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Mathematical Models of Chemotherapy

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Abstract

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Several mathematical models are developed to describe the effects of chemotherapy on both cancerous and normal tissue. Each model is defined by either a single homogeneous equation or a system of heterogeneous equations which describe the states of the normal and/or cancer cells. Periodic terms are added to model the effects of the chemotherapy. What we obtain are regions, in parameter space (dose and period), of acceptable drug regimens.

The models take into account various aspects of chemotherapy. These include, interactions between the cancer and normal tissue, cell specific chemotherapeutic drug, the use of non-constant parameters to aid in modeling specific chemotherapeutic processes, and drug resistance. By studying the models we can obtain a better understanding of the dynamics of the chemotherapeutic drugs and how better to implement them.

The mathematical methods used are mostly in the area of dynamical systems in particular Floquet Theory. These methods are used on either a single equation or a system of periodic ordinary differential equations which model the chemotherapeutic process. These are reduced to difference equations that describe the state of the cancer at the beginning of each period. By studying the characteristic multipliers, we

are able to determine the bifurcation between successful and unsuccessful regimens, if existing drug regimens seem reasonable from a mathematical model standpoint, and suggest ways to better implement the existing chemotherapeutic drugs.

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Chapter 1

Introduction

Mathematics gives a good basis for discussing the various effects of cytotoxic drugs on both cancer and normal tissue. By developing more sophisticated mathematical models that more accurately fit known chemotherapeutic responses, we can better understand how to control the proliferation of cancerous cells. The purpose of this dissertation is to discuss a variety of mathematical models of cancer chemotherapy and how they may help clinicians better design drug regimens to effectively control cancer. There are a variety of factors that must be taken into account in this process, including cell kinetics (how different cells grow), chemotherapeutic kinetics (how the cytotoxic drugs kill cells), chemotherapeutic resistance (how cancer cells develop resistance to cytotoxic drugs), and effects of chemotherapy on normal tissue such as bone marrow. The various models that will be described take into account one or more of these factors and show some of the mathematical ideas that can be used to help understand how they function.

The need for these mathematical models is becoming more widely appreciated.

As stated by Birkhead and Gregory [9]:

> While certain agreed treatment principles seem to have emerged from empirical experimentation, for some diseases these have failed to produce any significant improvements in the rate of clinical response, survival, or cure, and for others, initial progress has not been consolidated. There is a need, in such cases, to provide insights to help the clinician understand the reasons for failure and to help him make a rational choice of his next strategy.

The models described in this dissertation show specific regions of acceptable drug regimens that are related to the period in which drugs are delivered and strength of the dose. This **qualitative** knowledge may help clinicians make choices on how to better design chemotherapeutic regimens.

1.1 Literature Review

The literature on mathematical modeling of cancer chemotherapy is an informative basis for the present study. To begin with, there are a variety of books and papers that give an insightful overview of the topic. One of the earliest papers is by Aroesty *et al.* [5]. They investigate quantitative ways of estimating cell kinetic parameters, such as the growth rate, along with descriptions of the cell cycle which help in understanding the idea of cycle-specific chemotherapy. In his book, Swan [61] discusses various models of tumor growth curves including diffusion, stochastic, and age-structured models (many of these ideas are not covered in this dissertation),

along with topics on cell ecology models and immune response models which will be a part of this study. Works by Eisen [23], Swan [63, 64], and Knolle [38] also give descriptions of various models of the cell-cycle and chemotherapy. Skipper [60] investigates some of the critical variables in combination chemotherapy regimens. In particular, he studies the average relative dose intensity of drugs administered in combination, and matching of doses for the largest decay in tumor mass. He shows many graphs from various experiments with these drug regimens which give considerable insight as to the effects of combination chemotherapy.

One area in which much research has been carried out is that of tumor-normal cell interaction. Much of the work done has involved investigation of the interaction between the tumor and the immune system. Earlier work by Swan [62] investigates a mathematical model of tumor-lymphocyte interaction, and Albert *et al.* [4], who present a simple predator-prey model of the tumor-immune system interaction. A later study by Bellomo and Forni [6] also develops a model of the tumor-immune system interaction in the form of a predator-prey model. They also include some simulations and experimental results. A more immunologically-based view of the interaction can be seen in De Boer *et al.* [20, 21], and a more recent work by Kuznetsov *et al.* [41] studies the immune response to a tumor using some interesting nonlinear dynamics. An interesting model by Adam [1] (based on work of Prigogine and Lefever [59]) studies the one-dimensional spatio-temporal dynamics of cancer growth with an immune response. Traveling wave solutions are investigated and lower bounds on wave speeds for wavefronts linking stable tumoral states to unstable cancer-free states were found.

There also has been a variety of recent literature on more general tumor-host interaction models. Some early clinical studies by Paschkis *et al.* [58] and Fisher and Fisher [25] describe the interaction between hepatic tissue (liver) and tumor metastases. Both studies indicate that after a partial hepatectomy not only does the hepatic tissue start to grow back (because of growth factors produced), but hepatic metastases also show more rapid growth, thus leading them to believe there is some positive interaction between the regenerating liver and the cancer cells. More recent work in the tumor-host interaction has been done by Gatenby [27, 28], who studies how population ecology models can be applied to tumor-host interaction. Also, Cornil *et al.* [16] study the interaction of normal dermal fibroblasts with human melanoma cells.

Another area of emphasis in the research on chemotherapy modeling is in describing the cell-cycle and the use of cycle-specific chemotherapeutic drugs to take advantage of the differences in the cancer and normal tissue's cell-cycle. Some general references that discuss the cell-cycle and its importance in chemotherapy are Eisen [24, 23] and Knolle [38]. More specific models on cycle-specific chemotherapy are given in Webb [66] which describes a linear two compartment model (both proliferating and quiescent cells present) of the chemotherapeutic effects, and in Webb [67] and Gyllenberg and Webb [33] which describe a non-linear two compartment model. The basis for these models is developed by Gyllenberg and Webb [32]. Two other papers which also discuss the toxicity effects of drugs on normal tissue (such as bone marrow) are Agur *et al.* [3] and Cojocaru and Agur [13]. Their models examine the reduction in damage to bone marrow by examining the relation between

the period over which drugs are delivered and the cell-cycle times for the tumor and bone marrow cells.

Other methods used to help reduce the effects of cytotoxic drugs include the administration of various types of growth factors, in particular, Hemopoietic growth factors (HGF's). Examples of these methods are described in Bhalla *et al.* [8] and Demetri [22].

One major disadvantage of many chemotherapeutic regimens is the development of tumor resistance to the cytotoxic drugs. Some of the original mathematical research done in this area was carried out by Goldie and Coldman [29] who use a probabilistic model to show how, as the number of tumor cells increases, the probability of eradicating them before resistant cells take over radically drops. Goldie *et al.* [30], also discuss strategies of delivering non-cross-resistant chemotherapy that reduce the risk of developing totally resistant tumor cells. Swan [63] investigates a model of radiotherapeutic resistance with resistant and sensitive cell populations modeled by first order (linear) kinetics, and compares the advantages and disadvantages of periodic and continuous irradiation. Birkhead and Gregory [9] develop a difference equation model of chemotherapy with drug resistance. They study the ratio of sensitive tumor cells to total number of tumor cells, which can be found clinically, and use it to predict tumor size and to estimate model parameters. They also show the point at which a drug becomes ineffective against a resistant tumor. In the case of non-cross-resistant therapy, they discuss patterns of administration and give conditions for administration strategies. Birkhead *et al.* [10, 11] and Gregory *et al.* [31], also relate the foregoing model to various clinical trials. In addition,

Birkhead *et al.* [12] develop a linear four compartment differential equation model which also includes resistance to chemotherapy. Here they model each compartment of the cell-cycle (sensitive resting and proliferating along with resistant resting and proliferating) with a linear differential equation instead of a difference equation to describe more directly the effects of resistance. Another interesting approach to modeling drug resistance is given by Michelson and Slate [54], who discuss a multi-drug resistance as an efflux pump which basically pumps the drugs out of the cell. Also, Martin *et al.* [43, 44] study both single and non-cross-resistant chemotherapy from an optimization theory standpoint.

Heterogeneous tumor models (i.e. with both sensitive and resistant compartments) are another approach to investigating drug resistance. Michelson and Leith [50] summarize this approach by discussing the various types of tumor heterogeneity and including much of the theoretical background. A more mathematical view of this area can start with Jansson and Révész [37] whose model is further developed by Michelson *et al.* [53]. These models describe the competitive interactions between two different types of tumor cell masses (usually one mutating from the other). Variations on these topics are continued in Michelson and Leith [46], who study the effects of varying the growth rates of the subpopulations; Michelson *et al.* [45], who examine stochastic models of subpopulation emergence; and Michelson and Leith [47], wherein composition of the heterogeneous tumor in the presence of Mitomycin C (a chemotherapeutic drug) is investigated.

Non-constant parameters are used to increase the generality of the earlier models. Several preliminary mathematical papers which include periodic non-constant

parameters (particularly in logistic and competition environments) are provided by Cushing [19, 17, 18], Coleman [14], Coleman *et al.* [15], Hallam and Clark [36], and Zhien and Hallam [68]. In these papers, the authors start with constant coefficient systems and incorporate periodically-varying parameters. They also discuss existence of periodic solutions along with conditions needed for these solutions. In works more related to tumor growth and chemotherapy, Michelson and Leith [46, 48, 49] and Gyori and Michelson [34] discuss how varying different parameters of existing models may result in a better fit to tumor growth and chemotherapeutic kinetics. Recently Michelson and Leith [52] discuss the need for non-constant parameters to describe the interaction between liver tumors and the liver.

1.2 Topics

This dissertation covers four areas of chemotherapy: (i) tumor-host interaction in the presence of chemotherapeutic drugs, (ii) cell-specific chemotherapy, (iii) non-constant parameters, and (iv) drug resistance and heterogeneous tumors. Through the models developed in these areas, it is hoped to gain a **qualitatively** better understanding as to how chemotherapeutic drugs affect the growth dynamics of cancer cells (usually in terms of the dose and period) and how we may take advantage of this knowledge to better design chemotherapeutic regimens. In each case the tumor growth is described by a single or system of differential equations. Added to these equations are the effects of the chemotherapeutic drug. These are modeled either by a periodic pulsing function (instant removal of cells) or a piecewise-periodic function (removal over a

period of time) which is more realistic. In all cases the constraining effects of the drugs on normal tissue are discussed.

1.2.1 Tumor-Host Interaction

This chapter investigates the tumor-normal cell interaction with the added effects of periodically-pulsed chemotherapy. The model used in this case is the standard competition model from population dynamics in which the competition or interaction in the cancer model occurs between the tumor and normal tissue. Some examples of this interaction can be, competition for resources, immune response, or growth factor signals from either the tumor or normal tissue. The model describes parameter conditions needed to prevent relapse following attempts to remove the tumor or tumor metastasis (remote small secondary tumor growth).

1.2.2 Cell-Specific Chemotherapy

In this chapter a linear system of ordinary differential equations is used to discuss the effects of cell-specific chemotherapy. Cell-specific drugs act primarily on proliferating cells. Since tumor tissue has a higher percentage of cells in the proliferating compartment as compared to most normal tissue, the cell-specific drugs can be an advantageous method for reducing the tumor mass without overly destroying normal tissue. Thus this model studies the cell-cycle of the tumor mass, but also includes a constraint equation describing the effects of the drugs on sensitive normal tissue (such as bone marrow). This model, as the one in chapter 2, uses periodically-pulsed chemotherapeutic effects to calculate the parameter regions of acceptable dose and

period. It also identifies the optimal period needed for maximal tumor reduction. Examples are included concerning the use of growth factors and how they may enhance the cell kill of the chemotherapeutic drugs.

In trying to improve the success of a drug regimen, the clinician can attempt to give a larger dose, but because of its effects on the bone marrow, the clinician may not be able to administer the drug at its optimal period, that is, the period which obtains the highest reduction in tumor mass per dose. There are various methods to alleviate this problem. For example, bone marrow transplants are given to patients with various types of cancers including Acute Myeloid Leukemia (AML) after high doses of chemotherapeutic drugs. Another approach is to increase the rate at which bone marrow reproduces (makes leukocytes, white blood cells). This is done with various Hemopoietic Growth Factors (HGF). This model shows how, when the growth rate of bone marrow is increased, we can give the drug at a higher dose at its optimal period, thus, leading to an overall larger reduction in cancerous tissue. These methods may seem counter-intuitive, but as we will show, they dramatically increase the effectiveness of the chemotherapy.

1.2.3 Non-Constant Parameters

The need for non-constant parameters in the previous models is discussed in this chapter. This includes both effects such as the tumors ability to manipulate its environment with growth factors, the residual effects of drugs, and the use of periodic chemotherapeutic drugs. For example, as a drug is given, over time there will be toxic buildup in the body, waste from the dead cells, etc. This can be modeled by a

declining carrying capacity for both the normal and tumor cells. Also, a phenomenon known as the tumor bed effect (TBE) may occur, wherein the tumor, via growth factors, can increase its carrying capacity. Other examples of the need for non-constant parameters is with the interaction of the liver tumor with the liver, each has the ability to manipulate the other. The actual dynamics of these interactions may be observed by letting either the growth rate or carrying capacity vary.

In the case of the chemotherapeutic drugs, a logistic differential equation is utilized along with both a linear and non-linear system of differential equations with time-varying periodic parameters. The chemotherapeutic effects are modeled by a periodic parameter that modifies the growth rate of the cell tissue. A negative growth rate represents the detrimental effects of the drugs. Simple criteria are obtained for the effects of the chemotherapy.

1.2.4 Resistance and Heterogeneous Tumors

Resistance to various chemotherapeutic drugs is a major cause for failure of chemotherapeutic regimens. One type of resistance is discussed in chapter 3 where resting cells are not affected by the cytotoxic drugs. In this chapter, we will study a different form of resistance, cells become resistant to a drug not because of the phase of the cell-cycle that they are in, but because of physical changes (mutations) caused by chemotherapeutic drugs to the makeup of the surviving cells. They may also be inherent a priori and be selected without mutation. There are various types of resistance and here we will discuss induced or acquired resistance, i.e. resistance that arises as a result of cell mutations induced by the drug. We investigate both

homogeneous and heterogeneous models of resistance. In the case of the homogeneous model, the cell population is modeled as a whole, not taking into account the various types of sensitive and resistance cells in the tumor. The heterogeneous tumor model will take these into account. Conditions are developed for either eliminating the tumor or, in the case where the tumor cannot be eliminated with the specified regimen, specifying the number of acceptable doses (*nadir*) that can be administered before tumor regrowth due to resistance occurs.

Chapter 2

Tumor-Host Interaction

2.1 Introduction

Mathematical models of cancer chemotherapy can indicate how micro-environmental interactions between tumor and normal cells can affect the outcome of the chemotherapy and the ability of a tumor to recur or metastasize. As stated by Knolle [38], knowing how model parameters affect both the tumor and the normal cells can help take advantage of kinetic differences between the cells and how they may react to chemotherapy. Eisen [23] also notes that the mathematics can help "discover ways to use existing drugs more efficiently," pointing out that even a good drug can appear useless if administered inappropriately.

One of the earlier steps in developing dose-response curves of the effects of chemotherapeutic drugs on tumor and normal tissue is discussed by Berenbaum [7]. He takes a straightforward approach to modeling these effects. He derives basic criteria for reducing tumor size without overly destroying the normal tissue. These criteria

include administration of the proper dosage and the timing of the dosage. Another common approach to investigating chemotherapy and its effects on normal tissue is via optimization theory. Murray [55] models the cell populations with Gompertz growth and continuous cell-kill and minimizes the tumor population while keeping normal cells above and toxicity below acceptable levels.

Unfortunately, none of these studies takes into account the possible interaction between tumor and normal cells (tumors do not grow in an environment isolated from normal cells; they compete for the available resources and they both develop growth factors that can affect each other). Adding this feature to the model will make it more realistic.

This type of interaction does not occur with all forms of cancer. For example, both brain and lung tumors show little or no interaction with their local environment. Chemotherapeutic drugs used to eliminate these cancers are in many cases cell-specific (they only kill cells in their growing phase). The tissue local to the tumor is differentiated (not growing), and as such, it shows little negative effects to the treatment. But, there are some cases where this type of local interaction is occurring. This includes tumors in the liver as discussed by Fisher and Fisher [25], Paschkis *et al.* [58], and Michelson and Leith [52], along with a variety of other forms of interactions. For example, Gatenby [27, 28] investigates this tumor-host relationship considering the interaction to be both the effects of the immune system (for small tumor mass) and interaction for resources by epithelial (cells lining the internal and external surfaces) and mesenchymal cells (connective tissue). In particular, he considers the interaction with a small number of cancer cells. Bellomo and Forni [6]

develop a model of the interactions between the tumor, host, and immune system. They show that for small tumor mass, the immune system can retard the growth of the tumor. It can also be noted that lung tumors do interact with the immune system response as opposed to other tissue in their local environment. Cornil *et al.* [16] address the question of the effects that adjacent normal tissue such as fibroblasts have on human melanoma cells. Furthermore, Liotta [42] discusses how various growth factors produced by both normal and tumor tissues may either suppress or stimulate cell growth.

Interestingly, none of these models takes into account the effects of the drug on the normal tissue. Therefore, we extend the basic models of homogeneous tumor growth to include chemotherapy and normal cell interaction. The following models examine the effects of cycle non-specific (a drug that kills tumor cells at all stages of the cell cycle) periodically-pulsed chemotherapy in a local tumor-normal cell environment. Works by Webb [67, 66], Agur *et al.*[3], Cojocaru and Agur [13], and Panetta and Adam [57] are directed to model various types of cycle-specific drug dynamics and are **not** covered in this chapter. Most importantly, the model in this chapter will investigate the use of chemotherapy to eliminate either (i) a **small** tumor burden left after attempts to remove the main tumor mass have been made, or (ii) a metastasized tumor mass, and in so doing will provide parameter conditions for tumor relapse. From these conditions we show that the interaction term along with the normal cell carrying capacity has a significant effect on the outcome of the therapy. Knowing these conditions can help in understanding and developing effective drug treatments.

2.2 The Model

Competition models from population biology have sometimes been used to model cell interactions. Gatenby [27, 28] investigates models of tumor-normal cell interaction, while Jansson and Révész [37], Michelson *et al.* [46, 49, 53], and Gyori *et al.* [34] examine interaction in heterogeneous tumor populations. Of particular interest is the review of heterogeneous tumor populations by Michelson and Leith [50], who cover a wide variety of topics including the biological implications of the models. These heterogeneous models will be investigated in §5.2 where we will deal with tumor resistance. For now, we will study the homogeneous case, i.e. just one tumor cell population. As Michelson *et al.* [48, 49] mention, logistic growth with constant parameters is not the best approach in modeling tumor growth. They suggest that models with non-constant parameters that account for adaptational signals (autocrine and paracrine in their models) may better describe these complex dynamics. However, as a first approximation, the constant case does allow some freedom since it is not as difficult as other models to analyze in closed form.

We will assume normal and tumor cells interact in the local environment as described by the competition model from population biology with constant parameters. As noted in the introduction, this interaction can be described in various ways given by Cornil *et al.* [16], Gatenby [28], and Liotta [42]. It is important to note that in some of these cases the parameters will not be constant, but depend on various other tumor factors. However, we will only deal with constant parameters, and let the competition term represent general interactions between tumor and nor-

mal cells. Periodically-pulsed survival conditions are added to model the effects of chemotherapy on interacting populations. Kot and Funasaki [39] views a simplified predator-prey in a pulsed chemostat in a similar way.

We assume that (1) the drug is cycle non-specific, (2) there is instantaneous cell kill by the drug, (3) the parameters are constant, (4) there is no drug build-up in the environment, and (5) there is no build-up of dead cells.

The basic set of equations that will be studied is:

$$\frac{dX}{dT} = r_1 X(1 - X/K_1 - \lambda_1 Y) \tag{2.2.1}$$

$$\frac{dY}{dT} = r_2 Y(1 - Y/K_2 - \lambda_2 X) \tag{2.2.2}$$

$$X(n\tau^+) = F(D)X(n\tau^-) \tag{2.2.3}$$

$$Y(n\tau^+) = \overline{F}(D)Y(n\tau^-), \tag{2.2.4}$$

The variables and parameters are:

X: Normal cell biomass.

Y: Tumor cell biomass.

r_1, r_2: Growth rates of the normal and tumor cells respectively.

K_1, K_2: Carrying capacity of the normal and tumor cells respectively.

λ_1, λ_2: Interactive parameter of normal and tumor cells respectively.

τ: Period of dose. τ^- and τ^+ denote the time just before and after a pulse respectively.

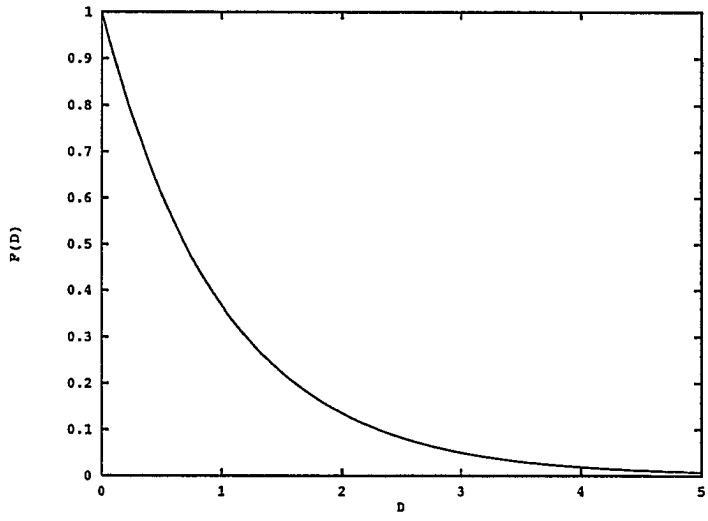

Figure 2.1: Exponential

$F(D), \overline{F}(D)$: Survival fraction of normal and tumor cells respectively for a given dose D. Note that $0 \leq F(D), \overline{F}(D) \leq 1$.

Some forms of $F(D)$ and $\overline{F}(D)$ are given in Berenbaum [7], e.g.:

1. Exponential: $F(D) = e^{-\alpha D}$, figure (2.1).

2. Exponential with shoulder: $F(D) = 1 - (1 - e^{-\alpha D})^{\beta}$, $\beta > 0$, figure (2.2).

3. Hyperbolic: $F(D) = \left(\frac{D}{D_0}\right)^{-\gamma}$, $\gamma > 0$, figure (2.3).

See Knolle [38, pp. 89–90] for indications of how the exponential dose-response curve is formulated.

