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Research Article

Analysis of a Delayed Free Boundary Problem with Application to a Model for Tumor Growth of Angiogenesis

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In this paper, we consider a time-delayed free boundary problem with time dependent Robin boundary conditions. The special case where $n = 3$ is a mathematical model for the growth of a solid nonnecrotic tumor with angiogenesis. In the problem, both the angiogenesis and the time delay are taken into consideration. Tumor cell division takes a certain length of time, thus we assume that the proliferation process leg behind as compared to the process of apoptosis. The angiogenesis is reflected as the time dependent Robin boundary condition in the model. Global existence and uniqueness of the nonnegative solution of the problem is proved. When $c > 0$ is sufficiently small, the stability of the steady state solution is studied, where c is the ratio of the time scale of diffusion to the tumor doubling time scale. Under some conditions, the results show that the magnitude of the delay does not affect the final dynamic behavior of the solutions. An application of our results to a mathematical model for tumor growth of angiogenesis is given and some numerical simulations are also given.

1. Introduction

In the past a few decades, there are a lot of focus on mathematical models with regard to tumor growth for biological and mathematical interests. Many researchers developed various mathematical models from different aspects to detail the process of tumor growth (see, e.g., [1–8]). The tumor growth process can be classified into two different stages: the stage without a necrotic core (see, e.g., [2, 9–13]) and the stage with a necrotic core (see, e.g., [3, 14–16]). Almost all mathematical models are established by using reaction-diffusion dynamics and mass conservation law for the processes of proliferation and apoptosis.

This paper focus on a time-delayed free boundary problem with the time dependent Robin boundary condition. The model is as follows:

$$c\frac{\partial \sigma}{\partial t} = \Delta_r \sigma - f(\sigma), \quad 0 < r < R(t), \ \ t > 0, \tag{1}$$

$$\frac{\partial \sigma}{\partial r}(0,t) = 0, \quad t > 0, \tag{2}$$

$$\frac{\partial \sigma}{\partial r} + \beta(\sigma - \bar{\sigma}) = 0, \quad r = R(t), \ \ t > 0, \tag{3}$$

$$\begin{aligned} R^{n-1}(t)R'(t) = &\int_0^{R(t-\tau)} g(\sigma(r,t-\tau))r^{n-1}dr \\ &- \int_0^{R(t)} h(\sigma(r,t))r^{n-1}dr, \quad t > 0, \end{aligned} \tag{4}$$

$$\sigma_0(r,t) = \psi(r,t), \quad 0 < r < R(t), \ -\tau \le t \le 0, \tag{5}$$

$$R_0(t) = \varphi(t), \quad -\tau \le t \le 0, \tag{6}$$

where $\sigma(r,t)$ and $R(t)$ are two unknown functions. c is a positive constant. ψ and φ are given functions, and

$$\Delta_r = \frac{\partial^2 \sigma}{\partial r^2} + \frac{n-1}{r}\frac{\partial \sigma}{\partial r}. \tag{7}$$

The special case where $n = 3$ is a mathematical model describing the growth of a nonnecrotic tumor with angiogenesis. In particular, when $n = 3$, the biological meaning is as follows: σ is the nutrient concentration at time t and radius r. $R(t)$ represents the outer radius of tumor at time t. c represents the ratio between time scale of the diffusion and time scale of the tumor doubling, and τ is a constant represents the time delay in the process of proliferation, i.e., τ is the average time required from the beginning of cell division to the completion of division. In order to obtain nutrients, tumors attract blood vessels at a rate proportional to β, so that $(\partial\sigma/\partial r) + \beta(\sigma - \bar{\sigma}) = 0$ holds on the boundary, where $\bar{\sigma}$ is the nutrients concentration outside the tumor. It should be pointed out that the boundary condition (3) is a time dependent Robin boundary condition since the boundary changes with time. Equation (4) describes the changes of the volume of the tumor. Equations (3), (2), (5), and (6) are boundary and initial conditions. f, g, and h are given functions. $f(\sigma)$ represents the nutrient consumption rate. It is assumed that the rate of nutrient consumption by tumor cells is an increasing function of nutrient concentration. $g(\sigma)$ represents the proliferation rate of tumor cells and $h(\sigma)$ represents the apoptosis rate of tumor cells. It is reasonable to assume that the rate of tumor cell proliferation is an increasing function of nutrient concentration and the rate of tumor cell apoptosis is a nonincreasing function of nutrient concentration.

The motivation for studying this model is as follows: Experiments have shown that changes in the proliferation rate modify apoptotic cell loss which does not occur immediately–there exists a time delay for this modification (see [1]), i.e., the proliferation process lags behind as compared to the process of apoptosis. As a result of this research, many researchers have grown interest in the study of mathematical models for tumor growth with time delays (see, e.g., [6, 11, 17–19] and their references). The idea of considering the time delay in the process of proliferation is motivated by the work of Byrne [1], Cui and Xu [11], Foryś and Bodnar [18] and Xu et al. [20] where either linear or constant functions f, g, and h are considered in the above mentioned papers. The motivation of considering the nonlinear functions f, g, and h is from the work of Cui [10] (where $n = 3$ and $\tau = 0$, i.e., the time delay is not considered). In this paper, we study a more general case, which not only considers both time-delay and nonlinear functions f, h, and h, but also takes n as any positive integer greater than or equal to 3. The main aim of this paper is to study the time-delayed problem (1)–(6) for Robin boundary conditions and general nonlinear functions f, g, and h.

It also should be pointed out that only Dirichlet boundary conditions are considered in [1, 10–12, 20]. In the recent work of Friedman and Lam [21], the authors studied the special case of the problem (1)–(6) where $\tau = 0$, the functions f and g are linear and h is a constant (but where β is a given function of t). The special cases of the model have been extensively studied by many researchers, such as for linear functions

$$f(\sigma) = \lambda\sigma, \quad g(\sigma) = \mu\sigma, \tag{8}$$

and $h(\sigma) = \mu\tilde{\sigma}$, where λ, μ, and $\tilde{\sigma}$ are positive constants, Xu et al. [20] have studied the model with Gibbs–Thomson relation, which appears as the Dirichlet boundary condition. In [20], by rigorous mathematical derivation and using theories of functional differential equations, the authors studied the asymptotic behavior of steady state solutions.

Throughout this paper, we suppose that the functions f, g, and h satisfy the following conditions:

(P1) $f, g, h \in C^{\infty}[0,\infty)$;
(P2) $f'(\sigma) > 0$ for all $\sigma \geq 0$ and $f(0) = 0$;
(P3) $g'(\sigma) > 0$, $h'(\sigma) \leq 0$ for all $\sigma \geq 0$ and there exists $a^* > 0$ such that $g(a^*) = h(a^*)$;
(P4) $\bar{\sigma} > a^*$.

Moreover, we suppose the initial value functions φ and ψ satisfy the following conditions:

(A_1) $\varphi \in C[-\tau, 0], \varphi(t) > 0$ for $-\tau \leq t \leq 0$.
(A_2) $\psi \in C([0,\infty] \times [-\tau, 0]), 0 \leq \psi \leq \bar{\sigma}$ and $\psi(r,0) = \psi_0(r) \in C^3[0, R(0)]$.
(A_3) $\sigma'(0) = 0$ and $\sigma_0'(R_0) = \beta(\bar{\sigma} - \sigma(R_0))$.

The paper is arranged as follows: Section 2 provides proof for the existence and uniqueness of a global solution to problem (1)–(6). Section 3 is devoted to studing asymptotic behavior of the solutions to problem (1)–(6). In the final section, an application of our results to a mathematical model for tumor growth of angiogenesis is given and some numerical simulations are also given.

2. Global Existence and Uniqueness

Lemma 1. *Let $(\sigma(r,t), R(t))$ be a solution to the problem (1)–(6). The following priori estimates are valid.*

$$0 \leq \sigma \leq \bar{\sigma}, \quad 0 \leq r \leq R(t), \quad t \geq -\tau, \tag{9}$$

$$\frac{M_1}{n} \leq \frac{\dot{R}(t)}{R(t)} \leq \frac{M_2}{n}, \quad t \geq 0, \tag{10}$$

$$R_0 \exp\left(\frac{M_1 t}{n}\right) \leq R(t) \leq R_0 \exp\left(\frac{M_2 t}{n}\right), \quad t \geq 0, \tag{11}$$

where $M_1 = -h(0)/n$ and $M_2 = (|\varphi|/R(0))^n \exp(h(0)\tau) g(\bar{\sigma})$, where $|\varphi| = \max_{-\tau\leq t\leq 0}\varphi$.

Proof. Obviously, $\sigma^* = \bar{\sigma}$ and $\sigma_* = 0$ are upper and lower solutions to the problem (1)–(3), by the maximum principle, we immediately have $0 \leq \sigma \leq \bar{\sigma}, 0 \leq r \leq R(t), t \geq -\tau$.

