# Analysis of a free boundary problem modeling spherically symmetric tumor growth with angiogenesis and a periodic supply of nutrients 

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#### Abstract

In this paper, we study a free boundary problem modeling spherically symmetric tumor growth with angiogenesis and a periodic supply of nutrients. The mathematical model is a free boundary problem since the external radius of the tumor denoted by $R(t)$ changes with time. The characteristic of this model is the consideration of both angiogenesis and periodic external nutrient supply. The cells inside the tumor absorb nutrient $u(r, t)$ through blood vessels and attracts blood vessels at a rate proportional to $\alpha$. Thus on the boundary, we have


$$
u_{r}(r, t)+\alpha(u(r, t)-\psi(t))=0, \quad r=R(t), t>0,
$$

where $\psi(t)$ is the nutrient concentration provided externally. Considering that the nutrient provided externally to the tumor are generally provided periodically, in this paper, we assume that $\psi(t)$ is a periodic function. Sufficient conditions for a tumor to disappear are given. We investigate the existence, uniqueness, and stability of solutions. The results show that when the nutrient concentration exceeds a certain value and $c$ is sufficiently small, the solutions of the model can be arbitrarily close to the unique periodic function as $t \rightarrow \infty$.

Keywords: Tumor growth; Free boundary problem; Angiogenesis; Asymptotic behavior; Periodic solution

## 1 Introduction

Over the past few decades, various mathematical models were proposed to study different stages and different effects on tumor growth, such as studies on avascular stage (see, e.g., $[1,2,5,6,9,10,12,16,17])$, studies on the stage with angiogenesis (see, e.g., $[11,13,14,20])$, studies on the effect of inhibitors [4, 7-9], studies on the effects of time delays [2, 3, 8, 9, 15 , 18, 19], and so on. The main goal of this paper is to study the effects of periodic nutrient supply on the dynamics of tumor growth with angiogenesis.
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In this paper, we study the following mathematical model:

$$
\begin{align*}
& c u_{t}=\Delta_{r} u-\lambda u \quad \text { in } r<R(t), t>0,  \tag{1.1}\\
& u_{r}(r, t)+\alpha(u(r, t)-\psi(t))=0 \quad \text { on } r=R(t), t>0,  \tag{1.2}\\
& \frac{d}{d t}\left(\frac{4 \pi R^{3}(t)}{3}\right)=4 \pi\left(\int_{0}^{R(t)} s u(r, t) r^{2} d r-\int_{0}^{R(t)} s \tilde{u} r^{2} d r\right), \quad t>0,  \tag{1.3}\\
& R(0)=R_{0},  \tag{1.4}\\
& u(r, 0)=u_{0}(r), \quad \text { where } u_{0}(r) \in[0, \psi(0)], \text { for } r \in\left[0, R_{0}\right], \tag{1.5}
\end{align*}
$$

where

$$
\Delta_{r} \cdot=\frac{1}{r^{2}} \frac{\partial}{\partial r}\left(r^{2} \frac{\partial \cdot}{\partial r}\right)
$$

In the model, $u(r, t)$ and $R(t)$ are two unknown functions, where $u(r, t)$ is the nutrient concentration, and $R(t)$ denotes the external radius; $\lambda u$ in equation (2.1) is the consumption rate of nutrient; $\alpha$ is a positive constant, which represents the density of blood vessels; $\psi(t)$ is a positive-valued function showing the concentration of nutrient outside the tumor; $s u$ is the proliferation rate; the first term on the right-hand side of equation (2.3) is the total volume increase caused by cell proliferation. The second term on the right-hand side of equation (2.3) is the total volume decrease caused by the natural death, and the natural death rate is $s \tilde{u}$, which is a constant. $c$ is a positive constant, which represents the ratio of the nutrient diffusion time scale to the tumor growth time scale; for details, see [9, 12]. From [4, 7] we know that $c \ll 1$.
The above model in the case where $\alpha=\infty$ and $c=0$ has been studied by Bai and Xu [1]. Under two-dimensional nonradial symmetric perturbations, the linear stability of periodic solutions is studied by Huang et al. [14]. Recently, He and Xing [13] extend the results of [1] and discussed the three-dimensional nonradially symmetric perturbations. The above model in the case where $\alpha=\infty$ and

$$
\begin{equation*}
\psi(t)=\bar{\sigma}\left(1-\gamma_{0} \kappa\right), \tag{1.6}
\end{equation*}
$$

induced by the Gibbs-Thomson relation, has been studied by Wu [16, 17], where $\bar{\sigma}$ and $\gamma_{0}$ are constants, $\kappa$ represents the mean curvature of the outer boundary of the tumor, and $\gamma_{0}$ describes cell-to-cell adhesiveness. The case where $\psi(t)$ is assumed to be a positive constant but $\alpha$ is considered more general and is a function of $t$ has been studied by Friedman and Lam [11]. In [11] the concentration of nutrient outside the tumor is assumed to be a constant, but in this paper, as we can see from (2.2), we assume that the nutrient provided externally to the tumor is generally provided periodically, so that $\psi(t)$ is a periodic function. This assumption is clearly more reasonable.

We give aufficient conditions for a tumor to disappear, and the results show that the tumor will tend to disappear when the average nutrient concentration provided by the outside is lower than a certain value within a cycle time (Theorem 3.1). We investigate the existence, uniqueness, and stability of solutions. We also study the asymptotic behavior of the solutions. The results show that when the nutrient concentration exceeds a certain
value and $c$ is sufficiently small, the solutions of the model can be arbitrarily close to the unique periodic function as $t \rightarrow \infty$ (Theorem 3.6).
The paper is arranged as follows: In Sect. 2, we prove the global existence and uniqueness of solutions to the system. In Sect. 3, we study the asymptotic behavior of the solutions.

