AIMS Mathematics

http://www.aimspress.com/journal/Math

AIMS Mathematics, 8(9): 22354–22370.
DOI: 10.3934/math.20231140
Received: 17 May 2023
Revised: 18 June 2023
Accepted: 25 June 2023
Published: 13 July 2023

Research article

Qualitative analysis of a time-delayed free boundary problem for tumor growth with Gibbs-Thomson relation in the presence of inhibitors

Huiyan Peng and Xuemei Wei*

Mathematics and Statistics, Guangdong University of Technology, Guangzhou 510520, China

* **Correspondence:** E-mail: wxm_gdut@163.com.

Abstract: In this paper, we study a time-delayed free boundary of tumor growth with Gibbs-Thomson relation in the presence of inhibitors. The model consists of two reaction diffusion equations and an ordinary differential equation. The reaction diffusion equations describe the nutrient and inhibitor diffusion within tumors and take into account the Gibbs-Thomson relation at the outer boundary of the tumor. The tumor radius evolution is described by the ordinary differential equation. It is assumed that the regulatory apoptosis process takes longer than the natural apoptosis and proliferation processes. We first show the existence and uniqueness of the solution to the model. Next, we further demonstrate the existence of the stationary solutions and the asymptotic behavior of the stationary solutions when the blood vessel density is a constant. Finally, we further demonstrate the existence of the stationary solutions and the asymptotic behavior of the stationary solutions when the blood vessel density is bounded. The result implies that, under certain conditions, the tumor will probably become dormant or will finally disappear. The conclusions are illustrated by numerical computations.

Keywords: time delay; tumor growth; free boundary problem; Gibbs-Thomson relation; stability
Mathematics Subject Classification: 35K57, 35Q92, 35R35

1. Introduction

The growth of the tumor is a very complicated phenomenon. In the last fifty years, a number of mathematical models have been proposed and studied from various angles to explain the growing process of tumors. In [1,2], Greenspan proposed and analyzed the non-vascularized solid tumor growth model under free boundary conditions. In 1995, Byrne and Chaplain proposed the following free boundary problem modeling tumor growth [3]:

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

$$\frac{\partial \sigma}{\partial r}(0,t) = 0, \;\; \sigma(R(t),t) = \sigma_R(t), \;\; t > 0,$$

$$\frac{dR}{dt} = \frac{1}{R^2}\int_0^{R(t)} S(\sigma) r^2 dr, \;\; t > 0,$$

$$\sigma(R(t),t) = \sigma_R(t), \quad \sigma(r,0) = \sigma_0(r), \quad 0 \le r \le R(0),$$

$$R(0) = R_0,$$

which is called the Byrne-Chaplain tumor model, where σ is nutrient concentration, $R(t)$ is the radius of the tumor and $S(\sigma)$ denotes the cell proliferation rate within the tumor. Based on this model, many researchers have analyzed it from different perspectives and reached some conclusions about the well-posedness of the stationary solution, the existence and uniqueness of the solution and asymptotic behavior of global solution, which can be seen in the literature [4–9] and so on.

Moreover, numerous experiments show that tumor cell proliferation does not occur instantly and that it requires mitosis, a process that takes some time. Following this idea, Byrne established the following time-delayed avascular tumor growth model [10]:

$$0 = \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 \frac{\partial \sigma}{\partial r}\Big) - \Gamma\sigma, \;\; 0 < r < R(t), \;\; t > 0,$$

$$\frac{\partial \sigma}{\partial r} = 0, \;\; \sigma(R(t),t) = \bar{\sigma}, \;\; t > 0,$$

$$\frac{dR(t)}{dt} = \eta(R(t), R(t-\tau)), \;\; t > 0,$$

$$R(t) = \varphi(t), \quad -\tau \le t \le 0,$$

where σ is nutrient concentration, $R(t)$ represents the radius of the tumor at time t, τ is a positive constant representing the time delay and the nonlinear smooth function η has a monotonic increase in the second variable. Cui and Xu studied the asymptotic behavior of mathematical model solutions for tumor growth with cell proliferation time delays in [11]. Xu and Feng [12] studied a mathematical model for tumor growth with a time delay in proliferation under the indirect influence of an inhibitor. Many researchers have taken an interest in the model and have published numerous research results about the well-posedness of the stationary solution, the existence and uniqueness of the solution and asymptotic behavior of global solution with the time-delays in [13–16].

In [17], the nutrients are hypothesized to be the energy needed to maintain the tightness of a tumor by cell-to-cell adhesion at the tumor boundary; thus, the nutrient concentration at the tumor boundary is smaller than the externally supplied nutrient concentration, and this difference satisfies the Gibbs-Thomson relation. However, Roose, Chapman and Maini [18] further found that tumor growth satisfied the modified Gibbs-Thomson relation, and the modified Gibbs-Thomson relation will be introduced in the following:

$$\Big[\frac{\partial \sigma}{\partial r}(r,t)+\alpha(\sigma-N(t))\Big]\Big|_{r=R(t)}=0,$$

where $N(t)$ fulfill the subsequent relationship

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

where $N(t)$ is induced by Gibbs-Thomson relation. $H(\cdot)$ is a smooth function on $(0,\infty)$, such that $H(x)=0$ if $x\leq\gamma$, $H(x)=1$ if $x\geq 2\gamma$ and $0\leq H'(x)\leq 2/\gamma$ for all $x\geq 0$. Continuing with this thinking, Wu analyzed the effect of the Gibbs-Thomson relation on tumor growth with the external nutrient supply [19]. Others have researched the Gibbs-Thomson relation and drawn some conclusions about stationary solutions and asymptotic behavior of the solution, which can be found in [20, 21].

Furthermore, the tumor will have a time delay during its growth, and the boundaries of the tumor model will also satisfy Gibbs-Thomson relation. Xu, Bai and Zhang [22] studied a free boundary problem for the growth of tumor with the Gibbs-Thomson relation and time delays. Xu and Wu [23] analyzed the problem of time-delayed free boundary of tumor growth with angiogenesis and the Gibbs-Thomson relation. Gaussian white noise is regarded as an inhibitor in [24–26]. At present, there is relatively limited research that considers a time-delayed free boundary of tumor growth with the Gibbs-Thomson relation, simultaneously. Hence, in this paper, we mostly examine how the external nutrient and inhibitor concentrations affect a time-delayed tumor growth under conditions that satisfy the Gibbs-Thomson relation.

