Bulletin of Mathematical Biology, Vol. 58, No. 3, pp. 425–447, 1996
Elsevier Science Inc.

0092-8240/96 $15.00 + 0.00

0092-8240(95)00346-0

A MATHEMATICAL MODEL OF PERIODICALLY PULSED CHEMOTHERAPY: TUMOR RECURRENCE AND METASTASIS IN A COMPETITIVE ENVIRONMENT

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A competition model describing tumor–normal cell interaction with the added effects of periodically pulsed chemotherapy is discussed. The model describes parameter conditions needed to prevent relapse following attempts to remove the tumor or tumor metastasis. The effects of resistant tumor subpopulations are also investigated and recurrence prevention strategies are explored.

1. Introduction. Mathematical models of cancer chemotherapy can indicate how micro-environmental interactions between tumor and normal cells can effect the outcome of the chemotherapy and the ability for a tumor to recur or metastasize. These interactions can include competition for nutrients, the effects of various growth factor or the effects of the immune system. As stated by Knolle (1988), 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 (1979) also noted 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. Also, Miller *et al.* (1981) stated that "Investigation of growth and control of neoplasia must take into account the natural control mechanisms existent for tumors."

There has been a variety of research done in this area. An early review article by Aroesty *et al.* (1973) gave a comprehensive description of many of the basic ideas in cell kinetics and chemotherapy. Berenbaum (1969) took a straightforward approach to modeling the effects of therapy. He derived

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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 is via optimization theory. Murray (1990) modeled the cell populations with Gompertz growth and continuous cell kill and minimized 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 or the effects of a resistant subpopulation on therapy. Though it is understood that some tumors such as lung or brain tumors do *not* show interative properties with their local environment, in many other cases as described forthwith, various local interactions can and do occur. Adding these features to the model will make it more realistic. Cornil *et al.* (1991) addressed the question of the effects that adjacent normal tissue such as fibroblasts have on human melanoma cells. In their *in vitro* experiments, they showed early stages of melanoma cells were *suppressed* by normal dermal fibroblasts (i.e. a negative growth factor from normal tissue) and advanced stages of melanoma cells were *stimulated* in the presence of normal dermal fibroblasts (i.e. a positive growth factor from the normal tissue). They note that this positive growth factor may be an explanation for the ability of a small but competent metastatic growth to "escape" from a local growth constraints. In another study, Miller *et al.* (1981) showed that preneoplastic cells are suppressed by normal mammary cells but stimulated by more advanced mammary carcinoma lesions. Gatenby (1991, 1994) investigated this tumor–host relationship by considering the interaction to be both the effects of the immune system (for small tumor mass) and competition for resources by epithelial and mesenchymal cells. In particular, he considered the competition with a small number of cancer cells. Bellomo and Forni (1994) developed a competition model that examined the interactions between the tumor, host, and immune system. They showed that for small tumor mass, the immune system can retard the growth of the tumor. Additionally, Liotta (1992) discussed how various growth factors produced by *both* normal and tumor tissues can either suppress or stimulate cell growth. Burger *et al.* (1994), Dotto *et al.* (1988) and La Rocca *et al.* (1989) also discussed various negative growth effects caused by various normal tissue to tumor cells. In terms of growth factors, Michelson and Leith (1993a) described how growth factor signals from the tumor, the local stroma, and the host can all affect the growth of the tumor.

Even more convincing evidence of the tumor–host interaction is discussed by Michelson and Leith (1995), where they described a similar signal process between the liver and the tumor after a partial hepatectomy. The

theoretical implications of this interaction between the tumor and the liver are *qualitatively* supported by studies by Paschkis *et al.* (1955), by Fisher and Fisher (1959) and, more recently, by Leith *et al.* (1992). It should be noted that (referring to the tumor–liver interaction) "At this point, we emphasize the fact that even though intriguing candidates for the signal processing elements in this system have been proposed, **no** experimental data explicitly defining these linkages has been generated" (Michelson and Leith, 1995). It is the hope that this and other theoretical work will encourage clinical tests that will more explicitly show the various interactions described in this and other papers.

Furthermore, resistant subpopulations are a major reason for failure of the chemotherapeutic regimens. Thus, adding resistance to the model can help us understand why the regimen is failing and help to find ways to eliminate the problem. Drug resistance must be taken into account because as tumors become resistant to drugs, the effects of the therapy are eventually reduced to ineffective levels. Two major types of drug resistance are applicable here: inherent and acquired. Inherent resistance refers to tumor cells that are resistant from the beginning of chemotherapy, whereas tumors cells which are initially susceptible to the drug, but develop resistance over time, are considered to acquire resistance. (We will only work with acquired resistance effects in this paper.)

Several researchers have modeled resistance. Swan (1981) investigated a model of radiotherapeutic resistance with resistant and sensitive cell populations modeled by first order (linear) kinetics, and compared the advantages and disadvantages of periodic and continuous irradiation. Goldie and Coldman (1979) showed the effect tumor size has on a tumor developing a resistant subpopulation. That is, the larger the tumor burden, the larger the probability the tumor will develop resistance. Birkhead and Gregory (1984) looked at a difference equation model of drug resistance, including non-cross-resistance (cell models which are not resistant to combinations of drugs). They looked at the ratio of sensitive tumor cells to total number of tumor cells, which can be found clinically, and used it to predict tumor size and to estimate model parameters. They also showed the point at which a drug becomes ineffective against a resistant tumor. In the case of non-cross-resistant therapy, Birkhead and Gregory discussed patterns of administration and gave conditions for administration strategies. Martin *et al.* (1992a, b) also looked at single and non-cross-resistant chemotherapy using optimization theory.

