



A Mathematical Model of Drug Resistance: Heterogeneous Tumors

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ABSTRACT

A mathematical model is developed to describe the growth and control of a heterogeneous tumor. The main aspect of the model is that it takes into account induced drug resistance. The mathematical model is a system of two ordinary differential equations that describes the growth of the cancer along with the effects of chemotherapy. The model is analyzed to determine what some of the critical parameters are; how we determine an effective treatment; how combination chemotherapy should be delivered; and how this model may help us develop more effective cancer chemotherapeutic treatments. © 1998 Elsevier Science Inc.

1. INTRODUCTION

A major cause of the failure of chemotherapeutic treatments for cancer is the development of resistance to drugs. If another non-cross-resistant drug is not available, then the cancer can grow unchecked and ultimately kill the patient. We would therefore like to get a better understanding of the growth kinetics of the cancer and, in particular, the growth kinetics that arise from the use of chemotherapy so that we may better understand the effects of drug resistance. The use of heterogeneous tumor models, which contain compartments for cells sensitive and cells resistant to the chemotherapeutic drugs will give us one way of modeling drug resistance. With these models, we hope to qualitatively define more efficient methods of delivering drugs when drug-resistant cancerous cells are present.

A variety of work has been done in the area of modeling heterogeneous tumors. One model designed to aid clinicians is by Birkhead et al. [1]. They set up a system of four linear differential equations that describe the dynamics of the sensitive, resistant, proliferating, and

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nonproliferating compartments of the cancer mass, thus modeling a heterogeneous cancer with four uniquely different types of cells. This model was originally developed for breast cancer, and in it they were looking not for detailed protocols but rather qualitative treatment strategies. They found parameter estimates and compared, through computer simulations, four various treatments, presenting the advantages of each.

The modeling of resistance is not without some controversy. Coldman and Goldie [2] developed a probabilistic model of cell mutations (which they suggest are a function of drug dose) resulting in drug resistance. With their model, they show that early detection and early therapy can lead to less chance of resistance because there is a fast change from a small to a large probability of resistance occurring as the tumor mass increases. They deduce that combination chemotherapy (alternating doses of non-cross-resistant drugs) should be as good as, and perhaps better than, sequential chemotherapy (m doses of first drug followed by n doses of second drug) in controlling drug resistance.

But Rosen [3] stated that he did not believe that, from their arguments, some of these conclusions can be drawn. In fact, he stated that they include "a number of incorrect hypotheses." He based this partly on the fact that he believes that resistance is *independent* of dose, whereas Coldman and Goldie state that "sensitive tumor cells have a fixed probability per division of acquiring resistance to a particular drug at a particular dose." That is, resistance is dose *dependent*. Rosen then proposes a simple differential equation model of tumor cell competition (i.e., a heterogeneous tumor with sensitive and resistant compartments), which he then simplifies to a model with first-order linear kinetics. He states that this would better model drug resistance. In a reply by Coldman and Goldie, they observe that he has *no* method of describing any form of drug resistance.

One of the problems in the preceding exchange is that there is some confusion on how they each define resistance. Coldman and Goldie's definition is in line with drug-*induced* resistance, whereas Rosen's definition follows that of *acquired* resistance—resistance resulting from genetic mutations independent of dose. Each type of resistance is physically different and thus modeled differently. Therefore, the methods of modeling drug resistance, along with how we define drug resistance, can vary widely and should be clarified before we embark on any model of drug resistance. In addition, part of the controversy is whether induced resistance even exists. Rosen suggests that resistance is due to selection (through cell competition) alone; that is, as sensitive cells are removed, the resistant cells have a better chance of competing and surviving. In fact, Birkhead et al. [1], Michelson et al. [4], and Michelson

and Leith [5, 6] consider mathematical models of acquired resistance including cell competition (see next paragraph). But, there is evidence that cancer cells are also induced to resistance by drugs. For example, in the mathematical model by Birkhead and Gregory [7], and subsequent clinical comparison with the model in Gregory et al. [8] and Souhami et al. [9], they investigate induced resistance in small cell lung cancer (SCLC). Their models and experiments indicated that as many as 36% of sensitive SCLC cells are induced to resistance per dose. In works by Schimke [10, 11], it is shown that Methotrexate (a chemotherapeutic drug) caused DHFR gene amplification, which in turn resulted in drug resistance.

Much of the mathematical work on tumor heterogeneity has been carried out by Michelson and colleagues. A good overview is given by Michelson and Leith [12], in which they review the theory and mathematics of much of the important literature in tumor heterogeneity, including much information on both induced and acquired resistance. Michelson and Leith [6] also present, in more mathematical detail, models that they developed in [4, 5]. Gyori et al. [13] considers the model in Michelson and Leith [6] with periodic doses. In each of these papers, the authors consider the effects of a single dose of Mitomycin C on the heterogeneous tumor system DLD-1 in nude mice. An interesting thing to note from their results is that the drug not only reduces the cancer cell mass, but alters the fundamental structure of the model by changing the model parameters. For example, they note that the Mitomycin C reduced the carrying capacity of the host (one of the model parameters) by 20–30%. Therefore, they note the importance of considering not only the direct effects of the drugs, but also the indirect effects. Each of the models that they examine is derived from the basic competition model in population dynamics with an added term to describe *acquired* resistance to the drugs as a result of cellular mutations. It should be noted that some of the models proposed and studied by Michelson and colleagues are similar to the model proposed by Rosen [3] in that all take into account cellular competition and acquired resistance.