$$c_1\frac{\partial u}{\partial t}=\Delta u-u,\qquad 0<r<R(t),\ \ t>0, \tag{1.1}$$

$$\frac{\partial u}{\partial r}+\alpha_1(t)\Big(u-N_1(t)\Big)=0,\qquad r=R(t),\ \ t>0, \tag{1.2}$$

$$c_2\frac{\partial v}{\partial t}=\Delta v-v,\qquad 0<r<R(t),\ \ t>0, \tag{1.3}$$

$$\frac{\partial v}{\partial r}+\alpha_2(t)\Big(v-N_2(t)\Big)=0,\qquad r=R(t),\ \ t>0, \tag{1.4}$$

$$\begin{aligned}\frac{d}{dt}\Big(\frac{4\pi R^3(t)}{3}\Big)=&4\pi\bigg(\int_0^{R(t-\tau)}\mu u(r,t-\tau)r^2dr-\int_0^{R(t)}\nu v(r,t)r^2dr\\&-\int_0^{R(t)}\mu\tilde{u}r^2dr\bigg),\qquad t>0,\end{aligned} \tag{1.5}$$

$$u_0(r,t)=\psi_1(r,t),\qquad 0\leq r\leq R(t),\ \ -\tau\leq t\leq 0, \tag{1.6}$$

$$v_0(r,t)=\psi_2(r,t),\qquad 0\leq r\leq R(t),\ \ -\tau\leq t\leq 0, \tag{1.7}$$

$$R(t)=\varphi(t),\quad -\tau\leq t\leq 0, \tag{1.8}$$

where u and v represent the concentration of nutrients and inhibitors, respectively; c_1 and c_2 are positive constants, and $c_i=T_{diffusion}/T_{growth}(T_{diffusion}\approx 1min, T_{growth}\approx 1day)$ represents the relationship between the tumor growth time scale and the nutrition and inhibitor diffusion time scales; r is the radial variable; τ is the time delay in cell proliferation; $R(t)$ is an unknown variable related to time t; $\alpha_1(t)$ and $\alpha_2(t)$ represent the blood vessel density. As there is just one vascular system in the tumor, it is logical to suppose that $\alpha_1(t) = \alpha_2(t) =: \alpha(t)$; μ, ν and $\tilde{u}$ are positive constants; ψ_1, ψ_2 and φ are given nonnegative functions. The three terms in (1.5) to the right are explained as follows: The first term is the overall volume increase caused by cell multiplication in a unit of time; μu is the rate of cell proliferation per unit volume. The second term is the total volume reduction caused by cell killing by the inhibitor in a unit time interval; νv is the rate of cell killing by the inhibitor per unit volume. The last term is the total volume contraction caused by apoptosis or cell death due to senescence in a unit time interval. $N_1(t) = \bar{u}(1 - \frac{\gamma}{R(t)})H(R(t))$ and $N_2(t) = \bar{v}(1 - \frac{\gamma}{R(t)})H(R(t))$ represent the functions satisfied by the external nutrient concentrations and the external inhibitor concentrations, respectively. Since the inhibitor has great side effects during tumor treatment, we need to control the inhibitor concentration without loss of generality, assuming that $\nu\bar{v} < \mu\bar{u}$.

From [3, 4] we know that $T^i_{diffusion} \approx 1 (i = 1, 2)$ min and $T_{growth} \approx 1$ day, noticing (1.1) and (1.3), so that $c_i \ll 1 (i = 1, 2)$. In this paper, we just take into account the limiting situation in where $c_i = 0 (i = 1, 2)$. The time-delayed free boundary mathematical model for tumor growth with angiogenesis and the Gibbs-Thomson relation studied in this paper are as follows:

$$\Delta u = u, \qquad 0 < r < R(t), \ \ t > 0, \tag{1.9}$$

$$\frac{\partial u}{\partial r} + \alpha(t)\Big(u - \bar{u}(1 - \frac{\gamma}{R(t)})H(R(t))\Big) = 0, \qquad r = R(t), \ \ t > 0, \tag{1.10}$$

$$\Delta v = v, \qquad 0 < r < R(t), \ \ t > 0, \tag{1.11}$$

$$\frac{\partial v}{\partial r} + \alpha(t)\Big(v - \bar{v}(1 - \frac{\gamma}{R(t)})H(R(t))\Big) = 0, \qquad r = R(t), \ \ t > 0, \tag{1.12}$$

$$\frac{d}{dt}\Big(\frac{4\pi R^3(t)}{3}\Big) = 4\pi\Big(\int_0^{R(t-\tau)} \mu u(r, t-\tau) r^2 dr - \int_0^{R(t)} \nu v(r, t) r^2 dr - \int_0^{R(t)} \mu\tilde{u} r^2 dr\Big), \ \ t > 0, \tag{1.13}$$

$$u_0(r, t) = \psi_1(r, t), \qquad 0 \le r \le R(t), \quad -\tau \le t \le 0, \tag{1.14}$$

$$v_0(r, t) = \psi_2(r, t), \qquad 0 \le r \le R(t), \quad -\tau \le t \le 0, \tag{1.15}$$

$$R(t) = \varphi(t), \quad -\tau \le t \le 0. \tag{1.16}$$

The organization of this paper is as follows: In Section 2, we present some preliminary findings. The existence and uniqueness of the solution to the Problem (1.9)–(1.16) are proved in Section 3. Section 4 is devoted to studying steady-state solutions and their stability. In Section 5, we give some numerical computations and have some discussions. In the last section, we give a conclusion.

2. Preliminaries

In this section, we present some preliminary results that will be used in our following analysis:

$$p(x) = \frac{x\coth x - 1}{x^2}, \qquad g(x) = xp(x) = \coth x - \frac{1}{x},$$

and

$$h(x) = x^3 p(x), \qquad D(x) = \frac{h(x)}{\alpha + g(x)}, \qquad l(x) = \frac{\alpha p(x)}{\alpha + g(x)}.$$

Lemma 2.1. (1) $p'(x) < 0$ for all $x > 0$, and $\lim_{x\to 0+} p(x) = \frac{1}{3}$, $\lim_{x\to\infty} p(x) = 0$.
(2) $h(x)$ and $g(x)$ are strictly monotone increasing for $x > 0$, and

$$g(0) = 0, \qquad \lim_{x\to\infty} g(x) = 1, \qquad g'(0) = \frac{1}{3}.$$

(3) For any $\alpha > 0$, $D(x)$ is strictly monotonely increasing for $x > 0$.
(4) For any $\alpha > 0$, $l(x)$ is strictly monotonely decreasing for $x > 0$.

Proof. For the proof of (1), (2) and (3) , please see [6, 7, 23].
(5) Through a simple differential calculation, we have

$$l'(x) = \frac{\alpha p'(x)\big(\alpha + g(x)\big) - \alpha p(x) g'(x)}{\big(\alpha + g(x)\big)^2} = \frac{(\alpha)^2 p'(x) - \alpha p^2(x)}{\big(\alpha + g(x)\big)^2} < 0,$$

where we have to take advantage of $p(x) > 0$ and $p'(x) < 0$. Therefore, $l(x)$ is strictly monotonely decreasing for $x > 0$. This completes the proof. □

Lemma 2.2. [11] Consider the initial value problem of a delay differential equation

$$\dot{x}(t) = G\big(x(t), x(t-\tau)\big), \quad t > 0, \tag{2.1}$$

$$x(t) = x^0(t), \quad -\tau \le t \le 0. \tag{2.2}$$

Assuming that the function G is defined and continuously differentiable in $R_+ \times R_+$ and strictly monotone increasing in the second variable, we have the following results:
(1) If x_s is a positive solution of the equation $G(x, x) = 0$ such that $G(x, x) > 0$ for x less than but near x_s, $G(x, x) < 0$ for x greater than but near x_s. Let (c, d) be the (maximal) interval containing only the root x_s of the equation $G(x, x) = 0$. If $x(t)$ is the solution of the problem of (2.1), (2.2) and $x^0(t) \in C[-\tau, 0]$, $c < x^0(t) < d$ for $-\tau \le t \le 0$, then

$$\lim_{t\to\infty} x(t) = x_s,$$

(2) If $G(x, x) < 0$ for all $x > 0$, then

$$\lim_{t\to\infty} x(t) = 0.$$

In the following, we will use the above properties to help us prove the main theorems.

