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Research article

Analysis of a free boundary problem for vascularized tumor growth with a time delay in the process of tumor regulating apoptosis

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Abstract: In this paper, we study a free boundary problem for vascularized tumor growth with a time delay in the process of tumor regulating apoptosis. The characteristic of this model is that both vascularization and apoptosis regulation is considered. In mathematical form, this model is expressed as a free boundary problem with Robin boundary. We prove the existence and uniqueness of the global solution and their asymptotic behavior. The effects of vascularization parameters and apoptosis regulation parameters on tumor are discussed. Depending on the importance of regulating the apoptosis rate, the tumor will tend to the unique steady state or eventually disappear. For some parameter values, the final results show that the dynamic behavior of the solutions of our model is analogous to the quasi-stationary solutions. Our results are also verified by numerical simulation.

Keywords: time delay; global solution; asymptotic behavior; angiogenesis; tumor growth
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1. Introduction

Tumor is multiple diseases that seriously threaten human life and health due to the complexity of their growth mechanism. It is essential to study tumor growth and change the rule using mathematical models. The study of tumor growth model has aroused the interest of many researchers. People have considered the mathematical models of tumor growth under different conditions and given rigorous mathematical analysis to these models [2–8, 10–14, 17, 19–24].

This paper focuses on a free boundary problem for vascularized tumor growth with a time delay in the process of tumor regulating apoptosis. First, we introduce the mathematical model to be studied in this paper. We denote the tumor region by $\Omega = \{(r,t) \mid 0 < r < R(t),\quad t > 0\}$ and its free boundary by $\Pi = \{(R(t),t) \mid\ t > 0\}$. It is natural to assume that the nutrient concentration σ in Ω satisfies the reaction-diffusion equation

$$c\frac{\partial\sigma}{\partial t} = \Delta_r\sigma - \Gamma\sigma, \tag{1.1}$$

where $\Delta_r\sigma = \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial\sigma}{\partial r}\Big)$, $c = T_{diffusion}/T_{growth} \ll 1$ represents the ratio between the time scale nutrient diffusion and tumor growth, $\Gamma\sigma$ represents the nutrient consumption rate, c and Γ are positive constants.

In the growth process of tumor cells, necrosis and apoptosis are different cell loss mechanisms. The proliferation rate of cells is determined by the balance between mitosis and cell death. However, the changes in proliferation rate will lead to changes in apoptosis loss, which is not instantaneous. Therefore, there is a time delay in regulating tumor cell apoptosis [7, 16]. According to the law of conservation of mass, the free boundary $r = R(t)$ satisfies the following equation with a time delay

$$\frac{\mathrm{d}}{\mathrm{dt}}\Big(\frac{4\pi R^3(t)}{3}\Big) = 4\pi\int_0^{R(t)}\lambda(\sigma(r,t)-\tilde{\sigma})r^2dr - 4\pi\int_0^{R(t-\tau)}\lambda\theta(\sigma(r,t-\tau)-\sigma_h)r^2dr, \quad t>0, \tag{1.2}$$

where $R(t)$ is the tumor radius, $\lambda\sigma$ is cell proliferation rate, $\lambda\tilde{\sigma}$ is apoptosis rate, τ is the time required for changes in the apoptotic process, θ is a parameter that describes the importance of regulating apoptosis and σ_h is the optimal growth rate of the tumor. Moreover, $\int_0^{R(t)}\lambda(\sigma(r,t)-\tilde{\sigma})r^2dr$ represents the net proliferation rate of cells, $\int_0^{R(t-\tau)}\lambda\theta(\sigma(r,t-\tau)-\sigma_h)r^2dr$ describes a cell undergoing regulatory apoptosis, and the process of apoptosis is time delay. If $\sigma < \sigma_h$, regulatory mechanisms reduce the loss of apoptotic cells, if $\sigma > \sigma_h$, regulatory mechanisms increase the loss of apoptotic cells, otherwise, regulatory mechanisms do not work.

The avascular tumor is the initial spread state of solid tumor. Angiogenesis plays a vital role in tumor growth. In this process, tumor cells secrete cytokines that stimulate the vascular system to grow toward the tumor [1]. Since nutrients σ enter the sphere by the vascular system, the tumor will attract blood vessel at a rate proportional to γ (γ is a positive constant). The boundary condition can be seen as follows

$$\frac{\partial\sigma}{\partial r}(0,t) = 0, \quad \frac{\partial\sigma}{\partial r}(R(t),t) + \gamma(\sigma(R(t),t)-\sigma_\infty) = 0, \tag{1.3}$$

where σ_∞ is the nutrient concentration outside the tumor. Based on this idea, many models of tumor growth with angiogenesis have been considered [1, 5, 15, 16]. The initial conditions of (1.1) and (1.2) are as follows

$$\sigma(r,t) = \chi(r,t), \quad 0 \le r \le R(t), \quad -\tau \le t \le 0, \tag{1.4}$$

$$R(t) = \phi(t), \quad -\tau \le t \le 0. \tag{1.5}$$

Various mathematical models describing tumor growth with time delays have been proposed and studied in recent years from different aspects. Time delays usually occur in the time required for cell differentiation, cell proliferation, the response of one cell to other cells, etc. The ordinary differential system model is widely used in time-delay tumor, such as the tumor-immune system of cell-to-cell interactions [2, 10, 11, 18] and the tumor immune system under drug treatment [8, 23]. In addition to these ordinary differential equation systems, there are also many studies on delayed tumor models on partial differential equations. H. M. Byrne [4] proposed two kinds of free boundary problems of tumor growth with time delays. One delay exists in the process of tumor cell proliferation, the other in the process of regulating apoptosis. A time-delayed mathematical model describing tumor growth with angiogenesis and Gibbs-Thomson relation was considered by Xu and Wu [17]. P. R. Nyarko1 and M. Anokye [12] developed an advection-reaction-diffusion system to describe interactions between tumor cells and extracellular matrix (ECM) at the macroscopic level. Zhou et al. considered the time delay tumor model with angiogenesis, the existence, uniqueness and stability of the solution have been proved [7]. However, the effect of regulating apoptosis was not considered. An avascular delayed tumor growth model with regulated apoptosis was considered in [16] by Xu et al., but the effect of vascularization was not considered. By rigorous mathematical analysis, the existence, uniqueness, and asymptotic behavior were obtained. He et al. [22] considered a three-dimensional model for multilayered tumor growth of the flat-shaped form, but did not consider the influence of angiogenesis and the regulation of apoptosis.

With the motivation of the above work, we will study the free boundary problem (1.1)–(1.5) for vascularized tumor growth with a time delay in the process of tumor regulating apoptosis. The characteristic of this model is that both vascularization and apoptosis regulation is considered. The model studied in this paper is modified from the model in [16]. During tumor growth, the boundary value conditions change from Dirichlet boundary condition to Robin boundary condition due to the generation of blood vessels. In a biological sense, compared to the Dirichlet condition in [16], Robin boundary condition is more realistic for vascularized tumor growth [1, 6, 7, 17]. In this paper, the model with the Robin boundary condition is studied. Mathematically, the model discussed in [16] is a special case of the model discussed in this paper where $\gamma = \infty$. At the same time, considering the Robin boundary condition makes the analysis of the problem much more difficult. It is mainly reflected in the following two aspects: on the one hand, it is reflected in the difficulty of calculation. Considering the Robin boundary condition makes the calculation of nutrient concentration more complicated, and at the same time, the discussion of the steady-state situation becomes more difficult. On the other hand, when analyzing the asymptotic behavior of the solution, it is necessary to overcome the difficulties caused by considering Robin boundary condition. When using the comparison principle, it is necessary to overcome some new difficulties in the verification of whether the conditions are met and the construction of auxiliary functions. The linearization theory of functional differential equations is used to study the local stability of positive constant steady state solutions. The global stability of solution is studied by the comparison principle and iterative technique of free boundary problems. The results demonstrate the effect of parameters regulating apoptosis on the asymptotic behavior of tumor growth.

