Hindawi Publishing Corporation
Abstract and Applied Analysis
Volume 2011, Article ID 980686, 10 pages
doi:10.1155/2011/980686

Research Article

Hopf Bifurcation of a Mathematical Model for Growth of Tumors with an Action of Inhibitor and Two Time Delays

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Received 3 November 2010; Accepted 25 January 2011

Academic Editor: Allan C. Peterson

A mathematical model for growth of tumors with two discrete delays is studied. The delays, respectively, represent the time taken for cells to undergo mitosis and the time taken for the cell to modify the rate of cell loss due to apoptosis and kill of cells by the inhibitor. We show the influence of time delays on the Hopf bifurcation when one of delays is used as a bifurcation parameter.

1. Introduction

Within last four decades, an increasing number of partial differential equation models for tumor growth or therapy have been developed; compare [1–9] and references cited therein. Most of those models are in form of free boundary problems. Rigorous mathematical analysis of such free boundary problems has drawn great interest, and many interesting results have been established; compare [10–20] and references cited therein. Analysis of such free boundary problems not only provides a sound theoretical basis for tumor medicine, but also greatly enriches the understanding of deferential equations.

In this paper, we study a mathematical model for growth of tumors with two discrete delays. The delays, respectively, represent the time taken for cells to undergo mitosis and the time taken for the cell to modify the rate of cell loss due to apoptosis and kill of cells by the inhibitor. The model is as follows:

$$\Delta_r \sigma = \Gamma_1 \sigma, \qquad 0 < r < R(t), \quad t > 0, \tag{1.1}$$

$$\frac{\partial\sigma}{\partial r}(0,t)=0, \qquad \sigma(R(t),t)=\sigma_\infty, \quad t>0, \tag{1.2}$$

$$\Delta_r\beta=\Gamma_2\beta, \qquad 0<r<R(t), \quad t>0, \tag{1.3}$$

$$\frac{\partial\beta}{\partial r}(0,t)=0, \qquad \beta(R(t),t)=\beta_\infty, \quad t>0, \tag{1.4}$$

$$\frac{d}{dt}\frac{4\pi R^3(t)}{3}=4\pi\int_0^{R(t-\tau_1)}\lambda\sigma(r,t-\tau_1)r^2dr-4\pi\int_0^{R(t-\tau_2)}\left[\lambda\widetilde{\sigma}+\mu\beta(r,t-\tau_2)\right]r^2dr, \quad t>0, \tag{1.5}$$

$$R(t)=\varphi(t), \qquad -\tau\le t\le 0, \tag{1.6}$$

where Γ_1, Γ_2, λ, μ, σ_∞, β_∞, $\widetilde{\sigma}$, τ_1, and τ_2 are positive constants, φ is a given positive function. $\Delta_r=(1/r^2)(\partial/\partial r)(r^2(\partial./\partial r))$. The term $\Gamma_1\sigma$ in (1.1) is the consumption rate of nutrient in a unit volume; $\Gamma_2\beta$ in (1.3) is the consumption rate of inhibitor in a unit volume; σ_∞ reflects constant supply of nutrient that the tumor receives from its surface; β_∞ reflects constant supply of inhibitor that the tumor receives from its surface. τ_1 represents the time taken for cells to undergo mitosis, and τ_2 represents the time taken for the cell to modify the rate of cell loss due to apoptosis and kill of cells by the inhibitor. The two terms on the right hand side of (1.5) are explained as follows: the first term is the total volume increase in unit time interval induced by cell proliferation; $\lambda\sigma$ is the cell proliferation rate in unit volume. The second term is total volume shrinkage in unit time interval caused by cell apoptosis (cell death due to aging) and the kills of cells by the inhibitor; the cell apoptosis rate is assumed to be constant; $\lambda\widetilde{\sigma}$ does not depend on either σ or β.