3. Existence and uniqueness of the solution to Problem (1.9)–(1.16)

In this section, we will discuss the existence and uniqueness of the solution to Problems (1.9)–(1.16).

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 (1.9)–(1.16) on interval $[-\tau, \infty)$.

*Proof.*Combined with (1.9) and (1.10), the solution is given explicitly in the form of

$$\begin{aligned} u(r,t) &= \frac{\alpha}{\alpha + R(t)p(R(t))}\frac{R(t)sinhr}{r\sinh R(t)}\bar{u}\Big(1-\frac{\gamma}{R(t)}\Big)H(R(t)) \\ &= \frac{\alpha\bar{u}}{\alpha + g(R(t))}\frac{R(t)\sinh r}{r\sinh R(t)}\Big(1-\frac{\gamma}{R(t)}\Big)H(R(t)). \end{aligned} \tag{3.1}$$

Similarly, the solution of (1.11) and (1.12) is given explicitly in the form of

$$\begin{aligned} v(r,t) &= \frac{\alpha}{\alpha + R(t)p(R(t))}\frac{R(t)sinhr}{r\sinh R(t)}\bar{v}\Big(1-\frac{\gamma}{R(t)}\Big)H(R(t)) \\ &= \frac{\alpha\bar{v}}{\alpha + g(R(t))}\frac{R(t)\sinh r}{r\sinh R(t)}\Big(1-\frac{\gamma}{R(t)}\Big)H(R(t)). \end{aligned} \tag{3.2}$$

Substituting (3.1) and (3.2) into (1.13), we deduce

$$\begin{aligned} \frac{dR}{dt} =&\mu\bar{u}R(t)\Bigg[\frac{\alpha R^3(t-\tau)p(R(t-\tau))}{\big(\alpha+g(R(t-\tau))\big)R^3(t)}\Big(1-\frac{\gamma}{R(t-\tau)}\Big)H(R(t-\tau)) \\ &-\frac{\nu\bar{v}}{\mu\bar{u}}\frac{\alpha p(R(t))}{\alpha+g(R(t))}\Big(1-\frac{\gamma}{R(t)}\Big)H(R(t))-\frac{\tilde{u}}{3\bar{u}}\Bigg]. \end{aligned} \tag{3.3}$$

If we denote $x(t) = R^3(t)$, then we have

$$\begin{aligned} \frac{dx}{dt} =&3\mu\bar{u}x(t-\tau)l(x^{\frac{1}{3}}(t-\tau))(1-\frac{\gamma}{x^{\frac{1}{3}}(t-\tau)})H(x^{\frac{1}{3}}(t-\tau)) \\ &-\Big[3\nu\bar{v}l(x^{\frac{1}{3}}(t))(1-\frac{\gamma}{x^{\frac{1}{3}}(t)})H(x^{\frac{1}{3}}(t))+\mu\tilde{u}\Big]x(t) \\ =&: G(x(t-\tau))-F(x(t)). \end{aligned} \tag{3.4}$$

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

$$x_0(t) = [\varphi(t)]^3, \quad -\tau \le t \le 0. \tag{3.5}$$

The ODE uniqueness of the solution of the initial value problem implies that the Problem (3.4), (3.5) has a unique solution $x(t)$ exists on $[0, \infty)$. Further, we use the prolongement method on intervals $[n\tau, (n+1)\tau]$, $n \in N$. Therefore, we obtain the solution of (3.4) exists on $[-\tau, \infty)$. Next, we need to show that the solution is nonnegative. Where

$$G(x(t-\tau)) = 3\mu\bar{u}x(t-\tau)l(x^{\frac{1}{3}}(t-\tau))\Big(1-\frac{\gamma}{x^{\frac{1}{3}}(t-\tau)}\Big)H(x^{\frac{1}{3}}(t-\tau)),$$

$$F(x(t)) = \Big[3\nu\bar{v}l(x^{\frac{1}{3}}(t))(1-\frac{\gamma}{x^{\frac{1}{3}}(t)})H(x^{\frac{1}{3}}(t))+\mu\tilde{u}\Big]x(t).$$

By a simple calculations, we derive

$$\begin{aligned}F'(x(t)) =&3\nu\bar{v}l(x^{\frac{1}{3}}(t))\Big(1-\frac{\gamma}{x^{\frac{1}{3}}(t)}\Big)H(x^{\frac{1}{3}}(t))+\mu\tilde{u}\\&+x(t)\Big[3\nu\bar{v}l'(x^{\frac{1}{3}}(t))\frac{1}{3}(x(t))^{-\frac{2}{3}}\Big(1-\frac{\gamma}{x^{\frac{1}{3}}(t)}\Big)H(x^{\frac{1}{3}}(t))\\&+3\nu\bar{v}l(x^{\frac{1}{3}}(t))\Big(\frac{\gamma}{3x^{\frac{4}{3}}(t)}\Big)H(x^{\frac{1}{3}}(t))+3\nu\bar{v}l(x^{\frac{1}{3}}(t))\Big(1-\frac{\gamma}{x^{\frac{1}{3}}(t)}\Big)H'(x^{\frac{1}{3}}(t))\frac{1}{3}(x^{-\frac{2}{3}}(t))\Big].\end{aligned}$$

From Lemma 2.1, we know that $F'(x(t)) > 0$ for all $x(t) > 0$. Because $\varphi(t)$ is continuous on intervals $[-\tau, 0]$, $x(t)$ is continuous on intervals $[-\tau, 0]$. Then, we derive that there exists a unique solution of (3.4) on $[0, \infty)$ (see [27]). From the Lemma 2.1, we have $G(x(t-\tau)) \geq 0$ for all $x(t-\tau) > 0$. By Theorem 1.1 in [28], we obtain the solution to Problem (3.4) and (3.5) is nonnegative on $[0, \infty)$, which completes our proof. □

4. The steady state solution and their stability

In this section, we will discuss the steady state solution and their stability with the $\alpha(t)$ division constant and bounded.

4.1. When $\alpha(t)$ is a constant

By discussing the existence of stationary solution by classifying the parameters, we have the following result.

Theorem 4.1. Assume that x^* is the unique solution to $J(x) = 0$. Then there exists a unique positive constant $3f(x^*)$ such that the following results are vaild:
(i) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, there exists two different stationary solutions $(u_{s1}(r), v_{s1}(r), R_{s1})$ and $(u_{s2}(r), v_{s2}(r), R_{s2})$ to Problem (1.9)–(1.16), where $R_{s1} < R_{s2}$.
(ii) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, there exists a unique stationary solution $(u_s(r), v_s(r), R_s)$ to Problems (1.9)–(1.16).
(iii) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, there are no stationary solutions to Problems (1.9)–(1.16).