## 2 Global existence and uniqueness

By the change of variables

$$
\hat{r}=\sqrt{\lambda} r, \quad \hat{u}=s u, \quad \hat{\psi}=s \psi, \quad \hat{\tilde{u}}=s \tilde{u}
$$

after dropping """, we simplify the problem to the following system:

$$
\begin{align*}
& c u_{t}=\Delta_{r} u-u \quad \text { in } r<R(t), t>0,  \tag{2.1}\\
& u_{r}(r, t)+\alpha(u(r, t)-\psi(t))=0 \quad \text { on } r=R(t), t>0,  \tag{2.2}\\
& R^{2}(t) R^{\prime}(t)=\int_{0}^{R(t)} u(r, t) r^{2} d r-\int_{0}^{R(t)} \tilde{u} r^{2} d r, \quad t>0,  \tag{2.3}\\
& R(0)=R_{0},  \tag{2.4}\\
& u(r, 0)=u_{0}(r), \quad \text { where } u_{0}(r) \in[0, \psi(0)], \text { for } r \in\left[0, R_{0}\right] . \tag{2.5}
\end{align*}
$$

In this paper, we assume that the following conditions are satisfied:
(A1) $\psi$ is a positive-valued differentiable function on $(0, \infty)$ and $\psi(t)=\psi(t+\omega)$, where $\omega>0$ is a constant. Moreover, there exists a positive constant $B_{0}>0$ such that $\left|\psi^{\prime}(t)\right| \leq B_{0}$ for $t \geq 0$.
(A2) $u_{0}(r)$ is a twice differentiable function.
We denote

$$
\bar{\psi}=\frac{1}{\omega} \int_{0}^{\omega} \psi(t) d t, \quad \psi^{*}=\max _{0 \leq t \leq \omega} \psi(t), \quad \psi_{*}=\min _{0 \leq t \leq \omega} \psi(t) .
$$

Let

$$
p(x)=\frac{x \operatorname{coth} x-1}{x^{2}}, \quad g(x)=x p(x)=\operatorname{coth} x-\frac{1}{x}, \quad \text { and } \quad G(x)=\frac{\alpha p(x)}{\alpha+g(x)} .
$$

Lemma 2.1 (1) $p^{\prime}(x)<0$ for all $x>0, \lim _{x \rightarrow 0+} p(x)=1 / 3$, and $\lim _{x \rightarrow \infty} p(x)=0$.
(2) $g^{\prime}(x)>0$ for $x \geq 0, \lim _{x \rightarrow 0^{+}} g(x)=0, \lim _{x \rightarrow \infty} g(x)=1$.
(3) $G^{\prime}(x)<0$ for $x>0, \lim _{x \rightarrow 0^{+}} G(x)=1 / 3, \lim _{x \rightarrow \infty} G(x)=0$.

Proof (1) See [12]. Property (2) is from [11]. (3) can be easily obtained from (1) and (2).

Lemma 2.2 Let $(u(r, t), R(t))$ be a solution of (2.1)-(2.5). Then for $0<c<\psi_{*} / B_{0}$, we have the following prior estimates:
(1) $0 \leq u(r, t) \leq \psi(t)$ for $r \leq R(t), t \geq 0$.
(2) $K_{1} R(t) \leq R^{\prime}(t) \leq K_{2} R(t)$, where $K_{1}=-\tilde{u} / 3$ and $K_{2}=\left(\psi^{*}-\tilde{u}\right) / 3$.
(3) $R_{0} e^{K_{1} t} \leq R(t) \leq R_{0} e^{K_{2} t}$ for all $t \geq 0$.

Proof (1) For $0<c<\psi_{*} / B_{0}$, it is easy to check that $u_{1}=0$ and $u_{2}=\psi(t)$ are lower and upper solutions to problem (2.1), (2.2), and (2.5). According to the comparison principle, it follows that $0 \leq u(r, t) \leq \psi(t)$ for $r \leq R(t), t \geq 0$.
(2) Using (1), from (2.5) we get

$$
\begin{equation*}
-\int_{0}^{R(t)} \tilde{u} r^{2} d r \leq R^{2}(t) R^{\prime}(t) \leq \int_{0}^{R(t)}[\psi(t)-\tilde{u}] r^{2} d r, \tag{2.6}
\end{equation*}
$$

which implies $K_{1} R(t) \leq R^{\prime}(t) \leq K_{2} R(t)$, where $K_{1}=-\tilde{u} / 3$ and $K_{2}=\left(\psi^{*}-\tilde{u}\right) / 3$.
(3) From (2), integrating the three parts separately, we readily get that $R_{0} e^{K_{1} t} \leq R(t) \leq$ $R_{0} e^{K_{2} t}$ for all $t \geq 0$. This completes the proof.

Theorem 2.3 For $c>0$ sufficiently small, problem (2.1)-(2.5) has a unique solution ( $u(r, t), R(t)$ ) for $t \geq 0$.

Proof First, the free boundary problem can be transformed into a fixed boundary problem by variable transformation $r \mapsto \frac{r}{R(t)}$, and then the existence and uniqueness of the solution follow by the Banach fixed point theorem. The proof is completely similar to that of Theorem 1.1 in [20], and we omit the details. This competes the proof.

## 3 Asymptotic behavior of the solutions

Theorem 3.1 If $\bar{\psi}<\tilde{u}$, then for any positive initial value $R_{0}$, we have $\lim _{t \rightarrow \infty} R(t)=0$.

