Modeling of Tumor Growth and its Control via Paclitaxel Using a Delay Differential Equation

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Abstract

Paclitaxel is shown to be antiangiogenic at low doses, but the extent of these effects is not known. A mathematical model that describes tumor growth and response to treatment with a continuous, low dose treatment of the anti-mitotic drug Paclitaxel is considered. The model considers three populations: system cells, proliferating tumor cells, and tumor cells in a resting phase. A delay differential equation model accounts for the time it takes for tumor cells to complete one cycle in the proliferation phase. The system is first analyzed without drug administration, and then analyzed numerically under different levels of drug administration. Finally, sensitivity analysis is performed on certain parameters to determine what the likely consequences of antiangiogenic effects.

1 Introduction

Studies have suggested that well-tolerated chemotherapy can exert a better antitumor effect than conventional high-dose, temporarily spaced-out chemotherapy [4]. Moreover, at lower doses the anti-mitotic drug Paclitaxel has been shown to have antiangiogenic effects. Since it is very hard to show the exact extent of those effects in clinical testing, we are creating a mathematical model of tumor growth with only the antimitotic effects. We can then do sensitivity analysis to determine the response of the stability of the equilibria to the antiangiogenic effects of Paclitaxel

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at low doses. Therefore, we consider a model that describes tumor growth with a continuous, low dose treatment of the anti-mitotic drug Paclitaxel.

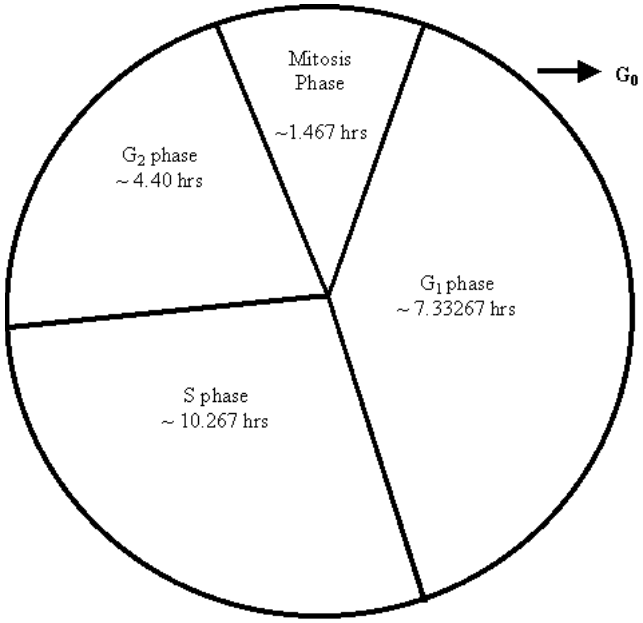

Figure 1: Cell Cycle.

To understand the dynamics of the drug we must understand the cell cycle. Interphase and mitosis are the two main components of a cell cycle. Interphase first involves the synthesis of proteins and cellular molecules, which is known as G_1. After cells leave G_1, their DNA starts to replicate, in what is known as the S phase. Cells then enter the last stage of interphase, G_2, which involves the production of more proteins. Finally, cells enter mitosis, where a cell divides into two identical daughter cells. It is important to note that 80% of cells are not in the cell cycle; instead, they are in the resting phase, G_0 [1]. During G_0 cells carry out functions normally, but do not replicate DNA and divide. Thus, G_0 phase of cells plays an important role in the dynamics of cell growth.

A delay differential equation model has been used in previous studies to analyze the role of the conventional chemotherapy treatment, and we see the delay necessary in understanding the full dynamics of tumor growth [8]. It was shown that the stability of a fixed point, representing an amount of tumor that is invariant under the growth model, can be affected by the delay [8]. That model, however, did not include a population that represented the quiescent, or G_0 phase, cells. This

assumption skews the dynamics of tumor growth away from a biologically correct representation since a large proportion of tumor cells are in the G_0 phase. For example, in bone marrow cancer, it has been shown that 90% of tumor cells are in G_0 [5]. The importance of the inclusion of this population can be seen in previous work [2]. Therefore, our mathematical model incorporates both T_{G_0} and delay to better understand the dynamics of tumor growth under low-dose Paclitaxel and the possible antiangiogenic effects of the drug.

2 Model Description

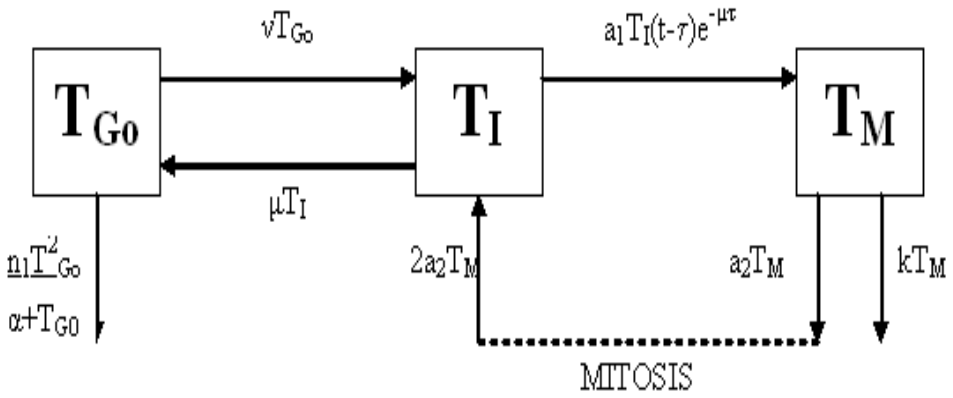

Figure 2: A three-compartment model of the cell cycle that includes cells in quiescent phase (T_{G_0}), interphase (T_I), and mitosis (T_M).

The model was made under the assumption of unbounded exponential growth. We therefore chose not to incorporate Gompertz or logarithmic growth because we were only interested in the portion of the growth that exhibited exponential growth. Usually by the time a tumor nears or reaches its carrying capacity the patient is either dead or in a state where treatment is of limited use.

Three compartments of cells model the dynamics of that population: quiescent (T_{G_0}), interphase (T_I), and mitosis (T_M). They allow for movement between subsequent and previous phases, natural cell death in the quiescent phase and drug-induced

death in the mitosis phase

$$\begin{cases} \dot{T}_{G_0} &= \mu T_I - \nu T_{G_0} - \frac{n_1 T_{G_0}^2}{\alpha + T_{G_0}} \\ \dot{T}_I &= \nu T_{G_0} + 2a_2 T_M - a_1 T_I(t-\tau)e^{-\mu\tau} - \mu T_I \\ \dot{T}_M &= a_1 T_I(t-\tau)e^{-\mu\tau} - a_2 T_M - kT_M \end{cases} \tag{1}$$

In our model, T_{G_0} represents the portion of tumor cells in G_0 phase. T_I represents the tumor cells in interphase. T_M represents the tumor cells in mitosis. n_1 is the death rate from necrosis in T_{G_0}, k is the kill rates due to chemotherapy, and τ is the average time that the tumor cells spend in interphase. a_1 is the rate at which cells leave interphase, while a_2 is the rate at which cells leave the mitosis phase. ν is rate at which cells leave the quiescent phase while μ is the rate at which cells leave interface into the quiescent phase. α is the rate at which necrosis rate approaches the maximum rate, n_1.

