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Analysis of a free boundary problem for tumor growth in a periodic external environment

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Abstract

In this paper a free boundary problem for solid avascular tumor growth in a periodic external environment is studied. The periodic environment means that the supply of nutrient and inhibitors is periodic. Sufficient conditions for the global stability of tumor free equilibrium are given. We also prove that if external concentration of nutrients is large, the tumor will not disappear. The conditions under which there exists a unique periodic solution to the model are determined, and we also show that the unique periodic solution is a global attractor of all other positive solutions.

Keywords: solid avascular tumor; periodic environment; stability; periodic solution

1 Introduction

The process of tumor growth and its dynamics has been one of the most intensively studied processes in the recent years. There have appeared many papers devoted to developing mathematical models to describe the process, *cf.* [1–15] and the references therein. Most of those models are based on the reaction diffusion equations and mass conservation law. Analysis of such mathematical models has drawn great interest, and many results have been established, *cf.* [16–27] and the references therein.

In this paper we study the following problem:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma}{\partial r}\right)=\Gamma_1\sigma,\qquad 0<r<R(t),t>0, \tag{1.1}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\beta}{\partial r}\right)=\Gamma_2\beta,\qquad 0<r<R(t),t>0, \tag{1.2}$$

$$\frac{\partial\sigma}{\partial r}(0,t)=0,\qquad \sigma\bigl(R(t),t\bigr)=\varphi(t),\qquad 0<r<R(t),t>0, \tag{1.3}$$

$$\frac{\partial\beta}{\partial r}(0,t)=0,\qquad \beta\bigl(R(t),t\bigr)=\phi(t),\qquad 0<r<R(t),t>0, \tag{1.4}$$

$$\frac{d}{dt}\left(\frac{4\pi R^3(t)}{3}\right)=4\pi\left(\int_0^{R(t)}\lambda\sigma(r,t)r^2\,dr-\int_0^{R(t)}\nu r^2\,dr-\int_0^{R(t)}\mu\beta(r,t)r^2\,dr\right),\quad t>0, \tag{1.5}$$

where $R(t)$ denotes the external radius of tumor at time t; the term $\Gamma_1\sigma$ in (1.1) is the consumption rate of nutrient in a unit volume; $\Gamma_2\beta$ in (1.2) is the consumption rate of inhibitors in a unit volume; $\varphi(t)$ denotes the external concentration of nutrients, which is assumed to be a periodic function, the period of which is ω. $\phi(t)$ denotes the external concentration of inhibitors, and it is also assumed to be a periodic function, the period of which is ω. The external concentration of nutrients and inhibitors is assumed to be periodic with the same period, which means that the tumor is in a periodic external environment. The three terms on the right-hand side of (1.5) are explained as follows: the first term is the total volume increase in a unit time interval induced by cell proliferation, the proliferation rate is $\lambda\sigma$; the second term is the total volume decrease in a unit time interval caused by natural death, and the natural death rate is ν; the last term is total volume shrinkage in a unit time interval caused by inhibitors, or cell death due to inhibitors, the rate of cell apoptosis caused by inhibitors is $\mu\beta$.

We will consider (1.1)-(1.5) together with the following initial condition:

$$R(0) = R_0. \tag{1.6}$$

Equations (1.1)-(1.4) are from Byrne and Chaplain [4]. The modification is that we consider the effect of the periodic supply of nutrients and inhibitors. In [4] the supply of nutrients and inhibitors is assumed to be a constant, so instead of that Eq. (1.4) is employed here, *i.e.*, in [4] $\varphi(t) = \sigma_\infty$, $\phi(t) \equiv \beta_\infty$, where σ_∞ and β_∞ are two constants. In this paper, as can be seen from Eq. (1.4), we assume that the supply of nutrient and inhibitors is periodic. This assumption is clearly more reasonable. We mainly study how the periodic supply of nutrient and inhibitors influences the growth of tumors. Note that in the original expressions of these equations in [4], besides some other terms reflecting the effect of vascular network of the tumor, there is a linear term of β in the diffusion equation for σ, reflecting the inhibitory action of the inhibitor to the nutrient. Here we remove such a term because it does not conform to the biological principle: If we add a linear term of β with a minus sign into the left-hand side of (1.1), then the solution of this equation may take negative values in some points, which contradicts the fact that it must be a nonnegative function. The effect of the vascular network in the tumor is neglected because here we only consider the growth of avascular tumors. However, the method developed in this paper can be easily extended to treat similar tumor models with the effect of vascular network involved. Equation (1.5) is based on ideas of Byrne [3], Byrne and Chaplain [4], and Cui [18].

The idea of considering the periodic supply of external nutrients and inhibitors is motivated by [28]. In [28], through experiments, the authors observed that after an initial exponential growth phase leading to tumor expansion, growth saturation is observed even in the presence of periodically applied nutrient supply. In this paper, we mainly discuss how the periodic supply of external nutrients and inhibitors affects the growth of avascular tumor growth.

