ASYMPTOTIC BEHAVIOR OF A NONLINEAR NECROTIC TUMOR MODEL WITH A PERIODIC EXTERNAL NUTRIENT SUPPLY

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Abstract. In this paper we study a nonlinear free boundary problem for the growth of radially symmetric tumor with a necrotic core. The proliferation of tumor cells depends on the concentration of nutrient which satisfies a diffusion equation within tumor and is periodically supplied by external tissues. The tumor outer surface and the inner interface of the necrotic core are both free boundaries. We give a sufficient and necessary condition for the existence and uniqueness of positive periodic solution, and show it is globally asymptotically stable under radial perturbations. Our analysis implies that tumor growth may finally synchronize the periodic external nutrient supply.

1. Introduction. Tumor is one of the most dangerous diseases nowadays. To understand the mechanism of tumor growth is a very challenging and interesting research program. In the past several decades, a lot of mathematical models have been proposed to describe the growth of various tumors in vitro and in vivo, and many illustrated results have been established, see [3], [7], [9], [10], [11], [13], [14], [15], [18], [19] and references cited therein.

In this paper, we focus on a mathematical model for necrotic tumors. It is observed that there may exist a necrotic core in the solid tumor. Byrne and Chaplain [3] proposed that the occurrence of necrosis is caused by the lack of nutrient supply, all dead cells are concentrated within the necrotic core, and living tumor cells are concentrated in the living region. Denote \( \Omega(t) = \{ r \leq R(t) \} \) by the tumor region at time \( t > 0 \), and \( \sigma(r,t) \) by the nutrient concentration. Let \( \sigma \) be a positive constant representing the nutrient level for necrosis, then the necrotic region and living region

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can be denoted by \( \{ \sigma(r, t) \leq \bar{\sigma} \} \) and \( \{ \sigma(r, t) > \bar{\sigma} \} \), respectively. By using the mass conservation law, we have the following mathematical model:

\[
\begin{aligned}
\frac{\partial^2 \sigma}{\partial r^2} + \frac{2 \sigma}{r} \frac{\partial \sigma}{\partial r} &= f(\sigma)H(\sigma - \bar{\sigma}) \quad \text{for } 0 < r < R(t), \ t > 0, \\
\sigma_r(0, t) &= 0, \quad \sigma(R(t), t) = \phi(t) \quad \text{for } t > 0, \\
R^2(t) \frac{dR(t)}{dt} &= \int_{\sigma(r, t) > \bar{\sigma}} g(\sigma(r, t)) r^2 dr - \int_{\sigma(r, t) \leq \bar{\sigma}} \nu r^2 dr \quad \text{for } t > 0, \\
R(0) &= R_0,
\end{aligned}
\]  

(1)

where \( H(\cdot) \) is the Heaviside function, i.e., \( H(x) = 0 \) for \( x \leq 0 \) and \( 1 \) for \( x > 0 \). \( \nu \) is a positive constant representing the removal rate of dead cells, \( \phi(t) \) is a given function representing nutrient concentration supplied by external tissues, \( f(\cdot) \) and \( g(\cdot) \) are also given functions representing the nutrient consumption rate and the tumor cell proliferating rate, respectively. \( R_0 > 0 \) is a given initial tumor radius. Obviously, the tumor outer surface \( r = R(t) \) is a free boundary, and if the necrotic tumor region \( \{ \sigma(r, t) \leq \bar{\sigma} \} \neq \emptyset \), then its interface can be denoted by \( r = \rho(t) \) for some \( 0 < \rho(t) < R(t) \), which is another free boundary.

Typically, functions \( \phi(t), f(\cdot) \) and \( g(\cdot) \) are given as follows:

\[
\phi(t) \equiv \bar{\sigma}, \quad f(\sigma) = \lambda \sigma, \quad g(\sigma) = \mu(\sigma - \bar{\sigma}),
\]  

(2)

where \( \lambda, \mu, \bar{\sigma} \) and \( \bar{\sigma} \) are positive constants (cf. [3]). Cui and Friedman [6] proved that problem (1) and (2) has a unique necrotic stationary solution, and it is asymptotically stable under some case of model parameters. Global well-posedness was also established in [4][5]. The existence of necrotic stationary solutions for nonlinear and strictly increasing functions \( f \) and \( g \) was established in [2][17]. Similarly, in this paper we always assume

(\( A1 \)) \( f \in C^1[0, +\infty) \) is strictly increasing and \( f' \) is bounded on \( [0, +\infty) \), and \( f(0) = 0 \);

(\( A2 \)) \( g \in C^1[0, +\infty) \) is strictly increasing and \( g(\bar{\sigma}) = 0 \) for some \( \bar{\sigma} \in (\bar{\sigma}, +\infty) \);

(\( A3 \)) \( g(\bar{\sigma}) + \nu \geq 0 \).

