells to divide.

Note that in reality, all parameters depend on the tumor type and the health of the person. The parameter values given in the paper [21] were obtained by fitting data collected from a patient by measuring the interaction of Paclitaxel and breast cancer cells. This particular set of parameters came from an individual with a rapidly growing tumor whose immune system was not able to control the cancer. The patient eventually died [21]. The following table can be found in [21] and provides the values for the non-dimensionalized parameters we shall use throughout this thesis.

τ	0.92
a_1	0.98
a_4	0.8
d_2	0.11
d_3	0.4
d_1	0.29
c_1	0.9
c_3	0.9
c_2	0.085
c_4	0.085
α	0.2
ρ	0.1
λ_1	126.12
λ_2	0.85
k	0.036
k_1	0.47
k_2	0.57
k_3	0.49
k_4	0.061
r_1	0.73
r_2	0.27

Table 2.1: Parameter Values

2.2 Model 2: Model of Quiescent Tumor Cells

As stated above Villasana and Ochoa's model does not include quiescent tumor cells. In the paper *Dynamics Analysis and Limit Cycle in a Delayed Model for Tumor Growth with Quiescence* [22] Yafia develops a delay differential equation model for the interactions of proliferating and quiescent tumor cells. However, this paper does not include the immune cells nor the impact of the administration of drugs. Most chemotherapeutic drugs do not only target cancer cells but they also attack other rapidly reproducing cells such as hair follicles and cells of the intestinal tract [20]. In fact, it may be important for cancer treatment to target these proliferating cells. On the other hand, it is not clear that including non-proliferating cells in the model will improve the understanding of the impact of a particular drug treatment that attacks only proliferating cells. However, including quiescent cells in the model should be more realistic and could provide additional insight into this complex system. In particular, some organs have a higher quiescent to proliferating cell ratio. Therefore, including quiescent cells in the model may give us a more flexible model that can be used to understand different kinds of cancer. For example, many neurons stay in the quiescent stage for a long time and hence a cancer model that attempts to comprehend nerve cancer, needs to include both quiescent and proliferating tumor cells. In order to develop a complete model that includes quiescent cells, we make use of the model developed by Yafia in [22].

Let $P(t)$ and $Q(t)$ represent the number of proliferating tumor cells and quiescent tumor cells, respectively. The total number of tumor cells is given by $N(t) = P(t) + Q(t)$. Let $\beta > 0$ be the division rate of the proliferating cells and $\mu_P > 0$ be the death rate of the proliferating cells. Thus, $b = \beta - \mu_P > 0$ is the intrinsic growth rate of the proliferating cells. Since quiescent cells do not reproduce, there is no parameter for their division rate. There is a mortality rate represented by $u_Q \leq 0$. The terms $r_P(N)$ and $r_Q(N)$ incorporate the transition of proliferating cells to quiescent cells and quiescent cells to proliferating cells, respectively. Finally, the time delay τ is the time it takes proliferating cells to divide. Yafia's model is described by the delay differential equations

$$\frac{dP(t)}{dt} = bP(t-\tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t) \tag{2.15}$$

$$\frac{dQ(t)}{dt} = r_P((N(t))P(t) - \mu_Q Q(t) - r_Q(N(t))Q(t), \tag{2.16}$$

with constant initial functions

$$P(s) \equiv P_0, \quad Q(s) \equiv Q_0, \ -\tau < s \leq 0. \tag{2.17}$$

Here $r_P(N)$ is nondecreasing and $r_Q(N)$ nonincreasing in bounded sets on N. If the delay is set to zero, i.e. $\tau = 0$, then the system reduces to an ODE system. We used this system to test and verify the code used in the numerical results section. In particular, the ODE system

$$\frac{dP(t)}{dt} = bP(t) - r_P(N(t))P(t) - r_Q(N(t))Q(t) \tag{2.18}$$

$$\frac{dQ(t)}{dt} = r_P(N(t))P(t) - \mu_Q Q(t) + r_Q(N(t))Q(t) \tag{2.19}$$

is a reasonable approximation to the DDE system (2.15)-(2.16) when $\tau \approx 0$. In the next section we combine the two previous models to produce a new model with quiescent cells, immune cells and drug treatment.

2.3 Model 3: An Integrated Model

The model proposed here combines the two previous models and includes additional terms to account for the impact of Paclitaxel on the quiescent cells. In particular, we combine the three equations (2.3)-(2.5) with the two equations (2.15)-(2.16) and additional control terms. We note (see [21]) that quiescent tumor cells are resistant to cytotoxic agents and so their inclusion will introduce resistance into the model. Let $T_Q(t)$ denote the population of tumor cells that are in the quiescent stage of their cell cycle and let $N(t) = T_Q(t) + T_I(t) + T_M(t)$ be the total cancer cell population. We restrict our study to the case where in equations (2.15)-(2.16), the transition rates $r_P(N) = a_5$ and $r_Q(N) = a_6$ are constants. The constant d_4 represent the natural death rate of the quiescent tumor cells and c_5 is the kill rate of quiescent cells by the cytotoxic T-cells.

Since Paclitaxel is a cycle specific drug, it targets tumor cells while they are in the interphase stage. These cells are not actually arrested until the next cellular stage, whether it be mitosis or quiescence. We take into account the fact that high doses of a cycle specific drug will damage or kill immune cells and other cells in different cycles. The resulting model is described by the system of delay differential equations

$$\begin{aligned}\frac{dT_Q(t)}{dt} &= a_5T_I(t-\tau) - a_6T_Q(t) - d_4T_Q(t) \\ &\quad -c_5I(t)T_Q(t) - u_1(t)T_Q(t)\end{aligned} \tag{2.20}$$

$$\begin{aligned}\frac{dT_I(t)}{dt} &= 2a_4T_M(t) - a_5T_I(t-\tau) + a_6T_Q(t) \\ &\quad -c_1T_I(t)I(t) - d_2T_I(t) - a_1T_I(t-\tau)\end{aligned} \tag{2.21}$$

$$\begin{aligned}\frac{dT_M(t)}{dt} &= a_1T_I(t-\tau) - d_3T_M(t) - a_4T_M(t) \\ &\quad -c_3T_M(t)I(t) - u_2(t)T_M(t)\end{aligned} \tag{2.22}$$

$$\begin{aligned}\frac{dI(t)}{dt} &= k + \frac{\rho I(t)(T_Q(t)+T_I(t)+T_M(t))^n}{\alpha + (T_Q(t)+T_I(t)+T_M(t))^n} - c_2I(t)T_I(t) \\ &\quad -c_4T_M(t)I(t) - c_6T_Q(t)I(t) - d_1I(t) - u_3(t)I(t)\end{aligned} \tag{2.23}$$

with initial conditions the same as provided in [21]

$$T_Q(s) \equiv 0.8, \quad -\tau < s \leq 0 \tag{2.24}$$

$$T_I(s) \equiv 1.3, \quad -\tau < s \leq 0 \tag{2.25}$$

$$T_M(s) \equiv 1.2, \quad -\tau < s \leq 0 \tag{2.26}$$

$$I(s) \equiv 0.9, \quad -\tau < s \leq 0. \tag{2.27}$$

All parameter values are in fractional amounts per day. The constants a_1 and a_4 represent the fraction of cells which cycle from interphase to mitosis and from mitosis to interphase, respectively. Both of these constants need to be between 0.2 and 1.0 per day. It is typical for these values to be between 0.7 and 1.0. The constants d_1, d_2 and d_3 represent fractions of natural cell death, or apoptosis, and should be between 0.1 and 0.3. The constants c_i model the losses of the cells due to an encounter with another cell. For immune cells these numbers are usually around 0.1. When an immune cell and a cancer cells bind, approximately 10% of the time the immune cell is lost. For cancer cells this lost is somewhere around 20% to 30%. As above, the term

$$\frac{\rho * I(t)(T_Q(t) + T_I(t) + T_M(t))^n}{\alpha + (T_Q(t) + T_I(t) + T_M(t))^n}$$

represents the nonlinear growth of the immune population due to the presence of a tumor.

The control terms $u_1(t)$, $u_2(t)$ and $u_3(t)$ are more general than the exponential terms in [21]. However, in order to compare our model to the existing literature, we set

$$\begin{aligned} u_1(t) &= k_5(1 - e^{-k_6 w(t)}) \\ u_2(t) &= k_1(1 - e^{-k_2 w(t)}) \\ u_1(t) &= k_3(1 - e^{-k_4 w(t)}), \end{aligned} \tag{2.28}$$

where, as before,

$$\frac{dw_1(t)}{dt} = -\lambda_1 w_1(t) + c(t), \quad w_1(0) = 0 \tag{2.29}$$

$$\frac{dw_2(t)}{dt} = -\lambda_2 w_2(t) + c(t), \quad w_2(0) = 0 \tag{2.30}$$

and

$$w(t) = r_1 w_1(t) + r_2 w_2(t). \tag{2.31}$$

The system (2.20)-(2.31) of delay differential equations is our new model. In this form, the parameters a_1, a_4, a_5, a_6, d_1, d_2, d_3, d_4, c_1, c_2, c_3, c_4, c_5 and c_6 are all positive an less than 1. For the numerical runs we used the parameters in the previous papers and selected the new parameters based on the values of similar parameters in the previous models. Thus, the following table contains all the parameters used in the numerical runs. Since some of these parameters had to be chosen without the benefit of data, parameter identification should be done to find parameters that would be match a patient. However, this is outside the scope of this thesis.

a_5	0.0001
a_6	0.00015
d_4	0.1
c_5	$50\text{x}10^{-3}$
c_6	$85\text{x}10^{-5}$
k_5	0.47
k_6	0.57

Table 2.2: Parameter Values for Integrated Model

Although quiescent tumor cells are resistant to drugs [20], there is no reason to believe that interphase tumor cells that will become quiescent cells are also drug resistant. Thus, we added the term $u_1(t)T_Q(t)$ to the model to account for the loss of quiescent cells due to drugs. If we let $k_5 = 0$, then we recover the scenario where the quiescent cells are not affected by the drug. Quiescent cells are also annihilated by the the immune system. The terms $c_5T_I(t)T_Q(t)$ denotes the losses of quiescent tumor cells caused by the immune system. The term $c_6I(t)T_Q(t)$ denotes the deactivation of immune cells by quiescent tumor cells. Again, by setting $c_6 = 0$ we can see what happens if the quiescent cells do not deactivate the immune cells. Also note that Yafia's model contains the term $bP(t-\tau)$ where b is the intrinsic rate of proliferation, so b = birth-death. However, the time delay corresponds to the time it takes the cells to proliferate. Since there is no delay in death, we decided to separate the birth rate and the death rate. That is, for the rate of change of tumor cells during mitosis we use the term $a_6T_I(t-\tau)$ to model the proliferation of the cells, with the delay corresponding to the time the cells spend in interphase before they replicate. We let $d_3T_M(t)$ represent the instantaneous death of the mitotic tumor cells. Note that if $T_Q(0) = 0$ and $a_5 = 0$, then the system (2.21)-(2.23) reduces to (2.3)-(2.5). We used this fact to also verify the model (2.20)-(2.31).

