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A Logistic Model of Periodic Chemotherapy

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Abstract—A logistic differential equation with a time-varying periodic parameter is used to model the growth of cells, in particular cancer cells, in the presences of chemotherapeutic drugs. The chemotherapeutic effects are modeled by a periodic parameter that modifies the growth rate of the cell tissue. A negative growth rate represents the detrimental effects of the drugs. A simple criterion is obtained for the behavior of the chemotherapy.

Keywords—Logistic growth, Periodic differential equation, Cancer, Chemotherapy, Bifurcation.

1. INTRODUCTION

The logistic growth model has been used in many cases as a basic model of both cell growth and more particularly tumor cell growth [1–5]. There are various methods to model the effects of chemotherapy with the logistic model. One of the easiest is to assume the drug kills instantly, thus giving a pulsing type action. This type of model is investigated by Berenbaum [6], Panetta [7], and Panetta and Adam [8]. A more realistic method of modeling chemotherapy is to assume that the chemotherapeutic effects are modeled by continuous or piecewise-continuous periodic functions which affect the growth rate in the logistic growth model [5]. These periodic functions alternate the growth rate between a negative rate when the drug is present and a positive rate during the recovery stage. This is the method investigated in this paper. Because of the availability of closed form solutions to the logistic equation, this chemotherapeutic problem can be handled with analytical methods. Numerical solutions to this model have been used in [8] to model the effects of the chemotherapy on bone marrow. A similar model is discussed by Hallam and Clark [9] which describes a deteriorating environment through the use of decreasing growth rates and carrying capacities, and by Coleman *et al.* [10] who investigate *positive* periodic growth rates and carrying capacities. The model in this paper investigates periodic forms of the growth rate parameter by allowing this growth rate to be *negative* to model periodic chemotherapy.

2. MODEL

The logistic growth model is modified so that there is a variable growth rate to take into account chemotherapy. The general form is

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

where $y(t)$ is the cell mass, r is the growth rate, K is the carrying capacity, and $b(t)$ is a periodic function representing the chemotherapeutic effects on the cell mass. If $b(t) \equiv 0$, then there are

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

$$\frac{dx(t)}{dt} = rx(t)\left([1-b(t)] - x(t)\right). \tag{2}$$

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

$$b(t) = \begin{cases} b, & n\tau \leq t < a + n\tau, \\ 0, & a + n\tau \leq t < (n+1)\tau, \end{cases} \tag{3}$$

or exponentially decaying piecewise periodic function

$$b(t) = be^{a(t-n\tau)}, \qquad n\tau \leq t < (n+1)\tau, \tag{4}$$

or the periodic function

$$b(t) = b\sin\left(\frac{2\pi t}{\tau}\right). \tag{5}$$

3. SOLUTIONS

There are various methods of solving equation (2) for specific cases of $b(t)$, but in general the equation is of Bernoulli type and can be solved exactly. The solution is

$$x(t) = \frac{x_0 e^{r\int^t (1-b(s))\,ds}}{1 + (x_0/r)\int^t e^{r\int^s (1-b(\xi))\,d\xi}\,ds}. \tag{6}$$

Using this solution and the fact that $b(t)$ is periodic, we can set up a difference equation, which is sometimes referred to as a first return map or Poincaré map, that describes the state of the cells at the beginning of each period. Equation (6) describes the growth of the tissue over each period where x_0 is the initial cell mass of the period. The difference equation is

$$x_{(n+1)\tau} = \frac{x_{n\tau} e^{r\int_{n\tau}^{(n+1)\tau} (1-b(s))\,ds}}{1 + (x_{n\tau}/r)\int_{n\tau}^{(n+1)\tau} e^{r\int^s (1-b(\xi))\,d\xi}\,ds}. \tag{7}$$

Of interest is the stable equilibrium of this difference equation. Solving the equation

$$x_{eq} = \frac{x_{eq} e^{r\int_{n\tau}^{(n+1)\tau} (1-b(s))\,ds}}{1 + (x_{eq}/r)\int_{n\tau}^{(n+1)\tau} e^{r\int^s (1-b(\xi))\,d\xi}\,ds} \tag{8}$$

for x_{eq}, we can determine the equilibria. They are

$$x_{eq} = 0, \tag{9}$$

$$x_{eq} = \frac{r\left(e^{r\int_{n\tau}^{(n+1)\tau} (1-b(s))\,ds} - 1\right)}{\int_{n\tau}^{(n+1)\tau} e^{r\int^s (1-b(\xi))\,d\xi}\,ds}. \tag{10}$$

Equation (10) is equal to zero for $\langle b(t)\rangle = 1$, which is the bifurcation from a positive stable equilibrium to a zero stable equilibrium. That is, for $0 \leq \langle b(t)\rangle \leq 1$, equilibrium (10) is stable

and equilibrium (9) is unstable. For $\langle b(t)\rangle > 1$, the stability switches and equilibrium (9) becomes stable while equilibrium (10) switches to unstable. Therefore, the cells have a zero equilibrium when

$$\langle b(t)\rangle > 1. \tag{11}$$

In the above, we define

$$\langle b(t)\rangle \equiv \frac{1}{\tau}\int_0^\tau b(t)\,dt \tag{12}$$

as the mean value of $b(t)$.

