Research article

Qualitative analysis of a time-delayed free boundary problem for tumor growth with angiogenesis and Gibbs-Thomson relation

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Abstract: In this paper we consider a time-delayed mathematical model describing tumor growth with angiogenesis and Gibbs-Thomson relation. In the model there are two unknown functions: One is $\sigma(r,t)$ which is the nutrient concentration at time t and radius r, and the other one is $R(t)$ which is the outer tumor radius at time t. Since $R(t)$ is unknown and varies with time, this problem has a free boundary. Assume $\alpha(t)$ is the rate at which the tumor attracts blood vessels and the Gibbs-Thomson relation is considered for the concentration of nutrient at outer boundary of the tumor, so that on the outer boundary, the condition

$$\frac{\partial \sigma}{\partial r} + \alpha(t)\left(\sigma - N(t)\right) = 0, \quad r = R(t)$$

holds, where $N(t) = \bar{\sigma}\left(1 - \frac{\gamma}{R(t)}\right)H(R(t))$ is derived from Gibbs-Thomson relation. $H(\cdot)$ is smooth on $(0, \infty)$ satisfying $H(x) = 0$ if $x \leq \gamma$, $H(x) = 1$ if $x \geq 2\gamma$ and $0 \leq H'(x) \leq 2/\gamma$ for all $x \geq 0$. In the case where α is a constant, the existence of steady-state solutions is discussed and the stability of the steady-state solutions is proved. In another case where α depends on time, we show that $R(t)$ will be also bounded if $\alpha(t)$ is bounded and some sufficient conditions for the disappearance of tumors are given.

Keywords: tumor growth; time delay; free boundary problem; Gibbs-Thomson relation; stability

1. Introduction

Tumor growth is a complex process. Many mathematical models have been established from different aspects to describe this process in recent years (see, e.g., [1–6]). There are several distinct stages of tumor growth, starting from the early stage without angiogenesis (see, e.g., [2, 7–11]) to the

process with angiogenesis (see, e.g., [12]). Experiments have shown that changes in the rate of tumor cell proliferation can lead to changes in the rate of apoptosis, which does not happen immediately: There is a time lag between the two changes (see [1]). Rencently, the study of mathematical models for tumor growth with time delays has attracted many interests of other researchers (see, e.g., [9, 13–15]). In this paper we consider a mathematical model for tumor growth with angiogenesis and Gibbs-Thomson relation. The model has a time delay and a free boundary that depends on time.

First, let us introduce the mathematical model. Suppose the tumor is spherical and occupies the following space:

$$\{r \mid r \leq R(t), \quad r = \sqrt{x_1^2 + x_2^2 + x_3^2}\},$$

where $R(t)$ is an unknown function which represents the outer tumor radius at time t. In the model there is another unknown function $\sigma(r, t)$ which is the concentration of nutrient at time t and radius r. It is assumed that the consumption rate of nutrient is proportional to the nutrient concentration at the corresponding local place, and the proportionality constant is Γ. Then σ satisfies the equation:

$$c\frac{\partial \sigma}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \sigma}{\partial r}\right) - \Gamma\sigma, \quad 0 < r < R(t), \quad t > 0,$$

where

$$c = T_{diffusion}/T_{growth} > 0 \tag{1.1}$$

is a constant which is the ratio of time scale of the nutrient diffusion to time scale of the tumor growth (see [2, 10, 13]). By the mass conservation law, R satisfies

$$\frac{d}{dt}\left(\frac{4\pi R^3}{3}\right) = S(t) - Q(t),$$

where $S(t)$ denotes the net rates of proliferation and $Q(t)$ is the net rates of natural apoptosis. From [1, 9, 13], we know that there is a time delay in the process of cell proliferation. The size of the time delay is the time required from the beginning of cell division to the completion of division. Assume that the proliferation rate is proportional to the corresponding local nutrient concentration and the coefficient of proportionality is μ, then

$$S(t) = \int_0^{2\pi} \int_0^{\pi} \int_0^{R(t-\tau)} \mu\sigma(r, t-\tau)r^2 \sin\theta dr d\theta d\varphi$$

where τ is the time delay in the process of cell proliferation. Suppose the rate of the apoptotic cell loss is $\mu\tilde{\sigma}$, then

$$Q(t) = \int_0^{2\pi} \int_0^{\pi} \int_0^{R(t)} \mu\tilde{\sigma}r^2 \sin\theta dr d\theta d\varphi.$$

Assume the boundary value condition on $r = R(t)$ is as follows:

$$\frac{\partial \sigma}{\partial r} + \alpha(t)(\sigma - N(t)) = 0,$$

where $\alpha(t)$ depends on the density of the blood vessels. Thus, it is a positive valued function. $N(t)$ is a given function which is the supply of nutrients outside the tumor. The special cases of the above

boundary value has been studied extensively. For the case where $\alpha(t) = \infty$ and $N(t)$ is a constant, Friedman and Reitich [10] gave a strict mathematical analysis of the spherically symmetric case of the corresponding model. They proved the existence, uniqueness and asymptotic stability of spherically symmetric steady state solutions. Cui [16] studied the generalized model of [10] where the cell proliferation rate and nutrients consumption rate are assumed to be nonlinear functions. From [17–19], we know that the energy would be consumed in maintaining the tumors compactness by cell-to-cell adhesion on the external boundary of the tumor and the nutrient acts as the source of energy, and the nutrient concentration on the external boundary satisfies a Gibbs–Thomson relation given by

$$N(t) = \bar{\sigma}\left(1 - \frac{\gamma}{R(t)}\right)H(R(t))$$

which denotes the concentration of nutrients at external boundaries, where $\gamma > 0$ is a constant describing the cell-to-cell adhesiveness. $H(\cdot)$ is smooth on $R_+ = (0, \infty)$ such that $H(x) = 0$ for $x \leq \gamma$, $H(x) = 1$ for $x \geq 2\gamma$ and $0 \leq H'(x) \leq 2/\gamma$ for $x \geq 0$. $N(t)$ is induced by Gibbs–Thomson relation ([11, 18, 19]).

