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GLOBAL ASYMPTOTIC STABILITY OF POSITIVE STEADY STATES OF A SOLID AVASCULAR TUMOR GROWTH MODEL WITH TIME DELAYS

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ABSTRACT. In this work, global stability of a free boundary problem modeling solid avascular tumor growth is studied. The model is considered with time delays during the proliferation process. We prove that the unique positive constant steady state is globally asymptotically stable under some assumptions. The proof uses the comparison principle and the iteration method.

1. Introduction. Over the last 40 years, a variety of free boundary problems of partial differential equations have been proposed to model the growth of solid tumors, cf., **[1, 3]**–**[6, 11, 12, 17]**–**[23]**. Numerical simulations and asymptotic analysis of these tumor growth free-boundary problems have shown satisfactory coincidence with experimental observations. Rigorous mathematical analysis of these free boundary problems has drawn great interest, and many interesting results have been obtained cf., **[2, 7]**–**[10, 13, 14, 15, 24, 25, 26]**.

In the model studied in this paper we assume that the tumor is nonnecrotic and consider two unknown functions:

- $\sigma(r,t)$ – the nutrient concentration at radius r and time t;
- $R(t)$ – the outer tumor radius at time t.

As was done in **[13]**, it is also assumed here that the nutrient is simply consumed by tumor cells with the constant rate a. Then, the changes

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of σ are described by the following reaction-diffusion equation:

$$d\frac{\partial\sigma}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma}{\partial r}\right) - a, \quad 0 < r < R(t),\ t > 0, \tag{1.1}$$

where $d = T_{\text{diffusion}}/T_{\text{growth}}$ is a positive constant which represents the ratio of the nutrient diffusion time scale to the tumor growth (e.g., tumor doubling) time scale. From [**4, 9, 13, 16**], we know that

$$T_{\text{diffusion}} \approx 1 \text{ min} \quad \text{and} \quad T_{\text{growth}} \approx 1 \text{ day},$$

so that $d \ll 1$. The changes of R are governed by the mass conservation law, i.e.,

$$\frac{d}{dt}\left(\frac{4\pi R^3}{3}\right) = S - Q, \tag{1.2}$$

where Q and S denote the net rates of natural apoptosis and proliferation, respectively. It is reasonable to assume that the proliferation rate is proportional to the local nutrient concentration. Denoting the coefficient of proportionality by s, we have

$$S = 4\pi \int_0^{R(t-\tau)} s\sigma(r, t-\tau)r^2 dr, \tag{1.3}$$

where we denote by τ the time delay in cell proliferation, i.e., τ is the length of the period that a tumor cell undergoes a full process of mitosis. It is assumed that the apoptotic cell loss occurs with a constant rate sc, i.e.,

$$Q = 4\pi \int_0^{R(t)} scr^2 dr. \tag{1.4}$$

The boundary conditions are as follows.

$$\frac{\partial\sigma}{\partial r}(0, t) = 0, \quad \sigma(R(t), t) = \sigma_e, \quad 0 < r < R(t),\ t > 0, \tag{1.5}$$

where σ_e denotes the external concentration of nutrients, which is assumed to be a constant.

We will consider (1.1)–(1.2), together with the following initial condition,

$$\sigma(r,t) = \psi(r,t), \quad 0 \le r \le R(t), \quad -\tau \le t \le 0, \tag{1.6}$$

$$R(t) = \varphi(t), \quad -\tau \le t \le 0. \tag{1.7}$$

In [**13**], the limiting case where $d = 0$ has been studied. Rigorous analysis of the problem is given in the framework of delay differential equations. The final mathematical formulation for the problem is a delay differential equation. The authors [**13**] discussed the dynamical behavior of solutions to the model. In the limiting case where $d = 0$, equations (1.1) and (1.5) can be precisely solved and the exact expression of the evolution equation for R can be obtained. This is clearly not the case for the present model, and the method used in [**13**] cannot be used for the present model. Using the Banach fixed point theorem, a comparison method and some mathematical techniques, the existence and uniqueness of the global solution to the problem has been proved in [**26**]. In this paper, we mainly prove, under some assumptions, the global asymptotic stability of positive steady states in the case $c < \sigma_e < (5/3)c$. In what follows, we always assume that $s = 1$ for simplicity of notation, and, for any positive constant s, the arguments of problems (1.1)–(1.7) are similar.