Note that \( \bar{\sigma} \) means the critical nutrient level for the balance of tumor cell apoptosis and mitosis, (\( A3 \)) means the volume loss rate of living cells at nutrient level \( \bar{\sigma} \) is less than the removal rate of dead cells. Obviously, the necrotic region \( \{ \sigma(r, t) \leq \bar{\sigma} \} \) may be empty, we call the corresponding solution by nonnecrotic solution. From [17], we see that under assumptions (\( A1 \))–(\( A3 \)), there exists a positive threshold nutrient concentration \( \sigma^* \in (\bar{\sigma}, +\infty) \), such that problem (1) with \( \phi(t) \equiv \bar{\sigma} \) has a unique necrotic stationary solution for \( \bar{\sigma} \geq \sigma^* \), and has a unique nonnecrotic stationary solution for \( \bar{\sigma} < \sigma^* \). Moreover, tumor will finally converge to the necrotic dormant state for \( \bar{\sigma} > \sigma^* \), or converge to the nonnecrotic dormant state for \( \bar{\sigma} < \sigma^* \), or finally disappear for \( \bar{\sigma} \leq \sigma^* \). For the existence of stationary solutions of a similar necrotic multilayered tumor model, we refer to [16].

From the point of view of mathematical modeling, since the tumor model was established based on the assumption that tumor cells consume nutrient and the growth rate depends only on the nutrient concentration, it is natural to ask whether tumor behavior can be controlled by external nutrient supply. The above mentioned results partially answered that the existence and stability of dormant tumor state can be controlled. Note that humans and many animals have regular living and
feeding activities, associated with the biological rhythm, the nutrient concentration in their blood may be periodically changing over time (cf. [8]). Motivated by this observation, later on we always assume

\[(A4) \quad \phi(t) \in C^1[0, +\infty) \quad \text{is a positive periodic function with period } \omega > 0.\]

It is interesting to address whether the tumor may be induced a periodic growth behavior, to synchronize the periodic external nutrient supply. In the limiting case \(\hat{\sigma} = 0\) of problem (1) with \((A4)\) and linear functions \(f, g\) given in (2), i.e., for a similar nonnecrotic tumor model, Bai and Xu [1] proved that if \(\min_{0 \leq t \leq \omega} \phi(t) > \hat{\sigma}\), then there exists a unique periodic nonnecrotic solution, and it is asymptotically stable under radial perturbations. Recently, Huang, Zhang and Hu [12] further proved the periodic nonnecrotic solution is linearly stable under small non-radial perturbations.

In this paper, we extend to study the necrotic tumor model (1) with assumptions \((A1)-(A4)\). Since there may exist a necrotic core, the tumor may have two free boundaries, and the nutrient consumption rate function and the tumor growth rate are discontinuous across the inner free boundary of the necrotic core. It makes the necrotic tumor model much more difficult than the corresponding nonnecrotic tumor model. By reducing problem (1) into a Cauchy problem for differential equation, we will give a sufficient and necessary condition for the existence and uniqueness of positive periodic solution, and show asymptotic behavior of all transient solutions for any positive initial values.

By our method, one can easily improve results of [1] and [12] to obtain that the corresponding nonnecrotic tumor model has a unique periodic solution if and only if \(\frac{1}{\omega} \int_0^\omega \phi(t) dt > \hat{\sigma}\), and it is also asymptotically stable under radial perturbations and linearly stable under small non-radial perturbations.

In the next section, we give our main results of the existence, uniqueness and asymptotic stability of the positive periodic solution. In the last section, we discuss some interesting biological implications.