We will consider the problem together with the following initial conditions

$$\sigma_0(r, t) = \psi(r, t), \quad r \in [0, R(t)], \quad t \in [-\tau, 0],$$

$$R_0(t) = \varphi(t), \quad t \in [-\tau, 0].$$

We assume that ψ and φ satisfy compatibility conditions. From [2, 7] we know that $T_{diffusion} \approx 1min$ and $T_{growth} \approx 1day$, noticing (1.1), so that $c \ll 1$. In this paper we only study the limiting case where $c = 0$. The model studied in this paper is as follows

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma}{\partial r}\right) = \Gamma\sigma, \quad 0 < r < R(t), \quad t > -\tau, \tag{1.2}$$

$$\frac{\partial\sigma}{\partial r} + \alpha\left(\sigma - \bar{\sigma}\left(1 - \frac{\gamma}{R(t)}\right)H(R(t))\right) = 0, \quad r = R(t), \quad t > -\tau, \tag{1.3}$$

$$\frac{d}{dt}\left(\frac{4\pi R^3(t)}{3}\right) = 4\pi\left(\int_0^{R(t-\tau)}\mu\sigma(r, t-\tau)r^2dr - \int_0^{R(t)}\mu\tilde{\sigma}r^2dr\right), \quad t > 0, \tag{1.4}$$

$$\sigma_0(r, t) = \psi(r, t), \quad 0 \leq r \leq R(t), \quad -\tau \leq t \leq 0, \tag{1.5}$$

$$R_0(t) = \varphi(t), \quad -\tau \leq t \leq 0. \tag{1.6}$$

Consider the compatibility of the problem, we assume Eqs (1.2) and (1.3) are hold for $t > -\tau$. The model (1.2)–(1.6) with the boundary condition (1.3) replaced by $\sigma = \bar{\sigma}\left(1 - \frac{\gamma}{R(t)}\right)H(R(t))$ on $r = R(t)$ (which is the case $\alpha = \infty$) was studied in [19] and in the model studied in [19], the time delay is not considered. In [19], the author established the global existence and uniqueness of the solution and discussed the stability of the stationary solutions. The model where $N(t)$ is a constant has been studied by Friedman and Lam [12]. In [12], the authors mainly discussed the dynamics behavior of the solutions.

The structure of this paper is as below. In section 2, some preliminaries are given. In section 3, the existence and uniqueness of the solution to Eqs (1.2)–(1.6) is proved. Section 4 is devoted to studying the case where $\alpha(t) = $ constant. In section 5, we discuss the case when $\alpha(t)$ is bounded. In the last section, we give some computer simulations and dscussions.

2. Preliminaries

First we introduce some functions which will be used in our analysis:
$$p(x) = \frac{x \coth x - 1}{x^2}, \quad q(x) = xp(x), \quad g(x) = \frac{p(x)}{\alpha + q(x)}, \quad f(x) = \alpha\left(1 - \frac{\gamma}{x}\right)g(x)H(x)$$
and
$$J(x) = \alpha[(x^2 - \gamma x)p'(x) + \gamma p(x)] + (2\gamma x - x^2)p^2(x),$$

where α is a positive constant.

Lemma 2.1. *(1)* $p'(x) < 0$ *for all* $x > 0$, *and* $\lim_{x\to 0+} p(x) = \dfrac{1}{3}$, $\lim_{x\to\infty} p(x) = 0$.

(2) The function $q(x) = xp(x)$ *satisfies:*
(i) $q(0) = 0$, *(ii)* $\lim_{x\to\infty} q(x) = 1$, *(iii)* $q'(0) = 1/3$, *(iv)* $q'(x) > 0$ *for* $x \geq 0$.

(3) $k(x) = x^3 p(x)$ *is strictly monotone increasing for* $x > 0$.

(4) $\left(\dfrac{xp''(x)}{p'(x)}\right)' < 0$ *and* $-2 < \dfrac{xp''(x)}{p'(x)} < 1$ *for* $x > 0$.

(5) For any $\alpha, \gamma > 0$, $J'(x) < 0$ *for* $x > \gamma$.

(6) For any $\alpha > 0$, $\left(x^3 g(x)\right)' > 0$ *for* $x > 0$.

Proof. (1) and (2) can be found in Lemma 2.1 and Lemma 2.2 [12]. For the proof of (3), please see [9]. In the following we prove (4), (5) and (6).

(4) From Lemma 3.3 [7], we know $\left(\dfrac{xp''(x)}{p'(x)}\right)' < 0$ for $x > 0$ and

$$\frac{xp''(x)}{p'(x)} = \frac{2(\sinh^3 x - x^3 \cosh x)}{(x^2 + x \cosh x \sinh x - 2\sinh^2 x)\sinh x} - 2.$$

By a simple calculation, we have $\lim_{x\to\infty} \dfrac{xp''(x)}{p'(x)} = -2$. Thanks to the fact $\lim_{x\to 0} \dfrac{xp''(x)}{p'(x)} = 1$ (see the proof of Lemma 2.1 in [20]), then $-2 < \dfrac{xp''(x)}{p'(x)} < 1$ for $x > 0$ follows.