Proof From Lemma 2.2(1) we obtain

$$
\begin{equation*}
-\frac{1}{R^{2}(t)} \int_{0}^{R(t)} \tilde{u} r^{2} d r \leq R^{\prime}(t) \leq \frac{1}{R^{2}(t)} \int_{0}^{R(t)}[\psi(t)-\tilde{u}] r^{2} d r, \quad t>0 . \tag{3.1}
\end{equation*}
$$

It follows that for $t \geq 0$,

$$
R(t) \geq R_{0} \exp (-\tilde{u} t / 3)>0
$$

and

$$
\begin{equation*}
\frac{R^{\prime}(t)}{R(t)} \leq \frac{\psi(t)-\tilde{u}}{3} \tag{3.2}
\end{equation*}
$$

For any $\zeta \in[0, \omega]$, integrating with respect to $t$ from $\zeta$ to $\zeta+n \omega$ both sides of (3.2), we obtain

$$
R(\zeta+n \omega) \leq R(\zeta) \exp \left(\frac{n(\bar{\psi}-\tilde{u}) \omega}{3}\right) \rightarrow 0 \quad \text { as } n \rightarrow \infty
$$

which implies $\lim _{t \rightarrow \infty} R(t)=0$, where we use the fact

$$
\int_{\zeta}^{\zeta+n \omega} \psi(t) d t=\int_{0}^{n \omega} \psi(t) d t=n \int_{0}^{\omega} \psi(t) d t=n \omega \bar{\psi}
$$

This completes the proof.

Let

$$
\begin{equation*}
\nu(r, t)=\frac{\alpha \psi(t)}{\alpha+g(R(t))} \frac{R(t) \sinh r}{r \sinh R(t)} . \tag{3.3}
\end{equation*}
$$

Then $v$ satisfies the following equations:

$$
\begin{align*}
& \Delta_{r} v=\frac{1}{r^{2}} \frac{\partial}{\partial r}\left(r^{2} \frac{\partial v}{\partial r}\right)=v \quad \text { in } r<R(t), t>0,  \tag{3.4}\\
& v_{r}(r, t)+\alpha(v(r, t)-\psi(t))=0 \quad \text { on } r=R(t), t>0 \tag{3.5}
\end{align*}
$$

Consider the following equation:

$$
\begin{equation*}
\frac{d \tilde{R}}{d t}=\tilde{R}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(\tilde{R}(t))} p(\tilde{R}(t))-\frac{\tilde{u}}{3}\right] \tag{3.6}
\end{equation*}
$$

By the comparison principle we get

$$
\begin{equation*}
\tilde{R} \geq \tilde{R}(0) \exp (-\tilde{u} t / 3)>0 \quad \text { for } t>0 \tag{3.7}
\end{equation*}
$$

Lemma 3.2 Let $\psi$ satisfies (A1). If $\bar{\psi}>\tilde{u}$, then
(1) there exists a unique positive $\omega$-periodic solution $\bar{R}(t)$ to (3.6).
(2) Let $\tilde{R}(t)$ be a positive solution of (3.6). Then there exist positive constants $C_{0}$ and $\gamma$ such that

$$
\begin{equation*}
|\tilde{R}(t)-\bar{R}(t)| \leq C_{0} \exp (-\gamma t) \tag{3.8}
\end{equation*}
$$

Proof (1) Since $G^{\prime}(x)<0$ and $G(x) \in(0,1 / 3)$ (see Lemma 2.1(3)), if $\tilde{u}<\bar{\psi} \leq \psi^{*}$, then

$$
\frac{\tilde{u}}{3 \bar{\psi}}, \frac{\tilde{u}}{3 \psi^{*}} \in(0,1 / 3) .
$$

Let

$$
b=G^{-1}\left(\frac{\tilde{u}}{3 \bar{\psi}}\right), \quad x_{1}=b / \exp \left(\frac{\psi^{*}-\tilde{u}}{3} \omega\right), \quad x_{2}=p^{-1}\left(\frac{\tilde{u}}{3 \psi^{*}}\right)
$$

For $R_{0} \in\left[x_{1}, x_{2}\right]$, let $\tilde{R}(t)$ be the solution of (3.6) with initial value $R_{0}$. Define the map $F:\left[x_{1}, x_{2}\right] \rightarrow(0, \infty)$ by $F\left(R_{0}\right)=\tilde{R}(T)$. First, we prove that $F$ maps $\left[x_{1}, x_{2}\right]$ into itself. For $R_{0} \in\left[x_{1}, x_{2}\right]$, it is obvious that $x_{2}$ is an upper solution of (3.6). It follows that

$$
\begin{equation*}
\tilde{R}(t) \leq x_{2} \quad \text { for all } t>0 \tag{3.9}
\end{equation*}
$$

Thus $\tilde{R}(\omega) \leq x_{2}$. Consider the following initial problem:

$$
\left\{\begin{array}{l}
\frac{d R_{1}}{d t}=R_{1}(t)\left[\frac{\alpha \psi(t)}{\alpha+g\left(R_{1}(t)\right)} p\left(R_{1}(t)\right)-\frac{\tilde{u}}{3}\right]  \tag{3.10}\\
R_{1}(0)=x_{1}
\end{array}\right.
$$

By the comparison principle we have

$$
\begin{equation*}
\tilde{R}(t) \geq R_{1}(t) \quad \text { for } t>0 \tag{3.11}
\end{equation*}
$$

Since $G(x)<1 / 3$ (see Lemma 2.1(3)), we get

$$
\frac{d R_{1}}{d t}=R_{1}(t)\left[\frac{\alpha \psi(t)}{\alpha+g\left(R_{1}(t)\right)} p\left(R_{1}(t)\right)-\frac{\tilde{u}}{3}\right] \leq R_{1}(t)\left(\frac{\psi^{*}}{3}-\frac{\tilde{u}}{3}\right) .
$$