In this paper, a linear system of two ordinary differential equations that model the sensitive and resistant tumor mass is proposed. Included are the effects of periodic chemotherapy, which are modeled either discretely (drug effects are instant) or piecewise continuously (see Figure 6). In the modeling process, we will take several justifiable assumptions. First, we will consider only the effects of the drug treatment on the cancerous tissue, though in previous work the effects of the treatment on normal tissue such as bone marrow have been taken into account [14, 16] (J. C. Panetta, Chemotherapeutic effects on hemato-

poiesis: a mathematical model. *Journal of Theoretical Medicine* (submitted)). Here, we are more concerned with the dynamics of the effects of the drugs on the heterogeneous tumor, and the addition of normal cell constraints will only make these dynamical issues harder to mathematically comprehend. However, it should be noted that combining this model with a constraint model such as that in (J. C. Panetta. Chemotherapeutic effects on hematopoiesis: a mathematical model. *Journal of Theoretical Medicine* (submitted)) could help in discussing the complete problem. Next, we will consider the model parameters constant, though they can be altered (in a constant fashion—i.e., not periodically) to account for known phenomena. We will also consider the parameters to be fixed for a particular drug regimen. Furthermore, we will consider only induced drug resistance. And finally, we will consider any combination of drugs to be non-cross-resistant, with no drug buildup over multiple doses.

With these models, we will answer several questions. First, what are the critical parameters in regard to effective drug treatment? This question is discussed by Skipper [17], who makes several deductions on the critical variables. He suggests that some of the critical parameters are: initial burden, mutation rates, doubling time, effectiveness of dose, and schedule of dose. And, in reference to combination chemotherapeutic regimens, he suggests that average relative dose intensity of the drugs in combination and time to overgrowth of cells resistant to one or more drugs in a combination are the important critical parameters. Second, what are some of the effective drug regimens? We will derive conditions with respect to some of the foregoing critical parameters that help in determining if a particular treatment will eradicate the tumor mass or at least how long the treatment will be effective. Third, what can the models tell us about methods of delivering drugs in combination? This question is perhaps the most difficult to answer and, according to Birkhead and Gregory [7], combination drug regimens are “proving difficult to evaluate.” They ask the question, Is it better to deliver combination doses of the form $A \Rightarrow B$ or $A \Rightarrow A$, where “A” and “B” are two non-cross-resistant drugs? In their paper, they conclude that the higher the rate of double resistance, the higher the B kill must be to make the switch to the drug B. We will consider a similar comparison of combination chemotherapy with the models developed here. As of now, there are a multitude of cancer drugs available for treatment, each having slightly different effects. Therefore, we cannot rely on trial-and-error methods of determining effective combinations of these drugs; the hope is that these models may help in determining which combinations might be more effective. Finally, we will compare these models with clinical results. Although the availability of relevant clinical data is

limited, we will show that the results of these models, at least in a qualitative sense, conform to the known clinical results.

2. THE MODEL

The general heterogeneous tumor model with induced resistance that we will consider is of the form

$$\frac{dx}{dt} = [r_1 - d_1(t)]x, \quad (1)$$

$$\frac{dy}{dt} = b_1 d_1(t)x + [r_2 - d_2(t)]y, \quad (2)$$

where x represents the sensitive cell mass and y represents the resistant cell mass. The various parameters are as follows. $0 \leq b_1 \leq 1$ is the induction rate due to the chemotherapeutic drug effective against the sensitive cells. This induction rate can range from almost zero to nearly 50% of the surviving sensitive cells. For example, for small cell lung cancer (Section 2.1.3), the induction rate can be as high as 36%. $d_1(t)$ and $d_2(t)$ are periodic functions of period τ_1 and τ_2 , respectively, which represent the rate of cell lost owing to the non-cross-resistant drugs effective against the sensitive and resistant cells, respectively. Note that, if y is totally resistant, then $d_2(t) \equiv 0$. For ease of notation, we will use the letter "A" to denote the drug effective against x -cells, the letter "B" to denote the drug effective against y -cells. Note that Equation (1) is decoupled from Equation (2); thus, we can examine just Equation (1) and then determine the dynamics of the resistant compartment, Equation (2), separately.

2.1. PULSED THERAPY CASE

A convenient method of simplifying the model to a very tractable state is to consider that the drug effects are instantaneous; there is an immediate reduction in cell mass with each dose. We call this pulsed therapy, although this is obviously not physically explicitly related to the kinetics of the drugs, it is practical in the sense that clinical data are collected in a discrete fashion; thus we model it in a discrete form. This model is only a slight modification of Equations (1) and (2) and is of the form

$$\frac{dx}{dt} = r_1 x, \quad x_{n\tau}^+ = [f(D)(1 - R(D))]x_{n\tau}^-, \quad (3)$$

$$\frac{dy}{dt} = r_2 y, \quad y_{n\tau}^+ = \tilde{f}(D)y_{n\tau}^- + AVG[\tilde{f}(D)f(D)]R(D)x_{n\tau}^-, \quad (4)$$

where $x_{n\tau}^-$ and $y_{n\tau}^-$ represent the cell masses just prior to the n th chemotherapeutic dose; $x_{n\tau}^+$ and $y_{n\tau}^+$ represent the cell masses just after

the n th chemotherapeutic dose; n represents the dose number; τ is the length of the dose; $f(D)$, a function of dose D , represents the survival fraction of cells sensitive to drug A—see Berenbaum [18] for possible forms of $f(D)$; $\tilde{f}(D)$, a function of dose D , represents the survival fraction of cells resistant to drug A but affected by the non-cross-resistant drug B; and $R(D)$ represents the percentage of cells *induced* to resistance as a function of dose (this can range from very small to about 50%). In Equation (3), $[f(D)(1 - R(D))]$ represents the percentage of sensitive cells that survive the n th dose of drug A and remain sensitive to it, whereas $AVG[\tilde{f}(D)f(D)]R(D)$ in Equation (4) represents the percentage of sensitive cells that survive a weighted average of both drugs A and B on the n th dose and become resistant. One suggested form of this weighted average is

$$AVG[\tilde{f}(D)f(D)] = f^\alpha(D)\tilde{f}^{1-\alpha}(D), \quad (5)$$

where, if $\alpha = 0$, then drug A has no effect on the induced cells but, if $\alpha = 1$, then drug B has no effect on the induced cells. In the absence of chemotherapy, the two subpopulations grow exponentially and independently. Therefore, the only interaction between the two populations in this specific model is through the sensitive cells being *induced* to resistance by the chemotherapeutic drugs.