Proof. The stationary solution of the Problem (1.9)–(1.16), denoted by $(u_s(r), v_s(r), R_s)$, must satisfy the following equation:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial u_s(r)}{\partial r}\Big) = u_s(r), \qquad 0 < r < R_s, \tag{4.1}$$

$$\frac{\partial u_s(r)}{\partial r} + \alpha\Big(u_s(r) - \bar{u}(1-\frac{\gamma}{R_s})H(R_s)\Big) = 0, \qquad r = R_s, \tag{4.2}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial v_s(r)}{\partial r}\Big) = v_s(r), \qquad 0 < r < R_s, \tag{4.3}$$

$$\frac{\partial v_s(r)}{\partial r} + \alpha\Big(v_s(r) - \bar{v}(1-\frac{\gamma}{R_s})H(R_s)\Big) = 0, \qquad r = R_s, \tag{4.4}$$

$$\int_0^{R_s}\mu u_s(r)r^2dr - \int_0^{R_s}\nu v_s(r)r^2dr - \int_0^{R_s}\mu\tilde{u}r^2dr = 0. \tag{4.5}$$

Combined with (4.1) and (4.2), the solution is given explicitly in the form of

$$u_s(r) = \frac{\alpha\bar{u}}{\alpha + g(R_s)}\frac{R_s \sinh r}{r \sinh R_s}(1 - \frac{\gamma}{R_s})H(R_s). \tag{4.6}$$

Similarly, the solution of (4.3) and (4.4) is given explicitly in the form of

$$v_s(r) = \frac{\alpha\bar{v}}{\alpha + g(R_s)}\frac{R_s \sinh r}{r \sinh R_s}(1 - \frac{\gamma}{R_s})H(R_s). \tag{4.7}$$

Thus, we obtain that the R_s satisfies

$$\Big[p(R_s) - \frac{\nu\bar{v}}{\mu\bar{u}}p(R_s)\Big]\frac{\alpha}{\alpha + g(R_s)}(1 - \frac{\gamma}{R_s})H(R_s) = \frac{\tilde{u}}{3\bar{u}}. \tag{4.8}$$

Let

$$f(x) = \Big(1 - \frac{\nu\bar{v}}{\mu\bar{u}}\Big)l(x)(1 - \frac{\gamma}{x})H(x).$$

After a direct differential computation, we derive

$$f'(x) = \Big(1 - \frac{\nu\bar{v}}{\mu\bar{u}}\Big)H(x)\frac{\alpha}{[\alpha + g(x)]^2x^2}J(x) + \Big(1 - \frac{\nu\bar{v}}{\mu\bar{u}}\Big)l(x)(1 - \frac{\gamma}{x})H'(x),$$

where

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

Next, we will discuss the classification according to the value range of x. If $x \geq 2\gamma$, then $H(x) = 1 \Rightarrow H'(x) = 0$. By a direct differential computation, we obtain

$$f'(x) = \Big(1 - \frac{\nu\bar{v}}{\mu\bar{u}}\Big)\frac{\alpha}{[\alpha + g(x)]^2x^2}J(x).$$

On the one hand, $0 \leq H'(x) \leq \frac{2}{\gamma}$ for all $x \geq 0$. On the other hand, $J(x)$ is strictly monotonely increasing for all $x > \gamma$ (The proof of monotonicity of $J(x)$ can be found on [23]) and $\lim_{x\to 2\gamma} J(x) = \alpha\gamma[2\gamma p'(2\gamma) + p(2\gamma)] = \alpha\gamma[xp(x)]'|_{x=2\gamma} = \alpha\gamma g'(x)|_{x=2\gamma} > 0$. Therefore, if $\gamma < x \leq 2\gamma$, we have $f'(x) > 0$ In the same way, we have $\lim_{x\to\gamma^+} J(x) = \alpha\gamma p(\gamma) + \gamma^2 p^2(\gamma) > 0$. Thanks to Range$\{g(x)\} \in (0, 1)$ and $g(x)$ is strictly monotonely increasing for all $x > 0$, which implies that there exists a constant $M_0 > 0$ such that $M_0 p(M_0) = g(M_0) > \frac{1}{2}$. Setting $M_1 = \max\{M_0 + 1, 3\gamma, 2\gamma(\alpha + 1)\}$, we have

$$\begin{aligned}
&\Big[\alpha\gamma + (2\gamma - M_1)M_1 p(M_1)\Big]p(M_1) \\
&< (\alpha\gamma + \frac{1}{2}(2\gamma - M_1))p(M_1) \\
&\leq \Big(\alpha\gamma + \frac{1}{2}(2\gamma - 2\gamma(\alpha + 1))\Big)p(M_1) = 0,
\end{aligned}$$

then $J(M_1) = \alpha[(M_1^2 - \gamma M_1)]p'(M_1) + [\alpha\gamma + (2\gamma - M_1)M_1 p(M_1)]p(M_1) < 0$. When $x > \gamma$, we have $J'(x) < 0$. The mean value theorem implies that we have a unique constant $x^* \in (\gamma, M_1)$ such that $J(x^*) = 0$; when $x > x^*$, we have $J(x) < 0$; when $x \in (\gamma, x^*)$, we have $J(x) > 0$.

Thus

$$f'(x) = (1 - \frac{\nu\bar{v}}{\mu\bar{u}})\frac{\alpha}{[\alpha + xp(x)]^2}J(x) + (1 - \frac{\nu\bar{v}}{\mu\bar{u}})l(x)(1 - \frac{\gamma}{x})H'(x),$$

$f'(x) > 0$ for $x \in (\gamma, x^*)$; $f'(x) = 0$ for $x = x^*$; $f'(x) < 0$ for $x > x^*$. Then $f(x^*) = \max_{x\in[\gamma,M_1]} f(x) \in (0, \frac{1}{3})$.
According to the analysis, we have the following conclusions:
(i) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, we can get that there exist two different stationary solutions $(u_{s1}(r), v_{s1}(r), R_{s1})$ and $(u_{s2}(r), v_{s2}(r), R_{s2})$ to Problems (1.9)–(1.16), where $R_{s1} < R_{s2}$.
(ii) If $\mu\bar{u} = \nu\bar{v}+\mu\tilde{u}$, we can get that there exists a unique stationary solution $(u_s(r), v_s(r), R_s)$ to Problems (1.9)–(1.16).
(iii) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, we know that there are no stationary solutions to Problems (1.9)–(1.16).

This completes the proof. □

After discussing the existence of stationary solutions, we then study the asymptotic behavior of stationary solutions.

For convenience, let $|\varphi| = \max_{-\tau\le t\le 0} \varphi(t)$ and $\min\varphi = \min_{-\tau\le t\le 0} \varphi(t)$. Together with Theorem 4.1 and the case where $\alpha(t)$ is a constant, it implies the following result.

Theorem 4.2. For any nonnegative initial value function φ that is continuous, when $-\tau \le t$, there is a nonnegative solution to Problems (3.3) and (1.16), and the dynamics of those solutions are as follows:
(I) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R_{s1}$, we can obtain $\lim_{t\to\infty} R(t) = 0$, when $\min\varphi > R_{s1}$, we have $\lim_{t\to\infty} R(t) = R_{s2}$.
(II) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R_s$, then $\lim_{t\to\infty} R(t) = 0$, when $\min\varphi > R_s$, we have $\lim_{t\to\infty} R(t) = R_s$.
(III) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, then $\lim_{t\to\infty} R(t) = 0$.