The following figures compare Model 3 to Model 1 for the delayed and non-delayed cases. Model 1 responses are denoted by the dotted lines and Model 3 responses are given by the solid lines. In general we observed that Model 1 produces values of $T_I(t)$ and $T_M(t)$ that are higher than the values of $T_I(t)$ and $T_M(t)$ produced by Model 3. Hence, the presence of quiescent cells does affect $T_I(t)$ and $T_M(t)$ but does not seem to have a significant effect on $I(t)$. We observe the same general behavior for the ODE models.

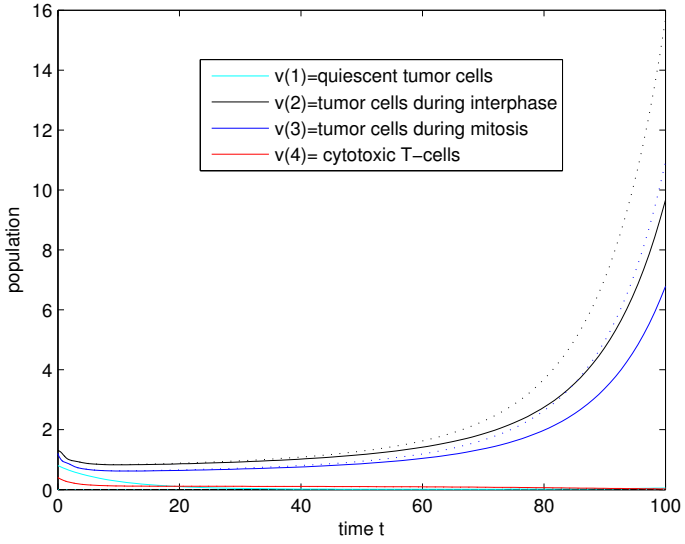

Figure 2.1: Comparison of DDE Model 1 and DDE Model 3

In order to demonstrate that the delay is significant, we compared the ODE Model 3 to the DDE Model 3 when the time delay is 0.92. Here the ODE responses are given by the dotted lines, while the DDE responses are denoted by the solid lines. In general we observed that the DDE model produces values of $T_I(t)$ and $T_M(t)$ that are higher than the values of

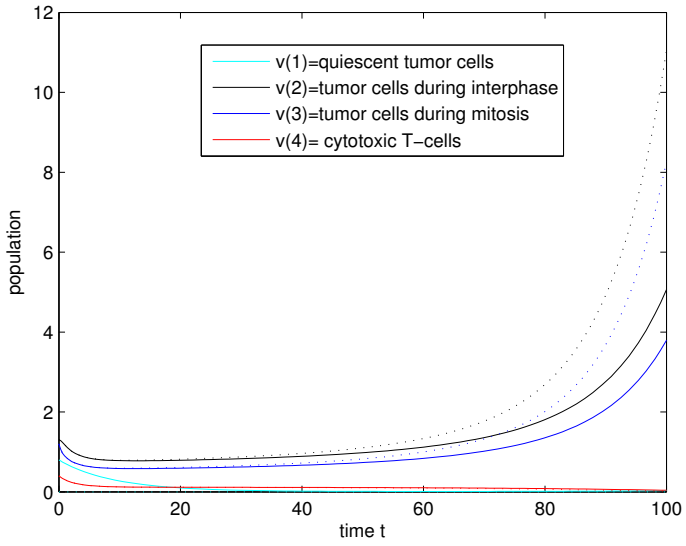

Figure 2.2: Comparison of ODE Model 1 and ODE Model 3

$T_I(t)$ and $T_M(t)$ produced by the ODE model. Hence, the delay is important.

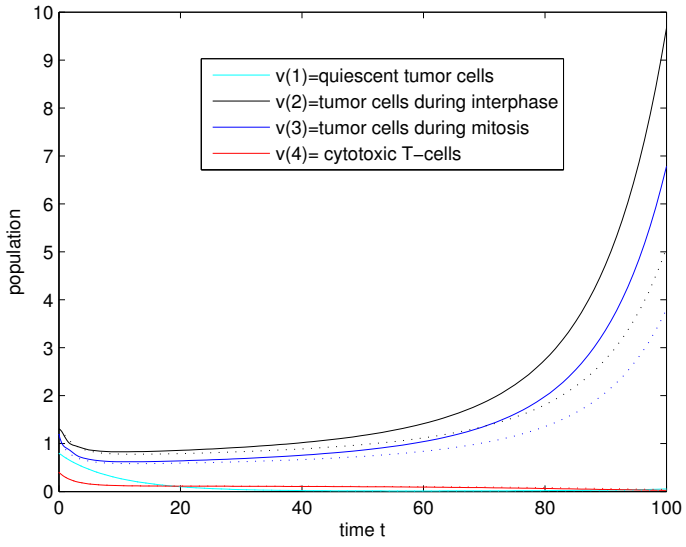

Figure 2.3: Comparison ODE and DDE versions of Model 3

2.4 Sensitivity Equations

During the initial numerical runs, we observed that the solutions to both systems (2.3)-(2.5) and (2.21)-(2.23) were very sensitive to the initial concentration of immune cells $I(0)$. In order to analyze this sensitivity, we fixed all the initial conditions except $I(0)$ and parameterized the initial condition $I(0)$ by setting $I(0) = \theta$. We derived the sensitivity/variational

equations for the sensitivities

$$ST_Q(t) \triangleq \frac{\partial}{\partial\theta}T_Q(t), \quad ST_I(t) \triangleq \frac{\partial}{\partial\theta}T_I(t),$$
$$ST_M(t) \triangleq \frac{\partial}{\partial\theta}T_M(t) \text{ and } SI(t) \triangleq \frac{\partial}{\partial\theta}I(t)$$

at $\theta = \theta_0$, the value of $I(0)$ of interest. The sensitivity equations for the system (2.21)-(2.23) are given by

$$\begin{aligned}\frac{dST_Q(t)}{dt} &= a_5ST_I(t-\tau) - a_6ST_Q(t) - d_4ST_Q(t) \\ &\quad -c_5[I(t)ST_Q(t) + SI(t)T_Q(t)] \\ &\quad -[u_1(t)ST_Q(t) + \frac{\partial}{\partial\theta}u_1(t)T_Q(t)]\end{aligned} \tag{2.32}$$

$$\begin{aligned}\frac{dST_I(t)}{dt} &= 2a_4ST_M(t) - a_5ST_I(t-\tau) + a_6ST_Q(t) \\ &\quad -c_1[T_I(t)SI(t) + ST_I(t)I(t)] \\ &\quad -d_2ST_I(t) - a_1ST_I(t-\tau)\end{aligned} \tag{2.33}$$

$$\begin{aligned}\frac{dST_M(t)}{dt} &= a_1ST_I(t-\tau) - d_3ST_M(t) - a_4ST_M(t) \\ &\quad -c_3[T_M(t)SI(t) + ST_M(t)I(t)] \\ &\quad -[u_2(t)ST_M(t) + \frac{\partial}{\partial\theta}u_2(t)T_M(t)]\end{aligned} \tag{2.34}$$

$$\begin{aligned}\frac{dSI(t)}{dt} &= \frac{num_\theta(t)dem(t) - num(t)dem_\theta(t)}{[dem(t)]^2} \\ &\quad -c_2[I(t)ST_I(t) + SI(t)T_I(t)] \\ &\quad -c_4[T_M(t)SI(t) + ST_M(t)I(t)] - c_6[T_Q(t)SI(t) + ST_Q(t)I(t)] \\ &\quad -d_1SI(t) - [u_3(t)SI(t) + \frac{\partial}{\partial\theta}u_3(t)I(t)],\end{aligned} \tag{2.35}$$

where

$$num(t) \triangleq \rho I(t)(T_Q(t) + T_I(t) + T_M(t))^n, \tag{2.36}$$
$$dem(t) \triangleq \alpha + (T_Q(t) + T_I(t) + T_M(t))^n, \tag{2.37}$$

$$\begin{aligned}num_\theta(t) \triangleq{}& \rho nI(t)(T_Q(t) + T_I(t) + T_M(t))^{n-1} \\ &\times (ST_Q(t) + ST_I(t) + ST_M(t)) \\ &+ \rho SI(t)(T_Q(t) + T_I(t) + T_M(t))^n,\end{aligned} \tag{2.38}$$

and

$$dem_\theta(t) \triangleq n(T_Q(t) + T_I(t) + T_M(t))^{n-1} \times (ST_Q(t) + ST_I(t) + ST_M(t)). \tag{2.39}$$