It follows that

$$
R_{1}(t) \leq x_{1} \exp \left(\left(\frac{\psi^{*}}{3}-\frac{\tilde{u}}{3}\right) t\right) \leq x_{1} \exp \left(\left(\frac{\psi^{*}}{3}-\frac{\tilde{u}}{3}\right) \omega\right)=b=G^{-1}\left(\frac{\tilde{u}}{3 \bar{\psi}}\right)
$$

for $0 \leq t \leq \omega$. Since

$$
\begin{aligned}
\frac{d R_{1}}{d t} & =R_{1}(t)\left[\frac{\alpha \psi(t)}{\alpha+g\left(R_{1}(t)\right)} p\left(R_{1}(t)\right)-\frac{\tilde{u}}{3}\right] \\
& \geq R_{1}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(b)} p(b)-\frac{\tilde{u}}{3}\right],
\end{aligned}
$$

we can get

$$
\begin{equation*}
R_{1}(\omega) \geq R_{1}(0) \exp \left(\frac{\omega \alpha \bar{\psi}}{\alpha+g(b)} p(b)-\frac{\tilde{u} \omega}{3}\right)=R_{1}(0)=x_{1} . \tag{3.12}
\end{equation*}
$$

From (3.9), (3.11), and (3.12) it follows that $\tilde{R}(\omega) \in\left[x_{1}, x_{2}\right]$. Thus $F$ maps $\left[x_{1}, x_{2}\right]$ into itself. Since the solution $\tilde{R}(t)$ depends continuously on the initial value $R_{0}$, it follows that $F$ is continuous. By Brouwer's fixed point theorem, $F$ has a fixed point $\bar{R}(0)$. It follows that the solution $\bar{R}(t)$ of (3.6) through the initial point $\left(0, R_{0}\right)$ is a positive $\omega$-periodic solution.

Next, we will prove that $\bar{R}(t)$ is a global attractor of all other positive solutions, which also implies the uniqueness of the periodic solution $\bar{R}(t)$.
(2) Let

$$
\bar{R}^{*}=\max _{0 \leq t \leq \omega} \bar{R}(t), \quad \bar{R}_{*}=\min _{0 \leq t \leq \omega} \bar{R}(t) .
$$

Inequality (3.7) implies that $\bar{R}^{*} \geq \bar{R}_{*}>0$.
The uniqueness of the solution of (3.6) and the comparison principle imply that if $\tilde{R}(0)>$ $\bar{R}(0)$, then there must be $\tilde{R}(t)>\bar{R}(t)$ for $t>0$, and if $\tilde{R}(0)<\bar{R}(0)$, then $\bar{R}(t)<\bar{R}$ for $t>0$. Assume that $\tilde{R}(t)>\bar{R}$ for $t>0$ (the proof of the case where $\tilde{R}(t)<\bar{R}$ for $t>0$ is similar and is omitted). Let

$$
\begin{equation*}
\tilde{R}(t)=\bar{R}(t) \exp (y(t)) \tag{3.13}
\end{equation*}
$$

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

$$
y^{\prime}(t)=\psi(t)\left[\frac{\alpha p(\bar{R}(t) \exp (y(t)))}{\alpha(t)+g(\bar{R}(t) \exp (y(t)))}-\frac{\alpha p(\bar{R}(t))}{\alpha+g(\bar{R}(t))}\right]
$$

$$
\begin{aligned}
& =\psi(t) G^{\prime}(\eta(t)) \bar{R}(t)(\exp (y(t)-1)) \\
& \leq-\psi_{*} A_{0} \bar{R}_{*}(\exp (y(t)-1)),
\end{aligned}
$$

where

$$
\eta(t)=\theta \bar{R}(t)+(1-\theta) \bar{R}(t) \exp (y(t)) \subseteq\left[\bar{R}_{*}, \bar{R}^{*} \exp (y(0)], \quad 0 \leq \theta \leq 1\right.
$$

and

$$
A_{0}=\min _{x \in \Omega}\left(-G^{\prime}(x)\right), \quad \text { where } \Omega=\left\{x \mid x \in\left[\bar{R}_{*}, \bar{R}^{*} \exp (y(0))\right]\right\}
$$

Therefore

$$
\begin{equation*}
\frac{(\exp (y(t))-1)^{\prime}}{\exp (y(t))-1} \leq-\psi_{*} A_{0} \bar{R}_{*} \tag{3.14}
\end{equation*}
$$

It follows that

$$
\begin{equation*}
\exp (y(t))-1 \leq(\exp (y(0))-1) \exp \left(\left(-\psi_{*} A_{0} \bar{R}_{*}\right) t\right) \tag{3.15}
\end{equation*}
$$

for $t>0$, and hence

$$
\begin{equation*}
\tilde{R}(t)-\bar{R}(t)=\bar{R}(t)(\exp (y(t))-1) \leq \bar{R}(t)(\exp (y(0))-1) \exp \left(\left(-\psi_{*} A_{0} \bar{R}_{*}\right) t\right) \tag{3.16}
\end{equation*}
$$

for $t>0$.
For the case $\tilde{R}(t)<\bar{R}$ for $t>0$, using similar arguments, it is not hard to get

$$
\begin{align*}
\bar{R}(t)-\tilde{R}(t) & =\bar{R}(t)(1-\exp (y(t))) \\
& \leq \bar{R}(t)(1-\exp (y(0))) \exp \left(\left(-\psi_{*} A_{1} \bar{R}_{*} \exp (y(0)) t\right)\right. \tag{3.17}
\end{align*}
$$

where

$$
\left.A_{1}=\min _{x \in \Omega}\left(-G^{\prime}(x)\right), \quad \text { where } \Omega=\left\{x \mid x \in\left[\bar{R}_{*} \exp (y(0)), \bar{R}^{*}\right)\right]\right\}
$$

Taking $\gamma=\min \left\{\psi_{*} A_{0} \bar{R}_{*} \exp \left(y(0), \psi_{*} A_{1} \bar{R}_{*} \exp (y(0)\}\right.\right.$ and $C_{0}=|1-\exp (y(0))| \bar{R}^{*}$, from (3.16) and (3.17) we easily get

$$
|\tilde{R}(t)-\bar{R}(t)| \leq C_{0} \exp (-\gamma t)
$$

for $t>0$. This completes the proof of Lemma 3.2.