Next, we consider how the parameters of the pulsed model relate to those of the original model. First, compare the sensitive cell mass for each model [Eqs. (1) and (3)]. Here, the terms $f(D)(1 - R(D))$ and $d_1(t)$ both describe the effects of the drug on the sensitive cells. If $f(D)(1 - R(D))$ is small, then few sensitive cells survive the dose. This is equivalent to a strong dose, which is represented in Equation (1) by a large $\langle d_1(t) \rangle_{\tau_1}$; that is, the mean value of $d_1(t)$ over one period of treatment [see Eq. (41)]. Therefore we observe that

$$f(D)(1 - R(D)) \propto \frac{1}{\langle d_1(t) \rangle_{\tau_1}}. \quad (6)$$

In a similar manner, we observe that, for the drug effects on the resistant cell mass in the pulsed model [Eq. (4)], small $\tilde{f}(D)$ again represents a strong dose; that is, few resistant cells survive the dose. This is equivalent in Equation (2) to a large $\langle d_2(t) \rangle_{\tau_2}$. Thus, for the resistant cell mass, we observe that

$$\tilde{f}(D) \propto \frac{1}{\langle d_2(t) \rangle_{\tau_2}}. \quad (7)$$

Finally, we can compare the induction parameters of the two forms of the model. The effects of induced resistance in Equations (2) and (4) are modeled by $bd_1(t)$ and $AVG[\tilde{f}(D)f(D)]R(D)$, respectively. Using Equations (5) and (6), we observe that

$$b \propto \left(\frac{\tilde{f}(D)}{f(D)} \right)^{1-\alpha} \frac{R(D)}{1-R(D)}. \quad (8)$$

From this, we see that small b is equivalent to either a small $R(D)$ —only a small percentage of sensitive cells are induced to resistance—or $\tilde{f}(D) \ll f(D)$ —drugs affecting the resistant cells are much stronger than those affecting the sensitive cells. (This is probably not the case.)

Now, we will analyze the pulsed model in a manner similar to that in [14] and [16]. First, note that Equation (3) decouples from Equation (4). Thus, we can first consider just the condition that will lead to sensitive cell destruction. Solving Equation (3) on the interval $n\tau \leq t < (n+1)\tau$, we obtain

$$x = x_{n\tau} e^{r_1(t-n\tau)}, \quad (9)$$

where $x_{n\tau}$ is the sensitive cell mass at time $n\tau$ (i.e., the initial value on the given interval). Taking into account the pulsed condition for Equation (3), we obtain the following difference equation:

$$x_{(n+1)\tau} = f(D)(1-R(D))e^{r_1\tau}x_{n\tau}, \quad (10)$$

which describes the state of the sensitive cells at the beginning of each dose. Thus, the condition for the sensitive cells to be destroyed is

$$f(D)(1-R(D))e^{r_1\tau} < 1. \quad (11)$$

Next, let us consider the effects on the resistant cell mass y . The solution to the resistant equation on the interval $n\tau \leq t < (n+1)\tau$ is

$$y = y_{n\tau} e^{r_2(t-n\tau)}, \quad (12)$$

where $y_{n\tau}$ is the resistant cell mass at time t . In this case, the difference equation describing the state of the resistant cells is

$$y_{(n+1)\tau} = [\tilde{f}(D)y_{n\tau}^- + AVG[\tilde{f}(D)f(D)]R(D)x_{n\tau}^-]e^{r_2\tau}, \quad (13)$$

and the condition for the resistant cells to be destroyed, given that sensitive cells are destroyed (a logical deduction), is

$$\tilde{f}(D)e^{r_2\tau} < 1. \quad (14)$$

Clearly, we can see that stronger doses [smaller $f(D)$ and $\tilde{f}(D)$] and shorter periods are better. An example of a successful regimen [conditions (11) and (14) holding] can be seen in Figure 1, left, and a unsuccessful regimen [condition (11) holds, but condition (14) does not] is shown in Figure 1, right. (Note that, in each of these graphs, interpolation lines are drawn between each dose so that it is easier to view.) These two results compare well with graphs of various clinical results given by Skipper [17].

From foregoing conditions on effective drug treatments, we can form conclusions on what some of the critical parameters are. That is, from Equations (11) and (14) we see that the dose, period, induction rate, and growth rate of the cells are important in determining effective drug treatments. Of these parameters, the two that are hardest to clinically predict are the induction rates and growth rates. With methods of measuring tumor mass by computed tomographic scans [8, 9], some of these parameters can be implicitly estimated. More importantly, there are two other questions that we will like to answer. First, if $\tilde{f}(D) \equiv 1$ (i.e., total resistance), when is the NADIR (the lowest obtainable cancer mass)? Second, what is the better method of giving combinations of non-cross-resistant drugs?

2.1.1. NADIR

If both conditions (11) and (14) hold, then the tumor will be eradicated. But, in many cases, $\tilde{f}(D) \equiv 1$ or at least condition (14) does not hold; that is, the drugs have little or no effect on the resistant cells. In this case, it is important to know how many doses of the drug can be administered before the *total* tumor mass stops regressing; that is, the NADIR. Mathematically, we use a definition similar to that of Skipper [17]; that is, the NADIR is the value of n (dose number) such that n solves

$$\frac{y_{n\tau}}{x_{n\tau}} = 1, \quad (15)$$

given that all the other parameters are fixed. Because we explicitly have both $x_{n\tau}$ and $y_{n\tau}$ for this model, we can analytically find the NADIR. First, note that

$$\begin{aligned} \frac{y_{(n+1)\tau}}{x_{(n+1)\tau}} &= \frac{\tilde{f}(D)}{f(D)(1-R(D))} e^{(r_2-r_1)\tau} \frac{y_{n\tau}}{x_{n\tau}} \\ &\quad + \frac{AVG[\tilde{f}(D)f(D)]R(D)}{f(D)(1-R(D))} e^{(r_2-r_1)\tau}. \end{aligned} \quad (16)$$