When the control input is given by (2.28)-(2.31), the partial derivatives $\frac{\partial}{\partial\theta}u_1(t)$, $\frac{\partial}{\partial\theta}u_2(t)$ and $\frac{\partial}{\partial\theta}u_2(t)$ are computed by solving (2.29)-(2.30) and using equations (2.28) where $w(t)$ is defined by (2.31). In this case the sensitivities $Sw_1(t) \triangleq \frac{\partial}{\partial\theta}w_1(t)$ and $Sw_2(t) \triangleq \frac{\partial}{\partial\theta}w_2(t)$ satisfy the homogenous linear equations with zero initial conditions

$$\frac{dSw_1(t)}{dt} = -\lambda_1 Sw_1(t), \quad w_1(0) = 0$$

and

$$\frac{dSw_1(t)}{dt} = -\lambda_1 Sw_1(t), \quad w_1(0) = 0,$$

respectively. Hence, $\frac{\partial}{\partial\theta}w_1(t) \equiv 0$, $\frac{\partial}{\partial\theta}w_2(t) \equiv 0$ and $\frac{\partial}{\partial\theta}w(t) = r_1\frac{\partial}{\partial\theta}w_2(t) + r_2\frac{\partial}{\partial\theta}w_2(t) \equiv 0$ and the sensitivity equations reduce to

$$\begin{aligned}\frac{dST_Q(t)}{dt} &= a_5 ST_I(t-\tau) - a_6 ST_Q(t) - d_4 ST_Q(t) \\ &\quad -c_5[I(t)ST_Q(t) + SI(t)T_Q(t)] - [u_1(t)ST_Q(t)]\end{aligned} \tag{2.40}$$

$$\begin{aligned}\frac{dST_I(t)}{dt} &= 2a_4 ST_M(t) - a_5 ST_I(t-\tau) + a_6 ST_Q(t) \\ &\quad -c_1[T_I(t)SI(t) + ST_I(t)I(t)] \\ &\quad -d_2 ST_I(t) - a_1 ST_I(t-\tau)\end{aligned} \tag{2.41}$$

$$\begin{aligned}\frac{dST_M(t)}{dt} &= a_1 ST_I(t-\tau) - d_3 ST_M(t) - a_4 ST_M(t) \\ &\quad -c_3[T_M(t)SI(t) + ST_M(t)I(t)] - [u_2(t)ST_M(t)]\end{aligned} \tag{2.42}$$

$$\begin{aligned}\frac{dSI(t)}{dt} &= \frac{num_\theta(t) \times dem(t) - num(t) \times dem_\theta(t)}{[dem(t)]^2} \\ &\quad -c_2[I(t)ST_I(t) + SI(t)T_I(t)] - c_4[T_M(t)SI(t) + ST_M(t)I(t)] \\ &\quad -c_6[T_Q(t)SI(t) + ST_Q(t)I(t)] - d_1 SI(t) - [u_3(t)SI(t)]\end{aligned} \tag{2.43}$$

where again $num(t)$, $dem(t)$, $num_\theta(t)$ and $dem_\theta(t)$ are defined by equations (2.36)-(2.39) above. The initial data for the sensitivity equations (2.40)-(2.43) is given by

$$ST_Q(s) \equiv 0.0, \quad ST_I(s) \equiv 0.0 \quad ST_M(s) \equiv 0.0 \quad SI(s) \equiv 1.0. \tag{2.44}$$

In the numerical computations, we use DDE23 to solve the coupled state and sensitivity equations defined by (2.20)-(2.31) and (2.40)-(2.43), respectively. Thus, we are able to compute the sensitivities $\frac{\partial}{\partial\theta}T_Q(t)$, $\frac{\partial}{\partial\theta}T_I(t)$, $\frac{\partial}{\partial\theta}T_M(t)$ and $\frac{\partial}{\partial\theta}I(t)$ with the same algorithm. We note that it is possible to obtain similar sensitivity equations with respect to any of the model parameters. However, sensitivity with respect to the delay leads to neutral functional differential equations and additional theoretical and numerical complexities (see [3] and [6]).

Chapter 3

Numerical Results

This chapter provides a summary of the numerical runs we conducted for Model 1 and our new Model 3. We first verify that both models reproduce known cases and then investigate the impact of Paclitaxel drug therapy on both models. Recall that Model 1 is defined by equations (2.3)-(2.14) and Model 3 is defined by equations (2.20)-(2.31).

3.1 Numerical Results for Model 1

In order to verify that Model 1 is consistent with various special cases we select initial data for which we know the exact solution. For example, if for $t \leq 0$ there are no cancer cells, then the the model should predict no new cancer cells and the immune cells should approach a steady state constant value. Thus, we take the initial function to be $[T_I(0), T_M(0), I(0)] = [0, 0, 0.9]$, set the drug concentration to zero (i.e. $c(t) = 0$) and use MATLAB's DDE23 to simulate Model 1 for $0 \leq t \leq 100$.

Figure 3.1 shows the results of this simulation. Here, $v(1) = T_I(t)$, $v(2) = T_M(t)$ and $v(3) = I(t)$. As predicted, the tumor cells remain at zero, the immune system is reproducing at a constant rate k and, as expected, the immune cells approach a steady state value of approximately 0.12.

We preformed another test of Model 1 and our code by considering the case with no drugs and no immune cells. As shown in Figure 3.2 there is a tremendous uncontrolled growth in the tumor cells. This also illustrates the rapid onset of cancer in patients with very compromised immune systems.

Figure 3.3 is a plot of a Model 1 simulation without the application of Paclitaxel. We use the initial condition $[1.3, 1.2, 0.9]$ also used in [21]. We see the initial levels of the tumor populations decreasing, then slowly rising after 20 days. This is similar to the results observed [21]. It is not clear that the tumor cells will stay bounded for longer times.

In order to check the code with a control input, again we use the initial function data in [21] and provide a unit step input similar to the inputs found in that paper. In particular, we set $c(t) = 1$ for t satisfying $0 \leq t \leq 10$, $20 \leq t \leq 30$ and $50 \leq t \leq 60$ and then set $c(t) = 0$, otherwise. This input is plotted in Figure 3.4 below and produces the response shown in Figure 3.5. We see an immediate decrease in the population of tumor cells in interphase and mitosis at $t = 0, 20$ and 50, which corresponds to the periodic pulsing of Paclitaxel. Again, it is not clear that the cancer will be reduced to zero as time continues.

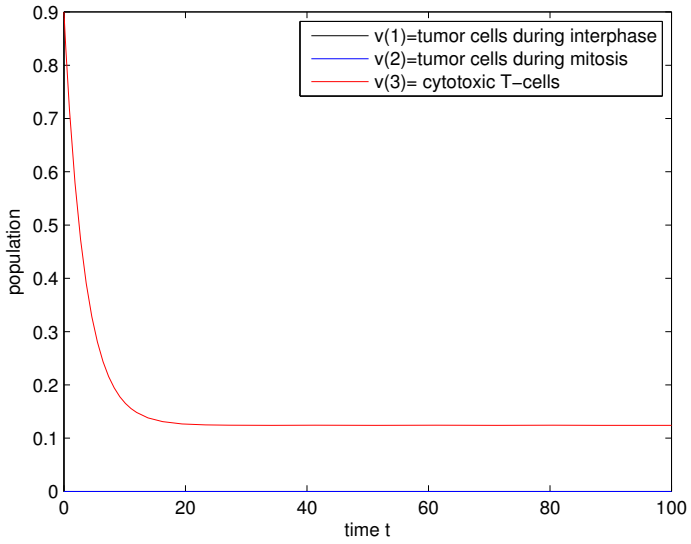

Figure 3.1: Model 1: Response with no tumor cells and no Paclitaxel

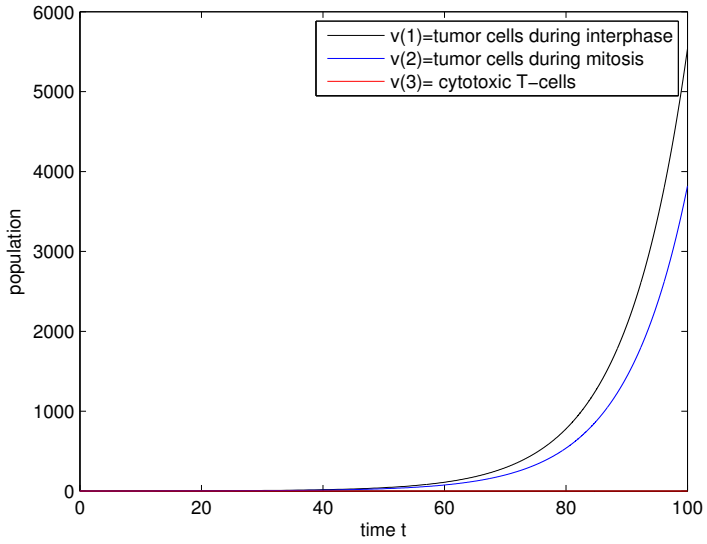

Figure 3.2: Model 1: Response with no immune cells and no Paclitaxel

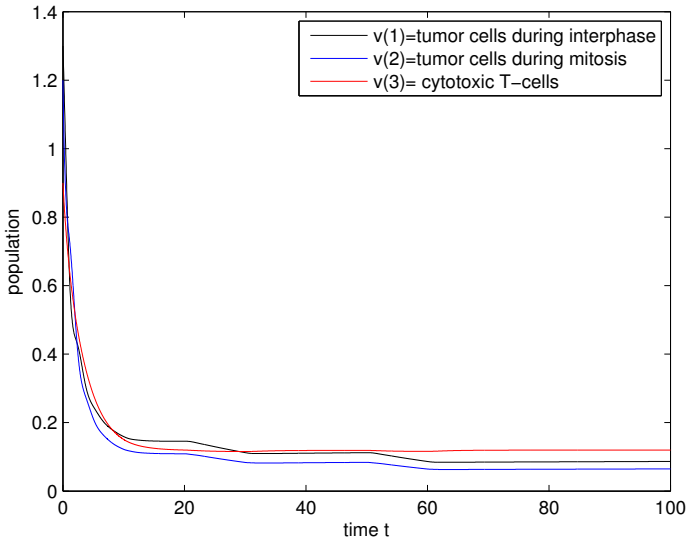

Figure 3.3: Model 1: Response for Initial Condition $[1.3, 1.2, 0.9]$ with no Drug

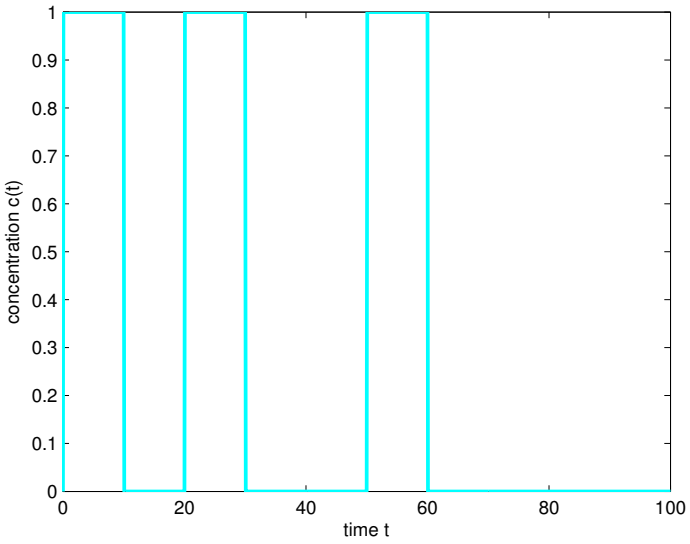

Figure 3.4: Paclitaxel Concentration Time History

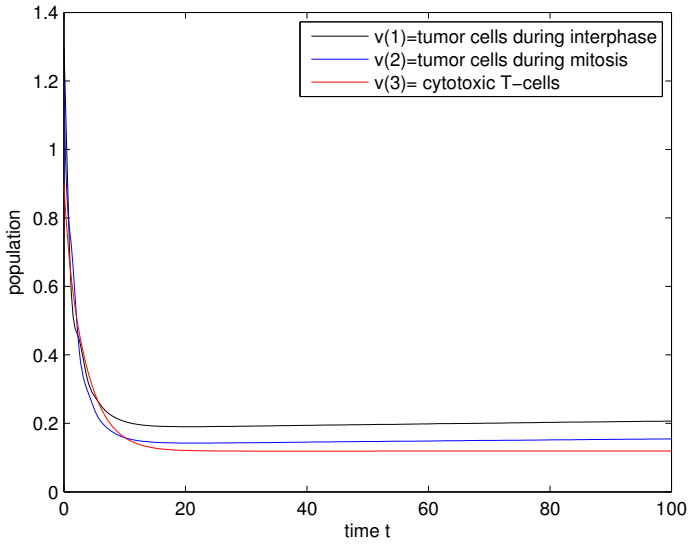

Figure 3.5: Model 1: Response to Pulsed Concentration of Paclitaxel for Initial Condition $[1.3, 1.2, 0.9]$