2. Global asymptotic stability. The constant stationary solution $(R_s, \sigma_s(r))$ to (1.1)–(1.7) satisfies the following equations:

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial \sigma_s}{\partial r}) = a, \quad 0 < r < R_s, \tag{2.1}$$

$$\frac{\partial \sigma_s}{\partial r}(0) = 0, \qquad \sigma(R_s) = \sigma_e, \tag{2.2}$$

$$\int_0^{R_s} \sigma_s(r) r^2 dr - \int_0^{R_s} cr^2 dr = 0. \tag{2.3}$$

From (2.1) and (2.2), we can get

$$\sigma_s(r) = \sigma_e - \frac{a}{6}(R_s^2 - r^2). \tag{2.4}$$

Substituting (2.4) for (2.3) yields that there exists a unique positive constant solution

$$R_s = \sqrt{\frac{15(\sigma_e - c)}{a}} \tag{2.5}$$

to equation (2.3) if $c < \sigma_e < (5/3)c$. Therefore, if $c < \sigma_e < (5/3)c$, the problem (1.1)–(1.7) has a unique positive constant stationary solution

$$(R_s, \sigma_s(r)) = \left(\sqrt{\frac{15(\sigma_e - c)}{a}}, \sigma_e - \frac{a}{6}(R_s^2 - r^2)\right), \quad 0 \le r \le R_s.$$

The next theorem comprises some of the main results of this paper.

Theorem 2.1. *Let* $(\sigma(r,t), R(t))$ *be the solution of system* (1.1)–(1.7). *If* $c < \sigma_e < (5/3)c$, *assume that the initial value function* φ *satisfies* $\delta_1 \le \varphi(t) \le \delta_2$ *for all* $-\tau \le t \le 0$, *where* δ_1 *and* δ_2 *are positive constants and*

$$\delta_2 < \sqrt{\frac{6\sigma_e}{a}} \frac{1}{\sqrt[3]{1 + \sigma_e \tau}} e^{-b\tau/3}, \quad b = \sigma_e + c.$$

Then, there exist corresponding positive constants d_0, γ, T_0 *and* C *such that*

$$\begin{aligned} |R(t) - R_s| &\le Ce^{-\gamma t}, \\ |R'(t)| &\le Ce^{-\gamma t}, \\ |\sigma(r,t) - \sigma_s(r)| &\le Ce^{-\gamma t} \end{aligned}$$

for all $t \ge T_0 + \tau$, $0 \le r \le R(t)$ *and* $0 < d \le d_0$.

Let $(v(r,t), R(t))$ be the solution to the limiting case, i.e., $d = 0$, of (1.1)–(1.7). Then,

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial v}{\partial r}\right) = a, \quad 0 < r < R(t),\ t > 0, \tag{2.6}$$

$$\frac{\partial v}{\partial r}(0,t) = 0, \quad v(R(t),t) = \sigma_e,\ t > 0, \tag{2.7}$$

$$\frac{d}{dt}\frac{4\pi R^3(t)}{3} = 4\pi \int\limits_0^{R(t-\tau)} v(r,t-\tau)r^2 dr - 4\pi \int\limits_0^{R(t)} cr^2 dr, \quad t>0. \tag{2.8}$$

The solution to (2.6) and (2.7) is

$$v(r,t) = \sigma_e - \frac{a}{6}(R^2(t) - r^2). \tag{2.9}$$

Lemma 2.2. *Let* $(\sigma(r,t), R(t))$ *is the solution to* (1.1)–(1.7), *and let* $v(r,t)$ *be the solution to the limiting case* (*i.e.*, $d = 0$) *of* (1.1) *and* (1.5), *where*

$$v(r,t) = \sigma_e - \frac{a}{6}(R^2(t) - r^2).$$

Assume that, for some $0 < T \le \infty$ *and* $\varepsilon > 0$,

$$|R'(t)| \le L \le L_0, \qquad \varepsilon \le R(t) \le \frac{1}{\varepsilon}, \quad 0 \le t < T, \tag{2.10}$$

where L_0 *is a fixed constant. Then, there exist positive constants* d_0 *and* C, *independent of* d, T, L *and* R_0 *but dependent on* ε, L_0 *and* M_0, *such that*

$$|\sigma(r,t) - v(r,t)| \le CLd\left(\frac{1}{\varepsilon^2} - r^2\right). \tag{2.11}$$

for arbitrary $0 \le r \le R(t)$, $0 \le t < T$ *and* $0 < d \le d_0$.