Arrangement of the rest part is as follows. We show some preliminary lemmas in Section 2. In Section 3, we study the quasi-stationary solution of system (1.1)–(1.5). In Section 4 and 5, we prove the global well-posedness and asymptotic behavior of the solution of Eqs (1.1)–(1.5). In Section 6, we will present numerical simulations of some parameters value. In the end, we draw biological implications from the mathematical results of this paper in Section 7.

2. Preliminaries

In this section, we introduce some preliminaries that we need to use in this paper. For convenience, we take

$$p(x) = \frac{x\coth x - 1}{x^2}, \quad m(x) = xp(x), \quad w_t(-\tau) = w(t-\tau).$$

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

(2) $m'(x) > 0$, $\lim_{x\to 0^+} m(x) = 0$, $\lim_{x\to\infty} p(x) = 1$ *for* $x > 0$.

(3) $h'(x) < 0$, $\lim_{x\to 0^+} h(x) = \frac{1}{3\gamma}$, $\lim_{x\to\infty} p(x) = 0$ *for* $x > 0$.

Proof. The proof of (1) and (2) see [13].

(3) Using (1) and (2), we deduce

$$h'(x) = \frac{p'(x)(\gamma + m(x)) - m'(x)p(x)}{(\gamma + m(x))^2} < 0.$$

Thus

$$\lim_{x\to 0^+} h(x) = \frac{1}{3\gamma}, \quad \lim_{x\to\infty} h(x) = 0.$$

□

Lemma 2.2. *[14] Consider the initial problem*

$$\dot{u}(t) = f(u(t), u_t(-\tau)), \quad t > 0, \tag{2.1}$$

$$u(t) = u_0(t), \quad -\tau \le t \le 0, \tag{2.2}$$

where $u_t(-\tau) = u(t-\tau)$. *Suppose* $f(u,w) \in C^1(R_+, R_+)$ *and* $\frac{\partial f}{\partial w} > 0$, *then*

(1) If $u_s \in (a,b) \subset (0,\infty)$ *is a positive solution of equation* $f(u,u) = 0$ *such that*

$$(u - u_s)f(u,u) < 0, \quad \textit{for } u \in (a,b) \textit{ and } u \ne u_s. \tag{2.3}$$

For $u_0(t) \in C[-\tau, 0]$ *and* $u_0(t) \in (a,b)$, $-\tau \le t \le 0$, *if* $u(t)$ *is a solution of the Eqs (2.1) and (2.2), then*

$$\lim_{t\to\infty} u(t) = u_s.$$

(2) Furthermore, we assume that $f(u,u) < 0$ *for* $u > 0$. *If (2.1) and (2.2) exis a solution for* $t \ge -\tau$, *then for any such initial function* $u_0(t) \in (0,\infty)$ *for all* $-\tau \le t \le 0$, *there holds*

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

Lemma 2.3. *[19] Linear time delay differential equations*

$$\dot{x}(t) + Ax(t) + Bx(t-\tau) = 0, \tag{2.4}$$

where A and B are constants, the following assertions hold

(1) If $A + B > 0$ *and* $A - B > 0$, *there exists a trivial solution of (2.4) that is asymptotically stable for any* $\tau > 0$.

(2) If $A + B < 0$, *the trivial solution of (2.4) for all* $\tau > 0$ *is instable.*

Lemma 2.4. *[5] Let $(\sigma(r,t), R(t))$ be a solution of problem (1.1)–(1.5) and set*

$$v(r,t) = \frac{\gamma\sigma_\infty}{\gamma + m(\sqrt{\Gamma}R(t))}\frac{R(t)\sinh(\sqrt{\Gamma}R(t)}{r\sinh(\sqrt{\Gamma}R(t))}, \ \ m(x) = \frac{x\coth x - 1}{x}.$$

We assume

$$|\dot{R}(t)| \le L, \ \ 0 \le t < T,$$
$$|\sigma_0(r) - v_0(r)| \le M\Big(1 - \frac{R_0\sinh(\sqrt{\Gamma}R_0)}{r\sinh(\sqrt{\Gamma}R_0)}\Big), \ \ 0 \le r \le R_0,$$

where $R_0 = R(0)$, $0 < L \le L_0$ and $0 < M \le M_0$. Then, there exists two constants C and c_0 independent $c,\ T,\ L,\ M,\ R_0$ and depend only on $L_0,\ M_0,\ \Gamma,\ \gamma,\ \sigma_\infty$, such that

$$|\sigma(r,t) - v(r,t)| \le \bar{C}(c' + e^{-\frac{\Gamma t}{c}}) \tag{2.5}$$

for all $0 < c \le c_0$, $0 \le r \le R(t)$ and $0 \le t \le T$, where $c' = \frac{cL}{M}$, $\bar{C} = CM\Big(1 + \frac{\sqrt{\Gamma}}{\gamma}\Big)$.

3. Quasi-steady-state solution

In this section, we will discuss the quasi-steady-state problem of (1.1)–(1.5) as follows

$$\Delta_r\sigma = \Gamma\sigma, \ \ 0 < r < R(t), \ \ t > 0, \tag{3.1}$$
$$\frac{\partial\sigma}{\partial r}(0,t) = 0, \ \ \frac{\partial\sigma}{\partial r}(R(t),t) + \gamma(\sigma(R(t),t) - \sigma_\infty) = 0, \ \ t > 0, \tag{3.2}$$
$$\frac{\mathrm{d}}{\mathrm{dt}}\Big(\frac{4\pi R^3(t)}{3}\Big) = 4\pi\int_0^{R(t)}\lambda(\sigma(r,t) - \tilde{\sigma})r^2dr - 4\pi\int_0^{R(t-\tau)}\lambda\theta(\sigma(r,t-\tau) - \sigma_h)r^2dr, \ \ t > 0, \tag{3.3}$$
$$R(t) = \phi(t), \quad -\tau \le t \le 0. \tag{3.4}$$

Solving (3.1) and (3.2), we obtain

$$\sigma(r,t) = \frac{\gamma\sigma_\infty}{\gamma + m(\sqrt{\Gamma}R(t))}\frac{R(t)\sinh(\sqrt{\Gamma}r)}{r\sinh(\sqrt{\Gamma}R(t))}. \tag{3.5}$$

Substitute (3.5) into (3.3), we get

$$\dot{\eta}(t) = a_1\eta(t)\Big[\Big(\frac{p(\eta(t))}{\gamma + m(\eta(t))} - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big) + \theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - \frac{p(\eta_t(-\tau))}{\gamma + m(\eta_t(-\tau))}\Big)\Big(\frac{\eta_t(-\tau)}{\eta(t)}\Big)^3\Big], \ \ t > 0, \tag{3.6}$$
$$\eta(t) = \psi(t), \quad -\tau \le t \le 0, \tag{3.7}$$

where $a_1 = \lambda\gamma\sigma_\infty$, $\sqrt{\Gamma}R(t) = \eta(t)$, $\sqrt{\Gamma}\phi(t) = \psi(t)$, and $\eta_t(-\tau) = \eta(t-\tau)$. Further, letting $\eta^3(t) = w(t)$, $\psi^3(t) = \varphi(t)$, $a = 3a_1$, we deduce

$$\dot{w}(t) = a\Big[\Big(\frac{p(w^{\frac{1}{3}}(t))}{\gamma + m(w^{\frac{1}{3}})} - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big)w(t) - \theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - \frac{p(w_t^{\frac{1}{3}}(-\tau))}{\gamma + m(w_t^{\frac{1}{3}}(-\tau))}\Big)w_t(-\tau)\Big], \ \ t > 0, \tag{3.8}$$

$$w(t) = \varphi(t), \quad -\tau \le t \le 0. \tag{3.9}$$

Therefore, the positive constant solutions of (3.8) are its stationary points satisfying

$$h(x) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty} + \frac{\theta\sigma_h}{3\gamma\sigma_\infty} - \theta h(x) = 0,$$

where $h(x) = \frac{p(x)}{\gamma+m(x)}$. Let $\theta \neq 1$, the stationary points are determined by

$$h(x) = \frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty(1-\theta)}. \tag{3.10}$$

If w_s is a solution of (3.10), then $x_s^{\frac{1}{3}} = w_s$.