2.3 Recurrence in the Absence of Chemotherapy

In the absence of chemotherapy, the two periodic conditions (2.2.3, 2.2.4) are removed and the problem reduces to the ordinary competition model. We must ask this

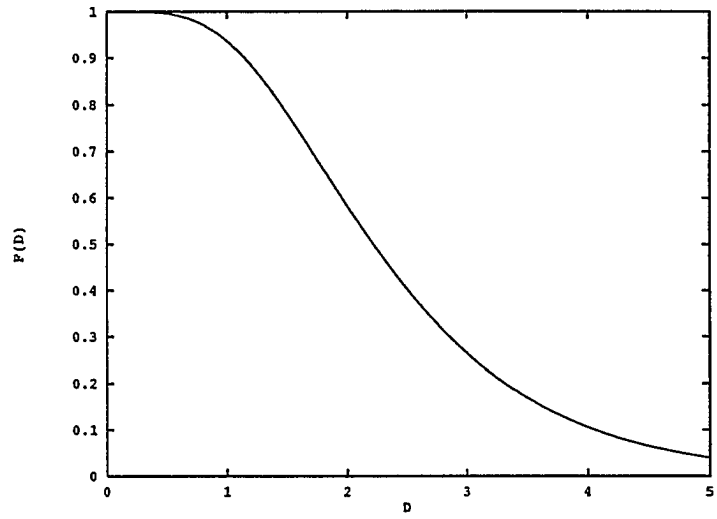

Figure 2.2: Exponential with shoulder

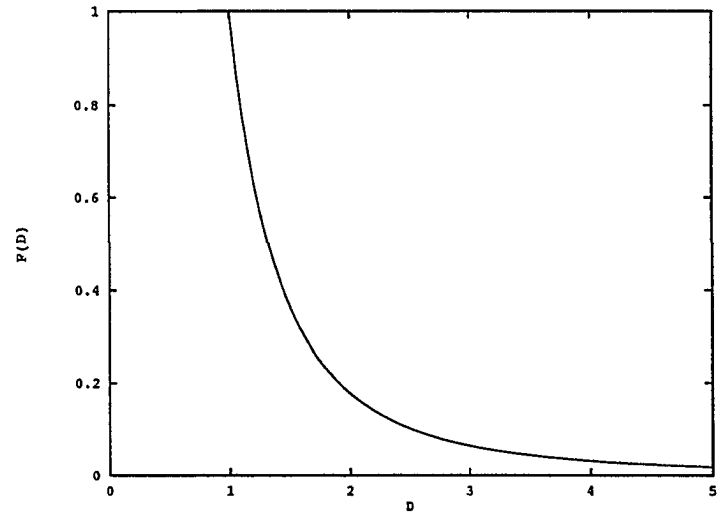

Figure 2.3: Hyperbolic

question: is the tumor-free case, $(K_1, 0)$, stable to small perturbations (compared to the normal cell mass)? In other words, can a small amount of tumor mass (perhaps remaining after surgery) survive or will the patient remain in the disease-free state? Linearizing about this equilibrium ($X = K_1 + \epsilon u$ and $Y = 0 + \epsilon v$ where ϵ is small compared to K_1) we obtain:

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} -r_1 & -\lambda_1 r_1 K_1 \\ 0 & r_2(1 - \lambda_2 K_1) \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix}. \tag{2.3.5}$$

From (2.3.5) it may be seen that the tumor population **can** recur if $K_1\lambda_2 < 1$ (the eigenvalue $1 - \lambda_2 K_1$ is positive). For more information on the relevant mathematical analysis see Waltman [65]. The term $K_1\lambda_2$ will be referred to as competitive pressure. Note that a similar result, derived differently, can also be found in Gatenby [28]. It can be seen that damaged normal tissue environment (reduced K_1) will be more susceptible to tumor recurrence along with poor competition for resources among the normal cells (small λ_2). If the parameters are non-constant, controlled by the growth factor signaling as in Michelson *et al.* [48, 49], then recurrence can be more difficult to visualize, but is also more realistic.

2.4 Recurrence with Pulsed Chemotherapy

Once chemotherapy is incorporated, it is very important to examine the effects it has, not only on the tumor cells, but also on normal cells. Otherwise, the regimen to destroy the tumor might also overly destroy the normal cells, and thus the patient. A commonly acceptable reduction in total normal tissue mass is about 50% of its

carrying capacity. So, first let us identify some basic conditions that must be placed on the therapy in the presence of normal cells only, and then examine the drugs effects on the tumor cells.

2.4.1 Normal Cell Growth

In the absence of any tumor cells, the system reduces to:

$$\frac{dX}{dT} = r_1 X(1 - X/K_1) \tag{2.4.6}$$

$$X(n\tau^+) = F(D)X(n\tau^-). \tag{2.4.7}$$

The solution which holds between pulses, which is the standard solution to the logistic differential equation, is:

$$X(t) = \frac{X_{n\tau} K_1}{X_{n\tau} + (K_1 - X_{n\tau})e^{-r_1(t-n\tau)}}; \qquad n\tau < t < (n+1)\tau \tag{2.4.8}$$

where $X_{n\tau} = X(n\tau)$. At the beginning of each successive pulse, the solution, using the pulsing condition (2.4.7), is:

$$X_{(n+1)\tau} = F(D)\frac{X_{n\tau} K_1}{X_{n\tau} + (K_1 - X_{n\tau})e^{-r_1\tau}}. \tag{2.4.9}$$

Equation (2.4.9) has two equilibrium points:

$$X_u^* = 0 \qquad X_s^* = \frac{K_1(F(D) - e^{-r_1\tau})}{(1 - e^{-r_1\tau})}. \tag{2.4.10}$$

Note that for X_s^* to exist and to be stable, $F(D) > e^{-r_1\tau}$. Otherwise X_u^* is the only equilibrium that exists, and it is stable. Since $F(D) > e^{-r_1\tau}$ allows even 99% of the normal cells to be killed and still have survival, then that condition in most cases is not acceptable and must be made more rigid. According to Berenbaum [7], an

acceptable level of cell kill for normal cells is about half the original state. This, in general, depends upon the type of normal cells that are being identified. Some can survive much larger cell kills than others. But to avoid specifying any particular type at this point, and to keep the model flexible, we will require $X_s^* > aK_1$, where a is the percentage of acceptable reduction from the steady state for normal cells. Using the above information, it can be seen that the survival fraction must be:

$$F(D) > a + e^{-r_1\tau}(1-a) \tag{2.4.11}$$

for there to be at least $a\%$ of the normal cells left. Substituting X_s^* into (2.4.8) we get the steady-state periodic solution:

$$X_s(t) = \frac{K_1(F(D) - e^{-r_1\tau})}{F(D) - e^{-r_1\tau} + (1-F(D))e^{-r_1(t-n\tau)}}; \qquad n\tau < t < (n+1)\tau. \tag{2.4.12}$$

2.4.2 Recurrence of the Tumor

Now, examine the recurrence of a small amount of tumor cells, $Y = 0 + \epsilon v$ (v is $O(1)$, and represents the tumor mass). As suggested earlier, this can be an $O(\epsilon)$ amount of tumor mass left after surgery. The question to be asked is, can the tumor continue to grow, or is the chemotherapy strong enough to eradicate it while maintaining the normal tissue above some acceptable level? To answer this, we linearize the original system about $(X_s(t), 0)$, and study the stability of the tumor mass. If the linear system is unstable in v, then the tumor can recur; otherwise the $(X_s(t), 0)$ state is stable and the chemotherapy prevents tumor recurrence. Letting $X = X_s(t) + \epsilon u$,

the linear system is:

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} r_1(1-2\frac{X_s(t)}{K_1}) & -r_1\lambda_1 X_s(t) \\ 0 & r_2(1-\lambda_2 X_s(t)) \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix}. \tag{2.4.13}$$

Thus, the stability of v can be determined by $v' = r_2(1-\lambda_2 X_s(t))v$. Since $X_s(t)$ is periodic with period τ, integrate over one period to get:

$$v_{(n+1)\tau} = \overline{F}(D) v_{n\tau} e^{r_2 \int_{n\tau}^{(n+1)\tau} 1-\lambda_2 X_s(t) dt} \tag{2.4.14}$$

or in a more useful form:

$$v_{(n+1)\tau} = v_{n\tau}\overline{F}(D) e^{\ln e^{r_2\tau} - r_2\lambda_2 \int_{n\tau}^{(n+1)\tau} X_s(t) dt}. \tag{2.4.15}$$

Calculating the above integral and simplifying, we get:

$$v_{(n+1)\tau} = v_{n\tau}\overline{F}(D) e^{\ln\left\{ \frac{e^{r_2\tau}}{F(D)^{\frac{r_2\lambda_2 K_1}{r_1}} e^{r_2\lambda_2 K_1 \tau}} \right\}} \tag{2.4.16}$$

or:

$$v_{(n+1)\tau} = v_{n\tau}\left\{ \frac{\overline{F}(D) e^{r_2\tau}}{F(D)^{\frac{r_2\lambda_2 K_1}{r_1}} e^{r_2\lambda_2 K_1 \tau}} \right\}. \tag{2.4.17}$$

If the characteristic multiplier of equation (2.4.17) (the term in brackets) is less then one, the tumor will regress. Thus, to prevent recurrence:

$$\overline{F}(D) < F(D)^{\frac{r_2\lambda_2 K_1}{r_1}} e^{-\tau r_2(1-\lambda_2 K_1)}. \tag{2.4.18}$$

Note that $\lambda_2 K_1 < 1$, since this is the condition for tumor survival without drug-therapy. In other words, if $\lambda_2 K_1 > 1$ then there is no need for any chemotherapy since the tumor is killed by competition with other cells (see § 2.3). To make it difficult for the tumor to recur, the right hand side of (2.4.18) must be large, close to

one. Therefore, either an increase in r_2 (tumor regrowth rate) or τ (period between treatments) will increase the ability of the tumor to recur, and an increase in r_1 (normal cell regrowth rate) or $\lambda_2 K_1$ (competitive pressure) will decrease the ability of the tumor to recur.

If $F(D) = e^{-\alpha_1 D}$ and $\overline{F}(D) = e^{-\alpha_2 D}$ then the conditions which prevent the tumor from recurring are:

$$D > \frac{\tau r_2(1-\lambda_2 K_1)}{\alpha_2 - \alpha_1 \lambda_2 K_1 r_2/r_1} \tag{2.4.19}$$

$$D < (-\alpha_1)^{-1} \ln\left(a + e^{-r_1 \tau}(1-a)\right) \tag{2.4.20}$$

where the first condition is derived from equation (2.4.18) and the second comes from (2.4.11). Note that both of these equations are affected by normal cell parameters (K_1, λ_2, r_1, α_1, a). For example, as the competitive pressure $\lambda_2 K_1$ increases, less of a dose is needed to prevent recurrence. For there to exist a region of acceptable dose and period, the graph of equation (2.4.20) must be above that of equation (2.4.19) for some region. For this to happen (noting that Dose=0 at $\tau = 0$), the slope of equation (2.4.20) at $\tau = 0$ must be larger then that of equation (2.4.19). To satisfy this, the following condition is needed:

$$\alpha_2 > \frac{\alpha_1 r_2(1 - a\lambda_2 K_1)}{r_1(1-a)}. \tag{2.4.21}$$

From this condition, we can see (as might be expected) that for the treatment to be effective, the chemotherapeutic drug must have more of an effect on the tumor cells then on the normal cells, unless the normal cells are able to grow back faster ($r_1 > r_2$).

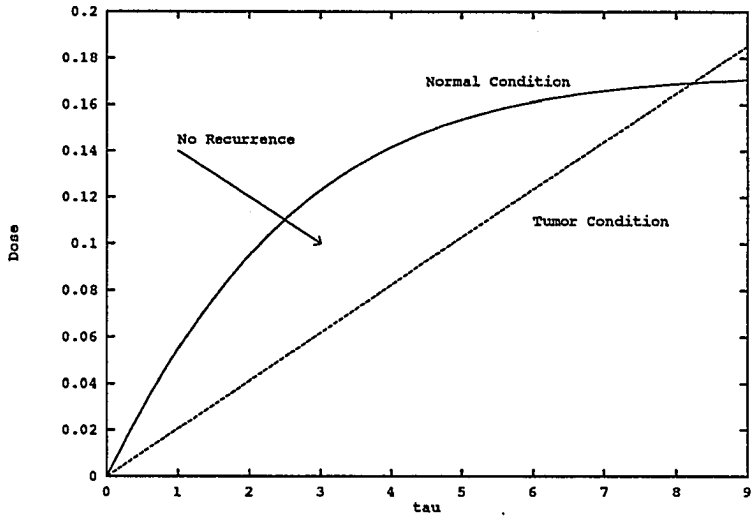

Figure 2.4: Dose-Response Curve: Dose vs. Period

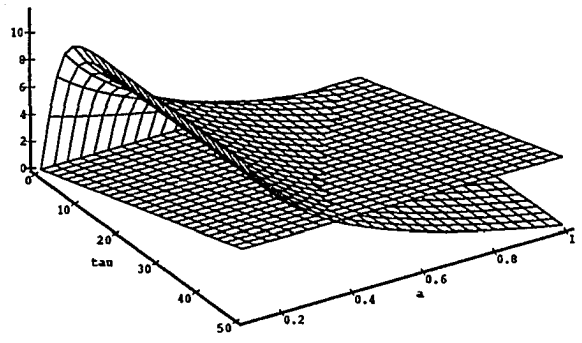

Figure 2.5: Dose-Response Curve: Dose vs. Period vs. Host Survival (a)

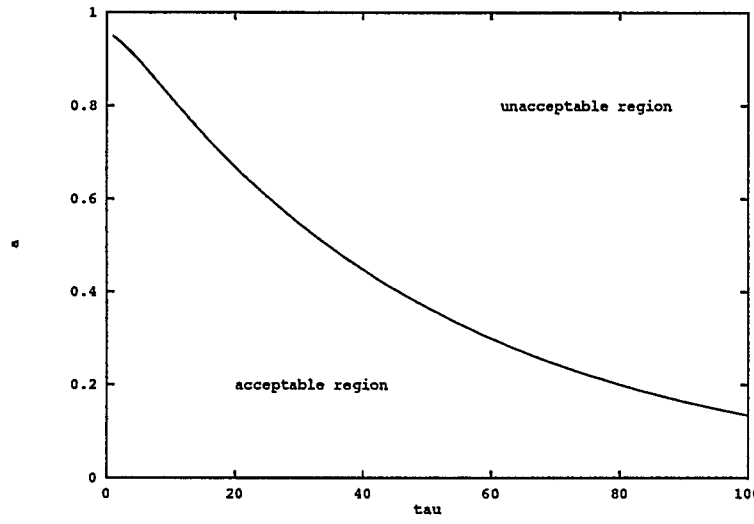

Figure 2.6: Dose-Response Curve: a vs. τ

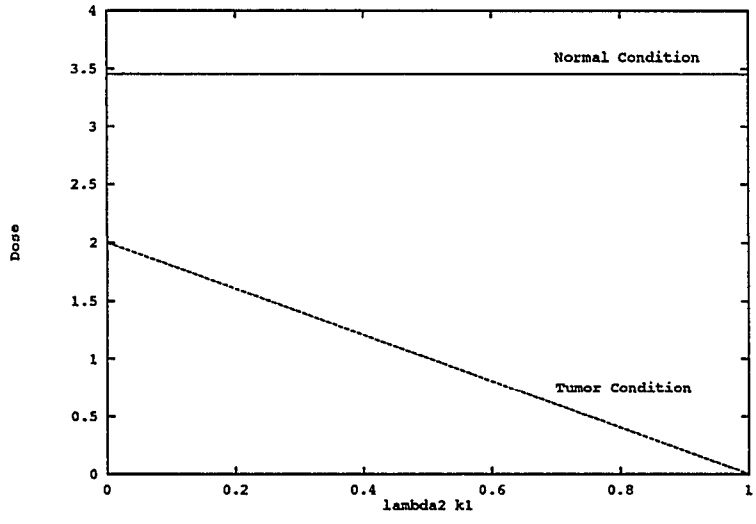

Figure 2.7: Dose-Response Curve: Dose vs. $\lambda_2 K_1$

Figure 2.4 gives one example of a region of acceptable dose and period. A dose and period chosen above the line, "Tumor Condition", and below the curve, "Normal Condition" will prevent the tumor from recurring and keep the normal cells above the specified level a. This also shows graphically the need for condition (2.4.21). Figure 2.5 gives a similar view with varying host survival (a). Here, we want to choose a dose and period above the plane and below the curved surface. It can be seen that as the condition on host survival (a) is increased, the region for successful treatment is decreased. In fact, Figure 2.6 shows where the graphs in Figure 2.5 cross. This forms the boundary between where a successful region exists and does not. Figure 2.7 shows the effect of varying $\lambda_2 K_1$. As predicted, for small values of $\lambda_2 K_1$, it will take a larger dose to prevent tumor recurrence. This can be interpreted as when the competitive pressure ($\lambda_2 K_1$) decreases, the drug therapy will need to be made more effective to continue to prevent recurrence. And if there is no competition at all, i.e. $\lambda_{1,2} = 0$ then the drug therapy must be able to eliminate the tumor alone.

2.5 Discussion and Conclusions

Since tumor cells are **not** isolated from their micro-environment, but are constantly competing with the host for resources, the models discussed here, which include tumor-normal cell interaction, are a step toward better describing chemotherapeutic effects. However, few researchers who have modeled chemotherapy have studied the effects the drugs have on normal tissue, or the effects of the normal tissue on the tumor. Since this first effect is possibly the most important constraint on the use

of chemotherapeutic drugs, it **must** be a part of any model that will accurately describe the interplay of the system.

The models in this chapter indicate that there are definite parameter regions of acceptable and unacceptable chemotherapeutic regimens, giving us a qualitative idea of how each parameter affects tumor recurrence. In particular, we show how the competitive pressure ($\lambda_2 K_1$) can control and even prevent tumor growth and recurrence. Also, we show how certain doses (D) and periods (τ) can lead to tumor regrowth.

Gatenby [27] points out that when therapy is withdrawn, the tumor will just grow back to its original size unless it is totally destroyed or the characteristics of the system have changed (by changing parameters through a critical point). As seen in this model, one of these changes can be an increase in $\lambda_2 K_1$ through the critical value of one which will make it impossible for the tumor to recur. A relevant topic in this regard is that of growth factors as discussed by Michelson *et al.* [48, 49]. In particular, the paracrine path, which can be described mathematically as the varying of the carrying capacity K_i by tumor growth factors, can change the recurrence condition significantly. Additionally, Gatenby [27] discusses how damage to the local tissue (normal cells) and devascularization (the preventing of blood vessels from growing into the tumor) can help the tumor mass emerge. That is, the carrying capacity is reduced because of dead cell buildup or increased levels of toxic drugs, thus making it easier for the tumor to emerge. These ideas give rise to the need for models with non-constant parameters.

Even though further work will be required to address the simplifications in these

models, they do provide a useful initial indication of the dynamics of tumor recurrence. The parameter conditions arising from these models define our expectations for the effective chemotherapeutic treatment of tumor recurrence, giving us more insight into how to administer the drugs more efficiently.

Chapter 3

Cell-Specific Chemotherapy

3.1 Introduction

Many chemotherapeutic drugs are cell-specific: they only destroy specific types of cells in specific phases of their cycle (usually proliferating cells). Some examples of these types of drugs are Cytosine Arabinoside (Ara-C), 5-fluorouracil and Prednisone which work in the G_1 and S phase of the cell-cycle and Vincristine and Bleomycin which work in the M phase of the cell-cycle. Most of the clinically-used methods of delivering chemotherapy have been developed empirically, and as stated by Birkhead *et al.* [12]: "In the absence of more effective new drugs there is an increasing need to define better treatment strategies with existing agents." The object of the model in this chapter is to give some qualitative ideas on how to better administer cell-specific chemotherapy. This model is not meant to dictate to the clinician which regimens of therapy are appropriate, for each individual patient is different and requires quantitatively different treatments. In fact, in most cases even approximate

ranges for parameters and drug effects are not known (R. Perry, private communication). But, it is hoped that this model will give some **qualitative** ideas on how to better implement cell-specific therapy.

Some of the more recent work done with mathematical models of cell-specific chemotherapy are by Webb [66, 67]. He develops both linear and non-linear models of cell-specific chemotherapy. In the case of the linear model, the advantages of periods of dose with shorter duration are investigated. Another work of interest is by Birkhead *et al.* [12] in which a four-compartment linear system is developed to model the cycling, resistant, and resting cells. Their results are limited to a few numerical calculations on four specific types of treatments. Swan [64] also examines cell-specific chemotherapy in his review article. In particular he concentrates on age-structured models which take into account the age of the cells in each compartment of the cell cycle. He also studies an age-structured chemotherapeutic model of acute myeloid leukemia AML. Eisen and Schiller [24] study a two-compartment model of tumor growth with non-constant growth rate. In addition, Kuzma *et al.* [40] examine a model with exponential growth for the tumor and both immediate and delayed effects of drugs. In their model they study a variety of results including the number of doses needed for a specific tumor reduction, the minimum initial dose needed for tumor reduction, and some toxicity effects. The issue not discussed in any of these articles is the effects of the drugs on normal tissue. An interesting approach to the problem of toxicity to bone marrow and other sensitive tissues has been investigated by Agur *et al.* [3] and Cojocaru and Agur [13] (this adds age structure to the previous). They develop criteria to maximize the tumor cell kill while

minimizing bone marrow damage. They accomplish this by examining the relation between the period in which the drugs are delivered and the cell-cycle time for the tumor and bone marrow cells. The idea is to administer the chemotherapeutic drug when the cancer cells are in a more vulnerable growth phase and the bone marrow is in a less vulnerable stage. These two articles also differ from the other above articles in that they only consider cells in the growth phase of the cell cycle, i.e. they do not consider the resting stage (G_0).

The model in this chapter will extend the linear models described in Webb [66], Birkhead *et al.* [12] and Eisen and Schiller [24] by adding both pulsed and piecewise-continuous chemotherapy, and by examining the effects of the cell-specific drug on the normal tissue. The tissues that will concern us in particular are the fast proliferating tissues such as bone marrow or those comprising the gastrointestinal tract. From this model we will identify parameter ranges, in terms of dose and period, needed to prevent further growth of the tumor.

One chemotherapeutic regimen used, as stated by Birkhead *et al.* [12], is "the maximally-tolerated dose is given as frequently as the rate of bone marrow recovery permits." Using the model developed in this chapter, we will investigate this chemotherapeutic regimen. The model will show for a given dose what the optimal period is to have maximal tumor cell kill. We will show that in some cases the model confirms Birkhead's regimen and in others this is not the "best" way to deliver the chemotherapeutic drugs.