As observed in Figure 3.3, given sufficient immune cells at time $t = 0$ the cytotoxic T-cells are able to reduce the tumor over a short time period. However, if we start with a lower level of cytotoxic T-cells we might expect the tumor will not be substantially reduced if no drugs are employed. Figure 3.6 confirms this observation. We set the initial function to $[1.3, 1.2, 0.46, 0, 0]$, applied no drugs and ran the simulation for 150 days. We observe a continual growth in tumor cells and a decline in immune cells. This observation supports the obvious fact that people with compromised immune systems are more likely to have cancer.

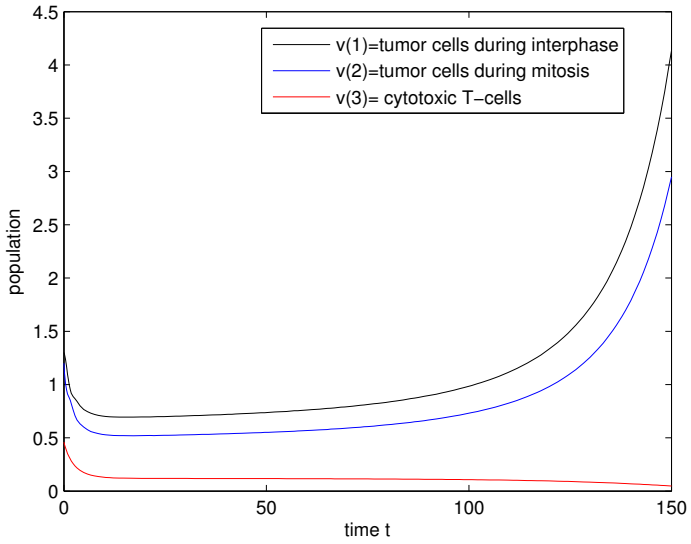

Figure 3.6: Model 1: Response for Initial Condition $[1.3, 1.2, 0.46]$ with no Drug

If we increase the initial number of immune cells from 0.46 to 0.48 we see a dramatic

change in the response. In Figure 3.7 we plot the response to this initial data with no drugs. Observe that we ran the simulation for 450 days and the tumor cells appear to be declining. However, as we shall see later a prediction based only on a simulation of this nature can be misleading. In any case, this simulation seems to imply that the initial data $[1.3, 1.2, 0.46]$ is within the basin of attraction of a stable steady state (again see the papers [19], [20] and [21]). This result implies that Model 1 is sensitive to the initial population of immune cells near this initial condition. A biological interpretation of this is that a slightly stronger immune system is able to drastically change the fight against cancer.

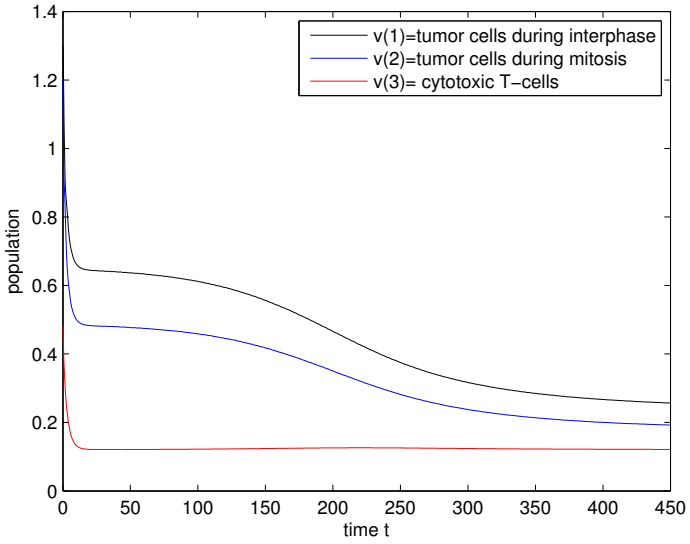

Figure 3.7: Model 1: Response for Initial Condition $[1.3, 1.2, 0.48]$ with no Drug

In order to evaluate the impact of an application of the drug Paclitaxel, we view the initial condition $[1.3, 1.2, 0.46]$ as a "struggling patient" on the edge of immune deficiency. In the next run we set the initial of cytotoxic T-cells back to 0.46 and provide a pulsed treatment of Paclitaxel. For this run we set $c(t) = 0.55$, for $0 \leq t \leq 3$, $20 \leq t \leq 23$, $48 \leq t \leq 50$ and $c(t) = 0$, otherwise. This input is plotted in Figure 3.8 and the response in plotted in Figure 3.9. Observe that a few treatments of Paclitaxel can reduce the cancer cells even when the initial population of immune cells is at or below the value 0.46.

We note that the pulsed treatments such as the one shown in Figure 3.8 are typical of the drug treatments suggested in [21]. One might guess that if the concentration level is reduced, then the drug treatments may no longer be effective. To illustrate this feature, we reduce the concentration level from 0.55 to 0.15 but retain the same pulsing sequence. This input is shown in Figure 3.10. Figure 3.11 shows the response to this control sequence. During a short initial period the cancer cells decline in response to the drug. However, by day 150 the impact of the drug treatment is reduced and there is a large growth in the tumor cells by day 180. Again, this example also illustrates that short time simulations may produce misleading conclusions. Therefore, long time simulations are essential to fully understand this model.

As noted in the papers [19], [20] and [21], both the concentration level and timing of the drug pulses are important. This can be illustrated by adding additional low level pulses to

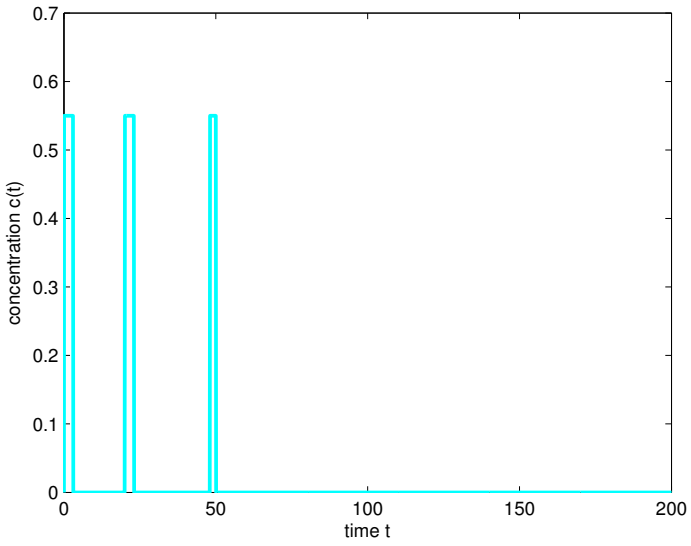

Figure 3.8: Paclitaxel Concentration Time History

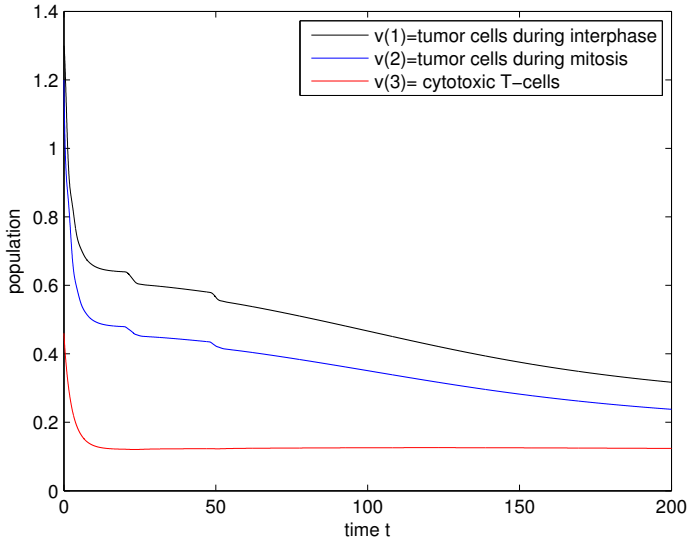

Figure 3.9: Model 1: Response for Initial Condition $[1.3, 1.2, 0.46]$ with Paclitaxel Concentration Levels of 0.55