Lemma 3.1. *(1) If $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, then w_s is the unique positive solution of (3.10).*

(2) If $\sigma_\infty < \sigma_h < \tilde{\sigma}$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta > 1$, (3.10) has no positive solution.

Proof. (1) Since $\tilde{\sigma} < \sigma_\infty < \sigma_h$, we have $\theta(\sigma_h - \sigma_\infty) > 0 > \tilde{\sigma} - \sigma_\infty$, which implies $\tilde{\sigma} - \theta\sigma_h < (1-\theta)\sigma_\infty$. If $0 < \frac{\tilde{\sigma}}{\sigma_h} < 1$, we see that

$$\frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty(\theta - 1)} \in (0, \frac{1}{3\gamma}),$$

by $\frac{\theta\sigma_h - \tilde{\sigma}}{\sigma_\infty(\theta-1)} < 1$. Using the properties of $h(x)$, there only exists a positive solutions of (3.10) and we remark it as w_s.

(2) Since $\frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty(\theta-1)} \in (0, \frac{1}{3\gamma})$ for $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, we conclude $\frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty(\theta-1)} > \frac{1}{3\gamma}$ or $\frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty(\theta-1)} < 0$ for $\sigma_\infty < \sigma_h < \tilde{\sigma}$, and $\frac{\tilde{\sigma}}{\sigma_h} > \theta > 1$. It is clearly that (3.10) has no positive solution. □

Theorem 3.2. *If $\sigma_h > \sigma_\infty > \tilde{\sigma}$, then the trivial solution of (3.8) and (3.9) is unstable, and the unique steady-state solution is asymptotically stable.*

Proof. Firstly, we linearize (3.8) at $x = 0$ and obtain

$$\dot{w} = a\Big(\frac{1}{3\gamma} - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big)w(t) + a\theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - \frac{1}{3\gamma}\Big)w(t-\tau). \tag{3.11}$$

By initial condition (3.9), we have

$$w(t) > \varphi(0)e^{\frac{1}{3\gamma}(1-\tilde{\sigma}/\sigma_\infty)t} \to \infty, \ \ t \to \infty,$$

where $\varphi(0) = \psi^3(0) > 0$. Thus, the trivial solution is unstable by Lemma 2.3.

Next, if $\theta < \frac{\tilde{\sigma}}{\sigma_h}$, (3.8) and (3.9) have a unique stationary solution w_s by Lemma 3.1. Letting $u(t) = w(t) - w_s$, we linearize (3.8) at $x = w_s$,

$$\dot{u}(t) = a\Big[h(w_s^{\frac{1}{3}}) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty} + \frac{1}{3}h'(w_s^{\frac{1}{3}})w_s^{\frac{1}{3}}\Big]u(t) + a\theta\Big[\frac{\sigma_h}{3\gamma\sigma_\infty} - h(w_s^{\frac{1}{3}}) - \frac{1}{3}h'(w_s^{\frac{1}{3}})w_s^{\frac{1}{3}}\Big]u(t-\tau). \tag{3.12}$$

characteristic equation of (3.12) is $\lambda + A + Be^{-\lambda\tau} = 0$, here $A = -a\Big[h(w_s^{\frac{1}{3}}) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty} + \frac{1}{3}h'(w_s^{\frac{1}{3}})w_s^{\frac{1}{3}}\Big]$, $B = -a\theta\Big[\frac{\sigma_h}{3\gamma\sigma_\infty} - h(w_s^{\frac{1}{3}}) - \frac{1}{3}h'(w_s^{\frac{1}{3}})w_s^{\frac{1}{3}}\Big]$. Since $h'(x) < 0$ and $h(x) \in \Big(0, \frac{1}{3\gamma}\Big)$, we obatin $B < 0$, $A + B = \frac{\theta-1}{3}ah'(w_s^{\frac{1}{3}})w_s^{\frac{1}{3}}$, which implies $A > 0$, $A + B > 0$ and $A - B > 0$. Therefore, we see that the trivial solution of (3.12) is asymptotically stable by Lemma 2.3. Applying the linearization theory of functional differential equations, (3.8) and (3.9) are asymptotically stable at $w_s^{\frac{1}{3}}$. □

Theorem 3.3. *The following assertions hold for $\varphi(t) > 0$, $-\tau \le t < 0$.*

(1) If $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, then the solution of (3.8) and (3.9) tends to w_s as $t \to \infty$, where $w_s = x_s^{\frac{1}{3}}$ is the unique stationary solution of (3.8).

(2) If $\sigma_\infty < \sigma_h < \tilde{\sigma}$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta > 1$, then the solution of (3.8) and (3.9) tends to 0 as $t \to \infty$.

Proof. Define a function

$$f(x,y) = a\Big[\Big(h(x^{\frac{1}{3}}) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big)x\Big] + a\theta\Big[\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(y^{\frac{1}{3}})\Big)y\Big].$$

Obviously,

$$\frac{\partial f}{\partial y} = a\theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(y^{\frac{1}{3}}) - \frac{1}{3}y^{\frac{1}{3}}h'(y^{\frac{1}{3}})\Big) > a\theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - \frac{1}{3\gamma} - \frac{1}{3}y^{\frac{1}{3}}h'(y^{\frac{1}{3}})\Big) > 0.$$

(1) If $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, (3.10) has a unique positive solution w_s by Lemma 3.1. Thanks to the following equation

$$f(x,x) = a\Big[h(x^{\frac{1}{3}})(1-\theta) + \frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty}\Big]x, \tag{3.13}$$

and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, we get

$$(i) f(x,x) > 0,\ 0 < x < w_s. \ (ii) f(x,x) = 0,\ x = w_s. \ (iii) f(x,x) < 0,\ x > w_s.$$

Hence, the conclusion (1) holds by Lemma 2.2.

(2) Under the condition of (2), for $x > 0$, we see that $f(x,x) < 0$ from (3.13). Applying Lemma 2.2, the solution of (3.8) and (3.9) tends to 0 as $t \to \infty$. The proof is completed. □

4. Global well-posedness

In this section, we will study the system (1.1)–(1.5), the well-posedness of global solution will be proved.

Theorem 4.1. *Assuming that $\chi(r,t)$ is a twice differentiable function in $[0,\infty]\times[-\tau,0]$, $\sigma_\infty \ge \chi(r,t) > 0$ when $R(t) \ge r$, or $\chi(r,t) = \sigma_\infty$ when $R(t) < r$. For a positive initial function $\phi(t)$ in $t \in [-\tau, 0]$, there exists a unique solution $(\sigma(r,t), R(t))$ of system (1.1)–(1.5). Moreover, the following estimates hold:*

(1) For $0 \le r \le R(t)$, $t > 0$, we obtain $0 \le \sigma(r,t) \le \sigma_\infty$.

(2) $\phi(0)\exp\{-\frac{\lambda\tilde{\sigma}t}{3}\} \le R(t) \le \sqrt[3]{1+\lambda\theta\sigma_h\tau}|\phi|\exp\{\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta\sigma_h)t}{3}\}$, where $|\phi| = \max_{-\tau\le t\le 0}\varphi(t)$.