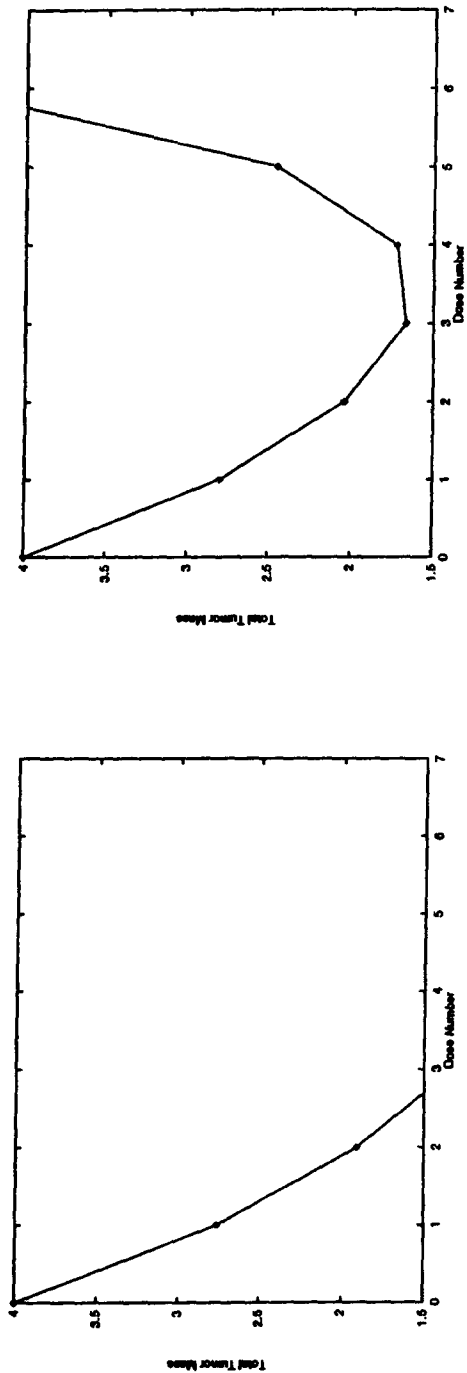
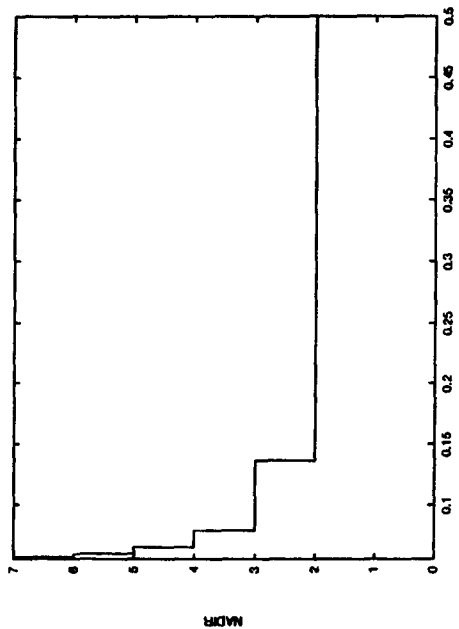
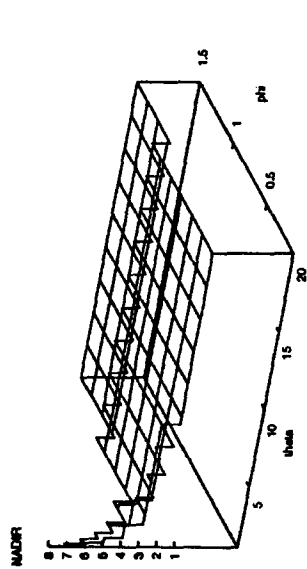
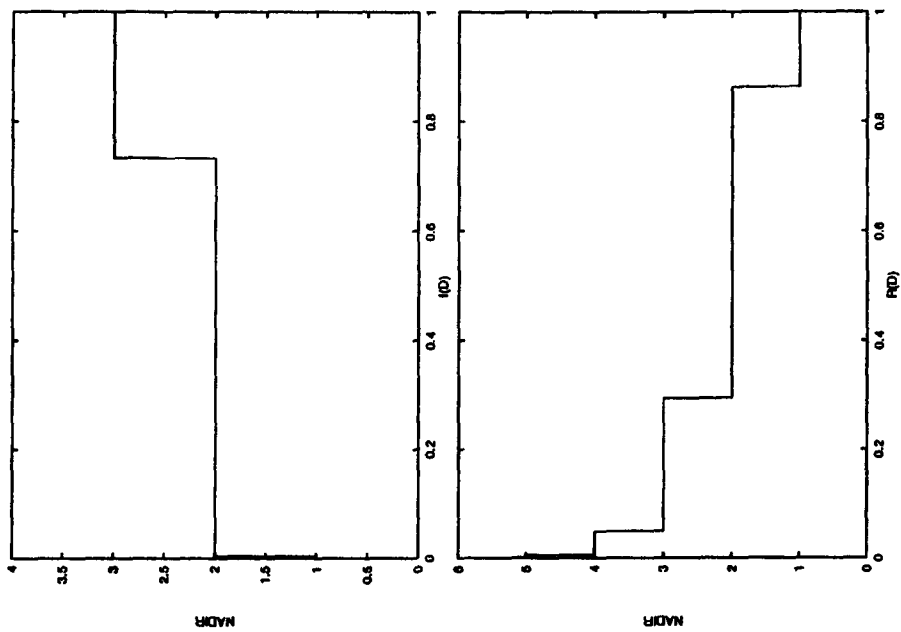


FIG. 1. Total tumor mass versus dose number: (left) successful regimen; (right) unsuccessful regimen.



