Analysis of a free-boundary tumor model with angiogenesis

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Abstract

We consider a free boundary problem for a spherically symmetric tumor with free boundary $r < R(t)$. In order to receive nutrients u the tumor attracts blood vessel at a rate proportional to $\alpha(t)$, so that $\frac{\partial u}{\partial r} + \alpha(t)(u - \bar{u}) = 0$ holds on the boundary, where $\bar{u}$ is the nutrient concentration outside the tumor. A parameter μ in the model is proportional to the 'aggressiveness' of the tumor. When α is a constant, the existence and uniqueness of stationary solution is proved. For the more general situation when α depends on time, we show, under various conditions (that are always satisfied if μ is small), that (i) $R(t)$ remains bounded if $\alpha(t)$ remains bounded; (ii) $\lim_{t\to\infty} R(t) = 0$ if $\lim_{t\to\infty} \alpha(t) = 0$; and (iii) $\liminf_{t\to\infty} R(t) > 0$ if $\liminf_{t\to\infty} \alpha(t) > 0$. Surprisingly, we exhibit solutions (when μ is not small) where $\alpha(t) \to 0$ exponentially in t while $R(t) \to \infty$ exponentially in t. Finally, we prove the global asymptotic stability of steady state when μ is sufficiently small.

1 Introduction

In a live tissue with uniformly distributed cells the concentration of nutrients, $\hat{u}$, satisfies a diffusion equation

$$c\frac{\partial \hat{u}}{\partial t} = \Delta \hat{u} + A(u_B - \hat{u}) - \lambda_0 \hat{u}$$

where $A(u_B - \hat{u})$ is the rate of nutrient concentration supplied by the vascular system and $\lambda_0 u$ is the consumption rate of nutrients by the cells. This model was proposed in [4] to describe the evolution of spherical tumors with uniformly distributed tumor cells. As a result of cells proliferation and death, the tumor region $\{r < R(t)\}$ varies in time; see also [1, 2, 3, 4, 5, 8], and the references therein, for other models developed over the last few decades where the tumor's evolution is represented in the form of a free-boundary problem.

We assume that the nutrient concentration outside the tumor is a constant $\bar{\bar{u}}$. Let $\tilde{\tilde{u}}$ denote the critical concentration below which cells cannot survive in the sense that

$$A(u_B - \tilde{\tilde{u}}) - \lambda_0 \tilde{\tilde{u}} < 0, \quad \text{or} \quad \tilde{\tilde{u}} > \frac{u_B}{1 + \lambda_0/A}.$$

We also assume that the proliferation (or death) rate of cells is proportional to $\hat{u} - \bar{\bar{u}}$, taking it to be $\nu(\hat{u} - \bar{\bar{u}})$ for some positive constant ν. The parameter ν, in the case of a tumor, represents aggressiveness of the tumor: large ν means faster proliferation rate, provided the tumor receives sufficient nutrients, i.e. provided $\hat{u} > \tilde{\tilde{u}}$.

Setting

$$u = \hat{u} - \frac{u_B}{1+\lambda_0/A}, \quad \tilde{u} = \tilde{\tilde{u}} - \frac{u_B}{1+\lambda_0/A}, \quad \bar{u} = \bar{\bar{u}} - \frac{u_B}{1+\lambda_0/A}, \quad \lambda = A + \lambda_0,$$

we get

$$c\frac{\partial u}{\partial t} = \Delta u - \lambda u \quad \text{in} \quad r < R(t).$$

Since nutrients enter the sphere by the vascular system, using homogenization [9] it is natural to assume that

$$\frac{\partial u}{\partial r} + \alpha(t)(u - \bar{u}) = 0 \quad \text{on} \quad r = R(t),$$

where $\alpha(t)$ is a positive-valued function which depends on the density of the blood vessels; this function may vary in time. Noting that $\nu(\hat{u} - \tilde{\tilde{u}}) = \nu(u - \tilde{u})$, we also have,

$$\frac{dR(t)}{dt} = \frac{\nu}{R(t)^2} \int_0^{R(t)} r^2 (u(r,t) - \tilde{u})\, dr.$$

By the maximum principle, if $0 \le u(r,0) \le \bar{u}$ then $0 \le u(r,t) \le \bar{u}$; hence if $\tilde{u} > \bar{u}$ then the tumor shrinks and $R(t) \searrow 0$ as $t \to \infty$. We shall henceforth exclude this case, and always assume that $\tilde{u} < \bar{u}$.

Tumor cells are known to secrete cytokines that stimulate the vascular system to grow toward the tumor, a process called *angiogenesis*, which results in an increase in $\alpha(t)$. On the other hand, if the tumor is treated with anti-angiogenic drugs, $\alpha(t)$ will decrease and may become very small and the starved tumor will shrink. In the limiting ischemic case where $\alpha(t) \to 0$, we expect that $R(t)$ will actually decrease to zero as $t \to \infty$.

The above system with the boundary condition $u = \bar{u}$ on $r = R(t)$ (which is formally the case $\alpha(t) = \infty$) was studied in [7].

In Section 3, we first show that for any $\alpha > 0$ and $\eta = \frac{\tilde{u}}{\bar{u}} \in (0,1)$ there exists a unique stationary solution $u_*(r)$ with radius R_* which depends only on the parameters α and η. Moreover, $R_* \to 0$ as $\alpha \to 0$, and R_* approaches the radius of the stationary solution studied in [7], as $\alpha \to \infty$.

We next consider the more general situation when α depends on t and show, under some conditions (which are always satisfied if $\frac{c\nu}{\lambda}$ is sufficiently small), that

(a) $R(t)$ remains bounded if $\alpha(t)$ is uniformly bounded (Section 4);

(b) $R(t) \to 0$ as $t \to \infty$ if $\alpha(t) \to 0$ as $t \to \infty$ (Section 5);

(c) $\liminf_{t\to\infty} R(t) > 0$ if $\liminf_{t\to\infty} \alpha(t) > 0$ (Section 6).

But, surprisingly, we give examples (Section 7) (when $\frac{c\nu}{\gamma}$ is not small) where $\alpha(t) \to 0$ as $t \to \infty$ while $R(t) \to \infty$ as $t \to \infty$. Finally in Sections 8 and 9 we prove, when $\alpha(t) \to \alpha_*$ for some $\alpha_* > 0$, that if $c\nu/\gamma$ is sufficiently small then the steady state solution corresponding to the case $\alpha = \alpha_*$ is globally asymptotically stable.

2 Preliminaries

We simplify the system of (u, R) in Section 1 by a change of variables:

$$v' = \sqrt{\lambda} r, \quad t' = \lambda/ct, \quad \alpha'(t') = \frac{\alpha(t)}{\sqrt{\lambda}}, \quad \mu = \frac{c\nu}{\lambda}, \quad u'(r', t') = u(r, t), \quad R'(t') = \sqrt{\lambda} R(t),$$

and after dropping the "$'$", we get the following simpler system:

$$\frac{\partial u}{\partial t} = \Delta u - u \quad \text{in} \quad r < R(t), \tag{1}$$

$$\frac{\partial u}{\partial r} + \alpha(t)(u - \bar{u}) = 0 \quad \text{on} \quad r = R(t), \tag{2}$$

$$\frac{dR}{dt} = \frac{\mu}{R(t)^2} \int_0^{R(t)} (u - \tilde{u}) r^2 \, dr, \quad \tilde{u} \in (0, \bar{u}). \tag{3}$$

We prescribe an initial condition:

$$u(r, 0) = u_0(r), \quad \text{where} \quad 0 \le u_0(r) \le \bar{u} \quad \text{for} \quad 0 \le r \le R(0). \tag{4}$$

As in [7] one can prove that the system (1) - (4) has a unique global solution, $0 < u(r, t) < \bar{u}$ if $0 \le r \le R(t)$, $t > 0$, and

$$-\frac{\mu \tilde{u}}{3} \le \frac{1}{R} \frac{dR}{dt} \le \frac{\mu(\bar{u} - \tilde{u})}{3} \quad \text{for all } t > 0. \tag{5}$$

Next, we introduce the functions

$$f(s) = \frac{\sinh s}{s}, \quad g(s) = \frac{f'(s)}{f(s)} = \coth s - \frac{1}{s} \quad \text{and} \quad h(s) = \frac{f'(s)}{s f(s)} = \frac{g(s)}{s}, \tag{6}$$

and note, by direct computation, that

$$f''(s) + \frac{2}{s} f'(s) = f(s). \tag{7}$$

The following three lemmas will be used in the paper.