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 and heterogeneous tumor growth to include chemotherapy and tumor–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 and resistant tumor–normal cell environment. Works by Panetta and Adam (1995), Webb (1992a, b), Agur *et al.* (1988), and Cojocaru and Agur (1992) were directed to model various types of cycle-specific drug dynamics and are *not* covered in this paper. Most importantly, the models will investigate the use of chemotherapy to eliminate either a *small* tumor burden left after attempts to remove the main tumor mass (such as a mastectomy) or metastasized tumor mass, and in so doing will provide parameter conditions to prevent 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. Also, in the case of resistance, we will show definite regions of resistant growth without sensitive growth, thus leading to death of the host. Knowing these conditions can help in understanding and developing effective drug treatments.

2. The Model. Competition models from population biology have been used to model cell interactions. Gatenby (1991, 1994) investigated competition models of tumor–normal cell interaction, Michelson and Leith (1988, 1993a, 1995) and Michelson *et al.* (1987) discussed the interactions with non-constant parameters describing various growth factor signals and Jansson and Révész (1977) and Gyori *et al.* (1988) examined competition in heterogeneous tumor populations. Of particular interest in the review of heterogeneous tumor populations by Michelson and Leigh (1993b), who covered a wide variety of topics including the biological implications of the models. These heterogeneous models will be investigated in section 5 where we discuss tumor resistance. For now, we will investigate the homogeneous case, i.e. just one tumor cell population. As Michelson and Leith (1991, 1993a) mentioned, logistic growth with constant parameters is not the best approach in modeling tumor growth. They suggested 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. 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 competi-

tion term represent general interactions between tumor and normal cells. Periodically pulsed survival conditions are added to model the effects of chemotherapy on interacting populations. Kot and Funasaki (1993) viewed a simplified predator–prey in a pulsed chemostat in a similar way.

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

The basic set of equations that will be studied are:

$$\frac{dX}{dT} = r_1 X\left(1 - \frac{X}{K_1} - \lambda_1 Y\right), \tag{1}$$

$$\frac{dY}{dT} = r_2 Y\left(1 - \frac{Y}{K_2} - \lambda_2 X\right), \tag{2}$$

$$X(n\tau^+) = F(D)X(n\tau^-), \tag{3}$$

$$Y(n\tau^+) = \bar{F}(D)Y(n\tau^-). \tag{4}$$

The variables and parameters are:

X: Normal (host) cell biomass.
Y: Tumor cell biomass.
r_1, r_2: Growth rates of the normal and tumor cells.
K_1, K_2: Carrying capacity of the normal and tumor cells.
λ_1, λ_2: Competitive parameters of the normal and tumor cells.
τ: Period of dose. τ^- and τ^+ denote the time just before and after a pulse, respectively.
$F(D), \bar{F}(D)$: Survival fraction of normal and tumor cells for a given dose D. Note $0 \leq F(D)$; $\bar{F}(D) \leq 1$.

The λ_is describe the various interactions discussed. For example, positive λ_1 describes the negative affects of the tumor on the host; negative λ_1 (though probably not physically meaningful) could describe any possible positive affects of the tumor on the host. Similarly, positive λ_2 describes the negative affects of the host on the tumor (i.e. the immune system or TFG-β; see Burger *et al.*, 1994, Dotto *et al.*, 1988 and La Rocca *et al.*, 1989), whereas negative λ_2 describes positive affects of the host on the tumor (i.e. growth factors such as those described in Cornil *et al.*, 1991, Michelson and Leith, 1995 and Miller *et al.*, 1981). If either $\lambda_i = 0$, then it is assumed there is no interaction or signal in that direction. Some forms of

$F(D)$ and $\bar{F}(D)$ are given in Berenbaum (1969):

1. Exponential: $F(D) = e^{-\alpha D}$.
2. Exponential with shoulder: $F(D) = 1 - (1 - e^{-\alpha D})^{\beta}$.
3. Hyperbolic: $F(D) = (D/D_0)^{-\lambda}$.

See Knolle [(1988), pp. 89–90] for indications of how the exponential dose–response curve is formulated.

3. Recurrence in the Absence of Chemotherapy. In the absence of chemotherapy, the two periodic conditions (3 and 4) are removed and the problem reduces to the ordinary competition model. We must ask this question: Is the tumor-free case $(K_1, 0)$ stable to small (compared to the normal cell mass) perturbations? In other words, can a small amount of tumor mass, left after surgery or due to metastasis, 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 get

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} -r_1 & -\lambda_1 r_1 K_1 \\ 0 & r_2(1 - \lambda_2 K_1) \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix}. \tag{5}$$

From (5) it can 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 mathematical analysis, see Waltman (1983). 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 (1994). It can be seen that the 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 positive λ_2). Therefore, $0 < K_1\lambda_2 < 1$ represents the tumor recurring but at an inhibited rate (caused by the normal tissue) as compared to the non-competitive case. However, if λ_2 is negative (positive growth factors), then $K_1\lambda_2 < 0$ is always true and the tumor *will* recur faster than in the non-competitive case ($\lambda_i = 0$). This case can represent the normal tissue stimulating the tumor mass.

These results are consistent with the *in vitro* experiments from Cornil *et al.* (1991), who concluded that non-metastatic melanoma cells (WM35) can be inhibited 3.5-fold (in five days; i.e. $0 \le K_1\lambda_2 < 1$) by dermal fibroblasts, whereas the metastatic melanoma cells (WM9) can be stimulated 1.6-fold (in five days; i.e. $K_1\lambda_2 < 0$) by dermal fibroblasts. More specifically, setting the parameters of our model at $r_1 = 0.212$, $r_2 = 0.42$, $K_1 = 10^7$, $K_2 = 10^5$, $X(0) = 10^7$, $Y(0) = 5000$, $\lambda_1 = 0$ and $\lambda_2 = 0$ (to conform with the experiments carried out in Cornil *et al. without* the dermal fibroblasts, i.e.