(5) Let $L_1(x) = (x^2 - \gamma x)p'(x) + \gamma p(x)$ and $L_2(x) = (2\gamma x - x^2)p^2(x)$. Then $J(x) = \alpha L_1(x) + L_2(x)$. In the following we prove that $L_i'(x) < 0$ ($i = 1, 2$) for all $x > \gamma$. First, we prove $L_1'(x) < 0$ for all $x > \gamma$. Direct computation yields

$$L_1'(x) = 2xp'(x) + (x^2 - \gamma x)p''(x) \tag{2.1}$$

$$= p'(x)\left(2x + (x - \gamma)\frac{xp''(x)}{p'(x)}\right). \tag{2.2}$$

Since $\left(\dfrac{xp''(x)}{p'(x)}\right)' < 0$ and $-2 < \dfrac{xp''(x)}{p'(x)} < 1$, one can get that

$$(x - \gamma)\frac{xp''(x)}{p'(x)} > -2(x - \gamma)$$

if $x > \gamma$. It follows that $2x + (x - \gamma)\dfrac{xp''(x)}{p'(x)} > 2x - 2(x - \gamma) = 2\gamma > 0$. By the fact that $p'(x) < 0$, we have $L_1'(x) < 0$. And then we prove $L_2'(x) < 0$ for $x > \gamma$. Since

$$L_2'(x) = 2(\gamma - x)p^2(x) + 2(2\gamma x - x^2)p(x)p'(x)$$
$$= 2p(x)[\gamma(p(x) + 2xp'(x)) - x(p(x) + xp'(x))]$$
$$< 2p(x)[\gamma(p(x) + xp'(x)) - x(p(x) + xp'(x))]$$
$$= 2p(x)(\gamma - x)(xp(x))',$$

where we used the fact $p'(x) < 0$, by the facts that $p(x) > 0$ and $(xp(x))' > 0$, we can get that for $x > \gamma$, $L_2'(x) < 0$. Thus,

$$J'(x) = \alpha L_1'(x) + L_2'(x) < 0$$

for $x > \gamma$.

(6) Since

$$
\begin{aligned}
(x^3 g(x))' &= \left(\frac{k(x)}{\alpha + q(x)}\right)' \\
&= \frac{k'(x)(\alpha + q(x)) - q'(x)k(x)}{(\alpha + q(x))^2} \\
&= \frac{\alpha k'(x)}{(\alpha + q(x))^2} + \left(\frac{k(x)}{q(x)}\right)' \frac{q^2(x)}{(\alpha + q(x))^2} \\
&= \frac{\alpha k'(x)}{(\alpha + q(x))^2} + 2x \frac{q^2(x)}{(\alpha + q(x))^2},
\end{aligned}
$$

it verifies that $(x^3 g(x))' > 0$ noticing $k'(x) > 0$. This completes the proof of Lemma 2.1.

The following lemma will be used to prove the global stability of steady-states.

Lemma 2.2. ([21]) *Consider the following initial value problem:*

$$\dot{x}(t) = G(x, x_\tau), \quad t > 0 \tag{2.3}$$

$$x(t) = x_0(t), \quad -\tau \le t \le 0. \tag{2.4}$$

where $x_\tau = x(t - \tau)$). Assume G is defined on $R_+ \times R_+$ and continuously differentiable. Assume further that G is strictly monotone increasing in the variable x_τ, then one can get the following results:

(1) Assume $G(x, x) = 0$ has a unique positive solution x_s in (c, d) such that $G(x, x) > 0$ for $a < x < x_s$ and $G(x, x) < 0$ for $x_s < x < b$, where c, d are two positive constants. If $x(t)$ be the solution to the problem of (2.3), (2.4), assume that $x_0(t) \in C[-\tau, 0]$, and $c < x_0(t) < d$ for $-\tau \le t \le 0$. Then $\lim_{t\to\infty} x(t) = x_s$.

(2) Assume $G(x, x) < 0$ for all $x > 0$, then $\lim_{t\to\infty} x(t) = 0$.

(3) Assume $G(x, x) = 0$ has a unique positive solution x_s in $(0, x_s]$ such that $G(x, x) < 0$ for $0 < x < x_s$ and $G(0, 0) = 0$. Let $x(t)$ be the solution to the problem of (2.3),(2.4), assume that $x_0(t) \in C[-\tau, 0]$ and $0 \le x_0(t) < x_s$ for $-\tau \le t \le 0$, then $\lim_{t\to\infty} x(t) = 0$.

(4) Assume $G(x, x) = 0$ has a unique positive solution x_s in $[x_s, \infty)$ such that $G(x, x) < 0$ for $x > x_s$. Let $x(t)$ be the solution to the problem of (2.3),(2.4), assume that $x_0(t) \in C[-\tau, 0]$ and $x_0(t) > x_s$ for $-\tau \le t \le 0$, then $\lim_{t\to\infty} x(t) = x_s$.

3. The existence and uniqueness of the solution to Eqs (1.2)–(1.6)

Theorem 3.1. *Assume $\varphi(t)$ is continuous and nonnegative on $[-\tau, 0]$. Suppose $\alpha(t)$ is continuous and positive on $[-\tau, \infty]$, then there exists a unique nonnegative solution to problem (1.2)–(1.6) on interval $[-\tau, \infty)$.*

Proof. Using scale transformation of the spatial variable, one can assume $\Gamma = 1$. Then, the solution to (1.2) and (1.3) is

$$\sigma(r, t) = \frac{\alpha\bar{\sigma}}{\alpha + q(R)} \frac{\zeta(r)}{\zeta(R(t))} \left(1 - \frac{\gamma}{R(t)}\right) H(R(t)), \tag{3.1}$$

where $\zeta(x) = \sinh x/x$. Substituting (3.1) into (1.4), we obtain

$$\frac{dR}{dt} = \mu\bar{\sigma}R \left[\frac{\alpha(t-\tau)}{\alpha(t-\tau) + q(R_\tau)} \frac{R_\tau^3 p(R_\tau))}{R^3} \left(1 - \frac{\gamma}{R_\tau}\right) H(R_\tau) - \frac{\tilde{\sigma}}{3\bar{\sigma}}\right] =: G(R(t), R_\tau). \tag{3.2}$$

where $R_\tau = R(t - \tau)$ and

$$G(x, y) = \mu\bar{\sigma}x \left[\frac{\alpha(t-\tau)}{\alpha(t-\tau) + q(y)} \frac{y^3 p(y))}{x^3} \left(1 - \frac{\gamma}{y}\right) H(y) - \frac{\tilde{\sigma}}{3\bar{\sigma}}\right].$$