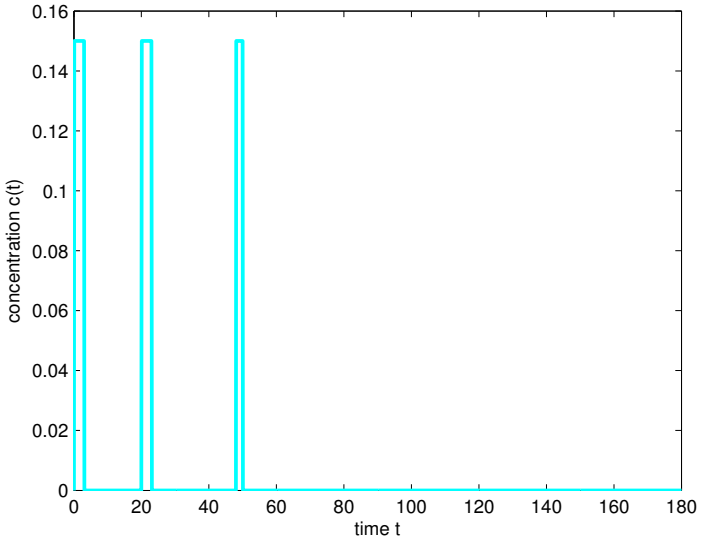

Figure 3.10: Paclitaxel Concentration Time History

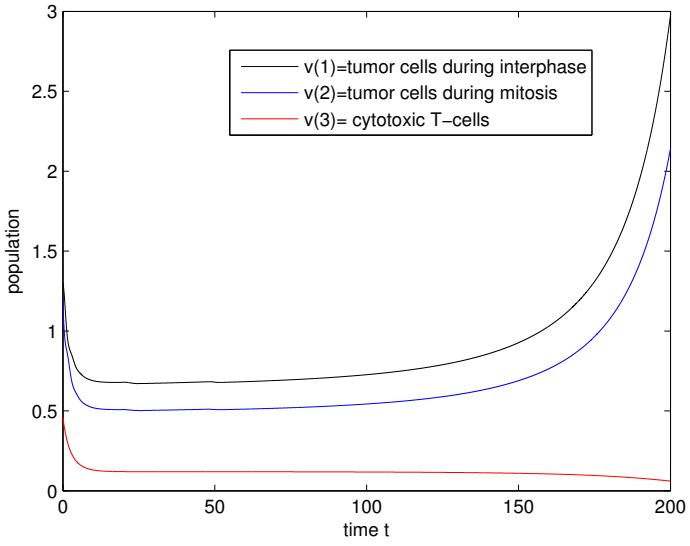

Figure 3.11: Model 1: Response for Initial Condition $[1.3, 1.2, 0.46]$ with Paclitaxel Concentration Levels of 0.15

the previous input. In the next run we add an additional low level pulse with concentration 0.15 between $7 \leq t \leq 9$ as shown in Figure 3.12. The response to this drug history is illustrated in Figure 3.13. We also conducted a run where the fourth pulse was added at a later time $68 \leq t \leq 70$. This input is shown in figure 3.14. Figure 3.13 shows the response to this control sequence. We see that even though in both cases the tumor cell population increases with time, when additional doses are added the growth rate of the tumor cells is reduced. Moreover, the earlier pulse seems to retard the growth more than the later. This supports the idea that early detection and treatment is extremely important.

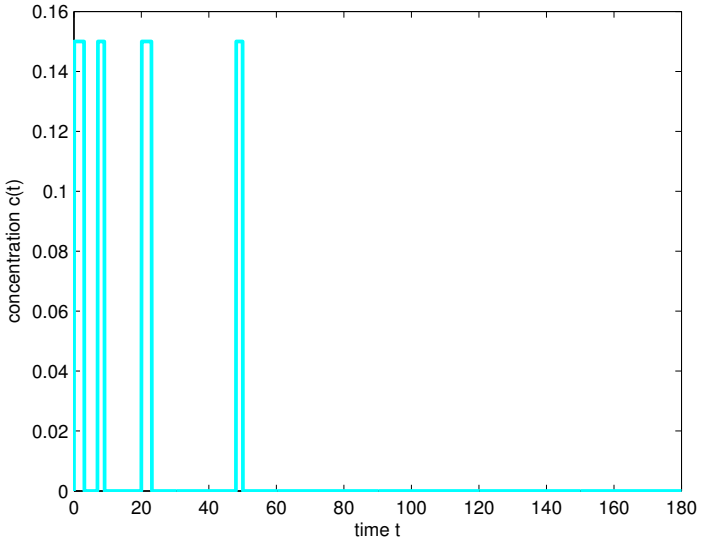

Figure 3.12: Paclitaxel Concentration Time History

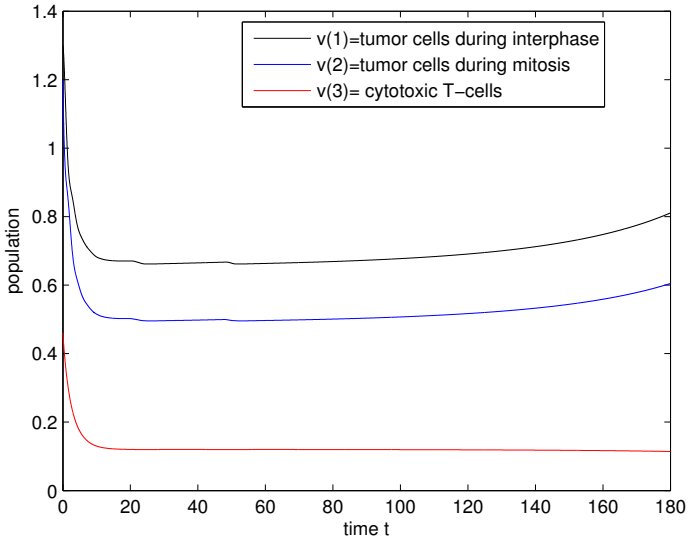

Figure 3.13: Model 1: Response for Initial Condition $[1.3, 1.2, 0.46]$ with Paclitaxel Concentration Levels of 0.15 and 4 Pulses

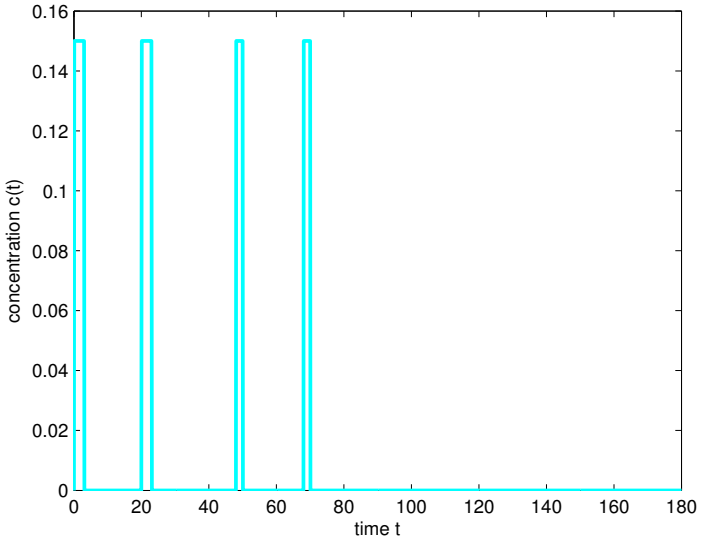

Figure 3.14: Paclitaxel Concentration Time History

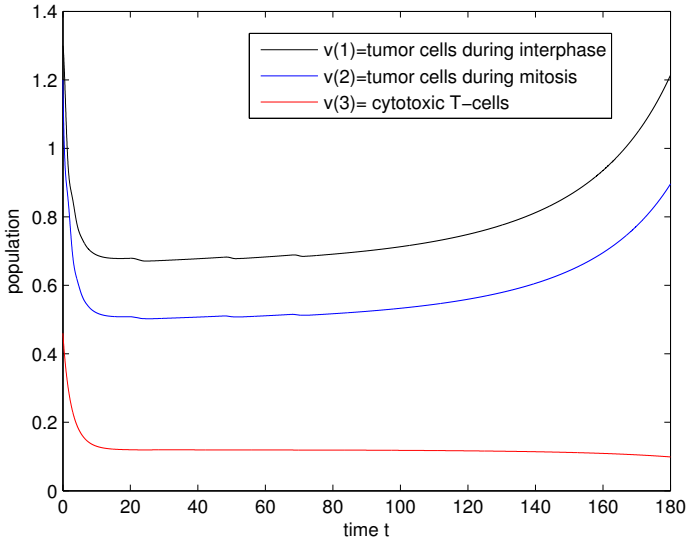

Figure 3.15: Model 1: Response for Initial Condition $[1.3, 1.2, 0.46]$ with Paclitaxel Concentration Levels of 0.15 and 4 Pulses

Clearly a fourth low level pulse does not control the long term cancer cell growth. However, by increasing the dose level one can reduce the initial tumor growth. We use the same pulse sequence as before, but raise the concentration level from 0.15 to 0.30 as shown in figure 3.16. Figure 3.17 shows the response to this control treatment. By doubling the concentration to 0.3 the tumor cells are appear to be better controlled.

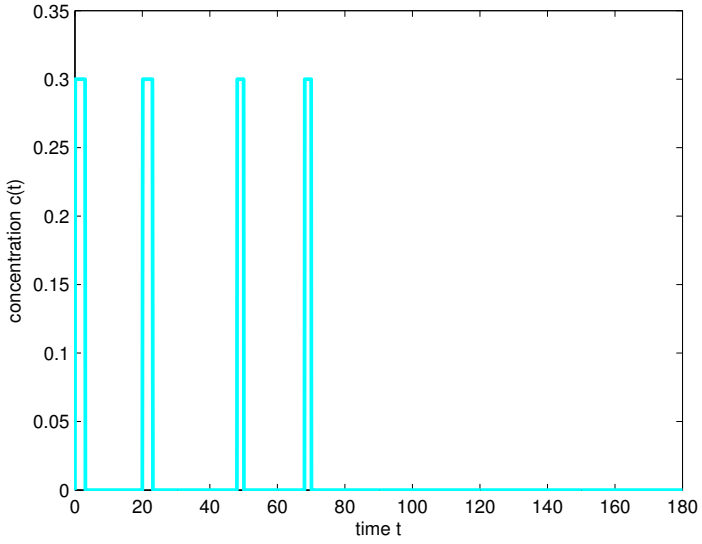

Figure 3.16: Paclitaxel Concentration Time History

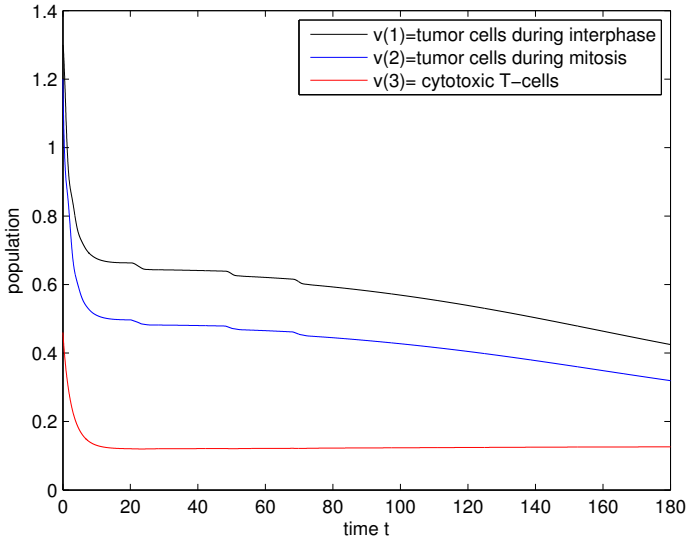

Figure 3.17: Model 1: Response for Initial Condition $[1.3, 1.2, 0.46]$ with Paclitaxel Concentration Levels of 0.3 and 4 Pulses

Remark: We complete this section with a warning about numerical error. Applying DDE23 to this model can produce no biological results for some initial data. For example,

if one sets the initial data to be $[1.3, 1.2, 4.9, 0, 0]$ and simulates the system with no drugs then, DDE23 produces the results shown in figure 3.18. The overshoot (i.e. the negative values of T_I) is due to numerical errors in DDE23. If one considers the non-delayed version of this problem and uses MATLAB's ODE23 solver, then a similar negative overshoot is observed. On the other hand, using MATLAB's stiff solver ODE23s we were not able to find initial conditions that produced this negative overshoot. This suggests that a stiff version of DDE23 might be needed to address this issue.