Lemma 3.3 Let $(u(r, t), R(t))$ be a solution of (2.1)-(2.5). Suppose that for $T_{0} \in(0, \infty)$ and $a>0$,

$$
\begin{equation*}
\max \left\{\left|(R \psi)^{\prime}\right|,\left|R^{\prime}(t)\right|\right\} \leq K \leq K_{0}, \quad a \leq R(t) \leq 1 / a . \tag{3.18}
\end{equation*}
$$

Suppose further that

$$
\begin{equation*}
\left|u_{0}(r)-v(r, 0)\right| \leq M \leq M_{0} \tag{3.19}
\end{equation*}
$$

Then there exists positive constant $C$ and $c_{0}$, depending only on a, $\alpha, K_{0}, L_{0}, M_{0}, \psi^{*}$, such that

$$
\begin{equation*}
|u(r, t)-v(r, t)| \leq C K\left(c+e^{-t / c}\right) \tag{3.20}
\end{equation*}
$$

for $0 \leq r \leq R(t), 0<t \leq T_{0}$, and $0<c \leq c_{0}$.
Proof Direct calculation yields

$$
\begin{aligned}
v_{t}(r, t)= & (R(t) \psi(t))^{\prime} \frac{\alpha}{\alpha+g(R(t))} \frac{\sinh r}{r \sinh R(t)} \\
& -R^{\prime}(t) \psi(t) \frac{\alpha\left(g^{\prime}(R) \sinh R+(\alpha+g(R)) \cosh R\right) R}{((\alpha+g(R)) \sinh R)^{2}} \cdot \frac{\sinh r}{r}
\end{aligned}
$$

By (3.18) we get that for $0 \leq r \leq R(t)$,

$$
\begin{equation*}
\left|v_{t}(r, t)\right| \leq C K \tag{3.21}
\end{equation*}
$$

where $C$ only depends on $\psi^{*}, \alpha$, and $a$.
Let

$$
u_{ \pm}(r, t)=v(r, t) \pm C K c \pm M e^{-t / c}
$$

Then

$$
c \frac{\partial u_{+}}{\partial t}-\Delta_{r} u_{+}+u_{+} \geq-C K c+C K c=0
$$

Since

$$
\begin{equation*}
\frac{\partial u_{+}}{\partial r}+\alpha\left(u_{+}-\psi(t)\right)=\alpha\left(C K c+M e^{-t / c}\right) \geq 0 \quad \text { on } r=R(t), t>0 \tag{3.22}
\end{equation*}
$$

and $u_{+}(r, 0) \geq u_{0}(r)$, by the comparison principle it follows that

$$
u_{+}(r, t) \geq u(r, t) \quad \text { for } 0 \leq r \geq R(t), 0<t \leq T
$$

Using similar arguments, we easily get

$$
u_{-}(r, t) \leq u(r, t) \quad \text { for } 0 \leq r \geq R(t), 0<t \leq T
$$

This completes the proof.
If $\psi_{*}>\tilde{u}$, then

$$
0<\frac{\tilde{u}}{3 \psi^{*}} \leq \frac{\tilde{u}}{3 \psi_{*}}<\frac{1}{3}
$$

Noticing that $G^{\prime}(x)<0$ and $G(x) \in(0,1 / 3)$, we can get that $G(x)=\frac{\tilde{u}}{3 \psi_{*}}$ and $G(y)=\frac{\tilde{u}}{3 \psi^{*}}$ have unique positive constants solutions $X_{0}$ and $Y_{0}$, respectively, and $X_{0} \leq Y_{0}$.

Lemma 3.4 Let $(u(r, t), R(t))$ be a solution of (2.1)-(2.5). Suppose that $R_{0} \in[a, 1 / a]$ for some $a>0$. When $\psi_{*}>\tilde{u}$, there exists a positive constant $c_{0}$, independent of $c$, such that

$$
\begin{equation*}
\frac{1}{2} \min \left\{X_{0}, a\right\} \leq R(t) \leq 2 \max \left\{Y_{0}, 1 / a\right\} \tag{3.23}
\end{equation*}
$$

for $t \geq 0$ and $c \in\left(0, c_{0}\right]$.

Proof If inequality (3.23) does not hold for some $t$, then there exists $T>0$ such that for $t \in[0, T)$,

$$
\frac{1}{2} \min \left\{X_{0}, a\right\} \leq R(t) \leq 2 \max \left\{Y_{0}, 1 / a\right\}
$$

and either $R(T)=2 \max \{\bar{R}, 1 / a\}$ or $R(T)=\frac{1}{2} \min \{\bar{R}, a\}$.
If $R(T)=2 \max \left\{Y_{0}, 1 / a\right\}$, then it follows that $R^{\prime}(T) \geq 0$. From (3.1) notice that for $0 \leq t<$ $T$,

$$
\frac{1}{2} \min \left\{X_{0}, a\right\} \leq R(t) \leq 2 \max \left\{Y_{0}, 1 / a\right\}
$$

and we get that $\left|R^{\prime}(t)\right| \leq K_{0}$, where $K_{0}$ is a positive constant independent of $c$ and $T$. It is obvious that $|u(r, 0)-v(r, 0)| \leq \psi^{*}$. Then by Lemma 3.3,