Lemma 2.1. *The function $g(s)$ has the following properties:*

$$\text{(i) } g(0) = 0, \quad \text{(ii) } \lim_{s \to \infty} g(s) = 1, \quad \text{(iii) } g'(0) = \frac{1}{3}, \quad \text{(iv) } g'(s) > 0 \text{ for } s \ge 0.$$

Lemma 2.2. *The function $h(s)$ has the following properties:*

$$\text{(i) } h'(s) < 0 \text{ for } s > 0, \quad \text{(ii) } \lim_{s \to 0} h(s) = \frac{1}{3}, \quad \text{(iii) } \lim_{s \to \infty} h(s) = 0.$$

A direct consequence of Lemma 2.2 is the following:

Corollary 2.3. *For any $0 < \tilde{u} < \bar{u}$, there exists an $a_0 > 0$ such that*

$$h(a_0) = \frac{f'(a_0)}{a_0 f(a_0)} = \frac{1}{3} \frac{\tilde{u}}{\bar{u}}.$$

Lemma 2.4. *The following identity holds for any $k \in [0, 1]$:*

$$\int_{kR}^{R} r^2 f\left(\frac{ar}{R}\right) dr = \frac{R^3}{a} \left[f'(a) - k^2 f'(ka) \right].$$

The proofs of Lemmas 2.1, 2.2 and 2.4 are given in the appendix.

3 $\alpha(t) =$ constant

In this section we consider the case where $\alpha(t) \equiv$ const. $\equiv \alpha$, and establish the existence of a unique steady state solution. A (radially symmetric) steady state solution of (1) and (2) (with $\alpha(t) = \alpha$), must have the form

$$u_*(r) = \frac{\alpha \bar{u}}{\alpha + g(R_*)} \frac{f(r)}{f(R_*)} \quad \text{for } 0 < r < R_*, \tag{8}$$

where by (3)

$$\frac{1}{3}\tilde{u} R_*^3 = \int_0^{R_*} u_*(r) r^2 \, dr. \tag{9}$$

Substituting (8) into (9) and using Lemma 2.4, we find that

$$h(R_*) = \frac{g(R_*)}{R_*} = \frac{\eta}{3}\left(1 + \frac{g(R_*)}{\alpha}\right), \tag{10}$$

where $\eta = \frac{\tilde{u}}{\bar{u}}$ and $g(s)$ is defined in (6).

In [7] the problem (1) - (3) was considered with the boundary condition (2) replaced by the boundary condition $u = \bar{u}$. This corresponds formally to the case $\alpha = \infty$. The existence of a unique steady state was proved, with $u_* = \bar{u} f(r)/f(R)$ and radius $R = R_{*,D}$ given by (10) with $\alpha = \infty$.

Theorem 3.1. *For any $\alpha > 0$, and $0 < \tilde{u} < \bar{u}$, there exists a unique steady state solution of (1) - (3), given by (8), (10), i.e. there exists a unique solution R_* of (10). Furthermore, setting $\eta = \frac{\tilde{u}}{\bar{u}}$, the function $R_* = R_*(\alpha, \eta)$ is strictly increasing in α and strictly decreasing in η. Finally, for each $\eta \in (0,1)$, $R_* \to 0$ as $\alpha \to 0$, and $R_* \to R_{*,D}$, as $\alpha \to \infty$.*

Proof of Theorem 3.1. Define a function $\Lambda : [0,\infty) \to \mathbb{R}$ by

$$\Lambda(s) := g(s) - \frac{\tilde{u}}{3\bar{u}}\left(1 + \frac{g(s)}{\alpha}\right) s,$$

Lemma 3.2. *There exists $R_* > 0$ such that*

$$\Lambda(s) = g(s) - \frac{\tilde{u}}{3\bar{u}}\left(1 + \frac{g(s)}{\alpha}\right) s = \begin{cases} 0 & \text{when } s = 0, \text{ or } s = R_*, \\ > 0 & \text{when } 0 < s < R_*, \\ < 0 & \text{when } s > R_*. \end{cases} \tag{11}$$

Moreover, $\Lambda'(0) > 0 > \Lambda'(R_*)$.

Proof. Clearly, we have $\Lambda(0) = 0$. To prove the rest of (11), we first recall that, by Lemma 2.2, $g(s)/s = h(s)$ satisfies

$$\left(\frac{g(s)}{s}\right)' < 0 \text{ for } s > 0, \quad \lim_{s\to 0} \frac{g(s)}{s} = \frac{1}{3}, \quad \lim_{s\to\infty} \frac{g(s)}{s} = 0.$$

Using also the facts that $g'(s) > 0$ for all $s \geq 0$ and $\lim_{s\to\infty} g(s) = 1$, we deduce that $(\Lambda(s)/s)' < 0$ for all $s > 0$. Also, since $\lim_{s\to\infty} g(s) = 1$,

$$\lim_{s\to 0} \frac{\Lambda(s)}{s} = \frac{1}{3} - \frac{\tilde{u}}{3\bar{u}} > 0, \quad \lim_{s\to\infty} \frac{\Lambda(s)}{s} = -\frac{\tilde{u}}{3\bar{u}}\left(1 + \frac{1}{\alpha}\right) < 0,$$

Hence there exists a unique $R_* > 0$ such that (11) holds. Moreover,

$$\Lambda'(0) = \lim_{s\to 0} \frac{\Lambda(s)}{s} = \frac{1}{3}\left(1 - \frac{\tilde{u}}{\bar{u}}\right) > 0,$$

and that

$$\Lambda'(R_*) = \left[s\frac{\Lambda(s)}{s}\right]'\Big|_{s=R_*} = R_* \left(\frac{\Lambda(s)}{s}\right)'\Big|_{s=R_*} < 0.$$

□

By (10), for each $\alpha > 0$, the system (1) - (3) has a steady state solution with radius R_* if and only if $\Lambda(R_*) = 0$. Hence the theorem follows, by (11) and the monotonicity of $\Lambda(s)/s$ with respect to α and η. □

4 $R(t)$ is bounded

Theorem 4.1. *If $\alpha(t)$ is uniformly bounded, and*

$$\mu(\bar{u} - \tilde{u}) < 1, \tag{12}$$

then $R(t)$ is uniformly bounded.

Proof. Integrating (1) and using (2), we get

$$\begin{aligned}\int_0^{R(t)} r^2 u(r,t)\,dr &= \int_0^t R^2(t)u(R(t)t)\dot{R}(t)\,dt + \int_0^{R(0)} r^2 u_0(r)\,dr \\ &+ \int_0^t R^2(t)[-\alpha(t)(u(R(t),t) - \bar{u})]\,dt - \int_0^t \int_0^{R(t)} r^2 u(r,t)\,dr\,dt\end{aligned}$$

and, by (3),

$$\int_0^{R(t)} r^2 u(r,t)\,dr = \frac{1}{\mu}R^2(t)\dot{R}(t) + \frac{1}{3}R^3(t)\tilde{u}.$$

Setting $\rho(t) = \frac{1}{3}R^3(t)$ we can then write

$$\frac{1}{\mu}\rho'(t) = -\left(\tilde{u} + \frac{1}{\mu}\right)\rho(t) - \tilde{u}\int_0^t \rho(t)\,dt + \int_0^t \alpha(t)R^2(t)[\bar{u} - u(R(t),t)]\,dt + \int_0^t u(R(t),t)\rho'(t)\,dt + A_1 \tag{13}$$

where

$$A_1 = \int_0^{R(0)} r^2 u_0(r)\,dr + \frac{1}{\mu}\rho(0).$$

Claim 4.2. *Suppose for some t_0, $\dot{R}(t_0) = 0$ and $\ddot{R}(t_0) \geq 0$, then $R(t_0) < B := \frac{3\alpha(t_0)\bar{u}}{\tilde{u}}$.*

To prove the claim, we differentiate (13) at $t = t_0$ to obtain

$$\begin{aligned}\frac{1}{\mu}\rho''(t_0) &= -\left(\tilde{u} + \frac{1}{\mu}\right)\rho'(t_0) - \tilde{u}\rho(t_0) + \alpha(t_0)R^2(t_0)[\bar{u} - u(R(t_0),t_0)] + u(R(t_0),t_0)\rho'(t_0) \\ &< -\frac{\tilde{u}}{3}R^3(t_0) + \alpha(t_0)R^2(t_0)\bar{u} \\ &= \frac{\tilde{u}}{3}R^2(t_0)\left(-R(t_0) + \frac{3\alpha(t_0)\bar{u}}{\tilde{u}}\right).\end{aligned}$$

Noting that $\rho''(t_0) \geq 0$, we conclude that $R(t_0) < B$.