From Eq. (4), we have

$$-\frac{h(0)}{n} R(t) \leq \frac{dR(t)}{dt} \leq g(\bar{\sigma}) \frac{R(t)}{n} \left(\frac{R(t-\tau)}{R(t)}\right)^n, \quad t > 0. \tag{12}$$

It follows that $R(t) \geq R(0)\exp(-h(0)t/n)$ and

$$\frac{R'}{R} \geq \frac{1}{n}M_1, \tag{13}$$

where $M_1 = -h(0)$. Moreover, from the the inequality on the left-hand side of (12), we can get

$$\left(R\exp\left(\frac{h(0)t}{n}\right)\right)' \geq 0. \tag{14}$$

It infer that when $t \geq \tau$,

$$\left(\frac{R(t-\tau)}{R(t)}\right)^n \leq \exp(h(0)\tau). \tag{15}$$

For $0 \leq t \leq \tau$, by the fact that $R(t) \geq R(0)\exp(-h(0)t/n) \geq R(0)\exp(-h(0)\tau/n)$, one can get

$$\left(\frac{R(t-\tau)}{R(t)}\right)^n \leq \left(\frac{|\varphi|}{R(0)}\right)^n \exp(h(0)\tau), \tag{16}$$

where $|\varphi| = \max_{-\tau\leq t\leq 0}\varphi$. Noticing the inequality on the right-hand side of (12) and $(|\varphi|/R(0))^n \geq 1$, we have

$$\frac{R'}{R} \leq \frac{g(\bar{\sigma})}{n}\left(\frac{R(t-\tau)}{R(t)}\right)^n \leq \frac{1}{n}M_2, \tag{17}$$

where $M_2 = g(\bar{\sigma})\exp(h(0)\tau)(|\varphi|/R(0))^n$. The inequality (11) follows from (10). This completes the proof. □

Theorem 1. *Suppose the conditions (P_1), (P_2), and (P_3) are satisfied. Suppose further that the functions φ and ψ satisfy the conditions (A_1)–(A_3). Then, there exists a unique solution $(\sigma(r,t), R(t))$ to (1)–(6) for all $t \geq -\tau$.*

Proof. By setting $r = sR(t)$, one can change $r \in [0, R(t)]$ to $s \in [0,1]$. Let

$$u(s,t) = \sigma(sR(t),t), \quad s \in [0,1],\ t \in [0,\infty). \tag{18}$$

Then

$$\begin{aligned} \sigma(r,t) &= u\left(\frac{r}{R(t)},t\right), \quad \sigma_r = \frac{u_s}{R(t)}, \\ \sigma_t &= u_t - u_s\frac{rR'(t)}{R^2(t)} = u_t - u_s\frac{sR'(t)}{R(t)}, \\ \sigma_{rr} &= \frac{u_{ss}}{R^2(t)}. \end{aligned} \tag{19}$$

Let $T > 0$ which will be given later. Consider the problem (1)–(6), by (19), it is equivalent to the following problem:

$$c\frac{\partial u}{\partial t} = \frac{1}{R^2(t)}\Delta_r u + \frac{cs\dot{R}}{R(t)}\frac{\partial u}{\partial s} - f(u), \quad 0 < s < 1,\ 0 < t \leq T, \tag{20}$$

$$\frac{\partial u}{\partial r}(0,t) = 0, \quad 0 < t \leq T, \tag{21}$$

$$\frac{\partial u}{\partial r} + \beta(u - \bar{\sigma}) = 0, \quad s = 1,\ 0 < t \leq T, \tag{22}$$

$$\begin{aligned} R'(t) = R(t)\Bigg[&\left(\frac{R(t-\tau)}{R(t)}\right)^n \int_0^1 g(u(s,t-\tau))s^{n-1}ds \\ &- \int_0^1 h(u(s,t))s^{n-1}ds\Bigg], \quad 0 < t \leq T, \end{aligned} \tag{23}$$

$$u(s,t) = \psi(sR(t),t), \quad 0 < s < 1,\ -\tau \leq t \leq 0. \tag{24}$$

$$R(t) = \varphi(t), \quad -\tau \leq t \leq 0. \tag{25}$$

We define the following metric space (M_T, d): The set M_T consists of vector functions $(\sigma(r,t), R(t))$ satisfying

(I) $R \in C^1[0,T] \cap C[-\tau,T]$, $R(t) = \varphi(t)$ for $-\tau \leq t \leq 0$, and

$$\begin{aligned} -\frac{1}{n}M_1 &\leq \frac{R'(t)}{R(t)} \leq \frac{1}{n}M_2, \\ \left(\frac{R(t-\tau)}{R(t)}\right)^n &\leq \left(\frac{|\varphi|}{R(0)}\right)^n \exp(h(0)\tau), \quad 0 < t \leq T, \end{aligned} \tag{26}$$

where $M_1 = -h(0)$ and $M_2 = g(\bar{\sigma})\exp(h(0)\tau)(|\varphi|/R(0))^n$.

(II) $u \in C([0,\infty) \times [-\tau,T])$, and

$$0 \leq u(s,t) \leq \bar{\sigma}, \quad 0 \leq r \leq R(t), \quad 0 < t \leq T, \tag{27}$$

$$u(s,t) = \psi(sR(t),t), \quad 0 \leq s \leq 1,\ -\tau \leq t \leq 0. \tag{28}$$

Define a metric d by

$$\begin{aligned} d((u_1,R_1),(u_2,R_2)) = &\max_{(s,t)\in[0,1]\times[0,T]} |u_1(r,t) - u_2(r,t)| \\ &+ \max_{t\in[0,T]} |R_1(t) - R_2(t)|. \end{aligned} \tag{29}$$

It is obvious that (M_T, d) is a complete metric space.

Next, create a mapping $F : (\sigma, R) \to (\hat{\sigma}, \hat{R})$ as follows. For any $(u,R) \in M_T$, consider the following initial value problem:

$$\begin{aligned} \tilde{R}'(t) = \tilde{R}(t)\Bigg[&\left(\frac{R(t-\tau)}{R(t)}\right)^n \int_0^1 g(u(s,t-\tau))s^{n-1}ds \\ &- \int_0^1 h(u(s,t))s^{n-1}ds\Bigg], \quad 0 < t \leq T, \end{aligned} \tag{30}$$

$$\tilde{R}(t) = \varphi(t), \quad -\tau \leq t \leq 0. \tag{31}$$

Then, one can get

$$\tilde{R}(t) = R(0)\exp\left(\int_0^1 G(\xi)d\xi\right), \quad 0 \leq t \leq T, \tag{32}$$

where

$$G(t) = \left(\frac{R(t-\tau)}{R(t)}\right)^n \int_0^1 g(u(s,t-\tau))s^{n-1}ds - \int_0^1 h(u(s,t))s^{n-1}ds. \tag{33}$$

By the facts that $0 \leq \sigma \leq \bar{\sigma}$, and $(R(t-\tau)/R(t))^n \leq (|\varphi|/R(0))^n \exp(h(0)\tau)$, one can get that

$$-\frac{1}{n}M_1 \leq G(t) \leq \frac{1}{n}M_2, \tag{34}$$

where we use the monotonicity of the functions f, g and h. It follows that

$$R_0\exp\left(\frac{M_1 t}{n}\right) \le \tilde{R}(t) \le R_0\exp\left(\frac{M_2 t}{n}\right), \quad 0 \le t \le T. \tag{35}$$

Thus, $\tilde{R}$ satisfies the condition (I). Taking similar arguments as that in [24], it is not hard to prove F is a contractive mapping for $T > 0$ is sufficiently small. By the Banach fixed point theorem, we have the local existence and uniqueness of a solution to the problem (1)–(6). To prove global existence and uniqueness, we only need to prove that it is impossible for the local solution to blow up or tend to zero in a finite time. This follows from the priori estimates (see Lemma 1). The proof of Theorem 1 is complete. □

3. Asymptotic Stability of Steady State

First, we study the existence of a unique steady state solution of (1)–(6). If $(\sigma_s(r), R_s)$ is a steady state solution to (1)–(6), it must satisfy the following equations:

$$\Delta_r \sigma_s(r) = f(\sigma_s(r)), \quad 0 < r < R_s, \tag{36}$$

$$\frac{\partial \sigma_s(r)}{\partial r} = 0, \quad r = 0, \tag{37}$$

$$\frac{\partial \sigma_s(r)}{\partial r} + \beta(\sigma_s(r) - \bar{\sigma}) = 0, \quad r = R_s, \tag{38}$$

$$\frac{1}{R_s^{n-1}}\left(\int_0^{R_s} g(\sigma_s(r))r^{n-1}dr - \int_0^{R_s} h(\sigma_s(r))r^{n-1}dr\right) = 0. \tag{39}$$

Consider the auxiliary boundary problem

$$U_{rr}(r,R) + \frac{n-1}{r}U_r(r,R) = f(U(r,R)), \quad 0 < r < R, \tag{40}$$

$$U_r(0,R) = 0, \quad U_r(R,R) = \beta(\bar{\sigma} - U(R,R)), \tag{41}$$

where $U_{rr}(r,R) = \partial^2 U/\partial r^2$ and $U_r(r,R) = \partial U/\partial r$.