Proof. By direct computation, we have

$$\frac{\partial v}{\partial t} = -\frac{a}{3}R(t)R'(t).$$

Hypothesis (2.10) implies that

$$\left|\frac{\partial v}{\partial t}\right| \le CL, \tag{2.12}$$

for $0 < r < R(t)$, $t \ge 0$, where C depends only upon a and ε. Let

$$\sigma_{\pm}(r,t) = v \pm \frac{CLd}{6\varepsilon^2} \mp \frac{CLdr^2}{6}.$$

Then, by using (2.12) we have

$$\begin{aligned} d\frac{\partial\sigma_+}{\partial t} - \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma_+}{\partial r}\right) + a = d\frac{\partial v}{\partial t} - \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial v}{\partial r}\right) + a \\ + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial(CLdr^2/6)}{\partial r}\right) \\ \geq -CLd + CLd = 0. \end{aligned}$$

From (2.7) and (2.10), we have

$$\frac{\partial\sigma_+}{\partial r}(0,t) = \frac{\partial v}{\partial r}(0,t) = 0 \quad \text{for } t > 0,$$

$$\sigma_+(R(t),t) = v(R(t),t) + \frac{CLd}{6\varepsilon^2} - \frac{CLdR^2}{6} \geq \sigma_e \quad \text{for } t > 0,$$

and

$$\sigma_+(r,0) = v(r,0) + \frac{CLd}{6\varepsilon^2} - \frac{CLdr^2}{6} \geq v(r,0) \quad \text{for } 0 \leq r \leq R(0).$$

Then, by the comparison principle, we obtain

$$\sigma_+(r,t) \geq \sigma(r,t) \quad \text{for } 0 \leq r \leq R(t),\ 0 \leq t < T.$$

Similar arguments prove that

$$\sigma_-(r,t) \leq \sigma(r,t) \quad \text{for } 0 \leq r \leq R(t),\ 0 \leq t < T.$$

It follows that

$$|\sigma - v| \leq |\sigma_+ - v| + |\sigma_- - v| \leq CLd\left(\frac{1}{\varepsilon^2} - r^2\right). \tag{2.13}$$

Hence, (2.11) holds. This completes the proof. □

Lemma 2.3 ([**26,** Theorem 3.3])**.** *Let $(\sigma(r,t), R(t))$ be the solution to* (1.1)–(1.7)*. Then, the following estimates hold*:

(i) $\sigma_e - ar^2/6 \leq \sigma(r,t) \leq \sigma_e$, $0 \leq r \leq R(t)$, $t \geq 0$;

(ii) $\varphi(0)e^{-ct/3} \leq R(t) \leq Ae^{bt/3}$, *for* $t \geq 0$, *where* $A = \sqrt[3]{1+\sigma_e\tau}|\varphi|$, $|\varphi| = \max_{-\tau\leq t\leq 0}\varphi(t)$, $b = \sigma_e + c$.

Lemma 2.4. *Let* $(\sigma(r,t), R(t))$ *be the solution to* (1.1)–(1.7). *Let*

$$\delta_1, \delta_2 \left(< \sqrt{\frac{6\sigma_e}{a}} \frac{1}{\sqrt[3]{1+\sigma_e\tau}} e^{-b\tau/3} \right)$$

be positive constants such that $\delta_1 \leq \varphi(t) \leq \delta_2$, *where* $b = \sigma_e + c$. *Assume that* $c < \sigma_e < (5/3)c$ *holds. Then, there exists a positive constant* d_0 *such that*

$$\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3}) < R(t) < \sqrt{\frac{6\sigma_e}{a}} \tag{2.14}$$

for arbitrary $t > 0$ *and* $0 < d < d_0$, *where* $R_s = \sqrt{15(\sigma_e - c)/a}$.

Proof. By Lemma 2.3 (ii) and the assumption $\delta_1 \leq \varphi(t) \leq \delta_2$ for $-\tau \leq t \leq 0$, we have

$$\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3}) < R(t) < \sqrt{\frac{6\sigma_e}{a}}, \quad 0 \leq t \leq \tau.$$

Assume that (2.14) is not valid for some t. It follows that there exists a $T > \tau$ such that, for $0 \leq t < T$,

$$\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3}) < R(t) < \sqrt{\frac{6\sigma_e}{a}},$$

and either $R(T) = \sqrt{6\sigma_e/a}$ or $R(T) = (1/2)\min(R_s, \varphi(0)e^{-c\tau/3})$.

