1995

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Pergamon

Mathl. Comput. Modelling Vol. 22, No. 2, pp. 67–82, 1995

0895-7177/95 $9.50 + 0.00

0895-7177(95)00112-3

A Mathematical Model of Cycle-Specific Chemotherapy

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(Received March 1995; accepted April 1995)

Abstract—A mathematical model is used to discuss the effects of cycle-specific chemotherapy. The model includes a constraint equation which describes the effects of the drugs on sensitive normal tissue such as bone marrow. This model investigates both pulsed and piecewise-continuous chemotherapeutic effects and calculates 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 can enhance the cell kill of the chemotherapeutic drugs.

Keywords—Periodic differential equation, Cancer, Chemotherapy, Cell-cycle, Quiescence.

1. INTRODUCTION

Many chemotherapeutic drugs are cycle-specific: they only destroy cells in specific phases of their cycle. 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.* [1], "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 paper is to give some qualitative ideas on how to better administer cycle-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 cycle-specific therapy.

Some of the more recent work done with mathematical models of cycle-specific chemotherapy is by Webb [2,3]. He develops both linear and nonlinear models of cycle-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.* [1] 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 [4] also examines cycle-specific chemotherapy in his review article. In particular, he concentrates on age-structured

I would like to thank R. Perry for his extremely useful comments and discussions which helped me immensely in preparing this paper. Also, I would like to thank S. Michelson for his helpful insight into much of the mechanisms of cancer. This paper is a partial requirement for the completion of a Ph.D. in the Department of Mathematics and Statistics at Old Dominion University.

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 [5] study a two-compartment model of tumor growth with nonconstant growth rate. In addition, Kuzma *et al.* [6] 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.* [7] and Cojocaru and Agur [8] (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 phase (S) and the bone marrow is in a less vulnerable stage. These two articles also differ from the other above articles in the fact 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 paper will extend the linear models described in [1,2,5] by adding both pulsed and piecewise-continuous chemotherapy along with the constraint to the chemotherapeutic regimen obtained by examining the effects of the cycle-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.* [1], is "the maximally-tolerated dose is given as frequently as the rate of bone marrow recovery permits." Using the model developed in this paper, 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 cycle-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 is exogenous estrogen which is used in treating breast cancer. 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.* [9] state 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 [10] 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 cycle-specific chemotherapeutic agents.

2. MODEL

A two-dimensional linear differential equation with periodically pulsed and periodically piecewise-continuous chemotherapy is used to describe the effects of chemotherapy on a tumor. The basic model is similar to those described by Eisen and Schiller [5] who describe a two-compartment model, and Birkhead *et al.* [1] who include resistant compartments for both the cycling and noncycling cells, thus increasing the dimension of their model to four. Both examine similar

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

Some basic assumptions are made here to keep the model tractable. First, 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 nonlinear effects of logistic or Gompertz growth will be minimal, allowing us to use the simpler model. Birkhead *et al.* [1,11] and Kuzma *et al.* [6] also utilize exponential growth between doses. Second, the parameters will be constant (except for the case of growth factors). In their model, Eisen and Schiller [5] incorporate nonconstant growth, but we will avoid this and focus more on the chemotherapeutic aspects of the model. Third, we do not take into account 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 (note though that this model does take into account natural cell decay). Fourth, Swan [4] (along with many others) states that the cycling compartment has four subcompartments or phases including the gap period (G_1), the synthetic period (S), the second gap period (G_2), and mitosis (M) (see Figure 1). To eliminate undue complications, we will combine the four subcompartments of the cycling phase into one to yield a two-compartment model with both a cycling and a resting compartment. Finally, even with cycle-specific drugs there are actually no absolutely safe cells (both resting and proliferating cells are affected to some extent) though the faster proliferating cells will definitely be affected more by the drug. In the present model, we will nonetheless assume that the resting cells (G_0) are not effected 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 cycle-specific chemotherapy without the undue complexity of the detailed mathematics. 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.

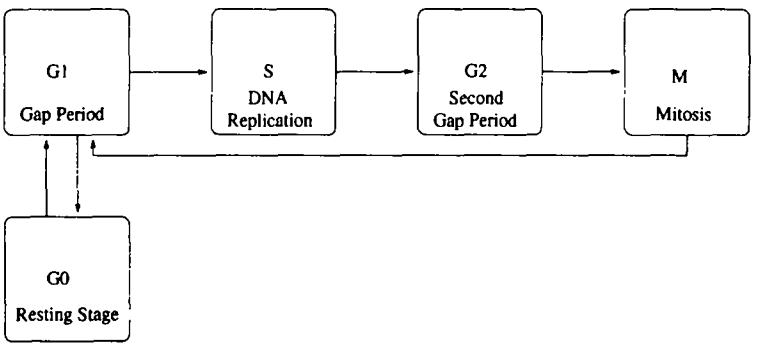

Figure 1. Cell-cycle.