2. Periodic solution and asymptotic behavior. We always assume that assumptions \((A1)-(A4)\) hold. Denote

\[M := \max_{0 \leq t \leq \omega} \phi(t).\]  (3)

At each time \(t > 0\), for any given \(R(t) > 0\), by the well-known theory of elliptic differential equations, we see that problem (1) \(_1\) and (1) \(_2\) has a unique solution \(\sigma(r, t) \in \bigcap_{p \geq 1} W^{2,p}(\Omega(t))\) satisfying \(0 < \sigma(r, t) \leq M\). Then by substituting this \(\sigma(r, t)\) into (1) \(_3\) we can reduce problem (1) into a Cauchy problem

\[\frac{dR}{dt} = F(R, t) \quad \text{for } t > 0, \quad R(0) = R_0.\]  (4)

It is easy to verify that \(R_0 \exp^{-\frac{1}{2}(|g(0)| + \nu)t} \leq R(t) \leq R_0 \exp^{\frac{1}{2}|g(M)|t}\), hence problem (1) has a unique global solution for all \(R_0 > 0\).

Next, we study properties of function \(F(R, t)\). For any given \(R > 0\), we first consider the following problem

\[\begin{cases}
\frac{d^2 \sigma}{dr^2} + \frac{2}{r} \frac{d\sigma}{dr} = f(\sigma)H(\sigma - \hat{\sigma}) & \text{for } 0 < r < R, \\
\sigma'(0) = 0, & \sigma(R) = \bar{\sigma}.
\end{cases}\]  (5)

Clearly, problem (5) has a unique solution \(\sigma(r) \equiv \bar{\sigma}\) for any \(0 < \bar{\sigma} \leq \hat{\sigma}\).
Lemma 2.1. Let (A1) be satisfied. For any given \( \hat{\sigma} > \hat{\sigma} \), there exists a unique positive number \( R_*(\hat{\sigma}) \), which is strictly increasing in \( \hat{\sigma} \), such that

(i) If \( 0 < R < R_*(\hat{\sigma}) \), then problem (5) has a unique classical solution denoted by \( \sigma = U(r, R, \hat{\sigma}) \) and \( U_r(r, R, \hat{\sigma}) > 0 \) for \( 0 < r < R \).

(ii) If \( R > R_*(\hat{\sigma}) \), then problem (5) has a unique solution denoted by \( \sigma = V(r, R, \hat{\sigma}) \) with \( V(r, R, \hat{\sigma}) \equiv \hat{\sigma} \) for \( 0 \leq r \leq \rho \) and \( V(r, R, \hat{\sigma}) > \hat{\sigma} \), \( V_r(r, R, \hat{\sigma}) > 0 \) for \( \rho < r < R \), where \( \rho = \rho(R, \hat{\sigma}) \) is uniquely determined by \( R \) and \( \hat{\sigma} \).

Proof. Consider

\[
\begin{align*}
\frac{d^2\sigma}{dr^2} + \frac{2}{r} \frac{d\sigma}{dr} &= f(\sigma) \quad \text{for } r > 0, \\
\sigma'(0) &= 0, \quad \sigma(0) = \hat{\sigma}. 
\end{align*}
\]

Since \( f(\sigma) \) is strictly increasing and \( f'(r) \) is bounded, we see problem (6) has a unique solution \( \sigma(r) \) on \([0, +\infty)\), and \( \lim_{r \to +\infty} \sigma(r) = +\infty \). Clearly, \( \sigma'(r) > 0 \). Then for any given \( \hat{\sigma} > \hat{\sigma} \), there exists a unique \( R_*(\hat{\sigma}) \) such that \( \sigma(R_*(\hat{\sigma})) = \hat{\sigma} \). Moreover, we have \( R_*(\hat{\sigma}) \) is strictly increasing on \((\hat{\sigma}, +\infty)\) and \( \lim_{\hat{\sigma} \to +\infty} R_*(\hat{\sigma}) = +\infty \).

We easily see that for any \( \hat{\sigma} > \hat{\sigma} \) and \( 0 < R < R_*(\hat{\sigma}) \), the solution of problem (6) is a lower solution to the following problem

\[
\begin{align*}
\frac{d^2\sigma}{dr^2} + \frac{2}{r} \frac{d\sigma}{dr} &= f(\sigma) \quad \text{for } 0 < r < R, \\
\sigma'(0) &= 0, \quad \sigma(R) = \hat{\sigma}. 
\end{align*}
\]

Obviously, \( \sigma(r) \equiv \hat{\sigma} \) is an upper solution. Thus by using the upper-lower solution method, for any \( \hat{\sigma} > \hat{\sigma} \), and \( \lim_{r \to +\infty} \sigma(r) = +\infty \), problem (7) has a unique solution denoted by \( \sigma = U(r, R, \hat{\sigma}) \), and we have \( \hat{\sigma} < U(r, R, \hat{\sigma}) < \hat{\sigma} \) for \( 0 < r < R \), and \( U_r(r, R, \hat{\sigma}) > 0 \).