(3) $-\frac{\lambda\tilde{\sigma}}{3} \le \frac{\dot{R}(t)}{R(t)} \le \frac{1}{3}\lambda(\sigma_\infty - \tilde{\sigma} + \theta\sigma_h\exp\{\lambda\tilde{\sigma}\tau\})$, $t > 0$.

(4) $\phi(0)\exp\{-\frac{\lambda\tilde{\sigma}t}{3}\} \le R(t) \le \phi(0)\exp\{\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta e^{\lambda\tilde{\sigma}\tau}\sigma_h)}{3}\}$, $t > 0$.

Proof. (1) Obviously, $\sigma(r,t) = 0$ and $\sigma(r,t) = \sigma_\infty$ is a pair of lower and upper solutions of (1.1) and (1.3), then by maximal principle, $0 \le \sigma \le \sigma_\infty$ holds.

(2) From (1.2), we have

$$-\frac{\lambda\tilde{\sigma}R(t)}{3} \le \dot{R}(t) \le \frac{\lambda}{3R^2(t)}[(\sigma_\infty - \tilde{\sigma})R^3(t) + \theta\sigma_h R^3(t-\tau)],\quad t > 0, \tag{4.1}$$

Integrating the left side of inequality (4.1), we deduce

$$R(t) \geq \phi_0 e^{-\frac{\lambda\tilde{\sigma}t}{3}}, \tag{4.2}$$

where $\phi_0 = \phi(0)$. By employing (4.1) and setting $\varsigma(t) = R^3(t)$, we get

$$\dot{\varsigma}(t) \leq \lambda(\sigma_\infty - \tilde{\sigma})\varsigma(t) + \lambda\theta\varsigma(t-\tau). \tag{4.3}$$

Applying Theorem 3.1 of [9] in chapter one to (4.3), $\varsigma(t) \leq A^3 e^{Bt}$, where $A = \sqrt[3]{1+\lambda\theta\sigma_h\tau}|\phi|$, $B = \lambda(\sigma_\infty - \tilde{\sigma} + \theta\sigma_h)$ and $|\phi| = \max_{-\tau\leq t\leq 0}\phi(t)$.

(3) By observing (4.1), we can obtain $\Big(R(t)\exp\{\frac{\lambda\tilde{\sigma}t}{3}\}\Big)' \leq 0$, which implies (4.4) hold

$$\Big(\frac{R_t(-\tau)}{R(t)}\Big)^3 \leq e^{\lambda\tilde{\sigma}\tau}, \tag{4.4}$$

then, $\theta\sigma_h\Big(\frac{R_t(-\tau)}{R(t)}\Big)^3 + (\sigma_\infty - \tilde{\sigma})$ is bounded. Since (4.1) hold, the estimate (3) holds.

(4) Integrating (3), we have $\phi_0\exp\{-\frac{\lambda\tilde{\sigma}t}{3}\} \leq R(t) \leq \phi_0\exp\{\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta e^{\lambda\tilde{\sigma}\tau}\sigma_h)}{3}\}$, $t > 0$.

Using Banach fixed point theorem and the extension theorem, similar to the proof of [5, 16], we get the existence and uniqueness of global solution. □

5. Asymptotic behavior

In this section, the asymptotic behavior of the solution of (1.1)–(1.5) will be proved. The steady-state solution of (1.1)–(1.5) satisfies the following problem

$$\Delta_r\sigma_s = \Gamma\sigma_s(r), \quad 0 < r < R_s, \tag{5.1}$$

$$\frac{\partial\sigma_s}{\partial r}(0,t) = 0, \quad \frac{\partial\sigma_s}{\partial r}(R_s) + \gamma(\sigma_s(R_s) - \sigma_\infty) = 0, \tag{5.2}$$

$$\int_0^{R_s}\lambda(\sigma_s(r) - \tilde{\sigma})r^2 dr - \int_0^{R_s}\lambda\theta(\sigma_s(r) - \sigma_h)r^2 dr = 0. \tag{5.3}$$

If $\sigma_h > \sigma_\infty > \tilde{\sigma}$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, (5.1)–(5.3) have a unique positive solution

$$(\sigma_s(r), R_s) = \Big(\frac{\gamma\sigma_\infty}{\gamma + m(\sqrt{\Gamma}R_s)}\frac{R_s\sinh(\sqrt{\Gamma}r)}{r\sinh(\sqrt{\Gamma}R_s)}, R_s\Big),$$

where R_s is determined by $h(\sqrt{\Gamma}R_s) = \frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty(\theta-1)}$. It is clear that $x_s = \sqrt{\Gamma}R_s$. In the sequence, we will prove that (σ_s, R_s) is asymptotically stable.

Lemma 5.1. *Let $(\sigma(r,t), R(t))$ be a solution of (1.1)–(1.5). When $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$ hold. Assuming for some $\epsilon > 0$, $-\tau \leq t \leq 0$, $\phi \in \Big(\epsilon, \frac{1}{\epsilon}\Big)$, c_0 (a positive constant) does not dependent on c and $\phi(t)$, then there exists*

$$\frac{1}{2}\min\Big\{R_s, \epsilon\exp\Big\{\frac{\lambda\tilde{\sigma}t}{3}\Big\}\Big\} < R(t) < 2\max\Big\{R_s, \frac{1}{\epsilon}\sqrt[3]{1+\lambda\theta\sigma_h\tau}\exp\Big\{\frac{\lambda(\sigma_\infty - \tilde{\sigma} + \theta\sigma_h\tau)}{3\epsilon}\Big\}\Big\}, \tag{5.4}$$

for any $t \geq 0$ and $0 < c \leq c_0$.

Proof. Using Theorem 4.1(2), $\varphi(t) \in \left(\epsilon, \frac{1}{\epsilon}\right)$ and $-\tau \leq t \leq 0$, we see that

$$\frac{\epsilon}{2}\exp\left\{\frac{\lambda\tilde{\sigma}t}{3}\right\} < R(t) < \frac{2}{\epsilon}\sqrt[3]{1+\lambda\theta\sigma_h\tau}\exp\left\{\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta\sigma_h)\tau}{3}\right\}, \tag{5.5}$$

and either

$$R(T) = 2\max\left\{R_s, \frac{1}{\epsilon}\sqrt[3]{1+\lambda\theta\sigma_h\tau}\exp\left\{\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta\sigma_h)\tau}{3}\right\}\right\},$$

or

$$R(T) = \frac{1}{2}\min\left\{R_s, \epsilon\exp\left\{\frac{\lambda\tilde{\sigma}t}{3}\right\}\right\}.$$