Denote $x = R^3$, then Eq (3.2) becomes

$$\frac{dx}{dt} = 3\mu\bar{\sigma}F(\sqrt[3]{x(t-\tau)}) - \mu\tilde{\sigma}x(t), \tag{3.3}$$

where

$$F(\sqrt[3]{x(t-\tau)}) = \frac{\alpha(t-\tau)x(t-\tau)p(\sqrt[3]{x(t-\tau)})}{\alpha(t-\tau) + q(\sqrt[3]{x(t-\tau)})} \left(1 - \frac{\gamma}{\sqrt[3]{x(t-\tau)}}\right) H(\sqrt[3]{x(t-\tau)}).$$

Then, the initial condition of $x(t)$ have the following form

$$x_0(t) = [\varphi(t)]^3, \quad -\tau \le t \le 0. \tag{3.4}$$

By the step method it is obvious that the problem (3.3), (3.4) has a unique solution $x(t)$ which exists on $[0, \infty)$, since we can rewrite the problem (3.3), (3.4) in the following functional form:

$$x(t) = x_0(0)e^{-\tilde{\sigma}t} + 3\mu\bar{\sigma} \int_0^t e^{-\tilde{\sigma}(t-s)} F(\sqrt[3]{x(s-\tau)})ds,$$

and solve it by using the step method (see, e.g., [22]) on intervals $[n\tau, (n+1)\tau], n \in N$. Thus, the solution of (3.3) exists on $[-\tau, \infty)$.

Next, we prove that the solution is nonnegative. Consider the following auxiliary problem:

$$\frac{dx}{dt} = -\mu\tilde{\sigma}x(t), \quad t > 0; \quad x(0) = x_0 \ge 0.$$

The solution is $x(t) = x_0 e^{-\mu\tilde{\sigma}t} \ge 0$. By Theorem 1.1 [23], to prove the solution of problem (3.3), (3.4) is nonnegative on the interval on which it exists, we only need to prove that $F(x) \ge 0$ for all $x \ge 0$ which follows from Lemma 2.1 and the fact $H \ge 0$. This completes the proof.

4. $\alpha(t) = $ constant

In this section, we study the case where $\alpha(t) = $ constant denoted by α. We will discuss the existence and stability of stationary solutions. The stationary solution denoted by $(\sigma_s(r), R_s)$ of the problem (1.2)–(1.6) must satisfy the following equations:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma_s(r)}{\partial r}\right) = \Gamma\sigma_s(r), \quad 0 < r < R_s, \tag{4.1}$$

$$\frac{\partial\sigma_s(r)}{\partial r} + \alpha\left(\sigma_s(r) - \bar{\sigma}\left(1 - \frac{\gamma}{R_s}\right)H(R_s)\right) = 0, \quad r = R_s, \tag{4.2}$$

$$\int_0^{R_s}\mu\sigma_s(r)r^2dr - \int_0^{R_s}\mu\tilde{\sigma}r^2dr = 0. \tag{4.3}$$

Using spatial scale transformation, one may assume $\Gamma = 1$. Then, the solution to (4.1) and (4.2) is

$$\sigma_s(r) = \frac{\alpha\bar{\sigma}}{\alpha + q(R_s)}\frac{\zeta(r)}{\zeta(R_s)}\left(1 - \frac{\gamma}{R_s}\right)H(R_s), \tag{4.4}$$

where $\zeta(x) = \sinh x/x$ and by (4.3), R_s satisfies

$$f(R_s) = \frac{\tilde{\sigma}}{3\bar{\sigma}}. \tag{4.5}$$

Theorem 4.1. *Let x^* be the unique solution to $J(x) = 0$, then there exists a unique positive constant ϑ^* which is determined by*

$$\vartheta^* = 3f(x^*)$$

such that the following conclusions are valid:

(i) If $0 < \tilde{\sigma} < \vartheta^*\bar{\sigma}$, there exist two different stationary solutions $(\sigma_{s1}(r), R_{s1})$ and $(\sigma_{s2}(r), R_{s2})$ to problem (1.2)–(1.6), where $R_{s1} < R_{s2}$.

(ii) If $\tilde{\sigma} = \vartheta^*\bar{\sigma}$, there exists a unique stationary solution $(\sigma_s(r), R_s)$ to problem (1.2)–(1.6).

(iii) If $\tilde{\sigma} > \vartheta^*\bar{\sigma}$, there is no stationary solutions to problem (1.2)–(1.6).