The study of effects of time delay in growth of tumors by using the method of mathematical models was initiated by Byrne [1]. Recently this study has drawn attention of some other researchers; compare Bodnar and Foryś [10], Fory and Bodnar [15], Foryś and Kolev [16], Sarkar and Banerjee [7] with one delay; and compare Piotrowska [18], Xu [19] with two delays. This mathematical model is established by modifying the model of Byrne [2] by considering two independent time delays effect as in [18, 19]. The modifications are based on biological considerations, see Cui and Xu [14] for details. In [14], the authors studied the problem (1.1)–(1.6) with only one delay in proliferation, that is, $\tau_2=0$, and showed that the dynamical behavior of solutions of the model with a delay in proliferation is similar to that of solutions for corresponding nondelayed problem. The aim of this paper is to investigate the influence of time delays on the Hopf bifurcation when τ_2 is used as a bifurcation parameter.

Denote $\theta=\sqrt{(\Gamma_2/\Gamma_1)}$. By rescaling the space variable, we may assume that $\Gamma_1=1$. Accordingly, we have $\theta=\sqrt{\Gamma_2}$. The solution of (1.1)–(1.4) is

$$\sigma(r,t)=\frac{\sigma_\infty R(t)}{\sinh R(t)}\frac{\sinh r}{r}, \qquad \beta(r,t)=\frac{\beta_\infty R(t)}{\sinh(\theta R(t))}\frac{\sinh(\theta r)}{r}. \tag{1.7}$$

Substituting (1.7) into (1.6) we obtain

$$\dot{R}(t)=R(t)\left[\lambda\sigma_\infty p(R(t-\tau_1))\left(\frac{R(t-\tau_1)}{R(t)}\right)^3-\left(\mu\beta_\infty p(R(t-\tau_2))+\frac{1}{3}\lambda\widetilde{\sigma}\right)\left(\frac{R(t-\tau_2)}{R(t)}\right)^3\right]; \tag{1.8}$$

here $p(x) = (x \coth x - 1)/x^2$. Set $\omega(t) = R^3(t)$, and we have

$$\dot{\omega}(t) = 3\lambda\sigma_\infty p\left(\omega^{1/3}(t-\tau_1)\right)\omega(t-\tau_1) - \left(3\mu\beta_\infty p\left(\omega^{1/3}(t-\tau_2)\right) + \lambda\tilde{\sigma}\right)\omega(t-\tau_2). \tag{1.9}$$

Using the step method (see, e.g., [21]), we can easily show that if there exists a solution for $t \in [(n-1)\tau_3, n\tau_3]$, then the solution for $t \in [n\tau_3, (n+1)\tau_3]$, where $n \in N$, $\tau_3 = \min(\tau_1, \tau_2)$, is defined by the formula

$$\omega(t) = \omega(n\tau_3) + \int_{n\tau_3}^{t} 3\lambda\sigma_\infty p\left(\omega^{1/3}(s-\tau_1)\right)\omega(s-\tau_1) - \left(3\mu\beta_\infty p\left(\omega^{1/3}(s-\tau_2)\right) + \lambda\tilde{\sigma}\right)\omega(s-\tau_2)ds. \tag{1.10}$$

Clearly the step method gives the existence of unique solution to (1.9) because of $s-\tau_1,\ s-\tau_2 \in [(n-1)\tau_3, n\tau_3]$.

Using Theorem 1.2 from [22], we can get nonnegative initial condition ω^0, and the solution of (1.9) can become negative in a finite time. Therefore, through the rest of the paper we assume that a positive solution of (1.9) with initial function ω^0 exists for every $t > 0$.

2. Stability of the Stationary Solutions and Existence of Local Hopf Bifurcation

In this section, we will study stability of the stationary solutions and existence of local Hopf bifurcation.

The first step is to find stationary solutions. Stationary solutions to (1.9) satisfy the equation

$$\left(3\lambda\sigma_\infty p\left(x^{1/3}\right) - 3\mu\beta_\infty p\left(\theta x^{1/3}\right) - \lambda\tilde{\sigma}\right)x = 0. \tag{2.1}$$

Clearly, (2.1) has the trivial solution $x = 0$. Next, we consider the positive solutions to (2.1). From [17] we know that $p(x)$ is strictly monotone decreasing for $x > 0$, and

$$\lim_{x\to 0+} p(x) = \frac{1}{3}, \qquad \lim_{x\to\infty} p(x) = 0. \tag{2.2}$$