2.1. Two-Compartment Model

The form of the two-compartment model as described in Figure 2 is

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{pmatrix} = \begin{pmatrix} \alpha - \mu - \eta & \beta \\ \mu & -\beta - \gamma \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, \tag{1}$$

where the parameters are all constant, positive, and defined as follows: α, cycling cells growth rate; μ, rate which cycling cells become noncycling; η, natural decay of cycling cells; β, rate which

noncycling cells become cycling; γ, natural decay of noncycling cells (optional). The elements of the vector $(x_1, x_2)^\top \equiv \vec{x}$ represents the cycling and noncycling 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 noncycling or quiescent compartment. Birkhead *et al.* [1] 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

$$\frac{d\vec{x}}{dt} = \begin{pmatrix} -a & \beta \\ \mu & -\beta \end{pmatrix} \vec{x}, \tag{2}$$

where $a, \beta, \mu \geq 0$. Birkhead *et al.* [1] give one set of parameter values from breast cancer data that fit the above conditions, namely, $\alpha = 0.5$, $\mu = 0.218$, $\eta = 0.477$, $\beta = 0.05$.

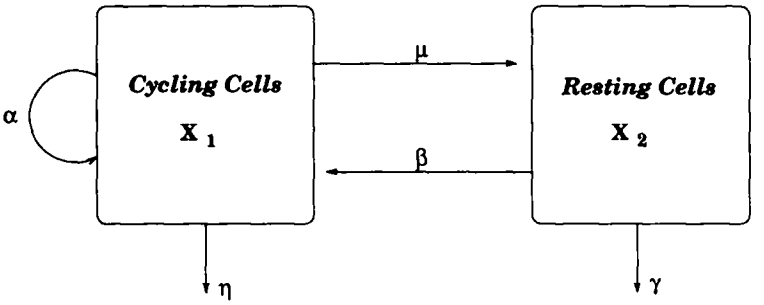

Figure 2. Two-compartment diagram.

Now we examine the periodic chemotherapeutic conditions. Since this model describes cycle-specific chemotherapy, the drugs will only affect the cycling cells, x_1. We will examine two types of chemotherapeutic effects. The first is similar to that used in [12], i.e., a pulsing condition. This describes a constant instantaneous cell kill at each period of dose. The pulsing periodic condition is

$$\vec{x}_{n\tau^+} = \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix} \vec{x}_{n\tau^-}, \tag{3}$$

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 [12]. Also, Birkhead *et al.* [1] examine $0.05 \leq f(D) \leq 0.4$.

For the piecewise continuous case, model (2) will be modified as

$$\frac{d\vec{x}}{dt} = \begin{pmatrix} -a & \beta \\ \mu & -\beta \end{pmatrix} \vec{x} - \begin{pmatrix} g(t) & 0 \\ 0 & 0 \end{pmatrix} \vec{x}. \tag{4}$$

The function $g(t)$ is a piecewise continuous function describing the chemotherapeutic effects on the tumor. Webb uses a similar model in his study [2], where he uses a step function to model the chemotherapeutic effects. We will investigate the model using the exponential decay function (Figure 3)

$$g(t) = he^{-\gamma(t-n\tau)}, \qquad n\tau \leq t < (n+1)\tau, \tag{5}$$

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

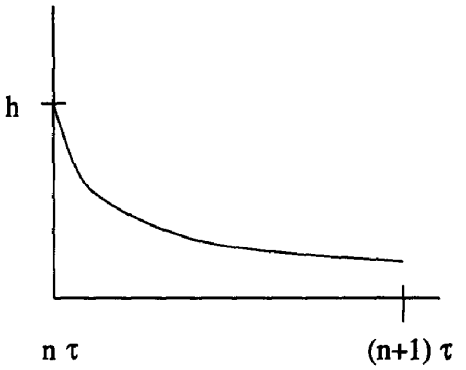

Figure 3. Exponential decay function.

2.2. Normal Cells

One of the major drawbacks of chemotherapy is that it also affects normal cell tissue. In the case of cycle-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 [12] examines the interaction between normal and tumor tissue and the effects of cycle-nonspecific drugs on them. In many cases such as with bone marrow, there is most likely 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, then a suitable constraint equation for pulsed therapy is

$$\dot{y} = \delta(K - y), \quad y_{n\tau+} = \tilde{f}(D)y_{n\tau-}, \qquad n\tau \leq t < (n+1)\tau, \tag{6}$$

where $\tilde{f}(D)$ is the survival fraction for the normal tissue and $\tilde{f}(D) > f(D)$. This means that, the drug affects the tumor cells more than the normal cells. Also in the above equation, δ is the growth rate of the normal tissue. For the piecewise case, the limited growth equation for normal tissue is

$$\dot{y} = \delta(K - y) - he^{-\gamma(t-n\tau)}, \qquad n\tau \leq t < (n+1)\tau. \tag{7}$$

Note that the above equations are still linear. Logistic growth can also be used to model the growth of the normal tissue though, in this case, the equation is nonlinear. The form of the logistic constraint equation for pulsed therapy is

$$\dot{y} = \delta y\left(1 - \frac{y}{K}\right), \quad y_{n\tau+} = \tilde{f}(D)y_{n\tau-}, \qquad n\tau \leq t < (n+1)\tau. \tag{8}$$

The logistic equation with pulsing is solved in [12] and the solution to the linear limited growth equation is similar and is solved in the following section. Finally, the logistic form for the piecewise case is

$$\dot{y} = \delta y\left(1 - \frac{y}{K}\right) - he^{-\gamma(t-n\tau)}y, \qquad n\tau \leq t < (n+1)\tau. \tag{9}$$

3. PULSED CASE

The first step in analyzing model (2) with pulsing condition (3) and constraint equation (8) is to develop solutions for (2) and (8) 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 [13]) that will describe the growth of the tumor at each pulse.