On the other hand, for any \( \hat{\sigma} > \hat{\sigma} \) and \( R > R_*(\hat{\sigma}) \), we can similarly show that there exists a unique solution \((\sigma, \rho) = (V(r, R, \hat{\sigma}), \rho(R, \hat{\sigma}))\) to the following problem

\[
\begin{align*}
\frac{d^2\sigma}{dr^2} + \frac{2}{r} \frac{d\sigma}{dr} &= f(\sigma) \quad \text{for } \rho < r < R, \\
\sigma'(\rho) &= 0, \quad \sigma(R) = \hat{\sigma}, \quad \sigma(r) = \hat{\sigma} \quad \text{for } 0 \leq r \leq \rho. 
\end{align*}
\]

For more details we refer to Lemma 2.1 and Lemma 2.2 of [17]. The assertion (ii) follows immediately and the proof is complete.

From the above Lemma, we see that for \( \hat{\sigma} > \hat{\sigma} \), the tumor is in the necrotic phase if its radius \( R > R_*(\hat{\sigma}) \), and in the nonnecrotic phase if \( R \leq R_*(\hat{\sigma}) \).

Define a function

\[
G(R, \hat{\sigma}) = \begin{cases} 
-\frac{\nu}{3R^3} & \text{for } R > 0, 0 < \hat{\sigma} \leq \hat{\sigma}, \\
\frac{1}{R^3} \int_0^R g(U(r, R, \hat{\sigma}))r^2dr & \text{for } 0 < R \leq R_*(\hat{\sigma}), \hat{\sigma} > \hat{\sigma}, \\
\frac{1}{R^3} \int_{\rho(R, \hat{\sigma})}^R g(V(r, R, \hat{\sigma}))r^2dr - \frac{\nu \rho^3(R, \hat{\sigma})}{3R^3} & \text{for } R > R_*(\hat{\sigma}), \hat{\sigma} > \hat{\sigma}.
\end{cases}
\]

The function \( G(R, \hat{\sigma}) \) is not continuous across the line \( \sigma = \hat{\sigma} \).

Lemma 2.2. Under assumptions (A1)–(A3), we have

(i) \( \partial_\hat{\sigma} G(R, \hat{\sigma}) > 0 \) and \( \partial_R G(R, \hat{\sigma}) < 0 \) for all \( R > 0 \) and \( \hat{\sigma} > \hat{\sigma} \).
(ii) For any given \( \bar{\sigma} > \hat{\sigma} \), \( \lim_{R \to 0^+} G(R, \bar{\sigma}) = \frac{1}{3}g(\bar{\sigma}) \) and \( \lim_{R \to +\infty} G(R, \bar{\sigma}) = -\frac{\nu}{3} \).

**Proof.** (i) For \( R > R_* (\bar{\sigma}) \), we set \( v(r) = \partial_\eta V(\rho, R, \bar{\sigma}) \) and \( \xi = \partial_\eta \rho(\bar{R}, \bar{\sigma}) \), then from problem (8) and by a standard computation, we see \( v(r) \) and \( \xi \) satisfy the following problem

\[
\begin{cases}
\frac{d^2 v}{dr^2} + \frac{2}{r} \frac{dv}{dr} = f'(V)v & \text{for } 0 < r < R, \\
v(\rho) = 0, \quad v(R) = 1, \quad v'(\rho) = -f(\bar{\sigma})\xi.
\end{cases}
\]  

(10)

By the comparison principle, since \( f'(V) \geq 0 \), we have \( v(r) = \partial_\eta V(\rho, R, \bar{\sigma}) > 0 \) for \( 0 < r < R \), and thus \( \xi = -v'(\rho)/f(\bar{\sigma}) < 0 \). Then by (A2) and (A3), we have for \( R \geq R_* (\bar{\sigma}) \),

\[
\partial_\sigma G(R, \bar{\sigma}) = \frac{1}{R^3} \left\{ \int_0^R g'(V(\rho, R, \bar{\sigma}))v(r)r^2 dr - (g(\bar{\sigma}) + \nu)\rho^2(\bar{R}, \bar{\sigma})\xi \right\} > 0.
\]

Similarly, by using the comparison principle to problem (7), we get \( \partial_\sigma G(R, \bar{\sigma}) > 0 \) for \( 0 < R \leq R_* (\bar{\sigma}) \) and \( \sigma > \bar{\sigma} \).

