Analysis of a mathematical model for tumor growth under indirect effect of inhibitors with time delay in proliferation

Shihe Xu\textsuperscript{a}, Zhaoyong Feng\textsuperscript{b,*}

\textsuperscript{a} Department of Mathematics, Zhaoqing University, Zhaoqing 526061, PR China
\textsuperscript{b} Department of Mathematics, Sun Yat-sen University, Guangzhou 510275, PR China

\section*{A R T I C L E   I N F O}

Article history:
Received 11 October 2009
Available online 25 August 2010
Submitted by P. Broadbridge

Keywords:
Tumor growth
Inhibitors
Time delay
Local stability
Global stability

\section*{A B S T R A C T}

In this paper, a mathematical model for tumor growth with time delay in proliferation under indirect effect of inhibitor is studied. The delay represents the time taken for cells to undergo mitosis. Nonnegativity of solutions is investigated. The steady-state analysis is presented with respect to the magnitude of the delay. Existence of Hopf bifurcation is proved for some parameter values. Local and global stability of the stationary solutions are proved for other ones. The analysis of the effect of inhibitor’s parameters on tumor’s growth is presented. The results show that dynamical behavior of solutions of this model is similar to that of solutions for corresponding non-retarded problems for some parameter values.

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1. Introduction

During last three decades, a variety of differential equation models for tumor growth or therapy have been developed, see [3–5,10,14,15,17–19]. The basic principles used to construct such models are based on reaction–diffusion equations and mass conservation law. Most of these models are in form of free boundary problems and are very diversified. Rigorous mathematical analysis of such free boundary problems has drawn great interest, and many interesting results have been established [2,6–9,11–13,20,21].

In this paper, we study a mathematical model modeling tumor growth with effect of inhibitor and time delay in proliferation. The idea of the model studied in this paper was initiated by Byrne [3], and recently this study has drawn attentions of some other researchers, cf. Bodnar and Forys [2], Forys and Bodnar [11], Cui and Xu [9] and Xu [21]. The model we study in this paper is established by modifying the model of Byrne and Chaplain [4] (see also in Cui [7] in which rigorous analysis of the model presented by Byrne and Chaplain [4] is given) by considering the time delay effect as in Byrne [3]. Introducing time delay in proliferation as in Byrne [3] to the scaled model studied by Cui and Friedman in [7] which had been initiated presented by Byrne and Chaplain [4] we have

\begin{align}
\frac{c_1}{\sigma_t} &= \Delta \sigma - \lambda \sigma - \beta, \\
\frac{c_2}{\beta_t} &= \Delta \beta - \gamma \beta, \\
\frac{\partial \sigma}{\partial r}(0, t) &= 0, \quad \sigma(R(t), t) = \sigma_\infty, \\
\frac{\partial \beta}{\partial r}(0, t) &= 0, \quad \beta(R(t), t) = \beta_\infty.
\end{align} 

\footnote{* Corresponding author. E-mail addresses: shihexu03@yahoo.com.cn (S. Xu), fzhao@sysu.edu.cn (Z. Feng).}

\textsuperscript{a} Corresponding author.

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doi:10.1016/j.jmaa.2010.08.043
\[
\frac{d}{dt} \frac{4\pi R^3(t)}{3} = 4\pi \int_0^{R(t)} \mu \sigma(r, t - \tau) r^2 dr - 4\pi \int_0^{R(t)} \mu \tilde{\sigma} r^2 dr. 
\] (1.1e)

\[
R(t) = \varphi(t), \quad -\tau \leq t \leq 0. 
\] (1.1f)

\[
\sigma(r, t) = \psi(t), \quad 0 < r < R(t), \quad -\tau \leq t \leq 0. 
\] (1.1g)

where \(0 < r < R(t), t > 0\) for Eqs. (1.1a)–(1.1d), and \(t > 0\) for Eq. (1.1e); \(\lambda, \gamma, \mu, \sigma, \beta, \tilde{\sigma}, \tau\) are positive constants. \(r\) is the radial variable scaled by the tumor-cell radius; the variables \(\tilde{\sigma}(r, t)\) and \(\beta(r, t)\), respectively, represent the scaled nutrient and inhibitor concentration at radius \(r\) and time \(t\); the variable \(R(t)\) represents the scaled radius of the tumor at time \(t\); \(\lambda, \gamma\) are scaled consumption coefficients of nutrient and inhibitor; \(\sigma, \beta\) reflect constant supply of nutrient and inhibitor that the tumor receives from its surface respectively; \(\tau\) is the time delay in cell proliferation, i.e., \(\tau\) is the length of the period that a tumor cell undergoes full process of mitosis. \(\varphi\) is a given positive function. \(\Lambda = \frac{1}{r^2} \frac{d}{dt} (\frac{T}{r^2})\). The two terms on the right hand side of (1.1e) are explained as follows: The first term is the total volume increase in a unit time interval induced by cell proliferation; \(\mu \tilde{\sigma}\) is the scaled cell proliferation rate in unit volume. The second term is total volume shrinkage in a unit time interval caused by cell apoptosis, or cell death due to aging; the cell apoptosis is assumed to be constant does not depend on \(\sigma\) or \(\beta\). \(c_1, c_2\) are positive constants. \(c_1 = T_{\text{diffusion}}/T_{\text{growth}}\) is the ratio of the nutrient diffusion time scale to the tumor growth (e.g., tumor doubling) time scale and \(c_2\) the ratio of the inhibitor diffusion time scale to the tumor growth (e.g., tumor doubling) time scale, for details see [7].