3.1. Normal Tissue

First, consider the linear case of limited normal tissue growth. Solving equation (6) yields the difference equation

$$y_{(n+1)\tau} = \widetilde{f}(D)\left\{K + (y_{n\tau} - K)\, e^{-\delta\tau}\right\}. \tag{10}$$

This has only one equilibrium:

$$y_s^* = \frac{K\widetilde{f}(D)\left(1 - e^{-\delta\tau}\right)}{1 - \widetilde{f}(D)e^{-\delta\tau}}. \tag{11}$$

Denoting $0 < \omega < 1$ as the acceptable fractional kill of the carrying capacity K, the constraint for limited growth on the chemotherapeutic regimen in terms of dose and period is

$$\omega \leq \frac{\widetilde{f}(D)\left(1 - e^{-\delta\tau}\right)}{1 - \widetilde{f}(D)e^{-\delta\tau}}. \tag{12}$$

Now, in a similar manner, the logistic constraint is also solved. Solving equation (8) yields the difference equation

$$y_{(n+1)\tau} = \widetilde{f}(D)\frac{y_{n\tau}K}{y_{n\tau} + (K - y_{n\tau})\, e^{-\delta\tau}}. \tag{13}$$

As shown in [12], this has two equilibrium points:

$$y_u^* = 0, \quad y_s^* = \frac{K\left(\widetilde{f}(D) - e^{-\delta\tau}\right)}{1 - e^{-\delta\tau}}. \tag{14}$$

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

$$\omega \leq \frac{\widetilde{f}(D) - e^{-\delta\tau}}{1 - e^{-\delta\tau}}. \tag{15}$$

In both cases, the cycle-specific chemotherapeutic drugs have less effect on these tissues, primarily since a much higher percentage of normal tissue is in the resting phase. Therefore, $\widetilde{f}(D) > f(D)$ since more normal than cancerous tissue survives each dose.

3.2. Effects on Tumor

First, examine equation (2). Hale and Koçak [13, 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 right-hand side matrix of (2). This solution is defined on the interval $n\tau \leq t < (n+1)\tau$. By the choices of signs of the parameters on the right hand side matrix of equation (2), 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 will always be negative. It will be more convenient for us to write the solution in the form

$$\vec{x}(t) = P\begin{pmatrix} e^{\lambda_1(t-n\tau)} & 0 \\ 0 & e^{\lambda_2(t-n\tau)} \end{pmatrix} P^{-1}\vec{x}_{n\tau}, \qquad n\tau \leq t < (n+1)\tau, \tag{16}$$

where

$$P \equiv \left(\vec{\xi}_1 \mid \vec{\xi}_2\right) \tag{17}$$

is referred to as the transformation matrix and $\vec{x}_{n\tau}$ is the tumor mass at the beginning of the n^{th} period.

Now, adding pulsing condition (3), the following difference equation describes the tumor mass just after each pulse of drug:

$$\vec{x}_{(n+1)\tau} = P \begin{pmatrix} e^{\lambda_1 \tau} & 0 \\ 0 & e^{\lambda_2 \tau} \end{pmatrix} P^{-1} \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix} \vec{x}_{n\tau}. \tag{18}$$

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

$$P \begin{pmatrix} e^{\lambda_1 \tau} & 0 \\ 0 & e^{\lambda_2 \tau} \end{pmatrix} P^{-1} \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix}, \tag{19}$$

of equation (18), need to be investigated. We will define the eigenvalues of matrix (19) as $\overline{\lambda}_i$, which can be found in terms of $f(D)$ and τ. If

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

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

$$\max_{i=1,2} \left(\left| \overline{\lambda}_i(f(D), \tau) \right| \right) = 1, \tag{20}$$

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

Also, in the above region, there are some regimens that are more effective than others. The most effective chemotherapeutic regimen is therefore defined as

$$\min_{\tau} \left(\max_{i=1,2} \left(\left| \overline{\lambda}_i(f(D), \tau) \right| \right) \right) \tag{21}$$

for each fixed $f(D)$. This does not take into account the effect of the drugs on the normal tissue. We must investigate this expression along with inequalities (12) or (15) when developing effective chemotherapeutic regimens. This is carried out in the next section.

Define $\vec{\xi}_i \equiv (\xi_{i1}, \xi_{i2})^\top$. It can be observed that $\xi_{11}, \xi_{12} > 0$ and ξ_{21}, ξ_{22} have opposite signs (this is true because of the signs of a, β, and μ). We can write matrix (19) as

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

Call matrix (22) CM. The eigenvalues of CM are

$$\overline{\lambda}_i(f(D), \tau) \equiv \frac{\text{trace}(CM) \pm \sqrt{(\text{trace}(CM))^2 - \det(CM)}}{2}. \tag{23}$$

Calculating the trace(CM) and det(CM), we get

$$\det(CM) \equiv f(D) e^{(\lambda_1 + \lambda_2)\tau} > 0 \tag{24}$$

and

$$\text{trace}(CM) \equiv (gf(D) - h) e^{\lambda_1 \tau} - (hf(D) - g) e^{\lambda_2 \tau} > 0, \tag{25}$$

where

$$g \equiv \frac{\xi_{11}\xi_{22}}{\det(P)}, \quad \text{and} \quad h \equiv \frac{\xi_{12}\xi_{21}}{\det(P)}. \tag{26}$$

It can be seen that both trace(CM) and det(CM) are positive because of the signs of the elements of the eigenvectors. Therefore, $\max_i \left(\left| \overline{\lambda}_i(f(D), \tau) \right| \right) = \overline{\lambda}_1(f(D), \tau)$. 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.