If $R(T) = \sqrt{6\sigma_e/a}$, then

$$R'(T) \geq 0. \tag{2.15}$$

By equation (1.2) and the fact that, for $0 \leq t < T$,

$$\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3}) < R(t) < \sqrt{\frac{6\sigma_e}{a}},$$

we have $|R'(t)| \leq L_0$; L_0 is a positive constant independent of d and T. By Lemma 2.2, noting the facts $|R'(t)| \leq L_0$ and $R(t) < \sqrt{6\sigma_e/a}$, it follows that

$$|\sigma(r,t) - v(r,t)| \leq Cd\left(\frac{6\sigma_e}{a} - r^2\right) \tag{2.16}$$

for arbitrary $0 \le r \le R(t)$, $0 \le t < T$ and $0 < c \le c_0$. Then, we have, for $t > \tau$:

$$R'(t) = \frac{1}{R^2(t)}\left[\int_0^{R(t-\tau)} \sigma(r, t-\tau) r^2 dr - \int_0^{R(t)} cr^2 dr\right]$$

$$\le \frac{1}{R^2(t)}\left[\int_0^{R(t-\tau)} v(r, t-\tau) r^2 dr + \frac{2\sigma_e}{a} CdR^3(t-\tau)\right] - \frac{1}{3}cR(t)$$

$$= \frac{1}{R^2(t)}\left[\int_0^{R(t-\tau)} \left(\sigma_e - \frac{a}{6}(R^2(t-\tau) - r^2)\right) r^2 dr + \frac{2\sigma_e}{a} CdR^3(t-\tau)\right]$$
$$- \frac{1}{3}cR(t)$$
$$= \frac{1}{3R^2(t)}\left[\left(\sigma_e R(t-\tau) - \frac{a}{15}R^3(t-\tau)\right) R^2(t-\tau) + \frac{6\sigma_e}{a} CdR^3(t-\tau)\right]$$
$$- \frac{1}{3}cR(t).$$

Then, for d satisfying

$$0 < d < d_1 = \left(c - \frac{3}{5}\sigma_e\right)\frac{a}{6\sigma_e C},$$

noting that $R(T-\tau) < \sqrt{6\sigma_e/a}$, we can obtain

$$R'(T) \le \frac{1}{3}\left(-c + \sigma_e - \frac{6\sigma_e}{15} + \frac{6\sigma_e}{a} Cd\right)\sqrt{\frac{6\sigma_e}{a}} < 0,$$

for which we have used $c < \sigma_e < (5/3)c$ and the fact that the function

$$\left(\sigma_e x - \frac{a}{15}x^3\right)x^2 + \frac{6\sigma_e}{a} Cdx^3$$

is monotone increasing for

$$0 < d < d_1 = \left(c - \frac{3}{5}\sigma_e\right)\frac{a}{6\sigma_e C}$$

and $c < \sigma_e < (5/3)c$. Therefore, this contracts to the fact $R'(T) \ge 0$. Hence, the right hand side of inequality (2.14) is true.

Next, we prove the left hand side of inequality (2.14). If $R(T) = (1/2)\min(R_s, \varphi(0)e^{-c\tau/3})$, then

$$R'(T) \le 0. \tag{2.17}$$

From equation (1.2) and the fact that, for $0 \le t < T$,

$$\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3}) < R(t) < \sqrt{\frac{6\sigma_e}{a}},$$

we have $|R'(t)| \le L_0$; L_0 is a positive constant independent of d and T. By Lemma 2.2, noting the facts $|R'(t)| \le L_0$ and $R(t) < \sqrt{6\sigma_e/a}$, we obtain

$$|\sigma(r,t) - v(r,t)| \le Cd\left(\frac{6\sigma_e}{a} - r^2\right) \tag{2.18}$$

for arbitrary $0 \le r \le R(t)$, $0 \le t < T$ and $0 < c \le c_0$. Then, we have, for $t > \tau$,