From [4,7] we know that \(T_{\text{diffusion}} \approx 1\) min and \(T_{\text{growth}} \approx 1\) day, so that \(c_1, c_2 \ll 1\). For this reason and simplicity, we only consider the limiting case where \(c_1 = c_2 = 0\) in this paper. Thus we study a delayed mathematical model for tumor growth as follows:

\[
\Delta_t \sigma - \lambda \sigma - \beta = 0, 
\] (1.2a)

\[
\Delta_t \beta - \gamma \beta = 0, \quad 0 < r < R(t), \quad t > 0, 
\] (1.2b)

\[
\frac{\partial \sigma}{\partial r}(0, t) = 0, \quad \sigma(R(t), t) = \sigma_\infty, 
\] (1.2c)

\[
\frac{\partial \beta}{\partial r}(0, t) = 0, \quad \beta(R(t), t) = \beta_\infty, 
\] (1.2d)

\[
\frac{d}{dt} \frac{4\pi R^3(t)}{3} = 4\pi \int_0^{R(t)} \mu \sigma(r, t - \tau) r^2 dr - 4\pi \int_0^{R(t)} \mu \tilde{\sigma} r^2 dr, 
\] (1.2e)

\[
R(t) = \varphi(t), \quad -\tau \leq t \leq 0. 
\] (1.2f)

The model (1.1a)–(1.1g) without time delay and inhibitor’s effect (i.e. \(\beta = 0\) and \(\tau = 0\)) is studied by Friedman and Reitich [13] and in their model they assume \(\sigma_\infty > \tilde{\sigma} > 0\). The model (1.1a)–(1.1g) only without time delay (i.e. \(\tau = 0\)) is studied by Cui and Friedman [7]. In their model, the parameters \(\sigma_\infty, \tilde{\sigma}\) are allowed to be any real numbers. But for simplicity we assume that the parameters \(\sigma, \tilde{\sigma}\) are positive constants. The methods presented in this paper can be extended to the case that \(\sigma_\infty, \tilde{\sigma}\) are allowed to be any real numbers, but the results will be different. For simplicity, we always assume that \(\gamma \neq \lambda\) as in [7].

The solution of (1.2a)–(1.2d) is

\[
\sigma(r, t) = (1 - A_1) \frac{\sigma_\infty R(t)}{\sinh(\sqrt{\lambda} R(t))} \sinh(\sqrt{\lambda} r) + A_1 \frac{\sigma_\infty R(t)}{\sinh(\sqrt{\tau} R(t))} \sinh(\sqrt{\gamma} r), 
\] (1.3)

\[
\beta(r, t) = \frac{\beta_\infty R(t)}{\sinh(\sqrt{\tau} R(t))} \frac{\sinh(\sqrt{\gamma} r)}{r}. 
\] (1.3)

Substituting (1.3) into (1.2e) and letting \(\eta = \sqrt{\lambda} R\), we obtain

\[
3\eta^2(t) \dot{\eta}(t) = a[(1 - A_1)p(\eta(t - \tau)) + A_1 p(\phi \eta(t - \tau))] \eta^3(t - \tau) - a A_0 \eta^3(t), 
\] (1.4)

here \(p(x) = \frac{x \cosh x - 1}{x^2}, \phi = \sqrt{\gamma}, a = 3\mu \sigma_\infty, A_0 = \frac{\tilde{\sigma}}{\beta_\infty}\). Setting \(\omega(t) = \eta^3(t)\), we have

\[
\dot{\omega}(t) = a[(1 - A_1)p(\omega(t - \tau)) + A_1 p(\phi \omega(t - \tau))] \omega(t - \tau) - a A_0 \omega(t). 
\] (1.5)

Let

\[
g(x) = (1 - A_1)p(x) + A_1 p(\phi x). 
\] (1.6)
Then Eq. (1.5) can be written as follows:

\[ \dot{\omega}(t) = a\Lambda_0 \omega(t) - \omega(t) \frac{d}{dt} \left( \frac{x^2}{(x^2 + 1) \cosh x - x^2} \right) \]  

(1.7)

The paper is arranged as follows. In Section 2, nonnegativity of the solution to Eq. (1.5) for any nonnegative initial condition \( \omega(0) \) for \(- \leq t \leq 0\) is studied. In Section 3, we mainly discuss local stability of stationary solutions and existence of local Hopf bifurcation. Section 4 is devoted to global stability of stationary solutions for certain ranges of the parameters. In Section 5, the effect of inhibitor’s parameters on tumor’s growth is studied. In the last section, we give a conclusion.