no interaction terms), we show similar growth rates as in their experiments. That is, the initial cancerous tissue mass for both the Cornil *et al.* study and our model was set at $Y(0) = 5000$ and after five days they both grew to $Y(5) \approx 30{,}000$. By adding the effects of the dermal fibroblasts ($\lambda_2 \neq 0$), our model, for various choices of λ_2, compares well with the Cornil *et al.* study. In the case of the non-metastatic melanoma cells, choosing $\lambda_2 = 7.12 \times 10^{-8}$, the competitive pressure is $0 < K_1\lambda_2 = 0.712$, which is consistent with the theory since the dermal fibroblasts are inhibiting the growth of the melanoma cells. In this inhibited growth environment $Y(5) \approx 8000$, which compares well to the Cornil *et al.* study. In the case of the metastatic cells, choosing $\lambda_2 = -3.75 \times 10^{-8}$, the competitive pressure is $K_1\lambda_2 = -0.375 < 0$, which is also consistent with the theory since the dermal fibroblasts are stimulating the growth of the melanoma cells. In this stimulated case, $Y(5) \approx 55{,}000$, which also compares well to the Cornil *et al.* study.

If the parameters are non-constant—controlled by the growth factor signaling as in Michelson and Leith (1991, 1993a, 1995)—then recurrence can be more difficult to see, but is also more realistic. For example, λ_2 can change from positive to negative (i.e. inhibitory to stimulatory effects) after a partial hepatectomy (Michelson and Leigh, 1995) or in the case of tumor "escape" as discussed by Cornil *et al.* (1991).

4. Recurrence with Pulsed Chemotherapy. It is common after a mastectomy or other surgical procedure to remove a tumor mass to administer chemotherapy to destroy any possible tumor metastasis. We now add these chemotherapeutic effects to our model.

Once chemotherapy is incorporated, it is very important to study the effects that it has not only on the tumor cells, but also on the normal cells. Otherwise, our solution to destroy the tumor might also destroy the normal cells, and thus the patient. So, first let us see what basic conditions must be placed on the therapy with just the normal cells; then we will examine the attempt of tumor cells to recur. Solving equations (1)–(4) (see Appendix A) we find that the condition on the survival fraction for the normal tissue to survive is

$$F(D) > a + e^{-r_1\tau}(1-a), \tag{6}$$

where $(1-a)$ represents the percentage of allowable normal cell kill (usually about 50%).

Now, examine the recurrence of a small amount of tumor cells. 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 $(X_s(t), 0)$, to study the stability of the tumor mass (see Appendix B). The condition to prevent recurrence (Appendix B) is

$$\bar{F}(D) < F(D)^{r_2\lambda_2 K_1/r_1} \exp\bigl(-\tau r_2(1-\lambda_2 K_1)\bigr). \tag{7}$$

Note that $\lambda_2 K_1 < 1$ 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 section 3). To make it difficult for the tumor to recur, the right-hand side of (7) must be large, close to 1. 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 λ_2 is positive and increase the ability to recur if it is negative. Also, many of the chemotherapeutic drugs used are immuno-suppressive. In this model this can be described by decreasing the size of λ_2, thus making it harder to prevent tumor recurrence without larger doses of the drugs.

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

$$D > \frac{\tau r_2(1-\lambda_2 K_1)}{\alpha_2 - \alpha_1 \lambda_2 K_1 r_2/r_1} \tag{8}$$

$$< \frac{-1}{\alpha_1} \ln(a + e^{-r_1\tau}(1-a)), \tag{9}$$

where the first condition is derived from equation (7) and the second comes from (6). Note that both of these equations are affected by normal cell parameters $(K_1, \lambda_2, r_1, \alpha_1, a)$. For example, as the competitive pressure $\lambda_2 K_1$ increases ($\lambda_2 > 0$), less of a dose is needed to prevent recurrence. For there to exist a region of acceptable dose and period, the graph of equation (9) must lie above that of equation (8) for some region. For this to happen, the slope of equation (9) at $\tau = 0$ must be larger than that of equation (8). To satisfy this, the following condition is needed:

$$\alpha_2 > \frac{\alpha_1 r_2(1 - a\lambda_2 K_1)}{r_1(1-a)}. \tag{10}$$

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 affect on the tumor cells than on the normal cell unless the normal cells are able to grow back faster ($r_1 > r_2$).

Figure 1 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 (10). Figure 2 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, Fig. 3 shows where the graphs in Fig. 2 cross. This forms the boundary between where a successful region does and does not exist. Figure 4 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. In fact, we can see that as the competitive pressure becomes increasingly negative, that is, stimulatory affects by the normal tissue, the region of acceptable dose gets smaller until it disappears around $\lambda_2 K_1 \approx -0.6$.