Proof. Let

$$Q(x, y) = x\left[\frac{\alpha}{\alpha + g(y)}\frac{y^3 p(y)}{x^3}(1 - \frac{\gamma}{y})H(y) - \frac{\nu\bar{v}}{\mu\bar{u}}\frac{\alpha p(x)}{\alpha + g(x)}(1 - \frac{\gamma}{x})H(x) - \frac{1}{3}\frac{\tilde{u}}{\bar{u}}\right]\mu\bar{u}, \tag{4.9}$$

then we have

$$\frac{\partial Q}{\partial y} = \frac{\mu\bar{u}\alpha}{x^2}\left[\gamma y l(y)H(y) + H'(y)y^3 l(y)(1 - \frac{\gamma}{y}) + (y^3 l(y))'(1 - \frac{\gamma}{y})H(y)\right]. \tag{4.10}$$

By the Lemma 2.1, we can get $\frac{\partial Q}{\partial y} > 0$. Thus, we know that Q is a function of monotonically increasing values about the variable y. According to (4.9), we get

$$\begin{aligned} Q(x, x) &= x\left[\frac{\alpha}{\alpha + g(x)}\frac{x^3 p(x)}{x^3}(1 - \frac{\gamma}{x})H(x) - \frac{\nu\bar{v}}{\mu\bar{u}}\frac{\alpha p(x)}{\alpha + g(x)}(1 - \frac{\gamma}{x})H(x) - \frac{1}{3}\frac{\tilde{u}}{\bar{u}}\right]\mu\bar{u} \\ &= \mu\bar{u}x[f(x) - \frac{1}{3}\frac{\tilde{u}}{\bar{u}}]. \end{aligned} \tag{4.11}$$

Therefore, we can obtain that
(a) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, we can easily get $Q(x, x) < 0$ for all $x < R_{s1}$, $Q(x, x) > 0$ for all $R_{s1} < x < R_{s2}$ and $Q(x, x) < 0$ for all $x > R_{s2}$.
(b) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, we can easily get $Q(x, x) < 0$ for all $x \neq R_s$.
(c) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, we can easily get $Q(x, x) < 0$ for all $x > 0$.
Combined with (a)-(c) and Lemma 2.2, we know that the Theorem 4.2 is true. The proof is complete. □

4.2. When $\alpha(t)$ is bound

There exist two constants m, M $(0 \leq m < M)$ so that $m \leq \alpha(t) \leq M$.

4.2.1. When $\alpha(t)$ has a upper bound

According to (3.3), we have

$$\begin{aligned}\frac{dR}{dt} \leq &\mu\bar{u}R(t)\Big[\frac{MR^3(t-\tau)p(R(t-\tau))}{\big(M+g(R(t-\tau))\big)R^3(t)}\Big(1-\frac{\gamma}{R(t-\tau)}\Big)H(R(t-\tau)) \\ &-\frac{\nu\bar{v}}{\mu\bar{u}}\frac{Mp(R(t))}{M+g(R(t))}\Big(1-\frac{\gamma}{R(t)}\Big)H(R(t))-\frac{\tilde{u}}{3\bar{u}}\Big].\end{aligned} \tag{4.12}$$

Furthermore, we consider the following initial value problem

$$\begin{aligned}\frac{d\tilde{R}}{dt} = &\mu\bar{u}\tilde{R}(t)\Big[\frac{M\tilde{R}^3(t-\tau)p(\tilde{R}(t-\tau))}{\big(M+g(\tilde{R}(t-\tau))\big)\tilde{R}^3(t)}\Big(1-\frac{\gamma}{\tilde{R}(t-\tau)}\Big)H(\tilde{R}(t-\tau)) \\ &-\frac{\nu\bar{v}}{\mu\bar{u}}\frac{Mp(\tilde{R}(t))}{M+g(\tilde{R}(t))}\Big(1-\frac{\gamma}{\tilde{R}(t)}\Big)H(\tilde{R}(t))-\frac{\tilde{u}}{3\bar{u}}\Big], \quad t>0,\end{aligned} \tag{4.13}$$

$$\tilde{R}_0(t) = \varphi(t), \quad -\tau \leq t \leq 0. \tag{4.14}$$

Define

$$\begin{aligned}G_1(x,y) = &\mu\bar{u}x\Big[\frac{My^3p(y)}{\big(M+g(y)\big)x^3}\Big(1-\frac{\gamma}{y}\Big)H(y) \\ &-\frac{\nu\bar{v}}{\mu\bar{u}}\frac{Mp(x)}{M+g(x)}\Big(1-\frac{\gamma}{x}\Big)H(x)-\frac{\tilde{u}}{3\bar{u}}\Big], \quad t>0.\end{aligned}$$

In the same way that $\alpha(t)$ is a constant, there exists a unique constant $X*$ satisfies the following equation:

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

Let $f_1(x) = \Big(1-\frac{\nu\bar{v}}{\mu\bar{u}}\Big)l(x)(1-\frac{\gamma}{x})H(x)$, then the following analysis and results is similar that $\alpha(t)$ is a constant.

Lemma 4.3. Assume that X^* be the unique solution to $J_1(x) = 0$. Then there exists a unique positive constant $3f_1(X^*)$ such that the following results hold true:
(i) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, there exist two different stationary solutions $(u^M_{s1}(r), v^M_{s1}(r), R^M_{s1})$ and $(u^M_{s2}(r), v^M_{s2}(r), R^M_{s2})$ to Problem (1.9)–(1.16), where $R^M_{s1} < R^M_{s2}$.
(ii) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, there exists a unique stationary solutions $(u^M_s(r), v^M_s(r), R^M_s)$ to Problem (1.9)–(1.16).
(iii) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, there are no stationary solutions to Problems (1.9)–(1.16).

Lemma 4.4. For any nonnegative initial value function φ that is continuous, when $-\tau \leq t$, there is a nonnegative solution to Problems (4.13) and (4.14), and the dynamics of those solutions are as follows:

(I) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^M_{s1}$, we can obtain $\lim_{t\to\infty} R^M(t) = 0$, when $\min\varphi > R^M_{s1}$, we have $\lim_{t\to\infty} R^M(t) = R^M_{s2}$.
(II) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^M_s$, then $\lim_{t\to\infty} R^M(t) = 0$, when $\min\varphi > R^M_s$, we have $\lim_{t\to\infty} R^M(t) = R^M_s$.
(III) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, then $\lim_{t\to\infty} R^M(t) = 0$.

Combined proof of Theorem 4.2, Lemma 4.3 and Lemma 4.4, we can proof of Theorem 4.5.

When $\alpha(t)$ has an upper bounded, we combined the Theorem 4.2 with the comparative principle of the ODE, we have the result shown bellow.

Theorem 4.5. For any nonnegative initial value function φ that is continuous, when $-\tau \le t$, there is a nonnegative solution to Problems (4.13) and (4.14). Moreover, if $\alpha(t)$ has a upper bound, the dynamics of those solutions are as follows:
(I) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^M_{s1}$, we can obtain $\lim_{t\to\infty} R(t) = 0$ and when $\min\varphi > R^M_{s1}$, we have $\limsup_{t\to\infty} R(t) \le R^M_{s2}$.
(II) If $\mu\bar{u} = \nu\bar{v}+\mu\tilde{u}$, when $|\varphi| < R^M_s$, then $\lim_{t\to\infty} R(t) = 0$ and when $\min\varphi > R^M_s$, we have $\limsup_{t\to\infty} R(t) \le R^M_s$.
(III) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, then $\lim_{t\to\infty} R(t) = 0$.