2. Existence and nonnegativity of the solution to Eq. (1.5)

It is obviously that every solution of Eq. (1.5) exists for \( t > 0 \), because we may rewrite this equation in the following functional form

\[ \omega(t) = \omega(0) e^{-a\Lambda_0 t} + \sum_{k=0}^{t} e^{a\Lambda_0 \xi} \left( \frac{d}{d\xi} \left( \frac{x^2}{(x^2 + 1) \cosh x - x^2} \right) \right) d\xi \]  

(2.1)

and solve it using the step method (see e.g. [16]) on intervals \([n\tau, (n + 1)\tau], n \in \mathbb{N}\). In the rest of this section, we study the nonnegativity of the solution to Eq. (1.5).

**Lemma 2.1.**

1. \( x' = x - \frac{3}{2} x^2 \), \( \lim_{x \to 0} x' = 0 \).
2. \( p' < 0 \) for all \( x > 0 \).
3. \( \lim_{x \to \infty} p(x) = 1 \), \( \lim_{x \to \infty} \frac{p(x)}{x} = 0 \).
4. \( \frac{p''}{p'(x)} \) is strictly monotone decreasing for all \( x > 0 \).
5. \( xp(x) \) is monotonically increasing and \( x^2 p(x) > 0 \) for all \( x > 0 \).

For the proof of (1) see [21], and the proof of (2) and (3) see [13], (4) and (5), respectively, see [7] and [9]. We set \( G(x) = xp'(x) \) and define \( G(0) = 0 \). Clearly, with this assumption \( G(x) \) is continuous on the closure of \( \mathbb{R}_+ \).

**Lemma 2.2.** The function

\[ m(x) = \frac{p(x)}{xp'(x)} \]

is strictly monotone increasing for all \( x > 0 \) (i.e. \( m'(x) > 0 \) for all \( x > 0 \)).

**Proof.** By direct computation, we get

\[ m(x) = \frac{(x \cosh x - \sinh x) \sinh x}{2 \sinh^2 x - x \cosh x \sinh x - x^2} \]

\[ m'(x) = \frac{q(x)}{[2 \sinh^2 x - x \cosh x \sinh x - x^2]} \]

where

\[ q(x) = x \sinh^2 x + x \cosh x \sinh x - x^3 (\cosh x)^2 - x^3 (\sinh x)^2 - 2x \sinh x \]

Thus we only need to show that \( q(x) > 0 \) for all \( x > 0 \). By direct computation, we have

\[ q(x) = \sum_{k=3}^{\infty} \frac{1}{(2k + 3)!} M(k) x^{2k + 3} \]

here \( M(k) = [4^k (8 \times 4^k - (2k + 1)(2k + 2)(2k + 3))] + [4^k (6k - 6)(2k + 3) + 2 \times 4^k (6k + 7)] \), where identities \( 2 \sinh^2 x = \cosh(2x) - 1 \), \( \sinh(2x) = 2 \sinh x \cosh x \) and the Taylor expansions

\[ \sinh x = \sum_{k=0}^{\infty} \frac{x^{2k + 1}}{(2k + 1)!} \quad \text{and} \quad \cosh x = \sum_{k=0}^{\infty} \frac{x^{2k}}{(2k)!} \]

have been used. It is easy to verify that \( 8 \times 4^k - (2x + 1)(2x + 2)(2x + 3) > 0 \) for all \( x > 3 \), then \( M(k) > 0 \) for all \( k \geq 3 \). Then \( q(x) > 0 \) for all \( x > 0 \) follows. \( \Box \)
Corollary 2.3. Let \( l(x) = x^3 p(x) \), then the function

\[
k(x) = \frac{x^3 p''(x)}{p'(x)}
\]

is strictly monotone decreasing for all \( x > 0 \).

Proof. Indeed,

\[
k(x) = \frac{x^3 p''(x) + 6xp'(x) + 6p(x)}{xp'(x) + 3p(x)} = \frac{n(x) + 4}{1 + 3m(x)} + 2
\]

here \( m(x) = \frac{p(x)}{xp'(x)} \), \( n(x) = \frac{xp''(x)}{p'(x)} \). By Lemma 2.1(4), we know that the function \( n(x) \) is strictly monotone decreasing for all \( x > 0 \), then the assertion follows from that \( m(x) \) is strictly monotone increasing for all \( x > 0 \). \( \square \)

Corollary 2.4. If \( \phi > 1 \) (\( 0 < \phi < 1 \)), then

\[
d \frac{l'(\phi x)}{\Gamma(x)} < 0 \quad (> 0)
\]

for all \( x > 0 \).