$$\begin{aligned}
R'(t) &= \frac{1}{R^2(t)}\left[\int_0^{R(t-\tau)} \sigma(r, t-\tau)r^2dr - \int_0^{R(t)} cr^2dr\right] \\
&\ge \frac{1}{R^2(t)}\left[\int_0^{R(t-\tau)} v(r, t-\tau)r^2dr - \frac{2\sigma_e}{a}CdR^3(t-\tau)\right] - \frac{1}{3}cR(t) \\
&= \frac{1}{R^2(t)}\left[\int_0^{R(t-\tau)} \left(\sigma_e - \frac{a}{6}(R^2(t-\tau) - r^2)\right)r^2dr - \frac{2\sigma_e}{a}CdR^3(t-\tau)\right] \\
&\quad - \frac{1}{3}cR(t) \\
&= \frac{1}{3R^2(t)}\left[\left(\sigma_e R(t-\tau) - \frac{a}{15}R^3(t-\tau)\right)R^2(t-\tau) - \frac{6\sigma_e}{a}CdR^3(t-\tau)\right] \\
&\quad - \frac{1}{3}cR(t).
\end{aligned}$$

Then, for d satisfying

$$0 < d < d_2 = \frac{a(\sigma_e - c)}{12\sigma_e C},$$

$$R'(T) \geq \frac{1}{6}\bigg(-c + \sigma_e - \frac{a}{30}R_s^2 - \frac{6\sigma_e}{a}Cd\bigg)R_s > 0,$$

for which we have used $c < \sigma_e < (5/3)c$ and the fact that the function

$$\bigg(\sigma_e x - \frac{a}{15}x^3\bigg)x^2 + \frac{6\sigma_e}{a}Cdx^3$$

is monotone increasing for

$$0 < d < d_2 = \frac{a(\sigma_e - c)}{12\sigma_e C}$$

and $c < \sigma_e < (5/3)c$. Therefore, this contradicts to the fact $R'(T) \leq 0$. Hence, the left hand side of inequality (2.14) is true. Let $d_0 = \min(d_1, d_2)$. This completes the proof. $\square$

Lemma 2.5. *Let* $(\sigma(r,t), R(t))$ *be the solution to* (1.1)–(1.7)*. Assume that the initial value function* φ *satisfies* $\delta_1 \leq \varphi(t) \leq \delta_2$ *for all* $-\tau \leq t \leq 0$*, where* δ_1 *and* δ_2 *are positive constants and*

$$\delta_2 < \sqrt{\frac{6\sigma_e}{a}}\frac{1}{\sqrt[3]{1+\sigma_e\tau}}\,e^{-b\tau/3}, \quad b = \sigma_e + c.$$

If $c < \sigma_e < (5/3)c$*, then there exist positive constants* d_0*,* θ*,* T_0 *and* C *independent of* d *such that the following assertions hold: if* $0 < d \leq d_0$*, for any* $\alpha \in (0, \alpha_0]$*, if the inequalities*

$$|R(t) - R_s| \leq \alpha, |\sigma(r,t) - \sigma_s(r)| \leq \alpha \tag{2.19}$$

hold for all $0 \leq r \leq R(t)$*,* $t \geq -\tau$ *and* $|R'(t)| \leq \alpha$ *hold for all* $0 \leq r \leq R(t)$*,* $t \geq 0$*, where* $(R_s, \sigma_s(r))$ *denotes the unique positive stationary solution to problem* (1.1)–(1.7)*, then also the inequalities*

$$\begin{aligned} |R(t) - R_s| &\leq C\alpha(d + e^{-\theta t}), \\ R'(t)| &\leq C\alpha(d + e^{-\theta t}), \\ |\sigma(r,t) - \sigma_s(r)| &\leq C\alpha(d + e^{-\theta t}) \end{aligned} \tag{2.20}$$

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

Proof. Since the initial value function φ satisfies $\delta_1 \leq \varphi(t) \leq \delta_2$ for all $-\tau \leq t \leq 0$, where δ_1 and δ_2 are positive constants and

$$\delta_2 < \sqrt{\frac{6\sigma_e}{a}} \frac{1}{\sqrt[3]{1+\sigma_e \tau}} e^{-b\tau/3},$$

by Lemma 2.4, we can obtain that

$$\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3}) < R(t) < \sqrt{\frac{6\sigma_e}{a}}$$

for arbitrary $t > 0$, $0 < d < d_0$, where $R_s = \sqrt{15(\sigma_e - c)/a}$. Direct computation yields
(2.21)

$$\frac{1}{R^2(t)}\left[\int\limits_0^{R(t-\tau)} v(r,t-\tau)r^2 dr - \int\limits_0^{R(t)} cr^2 dr\right] = R(t)G(R(t), R(t-\tau)),$$

where

$$G(R(t), R(t-\tau)) = \frac{1}{3}\left[\left(\sigma_e - \frac{a}{15}R^2(t-\tau)\right)\frac{R^3(t-\tau)}{R^3(t)} - c\right].$$