Making the following substitutions,

$$u_n = \frac{y_{n\tau}}{x_{n\tau}}, \quad (17)$$

$$\Theta = \frac{\tilde{f}(D)}{f(D)(1-R(D))} e^{(r_2-r_1)\tau}, \quad (18)$$

$$\Phi = \frac{AVG[\tilde{f}(D)f(D)]R(D)}{f(D)(1-R(D))} e^{(r_2-r_1)\tau}, \quad (19)$$

we arrive at the difference equation

$$u_{n+1} = \Theta u_n + \Phi, \quad (20)$$

which has the solution

$$u_n = \Theta^n u_0 + \Phi \left(\frac{\Theta^n - 1}{\Theta - 1} \right). \quad (21)$$

To find the NADIR, set Equation (21) equal to 1 and solve for n . Doing this, we find that

$$n = \frac{\ln \left[\frac{\Theta - 1 + \Phi}{(\Theta - 1)u_0 + \Phi} \right]}{\ln \Theta} \quad (22)$$

and the NADIR is

$$NADIR = \text{integer part} \left(\frac{\ln \left[\frac{\Theta - 1 + \Phi}{(\Theta - 1)u_0 + \Phi} \right]}{\ln \Theta} \right) + 1. \quad (23)$$

From Figure 2, upper left, we observe that the NADIR is higher for Θ near 1 and Φ near 0. This can relate to $R(D)$ being small (small induced resistance) and $f(D) \approx \tilde{f}(D)$ (drug kills are very similar). Figure 2, upper right, lower left, and lower right), shows the NADIR with respect to $f(D)$, $\tilde{f}(D)$, and $R(D)$, using the average defined in Equation (5) with $\alpha = 0.8$.

FIG. 2. (Upper left) NADIR versus Θ and Φ ; (upper right) NADIR versus $F(D)$; (lower left) NADIR versus $\tilde{F}(D)$; (lower right) NADIR versus $R(D)$.

2.1.2. Combination Chemotherapy

One question not fully understood either mathematically or clinically is, In what combination should multiple chemotherapeutic drugs be given? We will use the pulsed version of our model to help understand what can be required in making the decision on how to administer combination chemotherapy.

One way to ask the question is; is it better to give combinations of non-cross-resistant drugs (A and B) in sequence ($A \Rightarrow A \Rightarrow A \cdots B \Rightarrow B \Rightarrow B \cdots$) or in combination ($A \Rightarrow B \Rightarrow A \Rightarrow B \cdots$)? To help answer this question, we first need to define a way to describe the group or combination of treatments. We will define a *cycle* as the time needed to give a complete combination of drugs; for example, ($A \Rightarrow B \Rightarrow A \Rightarrow B \cdots$) has a cycle of 2τ and ($A \Rightarrow A \Rightarrow B \Rightarrow B \Rightarrow A \Rightarrow A \Rightarrow B \Rightarrow B \cdots$) has a cycle of 4τ , where τ is the period of each treatment.

First, we will compare case 1, giving two drugs simultaneously every 2τ (i.e., $AB \Rightarrow AB \Rightarrow AB \cdots$) with case 2, alternating drugs every τ ($A \Rightarrow B \Rightarrow A \Rightarrow B \cdots$). For case 1, the difference equations [Eqs. (11) and (14)] are modified to be

$$x_{(n+2)\tau} = f(D)(1 - R(D))e^{2r_1\tau}x_{n\tau}, \quad (24)$$

$$y_{(n+2)\tau} = e^{2r_2\tau}(\tilde{f}(D)y_{n\tau} + \tilde{f}(D)^{1-\alpha}f^\alpha(D)R(D)x_{n\tau}) \quad (25)$$

[using Eq. (5) for the function $AVG(\tilde{f}(D), f(D))$]. For case 2, the difference equations are

$$x_{(n+4)\tau} = [f(D)(1 - R(D))e^{2r_1\tau}]^2 x_{n\tau}, \quad (26)$$

$$y_{(n+4)\tau} = e^{2r_2\tau}\tilde{f}(D)\left[e^{2r_2\tau}\tilde{f}(D)y_n + f^\alpha(D)R(D)\{e^{2r_2\tau}\tilde{f}(D) + f(D)(1 - R(D))e^{2r_1\tau}\}x_n\right]. \quad (27)$$

Both have the same conditions for tumor eradication; that is,

$$f(D)(1 - R(D))e^{2r_1\tau} < 1, \quad (28)$$

$$\tilde{f}(D)e^{2r_2\tau} < 1. \quad (29)$$

But this does not indicate which case will eradicate the cancer faster. To do this, we will compare the results of each case over one cycle, with the initial tumor burden being totally sensitive. Using Equations (24)–(27), we can show that, for $\alpha = 0$, case 1 and case 2 are equivalent at the end of each cycle and, for $0 < \alpha \leq 1$, case 2 has a smaller cancer mass than case 1 at the end of the cycle (Figure 3).