Proof. By simple computation, we obtain

\[
\frac{d}{dx} \frac{l'(\phi x)}{\Gamma(x)} = \frac{\phi l'(\phi x) - l(\phi x)l''(x)}{(\Gamma(x))^2} = \left( \frac{\phi l''(\phi x)}{\Gamma(x)} - \frac{x l''(x)}{\Gamma(x)} \right) \frac{l'(\phi x)}{\Gamma(x)}.
\]

Since \( \frac{l'(\phi x)}{\Gamma(x)} \) is positive by Lemma 2.1(5), the assertions follow from Corollary 2.3. \( \square \)

Theorem 2.5. Set the function

\[
H(x) = x^3 \left[ (1 - A_1)p(x) + A_1 p(\phi x) \right] = x^3 g(x).
\]

Then

(i) If \( (\phi - 1) A_1 \leq \phi \) holds, then \( H(x) \) is strictly monotone increasing for all \( x > 0 \). Moreover, \( H(x) > 0 \) for all \( x > 0 \).
(ii) If \( (\phi - 1) A_1 > \phi \) holds, then there exists a unique \( x_0 \) such that

\[
H'(x) > 0 \quad \text{for} \ 0 < x < x_0, \quad H'(x) < 0 \quad \text{for} \ x > x_0
\]

and there exists a unique \( x_1 > x_0 \) such that

\[
H(x_1) = 0, \quad H(x) > 0 \quad \text{for} \ 0 < x < x_1, \quad H(x) < 0 \quad \text{for} \ x > x_1.
\]

Proof. Note that

\[
H(x) = (1 - A_1) l(x) + A_1 \frac{1}{\phi^2} l(\phi x),
\]

then

\[
H'(x) = l'(x) \left[ (1 - A_1) + \frac{A_1}{\phi^2} \frac{l'(\phi x)}{\Gamma(x)} \right].
\]

By simple computation, we have

\[
\lim_{x \to 0} \frac{l'(\phi x)}{\Gamma(x)} = \phi^2, \quad \lim_{x \to \infty} \frac{l'(\phi x)}{\Gamma(x)} = \phi.
\]

Then by Corollary 2.4, if \( \phi > 1 \) (\( \Leftrightarrow A_1 > 0 \)),

\[
\phi < \frac{l'(\phi x)}{\Gamma(x)} < \phi^2
\]

and if \( \phi < 1 \) (\( \Leftrightarrow A_1 < 0 \)),

\[
\phi^2 < \frac{l'(\phi x)}{\Gamma(x)} < \phi.
\]
Then
\[
H'(x) > l'(x) \left[ (1 - A_1) + \frac{A_1}{\phi} \right] = l'(x) \frac{\phi - (\phi - 1)A_1}{\phi} \geq 0,
\]
if \((\phi - 1)A_1 \leq \phi\) holds.

In the following, we shall prove (ii). Actually, by Lemma 2.1(2) and (2.4), we see that
\[
H'(x) \sim l'(x)[1 - A_1 + A_1] = l'(x) > 0
\]
if \(x\) near 0, and
\[
H'(x) \sim l'(x) \left[ 1 - A_1 + \frac{A_1}{\phi} \right] < 0
\]
if \(x\) near \(\infty\). We deduce that \(H'(x) = 0\) has only one positive solution \(x_0\) by Corollary 2.4. By Theorem 3.5(ii) in [7] and the fact \(\lim_{x \to \infty} g(x) = 0\) (by Lemma 2.1(3)), if \((\phi - 1)A_1 > \phi\) holds, there exists \(x_1 > 0\) such that \(g(x_1) = 0, g(x) > 0\) for \(x < x_1\), \(g(x) < 0\) for \(x > x_1\). Noticing that \(H(x) = x^3 g(x)\), we have
\[
H(x_1) = 0, \quad H(x) > 0 \quad \text{for} \quad 0 < x < x_1, \quad H(x) < 0 \quad \text{for} \quad x > x_1,
\]
and \(x_1 > x_0\) is obvious. \(\square\)

Using Theorem 1.2 from [1] and the property of \(H(x)\), we can conclude that the following assertions hold:

**Theorem 2.6.**

1. If \((\phi - 1)A_1 \leq \phi\) holds, for any nonnegative initial condition \(\omega(t)\) for \(-\tau \leq t \leq 0\), the solution to Eq. (1.5) will be nonnegative for all \(t > -\tau\).
2. If \((\phi - 1)A_1 > \phi\) holds, there exists a positive initial condition \(\omega(t)\) for \(-\tau \leq t \leq 0\) such that the solution to (1.5) becomes negative in a finite time interval.