Lemma 4.3. *Suppose that for some* $0 \le \tau_1 < \tau_2$, $\dot{R}(t) \ge 0$ *in* (τ_1, τ_2) *and* $R(\tau_1) \ge 3(\sup_{\tau_1<t<\tau_2} \alpha)\frac{\bar{u}}{\tilde{u}}$, *then*

$$\frac{1}{\mu}\rho'\Big|_{\tau_1}^{\tau_2} \le \left(\bar{u} - \tilde{u} - \frac{1}{\mu}\right)\rho\Big|_{\tau_1}^{\tau_2}. \tag{14}$$

Proof. We set $t = \tau_i$ $(i = 1, 2)$ in (13), and subtract, to obtain (after canceling A_1)

$$\frac{1}{\mu}\rho'\Big|_{\tau_1}^{\tau_2} = -\left(\tilde{u} + \frac{1}{\mu}\right)\rho\Big|_{\tau_1}^{\tau_2} - \tilde{u}\int_{\tau_1}^{\tau_2}\rho(t)\,dt + \int_{\tau_1}^{\tau_2}\alpha(t)R^2(t)[\bar{u} - u(R(t),t)]\,dt + \int_{\tau_1}^{\tau_2}u(R(t),t)\rho'(t)\,dt. \tag{15}$$

Using the inequality $\int_{\tau_1}^{\tau_2} u(R(t),t)\rho'(t)\,dt \le \bar{u}\rho\big|_{\tau_1}^{\tau_2}$, which follows from $\dot{R} \ge 0$, we deduce that

$$\frac{1}{\mu}\rho'\Big|_{\tau_1}^{\tau_2} \le \left(\bar{u} - \tilde{u} - \frac{1}{\mu}\right)\rho\Big|_{\tau_1}^{\tau_2} - \tilde{u}\int_{\tau_1}^{\tau_2}\rho(t)\,dt + \bar{u}\int_{\tau_1}^{\tau_2}\alpha(t)R^2(t)\,dt. \tag{16}$$

Since $R(\tau_1) \ge 3(\sup_t \alpha)\frac{\bar{u}}{\tilde{u}}$, the sum of last two terms is non-positive, and (14) follows. □

We proceed to show that $R(t)$ is uniformly bounded. Suppose to the contrary that $\sup_t R = +\infty$, then one of the following two scenarios holds:

(a) There exists a $T_0 > 0$ such that $\dot{R}(t) \ge 0$, for all $t \ge T_0$.

(b) There exists a sequence of intervals (s_n, t_n) such that

$$R'(t) > 0 \quad in \quad (s_n, t_n), \quad R(s_n) \le B, \quad \dot{R}(s_n) = 0, \quad R(t_n) \to +\infty.$$

where $B = \frac{3\bar{u}}{\tilde{u}}(\sup_t \alpha)$.

To see that this exhausts all the possibilities, suppose that (a) does not hold, i.e., there exists a sequence $\bar{t}_n \to \infty$ such that $\dot{R}(\bar{t}_n) < 0$. This, together with $\sup_t R = +\infty$, imply that there is a sequence of local maximum points $\tilde{t}_n \to \infty$ such that $R(\tilde{t}_n) \to \infty$. Hence we can choose, for each n, a maximal interval (s_n, t_n) such that

$$R(t_n) > \max\{R(t_{n-1}), n, B\}, \quad \dot{R}(s_n) = \dot{R}(t_n) = 0, \quad \dot{R}(t) > 0 \quad \text{in} \quad (s_n, t_n).$$

Noting that $\ddot{R}(s_n) \ge 0$, we conclude by Claim 4.2 that $R(s_n) \le \frac{3\bar{u}}{\tilde{u}}\alpha(s_n) \le B$, which yields the case (b).

We proceed to treat each case separately.

Case (a). By increasing T_0, we may assume without loss of generality that $R(T_0) \ge 3(\sup_t \alpha)\frac{\bar{u}}{\tilde{u}}$. Therefore, for any $t > T_0$, by setting $\tau_1 = T_0$ and $\tau_2 = t$, Lemma 4.3 yields

$$\rho'(t) - \rho'(T_0) < -\beta(\rho(t) - \rho(T_0)), \quad \text{where} \quad \beta = 1 + \mu(\tilde{u} - \bar{u}) > 0.$$

Multiplying both sides by $e^{\beta t}$, and rearranging, we have

$$(e^{\beta t}\rho(t))' < e^{\beta t}(\rho'(T_0) + \beta\rho(T_0)).$$

Integrating both sides from T_0 to t, we get

$$e^{\beta t}\rho(t) - e^{\beta T_0}\rho(T_0) < \frac{1}{\beta}(e^{\beta t} - e^{\beta T_0})(\rho'(T_0) + \beta\rho(T_0)),$$

so that for any $t > T_0$,

$$\rho(t) < e^{-\beta(t-T_0)}\rho(T_0) + \frac{1}{\beta}(1 - e^{-\beta(t-T_0)})(\rho'(T_0) + \beta\rho(T_0)).$$

But this implies that $\rho(t) = \frac{1}{3}R^3(t)$ remains uniformly bounded for all $t > T_0$, which is a contradiction to $\sup_t R = +\infty$.

Case (b). By replacing s_n by some $s'_n \in (s_n, t_n)$, we may assume that $R(s_n) = B$. Lemma 4.3 then implies that

$$\rho'(t) < -\beta(\rho(t) - \rho(s_n)) + \rho'(s_n) \quad \text{for any } s_n < t < t_n.$$

Multiplying both sides by $e^{\beta t}$, we get

$$(e^{\beta t}\rho(t))' < e^{\beta t}(\beta\rho(s_n) + \rho'(s_n)) = e^{\beta t}(\beta B_1 + \rho'(s_n)),$$

where $B_1 = \frac{1}{3}B^3 = 9\left(\frac{\bar{u}\sup_t \alpha}{\tilde{u}}\right)^3$. Using also the inequality $\rho' \leq \mu(\bar{u} - \tilde{u})\rho$, which follows from (3), we find that

$$(e^{\beta t}\rho(t))' < e^{\beta t}[\beta B_1 + \mu(\bar{u} - \tilde{u})\rho(s_n)] = e^{\beta t}B_1[\beta + \mu(\bar{u} - \tilde{u})].$$

Integrating from s_n to t_n, we deduce that

$$e^{\beta t_n}\rho(t_n) - e^{\beta s_n}B_1 < (e^{\beta t_n} - e^{\beta s_n})B_1\left[1 + \frac{\mu(\bar{u} - \tilde{u})}{\beta}\right],$$

so that

$$\rho(t_n) \leq e^{-\beta(t_n - s_n)}B_1 + (1 - e^{-\beta(t_n - s_n)})B_1\left[1 + \frac{\mu(\bar{u} - \tilde{u})}{\beta}\right] < B_1\left[1 + \frac{\mu(\bar{u} - \tilde{u})}{\beta}\right].$$

This implies again that $\rho(t_n)$ is bounded uniformly in n, which is a contradiction. This completes the proof of Theorem 4.1. □

Remark 4.4. *The last inequality implies that if $R(t)$ is uniformly bounded in t but is not monotone increasing for all large t (that is, we are in* Case (b) *with $R(t_n) \to \infty$ dropped) then*

$$\limsup_{t\to\infty} R(t) \leq \left\{3B_1\left[1 + \frac{\mu(\bar{u} - \tilde{u})}{\beta}\right]\right\}^{\frac{1}{3}} = \left(\frac{3\bar{u}\sup_t \alpha}{\tilde{u}}\right)\left[1 + \frac{\mu(\bar{u} - \tilde{u})}{\beta}\right]^{\frac{1}{3}}.$$

Indeed this follows by taking the t_n such that $\lim_{t\to\infty} R(t_n) = \limsup_{t\to\infty} R(t)$.

In the next theorem we prove the uniform boundedness of $R(t)$ under different assumptions than in Theorem 4.1, and by an entirely different method. Recall that $h(s) = \frac{\coth s}{s} - \frac{1}{s^2}$, and that, by Lemma 2.2, h^{-1} is well-defined in the interval $(0, \frac{1}{3})$.

Theorem 4.5. *Let $\eta = \frac{\tilde{u}}{\bar{u}} \in (0,1)$ and h be given as in (6). If*

$$\mu(\bar{u} - \tilde{u}) < \frac{9}{\eta h^{-1}(\frac{\eta}{3})^2} \tag{17}$$

then $R(t)$ remains uniformly bounded.