The paper is arranged as follows. In Section 2 we prove global stability of tumor free equilibrium to system (1.1)-(1.6). Section 3 is devoted to the existence, uniqueness and stability of periodic solutions to system (1.1)-(1.6). In the last section we give some conclusion and discussion.

2 Global stability of tumor free equilibrium

Denote $\theta = \sqrt{\frac{\Gamma_2}{\Gamma_1}}$. By re-scaling the space variable we may assume that $\Gamma = 1$. Accordingly, the solution to (1.1)-(1.4) is

$$\sigma(r,t) = \frac{\varphi(t)R(t)}{\sinh R(t)}\frac{\sinh r}{r}, \qquad \beta(r,t) = \frac{\phi(t)R(t)}{\sinh(\theta R(t))}\frac{\sinh(\theta r)}{r}. \tag{2.1}$$

Substituting (2.1) to (1.5), one can get

$$\frac{dR}{dt} = R(t)\left[\lambda\varphi(t)p\bigl(R(t)\bigr) - \frac{\nu}{3} - \mu\phi(t)p\bigl(\theta R(t)\bigr)\right], \tag{2.2}$$

where $p(x) = \frac{x\coth x-1}{x^2}$. Denote $x = R^3$. Then Eq. (2.2) takes the form

$$\frac{dx}{dt} = \bigl[F(x) - \nu\bigr]x(t) =: H(x,t), \tag{2.3}$$

where $F(x) = 3\lambda\varphi(t)p(\sqrt[3]{x}) - 3\mu\phi(t)p(\theta\sqrt[3]{x})$. Accordingly, the initial condition takes the form

$$x(0) = x_0 = R_0^3. \tag{2.4}$$

Lemma 2.1 *For the function* $p(x) = \frac{x\coth x-1}{x^2}$, *the following assertions hold*:

(1) *$p(x)$ is monotone decreasing for all $x > 0$ and* $\lim_{t\to 0+} p(x) = \frac{1}{3}$, $\lim_{t\to +\infty} p(x) = 0$. *Therefore, if we define $p(0) = \frac{1}{3}$, then the function $p(x)$ is continuous on* $[0,+\infty)$.

(2) *The function $x^3p(x)$ is monotone increasing for all* $x > 0$.

(3) *The function $\frac{p'(\theta x)}{p'(x)}$ is strictly monotone increasing* (*respectively decreasing*) *if* $0 < \theta < 1$ (*respectively* $\theta > 1$), *and*

$$\lim_{t\to 0+}\frac{p'(\theta x)}{p'(x)} = \theta, \qquad \lim_{t\to +\infty}\frac{p'(\theta x)}{p'(x)} = \theta^{-2}.$$

Proof For (1) please see [29], (2), see [21], (3), see [19]. This completes the proof. □

In what follows, we always denote

$$\bar{\varphi} = \frac{1}{\omega}\int_0^\omega \varphi(t)\,dt, \qquad \varphi^* = \max_{0\le t\le\omega}\varphi(t), \qquad \varphi_* = \min_{0\le t\le\omega}\varphi(t) \ge 0,$$
$$\bar{\phi} = \frac{1}{\omega}\int_0^\omega \phi(t)\,dt, \qquad \phi^* = \max_{0\le t\le\omega}\phi(t), \qquad \phi_* = \min_{0\le t\le\omega}\phi(t) \ge 0.$$

Looking for (2.2), as $0 \le p(x) \le 1/3$, one can easily get if ν is sufficiently large ($\nu \ge \lambda\varphi^*$), then the trivial steady state of (2.2) is globally asymptotically stable. Actually, since

$$\frac{dR}{dt} \le R(t)\left[\frac{\lambda\varphi^*}{3} - \frac{\nu}{3}\right],$$

and the solutions to $\frac{dR}{dt} = R(t)[\frac{\lambda\varphi^*}{3} - \frac{\nu}{3}]$ tend to zero as $t \to \infty$ if $\nu \ge \lambda\varphi^*$, by the comparison principle one can get that the trivial steady state of (2.2) is globally asymptotically stable.

Our main results of this section are the following three theorems.

Theorem 2.2 *If* $0 < \theta \le 1$, *the zero steady state of* (2.3) *is globally stable if* $\bar{\phi} > \frac{1}{\mu}(\lambda\bar{\varphi} - \nu)$ *and one of two conditions*

- *either* $\lambda\varphi(t) - \mu\phi(t) \ge 0$
- *or* $\lambda\varphi(t) - \mu\phi(t) \le 0$

holds for $t \in [0,\omega]$.

Theorem 2.3 *If* $\theta > 1$, *assume that* $\lambda\varphi(t) - \mu\phi(t) \ge 0$ *for* $t \in [0,\omega]$ *holds. If the zero steady state of* (2.3) *is globally stable, then* $\bar{\phi} \ge \frac{1}{\mu}(\lambda\bar{\varphi} - \nu)$.

Theorem 2.4 (A1) *If* $0 < \theta \le 1$ *and one of two conditions*

- *either* $\phi_* \ge \lambda\varphi^*/(\theta^2\mu)$
- *or* $\phi_* < \lambda\varphi^*/(\theta^2\mu)$ *and* $\nu \ge \lambda\varphi^* - \mu\phi_*$

holds.