Proof. Through a simple calculation, one can get that if $\gamma < x \le 2\gamma$,

$$f'(x) = \frac{\alpha}{x^2}[\gamma g(x) + (x^2 - \gamma x)g'(x)] + \alpha\left(1 - \frac{\gamma}{x}\right)g(x)H'(x)$$

$$= \frac{\alpha}{x^2[\alpha + xp(x)]^2}J(x) + \alpha\left(1 - \frac{\gamma}{x}\right)g(x)H'(x)$$

and if $x \ge 2\gamma$,

$$f'(x) = \frac{\alpha}{x^2}[\gamma g(x) + (x^2 - \gamma x)g'(x)]$$

$$= \frac{\alpha}{x^2[\alpha + xp(x)]^2}J(x)$$

where

$$J(x) = \alpha[(x^2 - \gamma x)p'(x) + \gamma p(x)] + (2\gamma x - x^2)p^2(x).$$

Since $0 \le H'(x) \le 2/\gamma$ for $x \ge 0$, noting $J(x)$ is strictly monotone decreasing and

$$\lim_{x \to 2\gamma} J(x) = \alpha\gamma[2\gamma p'(2\gamma) + p(2\gamma)] = \alpha\gamma \left[xp(x)\right]'_{|x=2\gamma} = \alpha\gamma q'(x)_{|x=2\gamma} > 0,$$

where we have used $q'(x) > 0$ for $x \ge 0$ (see Lemma 2.1 (2)), then $f'(x) > 0$ for $\gamma < x \le 2\gamma$. By a simple computation, $\lim_{x \to \gamma+} J(x) = \alpha\gamma p(\gamma) + \gamma^2 p^2(\gamma) > 0$. Since $\lim_{x \to \infty} q(x) = \lim_{x \to \infty} xp(x) = 1$, there exists a positive constant M_0, such that $xp(x) > \dfrac{1}{2}$. Choose $M_1 = \max\{M_0 + 1, 3\gamma, 2\gamma(\alpha + 1)\}$, it follows that

$$
\begin{aligned}
[\alpha\gamma + (2\gamma - M_1)M_1 p(M_1)]p(M_1) &< \left(\alpha\gamma + \frac{1}{2}(2\gamma - M_1)\right)p(M_1) \\
&\le \left(\alpha\gamma + \frac{1}{2}(2\gamma - 2\gamma(\alpha + 1))\right)p(M_1) = 0.
\end{aligned}
$$

Then

$$J(M_1) = \alpha[(M_1^2 - \gamma M_1)]p'(M_1) + [\alpha\gamma + (2\gamma - M_1)M_1 p(M_1)]p(M_1) < 0.$$

Since $J'(x) < 0$ for $x > \gamma$, by the mean value theorem, we have there exists a unique constant $x^* \in (\gamma, M_1)$ such that $J(x^*) = 0$; $J(x) < 0$ for $x > x^*$ and $J(x) > 0$ for $\gamma < x < M_1$. It follows that

$$f'(x) = \frac{\alpha}{x^2[\alpha + xp(x)]^2}J(x) + \alpha\left(1 - \frac{\gamma}{x}\right)g(x)H'(x)
\begin{cases}
> 0, & \gamma < x < x^*, \\
= 0, & x = x^*, \\
< 0, & x > x^*.
\end{cases}$$

Then

$$\vartheta^* =: 3f(x^*) = 3 \max_{x \in [\gamma, M_1]} f(x).$$

Since $f(x) = \alpha\left(1 - \dfrac{\gamma}{x}\right)g(x)$ and $\alpha g(x) < p(x) < 1/3$, one can get

$$\vartheta^* = 3f(x^*) \in (0, 1).$$

Noticing (4.5), we can get (i), (ii) and (iii). This completes the proof.

For simplicity of notation, in the following of the paper, let's denote $|\varphi| = \max_{-\tau \le t \le 0} \varphi(t)$ and write $\min_{-\tau \le t \le 0} \varphi(t)$ simply as $\min \varphi$.

Theorem 4.2. *For any continuous nonnegative initial value function φ, the nonnegative solution of (3.2) and (1.6) exists for $t \ge -\tau$ and the dynamics of solutions to problem (3.2) and (1.6) are as follows:*

(I) If $\tilde{\sigma} > \vartheta^*\bar{\sigma}$, then $\lim_{t \to \infty} R(t) = 0$.

(II) If $\tilde{\sigma} = \vartheta^*\bar{\sigma}$, when $|\varphi| < R_s$, then $\lim_{t \to \infty} R(t) = 0$ and when $\min \varphi > R_s$, we have $\lim_{t \to \infty} R(t) = R_s$.

(III) If $0 < \tilde{\sigma} < \vartheta^*\bar{\sigma}$, when $|\varphi| < R_{s1}$, we have $\lim_{t \to \infty} R(t) = 0$ and when $\min \varphi > R_{s1}$, then $\lim_{t \to \infty} R(t) = R_{s2}$.

Proof. By Theorem 3.1, for any continuous initial value function φ, we know that the nonnegative solution of (3.2) and (1.6) exists for $t \ge -\tau$. Next, we study the dynamics of solutions to Eq (3.2) where α is a constant. By a direct computation, one can get

$$\frac{\partial G}{\partial y} = \frac{\mu\alpha\bar{\sigma}}{x^2}\left[\gamma y g(y)H(y) + H'(y)y^3 g(y)(1 - \frac{\gamma}{y}) + (y^3 g(y))'(1 - \frac{\gamma}{y})H(y)\right]. \tag{4.6}$$
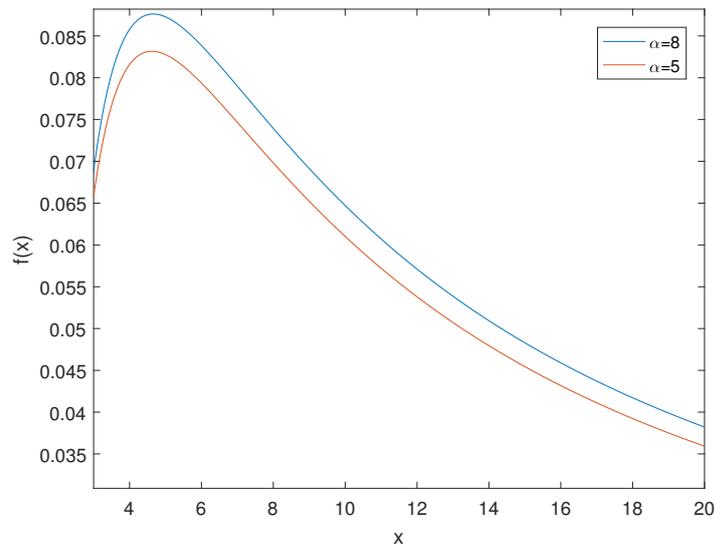
Figure 1. An example of the function f for $\gamma = 2$ and $\alpha = 5, 8$ respectively.