If $R(T) = 2\max\left\{R_s, \frac{1}{\epsilon}\sqrt[3]{1+\lambda\theta\sigma_h\tau}\exp\left\{\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta\sigma_h)\tau}{3}\right\}\right\}$, then

$$\dot{R}(T) \geq 0. \tag{5.6}$$

Obviously, by Theorem 4.2 (3), we obtain

$$\dot{R}(t) \leq L, \ \ 0 \leq t \leq T, \tag{5.7}$$

where L (a positive constant) does not dependent on T and c. Setting

$$v(r,t) = \frac{\gamma\sigma_\infty}{\gamma+m(\sqrt{\Gamma}R(t))}\frac{R(t)\sinh(\sqrt{\Gamma}r)}{r\sinh(\sqrt{\Gamma}R(t)},$$

we conclue

$$|\sigma_0(r)-v_0(r)| \leq M\Big(1-\frac{\phi(0)\sinh(\sqrt{\Gamma}r)}{r\sinh(\sqrt{\Gamma}\phi(0))}\Big), \ \ 0 \leq r \leq \varphi(0),$$

where $\sigma_0(r) = \sigma(r,0)$, $v_0(r) = v(r,0)$. By Lemma 2.4, we deduce

$$|\sigma(r,t)-v(r,t)| \leq \bar{C}(c'+e^{-\frac{\Gamma\tau}{c}}), \ \ 0 \leq r \leq R(t), \ \ 0 \leq t < T, \tag{5.8}$$

where $\bar{C} = CM\Big(1+\frac{\sqrt{\Gamma}}{\gamma}\Big)$, $c' = \frac{cL}{M}$, $0 < c \leq c_0$, $0 < M \leq M_0$. For $t > \tau$, we compute

$$\begin{aligned}\dot{R}(t) \leq &\frac{1}{R^2(t)}\Big[\int_0^{R(t)}\lambda(v(r,t)-\tilde{\sigma})r^2dr - \int_0^{R(t-\tau)}\lambda\theta(v(r,t-\tau)-\sigma_h)r^2dr\Big]\\ &+\frac{1}{3}\Big[\lambda\bar{C}\Big(c'+\exp\Big\{-\frac{\Gamma t}{c}\Big\}\Big)+\lambda\theta\bar{C}\Big(c'+\exp\Big\{\frac{\Gamma(\tau-t)}{c}\Big\}\Big)\Big]R(t)\\ &= R(t)F(R(t),R_t(-\tau)),\end{aligned}$$

where

$$F(x,y) = \frac{a_1}{\gamma}x\Big[\Big(h(\sqrt{\Gamma}x)-\frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big)+\theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty}-h(\sqrt{\Gamma}y)\Big)\Big(\frac{y}{x}\Big)^3+\Upsilon(t)\Big],$$

$$\Upsilon(t) = \frac{1}{3}\Big[\lambda\bar{C}\Big(c' + e^{-\frac{\Gamma t}{c}}\Big) + \lambda\theta\bar{C}\Big(c' + e^{-\frac{\Gamma(t-\tau)}{c}}\Big)\Big].$$

Letting $G(y) = \left(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(y)\right)y^3$ for $\tilde{\sigma} < \sigma_\infty < \sigma_h$, we obtain

$$\frac{\partial G(y)}{\partial y} = 3\Big[\frac{\sigma_h}{3\gamma\sigma_\infty} - h(y)\Big]y^2 - h'(y)y^3 > 0.$$

Obviously, $f(x, x) < 0$ for $x > w_s$, we see that if $R_s < R(T)$, then $F(R(T), R(T)) < 0$ for $0 < c \le c_0$ (c_0 is sufficiently small). Hence,

$$R(T)F(R(T), R(T)) \ge R(T)F(R(T), R_T(-\tau)) \ge \dot{R}(t), \quad \tau < T,$$

which is contradiction with (5.6).

If $R(T) = \frac{1}{2}\min\left\{\epsilon e^{-\frac{\lambda\tilde{\sigma}t}{3}}, R_s\right\}$, one can proof it in the same way and we omit here. □

Set

$$L(x, y) = \frac{a_1}{\gamma}\sqrt{\Gamma}\Big[\Big(h(\sqrt{\Gamma}x) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big) + \theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(\sqrt{\Gamma}y)\Big)\Big(\frac{x}{y}\Big)^3\Big],$$
$$g(x) = \Big(h(\sqrt{\Gamma}x) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big) + \theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(\sqrt{\Gamma}x)\Big).$$

Consider the initial value problems as follows

$$u_+'(t) = u_+(t)\{L(u_+(t), u_+(t-\tau)) + \bar{C}\alpha c'\}, \quad t > 0, \tag{5.9}$$
$$u_+(t) = \phi(t), \quad -\tau \le t \le 0, \tag{5.10}$$

and

$$u_-'(t) = u_-(t)\{L(u_-(t), u_-(t-\tau)) + \bar{C}\alpha c'\}, \quad t > 0, \tag{5.11}$$
$$u_-(t) = \phi(t), \quad -\tau \le t \le 0, \tag{5.12}$$

where $c' = \frac{cL}{M}$ and a positive constant $\bar{C} = CM\Big(1 + \frac{\sqrt{\Gamma}}{\gamma}\Big)$ is independent of α and c_0.

Lemma 5.2. *Assuming $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$ hold, $\phi(t)$ is a positive and continuous function in $-\tau \le t \le 0$. Setting $c' = \frac{cL}{M}$, there exists two positive constants c_0 and α_0 such that if $0 < c \le c_0$, $0 < \alpha \le \alpha_0$, then there exists two positive constants u_s^+ and u_s^- which are the unique solution of equations $L(x, x) + \bar{C}\alpha c' = 0$ and $L(x, x) - \bar{C}\alpha c' = 0$, respectively. Moreover, $\lim_{t\to\infty} u_\pm(t) = u_s^\pm$.*

Proof. Due to $g'(x) = (1-\theta)\sqrt{\Gamma}h'(\sqrt{\Gamma}x) < 0$ and Lemma 2.1, one can get that

$$\lim_{x\to 0^+} g(x) = \frac{1}{3\gamma} - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty} + \theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - \frac{1}{3\gamma}\Big) > 0,$$
$$\lim_{x\to\infty} g(x) = -\frac{\tilde{\sigma}}{3\gamma\sigma_\infty} + \frac{\theta\sigma_h}{3\gamma\sigma_\infty} = \frac{\theta\sigma_h - \tilde{\sigma}}{3\gamma\sigma_\infty} < 0.$$

Therefore, there exists positive constants α_0 and c_0 such that $g(x, x) \pm \bar{C}\alpha c' = 0$ has unique solution $u_s^\pm$, respectively, where $0 < \alpha \le \alpha_0$, $0 < c \le c_0$.

By a simple computation,

$$\frac{\partial L}{\partial y} = 3\lambda\sigma_\infty\theta x^{-3}y^2\Big[\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(\sqrt{\Gamma}y)\Big) - \frac{1}{3}\sqrt{\Gamma}yh'(\sqrt{\Gamma}y)\Big],$$

similarly with the proof of Theorem 3.3, we obtain $\frac{\partial L}{\partial y} > 0$. Thus, for $0 < \alpha \le \alpha_0$ and $0 < c \le c_0$, $L(x, x) \pm \bar{C}\alpha c' = 0$ has a unique solution $u_s^\pm$, respectively. Since $g'(x) < 0$, $f(x, x) = x[\lambda\sqrt{\Gamma}\sigma_\infty g(x) + \bar{C}\alpha c']$ and $f(u_s^\pm, u_s^\pm) = 0$, when $x \ne u_s^\pm$, we have $(x - u_s^\pm)f(x, x) < 0$. Using Lemma 2.2, we see that $u_\pm(t)$ will tends to $u_s^\pm$ as $t \to \infty$. □

Lemma 5.3. *$(\sigma(r, t), R(t))$ is a solution of (1.1)–(1.5), assuming*

$$K_1 \le R(t) \le K_2, \quad t > -\tau, \tag{5.13}$$

where K_1, K_2 independent on c and α are constants. If $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$ hold, there exists constants c_0, ν, T_0 and C independent of c, α such that if $|\dot{R}(t)| \le \alpha$ in $0 \le r \le R(t)$, $t \ge 0$ and

$$|R(t) - R_s| \le \alpha, \quad |\sigma(r, t) - \sigma_s| \le \alpha, \tag{5.14}$$

for $-\tau \le t$, $0 \le r \le R(t)$, then for $T_0 + \tau < t$,

$$|R(t) - R_s| \le \bar{C}\alpha(c' + e^{-\nu t}), \quad |\sigma(r, t) - \sigma_s| \le \bar{C}\alpha(c' + e^{-\nu t}). \tag{5.15}$$