Next, we study \( \partial_R G(R, \bar{\sigma}) \). For all \( R > R_* (\bar{\sigma}) \) and \( \bar{\sigma} > \sigma \), by letting \( s = r/R \) and \( \eta(R, \bar{\sigma}) = \rho(R, \bar{\sigma})/R \), from (9) we have

\[
G(R, \bar{\sigma}) = \int_{\eta(R, \bar{\sigma})}^1 g(V(sR, R, \bar{\sigma}))s^2 ds - \frac{\nu}{3} \eta^3(R, \bar{\sigma}).
\]

(11)

Rewrite \( u(s, R, \bar{\sigma}) = V(sR, R, \bar{\sigma}) \), then \((u, \eta)\) satisfies the following problem

\[
\begin{cases}
\frac{\partial^2 u}{\partial s^2} + \frac{2}{s} \frac{\partial u}{\partial s} = R^2 f(u) & \text{for } \eta < s < 1, \\
u|_{s=1} = \bar{\sigma}, \quad u|_{s=\eta} = \sigma, \quad \frac{\partial u}{\partial s}|_{s=\eta} = 0,
\end{cases}
\]

Set \( w(s) = \frac{\partial u}{\partial R}(s, R, \bar{\sigma}) \) and \( \zeta = \frac{\partial \eta}{\partial R}(R, \bar{\sigma}) \). By a linearization analysis, we see that \((w, \zeta)\) satisfies the following problem

\[
\begin{cases}
\frac{d^2 w}{ds^2} + \frac{2}{s} \frac{dw}{ds} - R^2 f'(u)w = 2Rf(u) & \text{for } \eta < s < 1, \\
w(1) = 0, \quad w(\eta) = 0, \quad w'(\eta) = -R^2 f(\bar{\sigma})\zeta.
\end{cases}
\]

By using (A1) and the comparison principle, we obtain

\[
w(s) = \frac{\partial u}{\partial R}(s, R, \bar{\sigma}) < 0 \quad \text{for } \eta < s < 1, \quad \text{and} \quad \zeta = \frac{\partial \eta}{\partial R} \geq 0.
\]

(12)

Thus from (11) and (12), we have for all \( R > R_* (\bar{\sigma}) \) and \( \bar{\sigma} > \sigma \),

\[
\partial_R G(R, \bar{\sigma}) = \int_{\eta(R, \bar{\sigma})}^1 g'(u(s, R, \bar{\sigma}))w(s)s^2 ds - (g(\bar{\sigma}) + \nu)\eta^2(R, \bar{\sigma})\zeta < 0.
\]

By a similar argument, we can also get \( \partial_R G(R, \bar{\sigma}) < 0 \), for \( 0 < R \leq R_* (\bar{\sigma}) \) and \( \bar{\sigma} > \hat{\sigma} \).

(iii) For any \( \bar{\sigma} > \hat{\sigma} \), since \( \lim_{R \to 0^+} U(r, R, \bar{\sigma}) = \bar{\sigma} \), we get \( \lim_{R \to 0^+} G(R, \bar{\sigma}) = \frac{1}{3}g(\bar{\sigma}) \).

On the other hand, by Lemma 2.2 (ii) of [17], there holds

\[
\lim_{R \to +\infty} \eta(R, \bar{\sigma}) = \lim_{R \to +\infty} \rho(R, \bar{\sigma})/R = 1.
\]

Hence by using (11) and \( \hat{\sigma} \leq V \leq \bar{\sigma} \), we get \( \lim_{R \to +\infty} G(R, \bar{\sigma}) = -\frac{\nu}{3} \). \qed
From Lemma 2.1 and (9), we define
\[ F(R, t) = RG(R, \phi(t)) \quad \text{for } R > 0, \ t > 0. \] (13)
Clearly, we see that problem (1) is equivalent to problem (4) with \( F(R, t) \) given by (13).