Let $g(x) = 3\lambda\sigma_\infty p(x^{1/3}) - 3\mu\beta_\infty p(\theta x^{1/3}) - \lambda\tilde{\sigma}$, $x > 0$. Then

$$\lim_{x\to 0+} g(x) = \lambda\sigma_\infty - \mu\beta_\infty - \lambda\tilde{\sigma},$$

$$g'(x) = x^{-2/3}\left(\lambda\sigma_\infty p'\left(x^{1/3}\right) - \theta\mu\beta_\infty p'\left(\theta x^{1/3}\right)\right) = -\theta\mu\beta_\infty x^{-2/3} p'\left(x^{1/3}\right)\left(\frac{p'(\theta x^{1/3})}{p'(x^{1/3})} - \frac{\lambda\sigma_\infty}{\theta\mu\beta_\infty}\right). \tag{2.3}$$

By [12], we know that $p'(\theta y)/p'(y)$ is strictly monotone increasing (resp., decreasing) if $0 < \theta < 1$ (resp., $\theta > 1$) and

$$\lim_{y\to 0+}\frac{p'(\theta y)}{p'(y)} = \theta, \qquad \lim_{y\to\infty}\frac{p'(\theta y)}{p'(y)} = \frac{1}{\theta^2}. \tag{2.4}$$

Using these results, we can easily prove the following lemma (see [11] or [14]).

Lemma 2.1. *Assume that $0 < \theta < 1$. Then the following assertions hold.*

(1) *If $\beta_\infty \ge \lambda\sigma_\infty/\theta^2\mu$ then there exist no positive solutions for* (2.1), *that is, the problem* (1.9) *has no positive stationary solutions.*

(2) *If $\beta_\infty < \lambda\sigma_\infty/\theta^2\mu$, then in the case $\widetilde{\sigma} \ge \sigma_\infty - \mu\beta_\infty/\lambda$ there exist no positive solutions for* (2.1), *that is, the problem* (1.9) *has no positive stationary solutions, and in the opposite case $\widetilde{\sigma} < \sigma_\infty - \mu\beta_\infty/\lambda$, there exists a unique positive solution $x = \omega_s$ for* (2.1), *that is, the problem* (1.9) *has a unique positive stationary solution $x = \omega_s$. Moreover $g'(\omega_s) < 0$.*

Assume that $\theta > 1$. Then the following assertions hold.

(3) *If $\beta_\infty \ge \theta\lambda\sigma_\infty/\mu$ then there exist no positive solutions for* (2.1), *that is, the problem* (1.9) *has no positive stationary solutions.*

(4) *If $\beta_\infty \le \lambda\sigma_\infty/\theta^2\mu$, then in the case $\widetilde{\sigma} \ge \sigma_\infty - \mu\beta_\infty/\lambda$ there exist no positive solutions for* (2.1), *that is, the problem* (1.9) *has no positive stationary solution, and in the opposite case $\widetilde{\sigma} < \sigma_\infty - \mu\beta_\infty/\lambda$, there exists a unique positive solution $x = \omega_s$ for* (2.1), *that is, the problem* (1.9) *has a unique positive stationary solution. Moreover $g'(\omega_s) < 0$.*

(5) *If $\lambda\sigma_\infty/\theta^2\mu < \beta_\infty < \theta\lambda\sigma_\infty/\mu$, then there exists a unique $x^* > 0$ such that*

$$\frac{p'(\theta y^*)}{p'(y^*)} = \frac{\lambda\sigma_\infty}{\theta\mu\beta_\infty}; \tag{2.5}$$

here $y^* = (x^*)^{1/3}$, and x^* is the maximum point of $g(x)$. Denote $g(x^*) = M$. Then if $\widetilde{\sigma} > 3M$ there exist no positive solutions for (2.1), *that is, the problem* (1.9) *has no positive stationary solutions. If $0 < \widetilde{\sigma} \le \sigma_\infty - \mu\beta_\infty/\lambda$ there exists a unique positive solution $x = \omega_s$ for* (2.1) *which satisfy $g'(\omega_s) < 0$, that is, the problem* (1.9) *has a unique positive stationary solution satisfying $g'(\omega_s) < 0$. If $\sigma_\infty - \mu\beta_\infty/\lambda < \widetilde{\sigma} < 3M$ there exist two positive solutions $x_1 = \omega_{s1} < x_1 = \omega_{s2}$ for* (2.1) *which satisfy $g'(\omega_{s1}) > 0$, $g'(\omega_{s2}) < 0$, that is, the problem* (1.9) *has two positive stationary solutions satisfying $g'(\omega_{s1}) > 0$, $g'(\omega_{s2}) < 0$, respectively.*