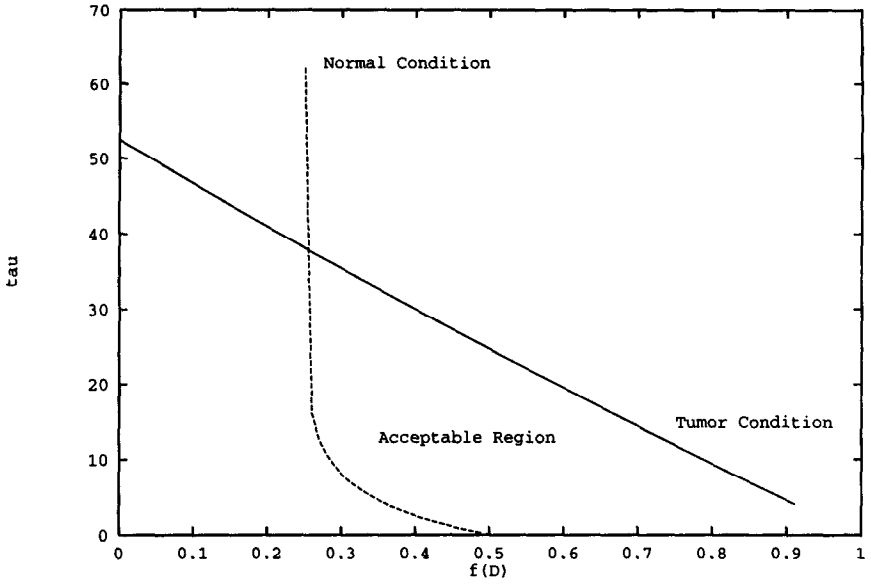

Figure 4. Bifurcation diagram: $\widetilde{f}(D) = 2f(D)$.

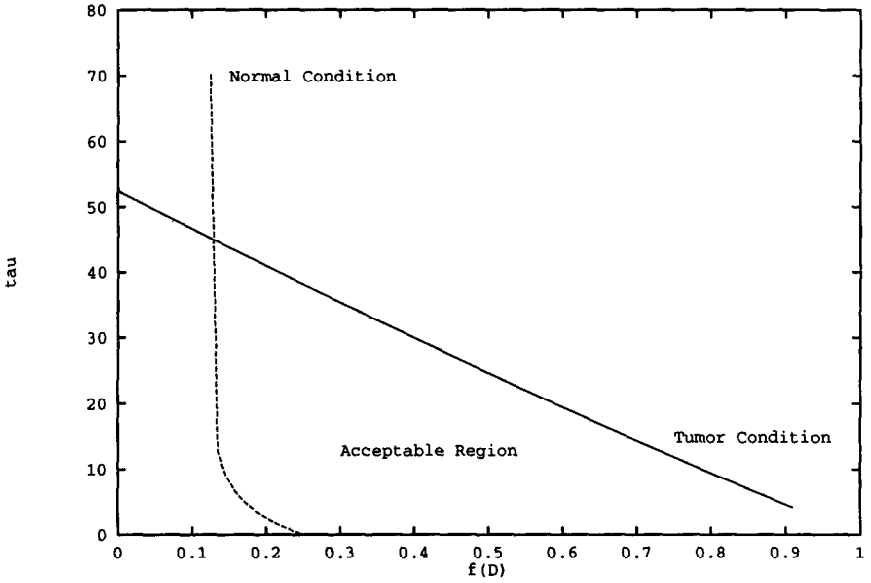

Figure 5. Bifurcation diagram: $\widetilde{f}(D) = 4f(D)$.

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, investigate the graph of the bifurcation equation (20) with $i = 1$ and the constraint equation (12) or (15). Using the parameters listed in Section 2.1, $\omega = 0.5$, and $\delta = 0.1$ along with the logistic constraint equation (15), we obtain Figure 4 for $\widetilde{f}(D) = 2f(D)$ (normal tissue survives twice as well as tumor tissue) and Figure 5 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 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 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 (21), it can be seen that the optimal period is actually greater than $\tau \approx 0$ (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 at too great a rate! 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 $\tau \approx 8$ ($\min \overline{\lambda}_1$ with respect to τ), see Figure 6, 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 7 for $0 < f(D) < 0.9$. As can be seen, more effective drugs (smaller $f(D)$) optimal periods are larger then less effective ones, thus allowing the normal tissue more time to recover.