Define a function
\[ h(x) = \begin{cases} \frac{-\nu}{3} & \text{for } 0 < x \leq \hat{\sigma}, \\ \frac{1}{3}g(x) & \text{for } x > \hat{\sigma}. \end{cases} \] (14)
By Lemma 2.2, we have
\[ G(R, \hat{\sigma}) \leq h(\hat{\sigma}) \quad \text{for } R > 0, \ \hat{\sigma} > 0. \] (15)
For a given function \( \phi(t) \) satisfying assumption (A4), we introduce a constant
\[ \omega := \int_0^\omega h(\phi(t))dt. \] (16)

**Theorem 2.3.** Suppose (A1)–(A4) hold, then the trivial solution \( R = 0 \) of problem (4) is globally stable if and only if \( \omega \leq 0 \).

**Proof.** Denote by \( R(t, R_0) \) the unique global solution of problem (4), for any given initial data \( R_0 > 0 \). By (13) and (15) we have \( \int_0^\omega G(R(t, R_0), \phi(t))dt \leq \omega \) for \( \omega < 0 \) and \( \int_0^\omega G(R(t, R_0), \phi(t))dt < \omega \) for \( \omega \geq 0 \). If \( \omega \leq 0 \), then for any \( t_0 \geq 0 \), we have
\[ \lim_{n \to +\infty} R(t_0 + n\omega, R_0) = \lim_{n \to +\infty} R(t_0, R_0) \exp \left\{ \int_{t_0}^{t_0 + n\omega} G(R(t, R_0), \phi(t))dt \right\} = 0. \]
It follows that \( \lim_{t \to +\infty} R(t, R_0) = 0. \)
On the other hand, if \( \lim_{t \to +\infty} R(t, R_0) = 0 \) and \( \omega > 0 \), then by Lemma 2.2 and (A2), there exists a large \( T > 0 \), such that for any \( t_0 > T \),
\[ \int_{t_0}^{t_0 + \omega} G(R(t, R_0), \phi(t))dt \geq \frac{\omega}{2} > 0. \]
It implies that \( R(t_0 + n\omega, R_0) \geq R(t_0, R_0) > 0 \), which contradicts to \( \lim_{t \to +\infty} R(t, R_0) = 0 \). The proof is complete. \( \square \)

Next, we study the positive periodic solution of problem (4), which is denoted by \( R_{per}(t) \). We have

**Theorem 2.4.** Suppose (A1)–(A4) hold. If \( \omega > 0 \), then problem (4) has a unique positive periodic solution \( R_{per}(t) \) with period \( \omega \), and for any initial value \( R_0 > 0 \), the solution \( R(t, R_0) \) will converge to \( R_{per}(t) \) in the following sense:
\[ \lim_{t \to +\infty} |R(t, R_0) - R_{per}(t)| = 0. \] (17)

**Proof.** Since \( \omega > 0 \), we see that \( g(M) > 0 \) where \( M = \max_{0 \leq t \leq \omega} \phi(t) \). By Lemma 2.2, there exists a unique \( R_M > 0 \) such that \( G(R_M, M) = 0 \). Moreover,
\[ F(R, t) = RG(R, \phi(t)) \leq RG(R_M, \phi(t)) \leq RG(R_M, M) = 0 \quad \text{for } R \geq R_M. \]
Thus for any \( R_0 > 0, 0 < R(t, R_0) \leq \max\{R_0, R_M\} \) for all \( t \geq 0 \).
We define \( R_n := R(n\omega, R_0) \) for \( n \in \mathbb{N} \). Clearly, we have \( R_n = R(\omega, R_{n-1}) \). By the uniqueness of the solution of problem (4), \( \{R_n\}_{n \geq 0} \) is a monotone sequence.
Then by the bounded monotone principle, \( \bar{R}_0 := \lim_{n \to +\infty} R_n \) exists. Since \( \varpi > 0 \), by Theorem 2.3, we see that \( 0 < \bar{R}_0 < +\infty \). Notice that by the uniqueness of the solution of problem (4), and the periodicity of \( \phi(t) \), we have

\[
R_{n+1} = R(\omega, R_n) = R_n \exp \left\{ \int_0^\omega G(R(t, R_n), \phi(t))dt \right\}.
\]