Another method of increasing the ability of cell-specific drugs to destroy the tumor (while not overly destroying normal tissue) is to provide growth factors to

the tumor and/or normal tissue. One such type of growth factor used in treating breast cancer is exogenous estrogen. This increases the tumor cell proliferation to make the tumor more susceptible to the chemotherapeutic drugs. Another class of growth factors used are the hemopoietic growth factors HGF such as granulocyte colony-stimulating factor G-CSF, granulocyte-macrophage colony-stimulating factor GM-CSF, and interleukin-3 IL-3. These growth factors are used in AML to increase the percentage of cells in the S phase (the phase which many chemotherapeutic drugs are most active) and in breast cancer to increase the levels of circulating leukocytes (white blood cells). Bhalla *et al.* [8] states that G-CSF, GM-CSF, and IL-3 increase about two to four times the number of AML blasts in the S phase while Demetri [22] states that these HGF's allow larger doses of chemotherapy to be safely given because of the increased circulating leukocytes. This model will take into account these growth factors, by varying appropriate parameters such as cell growth rates, and show how they increase the effectiveness of the cell-specific chemotherapeutic agents.

3.2 Model

A two-dimensional linear differential equation with periodically pulsed chemotherapy is used to describe the effects of chemotherapy on a tumor. The basic model is similar to the two-compartment model described in Eisen and Schiller [24], and to the model given in Birkhead *et al.* [12] who include resistant compartments for both the cycling and non-cycling cells, thus increasing the dimension of their model to four. Both

examine similar models to describe basic tumor growth. However, the model in this chapter not only identifies the chemotherapeutic effects more explicitly, but more importantly it models the effects of the drugs on normal tissue.

Some basic assumptions are made to keep the model tractable. Firstly, we only study a linear system (first-order kinetics) to describe tumor growth. This limits the model to either exponential growth or decay without any intermediate equilibrium. Nevertheless, this is an acceptable first approach since a successful chemotherapeutic regimen will prevent the tumor from growing near its carrying capacity, so that the non-linear effects of logistic or Gompertz growth will be minimal, allowing us to use the simpler model. Birkhead *et al.* [9, 12] and Kuzma *et al.* [40] also utilize exponential tumor growth between doses. Secondly, all the parameters are held constant (except for the case of growth factors). In their model Eisen and Schiller [24] incorporate non-constant growth, but we will avoid this and focus more on the chemotherapeutic aspects of the model. Thirdly, we ignore spatial or age effects. That is, the resources and chemotherapeutic drugs are assumed to reach all cells equally, and cells of all ages are affected uniformly (however, this model does take into account natural cell decay). Fourthly, even though the cycling compartment actually has four sub-compartments or phases including the gap period (G_1), the synthetic period (S), the second gap period (G_2), and mitosis (M) (see figure (3.1)), our model combines these four sub-compartments of the cycling phase into one to yield a two-compartment model containing a cycling and a resting compartment. Finally, even though cell-specific drugs still have some effect on resting cells (though the faster proliferating cells will definitely be more affected), we assume that resting

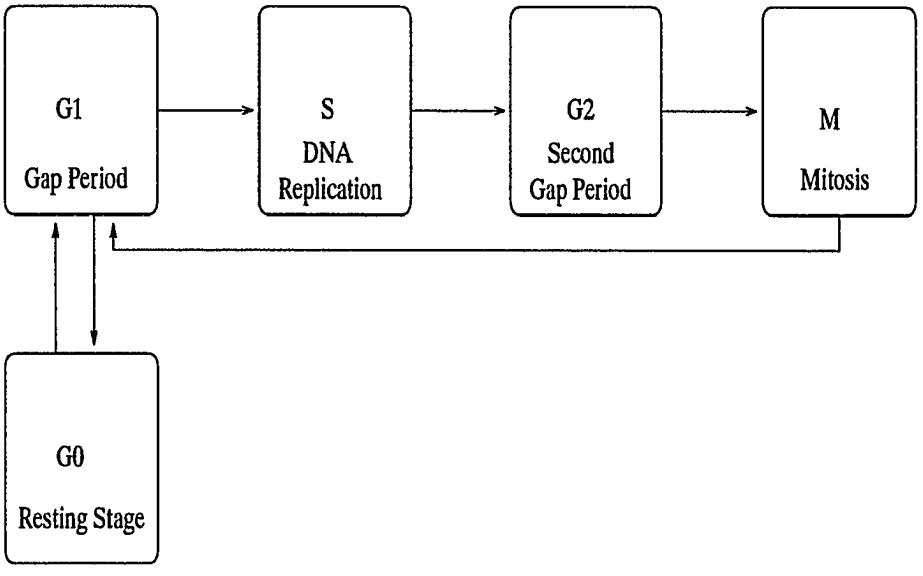

Figure 3.1: Cell-Cycle

cells (G_0) are not affected by the drugs. It is important to note that making the system more complex does not necessarily make it more useful. The simpler system allows us to view many interesting features of cell-specific chemotherapy without the undue mathematical complexity. Even with these assumptions, the model still shows many interesting dynamics and can address some of the major questions of chemotherapy such as: will the tumor grow or decay, how will the major parameters (dose and period) affect the outcome, and what is the optimal regimen to deliver the drugs.

3.2.1 Two-Compartment Model

The form of the linear two-compartment model as described in figure (3.2) is:

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{pmatrix} = \begin{pmatrix} \alpha - \mu - \eta & \beta \\ \mu & -\beta - \gamma \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, \tag{3.2.1}$$

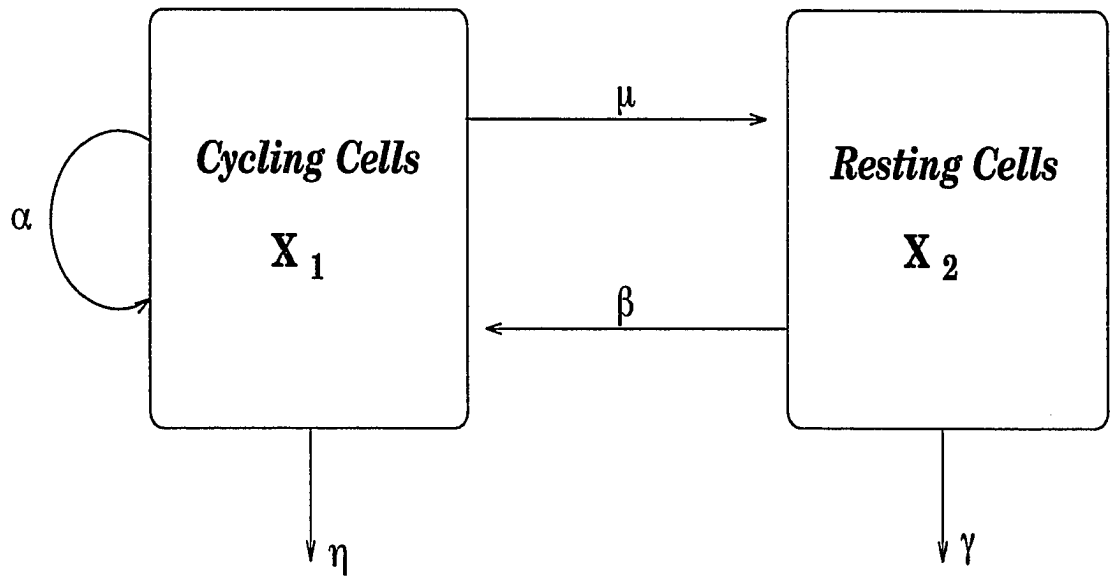

Figure 3.2: Two-Compartment Diagram

where the parameters are all constant, positive, and defined as follows: α, cycling cells growth rate; μ, rate which cycling cells become non-cycling; η, natural decay of cycling cells; β, rate which non-cycling cells become cycling; γ, natural decay of non-cycling cells (optional). The elements of the vector $(x_1, x_2)^T \equiv \vec{x}$ represents the cycling and non-cycling tumor cell mass respectively. We will assume that $\alpha > \eta$ (positive net growth rate), i.e. in the absence of chemotherapy, the tumor will grow without bound. We will also assume that $\alpha - \mu - \eta < 0$, i.e. a large number of cells move to the non-cycling or quiescent compartment. Birkhead *et al.* [12] suggest that only about 20% of the tumor cells are cycling. To simplify the form, let $a \equiv -(\alpha - \mu - \eta)$ and $\gamma \equiv 0$. Thus, the generalized linear system is:

$$\frac{d\vec{x}}{dt} = \begin{pmatrix} -a & \beta \\ \mu & -\beta \end{pmatrix} \vec{x} \tag{3.2.2}$$

where $a, \beta, \mu \geq 0$. Birkhead *et al.* [12] give one set of parameter values from breast cancer data that fit the above conditions, namely, $\alpha = 0.5, \mu = 0.218, \eta = 0.477, \beta = 0.05$.

Now we examine the periodic chemotherapeutic conditions. In this model of cell-specific chemotherapy, we assume the drugs only affect the cycling cells, x_1. We will model the chemotherapeutic effects with pulsed chemotherapy as in chapter 2. Again, this describes a constant instantaneous cell kill at each period of dose. The pulsing periodic condition is:

$$\vec{x}_{n\tau+} = \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix} \vec{x}_{n\tau-} \tag{3.2.3}$$

where $0 < f(D) < 1$ is the survival fraction (which is a decreasing function of dose D), and τ is the period between doses. τ^+ refers to the instant after the drug is given and τ^- refers to the instant prior to the dose of the drug. Specific forms of $f(D)$ can be found in Panetta [56]. Also, Birkhead *et al.* [12] examine $0.05 \leq f(D) \leq 0.4$.

3.2.2 Normal Cells

One of the major drawbacks of chemotherapy is that it also affects normal cell tissue. In the case of cell-specific chemotherapy, tissue like bone marrow which proliferates rapidly will be strongly affected by the drug and this will have to be taken into account when developing a chemotherapeutic regimen. There are a variety of ways to approach this problem. Panetta [56] examines the interaction between normal and tumor tissue and the effects of cell-non-specific drugs on them. In many cases, such as with bone marrow, there is probably no interaction with the tumor, but the

drugs still affect it. This is the case that we will examine in the present model. If we assume that the normal tissue has limited growth between pulses of the drug as described in equation 3.2.4, then a suitable linear constraint equation for pulsed therapy is:

$$\dot{y} = \delta(K - y), \quad y_{n\tau+} = \tilde{f}(D)y_{n\tau-}, \quad n\tau \leq t < (n+1)\tau, \tag{3.2.4}$$

where δ is the growth rate, K is the carrying capacity, $\tilde{f}(D)$ is the survival fraction for the normal tissue and $\tilde{f}(D) > f(D)$. This inequality means that the drug affects the tumor cells more than the normal cells. Logistic growth can also be used to model the growth of the normal tissue though, in this case, the equation is non-linear. The form of the logistic constraint equation for pulsed therapy is:

$$\dot{y} = \delta y(1 - \frac{y}{K}), \quad y_{n\tau+} = \tilde{f}(D)y_{n\tau-} \quad n\tau \leq t < (n+1)\tau. \tag{3.2.5}$$

The logistic equation with pulsing is solved in section 2.4.1 and in Panetta [56]; the solution to equation (3.2.4) is similar in form and is given in the following section.

3.3 Pulsed Case

The first step in analyzing model (3.2.2) with pulsing condition (3.2.3) and constraint equation (3.2.5) is to develop solutions for (3.2.2) and (3.2.5) over one period $n\tau \leq t < (n+1)\tau$. Once this is accomplished we can then apply the pulsing condition to arrive at a linear system of difference equations (sometimes referred to as the first return map or Poincaré map, see Hale and Koçak [35]) that will describe the growth of the tumor at each pulse.

3.3.1 Normal Tissue

First, consider the linear case of limited normal tissue growth. Solving equation (3.2.4) yields the difference equation:

$$y_{(n+1)\tau} = \tilde{f}(D)\{K + (y_{n\tau} - K)e^{-\delta\tau}\}. \tag{3.3.6}$$

This has a unique equilibrium:

$$y_s^* = \frac{K\tilde{f}(D)(1 - e^{-\delta\tau})}{1 - \tilde{f}(D)e^{-\delta\tau}}. \tag{3.3.7}$$

As in section 2.4.1, we require $y_s^* > \omega K$, where ω $(0 < \omega < 1)$ is the acceptable fractional kill of the carrying capacity K. Hence, the constraint for limited linear growth on the chemotherapeutic regimen in terms of dose and period is:

$$\omega \leq \frac{\tilde{f}(D)(1 - e^{-\delta\tau})}{1 - \tilde{f}(D)e^{-\delta\tau}}. \tag{3.3.8}$$

Now, in a similar manner, the logistic constraint is also solved. As in section 2.4.1, solving equation (3.2.5) yields the difference equation:

$$y_{(n+1)\tau} = \tilde{f}(D)\frac{y_{n\tau}K}{y_{n\tau} + (K - y_{n\tau})e^{-\delta\tau}}, \tag{3.3.9}$$

which has two equilibrium points:

$$y_u^* = 0 \quad y_s^* = \frac{K(\tilde{f}(D) - e^{-\delta\tau})}{1 - e^{-\delta\tau}}. \tag{3.3.10}$$

Thus, the constraint on the chemotherapeutic regimen in terms of dose and period is:

$$\omega \leq \frac{\tilde{f}(D) - e^{-\delta\tau}}{1 - e^{-\delta\tau}}. \tag{3.3.11}$$

In both cases, the cell-specific chemotherapeutic drugs have less effect on these tissues, primarily since a much higher percentage of normal tissue is in the resting phase, though this is **not** the case with bone marrow. Therefore $\tilde{f}(D) > f(D)$ since more normal than cancerous tissue survives each dose.

3.3.2 Effects on Tumor

First, examine equation (3.2.2). Hale and Koçak [35, chapter 8] provide a good account of the general solutions to linear systems such as this. The form of the solution given by many elementary ordinary differential equation texts is $\vec{x}(t) = c_1\vec{\xi}_1 e^{\lambda_1(t-n\tau)} + c_2\vec{\xi}_2 e^{\lambda_2(t-n\tau)}$ where the λ_i's are the eigenvalues, and $\vec{\xi}_i$'s are the corresponding eigenvectors to the coefficient matrix of (3.2.2). This solution is defined on the interval $n\tau \leq t < (n+1)\tau$. By our choice of signs of the parameters in the coefficient matrix, one eigenvalue must be positive (e.g. λ_1), with eigenvector $\vec{\xi}_1$ in the first quadrant. Thus, the tumor will grow in the absence of chemotherapy. The other eigenvalue must be negative. This can be observed by calculating the eigenvalues directly. They are:

$$\lambda_i = \frac{-(a+\beta) \pm \sqrt{(a+\beta)^2 - 4(a-\mu)}}{4(a-\mu)}. \tag{3.3.12}$$

Since $a, \beta, \mu > 0$ and $\alpha > \eta$, then $a - \mu < 0$. So, equation (3.3.12) has one positive and one negative eigenvalue. It will be more convenient for us to write the solution in the form:

$$\vec{x}(t) = P \begin{pmatrix} e^{\lambda_1(t-n\tau)} & 0 \\ 0 & e^{\lambda_2(t-n\tau)} \end{pmatrix} P^{-1}\vec{x}_{n\tau}, \quad n\tau \leq t < (n+1)\tau, \tag{3.3.13}$$

where

$$P \equiv (\vec{\xi}_1 | \vec{\xi}_2) \tag{3.3.14}$$

is the transformation matrix of eigenvectors and $\vec{x}_{n\tau}$ is the tumor mass at the beginning of the nth period.

Now, adding pulsing condition (3.2.3), the following difference equation describes the tumor mass just after each pulse of drug:

$$\vec{x}_{(n+1)\tau} = P \begin{pmatrix} e^{\lambda_1 \tau} & 0 \\ 0 & e^{\lambda_2 \tau} \end{pmatrix} P^{-1} \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix} \vec{x}_{n\tau}. \tag{3.3.15}$$

To determine whether the system is growing or decaying, the eigenvalues or characteristic multipliers of the characteristic matrix

$$P \begin{pmatrix} e^{\lambda_1 \tau} & 0 \\ 0 & e^{\lambda_2 \tau} \end{pmatrix} P^{-1} \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix}, \tag{3.3.16}$$

of equation (3.3.15) need to be investigated. We will define the eigenvalues of matrix (3.3.16) as $\overline{\lambda}_i$; these can be found in terms of $f(D)$, τ, and λ_i (fixed). If

$$\max_{i=1,2} (|\overline{\lambda}_i(f(D), \tau)|) < 1 \tag{3.3.17}$$

then the chemotherapeutic regimen will destroy the tumor; otherwise the tumor will grow. Therefore, we are interested in finding the bifurcation curve which separates growth from decay, i.e.

$$\max_{i=1,2} (|\overline{\lambda}_i(f(D), \tau)|) = 1, \tag{3.3.18}$$

in terms of the survival fraction $f(D)$ (or dose) and period τ.

Also, in region (3.3.17), there are some regimens that are more effective than others in destroying the tumor (e.g. by choosing the period which minimizes the

maximum value of $|\overline{\lambda}_i|$for a given dose). The most effective chemotherapeutic regimen is therefore defined as

$$\min_{\tau}\left(\max_{i=1,2}(|\overline{\lambda}_i(f(D),\tau)|)\right) \tag{3.3.19}$$

for each fixed $f(D)$. However, this does not take into account the effect of the drugs on the normal tissue. We must consider this expression along with inequalities (3.3.8) or (3.3.11) when developing effective chemotherapeutic regimens. This is carried out in the next section.

Now observe that the matrix (3.3.16) can be expressed in the form:

$$\frac{1}{det(P)}\begin{pmatrix} (\xi_{11}\xi_{22}e^{\lambda_1\tau}-\xi_{12}\xi_{21}e^{\lambda_2\tau})f(D) & -\xi_{11}\xi_{12}(e^{\lambda_1\tau}-e^{\lambda_2\tau}) \\ \xi_{21}\xi_{22}(e^{\lambda_1\tau}-e^{\lambda_2\tau})f(D) & (\xi_{11}\xi_{22}e^{\lambda_2\tau}-\xi_{12}\xi_{21}e^{\lambda_1\tau}) \end{pmatrix}. \tag{3.3.20}$$

Denoting this characteristic matrix (3.3.20) CM, its eigenvalues are:

$$\overline{\lambda}_i(f(D),\tau) \equiv \frac{trace(CM) \pm \sqrt{(trace(CM))^2 - det(CM)}}{2}. \tag{3.3.21}$$

Calculating the $det(CM)$ and $trace(CM)$, we obtain:

$$det(CM) \equiv f(D)e^{(\lambda_1+\lambda_2)\tau} > 0 \tag{3.3.22}$$

and

$$trace(CM) \equiv (gf(D)-h)e^{\lambda_1\tau} - (hf(D)-g)e^{\lambda_2\tau} > 0 \tag{3.3.23}$$

where

$$g \equiv \frac{\xi_{11}\xi_{22}}{det(P)}, \ and \ h \equiv \frac{\xi_{12}\xi_{21}}{det(P)}. \tag{3.3.24}$$

Because of the signs of the coefficient matrix of equation (3.2.2) $\xi_{11}, \xi_{12} > 0$ and ξ_{21}, ξ_{22} have opposite signs. Thus, it can be observed that both $trace(CM)$ and

$det(CM)$ are positive because of the signs of the elements of the eigenvectors. Therefore $\max_i(|\overline{\lambda}_i(f(D),\tau)|) = \overline{\lambda}_1(f(D),\tau)$. By the correct choice of the dose and period we are able to force $\overline{\lambda}_1(f(D),\tau) < 1$, thus eliminating the tumor.

3.3.3 Results for Pulsed Therapy

First, we will examine the bifurcation diagram of the model with respect to survival fraction $f(D)$ and period τ. That is, we investigate the graph of the bifurcation equation (3.3.18) with $i = 1$ and the constraint equation (3.3.8) or (3.3.11). Using the parameters $a\mu\beta$ listed in § 3.2.1, $\omega = 0.5$, and $\delta = 0.1$ along with the logistic constraint equation (3.3.11), we obtain figure 3.3 for $\widetilde{f}(D) = 2f(D)$ (normal tissue survives twice as well as tumor tissue) and figure 3.4 for $\widetilde{f}(D) = 4f(D)$ (normal tissue survives four times as well as tumor tissue). The tumor condition curve represents the bifurcation from tumor reduction to tumor growth and the normal condition curve represents the bifurcation from overdestruction of normal tissue to acceptable normal cell loss. From these curves we can see the area, in parameter space, of acceptable dose and period that will eliminate the cancer cells while maintaining the normal cells at a level of at least half their carrying capacity.