Lemma 2 (see Lemma 2.1 [22]). *Suppose that the conditions (P1)–(P4) are satisfied. For any $R > 0$, the problem (40) and (41) has a unique solution $U(r,R)$ and the following assertions hold:*

(1) *For all $0 \le r \le R$ and $R > 0$, $0 < U(r,R) < \bar{\sigma}$, $0 < U_{rr}(r,R) \le f(\bar{\sigma})$. For all $0 < r \le R$ and $R > 0$, $0 < U_r(r,R) \le f(\bar{\sigma})r/n$.*

(2) *For all $0 < r \le R$ and $R > 0$, $-f(\bar{\sigma})(1/\beta + R/n) \le U_R(r,R) \le 0$, $U_{rR}(r,R) \le 0$, where $U_{rR}(r,R) = (\partial^2 U/\partial r \partial R)(r,R)$.*

(3) *For any fixed $\rho \in (0,1)$, the function $(d/dR)U(\rho R, R) < 0$ for $R > 0$.*

(4) *For all $\rho \in (0,1)$, $\lim_{R\to 0^+} U(\rho R, R) = \bar{\sigma}$, and $\lim_{R\to\infty} U(\rho R, R) = 0$.*

Lemma 3. *Assume the conditions (P1)–(P4) are satisfied. Let*

$$F(R) = \int_0^1 [g(U(\rho R, R)) - h(U(\rho R, R))]\rho^{n-1}d\rho. \tag{42}$$

Then

(1) *If $g(\bar{\sigma}) > h(\bar{\sigma})$, there exists a unique steady state solution $(\sigma_s(r), R_s)$ to problem (1)–(6), where R_s is a unique solution of $F(R) = 0$ and $\sigma_s(r) = U(r, R_s)$. Moreover, $F(x) > 0$ for $0 < x < R_s$; $F(x) < 0$ for $x > R_s$.*

(2) *If $g(\bar{\sigma}) < h(\bar{\sigma})$, the problem (1)–(6) has none steady state solution.*

Proof. For given $R_s > 0$, the function $\sigma_s(r) = U(r, R_s)$ satisfies the equations (36)–(38). Substituting it into (39) and letting $r = \rho R_s$, one can get

$$F(R_s) = \int_0^1 [g(U(\rho R_s, R_s)) - h(U(\rho R_s, R_s))]\rho^{n-1}d\rho = 0. \tag{43}$$

Therefore, the problem (36)–(39) has a solution $(\sigma_s(r), R_s)$ iff the function $F(R) = 0$ has a solution $R_s > 0$. Noticing the facts that

$$\lim_{R\to 0^+} F(R) = \int_0^1 [g(\bar{\sigma}) - h(\bar{\sigma})]\rho^{n-1}d\rho = \frac{1}{n}[g(\bar{\sigma}) - h(\bar{\sigma})], \tag{44}$$

$$\lim_{R\to\infty} F(R) = \int_0^1 [g(0) - h(0)]\rho^{n-1}d\rho = \frac{1}{n}[g(0) - h(0)], \tag{45}$$

and

$$F'(R) = \int_0^1 [g'(U(\rho R, R)) - h'(U(\rho R, R))] \cdot \frac{d}{dR}U(\rho R, R)\rho^{n-1}d\rho < 0, \tag{46}$$

it follows that

(1) If $g(\bar{\sigma}) > h(\bar{\sigma})$, by intermediate value theorem, it can be inferred that the function $F(R) = 0$ has a unique solution $R_s > 0$.

(2) If $g(\bar{\sigma}) < h(\bar{\sigma})$, then $F(R) < 0$ for all $R > 0$ since $F'(R) < 0$. Thus, the problem (1)–(6) has none steady state solution. This completes the proof. □

Lemma 4 (see Lemma 3.1 in [23]). *Suppose that (P1)–(P4) are satisfied. Let $(\sigma(r,t), R(t))$ be the solutions of the problem (1)–(6) and let*

$$v(r,t) = U(r, R(t)), \quad 0 \le r \le R(t), \ t \ge 0, \tag{47}$$

where $U(r, R(t))$ is the unique solution to the following problem:

$$U_{rr}(r,R(t)) + \frac{n-1}{r}U_r(r,R(t)) = f(U(r,R(t))), \quad 0 < r < R, \tag{48}$$

$$U_r(0,R(t)) = 0, U_r(R(t),R(t)) = \beta(\bar{\sigma} - U(R(t),R(t))), \tag{49}$$

where $U_{rr}(r,R) = \partial^2 U/\partial r^2$ *and* $U_r(r,R) = \partial U/\partial r$. *Suppose further that for some* $\varepsilon > 0$, $0 < \alpha \le \alpha_0$ *and* $0 < T \le \infty$,

$$\left|\dot{R}(t)\right| \le \alpha \le \alpha_0, \quad \varepsilon \le R(t) \le \frac{1}{\varepsilon}, \quad 0 \le t < T, \tag{50}$$

and $|\psi(r,0) - v(r,0)| \le M \le M_0$ *for* $0 < r \le R(0)$. *Then there exists a positive constant* c_0, κ *and* C *independent of* c, T, α, M, *and* R_0 *(but may dependent on* ε, α_0 *and* M_0*) such that*

$$|\sigma(r,t) - v(r,t)| \le C\alpha c + M\exp\left(-\frac{\kappa t}{c}\right) \tag{51}$$

for all $0 \le r \le R(t), t \ge 0$, *and* $0 < c \le c_0$.

Let

$$G(R(t),R(t-\tau)) = \left(\frac{R(t-\tau)}{R(t)}\right)^n \int_0^1 g(w(s,t-\tau))s^{n-1}ds - \int_0^1 h(w(s,t))s^{n-1}ds, \tag{52}$$

where $w(s,t) = v(sR(t),t) = U(r,R(t)) = U(sR(t),R(t))$, $0 \le s \le 1$, $0 \le s \le 1, t \ge 0$. Therefore, G could be rewritten in the following form:

$$G(R(t),R(t-\tau)) = \frac{1}{R^n(t)}\left[\int_0^{R(t-\tau)} g(v(r,t-\tau))r^{n-1}dr - \int_0^{R(t)} h(v(r,t))r^{n-1}dr\right]. \tag{53}$$

Lemma 5. *Suppose the conditions (P1)–(P4) are satisfied. Suppose further that* $\partial G(x,y)/\partial y > 0$ *for* $x, y > 0$. *Consider the following two initial value problems*

$$\begin{aligned}&\dot{R}^{\pm}(t) = R^{\pm}(t)\left[G(R^{\pm}(t),R^{\pm}(t-\tau)) \pm C\alpha c\right], \quad t > 0;\\ &R^{\pm}(t) = \varphi(t), \quad -\tau \le t \le 0.\end{aligned} \tag{54}$$

Then there exists a unique solution $R^{\pm}(t)$ *to problem (54) and the following assertions hold: If* $g(\bar{\sigma}) > h(\bar{\sigma})$, *there exists* $c_0, \alpha_0 > 0$ *such that if* $0 < c \le c_0$ *and* $0 < \alpha \le \alpha_0$, *the problem (54) has a unique steady state solution* $R_s^{\pm}$, *where* $R_s^{\pm}$ *is a unique solution of* $G(x,x) \pm C\alpha c = 0$. *Moreover, the steady state solution* $R_s^{\pm}$ *is globally asymptotic stable, i.e., for any nonnegative continuous initial value function* φ,

$$\lim_{t\to\infty} R^{\pm}(t) = R_s^{\pm}. \tag{55}$$

Proof. Let $\eta = R^n$, then (54) takes the form:

$$\dot{\eta}(t) = H_1(\eta(t-\tau)) - H_2(\eta(t)), \tag{56}$$

where

$$H_1(\eta(t-\tau)) = n\eta(t-\tau)\int_0^1 g\left(U\left(s\sqrt[n]{\eta(t-\tau)}, \sqrt[n]{\eta(t-\tau)}\right)\right)s^{n-1}ds \tag{57}$$

and

$$H_2(\eta(t)) = n\eta(t)\int_0^1 h\left(U\left(s\sqrt[n]{\eta(t)}, \sqrt[n]{\eta(t)}\right)\right)s^{n-1}ds \pm nC\alpha c\eta. \tag{58}$$

From Lemma 2, we know $U(sR,R)$ is continuously differentiable on R. Since $g, h \in C^\infty[0,\infty)$, one can get that H_1, H_2 are continuous. It is apparent that the initial value problem (54) has one unique solution $\eta(t)$ which exists on $[0,\infty)$, since we may rewrite this problem in the following form:

$$\eta(t) = \eta(0)e^{-\int_0^t (H_2(\eta(\xi))\pm C\alpha c)d\xi} + \int_0^t e^{-\int_s^t (H_2(\eta(\xi))\pm C\alpha c)d\xi} H_1(\eta(s-\tau))ds, \tag{59}$$

and solve it using the method of steps (see, e.g., [24]) on intervals $[n\tau,(n+1)\tau], n \in N$. Since $H_1(s) > 0$ for $s > 0$. Thanks to Lemma 1.1 in [25], we obtain that the nonnegativity of the solution to equation (54) for any nonnegative initial value φ.

The steady state solution of (54) satisfies the equation

$$G(x,x) \pm C\alpha c = F(x) \pm C\alpha c = 0. \tag{60}$$

By (P3), we know that $g(0) - h(0) < 0$, then we have

$$\lim_{R\to\infty} F(R) = \int_0^1 [g(0) - h(0)]\rho^{n-1}d\rho = \frac{1}{n}[g(0) - h(0)] < 0. \tag{61}$$

Noticing $F(x)$ is strictly monotone decreasing (see the proof of Lemma 3) and when $g(\bar{\sigma}) > h(\bar{\sigma})$,

$$\lim_{R\to 0^+} F(R) = \int_0^1 [g(\bar{\sigma}) - h(\bar{\sigma})]\rho^{n-1}d\rho = \frac{1}{n}[g(\bar{\sigma}) - h(\bar{\sigma})] > 0. \tag{62}$$

Therefore, one can get that there exists $c_0, \alpha_0 > 0$ such that if $0 < c \le c_0$ and $0 < \alpha \le \alpha_0$, the problem (54) has a unique steady state solution $R_s^{\pm}$, where $R_s^{\pm}$ is a unique solution of $G(x,x) \pm C\alpha c = 0$.