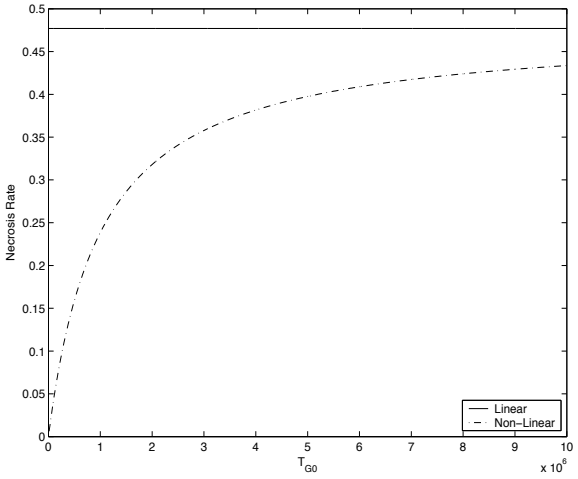

Figure 3: A linear necrosis rate vs. a non-linear necrosis rate for $\alpha = 1,000,000$.

n_1 is not in a linear relationship with T_{G_0} because necrosis is much more prominent when there are higher numbers of cells. As T_{G_0} gets large the death rate approaches the linear death rate. Poor vasculature and hypoxia, which lead to quiescent cell death, both increase as tumor size increases. See Figure 3 for a comparison between a linear death rate and the non-linear death rate in our model.

3 Parameter Estimation

Parameter	Definition	Value
a_1	rate at which cells leave interface	0.8470
a_2	rate at which cells leave mitosis	0.9159
n_1	death rate from necrosis	0.477
α	rate at which necrosis rate approaches maximum	10^4 to 10^6
k	kill rate due to chemotherapy	0 to 1
μ	rate cells leave the quiescent phase into mitosis	0.218
ν	rate cells leave mitosis into the quiescent phase	0.050
τ	time delay in days	0.9167

Table 1.

Values for a_1, a_2 and τ are taken from the values estimated in [8]. The death rate from necrosis,n_1, is taken from [3].

4 Analysis

4.1 Non-Delay Analysis

Both with the drug and without the drug, the system has two equilibria.

4.1.1 Analysis without drug

Without the drug, the equilibria are

$$(T_{G_0}, T_I, T_M) = (0, 0, 0)$$

and

$$(T_{G_0}, T_I, T_M) = (\frac{-\alpha\nu a_1}{\nu a_1 + n_1 a_1 - n_1\mu}, \frac{\alpha\nu^2 a_1}{\nu a_1^2 + n_1 a_1^2 + n_1\mu^2 - \nu a_1\mu - 2n_1 a_1\mu},$$

$$\frac{\alpha\nu^2 a_1^2}{\nu a_2 a_1^2 + n_1 a_1^2 a_2 + n_1\mu^2 a_2 - \nu a_2 a_1\mu - 2n_1 a_1 a_2\mu})$$

However, for the second equilibrium to make sense biologically, all three values for (T_{G_0}, T_I, T_M) must be greater than or equal to zero. If α is chosen between the values

given in Table 1, then it is necessary that

$$\begin{cases} n_1\mu & > & a_1(\nu + n_1) \\ n_1\mu^2 + a_1^2(n_1 + \nu) & > & a_1(2n_1 + \mu\nu) \end{cases} \tag{2}$$

Let us first consider the stability of the drug free, tumor free non-delay case.

First we must compute the characteristic equation of the linearization of the system around the tumor free equilibrium

$$0 = \lambda^3 + (a_1 + a_2 + \mu + \nu)\lambda^2 + (-a_1a_2 + \mu a_2 + a_2\nu + \nu a_1)\lambda - \nu a_1 a_2 \tag{3}$$

For this equilibrium to be stable under the Routh-Hurwitz criteria, it is necessary that

$$c_1 > 0, c_1c_2 > c_3, c_3 > 0 \tag{4}$$

where

$$0 = \lambda^3 + c_1\lambda^2 + c_2\lambda + c_3 \tag{5}$$

At this equilibrium

$$c_3 = -\nu a_1 a_2 < 0 \tag{6}$$

Since ν, a_1, and a_2 are all transition values, they must always be between 0 and 1. Therefore, at least one eigenvalue has a positive real part, making the tumor free equilibrium unstable. This leads to the following proposition:

Proposition 1 *The drug free, tumor free equilibrium is never stable.*

The analysis of the drug free, tumor present equilibrium will be covered in the next subsection after the analysis of the stability of the drug present, tumor present is performed.

4.1.2 Analysis with drug

When the drug is added into the system, the equilibria are

$$(T_{G_0}, T_I, T_M) = (0, 0, 0)$$

and

$$(T_{G_0}, T_I, T_M) = (\frac{(k - a_2)\nu a_1\alpha}{\nu a_1 a_2 + n_1 a_1 a_2 - \nu a_1 k - n_1 a_1 k - n_1\mu a_2 - n_1\mu k}, \\ \frac{\nu^2\alpha a_1(a_2 - k)(a_2 + k)}{P}, \frac{\nu^2\alpha a_1^2(a_2 - k)}{P})$$

where

$$P = \nu a_1^2 a_2^2 + \nu a_1^2 k^2 + n_1 a_1^2 a_2^2 + n_1 a_1^2 k^2 + n_1 \mu^2 a_2^2 + n_1 \mu^2 k^2 - 2\nu a_1^2 a_2 k - \nu a_1 a_2^2 \mu$$
$$+\nu a_1 k^2 \mu - 2n_1 a_1^2 a_2 k - 2n_1 a_1^2 a_2 \mu + 2n_1 a_1 k^2 \mu + 2n_1 \mu^2 a_2 k$$

We can calculate the stability of the tumor free, drug present equilibrium by first computing the characteristic equation of the linearized matrix

$$0 = \lambda^3 + (a_2 + \mu + a_1 + k + \nu)\lambda^2 + ((k + a_2)(\mu + \nu) + a_1(\nu - a_2 + k))\lambda - (a_1 a_2 \nu - k a_1 \nu) \quad (7)$$

This equation satisfies the Routh-Hurwitz criteria for stability stated in equation (4) if

$$a_2 < k \quad (8)$$

Thus if k is greater than the mitosis rate, then the tumor size will tend to zero.