(A2) *If* $\theta > 1$ *and one of two conditions*

- *either* $\phi_* \ge \lambda\theta\varphi^*/\mu$
- *or* $\phi_* \le \lambda\theta\varphi^*/\mu$ *and* $\nu \ge \lambda\varphi^* - \mu\phi_*$

holds.

(A3) *If* $\frac{\lambda\varphi^*}{\mu\theta^2} < \phi_* < \frac{\theta\lambda\varphi^*}{\mu}$ *and* $\nu > M_1$ *hold, where* $M_1 = g(x^*)$, $g(x) = 3\lambda\varphi^* p(\sqrt[3]{x}) - 3\mu\phi_* p(\theta\sqrt[3]{x})$, *and* x^* *is the unique solution to* $\frac{p'(\theta\sqrt[3]{x^*})}{p'(\sqrt[3]{x^*})} = \frac{\lambda\varphi^*}{\mu\theta\phi_*}$.

Then the zero steady state of (2.3) *is globally stable, i.e.*,

$$\lim_{t\to\infty} x(t) = 0. \tag{2.5}$$

Remark A (1) Some sufficient conditions (Theorem 2.2, Theorem 2.4) and necessary conditions (Theorem 2.3) for tumor free are given. Obviously, the sufficient conditions for tumor free of Theorem 2.2 and Theorem 2.4 do not contain each other except the case that $\varphi(t) = \sigma_\infty$, $\phi(t) \equiv \beta_\infty$, where σ_∞ and β_∞ are two constants.

(2) Since

$$\text{(A1)} \quad \Leftrightarrow \quad 0 < \theta \le 1, \quad \phi_* \ge \frac{\lambda\varphi^* - \nu}{\mu},$$

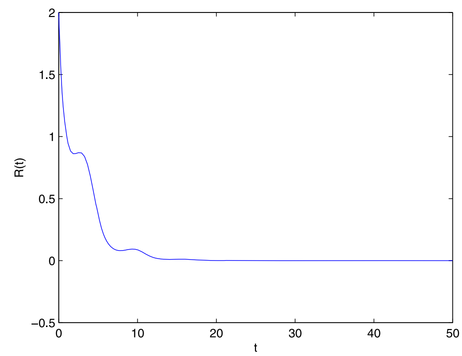
noticing $\bar{\phi} \ge \phi_*$, $\frac{\lambda\varphi^* - \nu}{\mu} \ge \frac{\lambda\bar{\varphi} - \nu}{\mu}$, then $\bar{\phi} \ge \phi_* \ge \frac{\lambda\varphi^* - \nu}{\mu} \ge \frac{\lambda\bar{\varphi} - \nu}{\mu}$. Thus Theorem 2.2 implies the part of Theorem 2.4(A1) for the cases either $\lambda\varphi(t) - \mu\phi(t) \ge 0$ or $\lambda\varphi(t) - \mu\phi(t) \le 0$. For example, the graph of $R(t)$ for $\varphi(t) = \sin t + 8$, $\phi(t) = \cos t + 6$, $\theta = 0.5$, $\omega = 2\pi$, $\lambda = \mu = 1$, $\nu = 3$ in Figure 1 and $\varphi(t) = \sin t + 8$, $\phi(t) = \cos t + 6$, $\theta = 0.5$, $\omega = 2\pi$, $\lambda = \mu = 1$, $\nu = 3$ which satisfy Theorem 2.2 but do not satisfy Theorem 2.4(A1).

The idea of the proof of Theorem 2.2 and Theorem 2.3 comes from [30, 31] where a delay differential equation is studied.

Proof of Theorem 2.2 Since $\bar{\varphi} = \frac{1}{\omega}\int_0^\omega \varphi(t)\,dt$, $\bar{\phi} = \frac{1}{\omega}\int_0^\omega \phi(t)\,dt$, for any $\xi \in [0,\omega]$,

$$\begin{aligned}
\int_\xi^{\xi+n\omega} \frac{dR}{R} &\le \int_\xi^{\xi+n\omega} \bigl[\lambda\varphi(t) - \mu\phi(t)\bigr] p\bigl(\theta R(t)\bigr)\,dt - \frac{1}{3}\int_\xi^{\xi+n\omega} \nu\,dt \\
&= \int_\xi^{\xi+n\omega} \bigl[\lambda\varphi(t) - \mu\phi(t)\bigr] p\bigl(\theta R(t)\bigr)\,dt - \frac{n\omega\nu}{3}.
\end{aligned}$$

Figure 1 **An example of the graph of $R(t)$ for $\varphi(t) = \sin t + 8$, $\phi(t) = \cos t + 6$, $\theta = 0.5$, $\omega = 2\pi$, $\lambda = \mu = 1$, $\nu = 3$ which satisfy Theorem 2.2.**



Then one can get

$$R(\xi + n\omega) \leq R(\xi)e^{\int_\xi^{\xi+n\omega}[\lambda\varphi(t)-\mu\phi(t)]p(\theta R(t))\,dt-\frac{n\omega}{3}\nu}. \tag{2.6}$$