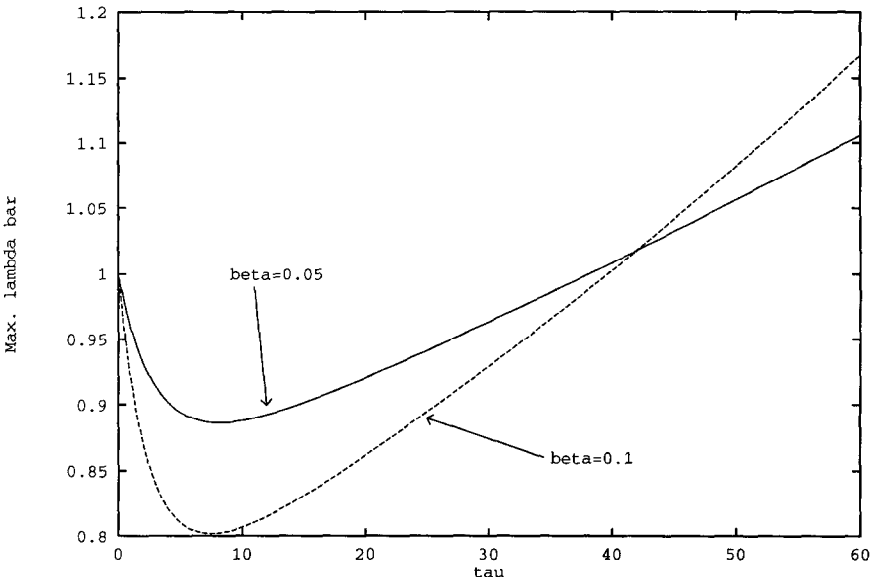

Figure 6. $\overline{\lambda}_1(f(D), \tau)$ vs. τ, $f(D) = 0.25$.

Now, consider the chemotherapeutic regimen stated by Birkhead *et al.* [1]. That is, "the maximally-tolerated dose is given as frequently as the rate of bone marrow recovery permits." Before seeing if our model agrees with this method, we need to consider what it is meant by this regimen. There are two possibilities; either administer the drug rapidly but do not use a strong dose, or allow higher doses but do not administer them as often. By looking at the bifurcation diagram for $\widetilde{f}(D) = 2f(D)$ (Figure 4) and the optimal period graph (Figure 7), we observe that the calculated optimal period is a better regimen if less of a dose (survival fraction $f(D) > 0.3$) is given more frequently and Birkhead's is better if the opposite holds true. This can be observed in Figure 8 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 only meant to be a qualitative look at the problem.

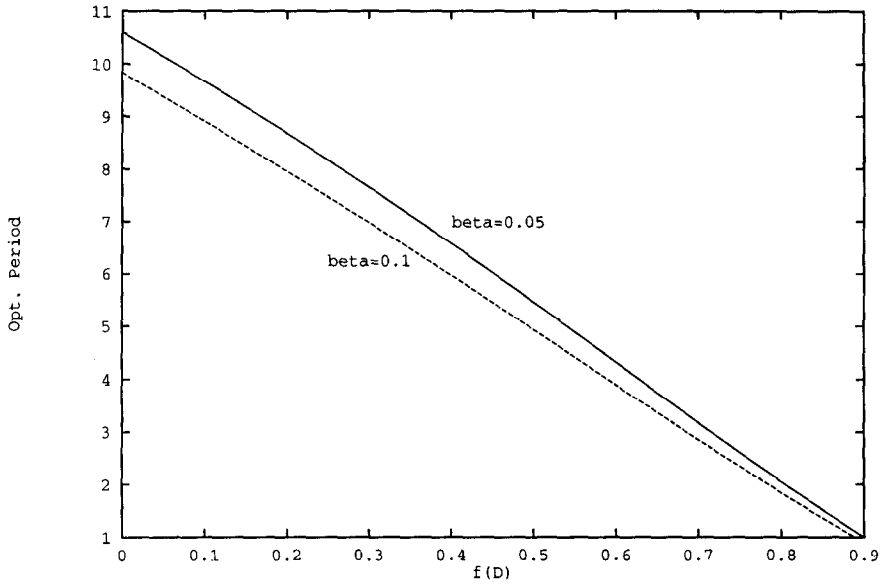

Figure 7. Optimal period vs. $f(D)$.

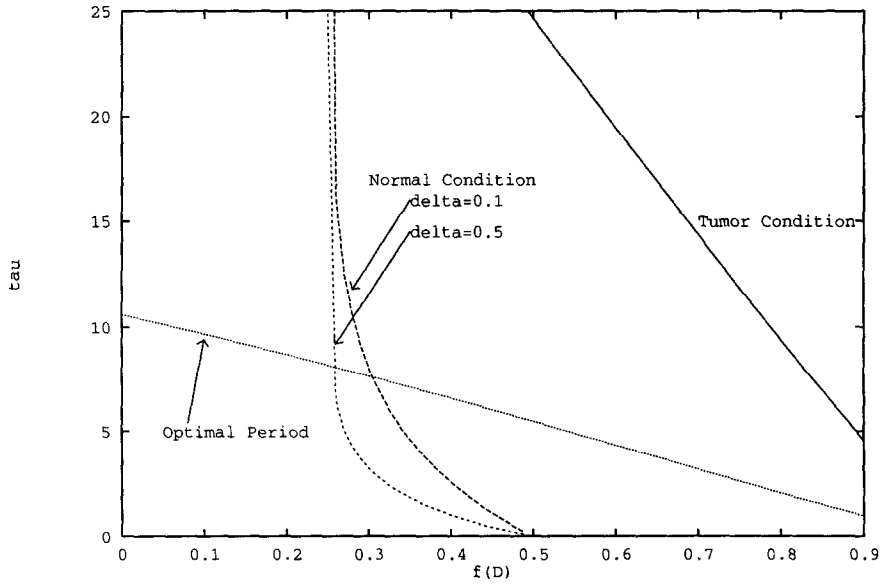

Figure 8. Bifurcation with optimal period.