Remark 4.6. *It is interesting to compare Theorem* 4.5 *with Theorem* 4.1*. If* $\eta = \frac{\tilde{u}}{\bar{u}}$ *is near 1 then* $a = h^{-1}(\eta)$ *is near* 0 *so that* (17) *is less restrictive than the condition* (12) *assumed in Theorem* 4.1*. On the other hand, if* η *is near* 0 *then* $a = h^{-1}(\eta)$ *is near* ∞*, and the condition* (17) *is more restrictive than the condition* (12)*. Note also that, in contrast with Theorem* 4.1*, Theorem* 4.5 *does not require the uniform boundedness of* $\alpha(t)$ *in* t*.*

Remark 4.7. *The case when formally* $\alpha(t) \equiv \infty$*, that is, when the boundary condition is* $u = \bar{u}$*, was considered in* [7] *where it was proved* (*see* [7, Theorem 5.1]) *that* $R(t)$ *is bounded if* $\mu(\bar{u} + e^{-1/\mu}) < 1$*. The proof of Theorem* 4.5 *is completely different from the proof in* [7]*, and it extends also to the case where* $u = \bar{u}$ *on the free boundary* (*under different conditions than in* [7])*.*

Proof of Theorem 4.5*.* Let $a_0 = h^{-1}(\frac{\eta}{3})$. By the assumption (17) and the monotonicity of h (Lemma 2.2), we may choose a positive constant a slightly greater than a_0 such that

$$\frac{\mu}{3}(\bar{u} - \tilde{u})a^2 h(a) < 1 \quad \text{ and } \quad h(a) = \frac{f'(a)}{af(a)} < \frac{\tilde{u}}{3\bar{u}}. \tag{18}$$

To prove the theorem, we suppose that $\limsup_{t\to\infty} R(t) = +\infty$, and derive a contradiction.

Claim 4.8. *For any* $M_0, T_0 > 0$*, there exist positive numbers* τ_1, τ_2 *such that*

$$\tau_2 - \tau_1 > T_0, \quad R(t) \geq M_0 \quad \textit{for all } t \in (\tau_1, \tau_2), \quad \textit{and} \quad \dot{R}(\tau_2) \geq 0.$$

It remains to show the claim for any $M_0 > \inf_{t>0} R(t)$. To prove the claim, take τ_0 such that $R(\tau_0) = M_0$ and fix $\tau_2 > \tau_0$ so that $R(\tau_2)/M_0 > \exp(\mu(\bar{u} - \tilde{u})T_0)$, and $\dot{R}(\tau_2) > 0$. Let $\tau_1 = \inf\{\tau_0 < t < \tau_2 : R(t') > M_0 \text{ for all } t' \in (t, \tau_2)\}$, then $R(\tau_1) = M_0$ and $R(t) \geq M_0$ for all $t \in (\tau_1, \tau_2)$. Also, from the fact $\dot{R}(t) \leq \mu(\bar{u} - \tilde{u})R(t)$, it follows that

$$\tau_2 - \tau_1 \geq \frac{1}{\mu(\bar{u} - \tilde{u})} \log\left(\frac{R(\tau_2)}{R(\tau_1)}\right).$$

Hence $\tau_2 - \tau_1 > T_0$ by our choice of τ_2. This completes the proof of the claim.

We are now going to construct a supersolution w for $\tau_1 < t < \tau_2$ and use it to estimate the right-hand side of (3) at $t = \tau_2$ and show that $\dot{R}(\tau_2) < 0$, which is a contradiction; this will complete the proof of the theorem. To construct the supersolution w we take M_0 such that

$$M_0^2 > \frac{a^2}{1 - a^2 h(a)\mu(\bar{u} - \tilde{u})/3}$$

which gives

$$-a^2 h(a) \cdot \frac{\mu}{3}(\bar{u} - \tilde{u}) + 1 - \frac{a^2}{M_0^2} > 0, \tag{19}$$

and choose (using (18)) a positive constant T_0 such that

$$T_0 > -\log\left(\frac{\tilde{u}}{\bar{u}} - 3h(a)\right),$$

which gives

$$\frac{\bar{u}e^{-t}}{3} - \frac{\tilde{u}}{3} + \bar{u}h(a) < 0 \quad \text{ for all } t \geq T_0. \tag{20}$$

Let

$$w := \bar{u}e^{-(t-\tau_1)} + \frac{\bar{u}}{f(a)} f\left(\frac{ar}{R(t)}\right).$$

We claim that w is a supersolution. We first check the differential inequality: For $t \in [\tau_1, \tau_2]$,

$$\begin{aligned}
&w_t - \Delta w + w \\
&= \frac{\bar{u}}{f(a)} f'\left(\frac{ar}{R(t)}\right) \cdot \frac{-ar}{R^2(t)} \dot{R}(t) + \left(1 - \frac{a^2}{R^2(t)}\right) \frac{\bar{u}}{f(a)} f\left(\frac{ar}{R(t)}\right) \\
&= \frac{\bar{u}}{f(a)} f\left(\frac{ar}{R(t)}\right) \left[-\frac{f'(\frac{ar}{R(t)})}{f(\frac{ar}{R(t)})} \frac{ar}{R(t)} \frac{\dot{R}(t)}{R(t)} + \left(1 - \frac{a^2}{R^2(t)}\right)\right].
\end{aligned}$$

Setting $w_1 := \frac{\bar{u}}{f(a)} f\left(\frac{ar}{R(t)}\right)$, we obtain

$$\begin{aligned}
&w_t - \Delta w + w \\
&\geq w_1 \left[-\left(\sup_{s\in(0,a)} \frac{f'(s)}{f(s)} s\right) \max\left\{0, \frac{\dot{R}(t)}{R(t)}\right\} + \left(1 - \frac{a^2}{R^2(t)}\right)\right] \\
&\geq w_1 \left[-a\frac{f'(a)}{f(a)} \cdot \frac{\mu}{3}(\bar{u} - \tilde{u}) + \left(1 - \frac{a^2}{R^2(t)}\right)\right] \\
&\geq w_1 \left[-a^2 h(a) \cdot \frac{\mu}{3}(\bar{u} - \tilde{u}) + 1 - \frac{a^2}{M_0^2}\right] > 0
\end{aligned}$$

by (19). Next, we observe that

$$[w_r + \alpha(t)(w - \bar{u})]\big|_{r=R(t)} > 0,$$

as $w_r(R(t), t) > 0$, $w - \bar{u} \geq 0$ and $\alpha(t) \geq 0$. Since also $u(r, \tau_1) < \bar{u} < w(r, \tau_1)$, we conclude, by comparison, that $u(r,t) \leq w(r,t)$ for $0 \leq r \leq R(t)$ and $t \in [\tau_1, \tau_2]$. Hence,

$$\begin{aligned}
\frac{\dot{R}}{R} &= \frac{\mu}{R^3} \int_0^R r^2 (u(r,t) - \tilde{u})\, dr \\
&\leq \frac{\mu}{R^3} \int_0^R r^2 (w(r,t) - \tilde{u})\, dr \\
&= \frac{\mu}{R^3} \int_0^R r^2 \left[\bar{u}e^{-(t-\tau_1)} + \frac{\bar{u}}{f(a)} f\left(\frac{ar}{R}\right) - \tilde{u}\right] dr.
\end{aligned}$$

By integration, using Lemma 2.4, we then get

$$\begin{aligned}
\frac{\dot{R}}{R} &\leq \frac{\mu}{R^3} \left\{ \frac{R^3}{3} [\bar{u}e^{-(t-\tau_1)} - \tilde{u}] + \frac{\bar{u}}{f(a)} \frac{R^3}{a} f'(a) \right\} \\
&= \mu \left\{ \frac{\bar{u}e^{-(t-\tau_1)} - \tilde{u}}{3} + \bar{u}h(a) \right\}.
\end{aligned}$$

Hence, by (20),

$$\frac{\dot{R}(\tau_2)}{R(\tau_2)} \leq \mu \left\{ \frac{\bar{u}e^{-(\tau_2-\tau_1)} - \tilde{u}}{3} + \bar{u}h(a) \right\} < 0,$$

which is a contradiction to the fact that $\dot{R}(\tau_2) \geq 0$. □

5 $R(t) \to 0$

Lemma 5.1. *If $R(t)$ is uniformly bounded and $\lim_{t\to 0} \alpha(t) = 0$, then $\liminf_{t\to\infty} R(t) = 0$.*

Proof. If the assertion is not true, then

$$R_1 \le R(t) \le R_2 \tag{21}$$

for some positive constants R_1, R_2 and all $t > 0$. Set

$$C_* = \sup_{R_1 \le r \le R_2} f(r), \quad c_0 = \inf_{R_1 \le r \le R_2} \frac{d}{dr} f(r) \tag{22}$$

where $f(r) = \frac{\sinh(r)}{r}$, and note that $c_0 > 0$.