Proof. According to (4.12) and the comparison principle [11], we only need to prove that $\frac{\partial G_1}{\partial y} > 0$. In fact,

$$\frac{\partial G_1}{\partial y} = \frac{\mu\bar{u}}{x^2}\Big[(y^3 l_1(y))'(1 - \frac{\gamma}{y})H(y) + y\gamma l_1(y)H(y) + H'(y)y^3 l_1(y)(1 - \frac{\gamma}{y})\Big], \tag{4.15}$$

where $l_1(y) = \frac{M}{M+g(y)}$. From Lemma 2.1, it is obvious that $\frac{\partial G_1}{\partial y} > 0$. Meanwhile, the comparison principle [11] indicates that

$$R(t) \le R^M(t). \tag{4.16}$$

By Lemma 4.3, noticing $R(t) \ge 0$ and taking upper limits for both $R(t)$ and $R^M(t)$ as $t \to \infty$, one can get Theorem 4.5. This completes the proof. □

Similarly, we consider the following initial value problem

$$\begin{aligned}\frac{d\bar{R}}{dt} =&\mu\bar{u}\bar{R}(t)\Big[\frac{m\bar{R}^3(t-\tau)p(\bar{R}(t-\tau))}{\big(m+g(\bar{R}(t-\tau))\big)\bar{R}^3(t)}\Big(1-\frac{\gamma}{\bar{R}(t-\tau)}\Big)H(\bar{R}(t-\tau))\\ &-\frac{\nu\bar{v}}{\mu\bar{u}}\frac{mp(\bar{R}(t))}{m+g(\bar{R}(t))}\Big(1-\frac{\gamma}{\bar{R}(t)}\Big)H(\bar{R}(t))-\frac{\tilde{u}}{3\bar{u}}\Big],\quad t>0,\end{aligned} \tag{4.17}$$

$$\bar{R}_0(t) = \varphi(t), \quad -\tau \le t \le 0. \tag{4.18}$$

Define

$$\begin{aligned}G_2(x,y) =&\mu\bar{u}x\Big[\frac{my^3p(y)}{\big(m+g(y)\big)x^3}\Big(1-\frac{\gamma}{y}\Big)H(y)\\ &-\frac{\nu\bar{v}}{\mu\bar{u}}\frac{mp(x)}{m+g(x)}\Big(1-\frac{\gamma}{x}\Big)H(x)-\frac{\tilde{u}}{3\bar{u}}\Big],\quad t>0,\end{aligned}$$

In the same way that $\alpha(t)$ is a constant, there exists a unique constant $X*$ satisfies the following equation:

$$J_2(x) = \alpha[(x^2 - \gamma x)p'(x) + \gamma p(x)] + (2\gamma x - x^2)p^2(x).$$

Let $f_2(x) = \left(1 - \frac{\nu\bar{v}}{\mu\bar{u}}\right) l_2(x)(1 - \frac{\gamma}{x})H(x)$, then the following analysis and results is similar that $\alpha(t)$ is a constant.

4.2.2. When $\alpha(t)$ has a lower bound

Similarly, we have

Lemma 4.6. Assume that X^* be the unique solution to $J_2(x) = 0$. Then there exists a unique positive constant $3f_2(X^*)$ such that the following results are valid:
(i) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, there exist two different stationary solutions $(u^m_{s1}(r), v^m_{s1}(r), R^m_{s1})$ and $(u^m_{s2}(r), v^m_{s2}(r), R^m_{s2})$ to Problem (1.9)–(1.16), where $R^m_{s1} < R^m_{s2}$.
(ii) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, there exists a unique stationary solutions $(u^m_s(r), v^m_s(r), R^m_s)$ to Problem (1.9)–(1.16).
(iii) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, there are no stationary solutions to Problems (1.9)–(1.16).

Lemma 4.7. For any nonnegative initial value function φ that is continuous, when $-\tau \le t$, there is a nonnegative solution to Problems (4.17) and (4.18), and the dynamics of those solutions are as follows:
(I) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^m_{s1}$, we can obtain $\lim_{t\to\infty} R^m(t) = 0$, when $\min\varphi > R^m_{s1}$, we have $\lim_{t\to\infty} R^m(t) = R^m_{s2}$.
(II) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^m_s$, then $\lim_{t\to\infty} R^m(t) = 0$, when $\min\varphi > R^m_s$, we have $\lim_{t\to\infty} R^m(t) = R^m_s$.
(III) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, then $\lim_{t\to\infty} R^m(t) = 0$.

Combined proof of Theorem 4.2, Lemma 4.6 and Lemma 4.7, we can proof of Theorem 4.8.

Similarly, when $\alpha(t)$ has an lower bounded, we combined the Theorem 4.2 with the comparative principle of the ODE, we have the result shown bellow.

Theorem 4.8. For any nonnegative initial value function φ that is continuous, when $-\tau \le t$, there is a nonnegative solution to Problems (4.17) and (4.18). Moreover, if $\alpha(t)$ $\alpha(t)$ has a lower bound, the dynamics of those solutions are as follows:
(I) If $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^m_{s1}$, we can obtain $\lim_{t\to\infty} R(t) = 0$ and when $\min\varphi > R^m_{s1}$, we have $\liminf_{t\to\infty} R(t) \ge R^m_{s2}$.
(II) If $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, when $|\varphi| < R^m_s$, then $\lim_{t\to\infty} R(t) = 0$ and when $\min\varphi > R^m_s$, we have $\liminf_{t\to\infty} R(t) \ge R^m_s$.
(III) If $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, then $\lim_{t\to\infty} R(t) = 0$.

Proof. According to (4.12) and the comparison principle [11], we only need to prove that $\frac{\partial G_2}{\partial y} > 0$. In fact,

$$\frac{\partial G_2}{\partial y} = \frac{\mu\bar{u}}{x^2}\left[(y^3 l_2(y))'(1 - \frac{\gamma}{y})H(y) + y\gamma l_2(y)H(y) + H'(y)y^3 l_2(y)(1 - \frac{\gamma}{y})\right], \tag{4.19}$$

where $l_2(y) = \frac{m}{m+g(y)}$. From Lemma 2.1, it is obvious that $\frac{\partial G_2}{\partial y} > 0$. Meanwhile, the comparison principle [11] indicates that

$$R(t) \ge R^m(t). \tag{4.20}$$

By Lemma 4.7, noticing $R(t) \ge 0$ and taking lower limits for both $R(t)$ and $R^m(t)$ as $t \to \infty$, then the Theorem 4.8 is true. The proof is complete. □

Therefore, the number of steady-state solutions varies in different value ranges. When the steady-state solution exists, it has a corresponding homeostasis.

5. Numerical computations

In this section, by using Matlab, we will present some numerical results to validate our theoretical results, see Figures 1–3. First, we give the values $\gamma = 2, \alpha = 5, 8$ and $\alpha = 8, \gamma = 2.5, 3$ for the two groups of parameters for the function $f(x)$, then we can obtain Figure 1. It is obvious that the function $f(x)$ is increasing in α and decreasing in γ.