4. STEP FUNCTION

We can examine the special case of the step function form of $b(t)$ (equation (3)) directly by examining the solution over each piece of the period τ. First, find the solution in the region $n\tau \le t < a + n\tau$; then match it to the solution in region $a + n\tau \le t < (n+1)\tau$. Doing this, we obtain

$$x(t) = \begin{cases} \dfrac{(1-b)x_{n\tau}}{x_{n\tau} + [(1-b) - x_{n\tau}]e^{-(1-b)r(t-n\tau)}}, & n\tau \le t < a + n\tau, \\ \dfrac{x_{(a+n\tau)}}{x_{(a+n\tau)} + [1 - x_{(a+n\tau)}]e^{-r(t-(a+n\tau))}}, & a + n\tau \le t < (n+1)\tau. \end{cases} \tag{13}$$

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

$$x_{(a+n\tau)} = \frac{(1-b)x_{n\tau}}{x_{n\tau} + [(1-b) - x_{n\tau}]e^{-(1-b)ar}}. \tag{14}$$

From this solution, we can find a difference equation that relates the size of $x(t)$ at the beginning of one period ($x_{n\tau}$) to that of the next period ($x_{(n+1)\tau}$). The Poincaré map for equations (13) is

$$x_{(n+1)\tau} = \frac{1}{1 + \left[\frac{x_{n\tau} + [(1-b) - x_{n\tau}]e^{-(1-b)ar}}{(1-b)x_{n\tau}} - 1\right] e^{-r(\tau - a)}}. \tag{15}$$

The equilibria for this difference equation are

$$x_{eq} = 0, \tag{16}$$

$$x_{eq} = \frac{1 - e^{r(ab-\tau)}}{1 - (1/(1-b))(e^{-ar(1-b)} - b)e^{-r(\tau-a)}}. \tag{17}$$

This is just a special case of equations (9) and (10) where the bifurcation from equilibrium (17) being stable to equilibrium (16) being stable is $ab = \tau$. (Note that this is the same result as $\langle b(t)\rangle = 1$.) Figure 1 shows the bifurcation diagram distinguishing between the stable and unstable equilibria.

5. CONCLUSIONS

Some variations can be made to this model to more accurately model chemotherapy. A few possibilities are varying the carrying capacity K (either increasing of decreasing) to model either the tumor bed effect (see [4,11]) or decaying carrying capacity due to cytotoxic build-up (see [9]). Another possibility is to allow cytotoxic effects to decay over each successive period. This can be due to drug resistance; the drugs have less affect on the cells over time. Incorporating these steps into the model can help it better model the effects of chemotherapy.

This model gives a concise and general form for the bifurcation between reduced steady state cell survival and cell destruction. It can be the basis for studying the chemotherapeutic effects on both cancerous cell tissue and normal cell tissue such as bone marrow. If it is used with cancerous tissue, then condition (11) describes the type of regimen needed to destroy the cancer cells. If it is used to model the chemotherapeutic effects on bone marrow, we might instead look for the point where the equilibrium is about half the carrying capacity since this is the limit of acceptable bone marrow destruction.

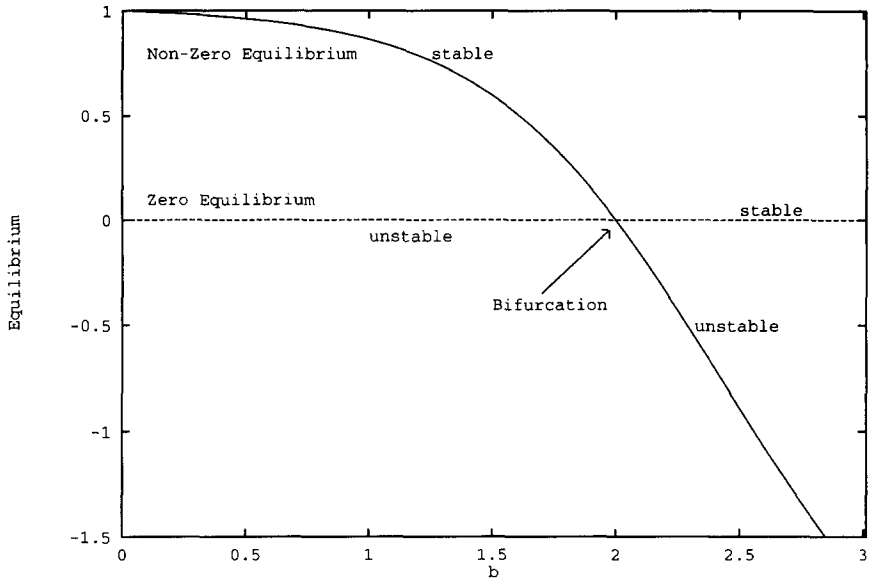

Figure 1. Bifurcation diagram, $a = 3$, $\tau = 6$, $r = 1$.

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