Since $p(x)$ is monotone decreasing for all $x > 0$ and $p(x) < \frac{1}{3}$, then one can get: If $\lambda\varphi(t) - \mu\phi(t) \geq 0$ (or $\lambda\varphi(t) - \mu\phi(t) \leq 0$) for $t \in [0, \omega]$, then

$$R(\xi + n\omega) \leq \max\bigl\{R(\xi)e^{\frac{n\omega}{3}(\lambda\bar{\varphi}-\mu\bar{\phi}-\nu)}, R(\xi)e^{-\frac{n\omega\nu}{3}}\bigr\} \to 0, \quad n \to \infty \tag{2.7}$$

if $\bar{\phi} > \frac{1}{\mu}(\lambda\bar{\varphi} - \nu)$. This completes the proof of Theorem 2.2. □

Remark B If $\phi(t) \equiv 0$, *i.e.*, there is no supply of inhibitors, then $\bar{\phi} = 0$ and the condition $\lambda\varphi(t) - \mu\phi(t) \geq 0$ is obviously satisfied since $\varphi_* = \min_{0\leq t\leq\omega}\varphi(t) \geq 0$. Thus, if $0 < \theta \leq 1$, the zero steady state of (2.3) is globally stable if $0 = \bar{\phi} > \frac{1}{\mu}(\lambda\bar{\varphi} - \nu)$ ($\Leftrightarrow \nu > \lambda\bar{\varphi} - \mu\bar{\phi} = \lambda\bar{\varphi}$). By the similar method as that of the proof of Theorem 2.2, one can also prove if the conditions $\theta > 1$ and $\phi(t) \equiv 0$ hold, the zero steady state of (2.3) is globally stable if $0 = \bar{\phi} > \frac{1}{\mu}(\lambda\bar{\varphi} - \nu)$ ($\Leftrightarrow \nu > \lambda\bar{\varphi} - \mu\bar{\phi} = \lambda\bar{\varphi}$). Therefore, if $\phi(t) \equiv 0$, the zero steady state of (2.3) is globally stable if $\nu > \lambda\bar{\varphi}$.

Actually, $\phi(t) \equiv 0$ is not necessary. By (2.2), one can get

$$\frac{dR}{dt} \leq R(t)\left[\lambda\varphi(t)p\bigl(R(t)\bigr) - \frac{\nu}{3}\right], \tag{2.8}$$

by the similar method as that of the proof of Theorem 2.2, and by use of the comparison principle, one can also prove that the zero steady state of (2.2) is globally stable if $\nu > \lambda\bar{\varphi}$. We omit the details here.

Proof of Theorem 2.3 Since the zero steady state is globally stable, *i.e.*, $\lim_{t\to\infty} R(t) = 0$, given $\varepsilon_0 > 0$, there exists $t_\varepsilon > 0$ such that $R(t) < \varepsilon_0$ for $t \geq t_\varepsilon$. Then

$$\begin{aligned}\frac{dR}{R} &\geq \left[\bigl(\lambda\varphi(t) - \mu\phi(t)\bigr)p\bigl(R(t)\bigr) - \frac{\nu}{3}\right] \\ &\geq \bigl(\lambda\varphi(t) - \mu\phi(t)\bigr)p(\varepsilon_0) - \frac{\nu}{3}, \quad t \geq t_\varepsilon,\end{aligned}$$

where we have used the fact that p is monotone decreasing. Therefore

$$\frac{R(t+\omega)}{R(t)} \geq e^{\omega((\lambda\bar{\varphi}-\mu\bar{\phi})p(\varepsilon_0)-\frac{\nu}{3})}.$$

We use the method of reduction to absurdity. If $\bar{\phi} < \frac{1}{\mu}(\lambda\bar{\varphi}-\nu)$, choose ε_0 sufficiently small such that $p(\varepsilon_0) > \frac{\nu}{3(\lambda\bar{\varphi}-\mu\bar{\phi})}$, then

$$\frac{R(t+\omega)}{R(t)} \geq e^{((\lambda\bar{\varphi}-\mu\bar{\phi})p(\varepsilon_0)-\frac{1}{3}\nu)} > 1.$$

Therefore, we construct a sequence $\{R(t_\varepsilon + n\omega)\}_n$ that is strictly increasing, which is contradicts the assumption that the zero steady state is globally stable. Thus $\bar{\phi} < \frac{1}{\mu}(\lambda\bar{\varphi}-\nu)$ does not hold. This completes the proof of Theorem 2.3. □

Let $f(x) = 3\lambda ap(\sqrt[3]{x}) - 3\mu bp(\theta\sqrt[3]{x}) - \nu$. Then, by Lemma 2.1(1), one can get

$$\lim_{x\to 0+} f(x) = \lambda a - \mu b - \nu, \qquad \lim_{x\to +\infty} f(x) = -\nu. \tag{2.9}$$

By direct computation,

$$f'(x) = \frac{1}{\sqrt[3]{x^2}}\left[\lambda ap'\left(\sqrt[3]{x}\right) - \mu\theta bp'\left(\theta\sqrt[3]{x}\right)\right] = -\mu\theta bp'\left(\sqrt[3]{x}\right)\left(\frac{p'(\theta\sqrt[3]{x})}{p'(\sqrt[3]{x})} - \frac{\lambda a}{\mu\theta b}\right).$$

By Lemma 2.1(3) and (2.9), one can easily get the following assertions (see [18]).