From Lemma 2.2, (1.2) and the fact that $|R'(t)| \leq \alpha$ holds for all $0 \leq r \leq R(t)$, $t \geq 0$, we can get for $t > \tau$:

$$\begin{aligned}
&|R'(t) - R(t)G(R(t), R(t-\tau))| \\
&\qquad = \left|\frac{1}{R^2(t)} \int\limits_0^{R(t-\tau)} [\sigma(r,t-\tau) - v(r,t-\tau)]r^2 dr\right| \\
&\qquad \leq R(t)\left[\frac{2\sigma_e}{a} C\alpha d \left(\frac{R(t-\tau)}{R(t)}\right)^3\right] \\
&\qquad \leq C_1 \alpha d R(t),
\end{aligned}$$

where

$$C_1 = \frac{2\sigma_e}{a} C \left(\frac{1}{2}\min(R_s, \varphi(0)e^{-c\tau/3})\right)^{-3} \sqrt{\frac{6\sigma_e}{a}}^{\,3}$$

and where C_1 is a positive constant independent of α and d. It follows that, for $t > \tau$:

$$\begin{aligned} R(t)[G(R(t), R(t-\tau)) - C_1\alpha d] &\le R'(t) \\ &\le R(t)[G(R(t), R(t-\tau)) + C_1\alpha d], \end{aligned} \tag{2.22}$$

where C_1 is a positive constant independent of α and d. Hereafter, for ease of notation, we use the same variable C to denote various different positive constants independent of d and α. Consider the initial value problems

$$R'^{\pm}(t) = R^{\pm}(t)[G(R^{\pm}(t), R^{\pm}(t-\tau)) \pm C\alpha d], \quad t > \tau, \tag{2.23}$$

$$R^{\pm}(t) = R(t), \quad 0 \le t \le \tau. \tag{2.24}$$

Since $G(x,x) = 0$ has a unique positive constant solution $x = \sqrt{15(\sigma_e - c)/a}$ if $c < \sigma_e < (5/3)c$, we can obtain that there exist positive constants α_0 and d_0 such that, for $\alpha \in (0, \alpha_0]$ and $d \in (0, d_0]$ the equation $G(x,x) \pm C\alpha c = 0$ has respectively unique solutions $R_s^{\pm}$. By similar arguments as [**26,** Lemma 2.4 (2)], the corresponding solutions of the equations to the above initial problem, which we respectively denote as $R^{\pm}(t)$, converge respectively to $R_s^{\pm}$ as $t \to \infty$.

From the fact $G(x,x)$ is monotone decreasing for all $x > 0$, we can get

$$|R_s^{\pm} - R_s| \le C\alpha d. \tag{2.25}$$

Actually, since $R_s^{\pm}$ respectively satisfies the equations $G(x,x) = \mp C\alpha c$ and R_s satisfies the equation $G(x,x) = 0$, by (2.14) and the fact that $G(x,x)$ is monotone decreasing for all $x > 0$, we readily obtain $|R_s^{\pm} - R_s| \le C\alpha d$.

Noting that

$$G(x,y) = \frac{1}{3}\left[\left(\sigma_e - \frac{a}{15}y^2\right)\frac{y^3}{x^3} - c\right], \quad x, y \le \sqrt{\frac{6\sigma_e}{a}},$$

we can get

$$\frac{\partial G}{\partial y} = \frac{y^2}{x^3}\left(\sigma_e - \frac{a}{9}y^2\right) > 0. \tag{2.26}$$

The comparison principle (see [**10,** Lemma 3.1]) implies, for all $t \ge 0$,

$$R^-(t) \le R(t) \le R^+(t). \tag{2.27}$$

By linearizing (2.23) at the stationary point R_s^+, we have

$$R'^{+}(t) = -aR^{+}(t) + bR^{+}(t-\tau), \tag{2.28}$$

where

$$a = \left[\sigma_e - \frac{a}{15}(R_s^+)^2\right], \qquad b = \left[\sigma_e - \frac{a}{9}(R_s^+)^2\right].$$