**Remark 2.7.** Also by Theorem 1.2 from [1] and the property of \(H(x)\), if \((\phi - 1)A_1 > \phi\) holds, assume that
\[
\omega(t) < x_1^3
\]
for all \(t\), we have for any nonnegative initial condition \(\omega(t)\) for \(-\tau \leq t \leq 0\), the solution to Eq. (1.5) will be nonnegative for all \(t > -\tau\). Hence we may assume that Eq. (1.5) is sensible only for \(\omega(t) < x_1^3\) and it is connected with the formation of necrotic core inside the tumor. Eq. (2.5) cannot be satisfied for all \(t > 0\) without additional assumptions.

3. Local stability of stationary solutions

**Lemma 3.1.** (See [4].)

1. If \(\bar{\sigma} > \sigma_\infty\) (i.e., \(A_0 > \frac{1}{3}\)), then Eq. (1.5) has no positive stationary solution and only has a trivial stationary solution.
2. If \(\bar{\sigma} < \sigma_\infty\) (i.e., \(0 < A_0 < \frac{1}{3}\)), then Eq. (1.5) has a unique positive stationary solution \(\omega_s\), and \(g'(\omega_s^2) < 0\).

**Theorem 3.2.**

1. If \(\bar{\sigma} > \sigma_\infty\) (i.e., \(A_0 > \frac{1}{3}\)), then the trivial solution to Eq. (1.5) is locally stable independent of \(\tau\).
2. If \(\bar{\sigma} < \sigma_\infty\) (i.e., \(0 < A_0 < \frac{1}{3}\)), then in the case \(2aA_0 + \frac{1}{3}g'(\omega_s^2)\omega_s^2 > 0\), the unique positive stationary solution \(\omega_s\) to Eq. (1.5) is locally stable independent of \(\tau\), and in the case \(2aA_0 + \frac{1}{3}g'(\omega_s^2)\omega_s^2 < 0\), there exists \(\tau_0 > 0\) such that the unique positive stationary solution \(\omega_s\) to Eq. (1.5) is stable for \(\tau < \tau_0\) and unstable for \(\tau > \tau_0\). The Hopf bifurcation occurs at \(\tau_0\).

**Remark 3.3.** (1) By Theorem 2.5(1) we know when \((\phi - 1)A_1 \leq \phi\), \(\frac{d}{dx}(x^3 g(x)) > 0\) for all \(x > 0\). Noticing that \(A_0 = g'(\omega_s^2)\), we get
\[
aA_0 + \frac{1}{3}g'(\omega_s^2)\omega_s^2 = a \left[ g(\omega_s^2) + \frac{1}{3}g'(\omega_s^2)\omega_s^2 \right] = \left[ \frac{1}{3x^3} \frac{d}{dx}(x^3 g(x)) \right]_{x=\omega_s^2} > 0.
\]
This means that \(\omega_s\) fulfills the inequality \(2aA_0 + \frac{1}{3}g'(\omega_s^2)\omega_s^2 > 0\) when \((\phi - 1)A_1 \leq \phi\).
(2) When \((\phi - 1)A_1 > \phi\), noticing that \(\Lambda_0 = g(\omega_s^1)\), and the fact \(\lim_{x \to 0} g(x) = \frac{1}{3}\) (by Lemma 2.1(3) and (1.6)), we see that in the case \(\Lambda_0\) less than but near \(\frac{1}{3}\) (i.e. \(\sigma\) is less than but near \(\sigma_\infty\)), then \(\omega_s\) is a small positive constant such that \(\omega_s < \chi_0^1\). Then

\[
a \Lambda_0 + a \frac{1}{3} g'(\omega_s^1) \omega_s^1 = a \left[ g(\omega_s^1) + \frac{1}{3} g'(\omega_s^1) \omega_s^1 \right] = \left[ \frac{1}{3} \frac{d}{dx} (x^3 g(x)) \right]_{x=\omega_s^1} > 0.
\]

This means that \(\omega_s\) fulfills the inequality \(2 a \Lambda_0 + a \frac{1}{3} g'(\omega_s^1) \omega_s^1 > 0\). And in another case \(\Lambda_0\) greater than but near \(0\) (i.e. \(\sigma\) is much smaller than \(\sigma_\infty\)), then we can get \(2 a \Lambda_0 + a \frac{1}{3} g'(\omega_s^1) \omega_s^1 < 0\) from Lemma 2.1(1) and (1.6).

**Proof of Theorem 3.2.** (1) Linearizing Eq. (1.5) at the trivial stationary solution, we get

\[
\dot{\omega}(t) + a \Lambda_0 \omega(t) - \frac{a}{3} \omega(t - \tau) = 0.
\]  
(3.1)

The characteristic equation of (3.1) is as follows

\[
z + A + Be^{-z \tau} = 0,
\]  
(3.2)

where \(A = a \Lambda_0\), \(B = -\frac{a}{3}\). Since

\[
A + B = a \left( \Lambda_0 - \frac{1}{3} \right), \quad A - B = a \left( \Lambda_0 + \frac{1}{3} \right).
\]

it is obviously that \(A - B > 0\), and \(A + B > 0\) if \(\Lambda_0 > \frac{1}{3}\). Therefore by a well-known result in the theory of retarded differential equations, we conclude that the trivial solution is stable independent of \(\tau\) if \(\Lambda_0 > \frac{1}{3}\) holds.