Noting properties of the function H and Lemma 2.1, n, one can easily get $\dfrac{\partial G}{\partial y} > 0$. By properties of $f(x)$ and noticing the fact

$$G(x, x) = \mu\bar{\sigma}x[f(x) - \frac{\tilde{\sigma}}{3\bar{\sigma}}], \tag{4.7}$$

it immediately follows that

(P1) If $\tilde{\sigma} > \vartheta^*\bar{\sigma}$, we have $f(x, x) < 0$ for all $x > 0$.

(P2) If $\tilde{\sigma} = \vartheta^*\bar{\sigma}$, we have $f(x, x) < 0$ for all $x \neq R_s$.

(P3) If $0 < \tilde{\sigma} < \vartheta^*\bar{\sigma}$, we have $f(x, x) < 0$ for all $x < R_{s1}$, $f(x, x) > 0$ for all $R_{s1} < x < R_{s2}$ and $f(x, x) < 0$ for all $x > R_{s2}$.

By (P1)–(P3) and Lemma 2.2, we can readily get (I)–(III). This completes the proof.

Remark. Since f, ϑ^* and R_s are functions depending on α and γ, we can rewrite them as $f(x, \alpha, \gamma)$, $\vartheta^*(\alpha, \gamma)$ and $R_s(\alpha, \gamma)$. Simple computation yields

$$\frac{\partial f}{\partial \alpha} = \frac{p(x)q(x)}{(\alpha + q(x))^2}(1 - \frac{\gamma}{x})H(x) > 0, \quad \frac{\partial f}{\partial \gamma} = -\frac{\alpha}{x}g(x)H(x) < 0, \quad x > \gamma, \tag{4.8}$$

which implies that $\dfrac{\partial \vartheta^*}{\partial \alpha} \geq 0$ and $\dfrac{\partial \vartheta^*}{\partial \gamma} \leq 0$. Moreover, for $0 < \tilde{\sigma} < \vartheta^*\bar{\sigma}$, by (4.8) we also can get that $\dfrac{\partial R_{s1}}{\partial \alpha} \leq 0, \dfrac{\partial R_{s2}}{\partial \alpha} \geq 0, \dfrac{\partial R_{s1}}{\partial \gamma} \geq 0$ and $\dfrac{\partial R_{s2}}{\partial \gamma} \leq 0$. From Theorem 4.2, we see that the stable stationary solution R_{s2} is decreasing in γ and increasing in α. Two examples are given (see Figure 1 for $\gamma = 2$ and $\alpha = 5, 8$ and Figure 2 for $\alpha = 8$ and $\gamma = 2.5, 3$). From Figures 1 and 2, it is obvious that the stable stationary solution R_{s2} (if it exists) is decreasing in γ and increasing in α.
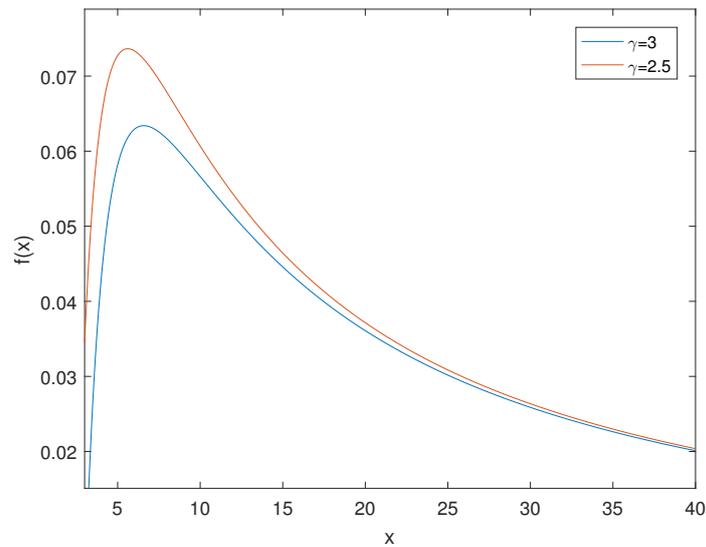
Figure 2. An example of the function f for $\alpha = 8$ and $\gamma = 2.5, 3$ respectively.

5. $\alpha(t)$ is bounded

If $\alpha(t)$ is bounded, there exists two constants m, M ($0 \leq m < M$) such that $m \leq \alpha(t) \leq M$. By Eq (3.2), we can get

$$\frac{dR}{dt} \leq \mu\bar{\sigma}R\left[\frac{M}{M + q(R_\tau)}\frac{R_\tau^3 p(R_\tau)}{R^3}\left(1 - \frac{\gamma}{R_\tau}\right)H(R_\tau) - \frac{\tilde{\sigma}}{3\bar{\sigma}}\right]. \tag{5.1}$$