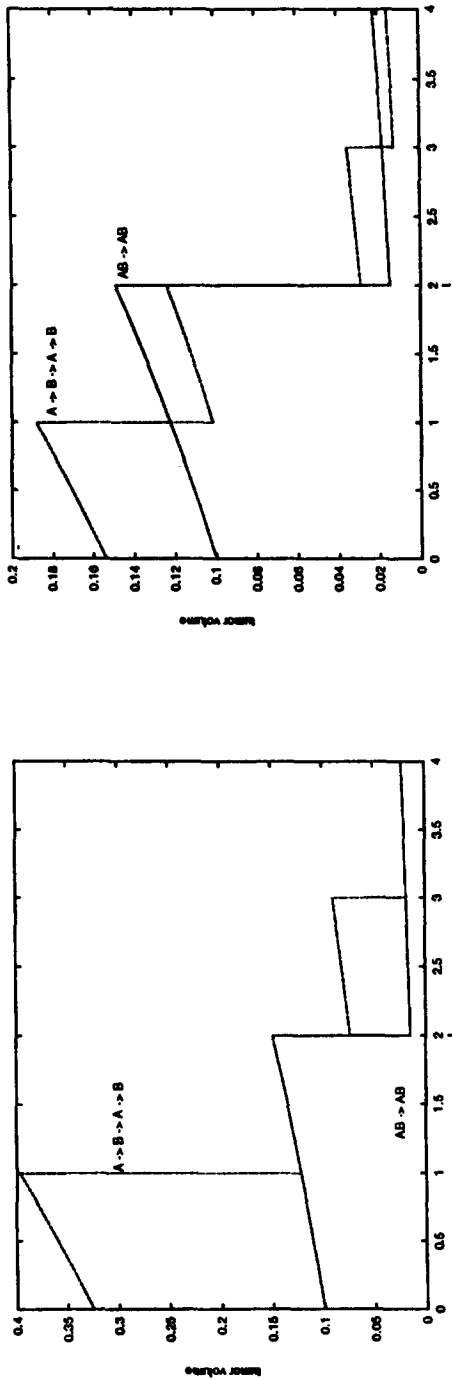


FIG. 3. Total tumor volume versus time: $\alpha = 0, \alpha = 0.5$.

Next, we will compare case 2 ($A \Rightarrow B \Rightarrow A \Rightarrow B \dots$) with case 3 ($A \Rightarrow A \Rightarrow B \Rightarrow B \Rightarrow A \Rightarrow A \dots$). Again, we will let the initial tumor burden be totally sensitive. For this, we will need to view the tumor mass every 4τ ; that is, the cycle is 4τ . The difference equations for case 3 are

$$x_{(n+4)\tau} = ([f(D)(1-R(D))]e^{2r_1\tau})^2 x_{n\tau}, \quad (30)$$

$$y_{(n+4)\tau} = e^{2r_2\tau} \tilde{f}^2(D) [e^{2r_2\tau} y_n + f^\alpha(D) R(D) e^{r_2\tau} \{e^{r_2\tau} + f(D)(1-R(D))e^{r_1\tau}\} x_n]. \quad (31)$$

Note that the conditions for tumor eradication do not change from conditions (28) and (29). Comparing case 2 and case 3, we find that, if

$$e^{r_1\tau} < \tilde{f}(D) e^{r_2\tau}, \quad (32)$$

case 2 ends with a smaller cancer mass than does case 3. But this condition cannot hold if the treatment is to be effective. This is because condition (14) must hold, which implies that $e^{r_1\tau} < 1$, and this is not true. Therefore, case 3 is *always* better than case 2 when starting with a tumor that is initially totally sensitive.

The preceding problem of determining which combination is better leads us to ask, Is it better to follow a dose of drug A with another dose of A ($A \Rightarrow A$) or to follow a dose of drug A with a dose of drug B ($A \Rightarrow B$)? Using the difference equations

$$x_{(n+2)\tau} = [f(D)(1-R(D))]^2 e^{2r_1\tau} x_{n\tau}, \quad (33)$$

$$y_{(n+2)\tau} = e^{r_2\tau} [e^{r_2\tau} y_n + f^\alpha(D) R(D) \{e^{r_2\tau} + f(D)(1-R(D))e^{r_1\tau}\} x_n] \quad (34)$$

to describe $A \Rightarrow A$ and the difference equations

$$x_{(n+2)\tau} = f(D)(1-R(D))e^{2r_1\tau} x_{n\tau}, \quad (35)$$

$$y_{(n+2)\tau} = \tilde{f}(D)e^{2r_2\tau} [y_n + f^\alpha(D) R(D) x_n] \quad (36)$$

to describe $A \Rightarrow B$, we can determine which method has the larger total cancer mass reduction over one cycle (2τ) in terms of the ratio of resistant to sensitive tumor cells $u_n = y_{n\tau} / x_{n\tau}$. The condition for it to be better to use $A \Rightarrow A$ over $A \Rightarrow B$ is

$$u_n < \frac{f(D)(1-R(D)) - [f(D)(1-R(D))]^2}{1 - \tilde{f}(D)} e^{2(r_1-r_2)\tau} - f^\alpha(D) R(D) - \frac{f^{\alpha+1}(D) R(D)(1-R(D))}{1 - \tilde{f}(D)} e^{(r_1-r_2)\tau}. \quad (37)$$

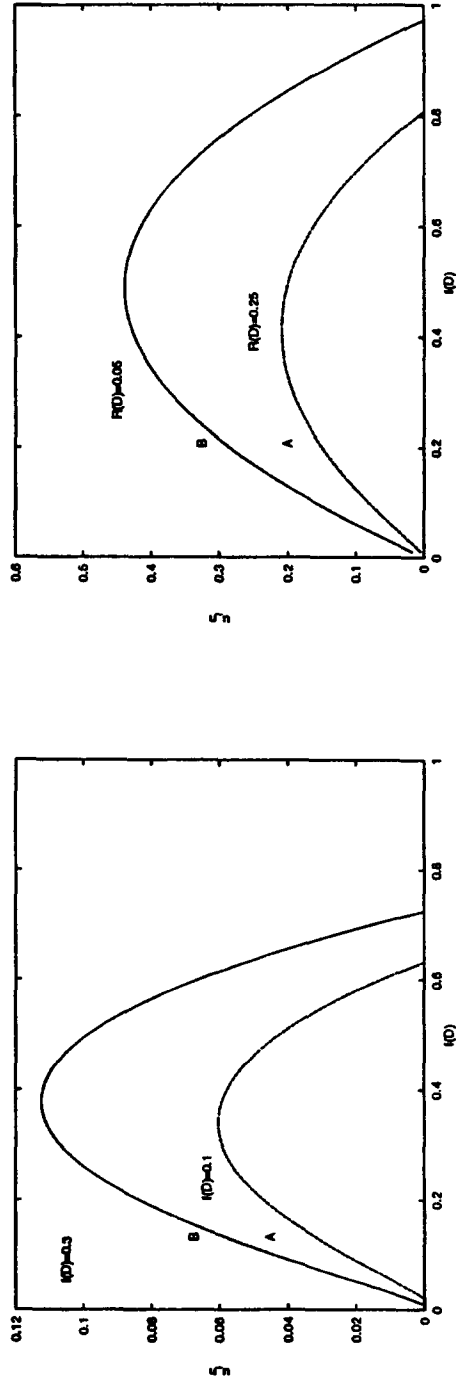


FIG. 4. u_n versus $f(D)$. Bifurcation curve: $A \Rightarrow B$ is the better regimen for values of u_n and $f(D)$ above the curve, and $A \Rightarrow A$ is the better regimen for values of u_n and $f(D)$ below the curve.