(2) Linearizing Eq. (1.5) at positive stationary solution \(\omega_0\), we obtain

\[
\dot{v} - a \left[ \frac{1}{3} g'(\omega_0^1) \omega_0^1 + g(\omega_0^1) \right] v(t - \tau) + a \Lambda_0 v(t) = 0.
\]  
(3.3)

The characteristic equation of (3.3) is of the form

\[
z + A + Be^{-z \tau} = 0,
\]  
(3.4)

where \(A = a \Lambda_0\), \(B = -a \left[ \frac{1}{3} g'(\omega_0^1) \omega_0^1 + g(\omega_0^1) \right]\).

Since

\[
A + B = a \Lambda_0 - a \left[ \frac{1}{3} g'(\omega_0^1) \omega_0^1 + g(\omega_0^1) \right] = -a \frac{1}{3} g'(\omega_0^1) \omega_0^1,
\]

\[
A - B = a \Lambda_0 + a \left[ \frac{1}{3} g'(\omega_0^1) \omega_0^1 + g(\omega_0^1) \right] = 2 a \Lambda_0 + a \frac{1}{3} g'(\omega_0^1) \omega_0^1
\]

where we have used \(\Lambda_0 = g(\omega_0^1)\). By \(g'(\omega_0^1) < 0\), we have \(A + B > 0\). Then we see that

\[
A - B > 0 \iff 2 a \Lambda_0 + a \frac{1}{3} g'(\omega_0^1) \omega_0^1 > 0.
\]

Therefore by a well-known result in the theory of retarded differential equations, we obtain that the positive stationary solution is stable independent of \(\tau\) if \(2 a \Lambda_0 + a \frac{1}{3} g'(\omega_0^1) \omega_0^1 > 0\) holds. Noting that \(A > 0\), we see that

\[
A - B < 0 \iff 2 a \Lambda_0 + a \frac{1}{3} g'(\omega_0^1) \omega_0^1 < 0 \iff |B| = -B > A.
\]

One uses Lemma 1 in [12] concluding: there exists

\[
\tau_0 = \frac{1}{\sqrt{B^2 - A^2}} \arccos \left( -\frac{A}{B} \right)
\]

such that the unique positive stationary solution \(\omega_s\) of Eq. (1.5) is stable for \(\tau < \tau_0\) and unstable for \(\tau > \tau_0\). The Hopf bifurcation occurs at \(\tau = \tau_0\). \(\square\)
4. Global stability of stationary solutions

In order to prove global stability of stationary solutions of Eq. (1.5), we shall use the following lemma from [9].

**Lemma 4.1.** Consider the initial value problem of a delay differential equation

\[
\begin{align*}
\dot{x}(t) &= f(x(t), x(t - \tau)) \quad \text{for } t > 0, \quad (4.1) \\
x(t) &= x^0(t) \quad \text{for } -\tau \leq t \leq 0. \quad (4.2)
\end{align*}
\]

Assuming that the function \( f \) is defined and continuously differentiable in \( \mathbb{R}_+ \times \mathbb{R}_+ \) and strictly monotone increasing in the second variable, we have the following results:

1. Let \( x_s \) be a positive solution of equation \( f(x, x) = 0 \) such that \( f(x, x) > 0 \) for \( x \) less than but near \( x_s \), \( f(x, x) < 0 \) for \( x \) greater than but near \( x_s \). Let \((c, d)\) be the maximal interval containing only the root \( x_s \) of equation \( f(x, x) = 0 \). Let \( x(t) \) be the solution of the problem of (4.1), (4.2) and \( x^0(t) \in C[-\tau, 0] \), \( c < x^0(t) < d \) for \( -\tau \leq t \leq 0 \), then

\[
\lim_{t \to -\infty} x(t) = x_s.
\]

2. If \( f(x, x) < 0 \) for all \( x > 0 \), then

\[
\lim_{t \to -\infty} x(t) = 0.
\]

Firstly, we consider global asymptotic behavior of the stationary solutions under the assumption that

\[
(\phi - 1) \Lambda_1 \leq \phi. \quad (4.3)
\]

Set

\[
F(x, y) = ag\left(\frac{1}{x}\right)y - a\Lambda_0 x, \quad (4.4)
\]

then we obtain the following results:

**Theorem 4.2.** Assume that \( (\phi - 1) \Lambda_1 \leq \phi \), then

1. If \( \sigma_\infty > \bar{\sigma} \), the equation \( F(x, x) = 0 \) has a unique positive solution \( \omega_s > 0 \) such that \( F(x, x) > 0 \) for \( 0 < x < \omega_s \), and \( F(x, x) < 0 \) for \( x > \omega_s \);

2. If \( \sigma_\infty < \bar{\sigma} \), \( F(x, x) < 0 \) for all \( x > 0 \).

**Proof.** (1) Noticing that \( F(x, x) = ax(g(x^\frac{1}{x}) - \Lambda_0) \), then by Lemma 2.1, we can easily get if \( \sigma_\infty > \bar{\sigma} \), the equation \( F(x, x) = 0 \) has a unique positive solution \( \omega_s > 0 \). By Theorem 3.5 in [7], we know that the function

\[
g(x) = (1 - \Lambda_1)p(x) + p(\phi x)
\]

is monotone decreasing (i.e., \( g'(x) < 0 \)) for all \( x > 0 \) under assumption that \( (\phi - 1) \Lambda_1 \leq \phi \). Then assuming that \( (\phi - 1) \Lambda_1 \leq \phi \), we have for all \( x > 0 \),

\[
\frac{dg(x^\frac{1}{x})}{dx} = \frac{1}{3}x^{-\frac{3}{2}}[(1 - \Lambda_1)p'(x^\frac{1}{x}) + \phi \Lambda_1 p'(\phi^\frac{1}{x})] = \frac{1}{3}x^{-\frac{3}{2}}g'(x^\frac{1}{x}) < 0.
\]

Then \( f(x, x) > 0 \) for \( 0 < x < \omega_s \), and \( f(x, x) < 0 \) for \( x > \omega_s \) follow immediately.

(2) By Lemma 2.1(3), we have \( \lim_{x \to 0} g(x^\frac{1}{x}) = \frac{1}{3} \) and from (1) above, we know

\[
\frac{dg(x^\frac{1}{x})}{dx} < 0.
\]

Then we get

\[
g(x^\frac{1}{x}) < \lim_{x \to 0} g(x^\frac{1}{x}) = \frac{1}{3} < \Lambda_0.
\]

Accordingly, \( f(x, x) = ax(g(x^\frac{1}{x}) - \Lambda_0) < 0 \) for all \( x > 0 \). \( \square \)

Using Lemma 4.1 and Theorem 4.2, we obtain the following theorem.
**Theorem 4.3.** Assuming that \((\phi - 1)A_1 \leq \phi\), the following assertions hold:

1. If \(\sigma_\infty > \hat{\sigma}\), for any nonnegative initial condition \(\omega^0(t)\) for \(-\tau \leq t \leq 0\), \(\lim_{t \to \infty} w(t) = \omega_\infty\).
2. If \(\sigma_\infty < \hat{\sigma}\), for any nonnegative initial condition \(\omega^0(t)\) for \(-\tau \leq t \leq 0\), \(\lim_{t \to \infty} w(t) = 0\).

**Proof.** In view of Lemma 3.1, it suffices to prove where \(\Lambda\)

\[\Lambda = \frac{\partial F}{\partial y} > 0\text{ for all } y > 0.\]

Next we consider global asymptotic behavior of the stationary solutions under the assumption that

\[(\phi - 1)A_1 > \phi\text{ and } \omega_3 < x^*,\]

where \((x^*)^3\) is the unique solution to equation \(H'(x) = 0\). \(\square\)

**Theorem 4.4.** If \((\phi - 1)A_1 > \phi\) and \(\omega_3 < x^*\) hold, the initial function \(\omega_0\) satisfies \(\omega_0 < x_1^3\), where \(x_1\) is the unique solution to equation \(H(x) = 0\), then the corresponding solution to (1.5) tends to \(\omega_3\) as \(t \to \infty\).

**Proof.** The proof is similar to that of Theorem 3.1 in [11], therefore we omit the details here. \(\square\)

5. The effect of inhibitor’s parameter on tumor’s growth

**Lemma 5.1.** (See [9].) Assume \(F\) satisfies conditions of Lemma 4.1, then we have the following comparison result: If two functions \(x(t), y(t) \in C[-\tau, T] \cap C^1(-\tau, T)\), where either \(T = \infty\) or \(0 < T < \infty\) satisfies the following relations:

\[
\begin{align*}
\dot{x}(t) &\geq F(x(t), x(t - \tau)), \\
\dot{y}(t) &\leq F(y(t), y(t - \tau)), \\
x(t) &> y(t) > 0 \text{ for } -\tau \leq t \leq 0,
\end{align*}
\]

where \(0 < t < T\) for inequalities (5.1a), (5.1b). Then \(x(t) \geq y(t)\) for \(-\tau \leq t < T\).