This leads to the following proposition:

Proposition 2 *The tumor free, drug present equilibrium is stable if $k > a_2$.*

The tumor present, drug present equilibrium is positive, and therefore makes sense biologically, if

$$\frac{a_2(\nu a_1 + n_1 a_1 - n_1 \mu)}{\nu a_1 + n_1 a_1 + n_1 \mu} < k < a_2 \quad (9)$$

Then by computing the corresponding linearized matrix of the system and then by computing its characteristic equation, conditions can be found that satisfy the Routh-Hurwitz criteria. After that, the equilibrium points are substituted back into the conditions. The resulting equation is then solved for k. This leads to the following proposition:

Proposition 3 *The tumor present, drug present equilibrium is stable if*

$$a_2\left(\frac{n_1(\mu^2 - 2a_1\mu + a_1^2) + \nu(a_1^2 - a_1\mu) + 2\sqrt{n_1 a_1^2 \mu^2 \nu - \nu a_1 \mu^3 n_1 + n_1^2 a_1^2 \mu^2 - 2n_1^2 a_1 \mu^3 + n_1^2 \mu^4}}{-3n_1\mu^2 + n_1 a_1^2 + \nu a_1^2 + 2n_1 a_1 \mu - \nu a_1 \mu}\right) < k < a_2 \quad (10)$$

As a consequence, a proposition of the drug free, tumor present equilibrium described in 4.1.1 follows:

Proposition 4 *The drug free, tumor present equilibrium is stable if conditions for*

its existence are met and the following is satisfied

$$\frac{n_1(\mu^2 - 2a_1\mu + a_1^2) + \nu(a_1^2 - a_1\mu) + 2\sqrt{n_1 a_1^2\mu^2\nu - \nu a_1\mu^3 n_1 + n_1^2 a_1^2\mu^2 - 2n_1^2 a_1\mu^3 + n_1^2\mu^4}}{-3n_1\mu^2 + n_1 a_1^2 + \nu a_1^2 + 2n_1 a_1\mu - \nu a_1\mu} \leq 0 \tag{11}$$

This is easily shown because the tumor present, drug free equilibrium is simply the tumor present, drug present equilibrium with $k = 0$.

4.2 Delay Analysis

4.2.1 Numerical Delay Analysis

To determine the stability of the equilibria, we calculate the characteristic polynomial in the usual way. For the trivial fixed point, the characteristic polynomial is

$$C(\lambda) = P(\lambda) + Q(\lambda)e^{-\tau\lambda} \tag{12}$$

where the roots of this equation in λ are eigenvalues. Here we choose $\tau = 0.9167$ based on data and we let k vary.

We define, using parameter estimates from [2] and [4] as described in Table 1,

$$\begin{cases} P(\lambda) = (-1.183900000 - k)\lambda^2 - (.2454612000 + .2680000000k)\lambda - \lambda^3 \\ Q(\lambda) = (-0.03467877475k + 0.03176228979) + (0.6005670211 - 0.6935754950k)\lambda - 0.6935754950\lambda^3 \end{cases} \tag{13}$$

To show the stability of the trivial equilibrium, it suffices to check that $\mathrm{Re}(\lambda) < 0$ when λ satisfies $C(\lambda) = 0$. For this computation we use a perturbation argument (See Proposition 5 in the Appendix). We first consider λ_i for i=1,2,3; where P(λ_i)+Q(λ_i)=0. Then we define $\lambda_{i,\tau} = \lambda_i e^{-\epsilon\tau}$, where

$$\epsilon = -\frac{Q(\lambda_i)}{\frac{\partial P}{\partial\lambda}|_{\lambda_i} + \frac{\partial Q}{\partial\lambda}|_{\lambda_i}}$$

We will generalize τ for now, then consider the meaning of our specified time delay. If $\mathrm{Re}(\lambda_{i,\tau}) < 0$ for i=1,2,3 then this suggests that the tumor free equilibrium will be stable. Using the formula for ϵ derived in the appendix and the parameters from Table 1 except for k and τ, we find that we must have the following conditions:

In the above table, a particular k is specified then the requirement that $\mathrm{Re}(\lambda_{i,\tau}) < 0$

Table 1: For a specific k given in the first column, we can derive $\lambda_{i,\tau}$ using Proposition 5 of the appendix. We then set $\mathrm{Re}(\lambda_{i,\tau}) < 0$ and solve for the inequality in τ. This will give regions where the real part of the eigenvalues of C(λ) may be negative. These regions are given in terms of τ with k increments of 0.01

k	$\tau <$ (for $\lambda_{1,\tau}$)	$\tau <$ (for $\lambda_{2,\tau}$)	$\tau <$ (for $\lambda_{3,\tau}$)
.9	-6170997923	$0.1964993751e^{11}$	$0.2187282630e^{11}$
.91	$-0.1347340274e^{11}$	$-0.1074434525e^{11}$	$0.1032543640e^{11}$
.92	-5702807894	$-0.1169206199e^{11}$	$-0.2575471146e^{11}$
.93	$-0.1522625963e^{11}$	$0.2553130717e^{11}$	$-0.1712817406e^{11}$
.94	-7419221435	$0.3453057356e^{11}$	$-0.1781915082e^{11}$
.95	-4551659579	$-0.1806366601e^{11}$	$-0.2428789777e^{11}$
.96	-4264983866	$0.2374235953e^{11}$	$-0.2541766121e^{11}$
.97	-7866578609	$-0.1158930896e^{11}$	$-0.2440033751e^{11}$
.98	-3230423581	$-0.3539375471e^{11}$	$-0.1126279423e^{11}$
.99	-3861664507	$-0.1880599737e^{11}$	$-0.3614801809e^{11}$

is reduced to an inequality for τ.

For the tumor present equilibrium, the characteristic equation takes on the same form as equation (13), with

$$P(\lambda) = -0.9687328679e - 2(3909829536.\mathrm{k}+6191954450\lambda - 0.2349966074e^{11}\lambda\mathrm{k}+0.7851600276e^{11}\lambda^2+ 0.7551516350e^{11}\lambda^3 - 0.2235616088e12\lambda^2\mathrm{k}+2591150838\mathrm{k}^2 + 4948330000.\lambda^2\mathrm{k}^2- 4254394243\lambda\mathrm{k}^2 + 0.4778263600e^{11}\lambda\mathrm{k}^3 + 0.2580690800e12\lambda^2\mathrm{k}^3 - 0.2791997763e12\lambda^3\mathrm{k}+ 0.2580690800e12\lambda^3\mathrm{k}^2 - 4660813282\mathrm{k}^3 - 2173645985)/(-27047 + 50000.\mathrm{k})^2 \tag{14}$$

$$Q(\lambda) = -2(0.2418789695e12\lambda\mathrm{k}-0.3634624607e12\lambda\mathrm{k}^2 + 0.1789903900e12\lambda^2\mathrm{k}^2 + 4517004898+ 0.5237546690e^{11}\lambda^2 - 0.1605355707e^{11}\mathrm{k}-0.5290245658e^{11}\lambda + 0.2011878167e^{11}\mathrm{k}^2 - 0.1936461231e12\lambda^2\mathrm{k}+ 0.1789903900e12\lambda\mathrm{k}^3 - 5879039580\mathrm{k}^3)/(-27047 + 50000\mathrm{k})^2 \tag{15}$$

We can calculate a similar table as above for the tumor present equilibrium:

Table 2: Just as in Table 1, a particular k is specified then the requirement that $\mathrm{Re}(\lambda_{i,\tau}) < 0$ is reduced to an inequality for τ.