After observing graphs of Equation (37) with respect to $f(D)$ (Figure 4), we see that, when the tumor is more x -like [point A on the graphs with $\tilde{f}(D) = 0.3$ and $R(D) = 0.05$], then $A \Rightarrow A$ is better. But, when the tumor is more y -like (point B on the graphs) then $A \Rightarrow B$ is better. Another observation is that the better drug B is, the more likely we should switch to it. For example, at point A on Figure 4, left, the model suggests that $A \Rightarrow A$ be used if $\tilde{f}(D) = 0.3$, but that $A \Rightarrow B$ be used if $\tilde{f}(D) = 0.1$. In addition, we can observe from Figure 4, right, that the larger $R(D)$ is, the more likely $A \Rightarrow B$ will be the better choice. That is, at point A with $R(D) = 0.05$, $A \Rightarrow A$ is better, but, if $R(D) = 0.25$, $A \Rightarrow B$ is better.

2.1.3. Clinical Results

One clinical test helpful in discussing these models is given in Gregory et al. [8] and Souhami et al. [9]. They calculate various critical parameters related to their model, such as drug kill and resistant proportion, using clinical data from SCLC patients. They derive these by delivering two doses of cyclophosphamide and measuring the tumor volume between each dose with a Computer Tomography (CT) scan. With an estimated cell doubling time of 30 days, the mean tumor volume reduction [$1 - f(D)$ in our model] per dose was 95% and the mean proportion of the tumor resistance after the first dose was approximately 15% [$R(D)$ in our model]. For a doubling time of 70 days, the mean tumor volume reduction was 91% and the mean proportion of tumor resistance after the first dose was approximately 36%. In both cases, the period between doses was 8 weeks. We would like to see how this specific clinical trial relates to our pulsed model.

First, by calculating the growth-rate parameter, we find that, for the doubling time of 30 days, $r_1 = 0.0231$ and, for the doubling time of 70 days, $r_1 = 0.0099$. For our model, we will let $r_1 = r_2$. Now, we would like to see how the parameters given in [8] and [9] relate to our conditions on tumor growth and decay; that is conditions (11) and (14). For the doubling time of 30 days, condition (11) is $0.155 < 1$. Therefore, our model would predict that the sensitive cells can be eradicated (they come to basically the same conclusion). For the doubling time of 70 days, condition (11) is $0.1000 < 1$ and again our model would predict that the sensitive cells would be eradicated. Next, if the drug has no effect on the resistant cells [$\tilde{f}(D) = 1$], then, for the doubling time of 30 days, condition (14) is $3.646 > 1$. Therefore the resistant compartment would *not* be eliminated. In fact, the model predicts that we would need a non-cross-resistant drug with $f(D) < 0.274$ to also eliminate the resistant compartment. For the doubling time of 70 days, condition (14) is $1.74 > 1$, and again the resistant compartment would *not* be elimi-

nated. Here, $\tilde{f}(D) < 0.574$ to eliminate the resistant compartment. This is in fact the result observed with SCLC; rapid initial success with treatment, but eventual relapse of the cancer.

Next, we calculated the NADIR for each case. In both cases we found that the NADIR was 2. Therefore, this model predicts that it is not practical to give more than the two doses of cyclophosphamide. Thus, it can be seen that there is a clear need for a non-cross-resistant drug if chemotherapy is to eradicate SCLC.

Possibly one of the more important aspects of the model is in helping determine methods of delivering combination chemotherapy. Gregory et al. [8] notes that it is clinically difficult to evaluate combination chemotherapy. Thus, we ask, What does our model suggest about methods of delivering combination chemotherapy in this specific clinical trial? That is, when should we start to give the second non-cross-resistant drug? Using the parameters calculated from this set of clinical data, we plot condition (37) with respect to $\tilde{f}(D)$. Figure 5 represents the bifurcation of $A \Rightarrow A$ or $A \Rightarrow B$ being better. Because the ratio of resistant to sensitive cells (u_n) at which we should switch to the non-cross-resistant drug ranges from 0% to 5.5% in the models of these

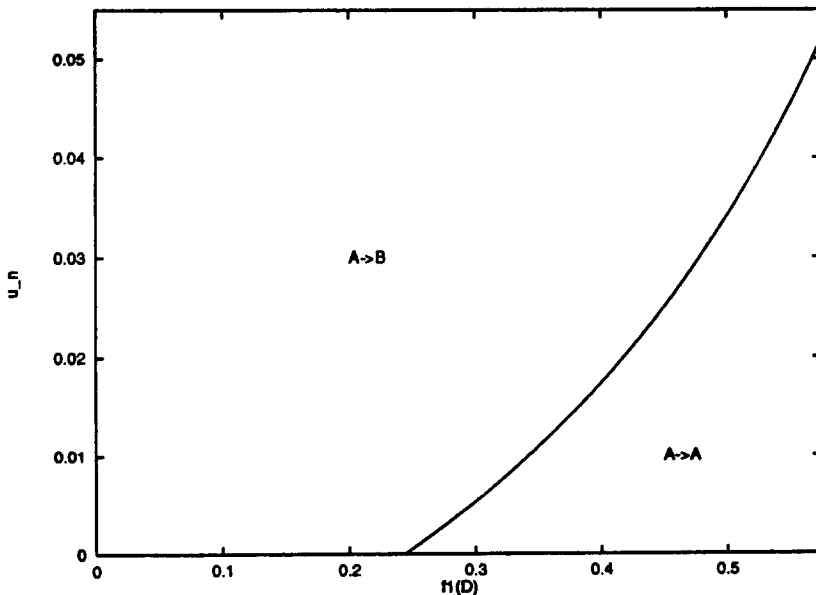


FIG. 5. u_n versus $\tilde{f}(D)$. Bifurcation curve: $A \Rightarrow B$ is the better regimen for values of u_n and $\tilde{f}(D)$ above the curve, and $A \Rightarrow A$ is the better regimen for values for u_n and $\tilde{f}(D)$ below the curve.

two cases, and the first dose induced between 15% and 36%, then this model predicts that it is important to deliver the non-cross-resistant drug next to effectively continue to reduce the total tumor mass. Thus, it is important not only to have the non-cross-resistant drug, but, in this case, to give it as soon as possible because of the high rate of induced resistance.