The next step is to study the stability and the Hopf bifurcation of (1.9). Linearizing (1.9) at positive stationary solutions, we obtain

$$\dot{\omega}(t) = -A_1\omega(t-\tau_1) - A_2\omega(t-\tau_2), \tag{2.6}$$

where $A_1 = -\lambda\sigma_\infty[\omega_s^{1/3}p'(\omega_s^{1/3}) + 3p(\omega_s^{1/3})]$, $A_2 = \mu\beta_\infty(\theta\omega_s^{1/3}p'(\theta\omega_s^{1/3}) + 3p(\theta\omega_s^{1/3})) + \lambda\widetilde{\sigma}$.

Similarly linearizing (1.9) at the trivial stationary solution we get

$$\dot{\omega}(t) = -B_1\omega(t-\tau_1) - B_2\omega(t-\tau_2), \tag{2.7}$$

where $B_1 = -\lambda\sigma_\infty$, $B_2 = \mu\beta_\infty + \lambda\widetilde{\sigma}$.

We claim $A_1 < 0$, $A_2 > 0$. Actually, for $y > 0$, $y^3p(y)$ is strictly monotone increasing in y (see [14]), that is, for $y > 0$,

$$\frac{d(y^3p(y))}{dy} > 0 \Longleftrightarrow y^2(y\dot{p}(y) + 3p(y)) > 0 \Longleftrightarrow y\dot{p}(y) + 3p(y) > 0. \tag{2.8}$$

This readily implies that $A_1 = -\lambda\sigma_\infty(y\dot{p}(y)+3p(y))|_{y=\omega_s^{1/3}} < 0$. Immediately, $A_2 = \mu\beta_\infty(y\dot{p}(y)+3p(y))|_{y=\theta\omega_s^{1/3}} + \widetilde{\sigma} > 0$. Hence the claim is true.

The characteristic of (2.6) is as follows:

$$z = -A_1e^{-z\tau_1} - A_2e^{-z\tau_2}. \tag{2.9}$$

From [14] we know that if $\tau_2 = 0$ then for arbitrary $\tau_1 > 0$, the dynamical behavior of solutions of problem (1.9) with nonnegative initial function is similar to that of solutions for corresponding nondelayed problem. By continuity, for sufficiently small $\tau_2 > 0$, the dynamical behavior of solutions of problem (1.9) with nonnegative initial function is also similar to that of solutions for corresponding nonretarded problem.

In the following, we will study stability of the stationary solutions and existence of local Hopf bifurcation. From biological point of view it is reasonable to take τ_2 as bifurcation parameter, for detail see [18] and the references therein.

The case when $B_1 < 0$, $B_2 > 0$ was studied in [23, 24], and the proof of the following lemma can be found in it.

Lemma 2.2. *Consider the equation*

$$\dot{x}(t) = f(x(t-\tau_1), x(t-\tau_2)), \tag{2.10}$$

with a nonnegative initial continuous function $\varphi : [-\tau, 0] \to R_+$, where τ_1, τ_2 are the positive constants, $\tau = \max(\tau_1, \tau_2)$, and f is a continuously differentiable nonlinear function. Assume that (2.10) *has the trivial stationary solution, that is, $f(0,0) = 0$. Let the linearized equation around the trivial solution of* (2.10) *be as follows:*

$$\dot{x}(t) = -B_1x(t-\tau_1) - B_2x(t-\tau_2). \tag{2.11}$$

Then

(1) *if $B_1 < 0$, $B_2 > |B_1|$, and $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$, then there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the trivial solution to* (2.10) *is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs;*

(2) *if $B_1 < 0$, $0 < B_2 < |B_1|$, the trivial solution to* (2.10) *is unstable independently on the values of both delays, and there is no Hopf bifurcation.*

Use Lemma 2.2, we easily have the following.