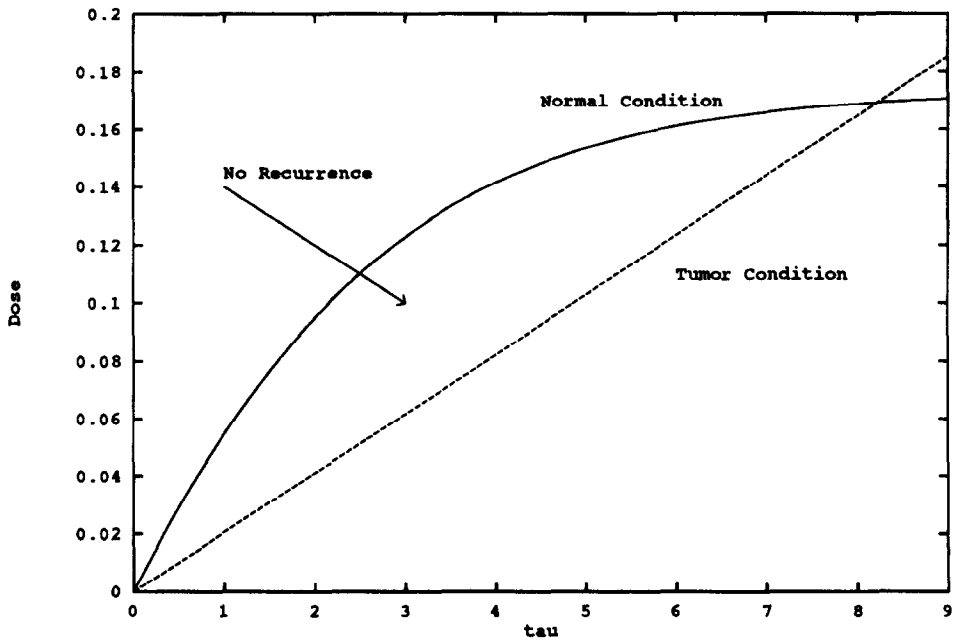

Figure 1. Dose–response curve: dose versus period.

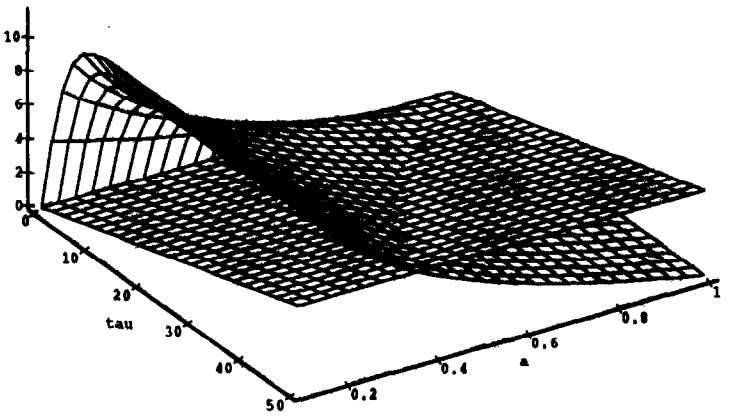

Figure 2. Dose–response curve: dose versus period versus host survival (a).

5. Resistant Subpopulations. If a resistant subpopulation occurs, 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 resistant cells are 100% resistant are discussed by Goldie and Coldman (1979). They show, by stochastic methods, that as the tumor burden is increased, there is a higher probability of

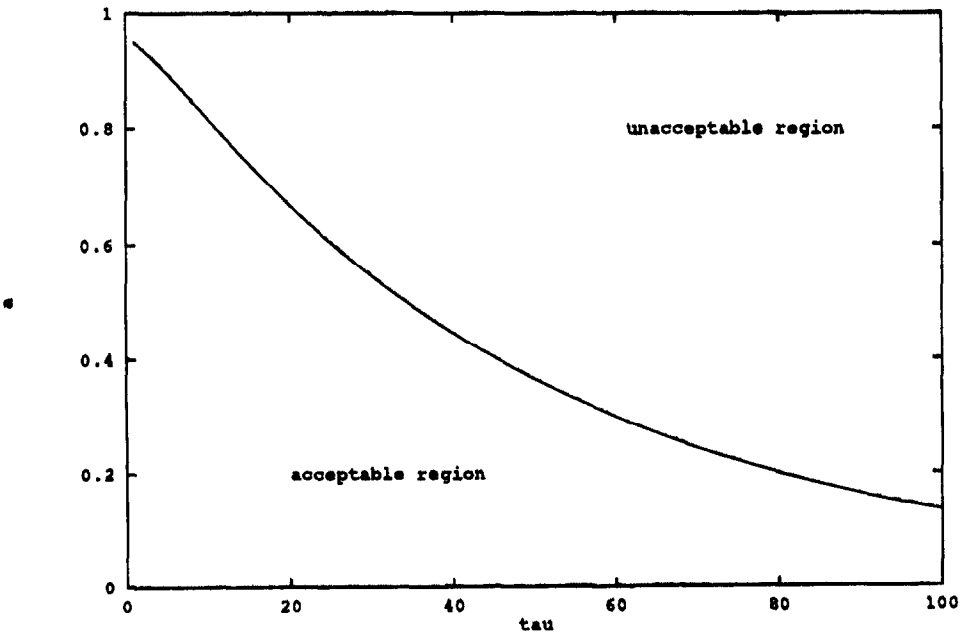

Figure 3. Dose–response curve: a versus τ.

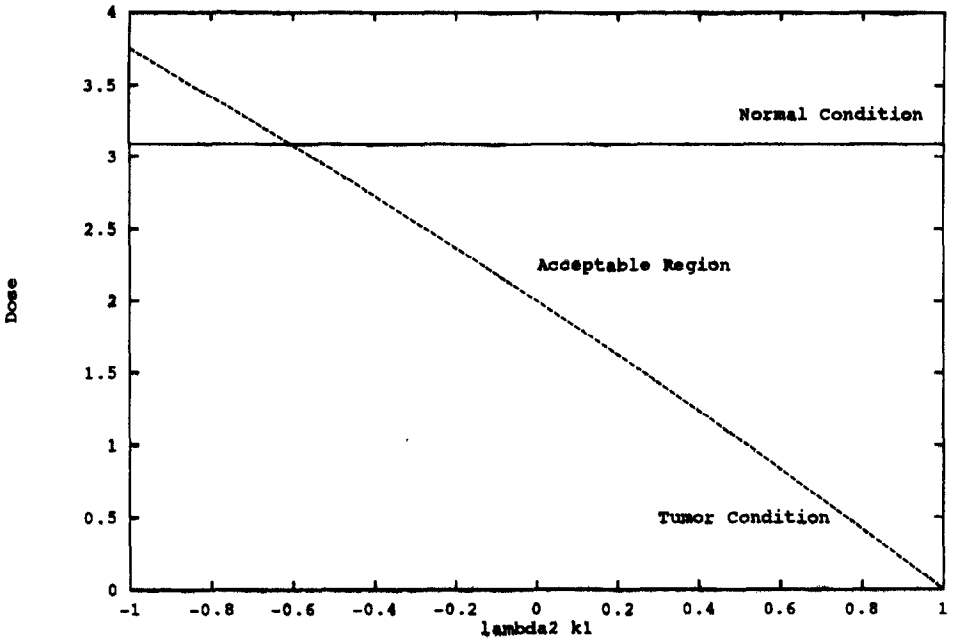

Figure 4. Dose–response curve: dose versus $\lambda_2 K_1$.