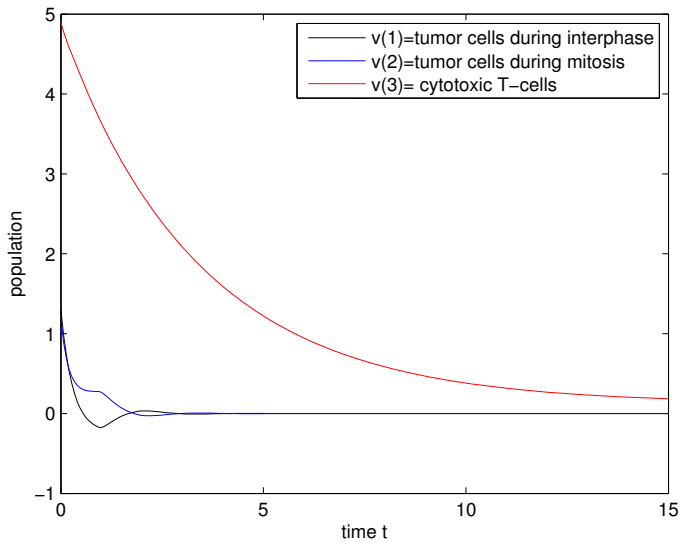

Figure 3.18: Model 1: Response for Initial Condition $[1.3, 1.2, 4.9]$ with no Drugs

One of the most important benefits of this model is that it provides some insight in the possible ways that drug administration can affect the tumor and the immune system. Ideally one would like to maximize the effect of the drug on the tumor so that it is properly eradicated while the immune system stays above some threshold as investigated in [20]. We turn now to the integrated model defined by (2.20)-(2.31).

3.2 Numerical Results for Model 3

In this section we present results based on the new Model 3 define by equations (2.20)-(2.31). As before we first conduct runs to verify the code. Again, if we assume that for $t \leq 0$ there are no cancer cells, then the the model should predict no new cancer cells and the immune cells should approach a steady state constant value. Thus, we take the initial function be $[T_Q(0), T_I(0), T_M(0), I(0)] = [0, 0, 0, 0.9]$ and set the drug concentration to zero (i.e. $c(t) = 0$). As shown in Figure 3.19, the immune cells approach a steady state value of about 0.12 which is exactly the same as produced by Model 1 (see figure 3.1). This suggests that the new model and code are consistent with Model 1 when there are no tumor cells.

Observe that Model 3 produces exactly the same response as Model 1 when the initial condition for $T_Q(0) = 0$ and $\alpha_5 = 0$. Thus, if we use $[0, 1.3, 1.2, 0.4]$ as the initial data in Model 3 we produce the same response as Model 1 with initial data $[1.3, 1.2, 0.4]$. The following runs provide a comparison of the response of the two models to the same concentration

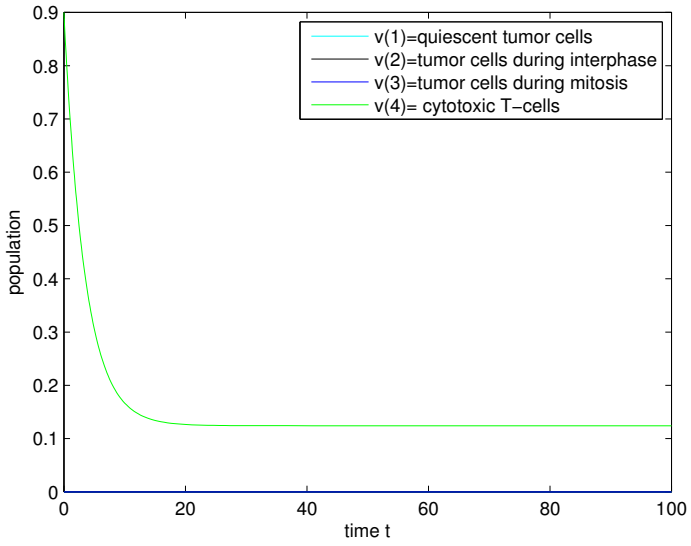

Figure 3.19: Model 3: Response with no tumor cells and no Paclitaxel

time history. We use the concentration of Paclitaxel as the input shown in Figure 3.20 with value 0.55 pulsed at times $0 \leq t \leq 10$, $20 \leq t \leq 30$, $60 \leq t \leq 70$ and 0 otherwise. The initial conditions for Model 1 with no quiescent cells is $[1.3, 1.2, 0.4]$ and the initial conditions for Model 3 are chosen to be $[1.8, 1.3, 1.2, 0.4]$.

This run is typical of the many numerical experiments of this type. Comparing Figures 3.22 and 3.21 we see that this particular concentration input decreases the cancer cells in both models. However, in Model 1 with no quiescent cells, the decrease in tumor cells is more rapid than predicted by Model 3 where there is a substantial population of quiescent cells at time $t = 0$. In particular, the levels of tumor cells in mitosis and interphase are slightly higher in Figure 3.22 than they are in Figure 3.21. **Thus, we conclude that the presence of quiescent cells does impact the response to a given drug therapy profile and the new Model 3 might provide a better basic for optimal therapy design.**

The next runs were produced with initial functions $[1, 1, 1, 1]$, $[0.1, 0.1, 0.1, 0.1]$ and $[0.01, 0.01, 0.01, 0.0$ respectively. As noted in these figures, if the initial population of immune cells is sufficiently high (see Figure 3.23) or the tumor cell population is sufficiently low (see Figure 3.25), then the immune response can control equivalent populations of tumor cells. However, there is the case as illustrated in Figure 3.34 where the quiescent cells will die out, while the other tumor cells continue to grow.

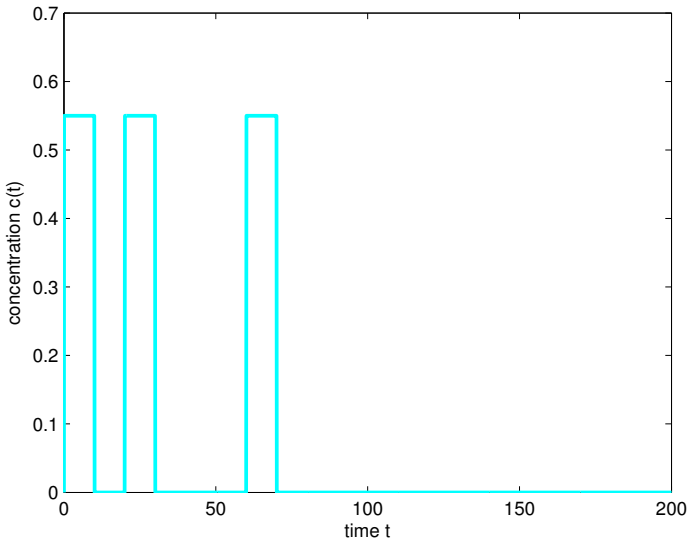

Figure 3.20: Paclitaxel Concentration Time History

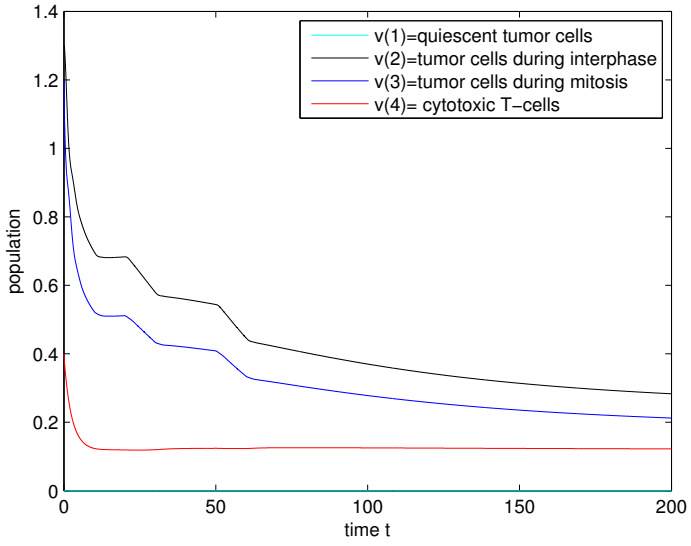

Figure 3.21: Model 1: Response for Initial Condition $[1.3, 1.2, 0.4]$ with Paclitaxel Concentration Levels of 0.55 and 3 Pulses

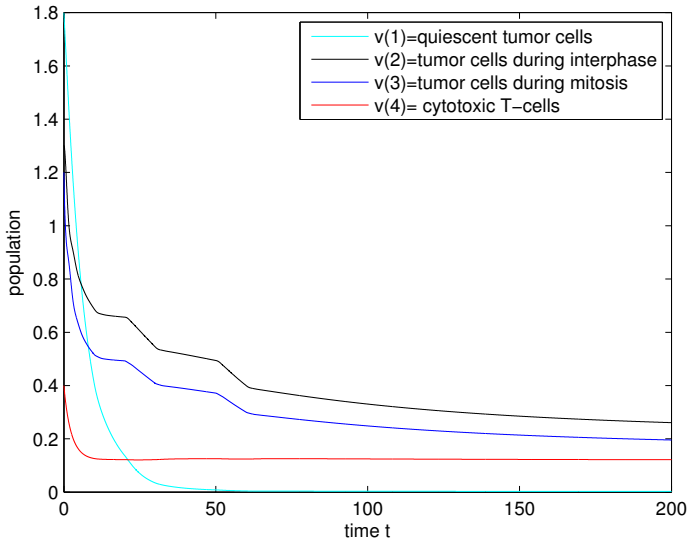

Figure 3.22: Model 3: Response for Initial Condition $[1.8, 1.3, 1.2, 0.4]$ with Paclitaxel Concentration Levels of 0.55 and 3 Pulses