Corollary 2.3. *Consider the equation*

$$\dot{x}(t) = f(x(t-\tau_1), x(t-\tau_2)), \tag{2.12}$$

with a nonnegative initial continuous function $\varphi : [-\tau, 0] \to R_+$, *where* τ_1, τ_2 *are the positive constants,* $\tau = \max(\tau_1, \tau_2)$, f *is a continuously differentiable nonlinear function. Assume that* (2.12) *has the positive stationary solution* $x = x_s$, *that is,* $f(x_s, x_s) = 0$. *Let the linearized equation around the positive stationary solution of* (2.10) *be as follows:*

$$\dot{x}(t) = -A_1 x(t-\tau_1) - A_2 x(t-\tau_2). \tag{2.13}$$

Then

(1) *if* $A_1 < 0$, $A_2 > |A_1|$, *and* $\tau_1 \in (0, \pi/2\sqrt{A_2^2 - A_1^2}]$, *then there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the positive stationary solution to* (2.10) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs;*

(2) *if* $A_1 < 0$, $0 < A_2 < |A_1|$, *the positive stationary solution to* (2.10) *is unstable independently on the values of both delays, and there is no Hopf bifurcation.*

Noticing $A_1 = -\lambda\sigma_\infty[\omega_s^{1/3} p'(\omega_s^{1/3}) + 3p(\omega_s^{1/3})]$, $A_2 = \mu\beta_\infty(\theta\omega_s^{1/3} p'(\theta\omega_s^{1/3}) + 3p(\theta\omega_s^{1/3})) + \tilde{\sigma}$ and $\omega_s > 0$ satisfy (2.1), by direct computation, we have

$$A_2 - |A_1| = A_2 + A_1 = -\lambda\sigma_\infty p'\left(\omega_s^{1/3}\right) + \theta\mu\beta_\infty p'\left(\theta\omega_s^{1/3}\right). \tag{2.14}$$

Since $p(x)$ is strictly monotone decreasing for $x > 0$, we are readily get

$$\begin{gathered} A_2 > |A_1| \Longleftrightarrow \frac{p'\left(\theta\omega_s^{1/3}\right)}{p'\left(\omega_s^{1/3}\right)} < \frac{\lambda\sigma_\infty}{\theta\mu\beta_\infty} \Longleftrightarrow g'(\omega_s) < 0, \\ A_2 < |A_1| \Longleftrightarrow \frac{p'\left(\theta\omega_s^{1/3}\right)}{p'\left(\omega_s^{1/3}\right)} > \frac{\lambda\sigma_\infty}{\theta\mu\beta_\infty} \Longleftrightarrow g'(\omega_s) > 0. \end{gathered} \tag{2.15}$$

Clearly $B_1 < 0$, by direct computation, we obtain

$$\begin{gathered} B_2 > |B_1| \Longleftrightarrow \tilde{\sigma} > \sigma_\infty - \frac{\mu\beta_\infty}{\lambda}, \\ B_2 < |B_1| \Longleftrightarrow \tilde{\sigma} < \sigma_\infty - \frac{\mu\beta_\infty}{\lambda}. \end{gathered} \tag{2.16}$$

Noticing

$$\beta_\infty < \frac{\lambda}{\mu}(\sigma_\infty - \tilde{\sigma}) \Longleftrightarrow \tilde{\sigma} > \sigma_\infty - \frac{\mu\beta_\infty}{\lambda} \Longleftrightarrow B_2 > |B_1|,$$
$$\beta_\infty > \frac{\lambda}{\mu}(\sigma_\infty - \tilde{\sigma}) \Longleftrightarrow \tilde{\sigma} < \sigma_\infty - \frac{\mu\beta_\infty}{\lambda} \Longleftrightarrow B_2 < |B_1|, \tag{2.17}$$

by Lemma 2.2, we can conclude the following.