k	$\tau < (for \lambda_{1,\tau})$	$\tau < (for \lambda_{2,\tau})$	$\tau < (for \lambda_{3,\tau})$
0	3467763.606	-33546072.63	3449046.970
.1	4179306.901	-118995816.8	3981478.998
.2	4386145.268	-70775929.44	4359440.263
.3	262976.0216	-56400824.45	253272.6320
.4	-506.6082611	8167377.113	-506.6955460
.5	-2.724158048	-104.3191532	-2.231667304
.6	0.1614817874	-1506285.697	.1121648851
.7	-18.10645400	610055770.3	-18.49967397
.8	-16.49011685	97362820.85	-16.47601960
.9	30.83018841	-35132018.38	30.97699415

We can see that the rate of drug administration, k, changes the dynamics of the system with respect to the value of the delay. For each equilibrium point, there corresponds a discrete table of values which outline three continuous graphs where τ is a function of k. We can assume continuity because we calculated the implicit equation that shows τ continuously depends on k(it is a rational function of exponentials and polynomials that does not blow up in finite time.) Therefore the intersection of the region below these three graphs represents the region where the roots of the characteristic equation have negative real parts, i.e. the equilibrium is stable. Because τ is fixed, namely at 0.9167 days, we can use the graphs to propose the optimal rate of drug administration to drive the tumor to either equilibrium. Note that this can only happen if there is some positive region bounded by all three curves that lies below τ=0.9167 (See figures 4,5,6).

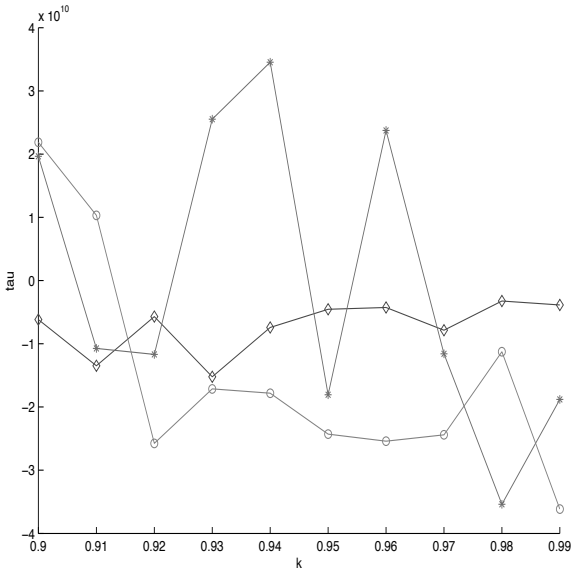

Figure 4: This figure represents the analysis with the perturbation algorithm on the trivial equilibrium. Again we note that positive regions bounded by all three curves represent regions of stability of the trivial equilibrium. Each curve corresponds to a different $\lambda_{i,\tau}$ and we use the calculated values in Table 1 for the discrete points on each curve. We see that in this case one of the curves is never positive. Because the time delay can never be negative, this equilibrium is always unstable.

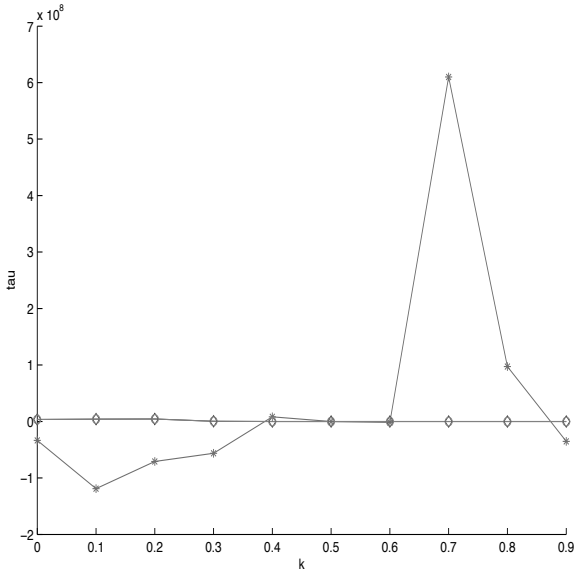

Figure 5: Similar to figure 4, this figure represents the analysis with the perturbation algorithm on the nontrivial equilibrium. We plot discrete points on each curve using the values in Table 2.

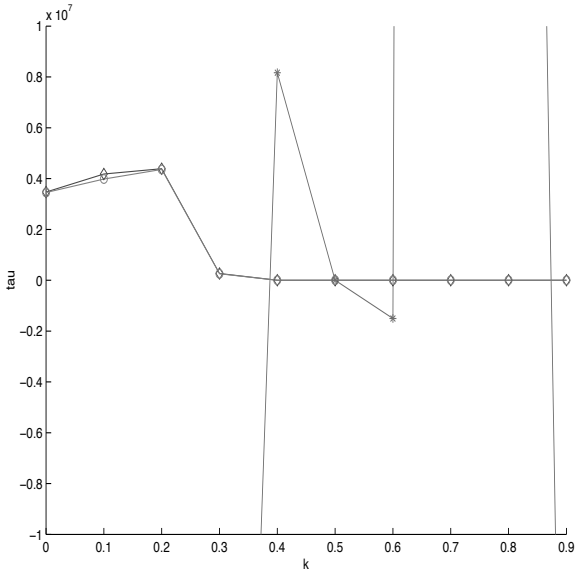

Figure 6: Figure 5 with a rescaled τ axis.

The above analysis with a k increment of 0.1 between 0 and .9 for the tumor present case and .01 between .9 and .99 for the tumor free case suggests neither of the equilibria will be stable in the delay case with the fixed parameters. However, one can show that there is a region of stability for either equilibria when the system is reduced to a non-delay case. When $\tau = 0$, there are values of k that cause either equilibria to be stable; these values of k correspond to values found in the non-delay analysis. If the delay analysis is done with increments on the order of 1/10000, we expect to find that there does exist some positive region bounded by all three approximated curves. For the k increments of 0.1 and 0.01, we found that neither tumor state represented by the equilibria will have invariant growth under the flow time. Although these results are hardly optimistic, we note that for different tumors there will be different parameter values which can change the characteristic polynomial and hence the stability. Here we have considered highly specific parameters estimated from clinical studies on breast carcinoma. For different types of cancer, this analysis will produce different regions of stability in the k-τ plane. From the figures below we can interpret the effect of the delay. Given a fixed delay, τ=τ_0, we can then correspond to it a horizontal line, τ=τ_0, in a continuously approximated discrete graph such as those illustrated in figures 5 and 6. This horizontal line will intersect a region of stability defined by the characteristic equation and perturbation analysis. This intersection determines the plausible values of k that will cause the equilibrium to be stable. For the case with no delay, the horizontal line will be the k-axis. For the case with a delay, the horizontal line will be shifted upward, possibly decreasing the plausible values for k. Essentially, this is interpreted to mean that the delay can decrease the amount of plausible drug rates for a given type of cancer.