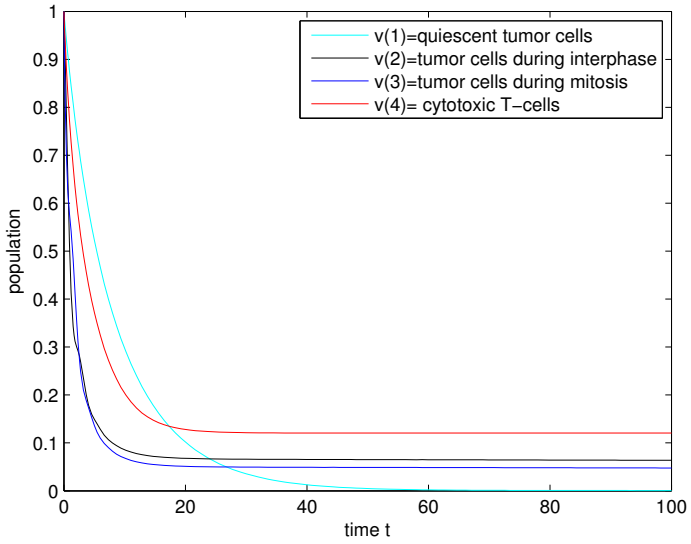

Figure 3.23: Model 3: Response for Initial Condition $[1, 1, 1, 1]$ without Paclitaxel

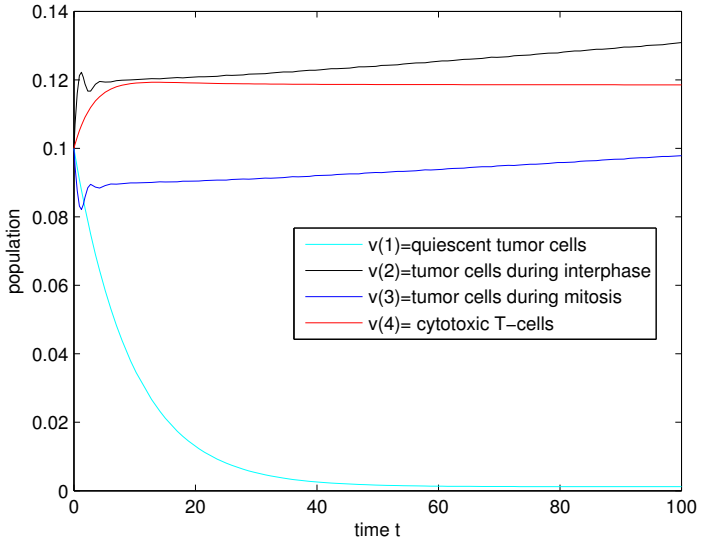

Figure 3.24: Model 3: Response for Initial Condition $[0.1, 0.1, 0.1, 0.1]$ without Paclitaxel

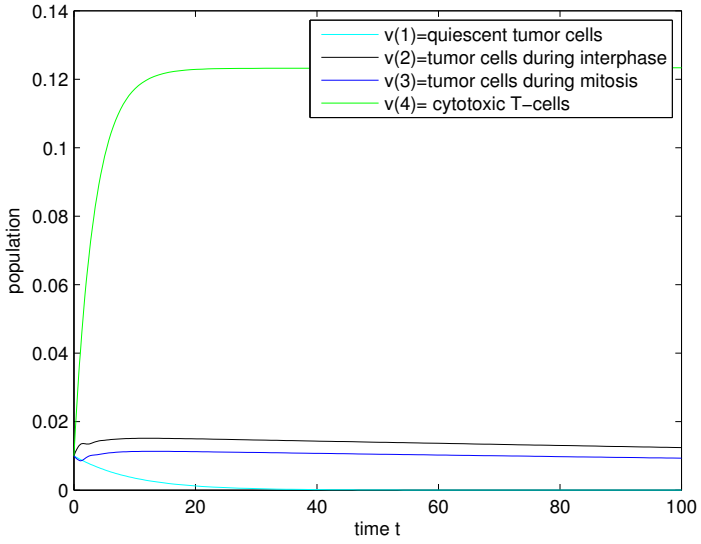

Figure 3.25: Model 3: Response for Initial Condition $[0.01, 0.01, 0.01, 0.01]$ without Paclitaxel

From Figures 3.23-3.25 it appears that for this range parameters, the immune system has a steady state value of approximately 0.12. Based on this, we will consider a person with an initial amount of immune cells equal to this value, a normally healthy person. We will now investigate the differences in the response of a person who is more healthy than normal, as well as a person who is less healthy than normal. For a person who is more healthy than normal we chose an initial amount of immune cells to be 25% more than usual, or .1488. For a person who is less healthy than normal we chose an initial amount of immune cells to be 25% less than usual, or .0912. The results can be seen in Figures 3.27-3.28, where it can be seen that although both patients are able to rid the body of tumor cells with the help of drugs, the healthy patient does it faster, and can also recover without the help of drugs, which the unhealthy cannot.

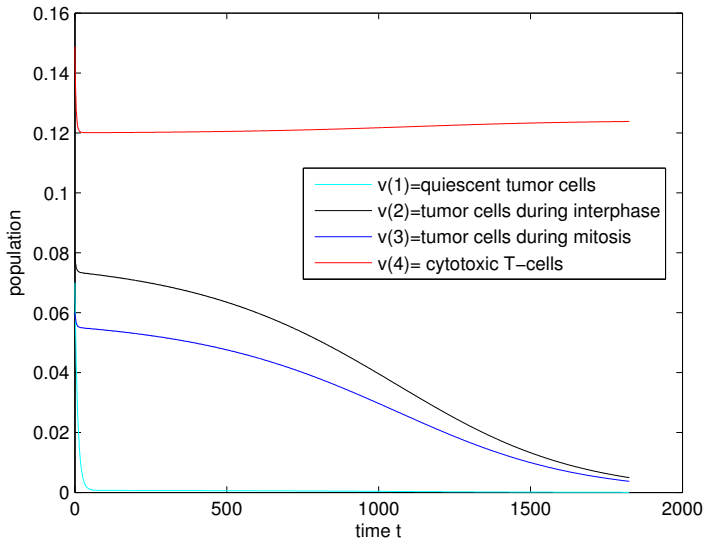

Figure 3.26: Model 3: Response of a healthy patient with no Paclitaxel

We take into consideration the immune deficient patient by setting the initial amount of immune cells equal to 0.06. The administration of Paclitaxel remains the same. When we look at the graph for 6 months we see that Paclitaxel is controlling the tumor cells for the first three months but it seems as if the tumor cells are begin to increase slowly after that. We can not be sure without further analysis that the tumor cells are completely under control. That is why we need to look at the sensitivity equations for more guidance.

Now if we look at the same simulation for 1 year then we become even more doubtful that the tumor cells will not emerge again. The sensitivity results will be able to guide us as to when we need to look at a longer timespan and when we do not.