Since $\partial G(x,y)/\partial y > 0$ for $x, y > 0$, $G(x,x) = F(x) > 0$ for $0 < x < R_s^{\pm}$ and $G(x,x) = F(x) < 0$ for $x > R_s^{\pm}$. By Lemma 3.2 in [11], we can get (24) hold. This completes the proof. □

Lemma 6. *Suppose (P1)–(P4) are satisfied and* $\partial G(x,y)/\partial y > 0$ *for* $x, y > 0$. *Let* $\sigma(r,t), R(t)$ *be the solutions of the problem (1)–(6). If* $g(\bar{\sigma}) > h(\bar{\sigma})$ *and* $\varepsilon \le |\varphi| =: \max_{-\tau\le t\le 0}\varphi(t) \le 1/\varepsilon$ *for some* $\varepsilon > 0$, *there exists a constant* c_0 *depending on* ε *such that*

$$\frac{\varepsilon}{2}\exp\left(\frac{M_1\tau}{n}\right) < R(t) < \frac{2}{\varepsilon}\exp\left(\frac{M_2\tau}{n}\right) \tag{63}$$

for all $t \ge 0$ *and* $c \in (0, c_0]$, *where* M_1 *and* M_2 *are as before.*

Proof. By (11), we can get that

$$\frac{\varepsilon}{2}\exp\left(\frac{M_1\tau}{n}\right) < \varepsilon\exp\left(\frac{M_1\tau}{n}\right) \le R(t) \le \frac{1}{\varepsilon}\exp\left(\frac{M_2\tau}{n}\right) < \frac{2}{\varepsilon}\exp\left(\frac{M_2\tau}{n}\right) \tag{64}$$

for all $t \in [0,\tau]$. If (53) is not true for some $t > \tau$. Then there exists $T > \tau$ such that

$$\frac{\varepsilon}{2}\exp\left(\frac{M_1\tau}{n}\right) < R(t) < \frac{2}{\varepsilon}\exp\left(\frac{M_2\tau}{n}\right), \tag{65}$$

for $-\tau \le t < T$ and either $R(T) = (2/\varepsilon)\exp(M_2\tau/n)$ or $R(T) = (\varepsilon/2)\exp(M_1\tau/n)$.

If $R(T) = (2/\varepsilon)\exp(M_2\tau/n)$, then $\dot{R}(t) \ge 0$. By (10) in Lemma 1, we obtain

$$\left|\dot{R}(t)\right| \le \frac{1}{n\varepsilon}\left(\left|M_1\right| + M_2\right) =: \alpha_0, \quad 0 \le t < T. \tag{66}$$

Noticing $\left|\psi(r,0) - v(r,0)\right| \le \bar{\sigma} =: M_0$ for $r \in (0, R(0)]$, by Lemma 4, one can get that there exists positive constants c_0, κ and C independent of c, T, α, M and R_0 (but may dependent on ε, α_0 and M_0) such that

$$|\sigma(r,t) - v(r,t)| \le C\alpha c + M\exp\left(-\frac{\kappa t}{c}\right) \le C\alpha\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right) \tag{67}$$

for all $0 \le r \le R(t)$, $t \ge 0$, and $0 < c \le c_0$. Denote $L_g = \max_{0\le\sigma\le\bar{\sigma}} g'(\sigma)$ and $L_h = \max_{0\le\sigma\le\bar{\sigma}} g'(\sigma)$. By using the differential mean value theorem, we obtain

$$\left|g(\sigma(r,t)) - g(v(r,t))\right| \le L_g C\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right), \tag{68}$$

$$|h(\sigma(r,t)) - h(v(r,t))| \le L_h C\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right) \tag{69}$$

for $0 \le r \le R(t)$, $0 \le t \le T$ and $0 < c \le c_0$. Therefore,

$$\begin{aligned}
\dot{R}(t) = {} & \frac{1}{R^{n-1}(t)}\left(\int_0^{R(t-\tau)} g(\sigma(r,t-\tau))r^{n-1}dr - \int_0^{R(t)} h(\sigma(r,t))r^{n-1}dr\right) \\
\le {} & \frac{1}{R^{n-1}(t)}\left(\int_0^{R(t-\tau)} g(v(r,t-\tau))r^{n-1}dr - \int_0^{R(t)} h(v(r,t))r^{n-1}dr\right) \\
& + \frac{R(t)}{n}L_g C\left(c + \exp\left(-\frac{\kappa(t-\tau)}{c}\right)\right)\left(\frac{R(t-\tau)}{R(t)}\right)^n \\
& + \frac{1}{n}L_h C\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right)R(t) \\
= {} & R(t)G(R(t), R(t-\tau)) + \frac{CR(t)}{n} \\
& \cdot\left[L_g\left(c + \exp\left(-\frac{\kappa(t-\tau)}{c}\right)\right)\left(\frac{R(t-\tau)}{R(t)}\right)^n + L_h\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right)\right].
\end{aligned} \tag{70}$$

Then for $T > \tau$

$$\begin{aligned}
\dot{R}(T) \le {} & R(T)G(R(T), R(T-\tau)) \\
& + \tfrac{CR(T)}{n}\left[L_g\left(c + \exp\left(-\tfrac{\kappa(T-\tau)}{c}\right)\right)\left(\tfrac{R(T-\tau)}{R(T)}\right)^n + L_h\left(c + \exp\left(-\tfrac{\kappa T}{c}\right)\right)\right] \\
\le {} & R(T)G(R(T), R(T)) + \tfrac{CR(T)}{n}\left[L_g\left(c + \exp\left(-\tfrac{\kappa(T-\tau)}{c}\right)\right) + L_h\left(c + \exp\left(-\tfrac{\kappa T}{c}\right)\right)\right] \\
\le {} & R(T)G(R(T), R(T)) + \tfrac{CcR(T)}{n}\left[L_g\left(1 + \tfrac{1}{\kappa(T-\tau)e}\right) + L_h\left(1 + \tfrac{1}{e\kappa T}\right)\right],
\end{aligned} \tag{71}$$

where $\partial G(x,y)/\partial y > 0$ for $x, y > 0$ has been used. Choosing ε small such that $R(T) = (2/\varepsilon)\exp(M_2\tau/n) > R_s$, one can get $G(R(T), R(T)) < 0$. Then there exists $c_0 > 0$ (sufficiently small), for $0 < c < c_0$, there holds $\dot{R}(T) < 0$ which is a contraction to the fact that $\dot{R}(T) \ge 0$.

If $R(T) = (\varepsilon/2)\exp(M_1\tau/n)$, by similar analysis, one can also show the contradiction. This completes the proof. ☐

Remark 1. When $\tau = 0$, $G(R(t), R(t-\tau)) = G(R(t), R(t)) = F(R(t))$. Thus, if $\partial G(x,y)/\partial y > 0$ for $x, y > 0$, Lemma 6 above extends Lemma 3.2 in [23] from the case $\tau = 0$ to the case $\tau > 0$. The assumption that $\partial G(x,y)/\partial y > 0$ could be satisfied for some special cases. For example, in [21], when $\tau = 0$, $f(\sigma) = \sigma$, $g(\sigma) = \mu\sigma$ and $h(\sigma) = \mu\tilde{\sigma}$, where μ, $\tilde{\sigma}$ are two constants, the existence, uniqueness, and stability of steady state solutions are proved. For the above special case, in the last section, we will prove $\partial G(x,y)/\partial y > 0$ for $x, y > 0$ and apply our results to prove the existence, uniqueness and stability of steady state solutions when $\tau > 0$.

Lemma 7. *Assume that (P1)–(P4) are satisfied and $\partial G(x,y)/\partial y > 0$ for $x, y > 0$. Let $(\sigma(r,t), R(t))$ be the solutions of the problem (1)–(6). If $g(\bar{\sigma}) > h(\bar{\sigma})$, assume that there exists $\varepsilon > 0$ such that*

$$\varepsilon \le \varphi(t) \le \frac{1}{\varepsilon} \tag{72}$$

for $-\tau \le t \le 0$. Then there exists positive constants c_0, T_0, θ and C independent of c, R and φ, for any $c \in (0, c_0]$ and $\alpha \in (0, \alpha_0]$, where α_0 is a given constant, when

$$|R(t) - R_s| \le \alpha, \ |\sigma(r,t) - \sigma_s(r)| \le \alpha, \tag{73}$$

for $0 \le r \le R(t)$, $t \ge -\tau$ and $\left|\dot{R}(t)\right| \le \alpha$ for $0 \le r \le R(t)$, $t \ge 0$, the following estimates

$$\left|R(t) - R_s\right| \le C\alpha(c + \exp(\theta t)), \left|\sigma(r,t) - \sigma_s(r)\right| \le C\alpha(c + \exp(\theta t)), \quad \left|\dot{R}(t)\right| \le C\alpha(c + \exp(\theta t)), \tag{74}$$

hold for $t \ge T_0$ and $0 \le r \le R(t)$.