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 arises in various ways. One is resistance that is *not* induced by the drugs. Since tumor heterogeneity is common (see Michelson and Leith, 1993b), this is a very likely case. This will be modeled by a *continuous* flow of cells, independent of the chemotherapy, from sensitive to resistant. The other is resistance induced by the drugs. That is, as the drugs are administered, some sensitive cells become resistant. This could be caused by genetic mutations. This will be modeled by a *discrete* flow of cells, dependent on the chemotherapy, from sensitive to resistant. As mentioned before, the present paper will look at this acquired resistance.

5.1. *Acquired resistance: Cell mutations.* Martin *et al.* (1992b) state that some types of drug resistant cells arise at a constant rate and are *not* induced by the chemotherapeutic drugs. This gives rise to heterogeneous tumors. Michelson and Leith (1988) and Michelson *et al.* (1987) have developed heterogeneous tumor models without normal cell interaction or chemotherapy and Gyori *et al.* (1988), using the model developed by Michelson *et al.*, added the effects of a time-dependent cytotoxic agent.

These models can be modified in the following way to account for normal cell interaction and periodically pulsed therapy:

$$\frac{dX}{dt} = r_1 X\left(1 - \frac{X}{K_1} - \lambda_1(Y_1 + Y_2)\right), \tag{11}$$

$$\frac{dY_1}{dt} = r_2 Y_1\left(1 - \frac{Y_1 + Y_2}{K_2} - \lambda_2(X + Y_2)\right) - mY_1, \tag{12}$$

$$\frac{dY_2}{dt} = r_3 Y_2\left(1 - \frac{Y_1 + Y_2}{K_2} - \lambda_3(X + Y_1)\right) + mY_1, \tag{13}$$

$$X(n\tau^+) = F(D)X(n\tau^-), \tag{14}$$

$$Y_1(n\tau^+) = \bar{F}(D)Y_1(n\tau^-), \tag{15}$$

$$Y_2(n\tau^+) = \tilde{F}(D)Y_2(n\tau^-), \tag{16}$$

where:

X: Normal cell biomass.
Y_1: Sensitive tumor cell biomass.
Y_2: Resistant tumor cell biomass.
m: Resistance parameter. Usually this is very small since cancer cells mutate at a rate of about 1 in every 10^6 cells (see Michelson and Leith, 1988).

Note that the λ_is can be either positive or negative as described before. We assume that two drugs are administered: both affect the sensitive cells with survival fraction $\bar{F}(D)$, while only one affects the resistant cells with survival fraction $\tilde{F}(D)$. This leads to the assumption $\bar{F}(D) < \tilde{F}(D)$, i.e. the drugs will have a stronger effect on the sensitive tumor cells than the resistant tumor cells.

5.1.1. *No therapy case.* Let us first look at the case with no chemotherapy. Michelson and Leith (1993b) noted that with 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. However, with the proper choices 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.

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

(11)–(13) about $X = K_1 + \epsilon u$, $Y_1 = 0 + \epsilon v$ and $Y_2 = 0 + \epsilon w$, we get

$$\begin{pmatrix} u' \\ v' \\ w' \end{pmatrix} = \begin{pmatrix} -r_1 & -r_1\lambda_1 K_1 & -r_1\lambda_1 K_1 \\ 0 & r_2(1-\lambda_2 K_1) - m & 0 \\ 0 & m & r_3(1-\lambda_3 K_1) \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix}. \tag{17}$$

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 no 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 *cannot* recur, although, typically $m \ll r_2$. The condition on resistant cell recurrence is $\lambda_3 K_1 < 1$. Although, if the sensitive cells recur, then the resistant cells *must* recur (see Michelson *et al.*, 1987), 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. However, 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.

5.1.2. *Resistant recurrence.* As before, we want to see what happens to small perturbations, caused by a small amount of tumor mass, to the tumor-free periodic solution given in section 3. The condition to prevent sensitive cell recurrence as shown in Appendix C is

$$\bar{F}(D) < F(D)^{((r_2-m)\lambda_2 K_1)/r_1} \exp\bigl(-\tau r_2(1-\lambda_2 K_1)\bigr). \tag{18}$$

Note that we assume $\lambda_2 K_1 < 1$ (see the previous section). As can be concluded, as m increases in size, the resistance has a larger affect in the outcome.

As in the no-drug case, resistant cells must recur if sensitive cells do, and there can be resistant cell recurrence even if the sensitive cells do not recur. The condition to prevent resistant recurrence as calculated in Appendix C is

$$\tilde{F}(D) < F(D)^{r_3\lambda_3 K_1/r_1} \exp\bigl(-\tau r_3(1-\lambda_3 K_1)\bigr). \tag{19}$$

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 they are competitively excluded ($K_1\lambda_3 > 1$), since the right-hand side of equation (53) is less than 1.