The characteristic equation of (2.28) is

$$z = -a + be^{-\tau z}. \tag{2.29}$$

Similarly, by linearizing equation (2.23) at the stationary point R_s^-, we have

$$R'^{-}(t) = -AR^{-}(t) + BR^{-}(t-\tau), \tag{2.30}$$

where

$$A = \left[\sigma_e - \frac{a}{15}(R_s^-)^2\right], \qquad B = \left[\sigma_e - \frac{a}{9}(R_s^-)^2\right].$$

The characteristic equation of (2.30) is

$$z = -A + Be^{-\tau z}. \tag{2.31}$$

Since $a - b = (2/45)(R_s^+)^2$ and $A - B = (2/45)(R_s^-)^2$, we have $a > b > 0$ and $A > B > 0$, provided $d \in (0, d_0]$ and $\alpha \in (0, \alpha_0]$. This implies that all complex roots of equations (2.29) and (2.31) are located in the left-half plane. Then, we have that there exist positive constants K, θ and T_0 $(\geq \tau)$ such that, for any $t \geq T_0$,

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

where $|\varphi| = \max_{-\tau \leq t \leq 0} \varphi(t)$. Then, noting (2.25), for any $t \geq T_0$:

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

By the mean value theorem, the fact that $v_s(r) = \sigma_s(r)$, and noting (2.14), we have

$$|v(r,t) - \sigma_s(r)| = |v(r,t) - v_s(r)| \le C|R(t) - R_s| \le C\alpha$$

for $0 \le r \le R(t)$, $t \ge 0$. It follows that

$$|\sigma(r,t) - v(r,t)| \le |\sigma(r,t) - \sigma_s(r)| + |v(r,t) - \sigma_s(r)| \le C\alpha$$

for $0 \le r \le R(t)$, $t \ge 0$. In particular, $|\sigma_0(r) - v(r,0)| \le C\alpha$ for $0 \le r \le R(0)$. Since $|R'(t)| \le \alpha$ for all $t \ge 0$, by Lemma 2.2, we have that there exists a positive constant d_0 independent of d and α such that

$$|\sigma(r,t) - v(r,t)| \le C\alpha d\left(\frac{6\sigma_e}{a} - r^2\right) \le C\alpha d\frac{6\sigma_e}{a} \tag{2.32}$$

for arbitrary $0 \le r \le R(t)$, $t \ge 0$ and $0 < d \le d_0$.

Set

$$f(t) = \frac{1}{R^3(t)}\left[\int_0^{R(t-\tau)} \sigma(r,t-\tau)r^2 dr - \int_0^{R(t)} cr^2 dr\right].$$

Then, we have, for $t \ge \tau$:

$$\begin{aligned}
&|R(t)f(t) - R(t)G(R(t), R(t-\tau))| \\
&\quad = \left|\frac{1}{R^2(t)} \int_0^{R(t-\tau)} [\sigma(r,t-\tau) - v(r,t-\tau)]r^2 dr\right| \\
&\quad \le R(t)\left[\frac{2\sigma_e}{a} Cd\left(\frac{R(t-\tau)}{R(t)}\right)^3\right].
\end{aligned}$$

Noting (2.14), we have, for $t \ge 2\tau$,

$$|R(t)f(t) - R(t)G(R(t), R(t-\tau))| \le C\alpha d. \tag{2.33}$$

By the mean value theorem and (2.14), we have, for $t \ge T_0 + \tau$,

$$\begin{aligned}
|G(R(t), R(t-\tau)) - G(R_s, R_s)| &\le C(|R(t) - R_s| + |R(t-\tau) - R_s|) \\
&\le C\alpha(d + e^{-\theta t}).
\end{aligned}$$

Then, using equations $R'(t) = R(t)f(t)$, inequality (2.14) and (2.33), it follows that $|R'(t)| \le C\alpha(d + e^{-\theta t})$. From (2.32), we have

$$|\sigma(r,t) - \sigma_s(r)| \le C\alpha(d + e^{-\theta t}).$$

The proof of Lemma 2.5 is complete. $\square$

Proof of Theorem 2.1. From Lemma 2.4, we see that there exists a positive constant d_0 such that, if $0 < d \le d_0$, then, for all $t \ge 0$,