In many cases, the clinician would prefer to give a larger dose then is acceptable by conventional methods. The problem, as can be seen in Figure 8, is that these large doses (small $f(D)$) must be administered over a larger then 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 (6) or (8)). As can be seen from Figure 8, a higher growth rate for the normal tissue increases the region of acceptable drug regimens, thus allowing higher doses of chemotherapeutic drugs to

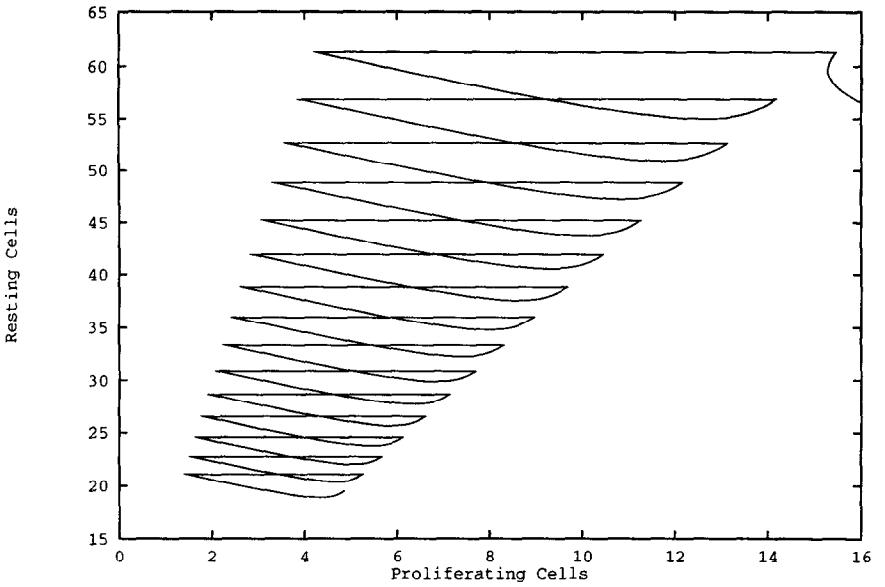

Figure 9. $\tau = 20$, $f(D) = 0.275$.

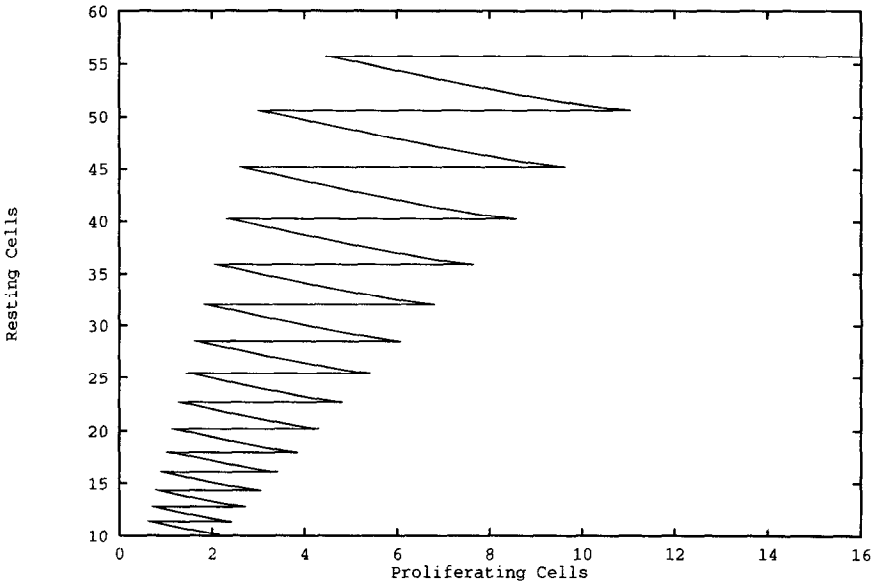

Figure 10. $\tau = 7.25$, $f(D) = 0.275$.

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 about a 64.7% 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 about a 82.2% reduction in tumor mass, which is a 27% increase in tumor reduction over the nonoptimal period! Figures 9 and 10 show the phase planes (resting vs. proliferating) for each case. Observing Figure 9, we can see why the nonoptimal period does not have as large of 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.

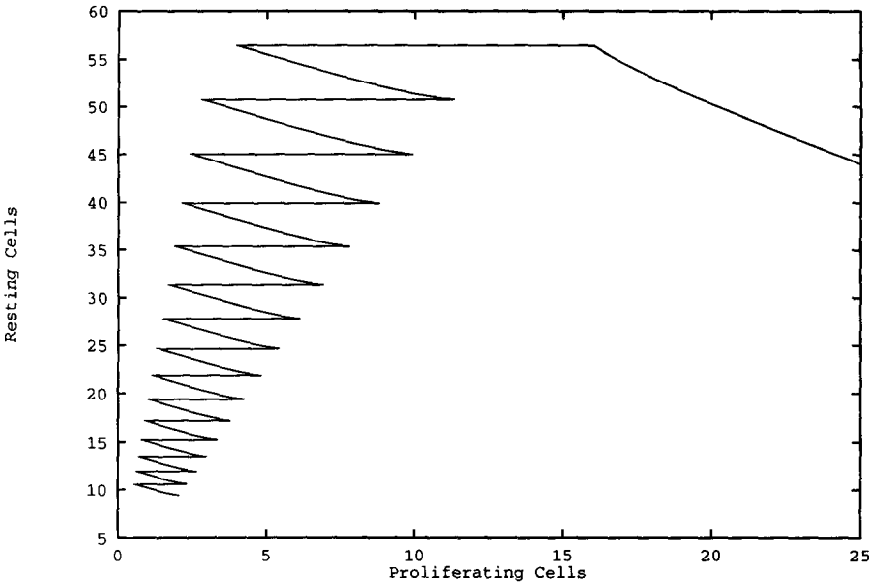

Figure 11. Beta = 0.05, 15 doses.