As before, choose the dose–response to be $F(D) = e^{-\alpha_1 D}$, $\bar{F}(D) = e^{-\alpha_2 D}$ and $\tilde{F}(D) = e^{-\alpha_3 D}$. Then the conditions to *prevent* both sensitive and resistant tumor recurrence while keeping the normal cells above the specified level a are

$$D > \frac{\tau r_2(1 - \lambda_2 K_1)}{\alpha_2 - \alpha_1 \lambda_2 K_1 (r_2 - m)/r_1} \tag{20}$$

$$> \frac{\tau r_3(1 - \lambda_3 K_1)}{\alpha_3 - \alpha_1 \lambda_3 K_1 r_3/r_1} \tag{21}$$

$$< \frac{-1}{\alpha_1} \ln(a + e^{-r_1 \tau}(1 - a)). \tag{22}$$

For there to be a region of resistant recurrence without sensitive recurrence, the graph of (20) (the equality) must be below that of (21), or the slope of (21) with respect to τ must be greater than that of (20). 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 $\alpha_3 > \alpha_2$ ($\bar{F}(D) > \tilde{F}(D)$, which is unrealistic), then, depending on the size of m, there will be a region (small if m is small) where resistant cells can recur without sensitive cells. If $\alpha_3 < \alpha_2$ ($\bar{F}(D) < \tilde{F}(D)$, 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 (10), we can see the minimum condition needed for the treatment to be able to prevent resistant tumor recurrence.

Figure 5 gives an example of two regions of dose versus period. One occurs where the tumor cannot recur and the other where only resistant tumor cells can do so. The upper line refers to equation (21) (the equality); the lower line refers to equation (20) and the curve is equation (22). 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.

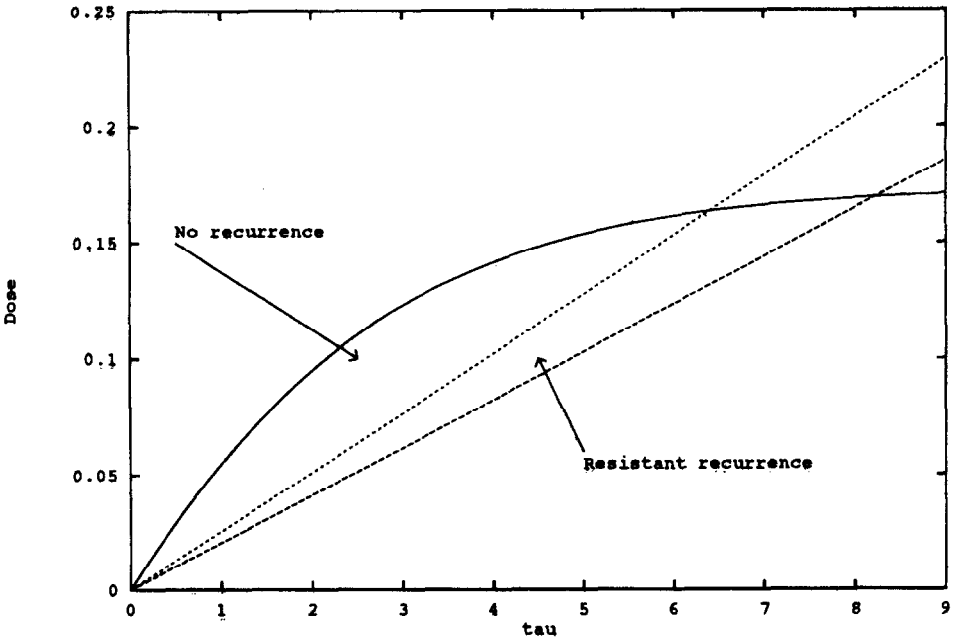

Figure 5. Dose–response curves: dose versus period.

5.2. *Induced resistance.* Birkhead and Gregory (1984) and Martin *et al.* (1992b) noted that tumor cells can mutate 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:

$$\frac{dX}{dt} = r_1 X\left(1 - \frac{X}{K_1} - \lambda_1(Y_1 + Y_2)\right), \tag{23}$$

$$\frac{dY_1}{dt} = r_2 Y_1\left(1 - \frac{Y_1 + Y_2}{K_2} - \lambda_2(X + Y_2)\right), \tag{24}$$

$$\frac{dY_2}{dt} = r_3 Y_2\left(1 - \frac{Y_1 + Y_2}{K_2} - \lambda_3(X + Y_1)\right), \tag{25}$$

$$X(n\tau^+) = F(D)X(n\tau^-), \tag{26}$$

$$Y_1(n\tau^+) = (\bar{F}(D) - R(D))Y_1(n\tau^-), \tag{27}$$

$$Y_2(n\tau^+) = \tilde{F}(D)Y_2(n\tau^-) + R(D)Y_1(n\tau^-), \tag{28}$$

where in equations (27) and (28) $R(D)$ is the fraction of cells mutating due to the dose of the drug. Note that $R(D)$ can be as large as 0.5, i.e. 50% of the surviving cells become resistant. Thus, induced resistance may have a great affect on the outcome of the therapy.

5.2.1. *Normal growth.* As in section 3, we are interested in the stability of the tumor-free case $(K_1, 0, 0)$. Linearizing (23)–(25) about the tumor-free state ($X = K_1 + \epsilon u$, $Y_1 = 0 + \epsilon v$ and $Y_2 = 0 + \epsilon w$), we get

$$\begin{pmatrix} u' \\ v' \\ w' \end{pmatrix} = \begin{pmatrix} -r_1 & -\lambda_1 r_1 K_1 & -\lambda_1 r_1 K_1 \\ 0 & r_2(1-\lambda_2 K_1) & 0 \\ 0 & 0 & r_3(1-\lambda_3 K_2) \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix}. \tag{29}$$

Note that this has similar conditions for recurrence as equation (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 just depends on the competition coefficient λ_i. Thus, prior to therapy, sensitive cell recurrence has no effect on the recurrence of resistant cells.