Lemma 2.5 *Suppose first that* $0 < \theta < 1$. *Then the following assertions hold*:

(1) *If* $b \geq \frac{\lambda a}{\mu\theta^2}$, *then* $f(x) < 0$ *for all* $x > 0$.

(2) *If* $b < \frac{\lambda a}{\mu\theta^2}$, *then in the case* $\nu \geq \lambda a - \mu b$ *we have* $f(x) < 0$ *for all* $x > 0$; *and in the opposite case there exists a unique* x_s *such that* $f(x_s) = 0$, $f(x_s) > 0$ *for* $0 < x < x_s$, *and* $f(x_s) < 0$ *for* $x > x_s$.

Suppose next that $\theta > 1$. *Then the following assertions hold*:

(3) *If* $b \geq \frac{\theta\lambda a}{\mu}$, *then* $f(x) < 0$ *for all* $x > 0$.

(4) *If* $b < \frac{\lambda a}{\mu\theta^2}$, *then in the case* $\nu \geq \lambda a - \mu b$ *we have* $f(x) < 0$ *for all* $x > 0$; *and in the opposite case there exists a unique* x_s *such that* $f(x_s) = 0$, $f(x_s) > 0$ *for* $0 < x < x_s$, *and* $f(x_s) < 0$ *for* $x > x_s$.

(5) *If* $\frac{\lambda a}{\mu\theta^2} < b < \frac{\theta\lambda a}{\mu}$, *then there exists a unique* $x^* > 0$ *such that*

$$\frac{p'(\theta\sqrt[3]{x^*})}{p'(\sqrt[3]{x^*})} = \frac{\lambda a}{\mu\theta b},$$

where x^* *is the maximum point of* $g(x)$. *Denote* $M = g(x^*)$. *If* $\nu > M$, *then* $f(x) < 0$ *for all* $x > 0$. *If* $0 < \nu \leq \lambda a - \mu b$, *there exists a unique* x_s *such that* $f(x_s) = 0$, $f(x_s) > 0$ *for* $0 < x < x_s$, *and* $f(x_s) < 0$ *for* $x > x_s$. *If* $\lambda a - \mu b < \nu < M$, *then there exist two positive numbers* $x_1^* < x_2^*$ *such that* $f(x_1^*) = f(x_2^*) = 0$, $f(x) < 0$ *for* $x < x_1^*$ *and* $x > x_2^*$, $f(x) > 0$ *for* $x_1^* < x < x_2^*$.

Suppose last that $\theta = 1$, *the following assertions hold*:

(6) *In the case* $\nu \geq \lambda a - \mu b, f(x) < 0$ *for all* $x > 0$; *and in the opposite case there exists a unique* x_s *such that* $f(x_s) = 0, f(x_s) > 0$ *for* $0 < x < x_s$, *and* $f(x_s) < 0$ *for* $x > x_s$.

Proof of Theorem 2.4 By (2.3), we have

$$\frac{dx}{dt} \leq \left[g(x) - \nu\right]x(t), \tag{2.10}$$

where $g(x) = 3\lambda\varphi^* p(\sqrt[3]{x}) - 3\mu\phi_* p(\theta\sqrt[3]{x})$ as before. Consider the following initial problem:

$$\frac{dx}{dt} = \left[g(x) - \nu\right]x(t); \qquad x(0) = x_0 = R_0^3. \tag{2.11}$$

Let $a = \varphi^*$, $b = \phi_*$. Then, by Lemma 2.5, one can get the following assertions: If one of the assumptions (A1), (A2) and (A3) holds, then $g(x) - \nu < 0$ for all $x > 0$. By the well-known results of ODEs, one can get if one of (A1), (A2) and (A3) holds, the solution to (2.11) denoted by $x_1(t)$ tends to zero as $t \to +\infty$. By the comparison principle, we have $x(t) \leq x_1(t)$ for all $t \geq 0$. Then

$$0 \leq \lim_{t\to+\infty} x(t) \leq \lim_{t\to+\infty} x_1(t) = 0.$$

This completes the proof of Theorem 2.4. □

Remark C For $\theta = 1$, by similar arguments as those for Theorem 2.4, one can get that if $\phi_* \geq \lambda\varphi^*/\mu$ the solution to (2.3), (2.4) tends to 0 as $t \to \infty$, *i.e.*, $\lim_{t\to\infty} x(t) = 0$. Thus (A1) can be replaced by $0 < \theta \leq 1$ and $\phi_* \geq \lambda\varphi^*/(\theta^2\mu)$.

3 Existence, uniqueness and stability of periodic solutions

In the following, we will give a result that Eq. (2.3) admits an oscillatory solution whose period matches that of $\varphi(t)$ and $\phi(t)$. The conditions under which there exists a unique periodic solution to the model would be determined, and we also will show that the unique periodic solution is a global attractor of all other positive solutions.