Proof. For the convenience of notation expression, in the following of the paper we use C to represents various constants independent of c and α. By Lemma 2 and (85), one can get

$$\left|v(r,t) - \sigma_s(r)\right| = \left|U(r, R(t)) - U(r, R_s)\right| \le C\left|R(t) - R_s\right| \le C\alpha, \tag{75}$$

for $0 \le r \le R(t), t \ge 0$. Then

$$|\sigma(r,t) - \nu(r,t)| \le |\sigma(r,t) - \sigma_s(r)| + |\nu(r,t) - \sigma_s(r)| \le C\alpha \tag{76}$$

for $0 \le r \le R(t), t \ge 0$. Specially,

$$|\psi(r,0) - \nu(r,0)| \le C\alpha, \quad 0 < r \le \varphi(0). \tag{77}$$

Noticing that $|\dot{R}(t)| \le \alpha$ for $t \ge 0$, by Lemma 4 we know that there exists positive constant c_0 and κ such that

$$|\sigma(r,t) - \nu(r,t)| \le C\alpha\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right) \tag{78}$$

for $0 \le r \le R(t), t \ge 0$ and $0 < c \le c_0$, where c_0 is independent of c and α.

Since

$$R(t)G(R(t), R(t-\tau)) = R(t)\left[\left(\frac{R(t-\tau)}{R(t)}\right)^n \int_0^1 g(u(s,t-\tau))s^{n-1}ds - \int_0^1 h(u(s,t))s^{n-1}ds\right] \tag{79}$$

by (78), we have

$$\begin{aligned}
&\left|\dot{R}(t) - R(t)G(R(t), R(t-\tau))\right| \\
&= \left|\frac{1}{R^{n-1}(t)}\left\{\int_0^{R(t-\tau)}[g(\sigma(r,t-\tau)) - g(\nu(r,t))]r^{n-1}dr - \int_0^{R(t)}[h(\sigma(r,t)) - h(\nu(r,t))]r^{n-1}dr\right\}\right| \\
&\le \frac{1}{n}R(t)\left[L_g C\alpha\left(c + \exp\left(-\frac{\kappa(t-\tau)}{c}\right)\right) + L_h C\alpha\left(c + \exp\left(-\frac{\kappa(t)}{c}\right)\right)\right] \\
&\le \frac{1}{n}R(t)\left[L_g C\alpha\left(c + \frac{c}{\kappa(t-\tau)}\right) + L_h C\alpha\left(c + \frac{c}{\kappa t}\right)\right] \\
&\le \frac{1}{n}R(t)\left[L_g C\alpha\left(c + \frac{c}{\kappa\tau}\right) + L_h C\alpha\left(c + \frac{c}{2\kappa\tau}\right)\right] \\
&\le C\alpha c R(t)
\end{aligned} \tag{80}$$

for $t \ge 2\tau$, where we have used the facts that $\exp(-x) < (xe)^{-1}$.

Consider the auxiliary initial value problem

$$\begin{aligned}
&\dot{R}^{\pm}(t) = R^{\pm}(t)[G(R^{\pm}(t), R^{\pm}(t-\tau)) \pm C\alpha c], t > 0; \\
&R^{\pm}(t) = \varphi(t), \quad -\tau \le t \le 0.
\end{aligned} \tag{81}$$

By Lemma 5, there exists unique solutions denoted by $R^{\pm}(t)$ to problem (81). Moreover, if $g(\bar{\sigma}) > h(\bar{\sigma})$, there exists $c_0, \alpha_0 > 0$ such that if $0 < c \le c_0$ and $0 < \alpha \le \alpha_0$, the problem (81) has unique steady state solutions $R_s^{\pm}$, where $R_s^{\pm}$ is a unique solution of $G(x,x) \pm C\alpha c = 0$. The steady state solutions $R_s^{\pm}$ are globally asymptotic stable, i.e.,

$$\lim_{t\to\infty} R^{\pm}(t) = R_s^{\pm} \tag{82}$$

for any nonnegative initial value function φ.

By the comparison principle (see Lemma 3.1 in [11]), we obtain that

$$R^{-}(t) \le R(t) \le R^{+}(t) \tag{83}$$

for all $t > -\tau$. Since $F(x)$ is decreasing, $F(R_s^{\pm}) \pm C\alpha c = 0$ and $F(R_s) = 0$, we can get

$$|R_s^{\pm} - R_s| \le C\alpha c. \tag{84}$$

For both stationary solutions $R_s^{\pm}$, using the linearization theorem, one can get that the characteristic equations are equal to

$$D^{\pm}(z) = -A + B\exp(-\tau z), \tag{85}$$

where

$$\begin{aligned}
A = &\, n\int_0^1 g(U(sR_s^{\pm}, R_s^{\pm}))s^{n-1}ds - R_s^{\pm}\int_0^1 g'(U(sR_s^{\pm}, R_s^{\pm})) \\
&- h'(U(sR_s^{\pm}, R_s^{\pm}))\frac{d}{dR}U(sR,R)|_{R=R_s^{\pm}}s^{n-1}ds
\end{aligned} \tag{86}$$

and

$$\begin{aligned}
B = &\, \frac{\partial G}{\partial y}(x,y)\Big|_{x=y=R_s^{\pm}} = n\int_0^1 g(U(sR_s^{\pm}, R_s^{\pm}))s^{n-1}ds \\
&+ R_s^{\pm}\int_0^1 g'(U(sR_s^{\pm}, R_s^{\pm}))\frac{d}{dR}U(sR,R)\Big|_{R=R_s^{\pm}}s^{n-1}ds.
\end{aligned} \tag{87}$$

Since $h'(x) \le 0, g'(x) > 0$ and $(d/dx)U(sx,x) < 0$ (see Lemma 2(3)) for $x > 0$, noticing that $\partial G(x,y)/\partial y > 0$ for $x, y > 0$, one can get that $A > B > 0$ which infers that all complex roots of Equation (85) have negative real parts. Then, there exists positive constant K, θ, and T_0 such that for any $t \ge T_0$

$$|R^{\pm}(t) - R_s^{\pm}| \le Ke^{-\theta t}|\varphi(t) - R_s^{\pm}|, \tag{88}$$

where $|\varphi(t) - R_s^{\pm}| = \max_{t\in[-\tau,0]}|\varphi(t) - R_s^{\pm}|$. It follows that

$$\begin{aligned}
|R(t) - R_s| &\le \max|R^{\pm}(t) - R_s| \\
&\le \max[|R^{\pm}(t) - R_s^{\pm}| + |R_s^{\pm} - R_s|] \\
&\le \max[Ke^{-\theta t}|\varphi(t) - R_s^{\pm}|] + C\alpha c \\
&\le [Ke^{-\theta t}(|\varphi(t) - R_s| + |R_s - R_s^{\pm}|)] + C\alpha c \\
&\le C\alpha(c + e^{-\theta t}).
\end{aligned} \tag{89}$$

By Lemma 2(2) and (72), using the differential mean value theorem, we obtain

$$|\nu(r,t) - \sigma_s(r)| = |\nu(r,t) - \nu_s(r)| \le C|R(t) - R_s| \le C\alpha \tag{90}$$

for $0 \le r \le R(t), t \ge 0$. Then

$$|\sigma(r,t) - \nu(r,t)| \le |\sigma(r,t) - \sigma_s(r)| + |\nu(r,t) - \sigma_s(r)| \le C\alpha \tag{91}$$

for $t \ge 0, 0 \le r \le R(t)$. Specially, $|\psi(r,0) - \nu(r,0)| \le C\alpha$ for $0 \le r \le \varphi(0)$. Noting $|R'(t)| \le \alpha$ for all $t \ge 0$, by Lemma 4, there exists a positive constant c_0 independent c and α such that

$$|\sigma(r,t) - \nu(r,t)| \le C\alpha\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right) \tag{92}$$

for arbitrary $t \ge 0, 0 \le r \le R(t)$ and $0 < c \le c_0$. Set

$$f(t) = \frac{1}{R^n(t)}\left[\int_0^{R(t-\tau)} g(\sigma(r,t-\tau))r^{n-1}dr - \int_0^{R(t)} h(\sigma(r,t))r^{n-1}dr\right]. \tag{93}$$

Then for $t \geq 2\tau$

$$\begin{aligned}
&\left|R(t)f(t) - R(t)G(R(t),R(t-\tau))\right| \\
&= \left|\frac{1}{R^{n-1}(t)}\int_0^{R(t-\tau)}[g(\sigma(r,t-\tau)) - g(v(r,t-\tau))]r^{n-1}dr \right.\\
&\quad \left. - \int_0^{R(t)}[h(\sigma(r,t)) - h(v(r,t))]r^{n-1}dr\right| \\
&\leq \frac{R(t)}{n}L_g C\alpha\left(c + \exp\left(-\frac{\kappa(t-\tau)}{c}\right)\right)\left(\frac{R(t-\tau)}{R(t)}\right)^n \\
&\quad + \frac{1}{n}L_h C\alpha\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right)R(t) \\
&= \frac{C\alpha R(t)}{n}\left[L_g\left(c + \exp\left(-\frac{\kappa(t-\tau)}{c}\right)\right)\left(\frac{R(t-\tau)}{R(t)}\right)^n \right.\\
&\quad \left. + L_h\left(c + \exp\left(-\frac{\kappa t}{c}\right)\right)\right] \\
&\leq \frac{C\alpha c R(t)}{n}\left[L_g\left(1 + \frac{1}{\kappa(t-\tau)e}\right) + L_h\left(1 + \frac{1}{e\kappa t}\right)\right] \\
&\leq C\alpha c.
\end{aligned} \tag{94}$$