As can be seen, this region is not small, so given that we have a prescribed dose to administer, what is the optimal period in which to deliver that dose? To answer this question we will minimize $\overline{\lambda}_1(f(D),\tau)$ with respect to τ. One might assume that for a given survival fraction the optimal frequency to administer the drug (without considering normal tissue) would be continuously. But, investigating equation (3.3.19), it can be seen that the optimal period is actually greater than $\tau \approx 0$

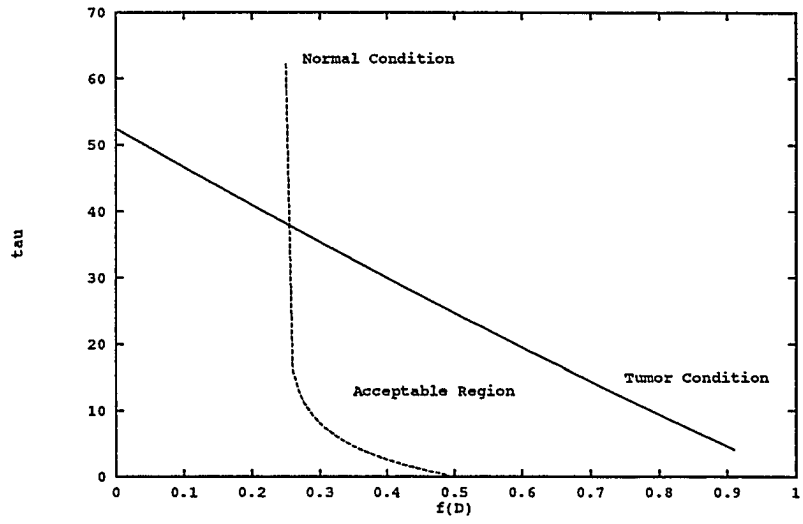

Figure 3.3: Bifurcation Diagram: $\tilde{f}(D) = 2f(D)$

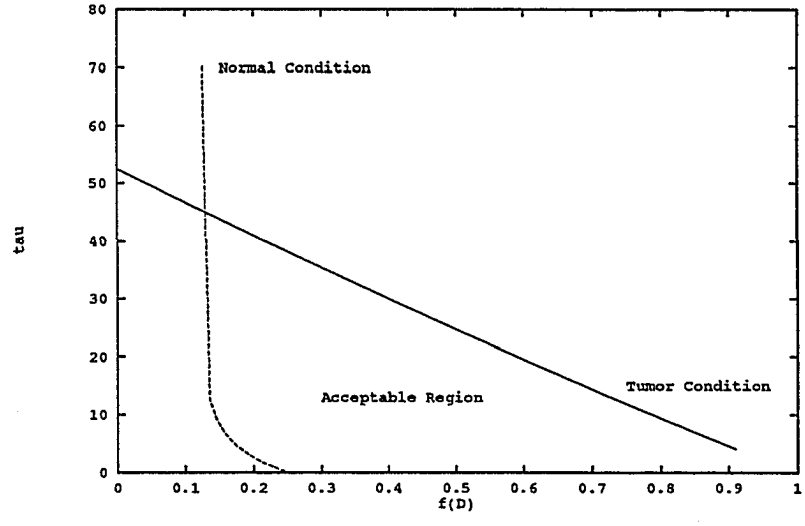

Figure 3.4: Bifurcation Diagram: $\tilde{f}(D) = 4f(D)$

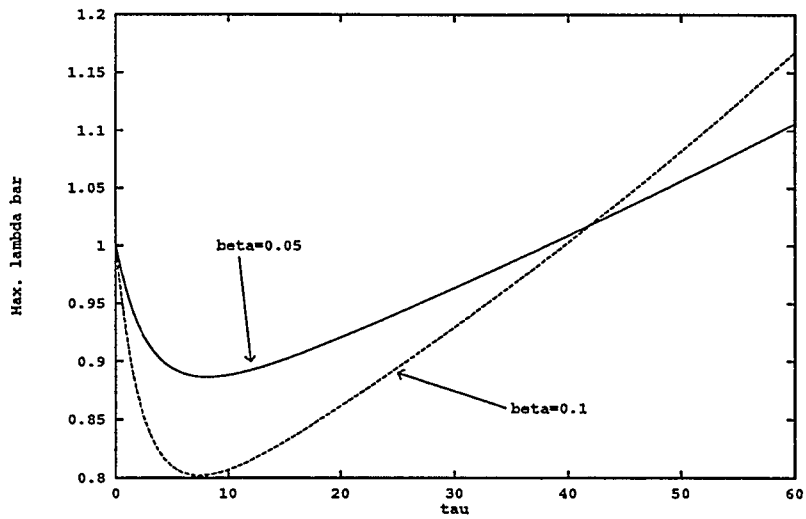

Figure 3.5: $\overline{\lambda}_1(f(D),\tau)$ vs. τ, $f(D) = 0.25$

(continuously delivering drugs). This is because by allowing some time between each dose, more resting cells are permitted to move to the cycling compartment, and so there are more cycling cells to be killed when the next dose is given. Also, it should be noted that giving the drugs at a very rapid rate will destroy the normal tissue too rapidly! Thus, a calculation of the optimal period is extremely practical. For example, with $f(D) = 0.25$, the optimal period to deliver the drug is $\tau \approx 8$ (i.e. this is the $\min \overline{\lambda}_1$ with respect to τ: see figure 3.5), while an acceptable period ($\overline{\lambda}_1 < 1$) ranges over the large interval $0 < \tau < 40$. In general, the optimal period is shown in figure 3.6 for $0 < f(D) < 0.9$. As can be seen, for more effective drugs (i.e. smaller $f(D)$) the optimal periods are larger than for less effective ones, thus allowing the normal tissue more time to recover.

Now, consider the chemotherapeutic regimen stated by Birkhead *et al.* [12]. That is, "the maximally-tolerated dose is given as frequently as the rate of bone marrow

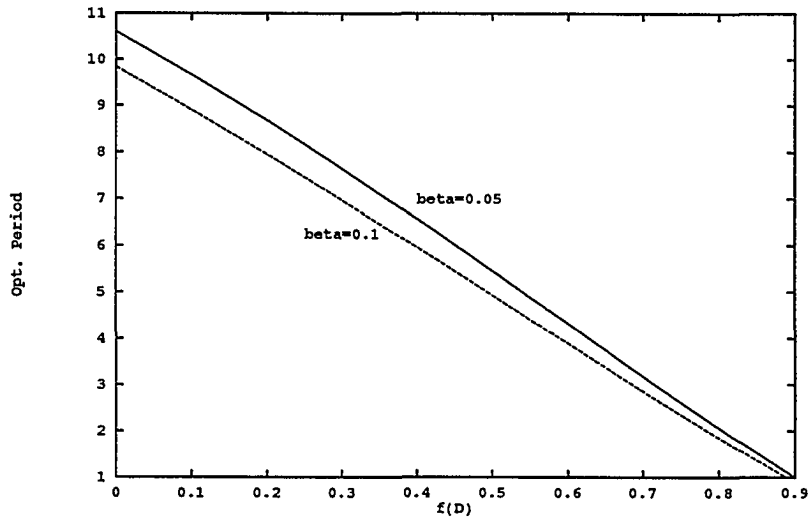

Figure 3.6: Optimal Period vs. $f(D)$

recovery permits." Before seeing if our model agrees with this protocol we need to consider what is implied by this regimen. There are two possibilities; either to administer the drug rapidly without using a strong dose, or to allow higher doses but administering them less frequently. By noting the bifurcation diagram for $\tilde{f}(D) = 2f(D)$ (figure 3.3) and the optimal period graph (figure 3.6), we observe that the calculated optimal period is a better regimen if a smaller dose (survival fraction $f(D) > 0.3$) is given more frequently; Birkhead's regimen is better if the opposite holds true. This can be observed in figure 3.7 by noting where the optimal period curve and the normal condition curve ($\delta = 0.1$) cross. If the survival fraction is to the right of this intersection then the optimal period is best, and if it is to the left then it is not. Of course the parameters chosen are just one possible acceptable set; thus, as stated above this is merely a qualitative examination of the problem.

In many cases the clinician would prefer to give a larger dose than is acceptable

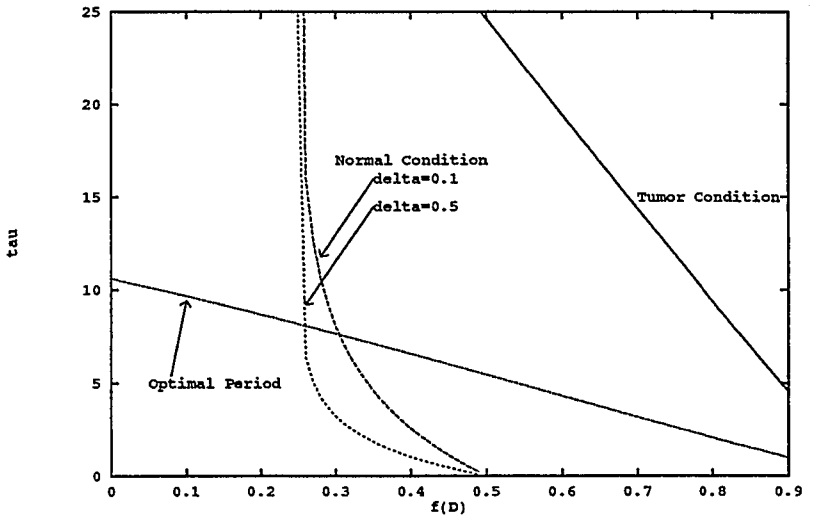

Figure 3.7: Bifurcation with Optimal Period

by conventional methods. The problem, as can be seen in figure 3.7, is that large doses (small $f(D)$) must be administered over a larger than optimal period to prevent overdestruction of the normal tissue. In the case of reduced leukocyte production because of damage to the bone marrow, HGF's are used to help counteract this problem by increasing leukocyte production. This process is modeled mathematically by increasing the growth rate, δ, of the normal tissue equation (either equation 3.2.4 or 3.2.5). As can be seen from figure 3.7, a higher growth rate for the normal tissue increases the region of acceptable drug regimens, thus allowing higher doses of chemotherapeutic drugs to be given at their optimal period. If $\tau = 20$ (the best period without growth factors, $\delta = 0.1$) and $f(D) = 0.275$, then there is approximately a 65% reduction in tumor mass. But, if growth factors are given ($\delta = 0.5$) then the optimal period of $\tau = 7.25$ can be used and there is approximately a 82% reduction in tumor mass, which is a 27% increase in tumor reduction over the non-optimal

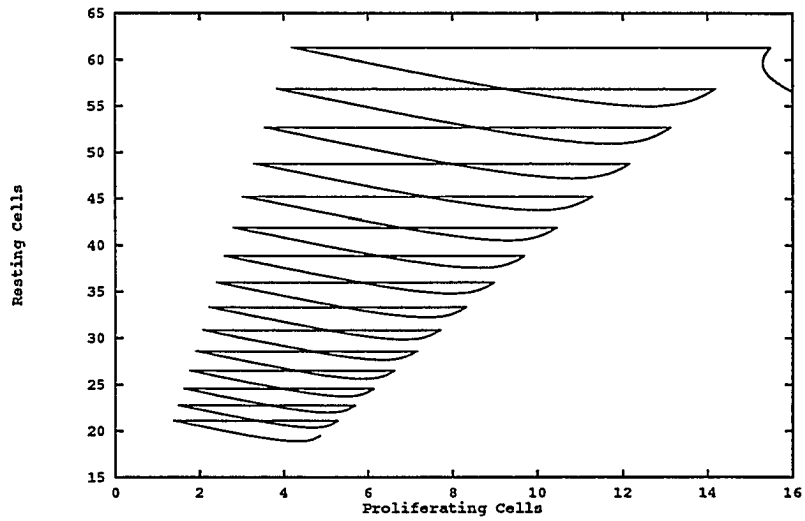

Figure 3.8: $\tau = 20$, $f(D) = 0.275$

period! Figures 3.8 and 3.9 show the phase planes (resting vs. proliferating) for each case. Observing figure 3.8 we can see why the non-optimal period does not have as large a cell kill as the optimal case. The graph shows that the proliferating cancer cells are able to start regrowth before the next dose is given. Thus, this regimen is not optimal since the dose is too large.

Another use of HGF's is with AML. They are used to increase the ratio of proliferating to resting cells, thus increasing the cell-kill of a cell-specific drug. This is modeled by an increase in the parameter β, which is the rate at which resting cells become proliferating. One question to be asked is: how does an increase in β affect the maximum eigenvalue of the characteristic polynomial? Examining the derivative of $\overline{\lambda}_1$ with respect to β, it can be seen that $\overline{\lambda}_1(\beta)$ is a decreasing function for $\beta > 0$. Thus, by increasing the rate at which resting cells become proliferating, the characteristic multiplier $\overline{\lambda}_1$ decreases, which means there is a larger cell-kill. This

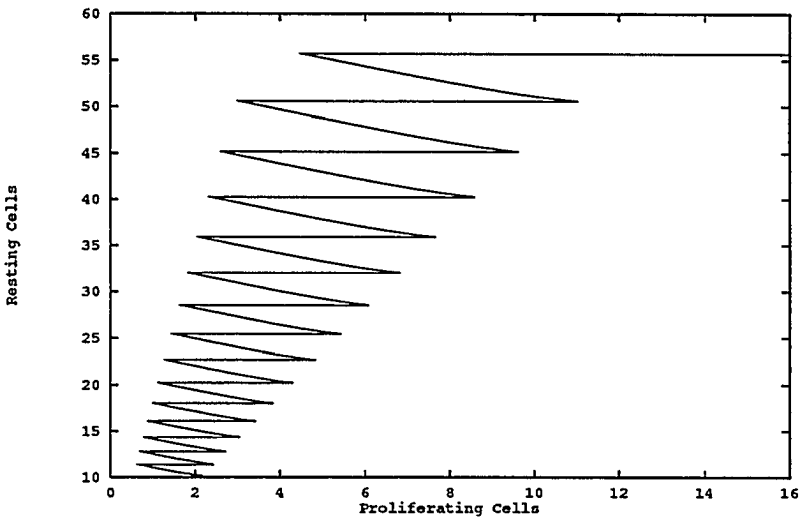

Figure 3.9: $\tau = 7.25$, $f(D) = 0.275$

can be seen in figure 3.5. Further, we note that the optimal period decreases as β is increased (see figure 3.6). This can be understood as the cells are moving into the cycling compartment faster so the optimal period is arrived at faster. The most important feature is that by introducing a growth factor the same number of doses can have a larger overall effect on the AML. This can be seen in figures 3.10 and 3.11. With the previously stated parameters it is calculated that fifteen doses of a drug with AML survival fraction of $f(D) = 0.25$, period of $\tau = 8$ and $\beta = 0.05$ will reduce the amount of AML by approximately 86%, while reducing it by 97% with $\beta = 0.1$. In this case there is a 13% increase in tumor reduction.

3.4 Discussion

For chemotherapeutic drugs to be useful they must be given to the patient at an appropriate interval with an effective dose. The clinician must also take into account

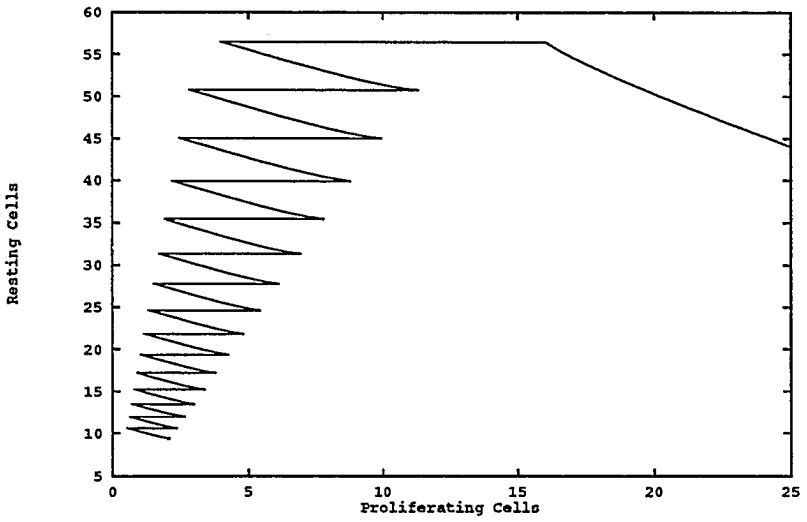

Figure 3.10: Beta=0.05, 15 doses

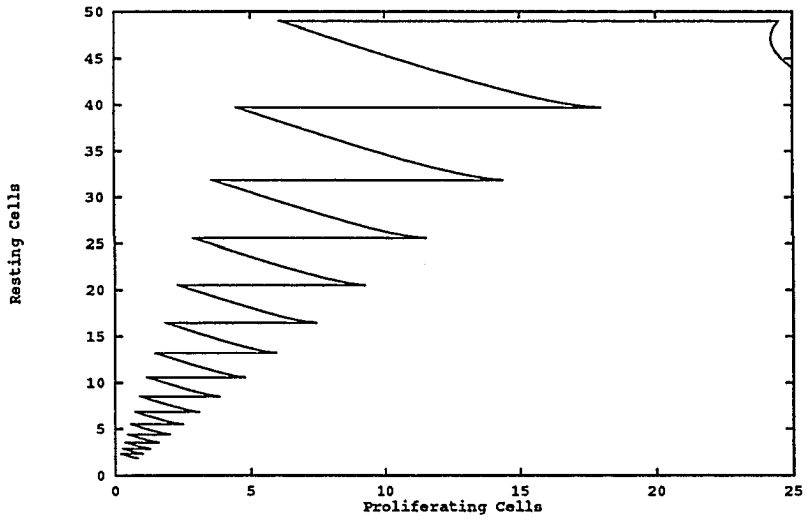

Figure 3.11: Beta=0.1, 15 doses

the effects of the drugs on the normal tissue. Otherwise, a given drug regimen might eliminate the tumor but also destroy the normal tissue, or even have no detrimental effect at all upon the tumor. Thus far, few of the mathematically constructed models have incorporated these features, and most drug protocols are developed empirically. It is our hope that this model gives some indication of how to better administer the drugs in order to more effectively destroy the cancerous cells.

The most basic question that can be asked about a chemotherapeutic regimen is, how much is enough and how much is **too** much? We have shown using the characteristic multipliers of the Poincaré maps that there is a bifurcation or boundary (in terms of survival fraction and period), separating regimens that will and will not eliminate the tumor mass. As noted earlier, this is only intended to be an essentially qualitative study, and quantitative details will of course vary from patient to patient. Clearly a bifurcation diagram is not sufficient to develop a good chemotherapeutic regimen because it includes modalities like continuously giving a very large dose of the drug. Obviously this will eliminate the tumor mass, **but** it will also kill the patient! Thus the use of the constraint equation that models the effects of the drugs on the normal tissues must be included.

However, with the constraint equation added, there is still a wide range of acceptable drug regimens. Thus we look for the optimal regimen. In doing this we have shown that the best drug protocol is <u>not</u> delivering the drug as often as possible and as strongly as possible, but rather there exists an optimal period and dose. Because of the constraint of normal tissue survival, this is not always possible with each dose (survival fraction). That is, for stronger doses, the period of delivery must

be broadened at non-optimal periods to prevent overly destroying the normal tissue, or a weaker dose must be administered.

Growth factors increasingly are being used to help cell-specific chemotherapeutic drugs work more effectively. This is one area where much medical research has been done, so in principle the medical results and the mathematical models can be closely compared to improve our understanding of how the various growth factors may affect the use of chemotherapeutic drugs on cancerous tissue. The pulsed model clearly shows that incorporating growth factors in AML increases the cell kill by 13%–14%, and reduces the number of doses needed to accomplish the same results, while in breast cancer growth factors allow larger doses of chemotherapy to be administered at optimal periods to obtain maximal cell kill. In this case the growth factors increased the cell kill to about 27% — a significant improvement.

One of the limitations of this model is it does not take into account varying parameters. For example, it is known that over time the chemotherapeutic doses have more effect on the the normal tissue and less effect on the tumor mass (resistance etc.); also the drugs reduce the carrying capacity of the normal tissue over time. Future work will include modifying some of these assumptions, thereby formulating a more comprehensive model. Even accepting the simplifications, this model illustrates some of the more important dynamics of chemotherapy. It identifies, for example, parameter regions of acceptable chemotherapeutic regimens, some of which reinforce regimens already developed empirically, and also it indicates the effects of the drugs on normal tissue and how this affects the chemotherapeutic process. The model also identifies how the use of growth factors increases the effectiveness of the drugs, again

reinforcing much of the clinical work done in the area of cancer chemotherapy.

Chapter 4

Non-Constant Parameters

4.1 Introduction

Though the models in the past two chapters reveal some interesting and useful insights into chemotherapy, many simplifying assumptions were made. In this chapter, by allowing various parameters to vary, we can remove some of those assumptions, thus creating, it is hoped, a more accurate model.

One of the most commonly known phenomena of tumor growth is the ability to manipulate the host environment. Without stressing the biological mechanics, let us try and gain some basic mathematical insights into the problem. Michelson and Leith discuss the need for non-constant parameters to accurately model the growth of the tumor. In their papers, [48, 49, 51], they state that parameters such as "K" (the carrying capacity) or "r" (the growth rate) should vary with respect to time due to various tumor effects such as the tumor bed effect (TBE) and growth factor signal processing. Also, Michelson and Leith [52] discuss how non-constant "K" and

"r" may be used to show the interplay between a liver tumor and the liver. In this case the parameters are functions of one or both of the cell masses.

A more realistic method (as opposed to pulsed therapy) to model the effects of a chemotherapeutic drug is to vary the growth rate of the cell population. This is done in a periodic fashion to represent periodic chemotherapy. The models developed give rise to systems of periodic differential equations and many of the existing methods of analyzing these solutions (such as Floquet theory and the averaging method) may be used here.

We will first investigate a homogeneous model, i.e. one that describes just one type of cell mass, using the logistic growth model. Once we have developed a good basis with the homogeneous logistic model, we can study the impact of piecewise-continuous periodic parameters on the heterogeneous cell-specific models. In this process we can develop a more sophisticated model and also discuss whether these modifications produce any new results or if they are qualitatively similar to the (mathematically simpler) model of pulsed therapy.

4.2 Non-Constant "K"

Because the tumor, through the use of growth factors etc., can manipulate its local environment, a constant carrying capacity, "K", can **not** accurately model growth of the tumor mass. To better model the growth of the tumor we allow "K" to be a non-constant function of the tumor mass. First investigate the Logistic equation:

$$\frac{dV}{dt} = rV\left(1 - \frac{V}{K(V)}\right). \tag{4.2.1}$$

The basic assumptions on $K(V)$ are:

1. $K(V)$ is monotone increasing

2. $K(V)$ is bounded by $0 < K_{min} \leq K(V) \leq K_{sat}$

3. $K(V) = V$ has a solution. This can be shown to be a consequence of (1.) and (2.).

First, note the existence of V^*, where V^* is a solution to $K(V) = V$. Because of the above conditions on $K(V)$, it can be shown that $K'(V) \to 0$ as $V \to \infty$. This is true because $K(V)$ is monotone increasing and bounded. Since $\frac{dV}{dV} = 1$ then $K(V)$ must cross V at least once because $K(V) > 0$.

Now, look at the stability of V^*. Linearize (4.2.1) about V^* to get:

$$V_l = -r(1 + K_V(V^*))V_l. \tag{4.2.2}$$

It can be seen that (4.2.2) is stable provided $K_V(V^*) > -1$. Since it is assumed that $K(V)$ is monotone increasing then this condition is always true.

Next, the steady state V^* is shown to be in the interval $0 < K_{min} \leq K^* \leq K_{sat}$. This can be shown by differential inequalities. Note that:

$$V' = rV\Big(1 - \frac{V}{K(V)}\Big) < rV\Big(1 - \frac{V}{K_{sat}}\Big) \tag{4.2.3}$$

$$V' = rV\Big(1 - \frac{V}{K(V)}\Big) \geq rV\Big(1 - \frac{V}{K_{min}}\Big) \tag{4.2.4}$$

therefore $K_{min} \leq V^* \leq K_{sat}$.

Similar results can be shown for the competition system of equations.

4.3 Piecewise Homogeneous Model

The logistic growth model has been used in many cases as a basic model of both cell growth and more particularly tumor cell growth (Eisen [23], Swan [63], Michelson *et al.* [53] and Michelson and Leith [48, 51]). There are various methods of modeling the effects of chemotherapy within the logistic model. One of the easiest is to assume that the drug kills cells instantly, thus giving a pulsing type action. This type of model is investigated by Berenbaum [7], and in chapters 2 and 3. A more realistic method of modeling chemotherapy is to assume that the chemotherapeutic effects are modeled by continuous or piecewise-continuous periodic functions which affect the growth rate (i.e. non-constant parameters) in the logistic growth model (Michelson and Leith [51]). These periodic functions alternate the growth rate between a negative rate when the drug is present and a positive rate during the recovery stage. This is the method investigated in the present chapter. Because of the availability of closed form solutions to the logistic equation, this chemotherapeutic problem can be handled with analytical methods. Numerical solutions to this model have been used in Panetta and Adam [57] to model the effects of the chemotherapy on bone marrow. A similar model is discussed by Hallam and Clark [36] which describes a deteriorating environment through the use of decreasing growth rates and carrying capacities, and by Coleman *et al.* [15] who investigate positive periodic growth rates and carrying capacities. The model in this chapter investigates periodic forms of the growth rate parameter by allowing this growth rate to be negative to more effectively model periodic chemotherapy.