It follows that

\[
\lim_{n \to +\infty} \exp \left\{ \int_0^\omega G(R(t, R_n), \phi(t))dt \right\} = \lim_{n \to +\infty} \frac{R_{n+1}}{R_n} = 1. \tag{18}
\]

We have

\[
\int_0^\omega G(R(t, \bar{R}_0), \phi(t))dt = \lim_{n \to +\infty} \int_0^\omega G(R(t, R_n), \phi(t))dt = 0. \tag{19}
\]

It implies that \( R(\omega, \bar{R}_0) = \bar{R}_0 \exp \left\{ \int_0^\omega G(R(t, \bar{R}_0), \phi(t))dt \right\} = \bar{R}_0 \), and \( R(t, \bar{R}_0) \) is a positive periodic solution of problem (4).

Define

\[
H(y) := \int_0^\omega G(R(t, y), \phi(t))dt \quad \text{for } y > 0.
\]

By Lemma 2.2 (i), we have

\[
\partial_R G(R, \tilde{\sigma}) \begin{cases} < 0 & \text{for } R > 0 \tilde{\sigma} > \hat{\sigma}, \\ = 0 & \text{for } R > 0, \tilde{\sigma} \leq \hat{\sigma}. \end{cases}
\]

Thus the equation \( H(y) = 0 \) has a unique positive root \( \bar{R}_0 \). Otherwise, there exists another \( \bar{R}_0 > 0 \) such that \( H(\bar{R}_0) = 0 \). Without loss of generality, we set \( \bar{R}_0 \geq \bar{R}_0 \), then \( R(t, \bar{R}_0) > R(t, \bar{R}_0) \). Due to \( \partial_R G(R, \tilde{\sigma}) \leq 0 \), we have \( 0 = H(\bar{R}_0) < H(\bar{R}_0) = 0 \).

It is a contradiction. On the other hand, from (18) and (19), we see that for any given \( R_0 \), \( \lim_{n \to +\infty} R(n\omega, R_0) \) exists and satisfies the equation \( H(y) = 0 \). It follows that \( \bar{R}_0 \) does not depend on \( R_0 \). Hence, problem (4) has a unique positive periodic solution \( R_{\text{per}}(t) = R(t, \bar{R}_0) \). Moreover, for any \( R_0 > 0 \), there holds \( \lim_{t \to +\infty} |R(t, R_0) - R_{\text{per}}(t)| = 0 \). The proof is complete.  

Since problem (4) is equivalent to problem (1), we see that problem (1) has a unique positive periodic solution if and only if \( \varpi > 0 \), and it is globally asymptotically stable.

3. Biological implications. In this paper, we study periodic growth of radially symmetric necrotic tumors with periodic external nutrient supplies. From Lemma 2.1, we see that at each time \( t > 0 \), if \( \phi(t) > \hat{\sigma} \), then for \( R_{\text{per}}(t) > R_*(\phi(t)) \), the tumor is in the necrotic phase, and for \( R_{\text{per}}(t) \leq R_*(\phi(t)) \), the tumor is in the nonnecrotic phase. Whether there exists a positive periodic solution is determined by the constant \( \varpi = \int_0^\omega h(\phi(t))dt \). By the definition (14) of function \( h(\cdot) \) and (15), we see that the constant \( \varpi \) represents the maximum of total growth amount of the tumor in the period \([0, \omega] \). By giving different types of periodic function \( \phi(t) \) with \( \varpi > 0 \), we can get periodic solutions all in necrotic phase, or all in nonnecrotic phase, or periodically mutual transition between the necrotic and nonnecrotic phases.

Our analysis implies that external nutrient supply is very important for the growth of solid tumors. If \( \varpi \leq 0 \), due to the lack of nutrient supply, the tumor volume will decrease and the tumor will finally disappear. If \( \varpi > 0 \), since the
nutrient supply is periodic, the tumor will be induced into a periodic growth state, and tumor growth will finally synchronize the periodic external nutrient supply. By adjusting the external nutrient concentration, we can not only control the size of the necrotic core within tumors (cf. [17]), but also control the growth pattern of tumors. These results may be useful for mathematical modeling of tumor growth and medical treatment.

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