Proof. Denote

$$\frac{\lambda}{R^2(t)}\Big[\int_0^{R(t)}(v(r, t) - \tilde{\sigma})r^2dr - \int_0^{R(t-\tau)}\theta(v(r, t-\tau) - \sigma_h)r^2dr\Big] = R(t)L(R(t), R_t(-\tau)), \tag{5.16}$$

where

$$v(r, t) = \frac{\gamma\sigma_\infty}{\gamma + m(\sqrt{\Gamma}R(t))}\frac{R(t)\sinh(\sqrt{\Gamma}r)}{r\sinh(\sqrt{\Gamma}R(t))},$$
$$L(x, y) = \frac{a_1\sqrt{\Gamma}}{\gamma}\Big[\Big(h(\sqrt{\Gamma}x) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty}\Big) + \theta\Big(\frac{\sigma_h}{3\gamma\sigma_\infty} - h(\sqrt{\Gamma}y)\Big)\Big(\frac{x}{y}\Big)^3\Big],$$

we obtain

$$\begin{aligned}&|\dot{R}(t) - R(t)L(R(t), R_t(-\tau))|\\ &= \Big|\frac{1}{R^2(t)}\Big[\int_0^{R(t)}\lambda(\sigma(r, t) - v(r, t))r^2dr - \int_0^{R(t-\tau)}\lambda\theta(\sigma(r, t-\tau) - v(r, t-\tau))r^2dr\Big]\Big|\\ &\le \frac{1}{3}R(t)\Big[\lambda\bar{C}\alpha(c' + e^{-\frac{\Gamma t}{c}}) + \lambda\theta\bar{C}\alpha(c' + e^{-\frac{\Gamma(t-\tau)}{c}})\Big(\frac{R_t(-\tau)}{R(t)}\Big)^3\Big].\end{aligned}$$

If $t \ge 2\tau$, we see that $e^{-\frac{\Gamma(t-\tau)}{c}} \le e^{-\frac{\Gamma t}{c}} \le \frac{c}{\Gamma\tau}$. Moreover, we deduce

$$R(t)[L(R(t), R_t(-\tau)) - \bar{C}\alpha c'] \le \dot{R}(t) \le R(t)[L(R(t), R_t(-\tau)) + \bar{C}\alpha c'],$$

where $\bar{C}$ (a positive constant) does not dependent on c and α. Consider the initial value problem

$$u'_{\pm}(t) = u_{\pm}(t)[L(u_{\pm}(t), u_{\pm}(t-\tau)) \pm \bar{C}\alpha c'],\quad t > 2\tau,$$
$$u_{\pm}(t) = R(t),\quad \tau \le t \le 2\tau.$$

We see that $\lim\limits_{t\to\infty} u_{\pm}(t) = u_s^{\pm}$ from Lemma 5.2. Applying comparison principle, we get

$$u_{-}(t) \le R(t) \le u_{+}(t). \tag{5.17}$$

For $g'(x) < 0$, we have $|u_s^{\pm} - R_s| \le \bar{C}\alpha c'$.

Indeed, $u_s^{\pm}$ and R_s are solutions of $\lambda\sigma_\infty\sqrt{\Gamma}g(x) = \mp\bar{C}\alpha c'$ and $\lambda\sigma_\infty\sqrt{\Gamma}g(x) = 0$, respectively, $K_1 \le R(t) \le K_2$, then we obtain $|u_s^{\pm} - R_s| \le \bar{C}\alpha c'$.

We linearize (5.9) at u_s^{+},

$$u'_{+}(t) = -au_{+}(t) + bu_{+}(t-\tau), \tag{5.18}$$

where

$$a = \frac{a_1\sqrt{\Gamma}}{\gamma}\Big[3\theta\Big(\frac{\sigma_h}{\gamma\sigma_\infty} - h(\sqrt{\Gamma}u_s^{+})\Big) - \sqrt{\Gamma}u_s^{+}h'(\sqrt{\Gamma}u_s^{+})\Big],$$
$$b = \frac{a_1\theta\sqrt{\Gamma}}{\gamma}\Big[3\Big(\frac{\sigma_h}{\gamma\sigma_\infty} - h(\sqrt{\Gamma}u_s^{+})\Big) - \sqrt{\Gamma}u_s^{+}h'(\sqrt{\Gamma}u_s^{+})\Big].$$

$z = -a + be^{-z\tau}$ is the characteristic equation of (5.18). In the same way, we can get the characteristic equation of linearized equation at u_s^{-} is $z = -A + Be^{-z\tau}$, where

$$A = \frac{a_1\sqrt{\Gamma}}{\gamma}\Big[3\theta\Big(\frac{\sigma_h}{\gamma\sigma_\infty} - h(\sqrt{\Gamma}u_s^{-})\Big) - \sqrt{\Gamma}u_s^{-}h'(\sqrt{\Gamma}u_s^{-})\Big],$$
$$B = \frac{a_1\theta\sqrt{\Gamma}}{\gamma}\Big[3\Big(\frac{\sigma_h}{\gamma\sigma_\infty} - h(\sqrt{\Gamma}u_s^{-})\Big) - \sqrt{\Gamma}u_s^{-}h'(\sqrt{\Gamma}u_s^{-})\Big].$$

Due to $\theta < \frac{\tilde{\sigma}}{\sigma_h} < 1$, we see that $0 < b < a$, $0 < B < A$, which implies their real part of the complex roots are negative. Therefore, there exists positive constants K, ν_1 and $2\tau \le T_1$ such that

$$|u^{\pm}(t) - u_s^{\pm}| \le Ke^{-\nu_1 t}|\phi(t) - u_s^{\pm}|,\quad T_1 \le t,$$

where $|\phi(t) - u_s^{\pm}| = \max_{-\tau\le t\le 0}|\phi(t) - R_s^{\pm}|$. Since $|u_s^{\pm} - R_s| \le \bar{C}\alpha c'$ for $t \ge T_0$, we have

$$\begin{aligned}|R(t) - R_s| &\le \max|u_{\pm}(t) - R_s|\\ &\le \max[|u_s^{\pm} - R_s| + |u_{\pm}(t) - u_s^{\pm}|]\\ &\le \max[Ke^{-\nu_1 t}(|R_s - u_s^{\pm}| + |\phi(t) - R_s|)] + \bar{C}\alpha c'\\ &\le \bar{C}\alpha(c' + e^{-\nu_1 t}).\end{aligned}$$

Note that $K_1 \le R(t) \le K_2$ and $\sigma_s(r) = v_s(r)$, thus

$$|v(r,t) - \sigma_s(r)| = |v(r,t) - v_s(r)| \le \bar{C}|R(t) - R_s| \le \bar{C}\alpha,\quad 0 \le r \le R(t),\quad t \ge 0.$$

It is clearly that

$$|\sigma(r,t)-v(r,t)|\le|\sigma(r,t)-\sigma_s(r)|+|v(r,t)-\sigma_s(r)|\le\bar{C}\alpha,\ \ 0\le r\le R(t),\ \ t\ge 0.$$

Specially, $|\sigma(r,0)-v(r,0)|\le\bar{C}\alpha$, $|\dot{R}(t)|\le\alpha$, applying Lemma 2.4, then

$$|\sigma(r,t)-v(r,t)|\le\bar{C}\alpha(c'+e^{-\frac{-\Gamma t}{c}})\le\bar{C}\alpha(c'+e^{\frac{-\Gamma\tau}{c_0}}),\ \ 0\le r\le R(t),\ \ t\ge 0,\ \ 0<c\le c_0. \tag{5.19}$$

Let

$$f(t)=\frac{1}{R^3(t)}\Big[\int_0^{R(t)}\lambda(\sigma(r,t)-\tilde{\sigma})r^2dr-\int_0^{R(t-\tau)}\lambda\theta(\sigma(r,t-\tau)-\sigma_h)r^2dr\Big].$$