4.3.1 The Model

The logistic growth model is modified to include a variable growth rate, thus mimicking the effects of chemotherapy. The general form is:

$$\frac{dy(t)}{dt} = ry(t)\left([1 - b(t)] - \frac{y(t)}{K}\right) \tag{4.3.5}$$

where $y(t)$ is the cell mass, r is the growth rate, K is the carrying capacity, and $b(t)$ is a periodic function representing the chemotherapeutic effects on the cell mass. If $b(t) \equiv 0$ then there are no chemotherapeutic effects and the equilibrium is K, while if $b(t) \equiv b < 1$ then the equilibrium is $(1 - b)K$. Conversely if $b(t) \equiv b \geq 1$ then the equilibrium is 0. If the term $[1 - b(t)]$ is positive for all t then there is tumor growth with a reduced growth rate and there will be an equilibrium between zero and K. Conversely, if $[1 - b(t)]$ is negative for some range of t then there are regions of negative growth or cell kill, and thus the possibility for a zero equilibrium. The object of this model is to determine conditions on $b(t)$ such that the equilibrium of equation (4.3.5) is zero. To reduce the problem to a simpler form, we scale equation (4.3.5) by writing $y(t) = Kx(t)$. The resulting equation is:

$$\frac{dx(t)}{dt} = rx(t)([1 - b(t)] - x(t)). \tag{4.3.6}$$

The function $b(t)$ can take on various periodic forms (with period τ), including the step type function of the form:

$$b(t) = \begin{cases} b, & n\tau \leq t < a + n\tau \\ 0, & a + n\tau \leq t < (n+1)\tau \end{cases}, \tag{4.3.7}$$

the exponentially decaying piecewise periodic function:

$$b(t) = be^{a(t-n\tau)}, \quad n\tau \leq t < (n+1)\tau, \tag{4.3.8}$$

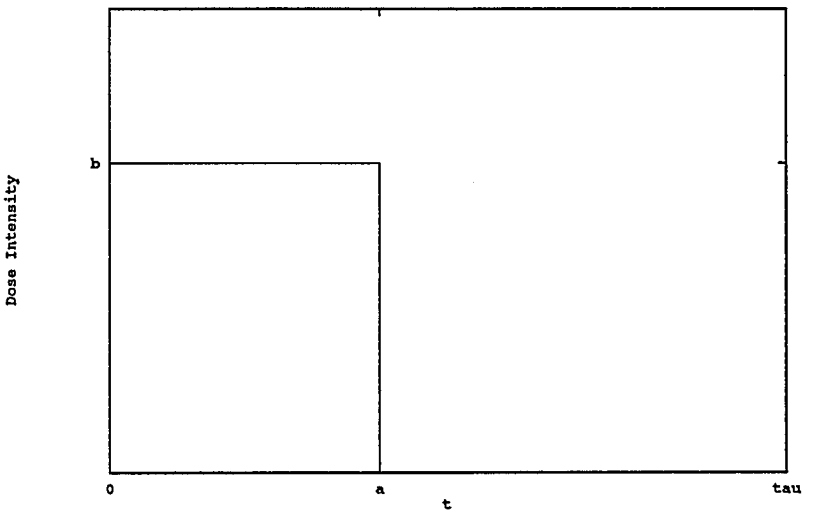

Figure 4.1: Step Function

or the modified exponentially decaying piecewise periodic function:

$$b(t) = b\left(e^{a(t-n\tau)} - e^{c(t-n\tau)}\right), \quad n\tau \leq t < (n+1)\tau. \tag{4.3.9}$$

See figures (4.1, 4.2, 4.3).

4.3.2 Solutions

There are various methods of solving equation (4.3.6) for specific cases of $b(t)$, but in general the equation is of Bernoulli type and can be solved exactly. The solution is:

$$x(t) = \frac{x_0 e^{r\int^t (1-b(s))ds}}{1 + \frac{x_0}{r}\int^t e^{r\int^s (1-b(\xi))d\xi}ds} \tag{4.3.10}$$

Using this solution and the fact that $b(t)$ is periodic, we can set up a difference equation (sometimes referred to as a first return map or Poincaré map), that describes the state of the cells at the beginning of each period. Equation (4.3.10) describes

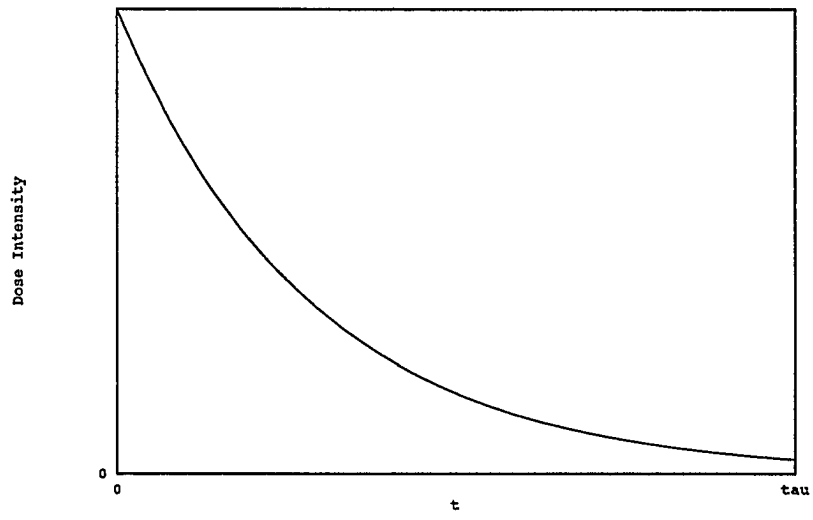

Figure 4.2: Exponential Function

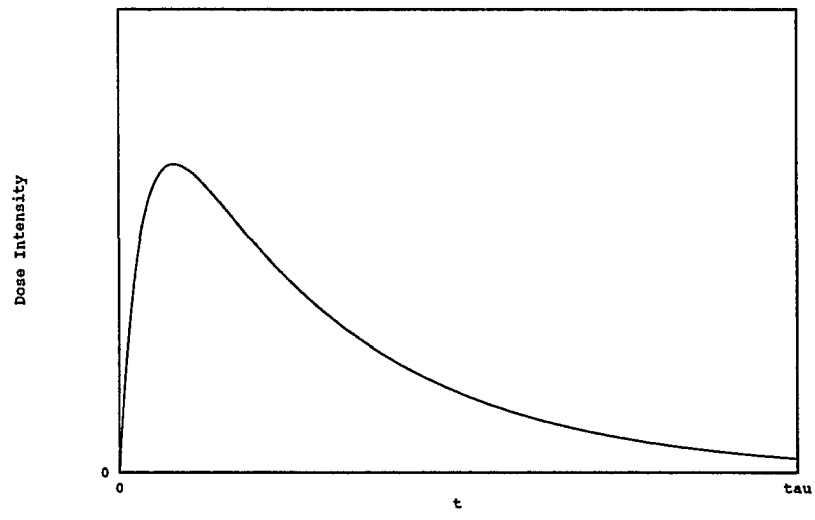

Figure 4.3: Modified Exponential Function

the growth of the tissue over each period, where x_0 is the cell mass at the beginning of the period. The resulting difference equation is:

$$x_{(n+1)\tau} = \frac{x_{n\tau} e^{r\int_{n\tau}^{(n+1)\tau}(1-b(s))ds}}{1+\frac{x_{n\tau}}{r}\int_{n\tau}^{(n+1)\tau} e^{r\int^{s}(1-b(\xi))d\xi}ds}. \tag{4.3.11}$$

Of interest is the stable equilibrium of this difference equation. Solving the equation for x_{eq} we find

$$x_{eq} = \frac{x_{eq} e^{r\int_{n\tau}^{(n+1)\tau}(1-b(s))ds}}{1+\frac{x_{eq}}{r}\int_{n\tau}^{(n+1)\tau} e^{r\int^{s}(1-b(\xi))d\xi}ds}, \tag{4.3.12}$$

and hence we can determine the equilibria. They are:

$$x_{eq} = 0 \tag{4.3.13}$$

$$x_{eq} = \frac{r\left(e^{r\int_{n\tau}^{(n+1)\tau}(1-b(s))ds}-1\right)}{\int_{n\tau}^{(n+1)\tau} e^{r\int^{s}(1-b(\xi))d\xi}ds}. \tag{4.3.14}$$

Next, we define:

$$\langle b(t)\rangle \equiv \frac{1}{\tau}\int_0^{\tau} b(t)dt. \tag{4.3.15}$$

as the mean value of $b(t)$. Equation (4.3.14) is equal to zero for $\langle b(t)\rangle = 1$, which is the bifurcation from a positive stable equilibrium to a zero stable equilibrium. That is, for $0 \leq \langle b(t)\rangle \leq 1$ equilibrium (4.3.14) is stable and equilibrium (4.3.13) is unstable. For $\langle b(t)\rangle > 1$ the stability switches and equilibrium (4.3.13) becomes stable while equilibrium (4.3.14) switches to unstable. Therefore the cells have a zero equilibrium when

$$\langle b(t)\rangle > 1. \tag{4.3.16}$$

4.3.3 Step Function

We can examine the special case of the step function form of $b(t)$ (equation (4.3.7)) directly by examining the solution over each piece of the period τ. First we find the

solution in the region $n\tau \leq t < a + n\tau$, and then match it to the solution in region $a + n\tau \leq t < (n+1)\tau$. Thus we obtain:

$$x(t) = \begin{cases} \dfrac{(1-b)x_{n\tau}}{x_{n\tau} + [(1-b) - x_{n\tau}]e^{-(1-b)r(t-n\tau)}} & n\tau \leq t < a + n\tau \\ \dfrac{x_{(a+n\tau)}}{x_{(a+n\tau)} + [1 - x_{(a+n\tau)}]e^{-r(t-(a+n\tau))}} & a + n\tau \leq t < (n+1)\tau \end{cases} . \quad (4.3.17)$$

Matching the two solutions at $a + n\tau$ we find:

$$x_{(a+n\tau)} = \frac{(1-b)x_{n\tau}}{x_{n\tau} + [(1-b) - x_{n\tau}]e^{-(1-b)ar}} \quad (4.3.18)$$

From this solution a difference equation can be found that relates the size of $x(t)$ at the beginning of one period ($x_{n\tau}$) to that of the next period ($x_{(n+1)\tau}$). The Poincaré map for equations (4.3.17) is:

$$x_{(n+1)\tau} = \frac{1}{1 + \left[\dfrac{x_{n\tau} + [(1-b) - x_{n\tau}]e^{-(1-b)ar}}{(1-b)x_{n\tau}} - 1\right] e^{-r(\tau-a)}}. \quad (4.3.19)$$

The equilibria for this difference equation are:

$$x_{eq} = 0 \quad (4.3.20)$$

$$x_{eq} = \frac{1 - e^{r(ab-\tau)}}{1 - \frac{1}{1-b}(e^{-ar(1-b)} - b)e^{-r(\tau-a)}} \quad (4.3.21)$$

This is just a special case of equations (4.3.13) and (4.3.14) where the bifurcation from equilibrium (4.3.21) being stable to equilibrium (4.3.20) being stable is $ab = \tau$. (Note that this is the same result as $\langle b(t) \rangle = 1$.) Figure (4.4) shows the bifurcation diagram distinguishing between the stable and unstable equilibria.

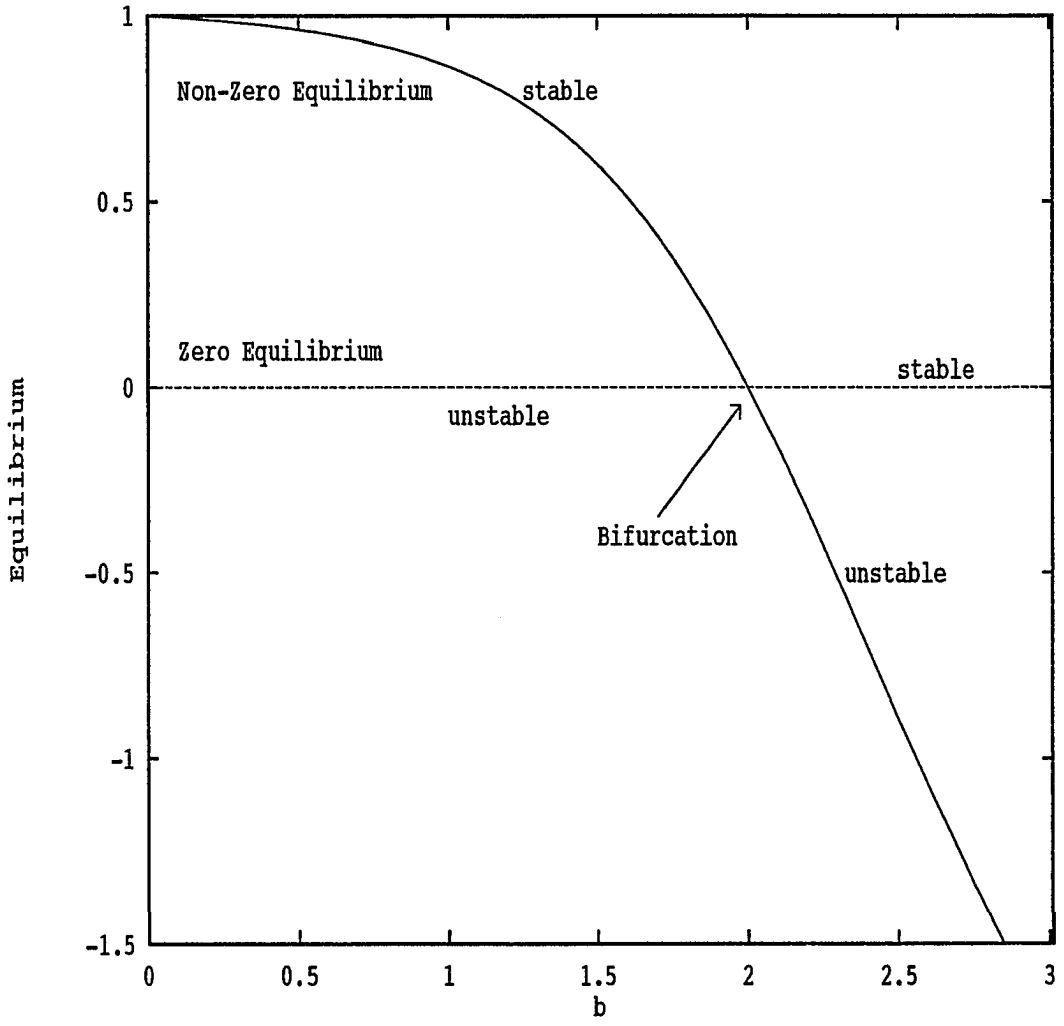

Figure 4.4: Bifurcation Diagram, $a = 3$, $\tau = 6$, $r = 1$

4.4 Piecewise Cell-Specific Model

For the piecewise continuous cell-specific case, model (3.2.2) will be modified as:

$$\frac{d\vec{x}}{dt} = \begin{pmatrix} -a & \beta \\ \mu & -\beta \end{pmatrix} \vec{x} - \begin{pmatrix} g(t) & 0 \\ 0 & 0 \end{pmatrix} \vec{x}. \tag{4.4.22}$$

The function $g(t)$ is a piecewise continuous function describing the chemotherapeutic effects on the tumor. Webb studies a similar model in his study [66], where he uses a step function to model the chemotherapeutic effects. We will investigate the model using the exponential decay function, (figure (4.2)):

$$g(t) = he^{-\gamma(t-n\tau)}, \ n\tau \leq t < (n+1)\tau, \tag{4.4.23}$$

where h is the cell kill parameter and γ is the decay of the drug. However as seen in Webb [67, 66] and in the previous sections, $g(t)$ may take on many other forms as considered appropriate. In this section, we will compare the results of this more realistic model of chemotherapy with the more mathematically tractable pulsed-therapy model.

4.4.1 Normal Tissue

For the piecewise case the limited growth equation for normal tissue is:

$$\dot{y} = \delta(K - y) - he^{-\gamma(t-n\tau)}, \ n\tau \leq t < (n+1)\tau. \tag{4.4.24}$$

Finally, the logistic form for the piecewise case is:

$$\dot{y} = \delta y(1 - \frac{y}{K}) - he^{-\gamma(t-n\tau)}y, \ n\tau \leq t < (n+1)\tau. \tag{4.4.25}$$

See section §4.3. In equations (4.4.24, 4.4.25) δ is the growth rate of the normal tissue and K is the carrying capacity.

4.4.2 Confluent Hypergeometric Solutions

The model that we investigate is based on equations (4.4.22, 4.4.23) and the normal tissue condition (4.4.25). Analytic solutions to the tumor equation can be found in terms of confluent hypergeometric functions. In particular, we are interested in comparing the results of the pulsed therapy with those of the piecewise therapy. This will help us understand, in a qualitative sense, if and when the more sophisticated model will be needed. Note that the parameter γ in the piecewise case describes the decay rate of the chemotherapeutic drug. A large value of γ (for fixed h) therefore, corresponds to the effects of the drug decaying away quickly. This is qualitatively equivalent to a high survival fraction, $f(D)$, in the pulsed case.

Analytic Solutions

Reformulating the system of differential equations (4.4.22, 4.4.23) as a Schrödinger equation in time, i.e.

$$\frac{d^2y}{dt^2} + \left(\tilde{\lambda} - V(t)\right) y = 0 \tag{4.4.26}$$

we may investigate analytic solutions to the piecewise chemotherapeutic case. With the choice of an exponentially decaying function representing the effects of chemotherapy on proliferating tumor cells (see figure (4.2)), the potential function $V(t)$ in equation 4.4.26 is a Morse-type potential, well-known in the quantum mechanical

literature (see Flügge [26]); and the solutions are obtainable in terms of confluent hypergeometric functions or the related Whittaker functions). Because the chemotherapy is administered periodically, the potential $V(t)$ is periodic also. Therefore, using existing Floquet theory as applied to scattering by periodic potentials in the quantum theory of solids, we find corresponding results in our chemotherapeutic case. More specifically, corresponding to the existence of "forbidden energy bands" in quantum theory, it appears that there are "forbidden" or inappropriate chemotherapeutic regimens also, in the sense that for some combinations of period, dosage, and cell parameters, no real solutions exist for the system of equations describing the time evolutions of cancer cells in each compartment. The mathematical details of these analytic ideas are contained in Adam and Panetta [2] and here we will concentrate on the numerical results of the next section.

Numerical Results

Using the same parameter values as in the pulsed case with the new parameter $h = 0.5$ for both the normal and tumor equations, we compare the bifurcation diagrams of the two cases. Note the similarities between figures (4.5) and (3.4). Both show similar regions in parameter space for acceptable period and strength. The main difference between the two is that in the pulsed case (which models instant removal of cells) there is a much more dramatic change in the normal cell bifurcation curve then in the piecewise case. This is because in the piecewise case the drugs destroy cells over the complete period, thus there is not an instantaneous drop in normal cell mass. Thus in the piecewise case we are not concerned about the cell

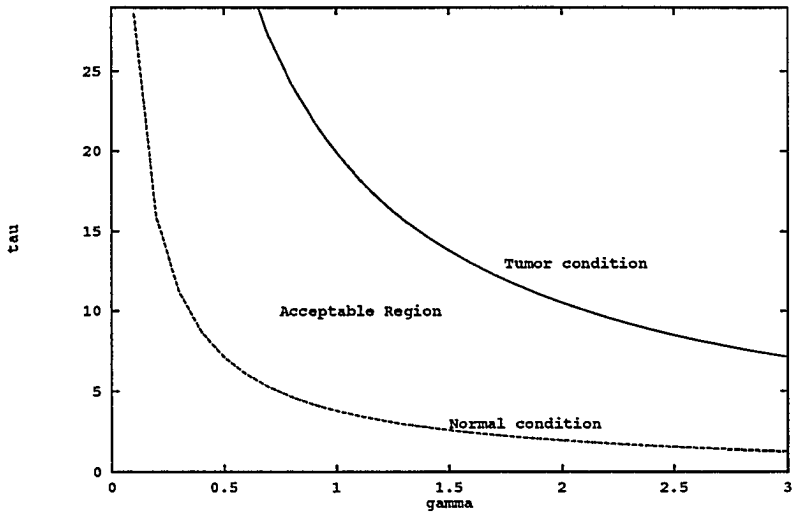

Figure 4.5: Bifurcation Curves

mass instantly dropping below its critical value; consequently this model allows for larger drug doses to be administered. Note next the similarities between figures (4.6) and (3.5). It should be recalled that the minimum eigenvalue means highest tumor reduction in figure (3.5). These two graphs compare very well, both showing that the optimal period is one that allows some time between doses. Finally, figure (4.7) shows the optimal period curve along with the bifurcation curves of both normal and cancerous tissue. A significant point to be made here is that the optimal period curve is completely in the acceptable region unlike the pulsed case. Therefore if we are to compare the optimal period in the piecewise case to the regimen stated by Birkhead *et al.* ("the maximally-tolerated dose is given as frequently as the rate of bone marrow recovery permits"), we may note that they are basically equivalent. Thus, if the clinician administers a strong dose (i.e. γ small), then the optimal period, and the smallest period that allows bone marrow recovery, are almost identical.