(i) Assume that $\beta_\infty < (\lambda/\mu)(\sigma_\infty - \tilde{\sigma})$ and $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ hold, then there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the trivial solution to (1.9) is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs.

(ii) Assume that $\beta_\infty > (\lambda/\mu)(\sigma_\infty - \tilde{\sigma})$ holds, the trivial solution to (1.9) is unstable independently on the values of both delays, and there is no Hopf bifurcation.

By simple computation, we have

$$\beta_\infty < \frac{\lambda}{\mu}(\sigma_\infty - \tilde{\sigma}), \qquad \beta_\infty < \frac{\lambda\sigma_\infty}{\mu\theta^2} \Longleftrightarrow$$
$$0 < \theta < 1, \quad \beta_\infty < \frac{\lambda\sigma_\infty}{\mu\theta^2}, \quad \tilde{\sigma} < \sigma_\infty - \frac{\mu\beta_\infty}{\lambda} \quad \text{or} \quad \theta > 1, \quad \beta_\infty < \frac{\lambda\sigma_\infty}{\mu\theta^2}, \quad \tilde{\sigma} < \sigma_\infty - \frac{\mu\beta_\infty}{\lambda} \tag{2.18}$$

$\Rightarrow$ (1.9) has a positive stationary solution ω_s and $g'(\omega_s) < 0 \Leftrightarrow A_2 > |A_1|$. Then by Corollary 2.3, we have the following. Assume that $\beta_\infty < (\lambda/\mu)(\sigma_\infty - \tilde{\sigma})$ and $\beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ hold, then for $\tau_1 \in (0, \pi/2\sqrt{A_2^2 - A_1^2}]$ there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the positive stationary solution to (1.9) is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs.

Since $0 < \theta < 1$ and $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2 \Leftrightarrow \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$, $\tilde{\sigma} > \sigma_\infty - \mu\beta_\infty/\lambda \Rightarrow B_2 > |B_1|$. From Lemma 2.1 we know that if $0 < \theta < 1$ and $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ hold, then (1.9) has no positive stationary solution. By Lemma 2.2, we readily have the following. Assume that $0 < \theta < 1$ and $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ hold, then for $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the trivial solution to (2.10) is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs.

Assume that $\theta > 1$, then we have the following.

If $\beta_\infty > (\theta\lambda\sigma_\infty/\mu)(> \lambda\sigma_\infty/\mu\theta^2) \Rightarrow \beta_\infty < (\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) \Rightarrow B_2 > |B_1|$;

if $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2 \Rightarrow \tilde{\sigma} > \sigma_\infty - \mu\beta_\infty/\lambda \Leftrightarrow B_2 > |B_1|$;

if $\lambda\sigma_\infty/\mu\theta^2 < \beta_\infty < \theta\lambda\sigma_\infty/\mu$ and if $\tilde{\sigma} > 3M \Rightarrow \tilde{\sigma} < \sigma_\infty - \mu\beta_\infty/\lambda \Leftrightarrow B_2 < |B_1|$; if $\tilde{\sigma} < \sigma_\infty - \mu\beta_\infty/\lambda \Rightarrow B_2 > |B_1|$; if $\sigma_\infty - \mu\beta_\infty/\lambda < \tilde{\sigma} < 3M \Rightarrow g'(\omega_{s2}) < 0$ and then by Lemma 2.2 and Corollary 2.3, we have the following.

(1) Assume that $\theta > 1$, $\beta_\infty > \theta\lambda\sigma_\infty/\mu$ or $\theta > 1$, $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ holds, then for $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the trivial solution to (2.10) is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs.

(2) Assume that $\theta > 1$, $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ hold. Then if $\tilde{\sigma} > 3M$, the trivial solution to (1.9) is unstable independently on the values of both delays, and there is no Hopf bifurcation; if $\tilde{\sigma} < \sigma_\infty - \mu\beta_\infty/\lambda$, then for $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the trivial solution to (2.10) is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs; if $\sigma_\infty - \mu\beta_\infty/\lambda < \tilde{\sigma} < 3M$, then for $\tau_1 \in (0, \pi/2\sqrt{A_2^2 - A_1^2}]$ there exists $\tau_2^0 > 0$ such that for $\tau_2 \in [0, \tau_2^0)$ the positive stationary solution ω_{s2} to (1.9) is asymptotically stable and for $\tau_2 = \tau_2^0$ the Hopf bifurcation occurs.