However, this type of numerical analysis has its limitations. The results here do not agree with the delay case bifurcation results and the numerical simulations done in Section 5. This is because the ϵ function does not work for $\tau = 0$ and may be too large a perturbation for other τ values. Therefore, we have decided to also analyze the delay equation analytically.

4.2.2 Analytical Delay Analysis

We conducted analytical delay analysis on the tumor free equilibrium. A similar analysis can be found in Xiao and Chen [9].

With the delay the chacteristic equation can be written as

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0 \tag{16}$$

For the tumor free equilibium, the characteristic equation can be decomposed into

$$\begin{aligned} P(\lambda,\tau) &= -[\lambda(\nu a_2 + \nu k + \mu a_2 + \mu k) + \lambda^2(\nu + \mu + a_2 + k) + \lambda^3] \\ Q(\lambda,\tau) &= -[\nu a_1 a_2 e^{-\mu\tau} + \nu a_1 k e^{-\mu\tau} + \lambda(\nu a_1 e^{-\mu\tau} - a_1 a_2 e^{-\mu\tau} + a_1 k e^{-\mu\tau}) + \lambda^2(a_1 e^{-\mu\tau})] \end{aligned} \tag{17}$$

Our objective is to show that all eigenvalues have negative real part. To do that we will introduce two lemmas and then construct a bounded region of stability.

Lemma 5 *All roots of (16) with* $Re(\lambda) \geq 0$ *lie in a bounded domain.*

Proof: From equation (16) we have

$$\mid \lambda^{-3} P(\lambda,\tau) \mid = \mid \lambda^{-3} Q(\lambda,\tau) e^{-\lambda\tau} \mid = \mid \lambda^{-3} Q(\lambda,\tau) \mid e^{-Re(\lambda)\tau} \tag{18}$$

We can then choose ρ_1 such that $\mid \lambda^{-3} P(\lambda,\tau \mid) > 0.5$ for $\mid \lambda \mid \geq \rho_1$. We can then choose ρ_2 such that $\mid \lambda^{-3} Q(\lambda,\tau) \mid e^{-\lambda,\tau} < 0.5$ for $\mid \lambda \mid > \rho_2$. Since $Q(\lambda,\tau)$ is of degree 2, there is a $\rho_2 > 0$ that satisfies the previous inequalities. Thus $Re(\lambda) \geq 0$. The equation (16) cannot hold for $\mid \lambda \mid \geq \max\{\rho_1, \rho_2\}$. Therefore, the conclusion of this lemma is true.

Lemma 6 *The tumor free characteristic equation has no purely imaginary roots for any* $\tau \geq 0$ *when*

$$k > a_2 \tag{19}$$

Proof: Let $\lambda = i\omega$, $\omega > 0$. We can then substitute into equation (16) for λ and separate the real parts from the imaginary parts.

$$\begin{aligned} -\omega^2(\mu + a_2 + k + \nu) &= (-\omega a_1 e^{-\mu\tau} + A)\cos\omega\tau + B\omega\sin\omega\tau \\ -\omega^3 + \omega(\nu+\mu)(a_2+k) &= B\omega\cos\omega\tau - (-\omega^2 a_1 e^{-\mu\tau} + A)\sin\omega\tau \end{aligned} \tag{20}$$

where

$$A = \nu a_1 e^{-\mu\tau}(k - a_2)$$

and

$$B = a_1 e^{-\mu\tau}(\nu + k - a_2)$$

When both sides are squared and added, we get

$$\omega^6 + m_1\omega^4 + m_2\omega^2 + m_3 = 0 \tag{21}$$

where

$$\begin{aligned} m_1 &= a_2^2 + \mu^2 + k^2 + \nu^2 + 2a_2k + 2\mu k \\ m_2 &= (\nu + \mu)^2(a_2 + k)^2 \\ m_3 &= 0 \end{aligned} \tag{22}$$

Let w be a root of (21). Since $m_1 > 0$, $m_2 > 0$, and $m_3 = 0$, no non-zero w can satisfy equation (21). If $w = 0$, the characteristic equation equalling zero is not satisfied for $k > a_2$. Thus equation (17) has no imaginary roots when the condition is satisfied.

Now we want to find the region of stability. Let us choose k and τ as parameters and fix values for a_1, a_2, μ, ν, and n_1. We know that the tumor free equilibrium always exists and that its characteristic equation never has purely imaginary roots. So let us then consider the region

$$S = \left\{(k, \tau) \in R_+^2 : a_2 < k, 0 \leq \tau\right\}$$

Theorem 7 *The tumor free equilibrium is asymtotically stable if* $(k, \tau) \in S$.

Proof: By the Routh-Hurwitz criteria, we know that all roots of (17) have negative real parts, and the equilibrium is therefore stable for $\tau = 0$. Since the characteristic equation never has purely imaginary roots and all roots with $Re(\lambda) > 0$ are bounded, we know that the roots of this equation never cross the y-axis in the real-imaginary plane. Therefore the equation will always have roots with $Re(\lambda) < 0$ and the equilibrium will therefore be stable for any τ.

A similar analysis can be done for the tumor present equilibrium to determine the region of $(k, \tau) \in R_+^2$ where the equilibrium is stable.

4.3 Sensitivity Analysis

Since Paclitaxel is antiangiogenic at low doses, we expect both n_1 and μ to increase because decreased vasculature would cause more cells to shift from cycling to quiescent and a higher death rate for those that are quiescent. Therefore, we would like to consider how a small shift in the parameters would change the stability of the tumor free equilibrium. We care only about the tumor free equilibrium because in a tumor present equilibrium that tumor itself will not grow, but it can metastasize to other areas. To find the effects of a small perturbation, we perform sensitivity analysis on the characteristic equation of the non-delay system with the drug. Sensitivity analysis involves taking partial derivatives of the equation with respect to the parameter

we want to test.

The characteristic equation of of the non-delay case with drug administration is

$$0 = \lambda^3 + (a_2 + \mu + a_1 + k + \nu)\lambda^2 + ((k + a_2)(\mu + \nu) + a_1(\nu - a_2 + k))\lambda - (a_1 a_2 \nu - k a_1 \nu) \quad (23)$$

Therefore, we want to find the sensitivity of these equations with respect to n_1 and μ

$$\begin{cases} c_1 &= (a_2 + \mu + a_1 + k + \nu \\ c_2 &= (k + a_2)(\mu + \nu) + a_1(\nu - a_2 + k) \\ c_3 &= -(a_1 a_2 \nu - k a_1 \nu) \end{cases} \quad (24)$$

The sensitivity index of each parameter, ξ_i, is given by

$$S_{\xi_i} = \frac{\xi_i}{c_j} \frac{\partial c_j}{\partial \xi_i} \quad (25)$$

for $i = 1, 2$ and $j = 1, 2, 3$.

4.3.1 Sensitivity of n_1

Since none of these equations depend on n_1 the partial derivatives are all zero and sensitivity index of n_1 is

$$S_{n_1} = 0 \quad (26)$$

Thus, any changes in n_1 will not cause any changes in the stability of the tumor free equilibrium.