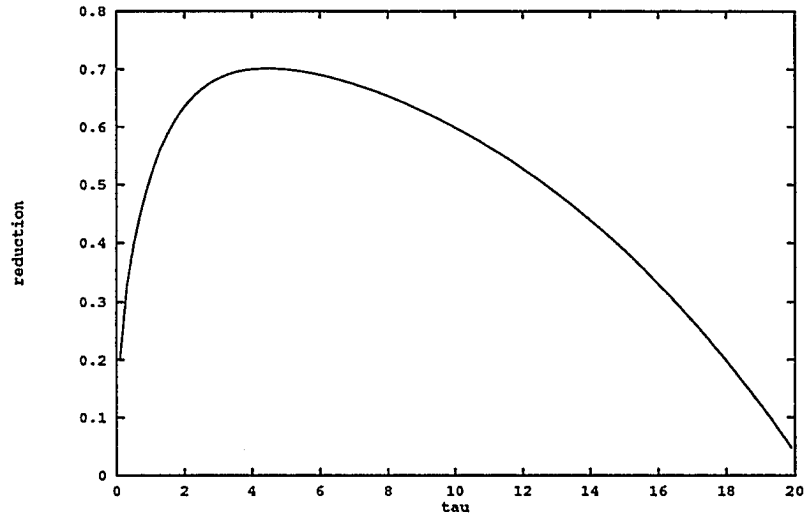

Figure 4.6: Tumor Reduction

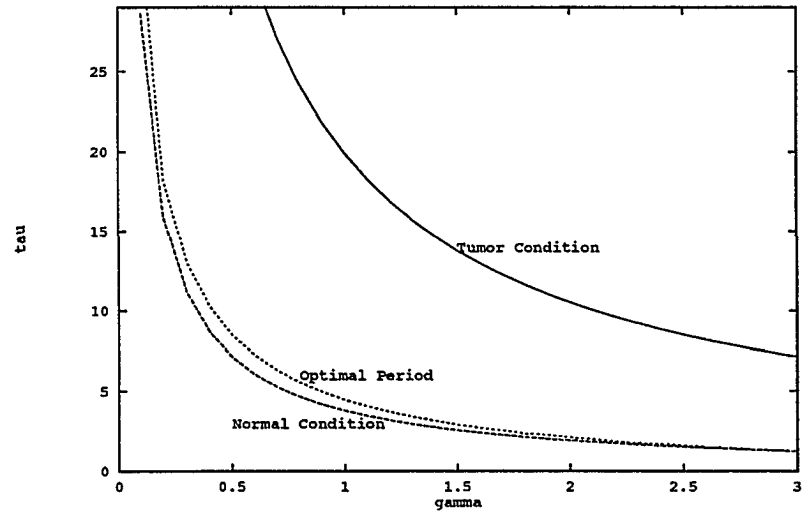

Figure 4.7: Bifurcation Curves with Optimal Period Curve

4.5 Discussion

Some variations can be made to this model to model chemotherapy even more effectively. A few possibilities include varying the carrying capacity K (either increasing or decreasing it) to model either the tumor bed effect (see Michelson and Leith [48, 49]) or allow a decaying carrying capacity due to cytotoxic build-up (see Hallam and Clark [36]). A further possibility is to allow cytotoxic effects to decay over each successive period. This can arise as a result of drug resistance because the drugs have less affect on the cells over time.

This model gives a concise and general form for the bifurcation between reduced steady state cell survival and cell destruction. It can be the basis for studying the chemotherapeutic effects on both cancerous cell tissue and normal cell tissue such as bone marrow. If it is used with cancerous tissue, then condition (4.3.16) describes the type of regimen needed to destroy the cancer cells. If it is used to model the chemotherapeutic effects on bone marrow, we might instead look for the point where the equilibrium is about half the carrying capacity since this is the limit of acceptable bone marrow destruction.

The piecewise model of chemotherapy is the more realistic of the two studied in this dissertation, but mathematically it is much more difficult to investigate. As noted above, it can be solved analytically, but this is mathematically very intensive especially when compared to the pulsed therapy case. By comparing the various bifurcation diagrams and optimal period diagrams, we can observe that the results obtained numerically from the piecewise model are qualitatively very similar to those

obtained from the pulsed case. Only a few differences are noted. Because of this, very similar **qualitative** results may be drawn from either model. Therefore in many situations it would be wise to choose the mathematically more appropriate model — the pulsed therapy model. However, if circumstances permit and a more realistic approach to the chemotherapeutic effects is desired, the piecewise model is the better choice.

Chapter 5

Tumor Resistance

5.1 Introduction

Resistance to cytotoxic drugs is a major cause for failure of chemotherapy (Goldie and Coldman [29, 30] and Michelson and Leith [50]). Thus, for a more realistic approach, the chemotherapeutic models should also incorporate the effects of resistance. Two major types of drug resistance to consider (though there are others) are: inherent and acquired. Inherent resistance refers to tumor cells that are resistant from the beginning of chemotherapy. Conversely, tumor cells which are initially susceptible to the drug, but develop resistance over time, are considered to have acquired resistance. (We will only work with acquired resistance effects here).

The first model we investigate is an extension of the tumor-normal cell interaction model in chapter 2. Instead of just having a tumor and normal cell compartment, we add a resistant compartment. We continue to use pulsed therapy in this case and define new parameter ranges of acceptable treatment.

A second approach used here to model drug resistance is by means of a decaying periodic chemotherapeutic term added to the logistic growth model (i.e. the non-constant parameter approach as opposed to the pulsed therapy). Thus, over each period the drugs will have less and less of an effect on the cancer tissue. As can be clearly seen, unless the drug regimen can destroy every cancer cell after a finite number of doses (which is not possible in these models given the nature of the differential equations being studied), no single drug will be able to control the growth of the cancer tissue. Consequently we are more interested in finding the appropriate number of doses while still reducing the size of the cancer cell mass (this is known as the *nadir*). Knowing the *nadir* can help in ascertaining when to switch to a different drug and how to better design drug regimens.

Finally, we model resistance with a heterogeneous two compartment model; one for sensitive cells, the other for resistant cells. Various forms for this model have been studied. Birkhead *et al.* [12] discuss a linear system of equations modeling sensitive and resistant cycling and quiescent cells. They carry out numerical experiments with various drug-delivery methods where the drugs are assumed to be effective instantly. Gyori *et al.* [34] investigate a non-linear two-compartment model where sensitive cells mutate to resistant cells, both as a result of the cytotoxic drugs and by spontaneous mutation. They study analytically the effects of one drug dose on the system and study numerically the full system. Panetta [56] studied a model similar to that of Gyori *et al.* but the chemotherapeutic effects are modeled by periodic instantaneous cell kill or pulsing. In this chapter we derive a model similar to these and include piecewise-continuous and continuous instantaneous chemotherapeutic

effects. Analytic results describing the bifurcation between tumor growth and decay are developed.

The models in these sections are compared to some clinical results on chemotherapy given by Skipper [60].

5.2 Pulsed Models

If a resistant subpopulation occurs (i.e. 100% resistant), then the tumor can never be killed off unless the drugs are altered to have an effect on the most resistant population. This will entail the use of non-cross-resistant drugs. Models that assume 100% resistant cells are discussed by Goldie and Coldman [29]. They show, by stochastic methods, that as the tumor burden is increased there is a higher probability of the tumor becoming resistant, and that there is a small critical time interval in which the probability of the tumor developing resistance goes from low to high.

Resistance may arise in various ways. One such way concerns resistance that is **not** induced by the applied drugs. Since tumor heterogeneity is common (see Michelson *et al.* [50]), this is a very common situation. This will be modeled by a continuous flow of cells, independent of the chemotherapy, from sensitive to resistant compartments. The other type of resistance is induced by the drugs; that is, as the drugs are administered, some sensitive cells become resistant. This could be caused for example by genetic mutations. This will be modeled by a discrete flow of cells, dependent on the chemotherapy, from sensitive to resistant.

5.2.1 Acquired Resistance: Cell Mutations

Martin *et al.* [44] state that some types of drug resistant cells arise at a constant rate and are **not** induced by the chemotherapeutic drugs. This gives way to heterogeneous tumors. Michelson *et al.* [46, 53] have developed heterogeneous tumor models without normal cell interaction or chemotherapy, and Gyori *et al.* [34], using the model developed by Michelson *et al.*, add the effects of a time-dependent cytotoxic agent. These models can be a modified in the following way to account for normal cell interaction and periodically-pulsed therapy: thus we write

$$\frac{dX}{dt} = r_1 X(1 - X/K_1 - \lambda_1(Y_1 + Y_2)) \tag{5.2.1}$$

$$\frac{dY_1}{dt} = r_2 Y_1(1 - (Y_1 + Y_2)/K_2 - \lambda_2(X + Y_2)) - mY_1 \tag{5.2.2}$$

$$\frac{dY_2}{dt} = r_3 Y_2(1 - (Y_1 + Y_2)/K_2 - \lambda_3(X + Y_1)) + mY_1 \tag{5.2.3}$$

$$X(n\tau^+) = F(D)X(n\tau^-) \tag{5.2.4}$$

$$Y_1(n\tau^+) = \overline{F}(D)Y_1(n\tau^-) \tag{5.2.5}$$

$$Y_2(n\tau^+) = \widetilde{F}(D)Y_2(n\tau^-) \tag{5.2.6}$$

where X is the normal cell biomass, Y_1 is the sensitive tumor cell biomass, Y_2 is the resistant tumor cell biomass, and m is the resistance parameter. Usually m is very small since cancer cells mutate at a rate of about 1 in every 10^6 cells (see Michelson *et al.* [46]). Note that λ_1 could be zero in the non-interactive case, but for the sake of generalization, we will keep it in.

We assume that two drugs are administered, both affecting the sensitive cells with survival fraction $\overline{F}(D)$, the resistant cells with survival fraction $\widetilde{F}(D)$ and the normal cells with survival fraction $F(D)$. This leads to the reasonable assumption

$\overline{F}(D) < \tilde{F}(D)$, i.e. the drugs will have a stronger effect on the sensitive tumor cells than the resistant tumor cells.

5.2.2 No Therapy Case

Let us first investigate the case with no chemotherapy. Michelson *et al.* [50] note that for this model, in the constant coefficient case, there is **no** equilibrium where the resistant cells, Y_2, are excluded and sensitive cells, Y_1, survive. But, with the proper choice of parameters, the coexistent equilibrium can be driven as close to the $Y_2 = 0$ case as possible. They note that in this limit, the deterministic model can break down (i.e. the model does not take into account small random fluctuations that can have a large affect on a small cell population).

As before, the stability of the tumor free case, $(K_1, 0, 0)$, is investigated and parameter ranges for tumor growth are given. Linearizing equations (5.2.1–5.2.3) about $X = K_1 + \epsilon u$, $Y_1 = 0 + \epsilon v$, and $Y_2 = 0 + \epsilon w$ we obtain:

$$\begin{pmatrix} u' \\ v' \\ w' \end{pmatrix} = \begin{pmatrix} -r_1 & -r_1\lambda_1 K_1 & -r_1\lambda_1 K_1 \\ 0 & r_2(1-\lambda_2 K_1) - m & 0 \\ 0 & m & r_3(1-\lambda_3 K_1) \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix}. \tag{5.2.7}$$

We investigate the stability by looking at the eigenvalues. In particular, we are interested in the second two equations of the system. Since they decouple from the first equation, we may focus on them alone. The condition on sensitive cell recurrence is $\lambda_2 K_1 < 1 - m/r_2$. This condition is more restrictive than that of the zero resistance case because of the presence of the m/r_2 term. As m increases it is harder for the sensitive cells to recur, and as r_2 increases the sensitive cells can grow

faster, thus making it easier for them to recur. Also, if $m > r_2$ then the sensitive cells can **not** recur, although, typically $m << r_2$. The condition on resistance cell recurrence is $\lambda_3 K_1 < 1$, although, if the sensitive cells recur, then the resistant cells **must** recur (see Michelson *et al.* [53]) even if $\lambda_3 K_1 > 1$. This can be seen by looking at the third equation ($w' = mv + r_3(1 - \lambda_3 K_1)w$). Since v is increasing then so must w. But if $\lambda_3 K_1 < 1$ and $\lambda_2 K_1 > 1 - m/r_2$ then the resistant cells will recur without the sensitive cells.

5.2.3 Resistant Recurrence

As before, we investigate the effect a small tumor burden has on the tumor free periodic solution given in § 2.3. Thus the system is linearized about $(X_s(t), 0, 0)$ and the stability of the sensitive and resistant subpopulations is investigated. In the same manner as before, we investigate the linear system

$$\begin{pmatrix} u' \\ v' \\ w' \end{pmatrix} = \begin{pmatrix} r_1(1 - 2\frac{X_s(t)}{K_1}) & -r_1\lambda_1 X_s(t) & -r_1\lambda_1 X_s(t) \\ 0 & r_2(1 - \lambda_2 X_s(t)) - m & 0 \\ 0 & m & r_3(1 - \lambda_3 X_s(t)) \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix}, \tag{5.2.8}$$

where $X = X_s(t) + \epsilon u$, $Y_1 = 0 + \epsilon v$, and $Y_2 = 0 + \epsilon w$. In this case the second two equations decouple and the second can be solved by integrating $v' = (r_2(1 - \lambda_2 X_s(t)) -$

$m)v$ over $n\tau < t < (n+1)\tau$. This gives:

$$v_{(n+1)\tau} = v_{n\tau}\left\{\frac{\overline{F}(D)e^{(r_2-m)\tau}}{F(D)^{\frac{r_2\lambda_2K_1}{r_1}}e^{r_2\lambda_2K_1\tau}}\right\}, \tag{5.2.9}$$

The condition to **prevent** sensitive cell recurrence is:

$$\overline{F}(D) < F(D)^{\frac{(r_2-m)\lambda_2K_1}{r_1}}e^{-\tau r_2(1-\lambda_2K_1)} \tag{5.2.10}$$

(i.e. the survival fraction for the sensitive tumor mass is less than the survival fraction for the normal tissue.) Note that we assume $r_2 >> m$ and $\lambda_2K_1 < 1$ (see the previous section). Since m is very small, it has very little effect on the outcome. Thus, this condition is almost identical to equation (2.4.18).

As in the zero-drug case, resistant cells must recur if sensitive cells do, and there can be resistant cell survival even if the sensitive cells do not recur. To find the condition for this, we must integrate $w' = r_3(1-\lambda_3X_s(t))w$ over the interval $n\tau < t < (n+1)\tau$ yielding:

$$w_{(n+1)\tau} = w_{n\tau}\left\{\frac{\tilde{F}(D)e^{r_3\tau}}{F(D)^{\frac{r_3\lambda_3K_1}{r_1}}e^{r_3\lambda_3K_1\tau}}\right\}. \tag{5.2.11}$$

Thus the condition to **prevent** resistance recurrence is:

$$\tilde{F}(D) < F(D)^{\frac{r_3\lambda_3K_1}{r_1}}e^{-\tau r_3(1-\lambda_3K_1)}. \tag{5.2.12}$$

It is important to note that if the resistant subpopulation goes undetected, and drugs are administered which kill only the sensitive cells then, $\tilde{F}(D) = 1$. In this case the resistant subpopulation will recur unless it is competitively excluded ($K_1\lambda_3 > 1$) since the right-hand side of equation (5.2.12) is less than one.

As before, the dose-response is chosen to be $F(D) = e^{-\alpha_1D}$, $\overline{F}(D) = e^{-\alpha_2D}$, and $\tilde{F}(D) = e^{-\alpha_3D}$ respectively. Then the conditions to **prevent** both sensitive and

resistant tumor recurrence while keeping the normal cells above the specified level $0 < a < 1$ are:

$$D > \frac{\tau r_2(1-\lambda_2 K_1)}{\alpha_2 - \alpha_1\lambda_2 K_1(r_2-m)/r_1} \tag{5.2.13}$$

$$D > \frac{\tau r_3(1-\lambda_3 K_1)}{\alpha_3 - \alpha_1\lambda_3 K_1 r_3/r_1} \tag{5.2.14}$$

$$D < \frac{-1}{\alpha_1}\ln\left(a + e^{-r_1\tau}(1-a)\right) \tag{5.2.15}$$

For there to be a region of resistant recurrence without sensitive recurrence the graph of (5.2.13) (the equality) must be below that of (5.2.14), or the slope of (5.2.14) with respect to τ must be greater than that of (5.2.13). In general, this will depend on the growth rates and competition parameters of the two populations along with the dose response parameters (α_i). In the special case where $r_2 = r_3$ and $\lambda_2 = \lambda_3$ (a biologically reasonable one) the condition is $\alpha_3 - \alpha_2 < \alpha_1\lambda_2 K_1 m/r_1$. If $\alpha_3 > \alpha_2$ ($\overline{F}(D) > \tilde{F}(D)$,which is unrealistic) then, since m is very small, there will only be a very small region where resistant cells can recur without sensitive cells. If $\alpha_3 < \alpha_2$ ($\overline{F}(D) < \tilde{F}(D)$, typically true) then there will **always** be a region of resistant recurrence without sensitive recurrence. Replacing α_2, r_2, λ_2 with α_3, r_3, λ_3 in equation (2.4.21), we can see

$$\alpha_3 > \frac{\alpha_1 r_3(1-a\lambda_3 K_1)}{r_1(1-a)} \tag{5.2.16}$$

is the minimum condition needed for the treatment to be able to prevent resistant tumor recurrence.

Figure 5.1 gives an example of two regions of dose vs. period. One occurs where the tumor cannot recur and the other where only resistant tumor cells can

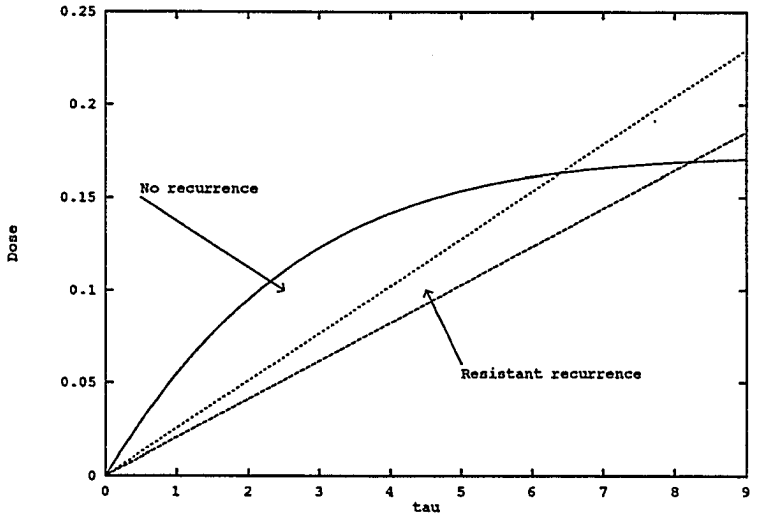

Figure 5.1: Dose-Response Curves: Dose vs. Period

do so. The upper line refers to equation (5.2.14) (the equality); the lower line refers to equation (5.2.13), and the curve is equation (5.2.15). From this graph we can see how the two regions are close together, thus showing how sensitive the results are to small changes in dose or period. Additionally, if the resistant population is undetected, then we can easily choose a dose and period to eliminate the tumor which actually falls in the range of resistant recurrence. Thus the tumor can recur even though it appears that we are administering an acceptable dose regimen.

5.2.4 Induced Resistance

Birkhead and Gregory [9] and Martin *et al.* [44] note that tumor cells can mutate or transition to resistant subpopulations as a result of exposure to chemotherapeutic drugs. With regard to this, a variation can be made to the above model to model

induced resistance:

$$\frac{dX}{dt} = r_1 X(1 - X/K_1 - \lambda_1(Y_1 + Y_2)) \tag{5.2.17}$$

$$\frac{dY_1}{dt} = r_2 Y_1(1 - (Y_1 + Y_2)/K_2 - \lambda_2(X + Y_2)) \tag{5.2.18}$$

$$\frac{dY_2}{dt} = r_3 Y_2(1 - (Y_1 + Y_2)/K_2 - \lambda_3(X + Y_1)) \tag{5.2.19}$$

$$X(n\tau^+) = F(D)X(n\tau^-) \tag{5.2.20}$$

$$Y_1(n\tau^+) = (\overline{F}(D) - R(D))Y_1(n\tau^-) \tag{5.2.21}$$

$$Y_2(n\tau^+) = \tilde{F}(D)Y_2(n\tau^-) + R(D)Y_1(n\tau^-) \tag{5.2.22}$$

where in equations (5.2.21, 5.2.22) $R(D)$ is the fraction of cells becoming resistant or induced due to the dose of the drug. Note that $R(D)$ can be a function of drug dose and in some cases could be as large as 0.5 (i.e. 50% of the surviving cells become resistant).

Normal Growth

As in §2.3, we are interested in the stability of the tumor free case, $(K_1, 0, 0)$. Linearizing (5.2.17, 5.2.18, 5.2.19) about the tumor free state ($X = K_1 + \epsilon u$, $Y_1 = 0 + \epsilon v$, and $Y_2 = 0 + \epsilon w$) we obtain:

$$\begin{pmatrix} u' \\ v' \\ w' \end{pmatrix} = \begin{pmatrix} -r_1 & -\lambda_1 r_1 K_1 & -\lambda_1 r_1 K_1 \\ 0 & r_2(1 - \lambda_2 K_1) & 0 \\ 0 & 0 & r_3(1 - \lambda_3 K_1) \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix}. \tag{5.2.23}$$

Note that this has similar conditions for recurrence as equation (2.3.5). That is, the sensitive cells will recur if $\lambda_2 K_1 < 1$ and the resistant cells will recur if $\lambda_3 K_1 < 1$. For this problem however, unlike the previous case, we can have sensitive cell recurrence

without resistant recurrence and the recurrence of one does not affect the other. It merely depends upon the competition coefficient λ_i. Thus prior to therapy, sensitive cell recurrence has no effect on the recurrence of resistant cells.

Induced Resistance with Chemotherapy

Continuing with the same approach as before we linearize the system about the tumor free periodic solution $(X_s(t), 0, 0)$. In this case we will solve the two decoupled equations, $v' = r_2(1 - \lambda_2 X_s(t))v$ and $w' = r_3(1 - \lambda_3 X_s(t))w$, by integrating over the period and applying the pulsing conditions (5.2.21) and (5.2.22). This gives us the system of difference equations:

$$v_{(n+1)\tau} = v_{n\tau}\left\{\frac{(\overline{F}(D) - R(D))e^{r_2\tau}}{F(D)^{\frac{r_2\lambda_2 K_1}{r_1}} e^{r_2\lambda_2 K_1\tau}}\right\} \tag{5.2.24}$$

$$w_{(n+1)\tau} = v_{n\tau}\left\{\frac{R(D)e^{r_2\tau}}{F(D)^{\frac{r_2\lambda_2 K_1}{r_1}} e^{r_2\lambda_2 K_1\tau}}\right\} + w_{n\tau}\left\{\frac{\tilde{F}(D)e^{r_3\tau}}{F(D)^{\frac{r_3\lambda_3 K_1}{r_1}} e^{r_3\lambda_3 K_1\tau}}\right\} \tag{5.2.25}$$

Now we examine the stability of this system. Note that the sensitive tumor cells **cannot** recur if:

$$\overline{F}(D) < F(D)^{\frac{r_2\lambda_2 K_1}{r_1}} e^{-\tau r_2(1-\lambda_2 K_1)} + R(D). \tag{5.2.26}$$

Note also that $R(D)$ increases the size of the right-hand side, thus making it easier to prevent sensitive cell recurrence. Depending on the size of $R(D)$, it will have varying affects on the outcome. Larger $R(D)$ (near 0.5) will make it vary easy to prevent sensitive cell recurrence while smaller $R(D)$ will have a minimal affect. Secondly, if the sensitive cells recur then the resistant cells will also recur because the second term on the right-hand side of equation (5.2.25) will grow in spite of the first term. Thus resistant tumor population recurrence does not depend on competitive pressure

if there is sensitive recurrence and continued dosing. But, sensitive cells recurring without continued dosing does not imply resistant recurrence. Finally the resistant tumor cells can recur even if the sensitive cells do not, provided that:

$$\widetilde{F}(D) > F(D)^{\frac{r_3\lambda_3 K_1}{r_1}} e^{-\tau r_3(1-\lambda_3 K_1)}. \tag{5.2.27}$$

This result is derived assuming that there are sensitive cells initially, which is very likely. Note that this result is consistent with condition (5.2.12) for non-induced resistance.