Consider the following initial value problem

$$\frac{dR}{dt} = \mu\bar{\sigma}R\left[\frac{M}{M + q(R_\tau)}\frac{R_\tau^3 p(R_\tau)}{R^3}\left(1 - \frac{\gamma}{R_\tau}\right)H(R_\tau) - \frac{\tilde{\sigma}}{3\bar{\sigma}}\right], \quad t > 0, \tag{5.2}$$

$$R_0(t) = \varphi(t), \quad -\tau \leq t \leq 0. \tag{5.3}$$

Define

$$G_1(x, y) = \mu\bar{\sigma}x\left[\frac{M}{M + q(y)}\frac{y^3 p(y))}{x^3}\left(1 - \frac{\gamma}{y}\right)H(y) - \eta/3\right].$$

where $\eta = \tilde{\sigma}/\bar{\sigma}$. By similar arguments as that in section 4, one can get there exists a unique positive constant X^* satisfies the following equation:

$$J_1(x) = M[(x^2 - \gamma x)p'(x) + \gamma p(x)] + (2\gamma x - x^2)p^2(x) = 0.$$

Let $f_1(x) = M\left(1 - \frac{\gamma}{x}\right)g(x)H(x)$, one can get the following two lemmas by similar arguments as that in section 4.

Lemma 5.1. *Let X^* be the unique solution to $J_1(x) = 0$, then there exists a unique positive constant θ^* which is determined by*

$$\theta^* = 3f_1(X^*)$$

such that the following conclusions are valid:

(i) If $0 < \tilde{\sigma} < \theta^* \bar{\sigma}$, there exist two stationary solutions $(\sigma_{s1}^M(r), R_{s1}^M)$ and $(\sigma_{s2}^M(r), R_{s2}^M)$ to problem (5.2)–(5.3), where $R_{s1}^M < R_{s2}^M$.

(ii) If $\tilde{\sigma} = \theta^* \bar{\sigma}$, there exists a unique stationary solution $(\sigma_s^M(r), R_s^M)$ to problem (5.2)–(5.3).

(iii) If $\tilde{\sigma} > \theta^* \bar{\sigma}$, there is no stationary solution to problem (5.2)–(5.3).

Lemma 5.2. *For any nonnegative initial value function φ, the nonnegative solution of (5.2) and (5.3) exists for $t \geq -\tau$ and the following conclusions can be drawn:*

(I) If $\tilde{\sigma} > \theta^* \bar{\sigma}$, then $\lim_{t \to \infty} R^M(t) = 0$.

(II) If $\tilde{\sigma} = \theta^* \bar{\sigma}$, when $|\varphi| < R_s^M$, then $\lim_{t \to \infty} R^M(t) = 0$ and when $\min \varphi > R_s^M$, we have $\lim_{t \to \infty} R^M(t) = R_s^M$.

(III) If $0 < \tilde{\sigma} < \theta^* \bar{\sigma}$, when $|\varphi| < R_{s1}^M$, we have $\lim_{t \to \infty} R^M(t) = 0$ and when $\min \varphi > R_{s1}^M$, then $\lim_{t \to \infty} R^M(t) = R_{s2}^M$.

Theorem 5.3. *For any nonnegative continuous $\varphi(t)$, the nonnegative solution of (5.2) and (5.3) exists for $t \geq -\tau$. Moreover, if $\alpha(t)$ is uniformly bounded, the dynamics of solutions to this problem are as follows:*

(1) If $\tilde{\sigma} > \theta^* \bar{\sigma}$, then $\lim_{t \to \infty} R(t) = 0$.

(2) If $\tilde{\sigma} = \theta^* \bar{\sigma}$, when $|\varphi| < R_s^M$, then $\lim_{t \to \infty} R(t) = 0$ and when $\min \varphi > R_s^M$, we have $\limsup_{t \to \infty} R(t) \leq R_s^M$.

(3) If $0 < \tilde{\sigma} < \theta^* \bar{\sigma}$, when $|\varphi| < R_{s1}^M$, we have $\lim_{t \to \infty} R(t) = 0$ and when $\min \varphi > R_{s1}^M$, then $\limsup_{t \to \infty} R(t) \leq R_{s2}^M$.

Proof. By (5.1) and the comparison principle (see, e.g. Lemma 3.1 in [9]), we just need to prove $\dfrac{\partial G}{\partial y} > 0$. Actually,

$$\frac{\partial G_1}{\partial y} = \frac{\mu M \bar{\sigma}}{x^2} \left[\gamma y g_1(y) H(y) + H'(y) y^3 g_1(y)(1 - \frac{\gamma}{y}) + (y^3 g_1(y))'(1 - \frac{\gamma}{y}) H(y) \right] \tag{5.4}$$

where $g_1(y) = \dfrac{1}{M + q(y)}$. Noting properties of the function H and Lemma 2.1, one can easily get $\dfrac{\partial G_1}{\partial y} > 0$. The comparison principle (see, e.g. Lemma 3.1 in [9]) implies that

$$R(t) \leq R^M(t). \tag{5.5}$$

By Lemma 5.2, noticing $R(t) \geq 0$ and taking upper limits for both $R(t)$ and $R^M(t)$ as $t \to \infty$, one can get (1), (2) and (3). This completes the proof.