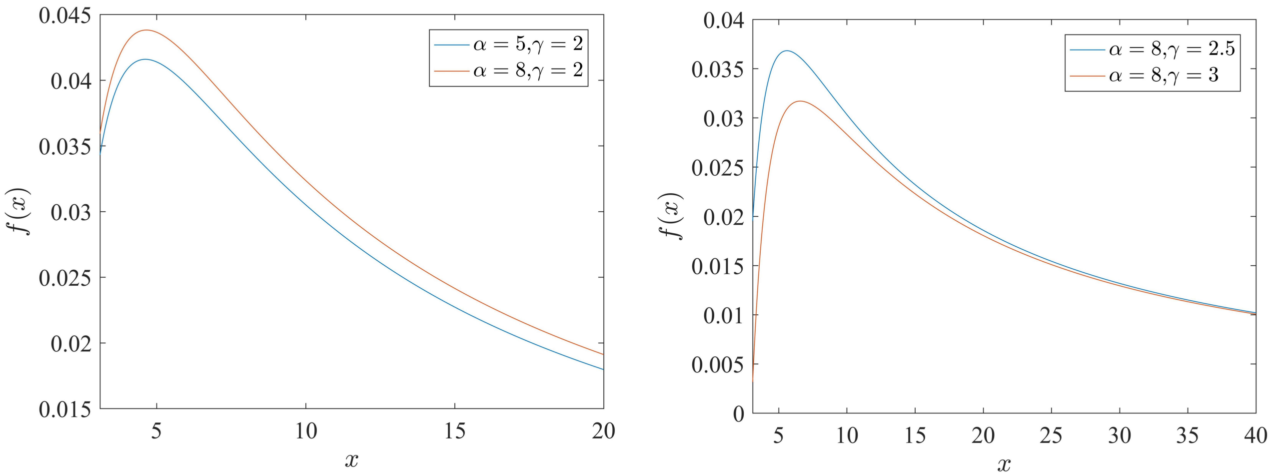

Figure 1. $\gamma = 2, \alpha = 5, 8$ and $\alpha = 8, \gamma = 2.5, 3$.

Figures 2 and 3 show that in some special cases, the steady-state solutions are larger than 2γ. In this case, $H(x) = 1$, hence,

$$f(x) = \Big(1 - \frac{\nu\bar{v}}{\mu\bar{u}}\Big)l(x)(1 - \frac{\gamma}{x}). \tag{5.1}$$

If the parameters in (3.4) are taken as

$$\bar{u} = 5, \bar{v} = 5, \tilde{u} = 10, \mu = 1, \nu = 1, \alpha = 8, \gamma = 2, \tau = 3, x_0 = 100, 1600, \tag{5.2}$$

then we can solve the equation $f(\sqrt[3]{x}) = \frac{\tilde{u}}{3\bar{u}}$, we get Figure 2.

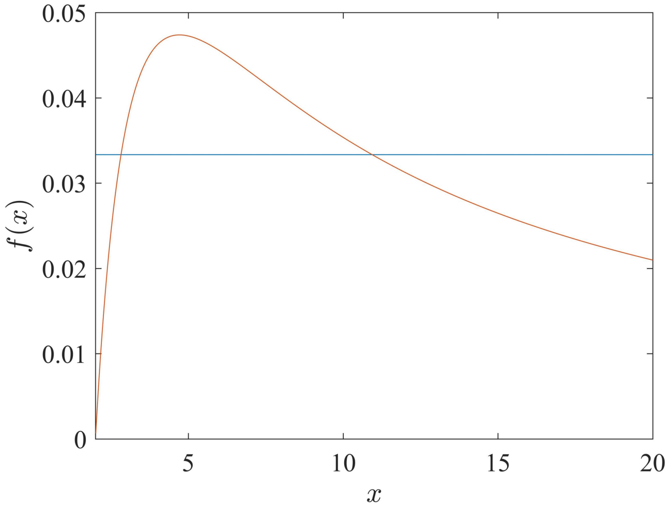

Figure 2. x-f(x).

The dynamics of the solution to (3.4) allow us to obtain Figure 3.

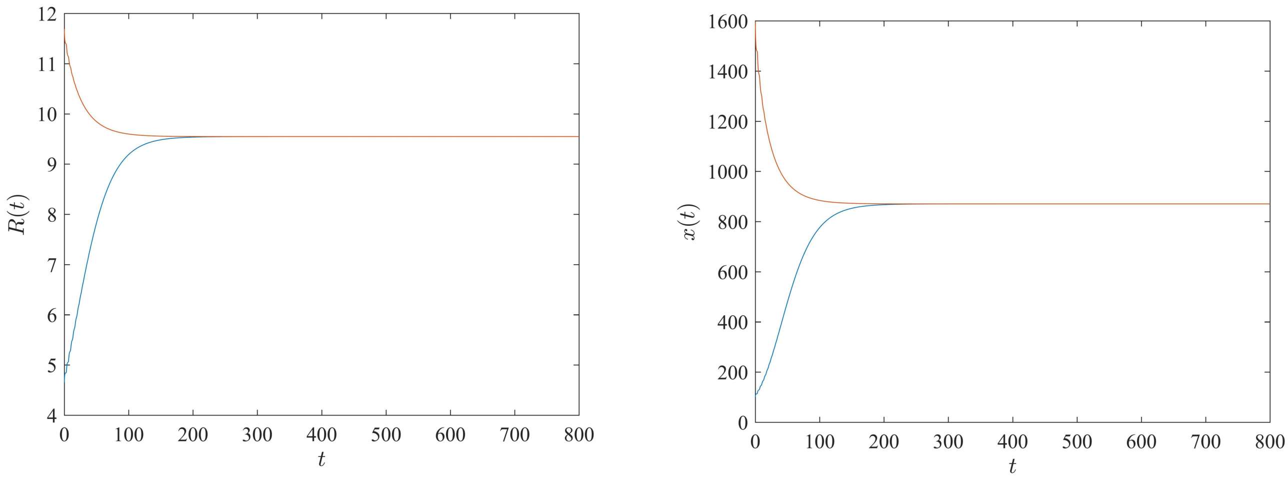

Figure 3. t-R(t) and t-x(t).

6. Conclusions

In this paper, we study how the external nutrient and inhibitor concentrations affect a time-delayed tumor growth under the Gibbs-Thomson relation.

This Problem (1.9)–(1.16) has a unique nonegative solution (Theorem 3.1).

(a) When $\alpha(t)$ is a constant, we further demonstrate the existence of the stationary solutions (Theorem 4.1) and the asymptotic behavior of the stationary solutions (Theorem 4.2);

(b) When $\alpha(t)$ is bounded, we also demonstrate the asymptotic behavior of the stationary solutions and their existence (Theorem 4.5 and Theorem 4.8).

From the biological point of view, the results show that
(i) if $\mu\bar{u} > \nu\bar{v} + \mu\tilde{u}$, there exists two different stationary solutions, for small initial function satisfying $\max\limits_{-\tau\le t\le 0}\varphi(t) < R_{s1}$, the tumor will disappear; for large function satisfying $\min\limits_{-\tau\le t\le 0}\varphi(t) < R_{s1}$, the tumor will not disappear and will tend to the unique steady-state;
(ii) if $\mu\bar{u} = \nu\bar{v} + \mu\tilde{u}$, there exists a unique stationary solution, for small initial function satisfying $\max\limits_{-\tau\le t\le 0}\varphi(t) < R_s$, the tumor will disappear; for large function satisfying $\min\limits_{-\tau\le t\le 0}\varphi(t) < R_s$, the tumor will not disappear and will tend to the unique steady-state;
(iii) if $\mu\bar{u} < \nu\bar{v} + \mu\tilde{u}$, there is no stationary solution, the tumor will disappear.