For $\tau\le T$, we have

$$|R(t)f(t)-R(t)L(R(t),R_t(-\tau))|\le\frac{1}{3}R(t)\Big[\lambda\bar{C}\alpha(c'+e^{-\frac{\Gamma t}{c}})+\lambda\theta\bar{C}\alpha(c'+e^{\frac{\Gamma(\tau-t)}{c}})\Big(\frac{R_t(-\tau)}{R(t)}\Big)^3\Big].$$

Hence,

$$|R(t)f(t)-R(t)L(R(t),R_t(-\tau))|\le\bar{C}\alpha(c'+e^{-\nu_2 t}),\ \ t\ge 2\tau, \tag{5.20}$$

where $\nu_2=\frac{\Gamma}{c_0}$. For $t\ge T_0+\tau$,

$$|L(R(t),R_t(-\tau))-L(R_s,R_s)|\le C(|R_t(-\tau)-R_s|+|R(t)-R_s|)\le\bar{C}\alpha(c'+e^{-\nu_1 t}).$$

Combining $\dot{R}(t)=R(t)f(t)$, (5.20) and $K_1\le R(t)\le K_2$, we see that $|\dot{R}(t)|\le\bar{C}\alpha(c'+e^{-\nu_1 t})$. Taking $\nu=\min\{\nu_1,\nu_2\}$, the proof is completed. □

Theorem 5.4. *Suppose that $(\sigma(r,t),R(t))$ is a solution of problem (1.1)–(1.5).*
(1) If $\tilde{\sigma}<\sigma_\infty<\sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_\infty}>\theta$, then

$$\lim_{t\to\infty}\dot{R}(t)=0,\ \ \lim_{t\to\infty}|R(t)-R_s|=0,\ \ \lim_{t\to\infty}|\sigma(r,t)-\sigma_s|=0,\ \ T_0+\tau\le t,\ \ 0\le r\le R(t).$$

(2) If $\sigma_\infty<\sigma_h<\tilde{\sigma}$ and $\frac{\tilde{\sigma}}{\sigma_h}-\frac{\sigma_\infty}{\sigma_h}>\theta>1$, then

$$\lim_{t\to\infty}R(t)=0,\ \ \varphi(t)\ge 0,\quad -\tau\le t\le 0.$$

Proof. (1) Thanks to (5.4), we set

$$K_1=\frac{1}{2}\min\{R_s,\epsilon e^{-\frac{\lambda\tilde{\sigma}t}{3}}\},\ \ K_2=2\max\{R_s,\frac{1}{\epsilon}\sqrt[3]{1+\lambda\theta\sigma_h\tau e^{-\frac{\lambda(\sigma_\infty-\tilde{\sigma}+\theta\sigma_h)\tau}{3}}}\},$$

then (5.5) holds. $|R(t)-R_s|\le K_2+R_s=\alpha_1$, $(t\ge 0)$. Minimize the absolute values of (4.1) both sides of the inequality, we have $|\dot{R}(t)|\le\frac{\lambda\sigma_\infty K_2}{3K_1}=\alpha_2$. Since $|\sigma(r,t)-\sigma_s(r)|\le 2\sigma_\infty$, we let $\alpha=\alpha_0=\max\{\alpha_1,\alpha_2,2\sigma_\infty\}$ in Lemma 5.3. Take τ and ν in according to Lemma 5.3, while c_0 sufficiently small and T_0 sufficiently large, then

$$|R(t)-R_s|\le\bar{C}\alpha(c'+e^{-\nu t})\le 2Cc\alpha,\ \ t\ge T_0+\tau,$$

$$|\dot{R}(t)| \le \bar{C}\alpha(c' + e^{-\nu t}) \le 2Cc\alpha, \quad t \ge T_0 + \tau,$$
$$|\sigma(r,t) - \sigma_s(r)| \le \bar{C}\alpha(c' + e^{-\nu t}) \le 2Cc\alpha, \quad 0 \le r \le R(t), \quad t \ge T_0 + \tau.$$

Setting $e^{-\nu(T_0+\tau)} = c'$, repeating the process, and we get

$$|R(t) - R_s| \le \bar{C}(2Cc\alpha)^{n-1}\alpha(c' + e^{-\nu(t-(n-1)T_0)}) \le (2Cc)^n\alpha, \quad t \ge nT_0 + \tau.$$

Similarly, for $0 \le r \le R(t)$ and $t \ge nT_0 + \tau$, we have $|\dot{R}(t)| \le (2Cc)^n\alpha$, $|\sigma(r,t) - \sigma_s| \le (2Cc)^n\alpha$.

Finally, denote $\beta > 0$, which satisfies $2Cc = e^{-\beta T_0} < 1$ for $2Cc < 1$. If n is sufficiently large and satisfies $nT_0 + \tau \le t \le (n+1)T_0 + \tau$, then

$$|R(t) - R_s| \le (2Cc)^n\alpha = \alpha e^{-n\beta T_0} = \alpha e^{-\beta t}e^{-\beta(nT_0-t)} \le \alpha e^{\beta(T_0+\tau)}e^{-\beta t} = Ce^{-\beta t}.$$

Repeating the process, the proof of (1) is completed.

(2) Let

$$\begin{aligned} \dot{\xi}(t) = f(\xi(t), \xi_t(-\tau)) = -\lambda(\tilde{\sigma} - \sigma_\infty)\xi(t) + \lambda\theta\sigma_h\xi_t(-\tau), \quad t > 0, \\ \xi(t) = \phi(t), \quad -\tau \le t \le 0, \end{aligned} \tag{5.21}$$

where $\xi_t(-\tau) = \xi(t-\tau)$. The characteristic equation of (5.21) is $z = -\lambda(\tilde{\sigma} - \sigma_\infty) + \lambda\theta\sigma_h e^{-\tau z}$, where $\lambda(\tilde{\sigma} - \sigma_\infty) > \lambda\theta\sigma_h > 0$. It is easy to see that

$$f(\xi(t), \xi(t)) \le \lambda(\sigma_\infty - \tilde{\sigma} + \frac{\tilde{\sigma} - \sigma_\infty}{\sigma_h}\sigma_h)\xi(t) < 0.$$

Applying Lemma 2.2, we have $\lim_{t\to\infty}\xi(t) = 0$. By (4.2), (4.3) and comparison principle, we obtain $\varsigma(t) \le \xi(t)$. Hence, $\lim_{t\to\infty} R(t) = 0$. The proof of Theorem 5.4 is completed. □

6. Numerical simulations

In this section, numerical simulation matching the theoretical results will be presented in Figures 1–3. In Figure 1, we take the parameter values as

$$c = 0, \quad a = 30, \quad \sigma_\infty = 10, \quad \sigma_h = 15, \quad \lambda = 1, \quad \Gamma = 1, \quad \gamma = 3, \quad \tilde{\sigma} = 6, \quad \theta = 0.3,$$

where are satisfied the conditions $\sigma_h > \sigma_\infty > \tilde{\sigma}$ and $\theta < \frac{\tilde{\sigma}}{\sigma_h}$ of Lemma 3.1. We see that there exists a unique root of $h(x) - \frac{\tilde{\sigma}}{3\gamma\sigma_\infty} + \frac{\theta\sigma_h}{3\gamma\sigma_\infty} - \theta h(x) = 0$, then Theorem 4.3 is verified.