By the differential mean value theorem and (72), we obtain that for $t \geq T_0 + \tau$

$$\begin{aligned}
&\left|G(R(t),R(t-\tau)) - G(R_s,R_s)\right| \\
&\leq C\left(\left|R(t) - R_s\right| + \left|R(t-\tau) - R_s\right|\right) \\
&\leq C\alpha\left(c + e^{-\theta t}\right).
\end{aligned} \tag{95}$$

Then by the equation $R'(t) = R(t)f(t)$ and the inequality (72), we have $|R'(t)| \leq C\alpha\left(c + e^{-\theta t}\right)$. By (93), we have

$$\left|\sigma(r,t) - \sigma_s(r)\right| \leq C\alpha\left(c + e^{-\theta t}\right). \tag{96}$$

This completes the proof of Lemma 7. □

Theorem 2. *Suppose that the conditions (P1)–(P4) are satisfied and $\partial G(x,y)/\partial y > 0$ for $x, y > 0$. Let $(\sigma(r,t), R(t))$ be the solution to the problem (1)–(6). If $g(\bar{\sigma}) > h(\bar{\sigma})$, then for any $\varepsilon > 0$, if $\varepsilon < |\varphi|$, $R_s < 1/\varepsilon$, there exist positive constants c_0, γ and C such that if $0 \leq c \leq c_0$, we have the following estimates:*

$$\left|R(t) - R_s\right| \leq Ce^{-\gamma t}, \left|R'(t)\right| \leq Ce^{-\gamma t}, \left|\sigma(r,t) - \sigma_s(r)\right| \leq Ce^{-\gamma t} \tag{97}$$

for all $t \geq T_0 + \tau$, $0 \leq r \leq R(t)$.

Proof. First, we prove that there exist positive constants c_0, γ and C such that if $0 < c \leq c_0$, (98) holds. Choosing ε sufficiently small such that $\varepsilon < |\varphi|$, $R_s < 1/\varepsilon$, by Lemma 6 we know there exists a positive constant c_0 such that.

$$\frac{\varepsilon}{2}\exp\left(\frac{M_1\tau}{n}\right) < R(t) < \frac{2}{\varepsilon}\exp\left(\frac{M_2\tau}{n}\right) \tag{98}$$

for all $t \geq 0$ and $0 < c \leq c_0$, where M_1 and M_2 are as before. Then

$$\left|R(t) - R_s\right| \leq \frac{2}{\varepsilon}\exp\left(\frac{M_2\tau}{n}\right) + R_s =: \alpha_1 \tag{99}$$

for all $t \geq 0$. By Lemma 1 and Equation (2.4), we obtain that for all $t \geq 0$,

$$\left|R'(t)\right| \leq \frac{2\left(\left|M_1\right| + M_2\right)}{n\varepsilon}\exp\left(\frac{M_2\tau}{n}\right) =: \alpha_2. \tag{100}$$

Obviously $|\sigma(r,t) - \sigma_s(r)| \leq 2\bar{\sigma}$ holds for all $0 \leq r \leq R(t), t \geq -\tau$. Therefore, the conditions of Lemma 7 are satisfied for $\alpha = \alpha_0 =: \max\{\alpha_1, \alpha_2, 2\bar{\sigma}\}$. Then by Lemma 7, one can get

$$\left|R(t) - R_s\right| \leq C\alpha\left(c + e^{-\theta t}\right) \leq 2Cc\alpha, \tag{101}$$

$$\left|R'(t)\right| \leq C\alpha\left(c + e^{-\theta t}\right) \leq 2Cc\alpha, \tag{102}$$

$$\left|\sigma(r,t) - \sigma_s(r)\right| \leq C\alpha\left(c + e^{-\theta t}\right) \leq 2Cc\alpha \tag{103}$$

hold for all $0 \leq r \leq R(t), t \geq T_0 + \tau$. For any given c satisfying $2Cc < 1$, we define T_0 by

$$e^{-\theta\left(T_0+\tau\right)} = c. \tag{104}$$

By induction, we obtain

$$\left|R(t) - R_s\right| \leq C\alpha(2Cc)^{n-1}\left(c + e^{-\theta\left(t-(n-1)T_0\right)}\right) \leq (2Cc)^n\alpha, \tag{105}$$

$$\left|R'(t)\right| \leq C\alpha(2Cc)^{n-1}\left(c + e^{-\theta\left(t-(n-1)T_0\right)}\right) \leq (2Cc)^n\alpha, \tag{106}$$

$$\left|\sigma(r,t) - \sigma_s(r)\right| \leq C\alpha(2Cc)^{n-1}\left(c + e^{-\theta\left(t-(n-1)T_0\right)}\right) \leq (2Cc)^n\alpha \tag{107}$$

hold for all $0 \leq r \leq R(t), t \geq nT_0 + \tau$.

Then, determine $\gamma > 0$ by using the following formula:

$$2Cc = e^{-\gamma T_0} < 1 \tag{108}$$

and for given $t > 0$, there exists an integer n satisfying $nT_0 + \tau \leq t \leq (n+1)T_0 + \tau$. It follows that

$$\begin{aligned}
\left|R(t) - R_s\right| &\leq \alpha(2Cc)^n\alpha = \alpha e^{-\gamma nT_0} = \alpha e^{-\gamma t}e^{-\gamma\left(nT_0 - t\right)} \\
&\leq \alpha e^{\gamma\left(T_0+\tau\right)}e^{-\gamma t} = Ce^{-\gamma t}.
\end{aligned} \tag{109}$$

By similar arguments, one can get $|R'(t)| \leq Ce^{-\gamma t}$, $|\sigma(r,t) - \sigma_s(r)| \leq Ce^{-\gamma t}$ for all $t \geq T_0 + \tau, 0 \leq r \leq R(t)$.

Next, we prove when $c = 0$, (109) is also valid. From (48) and (48), we know that

$$v(r,t) = U(r,R(t)), \quad 0 < r \leq R(t), \tag{110}$$

is the unique solution to (1)–(3). Substituting (110) into (4), we have

$$\frac{dR}{dt} = R(t)G(R(t),R(t-\tau)), \quad t > 0, \tag{111}$$

where $G(R(t),R(t-\tau))$ is defined in (52). Noting $G(x,x) = F(x)$, by Lemma 3, we have: If $g(\bar{\sigma}) > h(\bar{\sigma})$, there exists a unique steady state solution $\left(\sigma_s(r), R_s\right)$ to problem (1)–(6), where R_s is a unique solution of $G(x,x) = F(R) = 0$ and $\sigma_s(r) = U\left(r, R_s\right)$. Moreover, $G(x,x) = F(x) > 0$ for

$0 < x < R_s$; $G(x,x) = F(x) < 0$ for $x > R_s$. Since $G(x,y)$ is strictly monotone increasing in y, thanks to Lemma 3 [11], it follows that $\lim_{t\to\infty} R(t) = R_s$.

By using the linearization method, linearizing the equation (111) at the steady state solution R_s, one can get the characteristic equation of the linearized equation

$$L(z) = -A_1 + B_1 \exp(-\tau z), \tag{112}$$

where

$$\begin{aligned} A_1 = n\int_0^1 g(U(sR_s,R_s))s^{n-1}ds - R_s\int_0^1 \Big[g'(U(sR_s,R_s)) \\ - h'(U(sR_s,R_s))\Big] \frac{d}{dR}U(sR,R)\Big|_{R=R_s} s^{n-1}ds \end{aligned} \tag{113}$$

and

$$\begin{aligned} B_1 = \frac{\partial G}{\partial y}(x,y)\Big|_{x=y=R_s} = n\int_0^1 g(U(sR_s,R_s))s^{n-1}ds \\ + R_s\int_0^1 g'(U(sR_s,R_s)) \frac{d}{dR}U(sR,R)\Big|_{R=R_s} s^{n-1}ds. \end{aligned} \tag{114}$$

By the facts $g'(x) > 0, h'(x) \le 0$ and $(d/dx)U(sx,x) < 0$ (see Lemma 2(3)) for $x > 0$, noticing that $\partial G(x,y)/\partial y > 0$, one can get that $A_1 > B_1 > 0$ which infer that all complex roots of equation (112) have negative real parts. Therefore, there exits positive constant C, γ and T_0 such that such that for any $t \ge T_0$

$$|R(t) - R_s| \le Ce^{-\gamma t}. \tag{115}$$

From (115), one can get when T_0 is sufficiently large, $R_s/2 < R(t) > 3R_s/2$ for $t \ge T_0$. Notice that R is bounded, and when T_0 is sufficiently large, there is a positive lower bound of $R(t)$ for $t \ge T_0$, and notice that

$$R'(t) = R(t)|G(R(t), R(t-\tau)) - G(R_s,R_s)| \tag{116}$$

and

$$|\sigma(r,t) - \sigma_s(r)| = |U(r,R(t)) - U(r,R_s)|, \tag{117}$$

using the differential mean value theorem, one can get $|R'(t)| \le Ce^{-\gamma t}$, $|\sigma(r,t) - \sigma_s(r)| \le Ce^{-\gamma t}$ for all $t \ge T_0 + \tau$, $0 \le r \le R(t)$. The proof of Theorem 2 is complete. □