The result implies that, under certain conditions, the tumor will probably become dormant or will finally disappear. The conclusions are illustrated by numerical computations. We hope these results may be useful for future tumor research.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

This work was supported by the Characteristic Innovation Projects of Colleges and Universities in Guangdong Province, China (No. 2016KTSCX028), the High-Level Talents Project of Guangdong Province, China (No. 2014011).

Conflict of interest

All authors declare no conflicts of interest in this paper.

References

1. H. P. Greenspan, Models for the growth of solid tumor by diffusion, *Stud. Appl. Math.*, **51** (1972), 317–340. https://doi.org/10.1002/sapm1972514317
2. H. P. Greenspan, On the growth and stability of cell cultures and solid tumors, *J. Theoret. Biol.*, **56** (1976), 229–242. https://doi.org/10.1016/s0022-5193(76)80054-9
3. H. M. Byren, M. A. J. Chaplain, Growth of nonnecrotic tumors in the presence and absence of inhibitors, *Math. Biosci.*, **130** (1995), 151–181. https://doi.org/10.1016/0025-5564(94)00117-3
4. S. Cui, A. Friedman, Analysis of a mathematical model of the effect of inhibitors on the growth of tumors, *Math. Biosci.*, **164** (2000), 103–137. https://doi.org/10.1016/s0025-5564(99)00063-2
5. S. Cui, Analysis of a mathematical model for the growth of tumors under the action of external inhibitors, *J. Math. Biol.*, **44** (2002), 395–426. https://doi.org/10.1007/s002850100130
6. A. Friedman, F. Reitich, Analysis of a mathematical model for the growth of tumors, *J. Math. Biol.*, **38** (1999), 262–284. https://doi.org/10.1007/s002850050149
7. A. Friedman, K.-Y. Lam, Analysis of a free-boundary tumor model with angiogenesis, *J. Differ. Equ.*, **259** (2015), 7636–7661. https://doi.org/10.1016/j.jde.2015.08.032

8. H. Shen, X. Wei, A qualitative analysis of a free boundary problem modeling tumor growth with angiogenesis, *Nonlinear Anal.*, **5** (2019), 106–126. https://doi.org/10.1016/j.nonrwa.2018.10.004

9. J. Wu, S. Cui Asymptotic behaviour of solutions of a free boundary problem modelling the growth of tumours in the presence of inhibitors, *Nonlinearity*, **20** (2007), 2389. https://doi.org/10.1088/0951-7715/20/10/007

10. H. M. Byren, The effect of time delays on the dynamics of avascular tumor growth, *Math. Biosci.*, **144** (1997), 83–117. https://doi.org/10.1016/s0025-5564(97)00023-0

11. S. Cui, S. Xu, Analysis of mathematical models for the growth of tumors with time delays in cell proliferation, *J. Math. Anal. Appl.*, **336** (2007), 523–541. https://doi.org/10.1016/j.jmaa.2007.02.047

12. S. Xu, Z. Feng, Analysis of a mathematical model for tumor growth under indirect effect of inhibitors with time delay in proliferation, *J. Math. Anal. Appl.*, **374** (2011), 178–186. https://doi.org/10.1016/j.jmaa.2010.08.043

13. U. Fory's, M. Bodnar, Time delays in proliferation process for solid avascular tumour, *Math. Comput. Modelling.*, **37** (2003), 1201–1209. https://doi.org/10.1016/s0895-7177(03)80019-5

14. S. Xu, Analysis of tumor growth under direct effect of inhibitors with time delays in proliferation, *Nonlinear Anal.*, **11** (2010), 401–406. https://doi.org/10.1016/j.nonrwa.2008.11.002

15. S. Xu, D. Su, Analysis of a time-delayed free boundary problem for solid tumor growth with angiogenesis and direct influence of inhibitors, *Bound. Value Probl.*, **2020** (2020), 48. https://doi.org/10.1186/s13661-020-01350-3

16. S. Xu, F. Zhang, Q. Zhou, Analysis of a free boundary problem for solid avascular tumor growth with a time delay in regulatory apoptosis, *Int. J. Biomath.*, **15** (2022), 2250021. https://doi.org/10.1142/s1793524522500218

17. H. M. Byren, M. A. J. Chaplain, Modelling the role of cell-cell adhesion in the growth and development of carcinomas, *Math. Comput. Model.*, **24** (1996), 1–17. https://doi.org/10.1016/s0895-7177(96)00174-4

18. T. Roose, S. Chapman, P. Maini, Mathematical models of avascular tumor growth, *SIAM Rev.*, **49** (2007), 179–208. https://doi.org/10.1137/s0036144504446291

19. J. Wu, Stationary solutions of a free boundary problem modeling the growth of tumors with Gibbs-Thomson relation, *J. Differ. Equ.*, **260** (2016), 5875–5893. https://doi.org/10.1016/j.jde.2015.12.023

20. J. Wu, F. Zhou Asymptotic behavior of solutions of a free boundary problem modeling tumor spheroid with Gibbs-Thomson relation, *J. Differ. Equ.*, **262** (2017), 4907–4930. https://doi.org/10.1016/j.jde.2017.01.012

21. J. Wu, Analysis of a mathematical model for tumor growth with Gibbs-Thomson relation, *J. Math. Anal. Appl.*, **450** (2017), 532–543. https://doi.org/10.1016/j.jmaa.2017.01.051

22. S. Xu, M. Bai, F. Zhang, Analysis of a free boundary problem for tumor growth with Gibbs-Thomson relation and time delays, *Discrete Contin. Dyn. Syst. B*, **23** (2018), 3535–3551. https://doi.org/10.3934/dcdsb.2017213

23. S. Xu, J. Wu, Qualitative analysis of a time-delayed free boundary problem for tumor growth with angiogenesis and Gibbs-Thomson relation, *Math. Biosci. Eng.*, **16** (2019), 7433–7446. https://doi.org/10.3934/mbe.2019372
24. W. Duan, H. Fang, C. Zeng, The stability analysis of tumor-immune responses to chemotherapy system with gaussian white noises, *Chaos Solitons Fractals*, **127** (2019), 96–102. https://doi.org/10.1016/j.chaos.2019.06.030
25. W. Duan, The stability analysis of tumor-immune responses to chemotherapy system driven by Gaussian colored noises, *Chaos Solitons Fractals*, **141** (2020), 110303. https://doi.org/10.1016/j.chaos.2020.110303
26. W. Duan, L. Lin, Noise and delay enhanced stability in tumor-immune responses to chemotherapy system, *Chaos Solitons Fractals*, **148** (2021), 111019. https://doi.org/10.1016/j.chaos.2021.111019
27. T. Yi, L. Huang, Generalization of the Bernfeld-Chaddock conjecture and its proof, *Acta Math. Sinica*, **50** (2007), 261–270. https://doi.org/10.3321/j.issn:0583-1431.2007.02.003
28. M. Bodnar, The nonnegativity of solutions of delay differential equations, *Appl. Math. Lett.*, **13** (2000), 91–95. https://doi.org/10.1016/s0893-9659(00)00061-6