We summarize as follows.

Theorem 2.4. *(i) Assume that* $\beta_\infty < (\lambda/\mu)(\sigma_\infty - \tilde{\sigma})$ *and* $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ *hold, then there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the trivial solution to* (1.9) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs.*

(ii) Assume that $\beta_\infty > (\lambda/\mu)(\sigma_\infty - \tilde{\sigma})$ *holds, the trivial solution to* (1.9) *is unstable independently on the values of both delays, and there is no Hopf bifurcation.*

(iii) Assume that $\beta_\infty < (\lambda/\mu)(\sigma_\infty - \tilde{\sigma})$ *and* $\beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ *hold, then for* $\tau_1 \in (0, \pi/2\sqrt{A_2^2 - A_1^2}]$ *there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the positive stationary solution to* (1.9) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs.*

(iv) Assume that $0 < \theta < 1$ *and* $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ *hold, then for* $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ *there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the trivial solution to* (2.10) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs.*

(v) Assume that $\theta > 1$, $\beta_\infty > \theta\lambda\sigma_\infty/\mu$ *or* $\theta > 1$, $(\lambda/\mu)(\sigma_\infty - \tilde{\sigma}) < \beta_\infty < \lambda\sigma_\infty/\mu\theta^2$ *holds, then for* $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ *there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the trivial solution to* (2.10) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs.*

(vi) Assume that $\theta > 1$, $\lambda\sigma_\infty/\mu\theta^2 < \beta_\infty < \theta\lambda\sigma_\infty/\mu$ *hold. Then if* $\tilde{\sigma} > 3M$, *the trivial solution to* (1.9) *is unstable independently on the values of both delays, and there is no Hopf bifurcation; if* $\tilde{\sigma} < \sigma_\infty - \mu\beta_\infty/\lambda$, *then for* $\tau_1 \in (0, \pi/2\sqrt{B_2^2 - B_1^2}]$ *there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the trivial solution to* (2.10) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs; if* $\sigma_\infty - \mu\beta_\infty/\lambda < \tilde{\sigma} < 3M$, *then for* $\tau_1 \in (0, \pi/2\sqrt{A_2^2 - A_1^2}]$ *there exists* $\tau_2^0 > 0$ *such that for* $\tau_2 \in [0, \tau_2^0)$ *the positive stationary solution* ω_{s2} *to* (1.9) *is asymptotically stable and for* $\tau_2 = \tau_2^0$ *the Hopf bifurcation occurs.*

3. Conclusion

In this paper, we study a mathematical model for growth of tumors with two discrete delays. The delays, respectively, represent the time taken for cells to undergo mitosis and the time taken for the cell to modify the rate of cell loss due to apoptosis and kill of cells by the inhibitor. Final mathematical formulation of the model is retarded differential equation of the form

$$\dot{\omega}(t) = f(\omega(t - \tau_1), \omega(t - \tau_2)), \tag{3.1}$$

with a nonnegative initial continuous function $\varphi : [-\tau, 0] \rightarrow R_+$, where τ_1, τ_2, and $\tau = \max(\tau_1, \tau_2)$ are the positive constants, f is a continuously differentiable function. The results show that the two independent delays control the dynamics of the solution of the problem (3.1) and the dynamic behavior is different to the corresponding nonretarded ordinary equation

$$\dot{\omega}(t) = f(\omega(t), \omega(t)), \qquad x(0) = x_0 > 0, \tag{3.2}$$

or retarded differential equation with only one delay of the form

$$\dot{\omega}(t) = f(\omega(t-\tau), \omega(t)), \tag{3.3}$$

with a nonnegative initial continuous function $\varphi : [-\tau, 0] \rightarrow R_+$. However the dynamic behaviors of the problem (3.2) and (3.3) are similar, see [14].

Acknowledgments

The work of the third author is partially supported by NNSF (10926128), NSF, and YMF of Guangdong Province (9251064101000015, LYM10133).

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