4.3.2 Sensitivity of μ

In order to compute the sensitivity index of μ, we need to find the partial derivatives with respect to μ :

$$\begin{cases} \frac{\mu}{c_1}\frac{\partial c_1}{\partial \mu} &= \frac{\mu}{a_2+\mu+a_1+k+\nu} \\ \frac{\mu}{c_2}\frac{\partial c_2}{\partial \mu} &= \frac{\mu(k+a_2)}{(k+a_2)(\mu+\nu)+a_1(\nu-a_2+k)} \\ \frac{\mu}{c_3}\frac{\partial c_3}{\partial \mu} &= 0 \end{cases} \quad (27)$$

In order for the non-trivial equilibrium to be biologically feasible, then $k > a_2$ which in turn implies that $-a_2 + k > 0$, since μ, a_2, a_1, ν, $k > 0$. Since $\frac{\mu}{c_1}\frac{\partial c_1}{\partial \mu}$ and $\frac{\mu}{c_2}\frac{\partial c_2}{\partial \mu}$ are always positive, which means there is a positive correlation between μ, c_1, and c_2. When we let $\mu = 0$ the Routh-Hurwitz criteria are satisfied, and because the partial derivatives of c_1 and c_2 with respect to μ are strictly increasing, the Routh-Hurwitz criteria are satisfied for small μ perturbations. Therefore the stability of the tumor free equilibrium is not sensitive to small $\mu-$perturbations.

4.4 Bifurcation Analysis

We observe that all the six graphs exhibit transcritical bifurcation, in which an unstable and stable orbit collide and exchange stability [6].

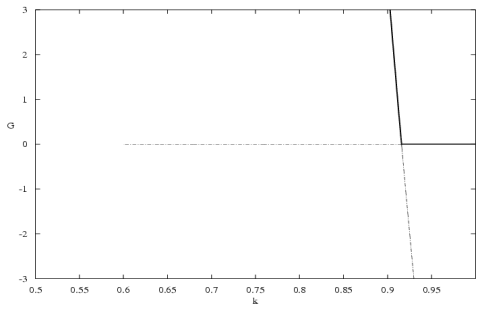

Figure 7: Transcritical bifurcation produced when k is graphed against the number of cells in T_{G_0} when there is no delay. Bold lines indicate stable equilibria, dashed lines unstable.

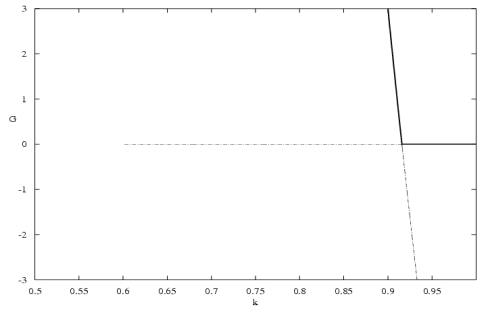

Figure 8: Transcritical bifurcation produced when k is graphed against the number of cells in T_{G_0} when there is delay.

The graphs of delay and non-delay of T_{G_0} are exactly the same as expected since there is no delay for cells in the quiescent phase.

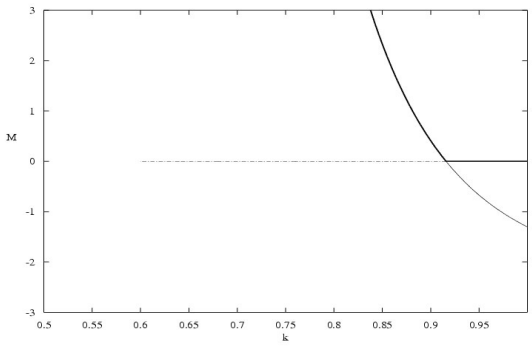

Figure 9: Transcritical bifurcation produced when k is graphed against the number of cells in mitosis when there is no delay. Bold lines indicate stable equilibria, dashed lines unstable.

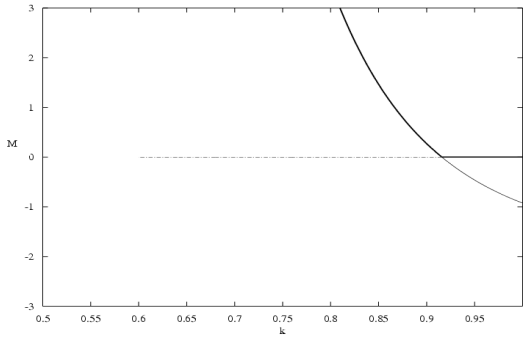

Figure 10: Transcritical bifurcation produced when k is graphed against the number of cells in mitosis when there is delay. Bold lines indicate stable equilibria, dashed lines unstable.

For the mitosis cell present case, the two graphs differ for the range of k for cells in mitosis and the range of k is narrower in nondelay than in delay. However, in the mitosis-cell free case, $k = .9159$ for both delay and nondelay.

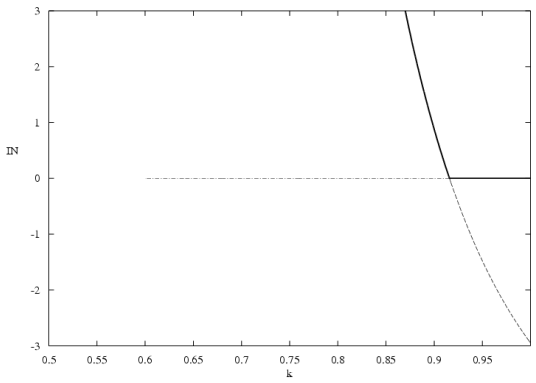

Figure 11: Transcritical bifurcation produced when k is graphed against the number of cells in interphase when there is no delay. Bold lines indicate stable equilibria, dashed lines unstable.

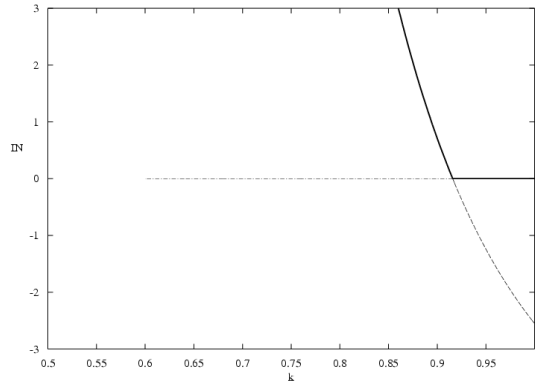

Figure 12: Transcritical bifurcation produced when k is graphed against the number of cells in interphase when there is delay. Bold lines indicate stable equilibria, dashed lines unstable.

We observe similar trends for interphase.