Let ϵ be a small number such that

$$\epsilon C_* < \frac{\tilde{u}}{3},$$

and choose a large number t_0 such that

$$\alpha(t) < c_1 := \frac{\epsilon c_0}{\bar{u}} \quad \text{if } t > t_0.$$

Consider the function

$$w(r,t) = \bar{u} e^{-(t-t_0)} + \epsilon f(r) \quad \text{for } t > t_0. \tag{23}$$

It satisfies (1) and $w(r, t_0) > \bar{u} \ge u(r, t_0)$. Since also

$$\frac{\partial w}{\partial r} + \alpha(t)(w - \bar{u}) > \epsilon \frac{d}{dr} f(r) - \alpha(t)\bar{u} > \epsilon c_0 - c_1 \bar{u} = 0 \quad \text{on } r = R(t),$$

we conclude that w is a supersolution for $t > t_0$, so that

$$u(r,t) < w(r,t) \quad \text{if} \quad t \ge t_0.$$

It follows that

$$u(r,t) - \tilde{u} < w(r,t) - \tilde{u} = \bar{u} e^{-(t-t_0)} + \epsilon C_* - \tilde{u} < -\frac{\tilde{u}}{3}$$

if $t \ge t_1$, where t_1 is chosen large enough such that

$$\bar{u} e^{-(t_1 - t_0)} = \frac{\tilde{u}}{3}.$$

Hence, for all $t > t_1$,

$$\frac{dR(t)}{dt} = \frac{\mu}{R(t)^2} \int_0^{R(t)} (u - \tilde{u}) r^2 \, dr < -\frac{\mu \tilde{u}}{9} R(t),$$

and $R(t)$ decreases exponentially to zero as $t \to \infty$, thus contradicting (21). ☐

Theorem 5.2. *If $\lim_{t\to 0} \alpha(t) = 0$ and (12) (i.e. $\mu(\bar{u} - \tilde{u}) < 1$) holds, then $R(t) \to 0$ as $t \to \infty$.*

Proof. We first note, by Theorem 4.1, that $R(t)$ is uniformly bounded.

Suppose the assertion of the theorem is not true, then, in view of Lemma 5.1, there exists a positive constant γ_0 and sequences $t_n, \tilde{t}_n \to \infty$ such that for all n

$$\tilde{t}_n < t_n < \tilde{t}_{n+1}, \quad \rho(t_n) > \gamma_0, \quad \rho(\tilde{t}_n) < \gamma_0, \quad \rho'(t_n) > 0 > \rho'(\tilde{t}_n),$$

where we recall that $\rho(t) = \frac{1}{3}R^3(t)$. Let

$$s_n = \inf\{s' : s' < t_n, \text{ and } \rho'(t) > 0 \text{ for all } t \in (s', t_n]\};$$

clearly $s_n \in (\tilde{t}_n, t_n)$, $s_n \to \infty$ as $n \to \infty$, $\rho'(s_n) = 0$ and $\rho''(s_n) \geq 0$. By Claim 4.2,

$$R(s_n) \leq \frac{3\bar{u}}{\tilde{u}}\alpha(s_n). \tag{24}$$

We conclude that there exists a sequence of disjoint intervals (s_n, t_n) such that

$$\rho'(t) > 0 \quad \text{in} \quad (s_n, t_n), \quad s_n \to \infty, \quad \rho(s_n) \leq 9\left(\frac{\tilde{u}}{\bar{u}} \sup_{(s_n,\infty)} \alpha\right)^3 \to 0, \tag{25}$$

and, by taking n sufficiently large, say $n \geq n_0$,

$$\rho(t_n) \geq \gamma_0 > 9\left(\frac{\tilde{u}}{\bar{u}} \sup_{(s_n,\infty)} \alpha\right)^3 > 0 \quad \text{for all } n \geq n_0. \tag{26}$$

By (25) and (26), we may choose $s'_n \in (s_n, t_n)$ such that

$$\rho(s'_n) = 9\left(\frac{\tilde{u}}{\bar{u}} \sup_{(s'_n,\infty)} \alpha\right)^3. \tag{27}$$

As $n \to \infty$, $s'_n \to \infty$ and hence the right-hand side of (27) tends to zero, and so does $\rho(s'_n)$. Therefore, for all n sufficiently large, we have

$$\rho(s'_n) < \frac{\gamma_0\beta}{2\beta + \mu(\bar{u} - \tilde{u})}, \tag{28}$$

where $\beta = 1 + \mu(\tilde{u} - \bar{u}) > 0$. In view of (25) and (27), the assumptions of Lemma 4.3 hold with $\tau_1 = s'_n$ and $\tau_2 \in [s'_n, t]$. Hence, by (14),

$$\rho'(t) - \rho'(s'_n) \leq -\beta(\rho(t) - \rho(s'_n)) \quad \text{for all } t \in [s'_n, t_n]. \tag{29}$$

By repeating the argument of Case (b) of Proof of Theorem 4.1, we then deduce that

$$\rho(t_n) < e^{-\beta(t_n - s'_n)}\rho(s'_n) + \rho(s'_n)(1 + \mu(\bar{u} - \tilde{u})/\beta).$$

Hence, by (28),

$$\rho(t_n) < \rho(s'_n)(2 + \mu(\bar{u} - \tilde{u})/\beta) < \gamma_0, \tag{30}$$

and this is a contradiction to the fact that $\rho(t_n) \geq \gamma_0$ for all n. □

6 $\liminf\limits_{t\to\infty} R(t) > 0$

In this section we show that if $\alpha(t) \not\to 0$ as $t \to \infty$, then $R(t)$ stays bounded away from zero for all $t \geq 0$. Moreover, there is a positive lower bound of $\liminf_{t\to\infty} R(t)$ that is independent of initial data (u_0, R_0).

Proposition 6.1. *If $\liminf_{t\to\infty} \alpha(t) = \alpha_1 > 0$, then there exists a positive constant $\delta_0 > 0$ independent of initial conditions (u_0, R_0) such that $\liminf\limits_{t\to\infty} R(t) \geq \delta_0$.*

Proof. Choose a small constant $\delta_0 > 0$ such that

$$f(\delta_0) < \frac{\bar{u}+\tilde{u}}{2\tilde{u}}, \qquad \frac{\sup_{r\in[0,\delta_0]} f'(r)}{f(\delta_0)} < \delta_0, \qquad \text{and} \qquad \frac{\bar{u}+\tilde{u}}{2}\delta_0 < \frac{\bar{u}-\tilde{u}}{2}\frac{\alpha_1}{2}. \tag{31}$$

This is indeed possible since

$$\lim_{s\to 0^+} f(s) = 1, \qquad \lim_{s\to 0^+} \frac{f'(s)}{sf(s)} = \lim_{s\to 0^+} h(s) = \frac{1}{3}, \qquad \text{and} \qquad \frac{\bar{u}+\tilde{u}}{2\tilde{u}} > 1.$$

Claim 6.2. *There exists a sequence $t_n \to \infty$ such that $R(t_n) > \delta_0$.*

Suppose to the contrary that there exists $t_0 > 0$ such that

$$R(t) \leq \delta_0 \qquad \text{and} \qquad \alpha(t) \geq \frac{\alpha_1}{2} \qquad \text{for all } t \geq t_0,$$

and introduce the function

$$w(r,t) = \frac{\bar{u}+\tilde{u}}{2}\frac{f(r)}{f(\delta_0)} - \bar{u}e^{-(t-t_0)}. \tag{32}$$

Then $w_t - \frac{1}{r^2}(r^2 w_r)_r + w = 0$, $w(r, t_0) \leq 0$ for all $r \in [0, R_0]$, and,

$$\begin{aligned}
(w_r + \alpha w)\big|_{r=R(t)} &= \frac{\bar{u}+\tilde{u}}{2}\left(\frac{f'(R(t))}{f(\delta_0)} + \alpha(t)\frac{f(R(t))}{f(\delta_0)}\right) - \alpha(t)\bar{u}e^{-(t-t_0)} \\
&\leq \frac{\bar{u}+\tilde{u}}{2}(\delta_0 + \alpha(t)) \\
&< \alpha(t)\bar{u}
\end{aligned}$$

where the last two inequalities follow from the last two inequalities in (31) and the fact that $\alpha(t) \geq \alpha_1/2$. Hence, by comparison, $u(r,t) \geq w(r,t)$ for all $0 < r < R(t)$ and $t > t_0$. But then

$$R(t)^2\dot{R}(t) \geq \int_0^{R(t)} (w(r,t) - \tilde{u})r^2\,dr \geq \int_0^{R(t)} \left(\frac{\bar{u}+\tilde{u}}{2f(\delta_0)} - \bar{u}e^{-(t-t_0)} - \tilde{u}\right) r^2\,dr. \tag{33}$$

Hence

$$\liminf_{t\to\infty} \frac{\dot{R}(t)}{R(t)} \geq \int_0^{R(t)} \left(\frac{\bar{u}+\tilde{u}}{2f(\delta_0)} - \tilde{u}\right) \frac{r^2}{R(t)^3}\,dr = \frac{1}{3}\left(\frac{\bar{u}+\tilde{u}}{2f(\delta_0)} - \tilde{u}\right),$$

where the right hand side is a positive constant, by the first condition in (31). This contradicts the assumption $R(t) \leq \delta_0$ for all $t \geq t_0$, which completes the proof of Claim 6.2

Next, choose δ_0 as above, and $\theta \in (0, 1)$ such that

$$\theta^{3/\tilde{u}} < \frac{1}{\bar{u}} \left[\frac{\tilde{u} + \bar{u}}{2f(\delta_0)} - \tilde{u} \right], \tag{34}$$

which is possible since the right hand side is positive by the first condition in (31).