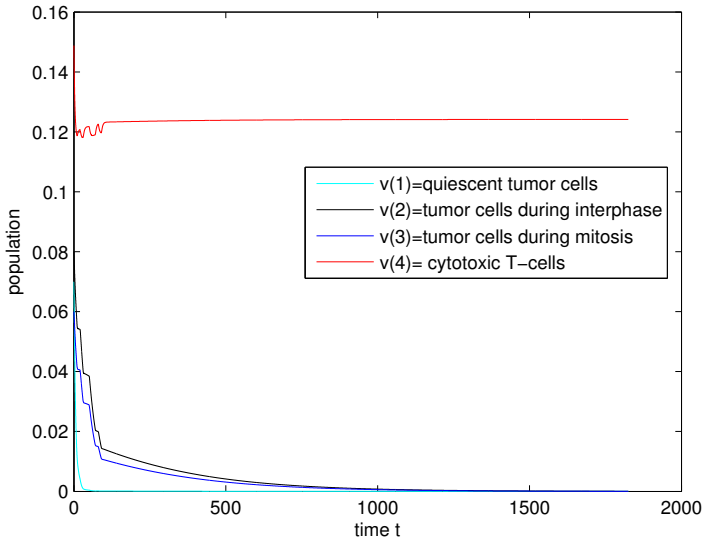

Figure 3.27: Model 3: Response of a healthy patient with Paclitaxel

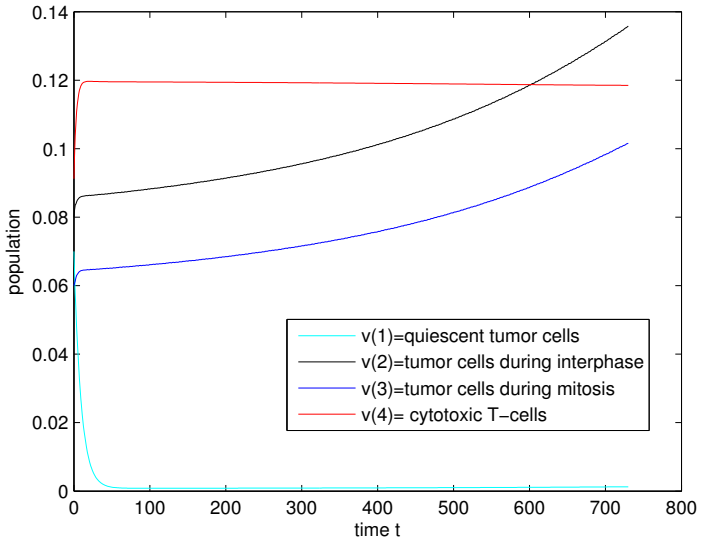

Figure 3.28: Model 3: Response of an unhealthy patient with no Paclitaxel

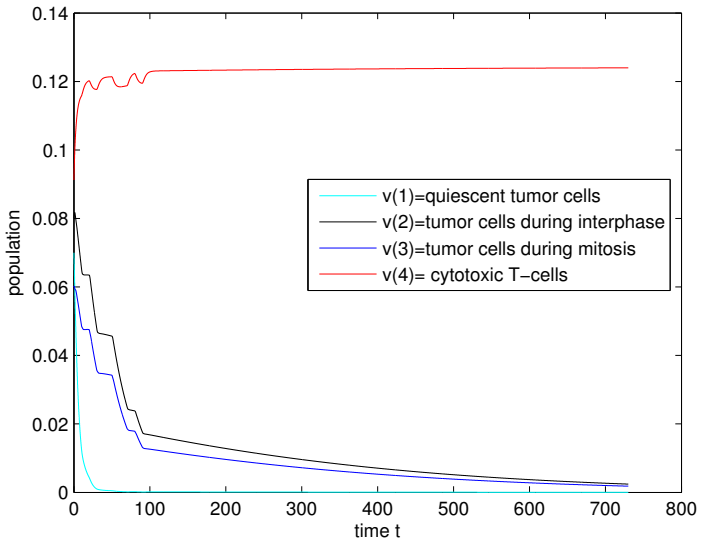

Figure 3.29: Model 3: Response of an unhealthy patient with Paclitaxel

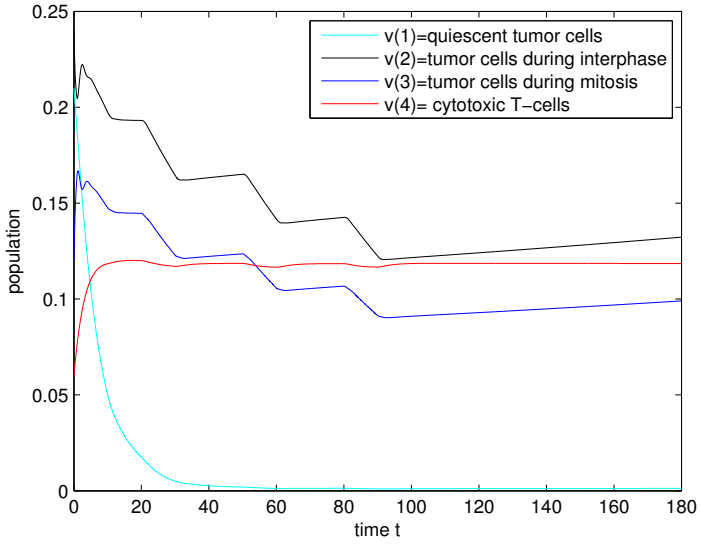

Figure 3.30: Model 3: Response of an immune deficient patient with Paclitaxel after 6 months

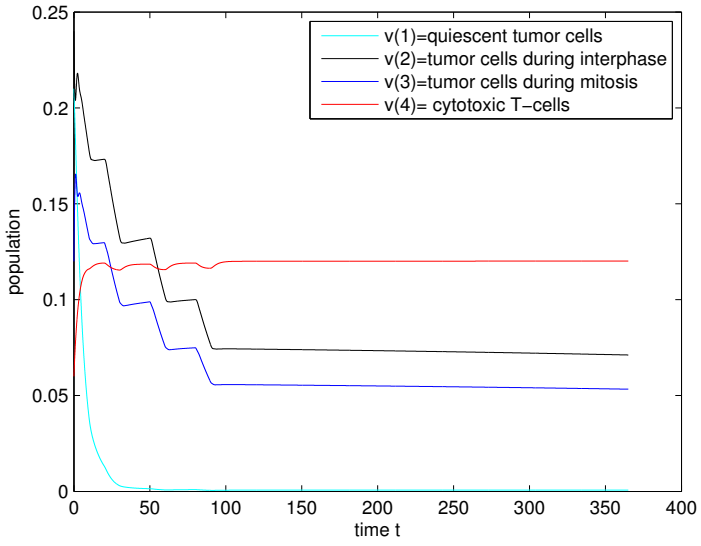

Figure 3.31: Model 3: Response of an immune deficient patient with Paclitaxel after 1 year

3.3 Sensitivity Results for Model 3

Previously, we observed that a small change in I(0), can produce significant changes in the levels of the tumor cells. Moreover, short time simulations can not always be used to predict long time behavior. In particular, a simulation on a short time may produce results that "appear" to have reached a steady state. In fact, a long time simulation may actually show that what first seems to be a successful drug treatment actually fails because the tumor cells eventually begin to grow out of control. In this case sensitivities can provide insight into a potential problem long before the problem is seen in a forward simulation.

To make this point more clear, we conducted a numerical experiment with initial data $[0.8, 1.3, 1.2, 0.40]$ for 100 days. Figure 3.32 shows the response to this initial data. Although the tumor cells are in decline for the first few days, it is clear that eventually the cancer cells begin to grow again by day 10. Therefore, if we had only simulated this system for 8 days we would see a response similar to the response illustrated in Figure 3.33. The challenge is to be able to predict when the simulation is actually producing a stable steady state from "short time" simulations.

In order to illustrate this point we present the results from two runs (typical for this model) without drugs. The first run uses the initial data $[0.8, 1.3, 1.2, 0.46]$ for which the immune response "appears" to kill off the tumor cells. As shown in Figure 3.33 after 200 days the tumor cells appear to be in decline. However, it is not possible to predict from this simulation that the tumor cells will continue to decline as time increases.

To fully address this problem we would have to discuss Lyapunov exponents (see [16]) and their computation. However, in some cases, raw sensitivities can be used to help with this problem. We illustrate this idea by using the sensitivity equations derived in Chapter 2 to compute the sensitivity of the solutions with respect to the initial condition $I(0)$.

Figure 3.34 shows a plot of the norm of tumor cell sensitivity with respect to I(0). The important observation is that the sensitivities show exponential growth on the interval $0 \leq t \leq 200$. In fact, this exponential growth is clear even on much shorter time intervals such as $0 \leq t \leq 10$. This exponential growth provides a warning that the initial decline of the tumor cells as seen in Figure 3.33 may not continue. This example is indicative of what happens in many such cases. Therefore, we suggest that it would be worthwhile to investigate how sensitivities and the corresponding Lyapunov exponents might be used as a method to verify long time behavior based on finite time simulations.

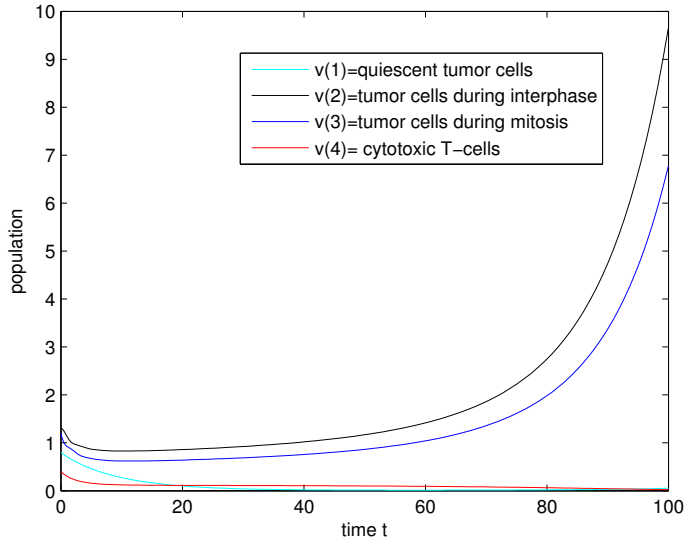

Figure 3.32: Model 3: Response for Initial Condition $[0.8, 1.3, 1.2, 0.4]$ Without Drugs

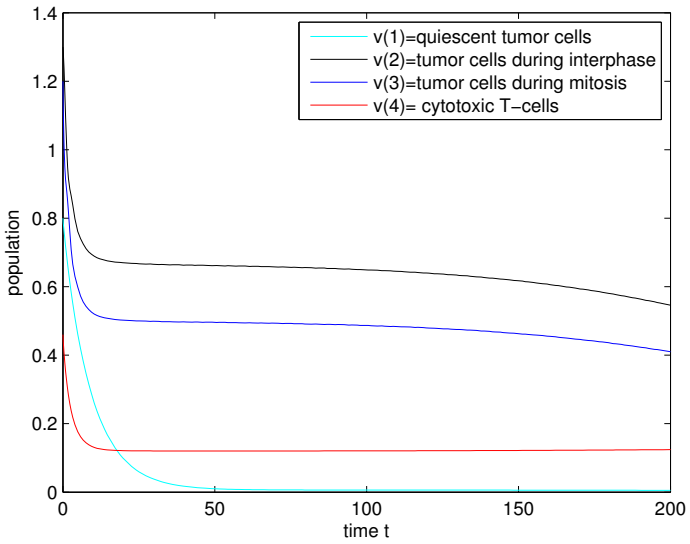

Figure 3.33: Model 3: Response for Initial Condition $[0.8, 1.3, 1.2, 0.46]$ Without Drugs

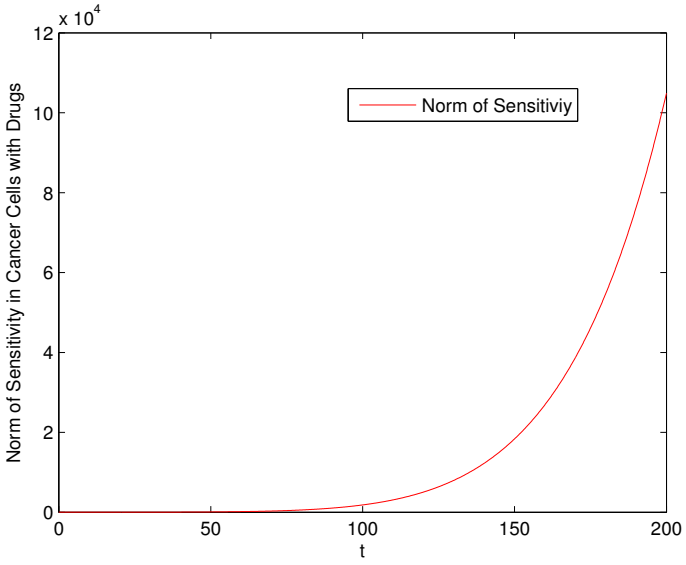

Figure 3.34: Model 3: Norm of Cancer Cell Sensitivity With Respect to $I(0)$ for Initial Condition $[0.8, 1.3, 1.2, 0.46]$ Without Drugs

Chapter 4

Conclusions and Suggestions for Future Research

The numerical results contained in this thesis illustrate the complexity of cancer modeling. There are many options in modeling cancer, and we opted to elaborate and modify ones that separated the tumor cells into their cell cycles. We observed the difference that Paclitaxel makes on the growth of the tumor cells and why an early detection can aid in controlling their growth. We introduced quiescent tumor cells into our model and simulated the systems with and without a healthy immune system. Although the inclusion of quiescent cells did not greatly alter the no drug response, in some cases the inclusion of quiescent cells into the model did seem to reduce the effectivness of the "optimal" drug treatments suggested in [21]. Perhaps one of the most interesting observations concerned the use of sensitivities to predict when the model was tending to a stable steady state. This preliminary result should be pursued in more detail. Also, we need to address the parameter identification problem in order to tune the new model. We also suggest that one investigate the behavior of the system and sensitivities for initial functions that are not constant. Non constant initial functions are more likely to occur in realistic cancer treatments. Finally, in order to deal with numerical difficulties (negative overshoots) that were observed when we used DDE23, we suggest that it would be worthwhile to write research code specifically to deal with this issue.

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Vita

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