6. Computer simulations and discussions

In this section, by using Matlab R2016a, we give some numerical simulations of solutions to Eq (3.3) for special parameter values (see Figures 3 and 4). We use matlab to find some special cases where the steady-state solutions are larger than 2γ. In this case $H(x) = 1$, therefore

$$f(x) = \alpha(1 - \frac{\gamma}{x}) g(x). \tag{6.1}$$

If the parameters in Eq (3.3) are taken values as

$$\bar{\sigma} = 5, \mu = 1, \tilde{\sigma} = 1, \alpha = 8, \gamma = 2, \tau = 3, x_0 = 100, 1600, \tag{6.2}$$
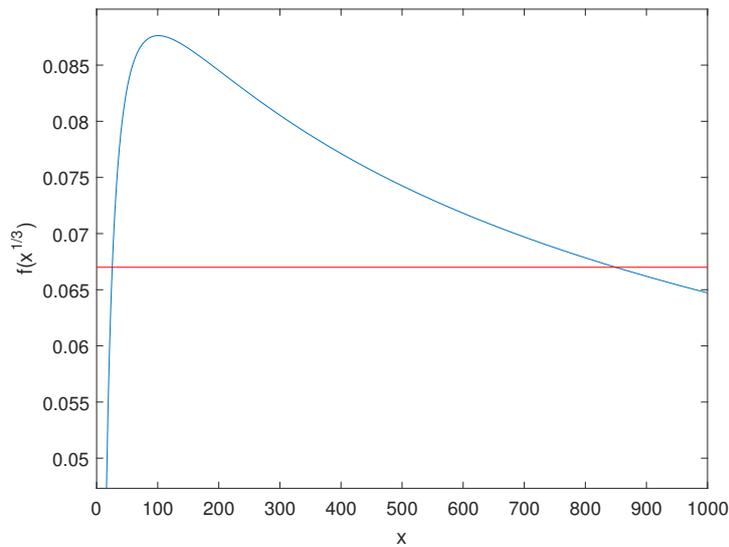
Figure 3. The curve of the function f for $\bar{\sigma} = 5, \mu = 1, \tilde{\sigma} = 1, \alpha = 8, \gamma = 2$.

by using Matlab R2016a, we can solve the equation

$$f(\sqrt[3]{x}) = \frac{\tilde{\sigma}}{3\bar{\sigma}}.$$

It has two positive solutions: The smaller one is $x_{s1} = 25.03$ and the larger one is $x_{s2} = 870.26$ (The curve of f is shown in Figure 3). Noticing (4.5), we have $R_{s1} = \sqrt[3]{25.03}$ and $R_{s2} = \sqrt[3]{870.26} > 2\gamma = 4$.

Since $\vartheta^* > 3 * 0.085$ (see Figure 3), it is obvious that

$$0 < \tilde{\sigma} = 1 < 3 * 0.085 * 5 = 1.275 < \vartheta^*\bar{\sigma}.$$

Therefore, the conditions of Theorem 4.2 (III) are satisfied. Since the initial conditions $x_0 = 100, 1600$ are larger than R_{s1} which third power is smaller than 100. Thus all the solutions of Eq (3.3) tend to $R_{s2} = \sqrt[3]{870.26}$. The dynamics of solution to Eq (3.3) for the parameters in Eq (3.3) are taken values as (6.2) are given by Figure 4.

In this paper considering the time-delay in the cell proliferation process and the Gibbs-Thomson relation in the boundary condition, we study a time-delayed free boundary problem describing tumor growth with angiogenesis. We prove the existence and uniqueness of time-varying solutions. When α is a positive constant, we discuss the existence of steady-state solutions and the number of steady-state solutions (Theorem 4.1), and prove the asymptotic behavior of solutions (Theorem 4.2). From the biological point of view, the result of Theorem 4.2 (I) means when $\tilde{\sigma}$ which represents the rate of apoptosis of tumor cells is less than a critical value $\vartheta^*\bar{\sigma}$, the tumor will disappear. The result of Theorem 4.2 (II) means when $\tilde{\sigma}$ is equal to the critical value $\vartheta^*\bar{\sigma}$, for small initial functions satisfying $\max_{-\tau \leq t \leq 0} \varphi(t) < R_s$, the tumor will disappear; for large initial functions satisfying $\min_{-\tau \leq t \leq 0} \varphi(t) > R_s$, the tumor will not disappear and will tend to the unique steady-state. The result of Theorem 4.2 (III) means that when $\tilde{\sigma}$ is relatively small (less than a critical value $\vartheta^*\bar{\sigma}$), whether the tumor will disappear or not depends on the value of the initial value function. When the minimum value of the initial value function is greater than R_{s1}, the tumor tends to the larger steady-state solution; when the maximum
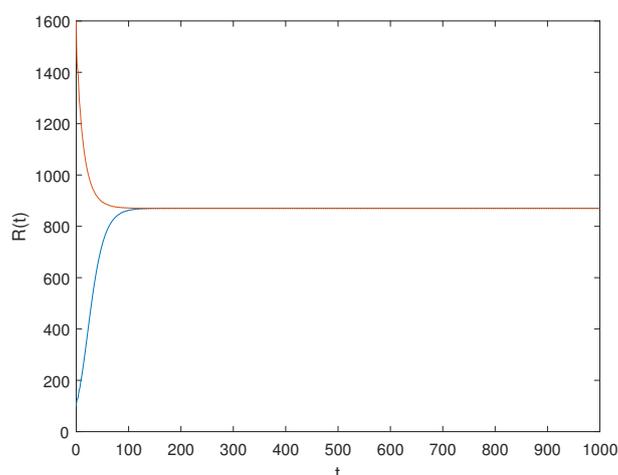
Figure 4. An example of the dynamics of solution to Eq (3.3) for $\bar{\sigma} = 5, \mu = 1, \tilde{\sigma} = 1, \alpha = 8, \gamma = 2, \tau = 3$ and $x_0 = 100, 1600$, respectively.

value of the initial value function is less than R_{s1}, the tumor will disappear. We prove that with the increase of α, the larger steady-state solution will increase when nutrients is sufficient (see Remark in section 4). According to the conclusion of the Theorem 4.2 (III) and the Remark in section 4, increasing α can increase the final volume of the tumor. Noting that α represents the ability of tumor to attract blood vessels, this indicate that the larger α is, the stronger it is to attract blood vessels, and the larger the tumor will be, which is consistent with biological phenomena. We also prove that when $\alpha(t)$ is bounded, tumors will not increase indefinitely and will remain bounded.

Acknowledgements

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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