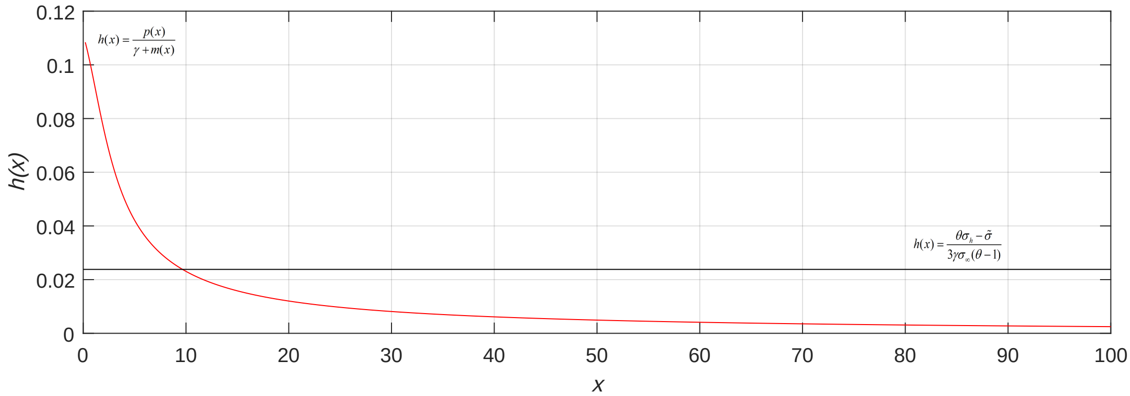

Figure 1. The stationary solution $x_s \approx 9.68$ to (3.10).

Figure 1 shows that the tumor radius is a fixed size in certain cases. In the sequence, Figures 2 and 3 show the asymptotic behavior of R with different values of the parameters.

For Figure 2, we take the parameter values as

$$c = 0, \;\; a = 30, \;\; \sigma_\infty = 10, \;\; \sigma_h = 15, \;\; \Gamma = 1, \;\; \gamma = 3,$$
$$\lambda = 1, \;\; \theta = 0.3, \;\; \tilde{\sigma} = 6, \;\; R_0^3 = 60, \; 1000, \; 2600, \;\; \tau = 3,$$

satisfy the condition of Theorem 3.3 (1), then the three lines represent the results obtained for the solution $w(t)$ of (3.8) under different initial values 2600, 1000 and 60, respectively. $w(t) = R^3(t)$ tends to the stationary solution $w_s \approx 906$ as $t \to \infty$. This indicates that the radius of the tumor gradually tends to a fixed value with the increase of time, and this state is consistent with the state described in Figure 1.

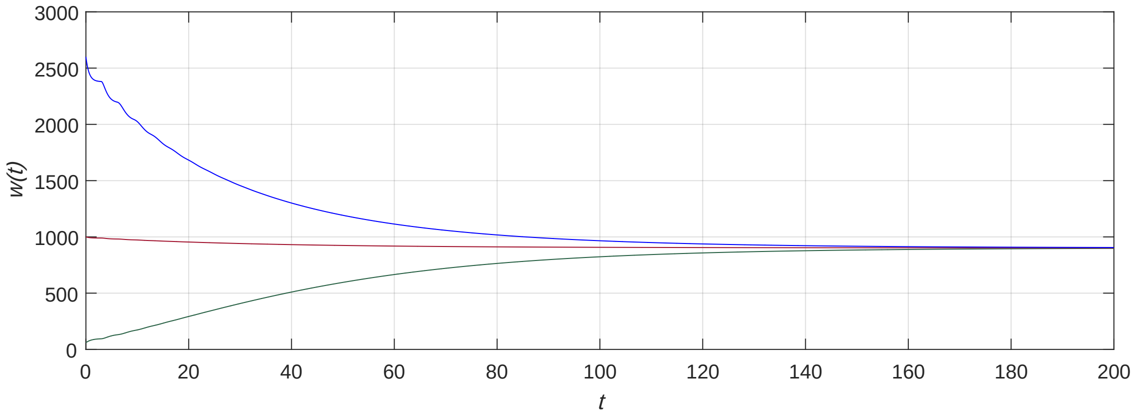

Figure 2. Asymptotic behavior of $w(t) = R^3(t)$ for $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$.

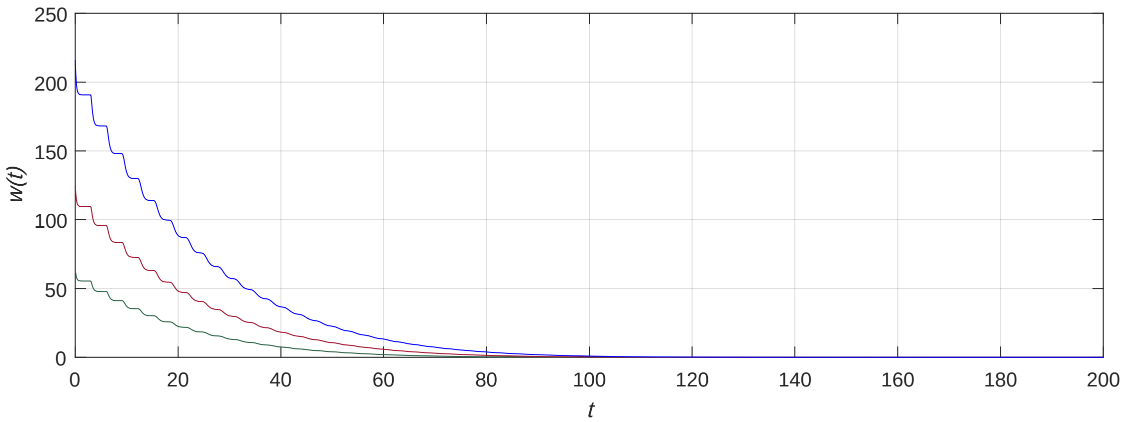

Figure 3. Asymptotic behavior of $w(t) = R^3(t)$ for $\sigma_\infty < \sigma_h < \tilde{\sigma}$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta > 1$.

For Figure 3, we take the parameter values as

$$c = 0, \;\; a = 30, \;\; \sigma_\infty = 10, \;\; \sigma_h = 15, \;\; \Gamma = 1, \;\; \gamma = 3,$$
$$\lambda = 1, \;\; \theta = 1.1, \;\; \tilde{\sigma} = 18, \;\; R_0^3 = 64, \; 125, \; 216, \;\; \tau = 3,$$

satisfy the condition of Theorem 3.3 (2), then the three lines represent the results obtained for the solution w(t) of (3.8) under different initial values 216, 125 and 64, respectively. $w(t) = R^3(t)$ tends to the stationary solution $w_s \approx 0$ as $t \to \infty$. In other words, the tumor in this condition will disappear with infinite time.

7. Conclusions

In this paper, we consider a Robin free boundary PDEs mathematical model in order to account for a vascularized tumor growth model with a time delay. We discussed the well-posedness of the stationary solution by rigorous analysis. The result shows that dynamical behavior of (1.1)–(1.5) is similar to corresponding quasi-stationary problem (see Theorems 3.3 and 5.4). For some parameter values, numerical simulations are also matching our results.

We assume that $\sigma(r, t)$ and $R(t)$ are radially symmetric, that in the development of solid tumor with a time delay in regulatory apoptosis, two situations may occur: it converges to a dormant state or disappears. On the one hand, if $\tilde{\sigma} < \sigma_\infty < \sigma_h$ and $\frac{\tilde{\sigma}}{\sigma_h} > \theta$, where the apoptosis rate $\tilde{\sigma}$ of cells and the degree of importance for regulating apoptosis rate is relatively small, then the tumor will converge to the unique steady state (dormant state, see Theorems 3.3 (1) and 5.4 (1)). On the other hand, the tumor will disappear (see Theorems 3.3 (2) and 5.4 (2)).

In our discussion, γ in (1.3) is taken as a constant. The case where γ is a bounded function or a periodic function is not studied. Interested readers and researchers can dig deeper into this in future works.

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Conflict of interest

Authors have no conflict of interest to declare.

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