Claim 6.3. $\liminf_{t \to \infty} R(t) \geq \delta_1 := \theta \delta_0$.

To prove Claim 6.3, suppose for contradiction that $\liminf_{t\to\infty} R(t) < \delta_1$. Then, by Claim 6.2, there exists a sequence $\tau_j \to \infty$ such that $\tau_{2j-1} < \tau_{2j} < \tau_{2j+1}$,

$$R(\tau_{2j-1}) > \delta_0, \quad R(\tau_{2j}) < \delta_1, \quad \text{and} \quad \dot{R}(\tau_{2j}) \leq 0.$$

Hence there exist $0 < t_0 < t_1$ such that $\alpha(t) \geq \alpha_1/2$ for all $t \geq t_0$, and

$$R(t_i) = \delta_i \text{ for } i = 0, 1, \quad \delta_1 < R(t) < \delta_0 \text{ for all } t \in (t_0, t_1), \quad \dot{R}(t_1) \leq 0, \tag{35}$$

and $\delta_1 = \theta\delta_0$. By (3), $\frac{\dot{R}(t)}{R(t)} \geq -\frac{\tilde{u}}{3}$, so that (35) implies the inequality

$$t_1 - t_0 \geq -\frac{3}{\tilde{u}} \log \theta. \tag{36}$$

The function $w(r, t)$ defined in (32) is a subsolution for $t \in [t_0, t_1]$. This implies, by comparison, that $u(r, t) \geq w(r, t)$ for all $0 < r < R(t)$ and $t_0 < t < t_1$. Hence by (33) and (36),

$$\dot{R}(t_1) \geq \int_0^{R(t_1)} \left(\frac{\bar{u} + \tilde{u}}{2f(\delta_0)} - \bar{u}\theta^{3/\tilde{u}} - \tilde{u} \right) r^2 \, dr.$$

But the right-hand side is positive by (34), which contradicts the fact that $\dot{R}(t_1) \leq 0$.

□

7 Blow up solutions

In this section we show a partial converse of Theorem 4.1.

Theorem 7.1. *Suppose $\mu\bar{u} > 1$. Then for any $\tilde{u}$ sufficiently small, there exist a function $\alpha(t)$ and initial conditions (u_0, R_0) such that $\lim_{t\to\infty} \alpha(t) = 0$ and the radius $R(t)$ of the solution (u, R) increases to infinity exponentially fast as $t \to \infty$.*

Proof. Define

$$\beta(a, k) = \bar{u} \left[\frac{f'(a) - k^2 f'(ka)}{af(a)} - \frac{1 - k^3}{3} \frac{f(ka)}{f(a)} - \frac{\tilde{u}}{3\bar{u}} \right]. \tag{37}$$

Claim 7.2. *There exist numbers $a > 0$ and $0 < k < 1$ such that for any $\tilde{u}$ sufficiently small,*

$$\mu\beta(a, k)g(ka)ka = \mu\beta(a, k)\frac{f'(ka)}{f(ka)}ka > 1. \tag{38}$$

To prove the claim, write the left-hand side of (38) as

$$\mu\bar{u}kg(ka)\left[g(a)-\frac{\tilde{u}}{3\bar{u}}a-k^2\frac{f'(ka)}{f(a)}-\frac{1-k^3}{3}\frac{f(ka)}{f(a)}a\right].$$

Fix some $k\in((\mu\bar{u})^{-1},1)$ and $c\in(1,\mu\bar{u}k)$, then as $\alpha\to+\infty$,

$$g(ka)\to 1,\quad g(a)\to 1,\quad \frac{f'(ka)}{f(a)}\to 0,\quad \text{and}\quad \frac{f(ka)}{f(a)}a\to 0,$$

which imply that there exists a positive constant a_1 such that

$$\mu\bar{u}kg(ka_1)\left[g(a_1)-\frac{\mu\bar{u}k-c}{\mu\bar{u}k}-k^2\frac{f'(ka_1)}{f(a_1)}-\frac{1-k^3}{3}\frac{f(ka_1)}{f(a_1)}a_1\right]\approx c>1. \tag{39}$$

If $\tilde{u}$ is sufficiently small such that

$$0<\tilde{u}\le\frac{\mu\bar{u}k-c}{\mu\bar{u}k}\frac{3\bar{u}}{a_1},$$

then (38) follows from (39).

Now, let a,k and $\tilde{u}$ be given as in Claim 7.2. Define a continuous function

$$w(r,t)=\begin{cases}0 & \text{for } 0\le r\le kR(t),\\ \frac{\bar{u}}{f(a)}\left[f\left(\frac{ar}{R(t)}\right)-f(ak)\right] & \text{for } kR(t)<r\le R(t).\end{cases}$$

Then one may compute, using Lemma 2.4, that

$$\frac{\mu}{R^3}\int_0^R(w(r,t)-\tilde{u})r^2\,dr=\mu\beta(a,k)>0\qquad\text{for all } t\ge 0. \tag{40}$$

We claim that for any initial condition $u_0>w(r,0)$ and any $\alpha(t)$ satisfying

$$\alpha(t)\ge\frac{f'(a)}{f(ka)}\frac{a}{R(0)}e^{-\mu\beta(a,k)t}, \tag{41}$$

the radius $R(t)$ of the solution (u,R) increases to ∞ exponentially fast as $t\to\infty$. To prove it we introduce the set

$$I_2=\left\{\tilde{t}\ge 0:\frac{\dot{R}(t)}{R(t)}\ge\mu\beta(a,k)\text{ for all } t\in[0,\tilde{t}]\right\},$$

and it suffices to show that $I_2=[0,+\infty)$, since then $R(t)\ge R(0)e^{\mu\beta(a,k)t}$ for all $t\ge 0$.

By using the fact that $u_0(r)<w(r,0)$ and (40) in (3), we have

$$\frac{\dot{R}(0)}{R(0)}=\frac{\mu}{R(0)^3}\int_0^{R(0)}(u_0(r)-\tilde{u})r^2\,dr>\frac{\mu}{R(0)^3}\int_0^{R(0)}(w(r,0)-\tilde{u})r^2\,dr=\mu\beta(a,k).$$

Hence $I_2\supset[0,\delta_1)$ for some $\delta_1>0$.

Next, suppose to the contrary that $I_2\ne[0,+\infty)$. By the closedness and connectedness of I_2, we may assume that $I_2=[0,T_0]$ for some $T_0>0$. We proceed to show that $w(r,t)$ is a subsolution for $0 \le t \le T_0 + \delta$ for some $\delta > 0$. In the region of (r, t) where $w(r, t) > 0$ (i.e. $kR(t) < r \le R(t)$),

$$
\begin{aligned}
& w_t - \frac{1}{r^2}(r^2 w_r)_r + w \\
&= \frac{\bar{u} f(\frac{ar}{R})}{f(a)} \left[-\frac{f'\left(\frac{ar}{R}\right)}{f\left(\frac{ar}{R}\right)} \frac{ar}{R} \frac{\dot{R}}{R} + \left(1 - \frac{a^2}{R^2}\right) - \frac{f(ka)}{f(a)} \frac{f(a)}{f(\frac{ar}{R})} \right] \\
&\le \frac{\bar{u} f(\frac{ar}{R})}{f(a)} \left[-\frac{f'(ka)}{f(ka)} ka \frac{\dot{R}}{R} + \left(1 - \frac{a^2}{R^2}\right) - \frac{f(ka)}{f(\frac{ar}{R})} \right] \\
&\le \frac{\bar{u} f(\frac{ar}{R})}{f(a)} \left[1 - \frac{f'(ka)}{f(ka)} ka \frac{\dot{R}}{R} \right] \\
&\le \frac{\bar{u} f(\frac{ar}{R})}{f(a)} \left[1 - \frac{f'(ka)}{f(ka)} ka \mu \beta(a, k) \right] < 0
\end{aligned}
$$

for all $0 \le t \le T_0$ and by our choice of k, a and $\tilde{u}$ in Claim 7.2. By continuity, $w_t - \frac{1}{r^2}(r^2 w_r)_r + w < 0$ also if $kR(t) < r < R(t)$, $0 \le t \le T_0 + \delta$ for some $\delta > 0$.

Next, by our choice of $\alpha(t)$, the boundary condition for a subsolution is also satisfied:

$$
\begin{aligned}
w_r + \alpha(t)(w - \bar{u})\big|_{r=R(t)} &= \bar{u} \frac{f'(a)}{f(a)} \frac{a}{R(t)} + \alpha(t) \left[\bar{u} \left(1 - \frac{f(ak)}{f(a)} \right) - \bar{u} \right] \\
&= \bar{u} \frac{f(ak)}{f(a)} \left[\frac{f'(a)}{f(ak)} \frac{a}{R(t)} - \alpha(t) \right] \\
&< \bar{u} \frac{f(ak)}{f(a)} \left[\frac{f'(a)}{f(ak)} \frac{a}{R(0)} e^{-\mu\beta(a,k)t} - \alpha(t) \right] \le 0
\end{aligned}
$$

for $0 \le t \le T_0$ and then, by continuity, for $0 \le t \le T_0 + \delta$.