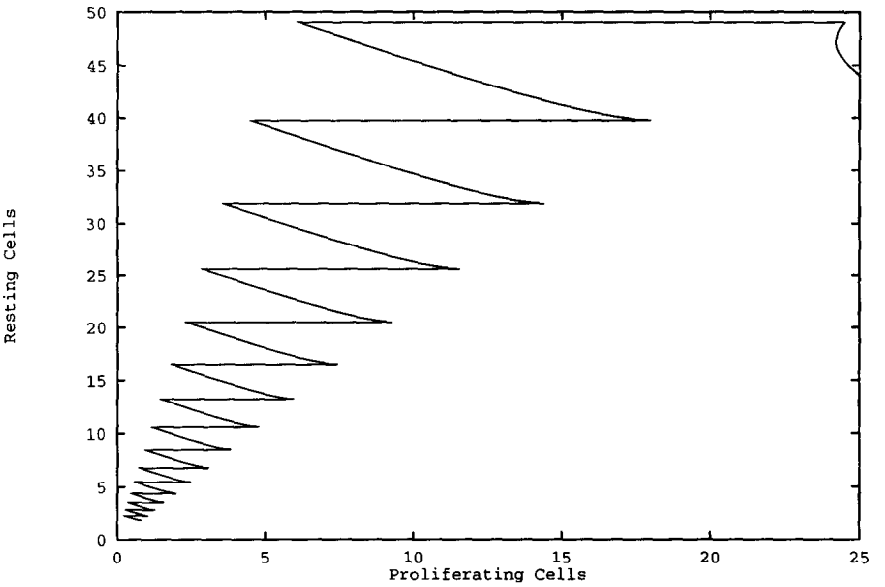

Figure 12. Beta = 0.1, 15 doses.

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 cycle-specific drug. This is modeled by an increase in the parameter β, which is the rate in which resting cells become proliferating, but can also be related to an increase in the cell growth rate. One question 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 of $\beta > 0$. 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 can be seen in Figure 6. Next, we note that the optimal period decreases as β is increased (see Figure 7). This can be understood as the cells

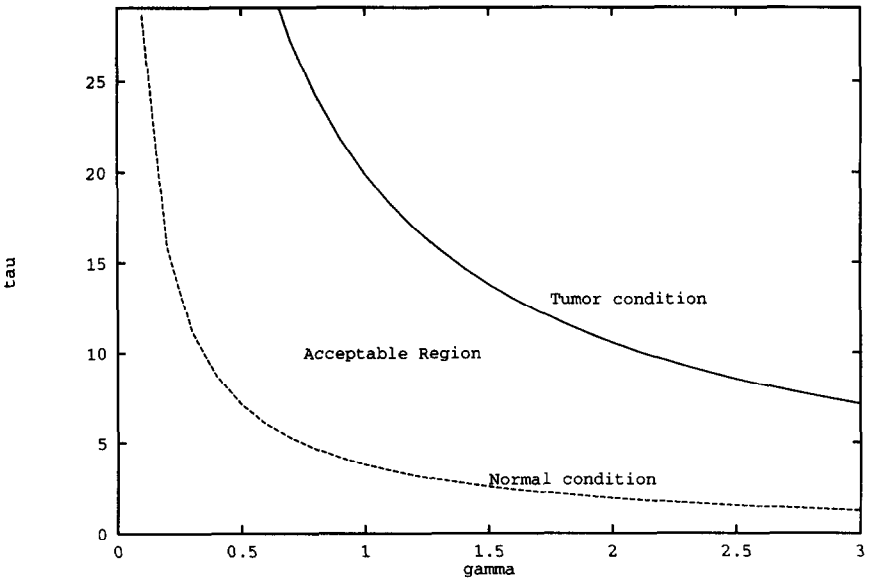

Figure 13. Bifurcation curves.