Lemma 3.1 (see Theorem 4.1 and Corollary 5.1 in [32]) *Consider the following ODE*:

$$\frac{dy}{dt} = G(y,t), \quad t \in R, \tag{3.1}$$

where $G : [a,c] \times R \to R$ *is continuous and* T*-periodic with respect to* t. *If, for all* $t \in [0,T]$, $G(a,t) \geq 0$ *and* $G(c,t) \leq 0$, *then* $[a,c]$ *is invariant under* G; *moreover, Eq.* (3.1) *admits a* T*-periodic solution*, $y : R \to [a,c]$.

Lemma 3.2 *For* $0 < \theta < 1$, *the function*

$$k(x) = \frac{p(y)}{p(\theta y)}$$

is monotone decreasing for any $y > 0$. *For* $\theta > 1$, *the function* $k(x)$ *is monotone increasing for any* $y > 0$.

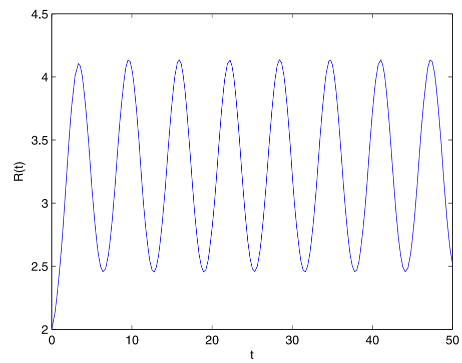


Figure 2 An example of the graph of $R(t)$ for $\varphi(t) = \sin t + 10$, $\phi(t) = \cos t + 4$, $\theta = 0.5$, $\omega = 2\pi$, $\lambda = \mu = 1$, $\nu = 3$ which satisfy Theorem 3.3.

Proof By direct computation,

$$\left(\frac{p(y)}{p(\theta y)}\right)' = \left(\frac{yp'(y)}{p(y)} - \frac{\theta yp'(\theta y)}{p(\theta y)}\right)\frac{p(y)}{yp(\theta y)}. \tag{3.2}$$

From Lemma 2.2 in [27], we know that the function $\frac{p(y)}{yp'(y)}$ is monotone increasing for any $y > 0$. Therefore $h(x) := \frac{yp'(y)}{p(y)}$ is monotone decreasing for any $y > 0$. It follows that

$$\frac{yp'(y)}{p(y)} - \frac{\theta yp'(\theta y)}{p(\theta y)} < 0\ (> 0)$$

for $0 < \theta < 1$ ($\theta > 1$) since $\frac{p(y)}{yp(\theta y)} > 0$. This completes the proof. □

Our main result of this section is Theorem 3.3.

Theorem 3.3 (Figure 2) *If the conditions* $0 < \theta < 1$, $\phi^* < \frac{\lambda\varphi_*}{\mu\theta^2}$ *and* $\nu < \lambda\varphi_* - \mu\phi^*$ *hold, then*

(I) *there exists a unique* ω*-periodic positive solution* $\bar{x}(t)$ *to Eq.* (2.3).

(II) *For any other positive solution* $x(t)$ *to Eq.* (2.3), *there holds*

$$\lim_{t\to\infty}\left[x(t) - \bar{x}(t)\right] = 0. \tag{3.3}$$

Proof Consider the following two problems:

$$\frac{dx}{dt} = \left[g(x) - \nu\right]x, \tag{3.4}$$

and

$$\frac{dx}{dt} = \left[g_1(x) - \nu\right]x, \tag{3.5}$$

where $g(x) = 3\lambda\varphi^* p(\sqrt[3]{x}) - 3\mu\phi_* p(\theta\sqrt[3]{x})$ as before and $g_1(x) = 3\lambda\varphi_* p(\sqrt[3]{x}) - 3\mu\phi^* p(\theta\sqrt[3]{x})$.

By Lemma 2.5, we obtain that if $(\phi_* \le)\phi^* < \frac{\lambda\varphi_*}{\mu\theta^2}$ and $\nu < \lambda\varphi_* - \mu\phi^*$ ($\le \lambda\varphi^* - \mu\phi_*$), there exist two positive constants c, d such that $g(c) - \nu = 0$ and $g_1(d) - \nu = 0$. Obviously,

$$H(c,t) = \big(F(c) - \nu\big)c \le \big(g(c) - \nu\big)c = 0, \qquad H(d,t) = \big(F(d) - \nu\big)d \ge \big(g_1(d) - \nu\big)d = 0.$$

By Lemma 3.2 we have $d < c$ since for $0 < \theta < 1$, the function $k(x) = \frac{p(y)}{p(\theta y)}$ is monotone decreasing and

$$\frac{p(\sqrt[3]{c})}{p(\theta\sqrt[3]{c})} = \frac{\mu\phi_*}{\lambda\varphi^*} < \frac{\mu\phi^*}{\lambda\varphi_*} = \frac{p(\sqrt[3]{d})}{p(\theta\sqrt[3]{d})}.$$

Then by Lemma 3.1 we have $[d, c]$ is invariant under H, moreover Eq. (2.3) admits a T-periodic solution. This completes the proof of Theorem 3.3.