Since also $w(r, 0) < u_0(r)$, we deduce that w is a subsolution for $0 \le t \le T_0 + \delta$, so that $w(r, t) < u(r, t)$ for all $0 < t \le T_0 + \delta$ and $0 \le r \le R(t)$. Hence,

$$
\frac{\dot{R}(t)}{R(t)} \ge \frac{\mu}{R(t)^3} \int_0^{R(t)} (w(r, t) - \tilde{u}) r^2 \, dr = \mu \beta(a, k) \qquad \text{for all } 0 \le t \le T_0 + \delta
$$

and this contradicts the maximality of T_0, and finishes the proof. □

Remark 7.3. *By the arguments presented in the proof of Theorem 7.1, a sufficient condition for blow-up of $R(t)$ is given by*

$$
\mu \sup_{a>0, 0<k<1} \beta(a, k) \frac{f'(ka)}{f(ka)} ka > 1,
$$

where $\beta(a, k)$ is given by (37).

8 Global Asymptotic Stability of Steady State

In this section we prove that the stationary solution $(u_*(r), R_*)$ defined by (8), (10) with $\alpha = \alpha_* > 0$ is globally asymptotically stable provided μ is sufficiently small independently of initial data; for clarity we first consider the case where $\alpha(t) = \text{const.} = \alpha_*$.

Theorem 8.1. *There exists a number μ_0 such that for any $\mu \in (0, \mu_0)$ and any initial data u_0, R_0, the solution of system* (1) - (4) *with $\alpha(t) \equiv \text{const.} = \alpha_*$ satisfies:*

$$\lim_{t\to\infty} R(t) = R_*, \qquad \text{and} \qquad \lim_{t\to\infty} u(r,t) = u_*(r).$$

Remark 8.2. *The case $\alpha = +\infty$, i.e. with the boundary condition $u = \bar{u}$, was considered in* [7]*, and the present proof follows the same procedure; however, in* [7] *the parameter μ_0 depends on initial conditions (namely, on bounds on $\|u_0\|_{L^\infty}$ and R_0), while in the present case we are able to show (using results from Section* 4*) that μ_0 does not depend on the initial data.*

Lemma 8.3. *Let δ_0, Γ be two given positive numbers, and assume, for some $\gamma \in (0, \Gamma]$, that*

$$|R(t) - R_*| \le \gamma, \quad R(t) \ge \delta_0, \quad \text{and} \quad |u(r,t) - u_*(r)| \le \gamma \quad \text{for all } t \ge 0.$$

Then there exist a number $\mu_0 > 0$ and constants A, β, depending on δ_0, Γ, but independent of $\mu, \gamma \in (0, \Gamma]$ such that if $\mu \in (0, \mu_0]$,

$$|R(t) - R_*| \le A\gamma(\mu + e^{-\beta t}), \quad |u(r,t) - u_*(r)| \le A\gamma(\mu + e^{-\beta t}). \tag{42}$$

Proof. Let $v = v(r,t)$ be defined by

$$v(r,t) = \frac{\alpha \bar{u}}{\alpha + g(R(t))} \frac{f(r)}{f(R(t))}.$$

Then

$$|u_*(r,t) - v(r,t)| \le A|R(t) - R_*|. \tag{43}$$

Introducing the differential operator $L[\phi] := \phi_t - \frac{1}{r^2}\left(r^2\phi_r\right)_r + \phi$, we have

$$\begin{aligned} L[v] &= v\dot{R}(t)\left[\frac{-g'(R(t))}{\alpha + g(R(t))} - \frac{f'(R(t))}{f(R(t))}\right] \\ &= v\mu\left(\int_0^{R(t)} \frac{r^2}{R(t)^2}(u(r,t) - \tilde{u})\,dr\right)\left[\frac{-g'(R(t))}{\alpha + g(R(t))} - g(R(t))\right]. \end{aligned}$$

By the assumptions of the lemma,

$$-A\gamma\mu \le L[v] \le A\gamma\mu$$

where here, and in the remainder of the proof, A denotes a generic constant depending on Γ but independent of μ and γ. This, in turn, implies that for all $K > 0$ and $\beta_1 \in (0, 1]$, that

$$L[v + A\gamma\mu + Ke^{-\beta_1 t}] \ge 0 \ge L[v - A\gamma\mu - Ke^{-\beta_1 t}], \tag{44}$$

and $(\frac{\partial}{\partial r} + \alpha)(v \pm (A\gamma\mu + Ke^{-\beta_1 t})) \gtreqless \alpha\bar{u}$ on the free boundary.

Next, by (43), (note here that the generic constant A may change from line to line, but remains independent of μ, and $\gamma \in [0, \Gamma]$)

$$\begin{aligned} |u(r,0) - v(r,0)| &\le |u(r,0) - u_*(r)| + |u_*(r) - v(r,0)| \\ &\le \gamma + A|R(0) - R_*| \le A\gamma. \end{aligned}$$

Taking $K = A\gamma$ in (44), we get, by comparison,

$$|u(r,t) - v(r,t)| \le A\gamma(\mu + e^{-\beta_1 t}). \tag{45}$$

We next note that, by Lemma 2.4,

$$\begin{aligned}
\int_0^{R(t)} (v(r,t) - \tilde{u})r^2\,dr &= \frac{\alpha\bar{u}}{\alpha + g(R(t))}\frac{1}{f(R(t))}\int_0^{R(t)} f(r)r^2\,dr - \frac{\tilde{u}}{3}R(t)^3 \\
&= \frac{\alpha\bar{u}}{\alpha + g(R(t))}\frac{R(t)^2 f'(R(t))}{f(R(t))} - \frac{\tilde{u}}{3}R(t)^3 \\
&= \frac{\alpha\bar{u}}{\alpha + g(R(t))}R(t)^2 g(R(t)) - \frac{\tilde{u}}{3}R(t)^3 \\
&= \frac{\alpha\bar{u}}{\alpha + g(R(t))}R(t)^3\left[\frac{g(R(t))}{R(t)} - \frac{\tilde{u}}{3\bar{u}}\left(1 + \frac{g(R(t))}{\alpha}\right)\right].
\end{aligned}$$

Thus, letting $E(t) = \frac{1}{R(t)^2}\int_0^{R(t)}(u(r,t) - v(r,t))r^2\,dr$, and using (3), we obtain

$$\begin{aligned}
\dot{R}(t) &= \frac{1}{R(t)^2}\int_0^{R(t)} (u(r,t) - \tilde{u})r^2\,dr \\
&= \frac{\alpha\bar{u}}{\alpha + g(R(t))}\left[g(R(t)) - \frac{\tilde{u}}{3\bar{u}}\left(1 + \frac{g(R(t))}{\alpha}\right)R(t)\right] + E(t).
\end{aligned}$$

Thus, the differential equations for $R = R(t)$ can be written in the form

$$\dot{R}(t) = G(R(t)) + E(t) \tag{46}$$

where

$$G(s) = \frac{\alpha\bar{u}}{\alpha + g(s)}\left[g(s) - \frac{\tilde{u}}{3\bar{u}}\left(1 + \frac{g(s)}{\alpha}\right)s\right].$$

and from (45),

$$|E(t)| \le A\gamma(\mu + e^{-\beta_1 t})R(t). \tag{47}$$

Let $G_{\pm\mu}(R) = G(R) \pm A\mu\gamma R$, then

$$G_{-\mu}(R(t)) - A\gamma e^{-\beta_1 t} \le G(R(t)) + E(t) \le G_{\mu}(R(t)) + A\gamma e^{-\beta_1 t}R(t).$$

Lemma 8.4. *There exists a positive constant $\mu_0 > 0$ (depending on Γ but independent of γ) such that for any $\mu \in (0, \mu_0]$, there exist numbers $R_{*,\pm\mu}$ for which the following holds:*

$$G'_{\pm\mu}(R_{*,\pm\mu}) < 0, \quad \textit{and} \quad G_{\pm\mu}(R) = \begin{cases} > 0 & \textit{when } 0 < R < R_{*,\pm\mu}, \\ = 0 & \textit{when } R = R_{*,\pm\mu}, \\ < 0 & \textit{when } R > R_{*,\pm\mu}, \end{cases} \tag{48}$$

Proof. By Lemma 3.2, there exists an $R_* > 0$ such that

$$G(R) = \begin{cases} = 0 & \text{when } R = 0, R_*, \\ > 0 & \text{when } 0 < R < R_*, \\ < 0 & \text{when } R > R_*, \end{cases} \quad \text{and} \quad G'(0) > 0 > G'(R_*).$$