5 Simulations

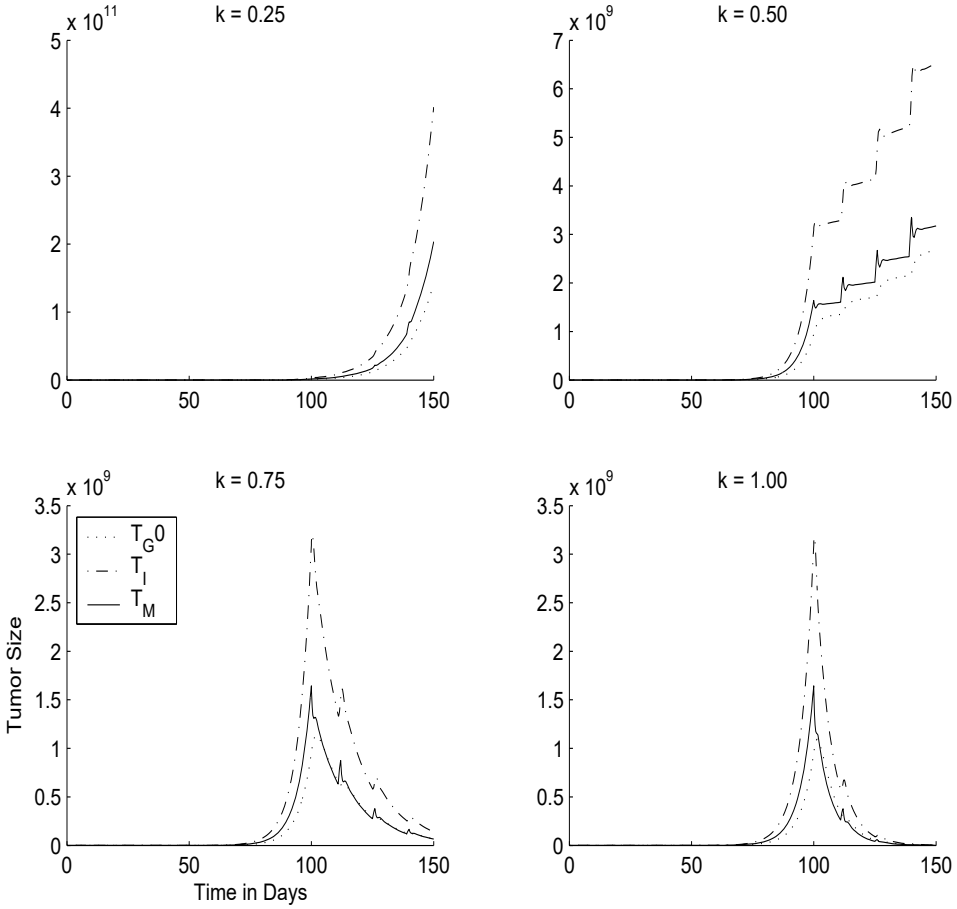

Figure 13: Pulsed chemotherapy with kill rates, k, ranging from 0.25 to 1. Drug given 13 days on, 1 day off after 100 days. α is fixed at 1,000,000. This produces periods of either decay or retarded growth, with short bursts of exponential growth between.

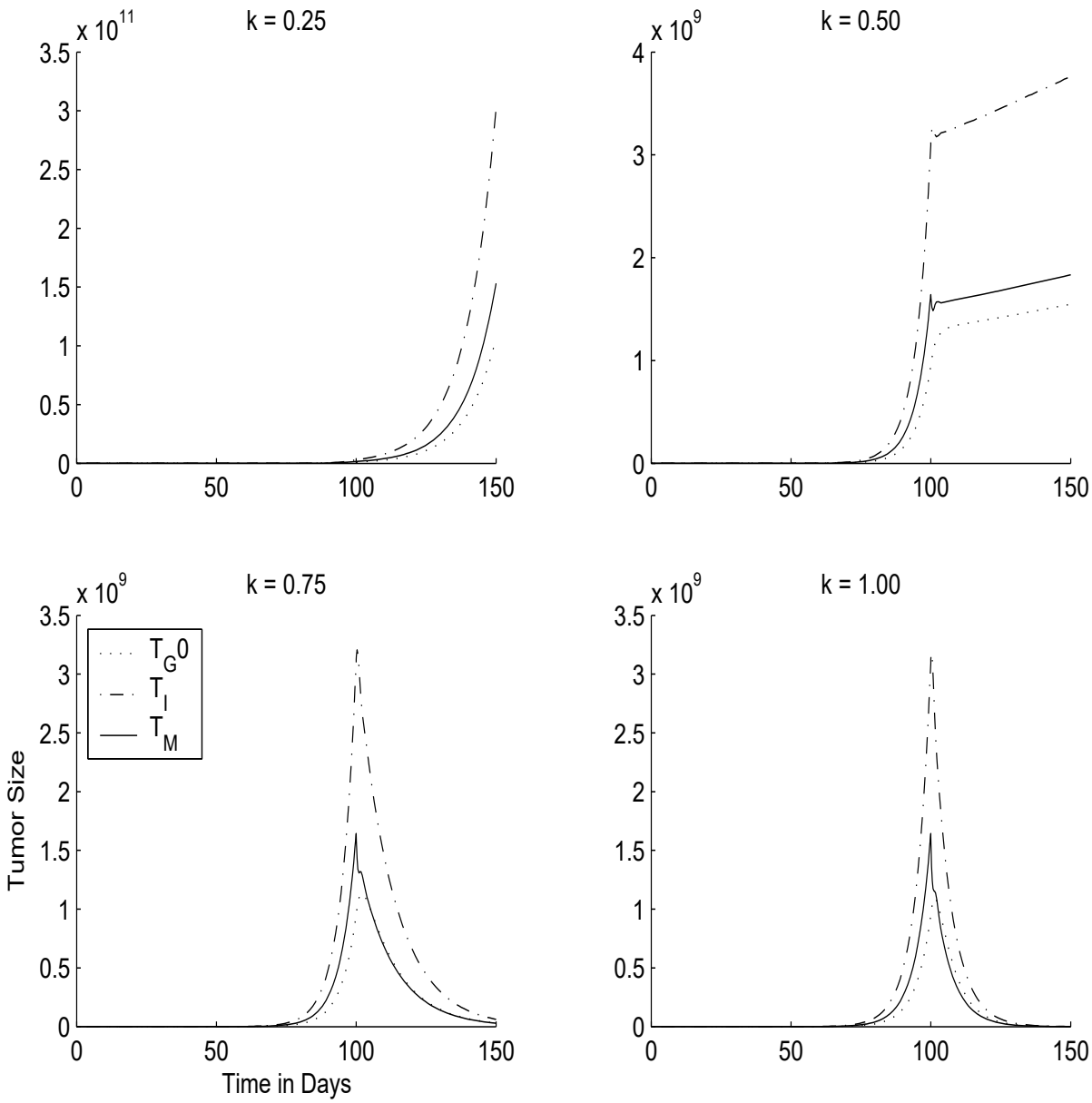

Figure 14: Non-Pulsed chemotherapy with kill rates, k, ranging from 0.25 to 1. Drug given continuously after 100 days. α is fixed at 1,000,000. This produces either steady growth or decay, depending on the value of k.