Theorem 3. *Suppose that the conditions (P1)–(P4) are satisfied and $\partial G(x,y)/\partial y > 0$ for $x, y > 0$. Let $(\sigma(r,t), R(t))$ be the solution to the problem (1)–(6). If $g(\bar\sigma) < h(\bar\sigma)$, then for any $c > 0$ and initial value function $\varphi(t) > 0, -\tau \le t \le 0$,*

$$\lim_{t\to\infty} R(t) = 0. \tag{118}$$

Proof. From Lemma 1(1) and Equation (4), we obtain

$$-\int_0^{R(t)} h(0)r^{n-1}dr \le R^{n-1}\frac{dR}{dt} \le \int_0^{R_\tau} g(\bar\sigma)r^{n-1}dr - \int_0^{R(t)} h(\bar\sigma)r^{n-1}dr, \tag{119}$$

where $R_\tau = R(t-\tau)$. It follows that

$$R(t) \ge \varphi(0)\exp\left(-\frac{h(0)}{n}t\right) \to 0, t \to \infty \tag{120}$$

and

$$R^{n-1}\frac{dR}{dt} \le g(\bar\sigma)\frac{R_\tau^n}{n} - h(\bar\sigma)\frac{R^n}{n}. \tag{121}$$

Let $x(t) = R^n(t)$, then (121) is reduced to the following equation:

$$\frac{dx}{dt} \le g(\bar\sigma)x(t-\tau) - h(\bar\sigma)x(t). \tag{122}$$

Consider the following auxiliary linear initial value problem

$$\frac{dX}{dt} = g(\bar\sigma)X(t-\tau) - h(\bar\sigma)X(t), X(t) = \varphi(t), \quad -\tau \le t \le 0, \tag{123}$$

Since $0 < g(\bar\sigma) < h(\bar\sigma)$, by a well known result of functional differential equations, one can get $\lim_{t\to\infty} X(t) = 0$. Let $G(x,y) = g(\bar\sigma)y - h(\bar\sigma)x$. Then G is strictly monotone increasing in y and $G(x,x) < 0$ for all $x > 0$. By using Lemma 2.1 [11], one can get $x(t) \le X(t)$. Then $\lim_{t\to\infty} x(t) = 0$ follows from (120) and $\lim_{t\to\infty} X(t) = 0$. On account of $x(t) = R^n(t) > 0$, we have $\lim_{t\to\infty} R(t) = 0$. This completes the proof. □

4. An Application

In this section, for the special case of the problem (1)–(6) where $n = 3$, $f(\sigma) = \sigma$, $g(\sigma) = \mu\sigma$ and $h(\sigma) = \mu\tilde\sigma$, we will apply our results to prove the existence, uniqueness and stability of steady state solutions when $\tau > 0$. In this section we assume $n = 3$, $f(\sigma) = \sigma$, $g(\sigma) = \mu\sigma$, $h(\sigma) = \mu\tilde\sigma$ and $\tau > 0$.

First, it is obvious that f, g, and h satisfy the conditions (P1) and (P2). Since $g'(\sigma) = \mu$, $h'(\sigma) = 0$ for $\sigma \ge 0$ and there exists $a^* = \tilde\sigma$ such that $g(a^*) = h(a^*) = \mu\tilde\sigma$, the functions f, g, and h satisfy the condition (P3). Therefore, by Theorem 2, if the initial value functions φ and ψ satisfy the conditions (A_1)–(A_3), then, problem (1)–(6) has a unique solution $(\sigma(r,t), R(t))$ for all $t \ge -\tau$.

For any $\beta > 0$ and $0 < \tilde\sigma < \bar\sigma$, by Theorem 3.1 in [21], we know that there exists a unique steady state solution denoted by $(\sigma_s(r), R_s)$ of (1)–(6) which is determined by

$$\sigma_s(r) = \frac{\beta\bar\sigma}{\beta + k(R_s)}\frac{\zeta(r)}{\zeta(R_s)} \tag{124}$$

and

$$\frac{\beta}{\beta + k(R_s)}p(R_s) = \frac{\eta}{3}, \tag{125}$$

where $\eta = \tilde\sigma/\bar\sigma$, $0 < r < R_s$, $k(x) = xp(x)$, $p(x) = (x\coth x - 1)/x^2$ and $\zeta(x) = \sinh x/x$.

The solution to problem (40) and (41) is

$$v(r,t) = U(r,R(t)) = \frac{\beta}{\beta + k(R(t))}\frac{\zeta(r)}{\zeta(R(t))}. \tag{126}$$

By (49) and a direct computation, one can get that

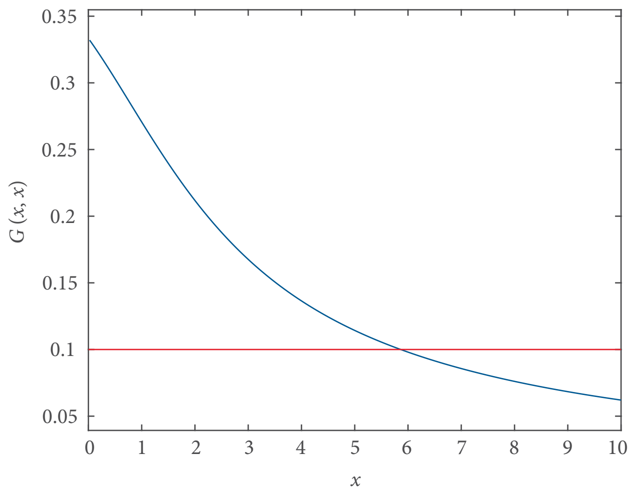

FIGURE 1: The curve of the function $f(x)$ for $\bar{\sigma} = 10, \mu = 1, \tilde{\sigma} = 3, \beta = 2$.

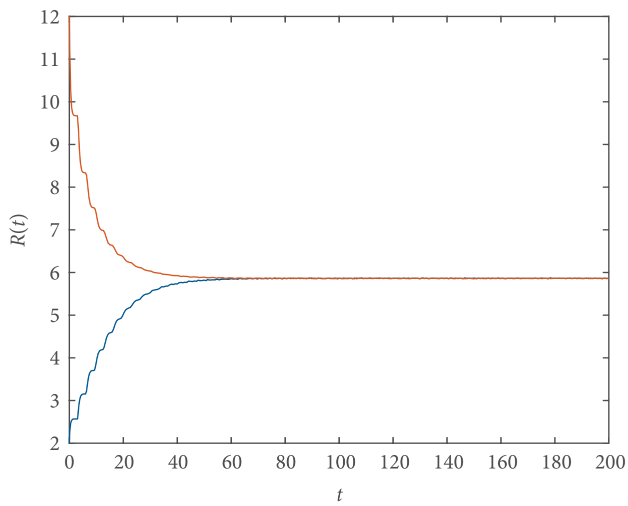

FIGURE 2: Asymptotic behavior of $R(t)$ for $c = 0, \bar{\sigma} = 10, \mu = 1, \tau = 3, \tilde{\sigma} = 3, \beta = 2, R_0 = 2, 12$.

$$G(R, R_\tau) = \frac{\mu\bar{\sigma}\beta}{\beta + k(R_\tau)} \frac{R_\tau^3 p(R_\tau)}{R^3} - \frac{\mu\tilde{\sigma}}{3}, \tag{127}$$

where $R_\tau = R(t - \tau)$. Thus,

$$G(x, y) = \frac{\mu\bar{\sigma}\beta}{\beta + k(y)} \frac{y^3 p(y)}{x^3} - \mu\tilde{\sigma}/3. \tag{128}$$

Next we prove $\partial G(x, y)/\partial y > 0$. From [11], we know $l'(y) = \left(y^3 p(y)\right)' > 0$ for $y > 0$. Therefore,

$$\begin{aligned} \frac{x^3}{\mu\bar{\sigma}} \frac{\partial G}{\partial y} &= \frac{l'(y)(\beta + k(y)) - k'(y)l(y)}{(\beta + k(y))^2} \\ &= \frac{\beta l'(y)}{(\beta + k(y))^2} + \left(\frac{l(y)}{k(y)}\right)' \frac{k^2(y)}{(\beta + k(y))^2} \\ &= \frac{\beta l'(y)}{(\beta + k(y))^2} + 2y \frac{k^2(y)}{(\beta + k(y))^2} > 0, \end{aligned} \tag{129}$$

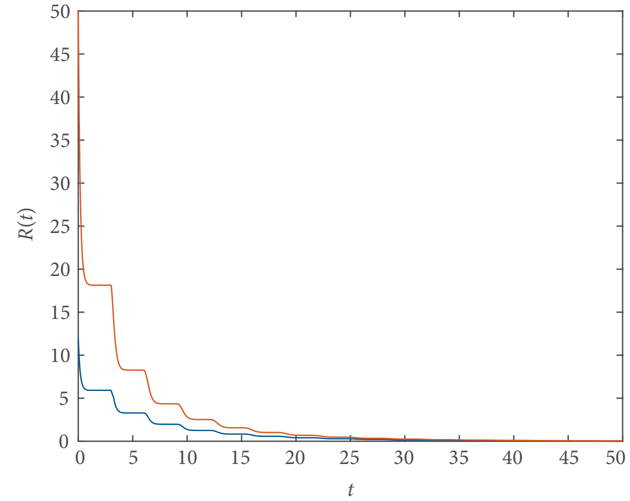

FIGURE 3: Asymptotic behavior of $R(t)$ for $c = 0, \bar{\sigma} = 5, \mu = 1, \tau = 3, \tilde{\sigma} = 6, \beta = 2, R_0 = 12, 50$.