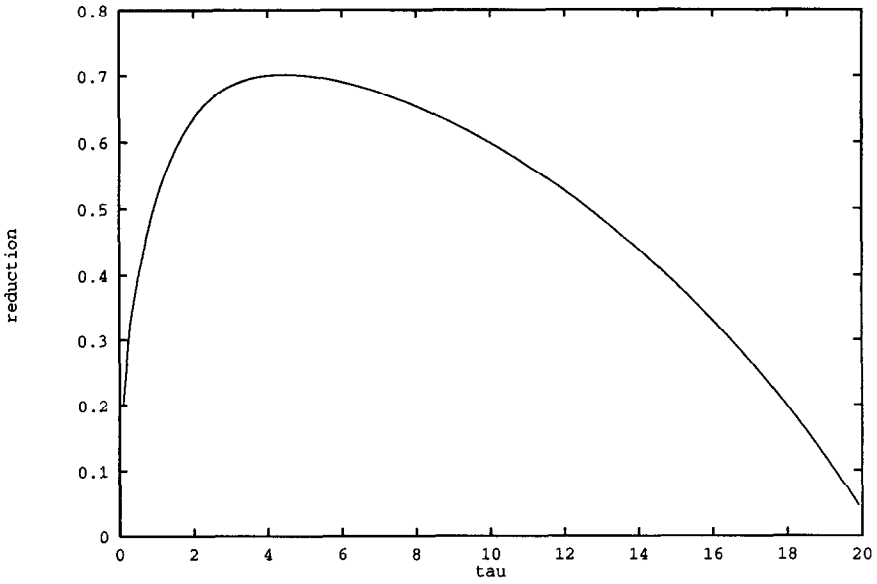

Figure 14. Tumor reduction.

are moving into the cycling compartment faster so we arrive at the optimal period faster. The most important fact 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 11 and 12. 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 about 85.6%, while reducing it 97.1% with $\beta = 0.1$. In this case, there is a 13.4% increase in tumor reduction.

4. PIECEWISE CASE

The model that we use in this case is based on equations (4),(5) and the normal tissue condition (9). Analytic solutions to the tumor equation can be found in terms of confluent hypergeo-

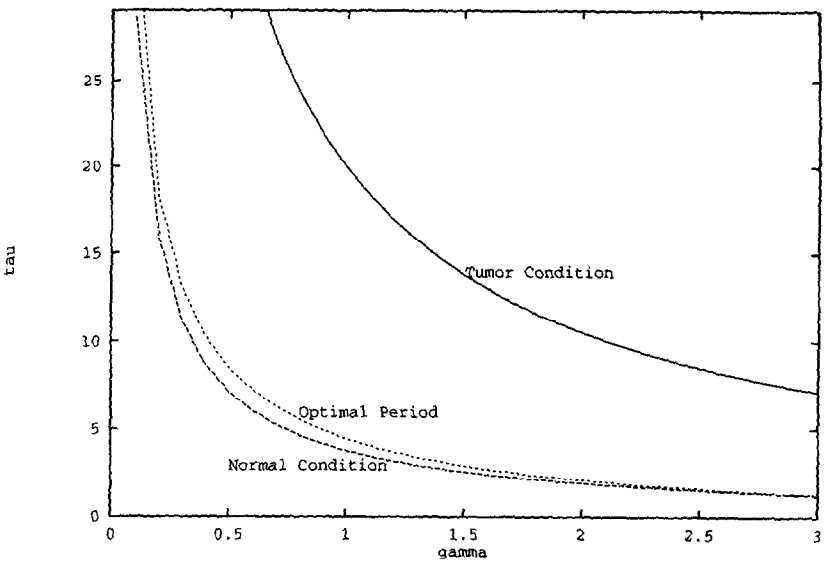

Figure 15. Bifurcation curves with optimal period curve.

metric functions (in preparation), but for the purposes of this article we only investigate numerical solutions to the above equations. In particular, we are interested in comparing the results of the pulsed therapy with those of the piecewise therapy. Note that the parameter γ in the piecewise case describes the decay rate of the chemotherapeutic drug. A large value of γ 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. First, the parameters are set as in the pulsed case with the new parameter $h = 0.5$ for both the normal and tumor equations. The first comparison of the two cases is with their bifurcation diagrams. Note the similarities between Figures 13 and 5. Both show similar regions in parameter space for acceptable period and strength. The main difference between the two is that in the piecewise case, since the drugs destroy cells over the complete period (not instantly as in the pulsed case), there is not the instantaneous drop in normal cell mass as there is in the pulsed case. Thus, in the piecewise case, we are not concerned about the cell mass instantly dropping below its critical value. Therefore, this model allows for larger drug doses. Note next the similarities between Figures 14 and 6. It should be recalled that the minimum eigenvalue means highest tumor reduction in Figure 6. Finally, Figure 15 shows the optimal period curve along with the bifurcation curves of both normal and cancerous tissue. The most interesting point to be made here is that unlike the pulsed case, the optimal period curve is completely in the acceptable region. 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 can see that they are basically equivalent. That is, if the clinician is to give a strong dose (γ small), then the optimal period and the smallest period that allows bone marrow recovery are almost identical.

5. 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 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 considered these situations, 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), between regimens that will and will not eliminate the tumor mass. As noted earlier, this is only intended to be a qualitative approach, and quantitative details will of course very from patient to patient. Clearly, a bifurcation diagram is not enough to develop a good chemotherapeutic regimen since 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 *not* delivering the drug as often as possible and as strongly as possible, but rather at the 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 nonoptimal periods to prevent overly destroying the normal tissue or a weaker dose must be administered.

Growth factors increasingly are being used to help cycle-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 are affecting the use of chemotherapeutic drugs on cancerous tissue. The pulsed model clearly shows that incorporating growth factors in (AML) increases the cell kill by about 13%–14%, and reduces the number of doses needed to accomplish the same results, while in breast cancer they 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.

The piecewise model of chemotherapy is the more realistic of the two studied in this paper, 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 using the piecewise model are qualitatively very similar to those obtained with the pulsed case. Only a few differences are noted. Because of this, very similar **qualitative** results may be drawn from either model. Therefore, 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.

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.) or 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.

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