5.2.2. *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 (27) and (28). This gives us the system of difference equations

$$v_{(n+1)\tau} = v_{n\tau}\left\{\frac{(\bar{F}(D) - R(D))e^{r_2\tau}}{F(D)^{r_2\lambda_2 K_1/r_1}\exp(r_2\lambda_2 K_2\tau)}\right\}, \tag{30}$$

$$w_{(n+1)\tau} = v_{n\tau}\left\{\frac{R(D)e^{r_2\tau}}{F(D)^{r_2\lambda_2 K_1/r_1}\exp(r_2\lambda_2 K_1\tau)}\right\} + w_{n\tau}\left\{\frac{\tilde{F}(D)e^{r_3\tau}}{F(D)^{r_3\lambda_3 K_1/r_1}\exp(r_3\lambda_3 K_1\tau)}\right\}. \tag{31}$$

Now, we will look at the stability results. First, the sensitive tumor cells *cannot* recur if

$$\bar{F}(D) < F(D)^{r_2\lambda_2 K_2/r_1}\exp(-\tau r_2(1-\lambda_2 K_1)) + R(D). \tag{32}$$

Note that $R(D)$ increases the size of the right-hand side (dramatically when $R(D)$ is large), thus making it easier to prevent sensitive cell recurrence. It can be seen that if $R(D)$ is large (close to 0.5), then tumor resistance will be hard to prevent. If the sensitive cells recur, then the resistant cells will also recur because the first term on the right-hand side of equation (31) will grow in spite of the second term. Thus, resistant tumor population recurrence does not depend on competitive pressure if there is sensitive recurrence. Last, the resistant tumor cells can recur even if the sensitive cells do not, provided

$$\tilde{F}(D) > F(D)^{r_3\lambda_3 K_1/r_1} \exp\bigl(-\tau r_3(1-\lambda_3 K_1)\bigr). \tag{33}$$

This is derived assuming that there are sensitive cells initially, which is very likely. Note that this result is consistent with condition (53) for non-induced resistance.

6. Discussion and Conclusions. Since tumor cells are *not* isolated from their micro-environment, but can be competing with the host for resources, affected by the immune system or by various growth factors, the models discussed in this paper, which include tumor–normal cell interaction, are a step toward better describing chemotherapeutic effects. For example, as stated by Miller *et al.* (1981):

> Investigation of growth and control of neoplasia must take into account the natural control mechanisms existent for tumors. For example, a much more vigorous therapeutic approach might be necessary to control a mammary tumor growing in a mammary fatpad than to control a mammary tumor growing at a s.c. (subcutaneous) site.

The model in this paper can help better qualify how vigorous the chemotherapy might need to be (i.e. in terms of dose and period) given a set of parameters that relate to the sites discussed by Miller *et al.* or others in which a tumor can grow. Along with the effects of the drugs on normal tissue, these are some of the more important constraints on the use of chemotherapeutic drugs and should be a part of any model that will accurately describe the mutual interplay within the system.

We show that data from studies on various tumor–host interactions have *suggested* that the type of interactions described in this paper can play an important role in the growth and control of tumors. As a result of this, many clinical studies have been and are being conducted to find the specific kinetics involved in these interactions, though, at this time these studies *cannot* specify the kinetics of these interactions, they do *strongly* suggest

that these interactions are very important and should be taken into account. Without having to know these specific kinetics, our model describes well both the suggested interactions along with more specific experimental data noted in this paper.

The models in this paper establish 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 ($\lambda_2 K_1$) (i.e. competition for resources, positive or negative growth factors and immune system effects) can control and even prevent tumor growth and recurrence, or possibly even enhance tumor growth (as seen in the case of a partial hepatectomy). Also, we show how certain doses (D) and period (τ) can lead to tumor regrowth including resistant regrowth.

The model is inappropriate if the tumor develops resistance that is untreatable (no drug affects it). However, 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 administered to give survival fractions $F(D)$ and $\bar{F}(D)$. However, because this does not give 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 be a result of resistant subpopulations, then heterogeneous tumor models are an appropriate approach to study drug resistance. Two different types of resistance are investigated: drug induced and non-induced. One of the main differences between these situations is in the no 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, whereas in the other case it does. When chemotherapy is added, both cases show a definite region of resistant recurrence with no sensitive recurrence. This region is important in that when planning a chemotherapeutic regimen, it can be avoided and thus not cause the tumor to become totally resistant, thereby killing the host. In both of these cases, the parameter region that will prevent recurrence is generally smaller than 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 significantly narrow the acceptable region of drug treatment. The main mathematical difference between these two resistance models is that the induced model allows for discrete mutations which can

have a significant affect on the outcome while the non-induced model has continuous mutations which usually are small compared to the chemotherapeutic effects.

Gatenby (1991) pointed 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. As seen in this model, one of these changes can be a variation of $\lambda_2 K_1$ through the critical value of 1, which will make it impossible for the tumor to recur. Another factor can be a change in sign of λ_2 (through growth factors, etc.), which will force the tumor to recur in the absence of chemotherapeutic drugs. A relevant topic in this regard is that of growth factors as discussed by Michelson and Leith (1991, 1993a, 1995). 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 (1991) discussed how damage to the local tissue (normal cells) and devascularization can help the tumor mass emerge. That is, the carrying capacity is reduced because of dead cell accumulation 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 simplification 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.