5.3 Piecewise-Continuous Models

Now, we study various ways to model drug induced resistance with piecewise-continuous chemotherapy.

5.3.1 Homogeneous Tumor

We model cancer cell growth with resistance by exponential growth instead of logistic growth. This is an acceptable simplifying assumption, since the carrying capacity for most cancerous tissue is much larger then the maximum tumor mass that the host can withstand. Thus exponential growth is an acceptable approximation to the growth between each period of treatment.

The model for decaying drug effects, most likely caused by the development of resistance to the drug, is:

$$\frac{dx(t)}{dt} = r\left(1 - \frac{b(t)}{\gamma n + 1}\right) x(t), \quad n\tau \le t < (n+1)\tau \tag{5.3.28}$$

where γ is the resistance parameter and n is an integer which represents the number of the dose that is being delivered. Large γ represents cells rapidly becoming resistant to the drug and small γ represents cells switching to resistance more slowly. To find the *nadir* we need to determine when $x_{(n+1)\tau} \geq x_{n\tau}$. This condition can be investigated by studying the the first return map of equation (5.3.28). This difference equation is:

$$x_{(n+1)\tau} = x_{n\tau} e^{r\tau\left(1-\frac{\langle b(t)\rangle}{\gamma n+1}\right)}, \tag{5.3.29}$$

or in terms of the initial value x_0:

$$x_{(n+1)\tau} = x_0 e^{(n+1)r\tau} \prod_{i=0}^{n} e^{r\tau\left(1-\frac{\langle b(t)\rangle}{\gamma i+1}\right)}. \tag{5.3.30}$$

Solving $x_{(n+1)\tau} \geq x_{n\tau}$ the condition on the number of doses that may be given before the cell mass will start to regrow instead of decline is:

$$n \geq \frac{1}{\gamma}(\langle b(t)\rangle - 1). \tag{5.3.31}$$

(See figure (5.2).) A more direct way of establishing the *nadir* is to just view the characteristic exponent of the first return map (5.3.29). When this is greater than or equal to zero the same condition for the *nadir* as above is obtained.

For a basic model of resistance, this fits very well to actual data given in Skipper [60]. Compare figure (5.3) with graphs of data in Skipper.

5.3.2 Heterogeneous Tumor

The general heterogeneous tumor model used is similar to that of Gyori *et al.* [34]. It is of the form:

$$x' = r_1 x(1 - x/K_1 - c_1 y) - (b_0 d_0(t) + b_1 d_1(t))x \tag{5.3.32}$$

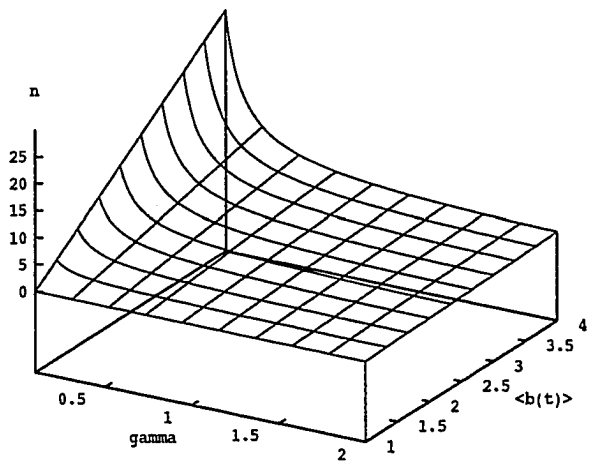

Figure 5.2: NADIR, Homogeneous Case

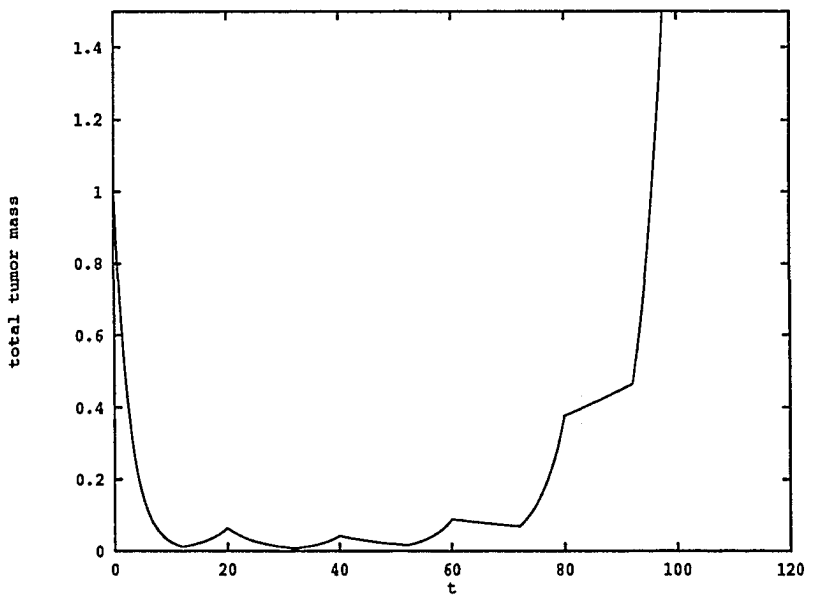

Figure 5.3: Tumor Mass vs. Time, Homogeneous Case

$$y' = b_0 d_0(t)x + r_2 y(1 - y/K_2 - c_2 x) - b_2 d_2(t)y, \qquad (5.3.33)$$

where x represents the sensitive cell mass and y represents the resistant cell mass. The various parameters are as follows: b_0 represents the induction rate of cell transformation (i.e. the rate at which they move from the sensitive to resistant compartments due to cytotoxic drugs), b_1 represents the effects of a cytotoxic drug that only affects the sensitive cells, b_2 represents the effects of a cytotoxic drug that can also affect the resistant cells, $d_{0,1}(t)$ are periodic functions of period τ_1, $d_2(t)$ is a periodic function of period τ_2 (these represent the periodic behavior of the chemotherapy), and the rest of the parameters are the regular parameters in a competition model. The induction rate of sensitive cells can range from almost zero to nearly 50% of surviving sensitive cells becoming resistant per dose.

5.3.3 Linear Model

As in the previous section we will eliminate the non-linear terms from equations (5.3.32, 5.3.33) for the following reasons. (i), The carrying capacity (K_i) of most tumors is much larger then the host can sustain; (ii) the drugs periodically destroy tumor mass keeping the tumor far from its carrying capacity (if the drugs do no do this the host will die); (iii) chemotherapy is often used in the adjuvant setting (post surgery) when the tumor burden is relatively low or to treat a metastatic burden; (iv) the linear system is much easier to handle analytically. Therefore, eliminating the non-linear terms from equations (5.3.32, 5.3.33) we obtain:

$$x' = (r_1 - (b_0 + b_1)d_0(t))x \qquad (5.3.34)$$

$$y' = b_0 d_0(t)x + (r_2 - b_2 d_2(t))y. \tag{5.3.35}$$

Note that equation (5.3.34) is decoupled from equation (5.3.35), therefore we can just examine equation (5.3.34) and determine separately the dynamics of the resistant compartment (equation (5.3.35)). Because of the possibility of different periods for the two drugs, we define the mean value function to be:

$$\langle f(t)\rangle_{\tau_i} = \frac{1}{\tau_i}\int_0^{\tau_i} f(t)dt, \quad i = 1, 2. \tag{5.3.36}$$

Note that the following is a useful relationship between the two means:

$$\langle f(t)\rangle_{\tau_1} = \frac{\tau_1}{\tau_2}\langle f(t)\rangle_{\tau_2}. \tag{5.3.37}$$

By integrating equation (5.3.34) over period τ_1 we get the condition required to destroy the sensitive cells. This condition is:

$$\frac{(b_0 + b_1)}{r_1}\tau_1\langle d_0(t)\rangle_{\tau_1} \geq 1. \tag{5.3.38}$$

If this condition holds (which it must if the therapy is to come even close to affecting the tumor), then the steady state effects of the resistant compartment can be studied by examining equation (5.3.35) with $x \equiv 0$. Therefore the condition that will also destroy the sensitive cells can be found by integrating equation (5.3.35) with $x \equiv 0$. This results in the condition:

$$\frac{b_2}{r_2}\tau_2\langle d_2(t)\rangle_{\tau_2} \geq 1. \tag{5.3.39}$$

Thus to have an effective drug regimen we need both condition (5.3.38) and (5.3.39) to be valid. Note that these conditions hold for both the linear model and the full non-linear model.

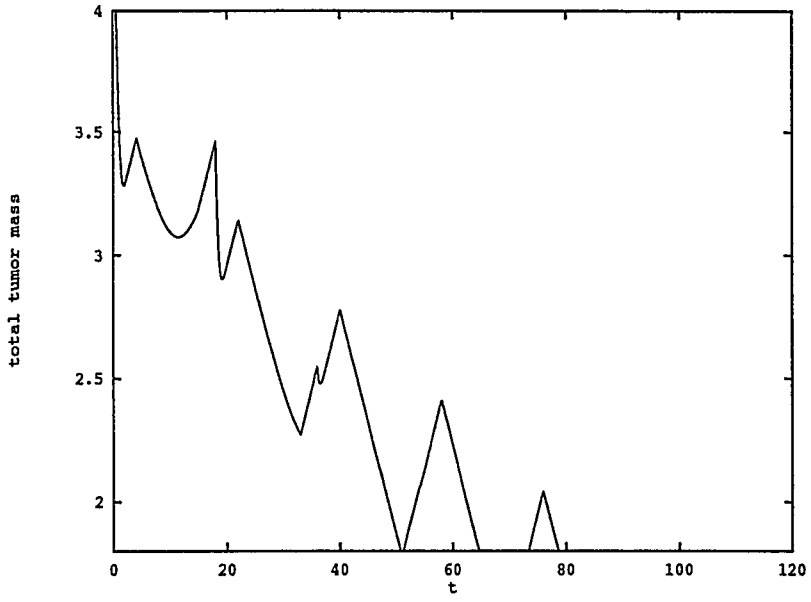

Figure 5.4: Tumor Mass vs. Time, Heterogeneous Case, Step Function

The following graphs give a clearer indication of how conditions (5.3.38) and (5.3.39) affect the growth of the cancer cells. It is assumed that condition (5.3.38) holds in all cases; thus we are interested in the bifurcation to resistant emergence. The most interesting feature of these graphs is that they qualitatively match actual studies of chemotherapeutic regimens listed in Skipper [60]. Although this model is only a linear version of a more realistic model, it nevertheless qualitatively fits the clinical results. Figure (5.4) shows an acceptable regimen of drugs, while figure (5.5) gives an unacceptable regimen. In both of these a step function (see figure (4.1)) is used to model the effects of the drug. In the case of the modified exponential function (see figure (4.3)), an unacceptable regimen has the form of figure (5.6).

In many cases (as noted above and by Skipper [60]), condition (5.3.39) will not hold, and hence the resistant cells will eventually take over, unless another drug

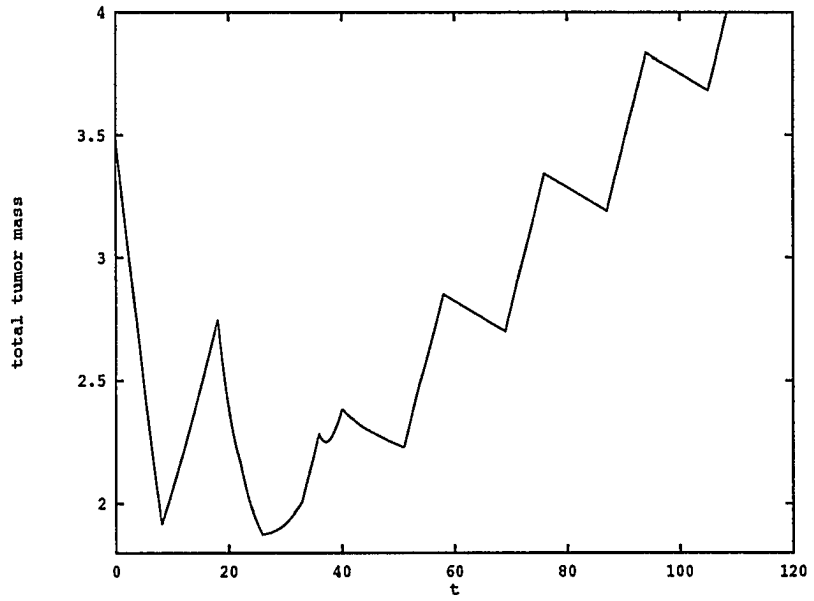

Figure 5.5: Tumor Mass vs. Time, Heterogeneous Case, Step Function

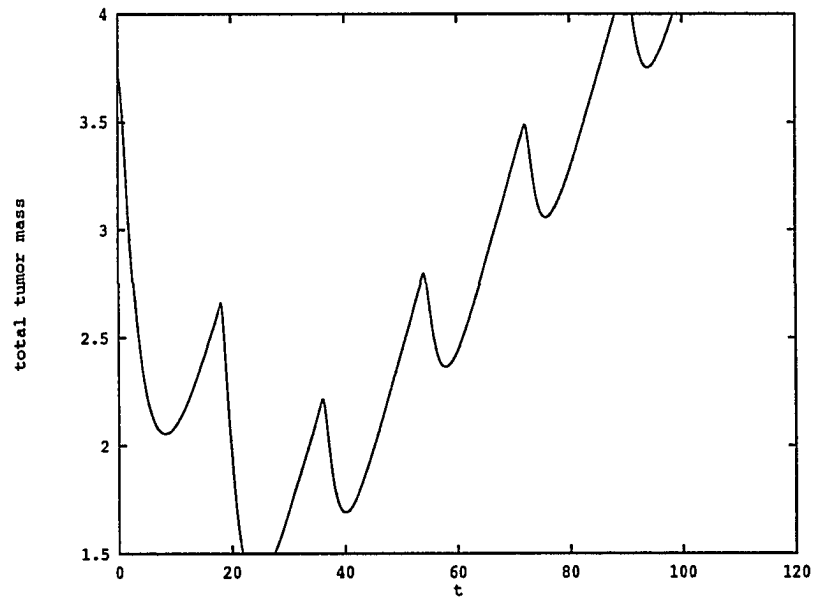

Figure 5.6: Tumor Mass vs. Time, Heterogeneous Case, Modified Exp. Function

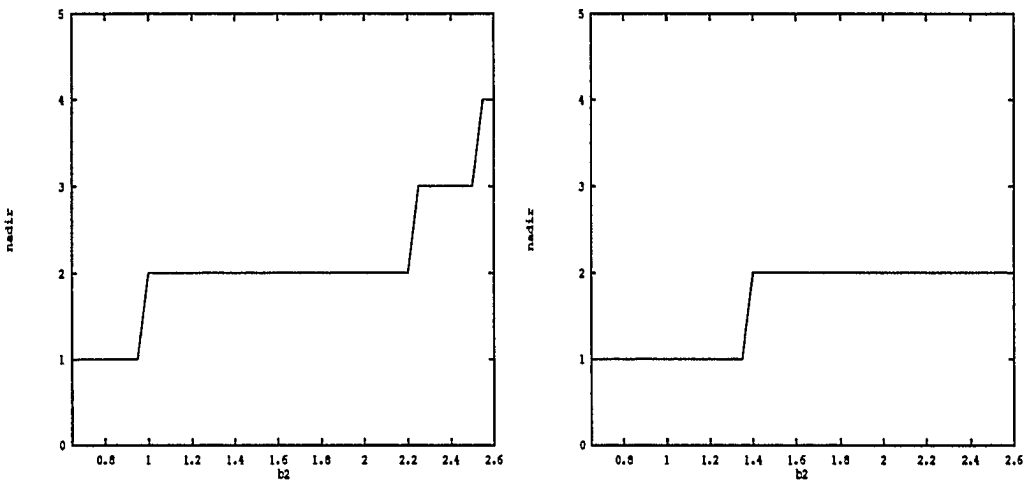

Figure 5.7: NADIR, linear model: $\tau = 18$, $b_1 = 1.475$ (left graph) and $b_1 = 1.75$ (right graph)

regimen is used that is more effective on the resistant cells. It is therefore important to know how many doses will have a positive effect on reducing the tumor mass. In this model the *nadir* will occur when:

$$\frac{x(t)}{y(t)} = 1. \tag{5.3.40}$$

At this point the total cell mass (sensitive plus resistant) will start to increase. An example of the *nadir* for fixed b_1 and varying b_2 in equations (5.3.34, 5.3.35) is given in figure (5.7). Also, comparing what happens when the period is varied with fixed b_i we get figure(5.8).

5.3.4 Non-Linear Model

To investigate the full model (equations (5.3.32, 5.3.33)), first let us study the constant parameter case, i.e. $d_i(t) \equiv 1$. This model has already been studied

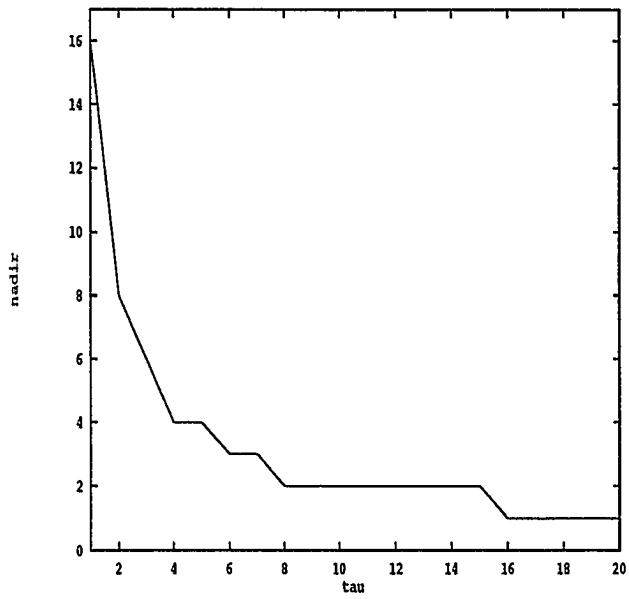

Figure 5.8: NADIR, linear model: $b_1 = 1.5$, $b_2 = 0.65$, vary τ

in detail by Michelson *et al.* [53, 46]. There are three equilibria; $E_0 \equiv (0,0)$, $E_1 \equiv (0,(r_2 - b_2)K_2/r_2)$, and $E_2 \equiv (x_e, y_e)$, where E_2 is the positive solution to (5.3.32,5.3.33) (see Michelson *et al.* [46]). Linearizing E_0, stability occurs provided:

$$r_1 < b_0 + b_1 \tag{5.3.41}$$

$$\textit{and } r_2 < b_2 \tag{5.3.42}$$

are both true. Note that conditions (5.3.38) and (5.3.39) reduce to these in the constant parameter case. If E_0 is unstable then either E_1 or E_2 will be stable. By linearizing about E_1 the condition for stability is:

$$(r_1 - (b_0 + b_1)) < \frac{r_1 c_1 K_2}{r_2}(r_2 - b_2), \tag{5.3.43}$$

and if this is not satisfied and E_0 is unstable, then E_2 is stable. (See Michelson *et al.* [53] for further details.)

Assuming that $d_i(t)$ is a non-constant periodic function of period τ, there exists a positive periodic solution of the equation for y, namely:

$$y' = r_2 y(1 - y/K_2) - b_2 d_2(t) y \tag{5.3.44}$$

provided $\langle d_2(t) \rangle < r_2/(\tau b_2)$ (see §(4.3)). Call the solution $Y_1(t)$. Note that this solution can be found analytically since this equation is in the form of a Bernoulli equation (see equation (4.3.10). Therefore $(0, Y_1(t))$ is a periodic solution to equations (5.3.32, 5.3.33). The stability may be studied in a manner similar to the constant coefficient case by linearizing about the equilibrium. In this case, the equilibrium E_1 is the periodic solution $(0, Y_1(t))$, and the variational matrix is:

$$\begin{pmatrix} r_1(1 - c_1 Y_1(t)) - (b_0 + b_1) d_0(t) & 0 \\ b_0 d_0(t) - r_2 c_2 Y_1(t) & r_2(1 - 2Y_1(t)/K_2) - b_2 d_2(t) \end{pmatrix}. \tag{5.3.45}$$

Since this is an uncoupled linear system, only an integration is required to find the condition for stability of $(0, Y_1(t))$. These stability conditions are:

$$r_1 - \tau(b_0 \langle d_0(t) \rangle + b_1 \langle d_1(t) \rangle) < r_1 c_1 \tau \langle Y_1(t) \rangle \tag{5.3.46}$$

$$r_2 - b_2 \tau \langle d_2(t) \rangle < \frac{2 r_2 \tau}{K_2} \langle Y_1(t) \rangle. \tag{5.3.47}$$

Note that this reduces to the conditions in the constant parameter case when $d_i(t)$ are constant.

Finally, it can be shown that if E_0 and $(0, Y_1(t))$ are unstable, then a periodic solution of the form $(X_c(t), Y_c(t))$ exist.