Next we prove the uniqueness. Let $Y = |x_1(t) - x_2(t)|$, where $x_1(t)$ and $x_2(t)$ are two solutions to Eq. (2.3), by the mean value theorem and noticing that every solution to Eq. (2.3) $x_1(t)$ and $x_2(t)$ satisfies $x_0e^{-(\lambda\phi^*+\nu)t} \leq x_i(t) \leq x_0e^{\lambda\varphi^*t}$, $i = 1, 2$. By direct computation, one can get

$$p'(x) = \frac{2\sinh^2 x - x^2 - x\sinh x\cosh x}{x^3\sinh^2 x},$$

then

$$\begin{aligned}\left|p'(\sqrt[3]{x})\right| &\leq \frac{2\sinh^2 y + y^2 + y\sinh y\cosh y}{y^3\sinh^2 y}\bigg|_{y=\sqrt[3]{x}} \\ &\leq \frac{2\sinh^2 y_0 + y_0^2 + y_0\sinh y_0\cosh y_0}{y_1^3\sinh^2 y_1} \\ &=: \delta_1(T)\end{aligned}$$

and

$$\begin{aligned}\left|p'(\theta\sqrt[3]{x})\right| &\leq \frac{2\sinh^2 y + y^2 + y\sinh y\cosh y}{y^3\sinh^2 y}\bigg|_{y=\theta\sqrt[3]{x}} \\ &\leq \frac{2\sinh^2(\theta y_0) + \theta^2 y_0^2 + \theta y_0\sinh(\theta y_0)\cosh(\theta y_0)}{\theta^3 y_1^3\sinh^2(\theta y_1)} \\ &=: \delta_2(T),\end{aligned}$$

where $y_0 = \sqrt[3]{x_0e^{\lambda\varphi^*T}}$, $y_1 = \sqrt[3]{x_0e^{-(\lambda\phi^*+\nu)T}}$. Since

$$\begin{aligned}Y'(t) &= \left|x_1'(t) - x_2'(t)\right| \\ &= \left|\left[F(x_1) - \nu\right]x_1 - F(x_2) - \nu]x_2\right| \\ &= \left|F(x_1)(x_1 - x_2) + \left(F(x_1) - F(x_2)\right) - \nu(x_1 - x_2)\right| \\ &\leq \left|F(x_1) + \nu\right||x_1 - x_2| + |x_2|\left|F'(\xi)\right||x_1 - x_2| \\ &\leq \left(\lambda\varphi^* + \mu\phi^* + \nu\right)Y(t) + |x_2|\left|F'(\xi)\right|Y(t) \\ &\leq \delta(T)Y(t),\end{aligned}$$

where ξ is between x_1 and x_2, $F'(x) = [\lambda\varphi(t)p'(\sqrt[3]{x}) - \theta\mu\phi(t)p'(\theta\sqrt[3]{x})]\frac{1}{\sqrt[3]{x^2}}$, and $\delta(T) = (\lambda\varphi^* + \mu\phi^* + \nu) + e^{(\lambda\varphi^*+\mu\phi^*+\nu)T}[\lambda\varphi^*\delta_1(T) + \theta\mu\phi^*\delta_2(T)]$. Since $Y(0) = 0$, by Gronwall's lemma we conclude that $Y(t) \equiv 0$ for $0 \leq t \leq T$. Hence $x_1(t) = x_2(t)$.

In the following we will prove (II). By the existence and uniqueness, assume that $x(t) > \bar{x}(t)$ for all t (the proof when $x(t) < \bar{x}(t)$ for all t is similar and will be omitted). Set

$$x(t) = \bar{x}(t)e^{y(t)}. \tag{3.6}$$

Then $y(t) > 0$ for all t, and

$$y'(t) = 3\lambda\varphi\bigl[p\bigl(\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\sqrt[3]{\bar{x}}\bigr)\bigr] - 3\mu\phi\bigl[p\bigl(\sqrt[3]{\theta\bar{x}e^{y}}\bigr) - p\bigl(\sqrt[3]{\theta\bar{x}}\bigr)\bigr]. \tag{3.7}$$

By simple computation, one can get

$$\bigl(\theta p(\theta z) - p(z)\bigr)' > 0 \quad\Leftrightarrow\quad \frac{p'(\theta z)}{p'(z)} < \frac{1}{\theta^2}. \tag{3.8}$$

By Lemma 2.1(3), we know that $p(x)$ is decreasing and for $0 < \theta < 1$, $(\theta p(\theta z) - p(z))' > 0$. Then we have

$$0 > \theta p\bigl(\theta\sqrt[3]{\bar{x}e^{y}}\bigr) - \theta p\bigl(\theta\sqrt[3]{\bar{x}}\bigr) > p\bigl(\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\sqrt[3]{\bar{x}}\bigr).$$