$$
|u(r, t)-v(r, t)| \leq C\left(c+e^{-t / c}\right)
$$

Then

$$
\begin{aligned}
R^{\prime}(t) & =\frac{1}{R^{2}(t)}\left(\int_{0}^{R(t)} u(r, t) r^{2} d r-\int_{0}^{R(t)} \tilde{u} r^{2} d r\right) \\
& \leq \frac{1}{R^{2}(t)}\left(\int_{0}^{R(t)} v(r, t) r^{2} d r+\frac{1}{3} C\left(c+e^{-t / c}\right) R^{3}(t)\right)-\frac{1}{3} \tilde{u} R(t) \\
& =\frac{R(t)}{3}\left(\frac{3 \alpha \psi(t)}{\alpha+g(R(t))} p(R(t))-\tilde{u}+C\left(c+e^{-t / c}\right)\right) \\
& \leq \frac{R(t)}{3}\left(\frac{3 \alpha \psi^{*}}{\alpha+g(R(t))} p(R(t))-\tilde{u}+C\left(c+e^{-t / c}\right)\right)
\end{aligned}
$$

In particular,

$$
R^{\prime}(T) \leq \frac{R(T)}{3}\left(\frac{3 \alpha \psi^{*}}{\alpha+g(R(T))} p(R(T))-\tilde{u}+C\left(c+e^{-T / c}\right)\right)
$$

Notice that

$$
\frac{3 \alpha \psi^{*}}{\alpha+g(R(T))} p(R(T))-\tilde{u}<\frac{3 \alpha \psi^{*}}{\alpha+g\left(Y_{0}\right)} p\left(Y_{0}\right)-\tilde{u}=0
$$

so choosing $c_{0}$ sufficiently small, for $c \in\left(0, c_{0}\right]$, we have

$$
\frac{\alpha \psi^{*}}{\alpha+g(R(T))} p(R(T))-\tilde{u}+C\left(c+e^{-T / c}\right)<0
$$

which implies $R^{\prime}(T)<0$, which contradicts with $R^{\prime}(T) \geq 0$.
If $R(T)=\frac{1}{2} \min \left\{X_{0}, a\right\}$, then the proof is similar, so we omit the details. This completes the proof.

Lemma 3.5 Let $(u(r, t), R(t))$ be a solution of (2.1)-(2.5), and let

$$
\begin{equation*}
\bar{v}(r, t)=\frac{\alpha \psi(t)}{\alpha+g(\bar{R}(t))} \frac{\bar{R}(t) \sinh r}{r \sinh \bar{R}(t)} . \tag{3.24}
\end{equation*}
$$

Suppose $\psi$ satisfies (A1) and suppose further that $R(t) \in[a, 1 / a]$ for some $a>0$. Then there exists positive constants $c_{0}, C$, and $T_{0}$, independent of $c$, such that the following statement holds: If for $c \in\left(0, c_{0}\right]$ and any $b \in\left(0, b_{0}\right]$,

$$
\begin{equation*}
|R(t)-\bar{R}(t)| \leq b, \quad \max \left\{\left|(R \psi)^{\prime}\right|,\left|R^{\prime}(t)\right|\right\} \leq b, \quad|u(r, t)-\bar{v}(r, t)| \leq b \tag{3.25}
\end{equation*}
$$

for $t \geq 0$ and $0 \leq r \leq R(t)$, then for $t \geq T_{0}$, we have

$$
\begin{equation*}
|R(t)-\bar{R}(t)| \leq C b\left(c+e^{-\gamma t}\right), \quad|u(r, t)-\bar{v}(r, t)| \leq C b\left(c+e^{-\gamma t}\right) \tag{3.26}
\end{equation*}
$$

and

$$
\begin{equation*}
\left|R^{\prime}(t)-\bar{R}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(\bar{R}(t))} p(\bar{R}(t))-\frac{\tilde{u}}{3}\right]\right| \leq C b\left(c+e^{-\gamma t}\right) \tag{3.27}
\end{equation*}
$$

for $0 \leq r \leq R(t)$.
Proof By the mean value theorem, using the facts that $R(t) \in[a, 1 / a]$ and $\bar{R}(t) \in\left[\bar{R}_{*}, \bar{R}^{*}\right]$, we get

$$
\begin{equation*}
|v(r, t)-\bar{v}(r, t)| \leq C|R(t)-\bar{R}(t)| \leq C b \tag{3.28}
\end{equation*}
$$

for $t \geq 0$ and $0 \leq r \leq R(t)$. We further denote by $C$ different constants independent of $c$ and $\eta$. Thus

$$
\begin{equation*}
|u(r, t)-\bar{v}(r, t)| \leq|u(r, t)-v(r, t)|+|v(r, t)-\bar{v}(r, t)| \leq C b \tag{3.29}
\end{equation*}
$$

for $t \geq 0$ and $0 \leq r \leq R(t)$. Particularly,

$$
\left|u_{0}(r)-\bar{v}(r, 0)\right| \leq C b \quad \text { for } 0 \leq r \leq R_{0}
$$

Since $\left|R^{\prime}(t)\right| \leq b$, by Lemma 3.3 there exists a constant $c_{0}$ such that

$$
\begin{equation*}
|u(r, t)-v(r, t)| \leq C b\left(c+e^{-t / c}\right) . \tag{3.30}
\end{equation*}
$$

Noticing that $t e^{-t} \leq 1$ for $t>0$, it follows that

$$
e^{-t / c} \leq c / t \leq c / T_{0} \quad \text { for } t \geq T_{0}>1 .
$$

By a simple calculation we obtain that

$$
\begin{equation*}
\frac{1}{R^{2}(t)} \int_{0}^{R(t)}(v(r, t)-\tilde{u}) r^{2} d r=R(t)\left[\frac{\alpha \psi(t)}{\alpha+g(R(t))} p(R(t))-\frac{\tilde{u}}{3}\right] \tag{3.31}
\end{equation*}
$$