Let us again assume that condition (5.3.39) does **not** hold. Do the non-linear effects modify the bifurcation significantly or is it qualitatively the same as in the

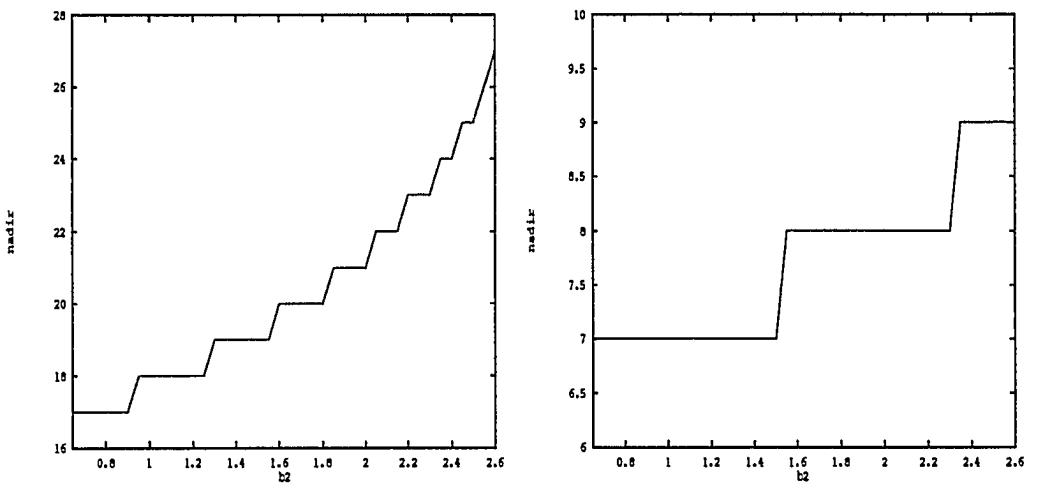

Figure 5.9: NADIR, non-linear model: $b_1 = 1.475$ (left graph), $b_1 = 1.75$ (right graph), $c_1 = 0.01$ and $c_2 = 0.01$

linear case? If condition (5.3.38) holds, then the equilibrium $(0, Y_1(t))$ is stable, otherwise, there is the possibility of a periodic coexistent solution. But, unlike the linear case, if condition (5.3.38) does **not** hold there is still the possibility of destroying the sensitive cells if the right hand side of condition (5.3.46) is large enough. In other words, either c_1 is larger (resistant cells more competitive) or $\tau\langle Y_1(t)\rangle$ is larger. Thus there exists the possibility of reducing the sensitive cells without administering such a large dose of chemotherapy.

More importantly, how do the non-linear terms affect the *nadir*? Using the same parameter ranges as in the linear case, the *nadir* is plotted vs. various parameters (see figure (5.9)). As can be seen, comparing graphs (5.7) and (5.9) we get qualitatively the same shape, but the non-linear form allows for higher *nadir*. Now, varying the competition parameter c_1 and c_2 in figure (5.10) shows how the competition parameters affects the *nadir*.

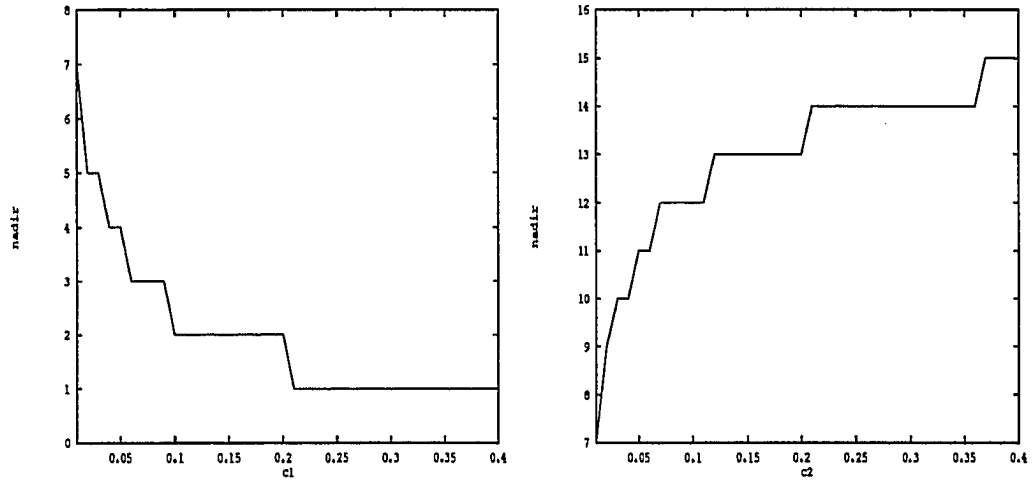

Figure 5.10: NADIR, non-linear model: $\tau = 18$, $b_1 = 1.75$, $b_2 = 0.65$

5.4 Conclusions

These models give a concise and general form for the bifurcation between reduced steady state cell survival, unlimited growth and cell destruction. It is hoped that they will provide cancer researchers with better qualitative ideas on how to optimize various clinical trials.

The model is inappropriate if the tumor develops resistance that is untreatable (i.e. no drug affects it). But if non-cross-resistant drugs are administered then it is still possible to continue to prevent tumor recurrence. One simplistic way to model this problem is to define the drugs to be a non-cross-resistant conglomeration: that is they are administered having survival fractions $F(D)$ and $\overline{F}(D)$. However, because this does not provide any insight into the mechanism of resistant recurrence, or how to control it, more sophisticated resistance models are needed.

Since most tumors are known to be heterogeneous and heterogeneity can result

in resistant subpopulations, heterogeneous tumor models are appropriate systems in which to study drug resistance. Two different types of resistance are investigated: drug induced and non-induced. One of the main differences between these situations arises in the zero therapy cases. That is, in the drug-induced no therapy case, growth of the sensitive cell population does not affect that of the resistant cell population while in the other case it does. When chemotherapy is added, both systems show a definite region of resistant recurrence with no sensitive recurrence. This region is important to identify in that it can be avoided when planning a regimen, thus not causing the tumor to become totally resistant (and thus killing the host). In both cases, it is seen that the cell mutations have a very small effect on the sensitive cell recurrence conditions, changing them only minimally. Again in both of these cases, the parameter region in which recurrence is prevented is generally smaller than in the homogeneous case, since the resistant cells are affected by fewer drugs. One of the most important points to note is that in all cases there are definite regions where the therapy will either succeed or fail. This should emphasize the importance of correct administration of chemotherapeutic drugs. Also, as pointed out earlier, it is important to account for the resistant subpopulation since it can narrow the acceptable region of drug treatment significantly. The main mathematical difference between these two resistance models is that the induced model has discrete induction events and the non-induced model has continuous induction. As we have demonstrated, these mathematical differences lead to only minimal differences in results.

Chapter 6

Conclusions

The need for mathematical models of chemotherapy is becoming more clear. As stated by Skipper [60],

> Over 20 years of experimental and clinical experience has demonstrated that intuitive or trial-and-error manipulations of doses, schedules, and combination of drugs—without guidance as to the effects of each manipulation—are apt to provide little or no improvement in combination chemotherapy designs.

The models developed in this dissertation give an uniquely different approach to discussing chemotherapeutic drug regimens. All the models show, in parameter space, proper and improper chemotherapeutic drug regimens in terms of dose and period, along with the bifurcation between these regimens. Some of the models verify that existing clinical regimens are a "good" way to deliver drugs while other results suggest that there could be other methods that may work better. All these models

are developed from the qualitative point of view. That is to say, we are not designing specific drug regimens, but rather defining general criteria to guide clinicians to more effective treatment schedules. In addition since one of the major limiting factors of a drug regimen is the negative effects on various normal tissues such as bone marrow, a constraint equation representing these effects is incorporated. This allows us to discuss delivery of proper regimens without them overly destroying normal tissue.

The first model described in Chapter 2 investigates the possible interaction between cancerous and normal tissue. Though this is not the case in all cancers, some examples of where this interaction may possibly occur were given, including the immune system or the liver. By using the pulsed therapy on a small metastisized tumor mass, we were able to develop parameter ranges of acceptable dose and period while preventing the over-destruction of the normal tissue.

The model in Chapter 3 discusses cell-specific chemotherapy. The most interesting result from this chapter is that fact that we actually want to have a gap between periods of drugs (which may seem counter-intuitive) to allow cells to "move" to the proliferating compartment. This model uses various known results from Floquet theory to help determine criteria such as the optimal period (i.e. the period which gives the largest cancer mass reduction per dose).

There have also been many medical advances in the use of HGF's to enhance the effectiveness of the chemotherapeutic drugs. By varying the parameters which relate to the effects of the HGF's, such as the growth rate of the bone marrow (rate of leukocyte production) or the transition rate from resting to cycling cells, the model in this chapter is extended to describe the dynamics of these HGF's. In fact this

particular model confirms what recent clinical results have shown, namely that the growth factors can increase the effectiveness of the chemotherapeutic drugs rather significantly.

Chapter 4 extends the idea of varying the parameters to better model the effects of chemotherapy. By means of a simple model of logistic growth with an increasing "K", the carrying capacity of the host for the tumor, we can observe how the tumors' ability to manipulate its environment can lead to uncontrolled growth. This can be related to the experiments with the tumor and the mouse, where the tumor is able to grow so large that it is as big as the mouse. This idea and the need for non-constant parameters is a continuing area of much research. This includes a recent publication by Michelson and Leith [52]. As described in this dissertation and in many publications, this area is extremely important in describing many of the interactions between various cells in cancer.

Other variations on the parameters were done by varying the growth rate of the cancer, which can also represent the effects of the chemotherapeutic drugs. Here bifurcation conditions were developed, again in terms of the dose and period, that identify regions of growth or decay. In the heterogeneous case, we were able to find analytic solutions of the equations to be in the form Confluent Hypergeometric functions. Also, using ideas from quantum mechanics we developed criteria for acceptable and unacceptable chemotherapeutic regions.

Chapter 5 covered one of the most important issues in developing chemotherapeutic regimens, namely drug resistance. The models developed in this chapter describe various ways of mathematically explaining drug resistance. Each of these models

fits well qualitatively with results discussed in Skipper [60]. These models identify important results such as how many doses may be given before resistance "takes over" and acceptable methods of delivering combination chemotherapy that control resistance. From this type of information, clinicians will better know how to deliver combinations of drugs more effectively to combat the effects of drug resistance.

There are many ways these models can be extended to more accurately model the chemotherapeutic effects. Some are for example: more accurate models of the immune system can be developed (i.e. take into better account their specific biological processes), more descriptive models of the cell-cycle can be used, more information on the mechanics of the (HGF's) can be discussed, more extensive analysis of the piecewise-continuous model can be investigated, and drug resistance may be added to all the models. It is the hope that the models in this dissertation along with some future development of these ideas will provide both mathematicians and clinicians a better view of how chemotherapeutic drug regimens work in theory and how to develop more effective drug regimens in the light of these results.

Bibliography

[1] John A. Adam. The dynamics of growth-factor-modified immune response to cancer growth: One dimensional models. *Mathl. Comput. Modelling*, 17(3):83–106, 1993.

[2] John A. Adam and John Carl Panetta. A simple mathematical model and alternative paradigm for certain chemotherapeutic regimens. Submitted to Mathematical and Computer Modelling, March 1995.

[3] Z. Agur, R. Arnon, and B. Schechter. Reduction of cytotoxicity to normal tissues by new regimens of cell-cycle phase-specific drugs. *Math. Biosci.*, 92(1):1–15, 1988.

[4] Arthur Albert, Marvin Freedman, and Alan S. Perelson. Tumors and the immune system: The effects of a tumor growth modulator. *Math. Biosci.*, 50(1/2):25–58, 1980.

[5] J. Aroesty, T. Lincoln, N. Shapiro, and G. Boccia. Tumor growth and chemotherapy: Mathematical methods, computer simulations, and experimental foundations. *Math. Biosci.*, 17:243–300, 1973.

[6] N. Bellomo and G. Forni. Dynamics of tumor interaction with the host immune system. *Mathl. Comput. Modelling*, 20(1):107–122, 1994.

[7] M. C. Berenbaum. Dose-response curves for agents that impair cell reproductive integrity. *Br. J. Cancer*, 23:434–445, 1969.

[8] Kapil Bhalla, Charles Holladay, Zalmen Arlin, Steven Grant, Ana Maria Ibrado, and Michelle Jasiok. Treatment with interleukin-3 plus granulocyte-macrophage colony-stimulating factors improves the selectivity of ara-c in vitro against acute myeloid leukemia blasts. *Blood*, 78(10):2674–2679, November 1991.

[9] B.G. Birkhead and W.M. Gregory. A mathematical model of the effects of drug resistance in cancer chemotherapy. *Math. Biosci.*, 72(1):59–69, 1984.

[10] B.G. Birkhead, W.M. Gregory, M.L. Slevin, and V.J. Harvey. Evaluating and designing cancer chemotherapy treatment using mathematical models. *Eur. J. Cancer. Clin. Oncol.*, 22(1):3–8, 1986.

[11] B.G. Birkhead, W.M. Gregory, and R.L. Souhami. A mathematical model of drug resistance applied to treatment for small-cell lung cancer. *Journal of Clinical Oncology*, 6(3):457–461, March 1988.

[12] B.G. Birkhead, E.M. Rakin, S. Gallivan, L. Dones, and R.D. Rubens. A mathematical model of the development of drug resistance to cancer chemotherapy. *Eur. J. Cancer. Clin. Oncol.*, 23(9):1421–1427, September 1987.

[13] L. Cojocaru and Z. Agur. A theoretical analysis of interval drug dosing for cell-cycle-phase-specific drugs. *Math. Biosci.*, 109(1):85–97, 1992.

[14] Bernard D. Coleman. Nonautonomous logistic equations as models of the adjustment of populations to environmental change. *Math. Biosci.*, 45(3/4):159–173, 1979.

[15] Bernard E. Coleman, Ying-Hen Hsieh, and Gregory P. Knowles. On the optimal choice of r for a population in a periodic environment. *Math. Biosci.*, 46(3/4):71–85, 1979.

[16] Isabelle Cornil, Dan Theodorescu, Shan Man, Meenhard Herlyn, J. Jambrosic, and R. S. Kerbel. Fibroblast cell interactions with human melanoma cells affect tumor cell growth as a function of tumor progression. *Proc. Natl. Acad. Sci.*, 88(14):6028–6032, July 1991.

[17] J. M. Cushing. Stable positive periodic solutions of the time-dependent logistic equation under possible hereditary influences. *J. Math. Anal. Appl.*, 60(6):747–754, 1977.

[18] J. M. Cushing. Two species competition in a periodic environment. *J. Math. Biol.*, 10(4):385–400, 1980.

[19] J.M. Cushing. Stable limit cycles of time dependent multispecies interactions. *Math. Biosci.*, 31(3/4):259–273, 1976.

[20] R. J. DeBoer, Pauline Hogeweg, Hub F. J. Dullens, Roel A. DeWeger, and Willem DenOtter. Macrophage T Lymphocyte interactions in the anti-tumor immune response: A mathematical model. *The Journal of Immunology*, 134(4):2748–2758, April 1985.

[21] R. J. DeBoer, Seth Michelson, and Pauline Hogeweg. Concomitant innumization by the fully antigenic counterparts prevents modulated tumor cells from escaping cellular immune elimination. *The Journal of Immunology*, 136(11):4319–4327, June 1986.

[22] George D. Demetri. The use of hematopoietic growth factors to support cytotoxic chemotherapy for patients with breast cancer. *Hematology and Oncology Clinics of North America*, 8(1):233–249, February 1994.

[23] Martin Eisen. *Mathematical Models in Cell Biology and Cancer Chemotherapy*, volume 30 of *Lecture Notes in Biomathematics*. Springer-Verlag, New York, 1979.

[24] Martin Eisen and John Schiller. Stability analysis of normal and neoplastic growth. *Bull. Math. Biol.*, 39(5):597–605, 1977.

[25] Bernard Fisher and Edwin R. Fisher. Experimental studies of factors influencing hepatic matastases. *Cancer*, 12:929–932, September 1959.

[26] S. Flügge. *Practical Quantum Mechanics*, volume I. Springer-Verlag, Berlin, 1971.

[27] Robert A. Gatenby. Population ecology issues in tumor growth. *Cancer Research*, 51:2542–2547, 1991.

[28] Robert A. Gatenby. Population ecology models of neoplastic growth: Implications for tumor biology and treatment. Private communication with Dr. John Adam, January 1994.

[29] J.H. Goldie and A.J. Coldman. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat. Rep.*, 63(11–12):1727–1733, 1979.

[30] J.H. Goldie, A.J. Coldman, and G.A. Gudauskas. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat. Rep.*, 66(3):439–449, March 1982.

[31] W.M. Gregory, R.H. Reznek, M. Hallett, and M.L. Slevin. Using mathematical models to estimate drug resistance and treatment efficacy via CT scan measurements of tumour volume. *Br. J. Cancer*, 62(4):471–475, October 1990.

[32] M. Gyllenberg and G.F. Webb. Quiescence as an explanation of gompertzian tumor growth. *Growth, Development & Aging*, 53:23–33, 1989.

[33] M. Gyllenberg and G.F. Webb. A nonlinear structured population model of tumor growth with quiescence. *J. Math. Biol.*, 28(6):671–694, 1990.

[34] Istvan Gyori, Seth Michelson, and John Leith. Time-dependent subpopulation induction in heterogeneous tumors. *Bull. Math. Biol.*, 50(6):681–696, 1988.

[35] J. Hale and H. Koçak. *Dynamics and Bifurcations.* Springer-Verlag, New York, 1991.

[36] T.G. Hallam and C.E. Clark. Non-autonomous logistic equations as models of populations in a deteriorating environment. *J. Theoret. Biol.*, 93:303–311, 1981.

[37] Birger Jansson and Laszlo Révész. Cell ecology: Deductive and dynamic models for proliferation, differentiation and competition of tumor cell populations. *J. Theoret. Biol.*, 68:43–51, 1977.

[38] Helmut Knolle. *Cell Kinetic Modelling and the Chemotherapy of Cancer*, volume 75 of *Lecture Notes in Biomathematics*. Springer-Verlag, New York, 1988.

[39] Mark Kot and Eric Funasaki. Invasion and chaos in a periodically pulsed mass-action chemostat. *Theoret. Population Biol.*, 44:203–224, 1993.

[40] Jan W. Kuzma, I. Valand, and Joseph Bateman. A tumor cell model for the determination of drug schedules and drug effect in tumor reduction. *Bull. Math. Biophysics*, 31(4):637–650, 1969.

[41] V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor, and A. S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bull. Math. Biol.*, 56(2):295–321, 1994.

[42] Lance A. Liotta. Cancer cell invasion and metastasis. *Scientific American*, pages 54–63, February 1992.

[43] R.B. Martin, M.E. Fisher, R.F. Michin, and K.L. Teo. Low-intensity combination chemotherapy maximizes host survival time for tumors containing drug-resistant cells. *Math. Biosci.*, 110:221–252, 1992.

[44] R.B. Martin, M.E. Fisher, R.F. Michin, and K.L. Teo. Optimal control of tumor size used to maximize survival time when cells are resistant to chemotherapy. *Math. Biosci.*, 110:201–219, 1992.

[45] Seth Michelson, K. Ito, H.T. Tran, and John T. Leith. Stochastic models for subpopulation emergence in heterogeneous tumors. *Bull. Math. Biol.*, 51(6):731–747, 1989.

[46] Seth Michelson and John T. Leith. Unexpected equilibria resulting from differing growth rates of subpopulations within heterogeneous tumors. *Math. Biosci.*, 91:119–129, 1988.

[47] Seth Michelson and John T. Leith. Effects of differential cell kill on the dynamic composition of heterogeneous tumors. *Computers Math. Applic.*, 20(4–6):149–159, 1990.

[48] Seth Michelson and John T. Leith. Autocrine and paracrine growth factors in tumor growth: A mathematical model. *Bull. Math. Biol.*, 53(4):639–656, 1991.

[49] Seth Michelson and John T. Leith. Growth factors and growth control of heterogeneous cell populations. *Bull. Math. Biol.*, 55(5):993–1011, 1993.

[50] Seth Michelson and John T. Leith. Tumor heterogeneity: A review of the theory. *Drug News & Perspectives*, 6(9):655–661, November 1993.

[51] Seth Michelson and John T. Leith. Dormancy, regression, and recurrence: Towards a unifying theory of tumor growth control. *J. Theoret. Biol.*, 169(4):327–338, 1994.

[52] Seth Michelson and John T. Leith. Interlocking triads of growth control in tumors. *Bull. Math. Biol.*, 57(2):345–366, 1995.

[53] Seth Michelson, B.E. Miller, A.S. Glicksman, and J.T. Leith. Tumor microecology and competitive interactions. *J. Theoret. Biol.*, 128(2):233–246, 1987.

[54] Seth Michelson and Doris Slate. A mathematical model of the p-glycoprotein pump as a mediator of multidrug resistance. *Bull. Math. Biol.*, 54(6):1023–1038, 1992.

[55] J.M. Murray. Some optimal control problems in cancer chemotherapy with a toxicity limit. *Math. Biosci.*, 100:49–67, 1990.

[56] John Carl Panetta. A mathematical model of periodically-pulsed chemotherapy: Tumor recurrence. Submitted to Bulletin of Mathematical Biology, March 1994.

[57] John Carl Panetta and John Adam. A mathematical model of cycle-specific chemotherapy. *Mathematical and Computer Modeling*, To Appear.

[58] Karl E. Paschkis, A. Cantarow, J. Stasney, and J. H. Hobbs. Tumor growth in partially hepatectomized rats. *Cancer Research*, 15:579–582, October 1955.

[59] I. Prigonine and R. Leferver. Stability problems in cancer growth and nucleation. *Comp. Biochem. Physiol.*, 67B:389–393, 1980.

[60] Howard E. Skipper. On mathematical modeling of critical variables in cancer treatment goals: Better understanding of the past and better planning in the future. *Bull. Math. Biol.*, 48(3/4):253–278, 1986.

[61] George W. Swan. *Some Current Mathematical Topics in Cancer Research.* University Microfilms International, Ann Arbor Michigan, 1977.

[62] George W. Swan. Immunological surveillance andd neoplastic development. *Rocky Mountain Journal of Mathematics*, 9(1):143–148, 1979.

[63] George W. Swan. *Optimization of Human Cancer Radiotherapy*, volume 42 of *Lecture Notes in Biomathematics*. Springer-Verlag, New York, 1981.

[64] George W. Swan. Tumor growth models and cancer chemotherapy. In James R. Thompson and Barry Brown, editors, *Cancer Modeling*, volume 83, chapter 3, pages 91–179. Marcel Dekker, New York, 1987.

[65] Paul Waltman. *Competition Models in Population Biology*, volume 45. Society for Industrial and Applied Mathematics, Philadelphia, PA, 1983.

[66] G. F. Webb. A cell population model of periodic chemotherapy treatment. *Biomedical Modeling and Simulation*, pages 83–92, 1992. Elsevier Science Publishers.

[67] G. F. Webb. A nonlinear cell population model of periodic chemotherapy treatment. *Recent Trends in Ordinary Differential Equations, Series in Applicable Analysis*, 1:569–583, 1992. World Scientific Publishing Company.

[68] Ma Zhien and Thomas G. Hallam. Effects of parameter fluctuations on community survival. *Math. Biosci.*, 86(1):35–49, 1987.

Biographical Statement

John Carl Panetta was born in Framingham Massachusetts in March of 1966. He received his B.S. (Cum Laude) in Applied Mathematics from Old Dominion University in May of 1988 and went on to complete his M.S. in May of 1990 in Mathematics from the University of Mississippi, where he was a teaching assistant from 1988 to 1990. He is currently completing his Ph.D. in Computational and Applied Mathematics at Old Dominion University, where he has been a teaching assistant from 1990 to 1995.

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