For $0 < \theta < 1$, direct computation yields

$$\begin{aligned}
y'(t) &= 3\lambda\varphi\bigl[p\bigl(\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\sqrt[3]{\bar{x}}\bigr)\bigr] - 3\mu\phi\bigl[p\bigl(\theta\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\theta\sqrt[3]{\bar{x}}\bigr)\bigr] \\
&\le 3\lambda\varphi_*\bigl[p\bigl(\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\sqrt[3]{\bar{x}}\bigr)\bigr] - 3\mu\phi^*\bigl[p\bigl(\theta\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\theta\sqrt[3]{\bar{x}}\bigr)\bigr] \\
&\le \frac{3\lambda\varphi_*}{\theta^3}\bigl[p\bigl(\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\sqrt[3]{\bar{x}}\bigr)\bigr] - \frac{3\mu\phi^*}{\theta}\bigl[\theta p\bigl(\theta\sqrt[3]{\bar{x}e^{y}}\bigr) - \theta p\bigl(\theta\sqrt[3]{\bar{x}}\bigr)\bigr] \\
&\le \left(\frac{3\lambda\varphi_*}{\theta^3} - \frac{3\mu\phi^*}{\theta}\right)\bigl[\theta p\bigl(\theta\sqrt[3]{\bar{x}e^{y}}\bigr) - \theta p\bigl(\theta\sqrt[3]{\bar{x}}\bigr)\bigr] \\
&= \left(\frac{3\lambda\varphi_*}{\theta^2} - 3\mu\phi^*\right)\bigl[p\bigl(\theta\sqrt[3]{\bar{x}e^{y}}\bigr) - p\bigl(\theta\sqrt[3]{\bar{x}}\bigr)\bigr] < 0,
\end{aligned}$$

where we have used the fact that $p(x)$ is monotone decreasing for all $x > 0$ and inequality (3.8). Thus, $y(t)$ is decreasing, and therefore the limit $\lim_{t\to\infty} y(t)$ exists, denote $\lim_{t\to\infty} y(t) = \alpha$, then $\alpha \in [0,\infty)$. Now we shall prove that $\alpha = 0$. If $\alpha > 0$, for any $\varepsilon > 0$ ($\varepsilon < \alpha$), there exists $T_\varepsilon > 0$ such that for $t \ge T_\varepsilon$, $0 < \alpha - \varepsilon < y(t) < \alpha + \varepsilon$. However, from (3.7), one can get

$$y'(t) < 3\lambda\varphi\bigl[p\bigl(\sqrt[3]{\bar{x}e^{(\alpha-\varepsilon)}}\bigr) - p\bigl(\sqrt[3]{\bar{x}}\bigr)\bigr] - 3\mu\phi\bigl[p\bigl(\sqrt[3]{\theta\bar{x}e^{(\alpha-\varepsilon)}}\bigr) - p\bigl(\sqrt[3]{\theta\bar{x}}\bigr)\bigr]. \tag{3.9}$$

Integrating (3.9) from T_ε to ∞ immediately gives a contraction since $3\lambda\varphi[p(\sqrt[3]{\bar{x}e^{(\alpha-\varepsilon)}}) - p(\sqrt[3]{\bar{x}})] - 3\mu\phi[p(\sqrt[3]{\theta\bar{x}e^{(\alpha-\varepsilon)}}) - p(\sqrt[3]{\theta\bar{x}})] < 0$. Hence $\alpha = 0$, and therefore $\lim_{t\to\infty} y(t) = 0$. Thus

$$\lim_{t\to\infty}\bigl[x(t) - \bar{x}(t)\bigr] = \lim_{t\to\infty}\bar{x}(t)\bigl[e^{y(t)} - 1\bigr] = 0.$$

This completes the proof of (II). □

4 Conclusion and discussion

In this paper a free boundary problem for solid avascular tumor growth in a periodic environment is studied. The periodic environment means that the supply of nutrient and inhibitors is periodic with the same period, and the periodic supply of inhibitors can be interpreted as a periodic treatment and $\phi(t)$ describes the external concentration of inhibitors. We mainly study how the periodic supply of inhibitors affects the growth of tumors. We have derived sufficient conditions (Theorem 2.2, Theorem 2.4) and necessary conditions (Theorem 2.3) for tumor free and proved the existence, uniqueness and stability of periodic solutions under some conditions (Theorem 3.3). Hence, in biology sense, the results of Theorem 2.2 and Theorem 2.4 have practical significance in terms of determining the amount of drug required to eliminate the tumor. From Theorem 3.3, we know that if external concentration of nutrients is large, the tumor will not disappear, and the conditions under which there exists a unique periodic solution to the model are determined. The result of Theorem 3.3 also shows that the unique periodic solution is a global attractor of all other positive solutions.

The periodic environment means that the supply of nutrient and inhibitors is periodic with the same period. As being pointed out by a referee, and I agree, the model used here can be extended to a more general one that the periods of the supply of nutrient and inhibitors are assumed to be different. If the periods of the supply of nutrient and inhibitors are assumed to be different, do these results remain true or not? This is an interesting but may be a challenging problem.

Competing interests
The author declares that they have no competing interests.

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