Then for $t \geq T_{0}>1$, we have

$$
\begin{aligned}
& \left|R^{\prime}(t)-R(t)\left[\frac{\alpha \psi(t)}{\alpha+g(R(t))} p(R(t))-\frac{\tilde{u}}{3}\right]\right| \\
& \quad=\frac{1}{R^{2}(t)} \int_{0}^{R(t)}(u(r, t)-v(r, t)) r^{2} d r \\
& \quad \leq \frac{1}{3 R^{2}(t)}\left(C b\left(c+e^{-t / c}\right) R^{3}(t)\right) \\
& \quad=\frac{R(t)}{3}\left(C b\left(c+e^{-t / c}\right)\right) \\
& \quad \leq \frac{R(t)}{3}\left(C b\left(c+\frac{c}{T_{0}}\right)\right) \\
& \quad \leq \operatorname{CbcR}(t)
\end{aligned}
$$

It follows that

$$
\begin{align*}
& \left|R^{\prime}(t)-\bar{R}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(\bar{R}(t))} p(\bar{R}(t))-\frac{\tilde{u}}{3}\right]\right|  \tag{3.32}\\
& \quad \leq C b c R(t)+\left\lvert\, R(t)\left[\frac{\alpha \psi(t)}{\alpha+g(R(t))} p(R(t))-\frac{\tilde{u}}{3}\right]\right. \\
& \left.\quad-\bar{R}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(\bar{R}(t))} p(\bar{R}(t))-\frac{\tilde{u}}{3}\right] \right\rvert\,  \tag{3.33}\\
& \quad \leq C b c+C|R(t)-\bar{R}(t)| . \tag{3.34}
\end{align*}
$$

If $\psi_{*}>\tilde{u}$, then there exists $c_{0}>0$ sufficiently small such that

$$
\psi_{*}>\tilde{u} \mp C b c
$$

for $c \in\left(0, c_{0}\right]$ and any $b \in\left(0, b_{0}\right]$. By arguments similar to those in the proof of Lemma 3.2, for the two initial value problems

$$
\left\{\begin{array}{l}
\frac{d R^{ \pm}}{d t}=R^{ \pm}(t)\left[\frac{\alpha \psi(t)}{\alpha+g\left(R^{ \pm}(t)\right)} p\left(R^{ \pm}(t)\right)-\frac{\tilde{u}}{3} \mp C b c\right], \quad t \geq T_{0}  \tag{3.35}\\
R^{ \pm}\left(T_{0}\right)=\bar{R}^{ \pm}\left(T_{0}\right) \exp \left( \pm C b T_{0}\right)
\end{array}\right.
$$

we can get the following statements: Assume that $\psi$ satisfies (A1). If $\psi_{*}>\tilde{u}$, then
(1) there exists a unique positive $\omega$-periodic solution $\bar{R}^{ \pm}(t)$ to (3.35).
(2) For any other positive solutions of (3.35), there exists a positive constant $\gamma_{1}$ such that

$$
\begin{equation*}
\left|R^{ \pm}(t)-\bar{R}^{ \pm}(t)\right| \leq C \exp \left(-\gamma_{1} t\right) \tag{3.36}
\end{equation*}
$$

where $C=\left|1-\exp \left(y\left(T_{0}\right)\right)\right|\left(\bar{R}^{ \pm}\right)^{*},\left(\bar{R}^{ \pm}\right)^{*}=\max _{0 \leq t \leq \omega} \bar{R}^{ \pm}(t)$, and $R^{ \pm}(t)=\bar{R}^{ \pm}(t) \exp (y(t))$. Then

$$
\left|1-\exp \left(y\left(T_{0}\right)\right)\right|\left(\bar{R}^{ \pm}\right)^{*} \leq C \mid\left(y\left(T_{0}\right) \mid \leq C b\right.
$$

since $\left|y\left(T_{0}\right)\right|=\left|\ln \exp \left( \pm C b T_{0}\right)\right| \leq C b$. Therefore

$$
\begin{equation*}
\left|R^{ \pm}(t)-\bar{R}^{ \pm}(t)\right| \leq C b \exp \left(-\gamma_{1} t\right) \tag{3.37}
\end{equation*}
$$

For $t \in\left[T_{0}, T_{0}+\omega\right]$ and $c$ sufficiently small,

$$
\begin{aligned}
& \mid \bar{R}^{+}(t)-\bar{R}^{-}(t) \mid \\
& \quad=\left|R\left(T_{0}\right)\right| \left\lvert\, \exp \left(\int_{0}^{t} \psi(\xi) G\left(\bar{R}^{+}(\xi)\right)-\frac{\tilde{u}}{3}-C b c\right) d \xi\right. \\
& \left.-\exp \left(\int_{0}^{t} \psi(\xi) G\left(\bar{R}^{-}(\xi)\right)-\frac{\tilde{u}}{3}+C b c\right) d \xi \right\rvert\, \\
& \quad \leq\left|R\left(T_{0}\right)\right|\left|\exp \left(\psi^{*} t / 3\right) \exp (-C b c t)-\exp (-\tilde{u} t / 3) \exp (C b c t)\right| \\
& \quad \leq\left|R\left(T_{0}\right)\right|\left(\left|\exp \left(\psi^{*} t / 3\right)(\exp (-C b c t)-1)\right|+|\exp (-\tilde{u} t / 3)(\exp (C b c t)-1)|\right) \\
& \quad \leq\left|R\left(T_{0}\right)\right|\left(\left|\exp \left(\psi^{*} \omega / 3\right)(\exp (-C b c \omega)-1)\right|+|(\exp (C b c \omega)-1)|\right) \\
& \quad \leq C b c
\end{aligned}
$$

where we used the fact that

$$
\left|e^{x}-1\right| \leq C|x|, \quad C>2 \text { for }|x|>0 \text { sufficiently small. }
$$