We ran simulations of tumor growth for the model with a delay under different regimes of drug treatment. For all simulations we let the tumor grow for one hundred days after starting with 10 cells in T_{G_0}, 20 cells in T_I, and 1 cell in T_M. After 100 days, one of two treatments was administered: either thirteen days on with one day off(Figure 8), or continual dosage(Figure 9).

We have shown that even with very small gaps in dosage administration can lead to tumor growth when the tumor would otherwise be controlled under a continuous treatment. This is because even in very small no-dosage gaps there is exponential growth, which can surpass the effect of the drug if the treatment gap is large enough. This suggests that even for higher dose treatment that the shorter the amount of time between treatments, the greater the chances of driving a tumor into either complete or partial remission.

6 Results and Discussions

In the non-delay case we computed the effect of different chemotherapy regimes on the presence and stability of equilibria. We found that the tumor free equilibrium was stable only when the drug was present and was at a level higher than the mitosis rate. The tumor free equilibrium was present and stable only under possibly a narrow range of certain conditions, presented above. Sensitivity analysis suggested that the most plausible effects of antiangiogenesis had no effect on the presence or stability of the tumor free equilibrium. However, because we know antiangiogenic drugs effectively reduce tumor growth, our findings suggest that they might reduce the rate of cells leaving the mitotic phase via mitosis.

For the delay case we computed the effect of different chemotherapy controls, i.e. different drug rates, on the stability of the equilibria numerically. One can carry out similar analysis by finding the equilibrium and stability thresholds in terms of other parameters. Analysis was done on varying k values because in practice this is the only parameter over which one has biological control. With numerical analysis, we see that different values of k may alter stability regions and that the same methods could be used to carry out very rough approximations for stability for models of different types of cancer. However, we found the inherent errors in such method for τ not being a small enough number. Thus, we calculated the stability of the delay case analytically, and found that time delay does not affect the stability of the tumor free equilibrium for $k > a_2$.

We would like to know how much chemotherapy is enough. At the tumors present equilibrium, tumors do not grow, but may metastasize to other parts of the body. Therefore, we are only interested to know the amount of chemotherapy enough to

reach the tumor-free equilibrium. Based on our analysis with delay and non-delay, we found that the kill rate of the chemotherapy greater than the mitosis rate is sufficient to make the tumor-free equilibrium stable..

Simulations showed that continual administration of drugs is preferable to pulsed administration, even when it consists of long pulses with short periods without the drug. This finding is expected because in the absence of chemotherapy the tumor grows at an exponential rate, which can quickly eliminate any benefits of chemotherapy. This finding has been supported by clinical research, where shorter periods between doses of chemotherapy have been shown to be more effective than the standard three weeks [7].

7 Conclusions and Future Work

The delay analysis includes a rough perturbation algorithm for calculating the real parts of the eigenvalues of the transcendental characteristic equation. This process itself is a rough approximation and has an inherent error; the continuous graph was approximated with large increments of k, namely 0.1. For future work, one can decrease the size of the increments to gain a more accurate portrait of the regions of stability. Also, there exist more efficient and more accurate perturbation algorithms. In our approximation we truncated to first order in the Taylor expansions in the proof of Proposition 5 in the appendix. If one uses a second order truncation in the proof of Proposition 5, greater accuracy can be achieved in the calculations. For future work we would want to compute under what circumstances the perturbation algorithm is valid and consider a new perturbation method.

The delay analysis also incorporated a continuous chemotherapy regiment in the model. Instead, one can analyze the effect of a periodic regiment of chemotherapy by considering a heavyside function in place of the linear drug term. This would provide more accurate models of more widely used chemotherapy practices and one can then compare them to the numerical results found in this paper.

A future model can incorporate different transition functions between the interphase and resting phase tumor cells. In this paper we assume linear, or nearly linear, transition rates. If one assumes Gompertz growth on the entire tumor cell population, a transition function can be calculated(See Kozusko and Bajzer, 2003). The parameters for the linear transition rates were approximated, but different functions would provide different dynamics, including the creation of a second tumor present equilibrium. The assumption of Gompertz growth on the entire system is more realistic because a tumor has a limited supply of resources from a host body, and therefore cannot grow exponentially for a long period.

It would also be of use to research the effects of combining Paclitaxel or any other anti-mitotic drug with another drug that retards the exit from the mitotic stage by mitosis. Our model shows that this would be the most effective target to reduce the level of chemotherapy needed.

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9 Appendix

Proposition 8

Suppose

$$P(\lambda_i) + Q(\lambda_i) = 0$$

Then

$$P(\lambda_{i,\tau}) + Q(\lambda_{i,\tau})e^{-\lambda_{i,\tau}\tau} = 0$$

where

$$\lambda_{i,\tau} = \lambda_i e^{-\varepsilon\tau} \text{ and } \varepsilon = -\frac{Q(\lambda_i)}{\frac{\partial P}{\partial \lambda}|_{\lambda_i} + \frac{\partial Q}{\partial \lambda}|_{\lambda_i}}$$

Proof: Let our solution have the form:

$$\lambda_{i,\tau} = \lambda_i e^{-\varepsilon\tau}$$

Then, if $\tau = 0$, we have $\lambda_{i,\tau} = \lambda_i$, i.e. $P(\lambda_i)+Q(\lambda_i) = 0$; and if τ is very small, we can use Taylor expansion to estimate $\lambda_{i,\tau} \approx \lambda_i(1-\varepsilon\tau)$ and $e^{-\lambda_{i,\tau}\tau} = e^{-\lambda_i e^{-\varepsilon\tau}\tau} \approx e^{-\lambda_i\tau}$.

Using a Taylor expansion again, we have that:

$$P(\lambda_{i,\tau}) = P(\lambda_i - \lambda_i\varepsilon\tau) \approx P(\lambda_i) - P_\lambda(\lambda_i)\lambda_i\varepsilon\tau$$

$$Q(\lambda_{i,\tau})e^{-\lambda_i\tau} = Q(\lambda_i - \lambda_i\varepsilon\tau) \approx Q(\lambda_i) - Q_\lambda(\lambda_i)\lambda_i\varepsilon\tau - \lambda_i\tau Q(\lambda_i)$$

Hence,

$$P(\lambda_{i,\tau}) + Q(\lambda_{i,\tau})e^{-\lambda\tau} = P(\lambda_i - \lambda_i\varepsilon\tau) + Q(\lambda_i - \lambda_i\varepsilon\tau)$$

$$P(\lambda_\tau) + Q(\lambda_\tau)e^{-\lambda_\tau} \approx P(\lambda_i) + Q(\lambda_i) - \varepsilon(P_\lambda(\lambda_i) + Q_\lambda(\lambda_i)) - Q(\lambda_i) = 0$$

Therefore,

$$P(\lambda_{i,\tau}) + Q(\lambda_{i,\tau})e^{-\lambda_{i,\tau}\tau} = 0$$

where

$$\lambda_{i,\tau} = \lambda_i e^{-\varepsilon\tau} \text{ and} \varepsilon = \frac{-Q(\lambda_i)}{P_\lambda(\lambda_i) + Q_\lambda(\lambda_i)}$$

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