APPENDIX A. NORMAL CELL GROWTH

In the absence of any tumor cells, system (1)–(4) reduces to

$$\frac{dX}{dT} = r_1 X\left(1 - \frac{X}{K_1}\right), \tag{A1}$$

$$X(n\tau^+) = F(D)X(n\tau^-). \tag{A2}$$

The solution which holds between pulses is

$$X(t) = \frac{X_{n\tau}K_1}{X_{n\tau} + (K_1 - X_{n\tau})\exp(-r_1(t - n\tau))}, \qquad n\tau < t < (n+1)\tau, \tag{A3}$$

where $X_{n\tau} = X(n\tau)$. At the beginning of each successive pulse, the solution, using the pulsing condition (A2), is

$$X_{(n+1)\tau} = F(D)\frac{X_{n\tau}K_1}{X_{n\tau} + (K_1 - X_{n\tau})e^{-r_1\tau}}. \tag{A4}$$

Equation (A4) has two equilibrium points:

$$X_u^* = 0, \qquad X_s^* = \frac{K_1(F(D) - e^{-r_1\tau})}{(1 - e^{-r_1\tau})}. \tag{A5}$$

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 (1969), 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 referred to. Some can survive much larger cell kills than others. However, to avoid specifying any particular type now and to keep the model flexible, we will require $X_s^* > aK_1$, where a is the proportion of acceptable reduction from the steady state for normal cells. Using the above information, it can be seen that the survival fraction must be

$$F(D) > a + e^{-r_1\tau}(1 - a) \tag{A6}$$

for there to be at least $a\%$ of the normal cells left. Substituting X_s^* into (A3) we get the steady-state periodic solution:

$$X_s(t) = \frac{K_1(F(D) - e^{-r_1\tau})}{F(D) - e^{-r_1\tau} + (1 - F(D))\exp(-r_1(t - n\tau))}, \qquad n\tau < t < (n+1)\tau. \tag{A7}$$

APPENDIX B. RECURRENCE OF THE TUMOR

Letting $X = X_s(t) + \epsilon u$ and $Y = 0 + \epsilon v$, then system (1)–(4) becomes

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} r_1\left(1 - 2\dfrac{X_s(t)}{K_1}\right) & -r_1\lambda_1 X_s(t) \\ 0 & r_2(1 - \lambda_2 X_s(t)) \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix}. \tag{B1}$$

If this system is stable in v, then the steady state $(X_s(t), 0)$ is stable and the chemotherapeutic regimen prevents tumor recurrence. The stability of v is determined by integrating

$$v' = r_2(1 - \lambda_2 X_s(t))v, \qquad n\tau < t < (n+1)\tau. \tag{B2}$$

Since $X_s(t)$ is periodic with period τ, integrate over one period to get

$$v_{(n+1)\tau} = \bar{F}(D)v_{n\tau} \exp\left(r_2 \int_{n\tau}^{(n+1)\tau} 1 - \lambda_2 X_s(t)\, dt\right) \tag{B3}$$

or, in a more useful form,

$$v_{(n+1)\tau} = v_{n\tau}\bar{F}(D)\exp\left(\ln e^{r_2\tau} - r_2\lambda_2 \int_{n\tau}^{(n+1)\tau} X_s(t)\, dt\right). \tag{B4}$$

Calculating the above integral and simplifying, we get

$$v_{(n+1)\tau} = v_{n\tau}\bar{F}(D)\exp\left(\ln\left\{\frac{r_2\tau}{F(D)^{r_2\lambda_2K_1/r_1}\exp(r_2\lambda_2K_1\tau)}\right\}\right) \tag{B5}$$

or

$$v_{(n+1)\tau} = v_{n\tau}\left\{\frac{\bar{F}(D)e^{r_2\tau}}{F(D)^{r_2\lambda_2K_1/r_1}\exp(r_2\lambda_2K_1\tau)}\right\}. \tag{B6}$$

If the characteristic multiplier of equation (B6) (term in brackets) is less than 1, the tumor will regress. Thus, to prevent recurrence,

$$\bar{F}(D) < F(D)^{r_2\lambda_2K_1/r_1}\exp(-\tau r_2(1-\lambda_2K_1)). \tag{B7}$$

APPENDIX C. ACQUIRED RESISTANCE RECURRENCE

Linearizing system (11)–(16) about $(X_s(t),0,0)$ the stability of the sensitive and resistant subpopulations is investigated. In the same manner as before, we look at the linear system

$$\begin{pmatrix} u' \\ v' \\ w' \end{pmatrix} = \begin{pmatrix} r_1\left(1-2\dfrac{X_s(t)}{K_1}\right) & -r_1\lambda_1X_s(t) & -r_1\lambda_1X_s(t) \\ 0 & r_2(1-\lambda_2X_s(t))-m & 0 \\ 0 & m & r_3(1-\lambda_3X_s(t)) \end{pmatrix}\begin{pmatrix} u \\ v \\ w \end{pmatrix}, \tag{C1}$$

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

$$v' = (r_2(1-\lambda_2X_s(t))-m)v, \qquad n\tau < t < (n+1)\tau. \tag{C2}$$

This gives

$$v_{(n+1)\tau} = v_{n\tau}\left\{\frac{\bar{F}(D)\exp((r_2-m)\tau)}{F(D)^{r_2\lambda_2K_1/r_1}\exp(r_2\lambda_2K_1\tau)}\right\}. \tag{C3}$$

The condition to *prevent* sensitive cell recurrence is

$$\bar{F}(D) < F(D)^{((r_2-m)\lambda_2K_1)/r_1}\exp(-\tau r_2(1-\lambda_2K_1)). \tag{C4}$$

To find the condition for resistant recurrence, we must integrate

$$w' = r_3(1-\lambda_3X_s(t))w, \qquad n\tau < t < (n+1)\tau, \tag{C5}$$

giving us:

$$w_{(n+1)\tau} = w_{n\tau}\left\{\frac{\bar{F}(D)e^{r_3\tau}}{F(D)^{r_3\lambda_3K_1/r_1}\exp(r_3\lambda_3K_1\tau)}\right\}. \tag{C6}$$

Thus, the condition to *prevent* resistance recurrence is

$$\tilde{F}(D) < F(D)^{r_3\lambda_3 K_1/r_1} \exp(-\tau r_3(1-\lambda_3 K_1)). \tag{C7}$$

I would like to thank Dr. Seth Michelson for his extremely useful comments and discussions which helped me immensely in preparing this paper. I would like to thank two anonymous reviewers whose comments greatly improved the presentation of this paper. I would also like to thank my advisor Dr. John Adam for his support in this research.

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Received 11 April 1994