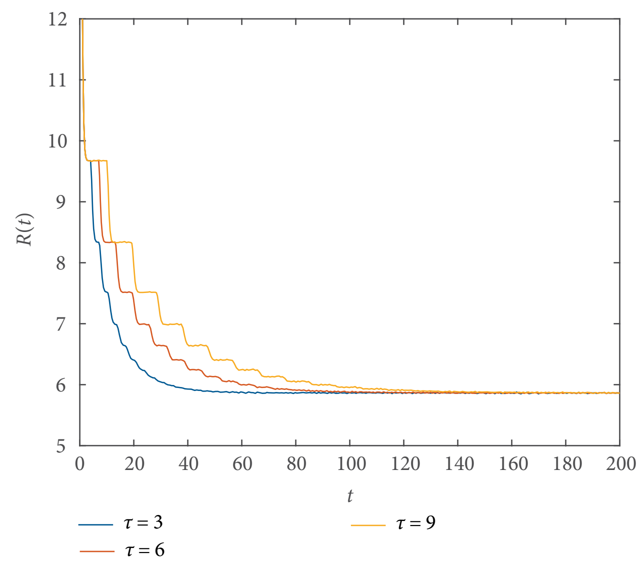

FIGURE 4: Asymptotic behavior of $R(t)$ for $c = 0, \bar{\sigma} = 10, \mu = 1, \tilde{\sigma} = 3, \beta = 2, R_0 = 12$ and $\tau = 3, 6, 9$ respectively.

where we used $k'(y) > 0$ for $y > 0$ (see Lemma 2.1 in [21]), it follows that $\partial G(x, y)/\partial y > 0$ for $x, y > 0$.

Since the condition (P4) $\bar{\sigma} > a^*$ and

$$\bar{\sigma} > a^* \Leftrightarrow 0 < \tilde{\sigma} < \bar{\sigma}, \tag{130}$$

then all conditions of Theorem 2 are satisfied. By Theorem 2, let $(\sigma(r, t), R(t))$ be the solution of the system (1)–(6). For any $\varepsilon > 0$ satisfying $\varepsilon < |\varphi|, R_s < 1/\varepsilon$, there exist corresponding positive constants c_0, γ and C such that if $0 \le c \le c_0$ such that

$$|R(t) - R_s| \le Ce^{-\gamma t}, \quad |R'(t)| \le Ce^{-\gamma t}, \quad |\sigma(r, t) - \sigma_s(r)| \le Ce^{-\gamma t} \tag{131}$$

for all $t \ge T_0 + \tau, 0 \le r \le R(t)$.

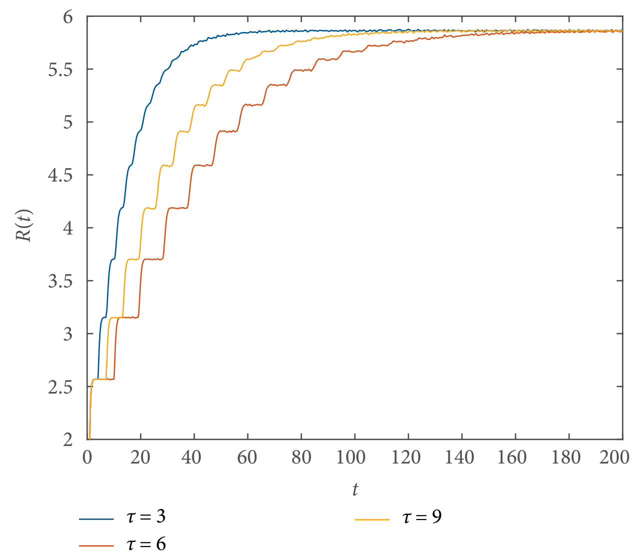

FIGURE 5: Asymptotic behavior of $R(t)$ for $c = 0, \bar{\sigma} = 10, \mu = 1, \tilde{\sigma} = 3, \beta = 2, R_0 = 2$ and $\tau = 3, 6, 9$ respectively.

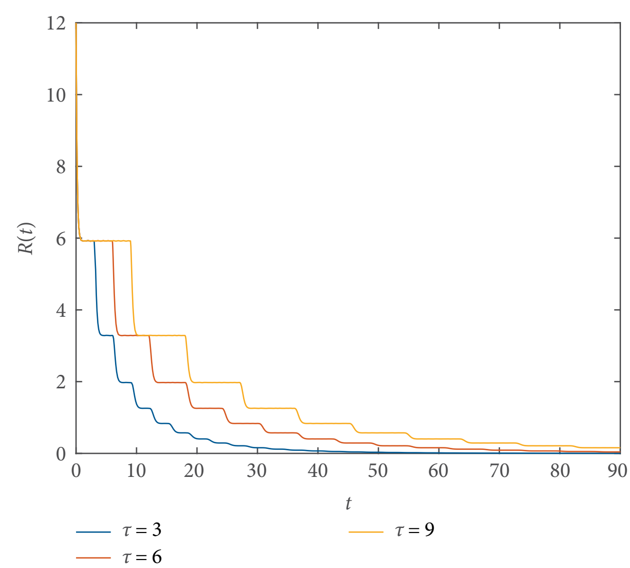

FIGURE 6: Asymptotic behavior of $R(t)$ for $c = 0, \bar{\sigma} = 5, \mu = 1, \tilde{\sigma} = 6, \beta = 2, R_0 = 12$ and $\tau = 3, 6, 9$ respectively.

Next, using Matlab R2016a, we will do some numerical simulation of the tumor growth model discussed above. First, we take the following parameter values:

$$c = 0, \quad \bar{\sigma} = 10, \quad \mu = 1, \quad \tau = 3, \quad \tilde{\sigma} = 3, \quad \beta = 2. \quad (132)$$

The steady state solution R_s is determined by (124). Let

$$f(x) = \frac{\beta}{\beta + k(x)} p(x), \quad (133)$$

where k and p are as before. In Figure 1, we plot the curve of f (the blue curve). As can be seen from Figure 1, noting the red curve is the curve of $\eta/3$, where $\eta = \tilde{\sigma}/\bar{\sigma}$, there is only one positive steady state solution, which can be solved by Matlab R2016a and $R_s \approx 5.86$. Figure 2 shows the dynamic change of tumor radius $R(t)$ with parameters taken as (126). From the above analysis, as well as notice

$$\bar{\sigma} = 10 > \tilde{\sigma} = 3 \Leftrightarrow g(\bar{\sigma}) = \mu\bar{\sigma} = 10 > h(\bar{\sigma}) = \mu\tilde{\sigma} = 3, \quad (134)$$

we know all conditions of Theorem 2 are satisfied. As can be seen from Figure 2, whether the initial value is taken $x_0 = 2$ or 12, all the solutions eventually tend to the unique steady state solution $R_s \approx 5.86$. This verifies the results of Theorem 2.

Next, if we take the parameter values as follows:

$$c = 0, \ \bar{\sigma} = 10, \ \mu = 1, \ \tau = 3, \ \tilde{\sigma} = 3, \ \beta = 2, \quad (135)$$

where

$$\bar{\sigma} = 5 < \tilde{\sigma} = 6 \Leftrightarrow g(\bar{\sigma}) = \mu\bar{\sigma} = 5 < h(\bar{\sigma}) = \mu\tilde{\sigma} = 6, \quad (136)$$

one can get all conditions of Theorem 3 satisfied. As can be seen from Figure 3, whether the initial value is taken $x_0 = 12$ or 50, all the solutions eventually tend to zero, which verifies the results of Theorem 3.

It can be seen from Theorems 2 and 3 that time delay does not affect the final tendency of tumor growth to the steady state or to disappear. In the following, by using the Figures 4–6, we show that the time delay has an effect on the speed of tumor growth towards to the steady state solution or toward extinction. In Figures 4–6, except for the size of time delay, the other parameters take the same value (please refer to captions of Figures 4–6). In Figures 4 and 6, the top curve of three curves corresponds to the larger τ where $\tau = 9$, the bottom curve of the three curves corresponds to a smaller τ where $\tau = 3$, the remaining curve corresponds $\tau = 6$. In Figure 5, the top curve of three curves corresponds to the smaller τ where $\tau = 3$, the bottom curve of the three curves corresponds to a larger τ where $\tau = 9$, the remaining curve corresponds $\tau = 6$. From Figures 4–6, we see that when other conditions remain unchanged, the larger the time delay, the slower the tumor tends to the steady state solution or tends to disappear.

Data Availability

No empirical data were used for this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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