Since $\bar{R}^{+}(t)$ and $\bar{R}^{-}(t)$ are periodic functions with the same period $\omega$, we have

$$
\left|\bar{R}^{+}(t)-\bar{R}^{-}(t)\right| \leq C b c
$$

for $t \geq T_{0}$. By the comparison principle it follows that

$$
R^{-}(t) \leq \bar{R}(t), \quad R(t) \leq R^{+}(t)
$$

and

$$
\bar{R}^{-}(t) \leq \bar{R}(t), \quad R(t) \leq \bar{R}^{+}(t)
$$

Therefore

$$
\begin{align*}
& |R(t)-\bar{R}(t)|  \tag{3.38}\\
& \quad \leq \max \left|R^{ \pm}(t)-\bar{R}(t)\right| \tag{3.39}
\end{align*}
$$

$$
\begin{align*}
& \leq \max \left|R^{ \pm}(t)-\bar{R}^{ \pm}(t)\right|+\max \left|\bar{R}^{ \pm}(t)-\bar{R}(t)\right|  \tag{3.40}\\
& \leq C b \exp \left(-\gamma_{1} t\right)+\left|\bar{R}^{+}(t)-\bar{R}^{-}(t)\right|  \tag{3.41}\\
& \leq C b\left(\exp \left(-\gamma_{1} t\right)+c\right) . \tag{3.42}
\end{align*}
$$

From (3.28) we obtain

$$
|v(r, t)-\bar{v}(r . t)| \leq C b\left(c+\exp \left(-\gamma_{1} t\right)\right)
$$

By (3.30) we get

$$
|u(r, t)-v(r . t)| \leq C b(c+\exp (-\gamma t))
$$

where $\gamma=\min \left\{\gamma_{1}, 1 / c_{0}\right\}$. Then (3.29) implies

$$
|u(r, t)-\bar{v}(r, t)| \leq C b(c+\exp (-\gamma t))
$$

Then (3.27) follows from (3.32)-(3.34) and (3.38)-(3.42). This completes the proof.

Theorem 3.6 Let $(u(r, t), R(t))$ be a solution of (2.1)-(2.5). Assume that $\psi_{*}>\bar{u}$. Suppose for some $a>0$, there holds $R_{0} \in[a, 1 / a]$. Then, for any $\epsilon>0$, there exist positive constant $c_{0}$ and $T_{0}$ such that if $c \in\left(0, c_{0}\right]$, there hold

$$
\limsup _{t \rightarrow \infty}|R(t)-\bar{R}(t)| \leq \epsilon, \quad \limsup _{t \rightarrow \infty}|u(r, t)-\bar{v}(r, t)| \leq \epsilon
$$

and

$$
\begin{equation*}
\limsup _{t \rightarrow \infty}\left|R^{\prime}(t)-\bar{R}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(\bar{R}(t))} p(\bar{R}(t))-\frac{\tilde{u}}{3}\right]\right| \leq \epsilon \tag{3.43}
\end{equation*}
$$

Proof From Lemma 3.4 we know that there exists a positive constant $c_{0}$, independent of $c$, such that

$$
\begin{equation*}
\frac{1}{2} \min \left\{X_{0}, a\right\} \leq R(t) \leq 2 \max \left\{Y_{0}, 1 / a\right\} \tag{3.44}
\end{equation*}
$$

for $t \geq 0$ and $c \in\left(0, c_{0}\right]$. Besides,

$$
|R(t)-\bar{R}(t)| \leq \frac{2}{a}+2 Y_{0}+\bar{R}^{*}=: b_{1}
$$

By Lemma 2.2(ii) we easily get that $\left|R^{\prime}(t)\right| \leq \frac{2}{a}\left(\left|M_{1}\right|+\left|M_{2}\right|\right)=: b_{2}$ for $0 \leq r \leq R(t)$. Then

$$
\left|(R \psi)^{\prime}\right| \leq\left|R^{\prime} \psi\right|+\left|R \psi^{\prime}\right| \leq b_{2} \psi^{*}+B_{0}\left(2 / a+2 Y_{0}\right)=: b_{3} .
$$

Clearly, $|u(r, t)-v(r, t)| \leq 2 \psi(t) \leq 2 \psi^{*}=b_{4}$. Let $b_{0}=\max \left\{b_{1}, b_{2}, b_{3}, b_{4}\right\}$. Then (3.25) holds for $0<b \leq b_{0}$. By Lemma 3.5 we obtain

$$
|R(t)-\bar{R}(t)| \leq C b_{0}\left(c+e^{-\gamma t}\right), \quad|u(r, t)-\bar{v}(r, t)| \leq C b_{0}\left(c+e^{-\gamma t}\right)
$$

and

$$
\left|R^{\prime}(t)-\bar{R}(t)\left[\frac{\alpha \psi(t)}{\alpha+g(\bar{R}(t))} p(\bar{R}(t))-\frac{\tilde{u}}{3}\right]\right| \leq C b_{0}\left(c+e^{-\gamma t}\right)
$$

Choose $c_{0}$ small enough and $T_{0}$ large enough such that

$$
e^{-\gamma T_{0}}+c_{0}<\frac{\epsilon}{C b_{0}}
$$

Thus, by taking the upper limit of the two sides of the above inequalities respectively, one can get the desired results. This completes the proof of Theorem 3.6.

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Not applicable.

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The authors declare no competing interests.

## Author contributions

Shihe Xu wrote the main manuscript text and Meng Bai did some analysis. All authors reviewed the manuscript.
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