**Lemma 5.2.** (See [7].) For each fixed \(x > 0\), the function

\[
L(\phi) = \begin{cases} 
\frac{p(\phi x) - p(x)}{\phi - 1} & \text{for } \phi \neq 1 (\phi > 0), \\
\frac{1}{2} xp'(x) & \text{for } \phi = 1
\end{cases}
\]

is continuous and strictly monotone increasing for \(\phi > 0\).

Actually, Eq. (1.5) can be written as the following equation

\[
\omega'(t) = aH(\omega^{\frac{1}{3}}(t - \tau)) - aA_1\omega(t).
\]

We shall write \(H(\omega^{\frac{1}{3}}(t - \tau))\) as \(H(\omega^{\frac{1}{3}}(t - \tau), \phi, \beta_\infty)\) to emphasize the dependence on the relevant parameters regarded as independent variables (i.e., \(H(\omega^{\frac{1}{3}}(t - \tau)) = H(\omega^{\frac{1}{3}}(t - \tau), \phi, \beta_\infty) = [(1 - A_1)p(\phi \omega^{\frac{1}{3}}(t - \tau)) + A_1p(\phi \omega^{\frac{1}{3}}(t - \tau))]\omega(t - \tau)\),

where \(A_1 = \frac{\beta_\infty}{\beta_\infty - \beta_\infty} = \frac{\beta_\infty}{\beta_\infty - \beta_\infty}\) as before.

In the following, we shall study the effect of inhibitor’s parameter on tumor’s growth under the assumption that

\[(\phi - 1)A_1 \leq \phi.\]

By direct computation, we have

\[
\frac{\partial H}{\partial \beta_\infty} = \frac{p(\phi \omega^{\frac{1}{3}}(t - \tau)) - p(\omega^{\frac{1}{3}}(t - \tau))}{\sigma_\infty \lambda (\phi^2 - 1)} \omega(t - \tau).
\]

Since \(p(x) < 0\) for \(x > 0\) (Lemma 2.1(2)) and \(\omega(t - \tau) > 0\) for all \(t > 0\) under condition (5.3) (Theorem 2.6(1)), it is easy to get

\[
\frac{\partial H}{\partial \beta_\infty} < 0.
\]
Then for $\beta_{1} < \beta_{2}$ and the other parameters $a, \gamma, \lambda, \sigma_{\infty}$ being fixed, we assume $x_{1}(t), x_{2}(t)$ are solutions of Eq. (1.5) with $A_{1} = \frac{A_{\infty}}{\lambda - \lambda \sigma_{\infty}}$ and $\frac{A_{\infty}}{\lambda - \lambda \sigma_{\infty}}, \gamma \neq \lambda$, respectively. Note that in Section 4 we have proved under assumption (5.3), that $F$ satisfies all conditions in Lemma 4.1, then by Lemma 5.1 we have $x_{1}(t) > x_{2}(t)$. We conclude: If $\beta_{\infty}$ is increasing then $\omega(t)$ and its limiting are decreasing.

Since $H(x, \phi, \beta_{\infty}) = \frac{p(x) - p(\phi)}{x^{2} - 1} \frac{\sigma_{\infty}}{\lambda \sigma_{\infty}}$, by Lemma 5.2, we have for $x > 0$,

$$\frac{\partial H}{\partial \phi} > 0.$$  (5.6)

Using similar arguments as above, we can get: If $\phi$ is decreasing then $\omega(t)$ and its limiting are also decreasing.

Above analysis shows that decreasing $\phi$ (i.e. decreasing $\gamma$ or (and) increasing $\lambda$) has a similar effect as increasing $\beta_{\infty}$.

6. Conclusions

Using rigorous analysis, we study the effects of time delay in cell proliferation on the tumor growth. The model considers the effects of time delay in cell proliferation in the presence of inhibitors. The results show: In the case $(\phi - 1)A_{1} \leq \phi$, time delay in proliferation does not change the tendency of the tumor towards evolving to a dormant state (see Theorem 4.3 and the corresponding results in [7, p. 115]). Moreover, we prove that decreasing $\phi$ (i.e. decreasing $\gamma$ or (and) increasing $\lambda$) has a similar effect as increasing $\beta_{\infty}$ which shows that inhibitor and parameter $\lambda$ always have good effect on tumor treatment in the sense that their administration can reduce tumors final size. However, parameter $\gamma$ always has bad effect on tumor treatment. In the opposite case $(\phi - 1)A_{1} > \phi$, the dynamical behavior of the solutions to (1.5) is more complex than corresponding non-retarded problem (see Theorems 3.2, 4.4 and the corresponding results in [7, p. 115]). More precisely, the time delay $\tau$ may change the tendency of the tumor towards evolving to a dormant state and may lead to a Hopf bifurcation.

Acknowledgments

This work is partially supported by NNSFC (Nos. 10771223, 10926128), GDSF (No. 9251064101000015) and the project sponsored by SRF for ROCS, SEM. The authors express their thanks to two anonymous references for their valuable suggestions on modification of the original manuscript.

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