One nice consequence of this model is that, when we have the parameters set for a particular patient, then the model can act as a predictor for how to proceed with the therapy. Thus, through the NADIR calculation along with the predicted time to switch to the second non-cross-resistant drug, we can help in determining the possible future course of chemotherapy.

2.2. PIECEWISE-CONTINUOUS THERAPY CASE

Next, we consider the chemotherapeutic drugs acting in a piecewise-continuous fashion governed by the piecewise-continuous functions $d_i(t)$ in Equations (1) and (2). The piecewise-continuous functions can be in the form of the step function [Eq. (38)], the exponential function [Eq. (39)], or the modified exponential function [Eq. (40); see Figure 6].

$$d_i(t) = \begin{cases} D_i, & n\tau \leq t < a_i + n\tau \\ 0, & a_i + n\tau \leq t < (n+1)\tau, \end{cases} \quad (38)$$

$$d_i(t) = D_i e^{-a_i(t-n\tau)}, \quad n\tau \leq t < (n+1)\tau, \quad (39)$$

$$d_i(t) = D_i(e^{-a_i(t-n\tau)} - e^{-c_i(t-n\tau)}), \quad n\tau \leq t < (n+1)\tau, \quad c_i > a_i, \quad (40)$$

where D is drug strength.

By defining the mean value function as

$$\langle f(t) \rangle_{\tau_i} = \frac{1}{\tau_i} \int_0^{\tau_i} f(t) dt, \quad i = 1, 2, \quad (41)$$

we are able to find the bifurcation from exponential growth to decay of Equations (1) and (2). Integrating Equation (1) over its period τ_1 , we obtain the condition

$$\frac{1}{r_1} \langle d_1(t) \rangle_{\tau_1} > 1, \quad (42)$$

which is required to prevent sensitive cell growth. If this condition does *not* hold, then there will be both sensitive and resistant cell growth. If this condition holds, then the sensitive cells will decay, and we find that

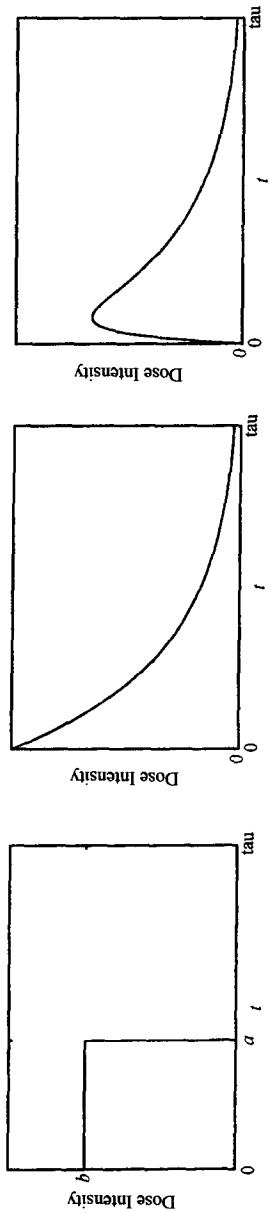


FIG. 6. Step function, exponential function, and modified exponential function.

the condition for the decay of the resistant cells is governed by

$$\frac{1}{r_2} \langle d_2(t) \rangle_{\tau_2} > 1. \quad (43)$$

In Section 2.1, we observed how the parameters for the pulsed model and this form of the model are related [see Eqs. (6)–(8)]. Here, we note that the two bifurcation equations in this section [Eqs. (42) and (43)] are also directly related to the bifurcation equations for the pulsed case [Eqs. (11) and (14)], given the proportionality relations in Equations (6) and (7).

3. CONCLUSIONS

In this paper, a heterogeneous tumor model with chemotherapy and induced drug resistance is discussed. It is the hope that, by a close investigation of these models, we will come to a better understanding of the kinetics of cancer chemotherapy and be able to help determine more effective methods of delivering combinations of chemotherapeutic drugs.

In these models, we have considered some of the main critical parameters including dose, period, induction rate, and growth rate. These parameters are important to know because, if the clinical data does not allow us to determine them either directly or implicitly, then the model will have little hope of being of any use in determining effective combination chemotherapeutic treatments. As noted earlier, with newer clinical techniques available (e.g., CT scans) for measuring tumor mass, we have a better hope of determining these critical parameters and thus more accurately modeling the chemotherapeutic effects. In fact, using these measurements in our model, we are able to derive conditions needed for tumor reduction. These basic conditions give us a place to start looking for effective treatment regimens. In fact, we have shown how these conditions fit well with clinical data from SCLC.

When we had determined these conditions on tumor growth and decay, we were able to find conditions for effective methods of delivering combination chemotherapy. In the pulsed therapy case, we analytically derived the condition to determine when we should switch to a second non-cross-resistant drug. This condition was related to the ratio of resistant to sensitive tumor cells. From this, we determined that we should switch to drug B sooner if the rate of induction is high or drug B is very effective. Note that this is a similar conclusion to that given by Birkhead and Gregory [7]: the higher the rate of double resistance, the higher the B kill must be to make the switch to drug B.

It is the hope that the models in this paper can form the basis for more mathematical models and may help qualitatively guide clinical

trials to help control the problem of drug resistance in cancer chemotherapy.

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