$$C_* \le R(t) \le C^*,$$

where $C_* = (1/2)\min(R_s, \varphi(0)e^{-c\tau/3})$, $C^* = \sqrt{6\sigma_e/a}$. It follows that $|R(t) - R_s| \le C^* + R_s =: \alpha_1$ for all $t \ge 0$. By Lemma 2.3 (i), we know that $\sigma \le \sigma_e$, and, from (1.2), we have, for all $t \ge 0$, $|R'(t)| \le s(\sigma_e + c)(C^*)^3/C_*^2 := \alpha_2$. Obviously, $|\sigma(r,t) - \sigma_s(r)| \le 2\sigma_e$ holds for all $0 \le r \le R(t)$, $t \ge -\tau$. We see that the conditions of Lemma 2.5 hold for $\alpha = \alpha_0 =: \max\{\alpha_1, \alpha_2, 2\sigma_e\}$. Then, by Lemma 2.5, and letting C and θ be as in (2.20) with T_0 larger (if necessary), we can obtain

$$\begin{aligned} |R(t) - R_s| &\le C\alpha(d + e^{-\theta t}) \le 2Cd\alpha, \\ |R'(t)| &\le C\alpha(d + e^{-\theta t}) \le 2Cd\alpha, \\ |\sigma(r,t) - \sigma_s(r)| &\le C\alpha(d + e^{-\theta t}) \le 2Cd\alpha \end{aligned}$$

hold for all $0 \le r \le R(t)$, $t \ge T_0 + \tau$. Taking d_0 smaller (if necessary), for any given d ($< d_0$) such that $2Cd < 1$, we define T_0 by

$$e^{-\theta(T_0 + \tau)} = d.$$

Iterating this result yields

$$\begin{aligned} |R(t) - R_s| &\le C(2Cd)^{n-1}\alpha(d + e^{-\theta(t-(n-1)T_0)}) \le (2Cd)^n\alpha, \\ |R'(t)| &\le C(2Cd)^{n-1}\alpha(d + e^{-\theta(t-(n-1)T_0)}) \le (2Cd)^n\alpha, \\ |\sigma(r,t) - \sigma_s(r)| &\le C(2Cd)^{n-1}\alpha(d + e^{-\theta(t-(n-1)T_0)}) \le (2Cd)^n\alpha \end{aligned}$$

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

Finally, defining $\gamma > 0$ by

$$2Cd = e^{-\gamma T_0} < 1$$

and, for a given $t > 0$, letting n be the largest integer that satisfies $nT_0 + \tau \le t \le (n+1)T_0 + \tau$, then it follows that

$$\begin{aligned}|R(t) - R_s| &\le \alpha(2Cd)^n \alpha = \alpha e^{-\gamma n T_0} = \alpha e^{-\gamma t} e^{-\gamma(nT_0 - t)} \\ &\le \alpha e^{\gamma(T_0+\tau)} e^{-\gamma t} = Ce^{-\gamma t}.\end{aligned}$$

Similar arguments yield $|R'(t)| \le Ce^{-\gamma t}$, $|\sigma(r,t) - \sigma_s(r)| \le Ce^{-\gamma t}$ for all $t \ge T_0 + \tau$, $0 \le r \le R(t)$. This completes the proof of Theorem 2.1. $\square$

3. Conclusions. In this paper, we studied the global stability of a free boundary problem modeling solid avascular tumor growth. The model studied is a PDE ($d > 0$) model describing tumor growth, which is a generalization of the existing ODE ($d = 0$) model in [**13**]. The ODE model is the quasi steady-state approximation of the PDE model. Using the Banach fixed point theorem, a comparison method and other mathematical techniques, the existence and uniqueness of the global solution to the problem was proven in [**26**]. In this paper, we mainly studied the asymptotic behavior of the solution and proved that, in the case where d (the ratio of the diffusion time scale to the tumor doubling time scale) is sufficiently small, it will evolve to a dormant state as $t \to \infty$.

From a biology standpoint, our main results (see Theorem 2.1) mean that, if the supply of nutrient σ_e that the tumor receives from its surface satisfying $c < \sigma_e < (5/3)c$, with initial radius $\varphi(t)$ satisfying $\varphi \in (\delta_1, \delta_2)$, where

$$0 < \delta_1, \delta_2 < \sqrt{\frac{6\sigma_e}{a}} \frac{1}{\sqrt[3]{1 + \sigma_e \tau}} e^{-b\tau/3},$$

$b = \sigma_e + c$, the tumor will not disappear, and its radius will tend to the unique positive constant steady state if d is sufficiently small. The results show that, under the conditions of Theorem 2.1, dynamical behavior of solutions to the model are similar to that of solutions for that of the corresponding problem $d = 0$ (refer to [**26,** Lemma 2.4 (2)] and Theorem 2.1).

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