The lemma then follows from this and the fact that

$$\lim_{R\to\infty}\frac{G(R)}{R}=\frac{\alpha\bar{u}}{\alpha+1}\left[-\frac{\tilde{u}}{3\bar{u}}\left(1+\frac{1}{\alpha}\right)\right]<0.$$

□

From the above proof we also have, for $\mu\in(0,\mu_0]$,

$$R_{*,-\mu}\le R_*\le R_{*,\mu}\quad\text{ and }\quad 0\le R_{*,\mu}-R_{*,-\mu}\le A\mu\gamma. \tag{49}$$

By Lemma 8.4 and by possibly taking μ_0 smaller, there exists positive constants c_0, C_0 such that for all $\mu\in(0,\mu_0]$,

$$\begin{cases} G_{\pm\mu}(R)\ge -c_0(R-R_{*,\pm\mu}) & \text{when } \max\{\delta_0,R_*-\Gamma\}<R<R_{*,\pm\mu},\\ G_{\pm\mu}(R)\le -c_0(R-R_{*,\pm\mu}) & \text{when } R_{*,\pm\mu}<R<R_*+\Gamma.\end{cases} \tag{50}$$

Using the fact that $R_{*,\pm\mu}$ are constants independent of t, we combine (46) and (47) to get

$$\frac{d}{dt}(R(t)-R_{*,\mu})\le G_\mu(R(t))+A\gamma e^{-\beta_1 t}R(t)$$

which, in view of (50) and the boundedness of $R(t)\le R_*+\Gamma$,

$$\frac{d}{dt}(R(t)-R_{*,\mu})\le -c_0(R(t)-R_{*,\mu})+A\gamma e^{-\beta_1 t}$$

whenever $R(t)>R_{*,\mu}$, with another constant A. By integration, we then conclude that for some $\beta_2\in(0,\beta_1]$, and another constant A,

$$R(t)-R_{*,\mu}\le A\gamma e^{-\beta_2 t},$$

and deduce, by (49), that

$$R(t)-R_*\le A\gamma(\mu+e^{-\beta_2 t}).$$

Similarly, using the lower bound for $E(t)$ in (47), one can prove that

$$R(t)-R_*\ge -A\gamma(\mu+e^{-\beta_2 t}).$$

This completes the proof of the first part of (42). The second part of (42) follows by combining (43) and (45). □

Proof of Theorem 8.1. We take $\mu<\frac{1}{\bar{u}-\tilde{u}}$ so that by Theorem 4.1, $R(t)$ is uniformly bounded. By Proposition 6.1 and Remark 4.4, we have $0\le u_0(r)\le\bar{u}$ for all r, and

$$\delta_0\le\liminf_{t\to\infty}R(t)\le\limsup_{t\to\infty}R(t)\le B_2:=\left(\frac{3\bar{u}\sup_t\alpha}{\tilde{u}}\right)\left[1+\frac{\mu(\bar{u}-\tilde{u})}{\beta}\right]^{\frac{1}{3}} \tag{51}$$

where $\delta_0>0$ is given in Proposition 6.1. Indeed, if (51) does not hold then, by Remark 4.4 and Proposition 6.1, we deduce that $R(t)$ is a monotone function for all large t, and $\lim_{t\to\infty}R(t)>0$. But then, by slightly modifying the proof of [6, Chapter 6, Theorem 5] we conclude that $\lim_{t\to\infty} R(t) = R_*$ and $\lim_{t\to\infty} u(r,t) = u_*(r)$, where (u_*, R_*) is the unique stationary solution corresponding to α_*.

We can now proceed with the proof of Theorem 8.1 assuming, for simplicity, that

$$0 \le u_0(r) \le \bar{u} \text{ for all } r, \quad \frac{\delta_0}{2} \le R(t) \le B_2 + 1 \quad \text{for all } t \ge 0. \tag{52}$$

We shall establish the stability of the stationary solution by repeated application of the Lemma 8.3. Indeed, combining (5) and Theorem 4.1 or Theorem 4.5, we know that for some μ_0 (depending on $\Gamma = B_2 + 1$ and $\delta_0 > 0$ as given in Proposition 6.1), the assumptions of the lemma hold true. Hence, we have

$$|R(t) - R_*| \le A\gamma(\mu + e^{-\beta t}) \le 2A\mu\gamma \quad \text{for } t \ge T_0 := -\frac{1}{\beta}\log\mu.$$

Next, fix any μ such that $2A\mu < 1$ and define $\beta_3 > 0$ by

$$2A\mu = e^{-\beta_3 T_0}.$$

Given $T > 0$, let n be the largest integer that satisfies $nT_0 \le t < (n+1)T_0$. Then

$$\begin{aligned} |R(t) - R_*| &\le \gamma(2A\mu)^n = \gamma e^{-\beta_3 n T_0} = \gamma e^{-\beta_3 t} e^{-\beta_3(nT_0 - t)} \\ &\le \gamma e^{\beta_3 T_0} e^{-\beta_3 t} = B_0 e^{-\beta_3 t}. \quad (B_0 = \gamma e^{B_3 T_0}.) \end{aligned}$$

It follows that $\lim_{t\to\infty} R(t) = R_*$ and by [6, Chapter 6, Theorem 5], $\lim_{t\to\infty} u(r,t) = u_*(r)$. □

We proceed to extend Theorem 8.1 to the case where $\alpha(t)$ is not constant.

Theorem 8.5. *Suppose for some positive constant α_*, $\lim_{t\to\infty}\alpha(t) = \alpha_*$. Then there exists a number μ_0 such that for any $\mu \in (0, \mu_0)$ and any initial data u_0, R_0, the solution of system* (1) - (4) *satisfies:*

$$\lim_{t\to\infty} R(t) = R_*, \quad \text{and} \quad \lim_{t\to\infty} u(r,t) = u_*(r).$$

Lemma 8.6. *Let δ_0, Γ be two given positive numbers, and assume, for some $\gamma \in (0, \Gamma]$, that*

$$|R(t) - R_*| \le \gamma, \quad R(t) \ge \delta_0, \quad \text{and} \quad |u(r,t) - u_*(r)| \le \gamma \quad \text{for all } t \ge 0.$$

Then there exist a number $\mu_0 > 0$ and constants A, β, depending on δ_0, Γ but independent of $\mu, \gamma \in (0, \Gamma]$ such that if $\mu \in (0, \mu_0]$, then

$$|R(t) - R_*| \le A\left[(\gamma + \vartheta)(\mu + e^{-\beta t}) + \vartheta\right], \tag{53}$$

and

$$|u(r,t) - u_*(r)| \le A\left[(\gamma + \vartheta)(\mu + e^{-\beta t}) + \vartheta\right], \tag{54}$$

where $\vartheta = \sup_{t>0}|\alpha(t) - \alpha_*|$.

Proof. Let $\alpha^+ = \sup_{t>0} \alpha(t)$ and $\alpha^- = \inf_{t>0} \alpha(t)$, and define $v^\pm = v^\pm(r,t)$ by

$$v^\pm(r,t) = \frac{\alpha^\pm \bar{u}}{\alpha^\pm + g(R(t))} \frac{f(r)}{f(R(t))},$$

then

$$|u_*(r,t) - v^\pm(r,t)| \le A(|R(t) - R_*| + \vartheta) \le A(\gamma + \vartheta). \tag{55}$$

Proceeding as in Lemma 8.3, with $K = A(\gamma + \vartheta)$, we get, by comparison,

$$|u(r,t) - v^\pm(r,t)| \le A(\gamma + \vartheta)(\mu + e^{-\beta_1 t}), \tag{56}$$

and then also

$$\dot{R}(t) = G^\pm(R(t)) + E^\pm(t), \tag{57}$$

where

$$G^\pm(s) = \frac{\alpha^\pm \bar{u}}{\alpha^\pm + g(s)} \left[g(s) - \frac{\tilde{u}}{3\bar{u}} \left(1 + \frac{g(s)}{\alpha^\pm} \right) s \right],$$

$E^\pm(t) = \frac{1}{R(t)^2} \int_0^{R(t)} (u(r,t) - v^\pm(r,t)) r^2 \, dr$, and

$$|E^\pm(t)| \le A(\gamma + \vartheta)(\mu + e^{-\beta_1 t}) R(t). \tag{58}$$

Let $G^\pm_\mu(R) = G^\pm(R) \pm A\mu(\gamma + \vartheta)R$, then

$$G^-_\mu(R(t)) - A(\gamma + \vartheta)e^{-\beta_1 t} \le G^\pm(R(t)) + E^\pm(t) \le G^+_\mu(R(t)) + A(\gamma + \vartheta)e^{-\beta_1 t}.$$

The proof of Lemma 8.4 can now be repeated and together with (57) we obtain, similarly to (50), the estimate

$$\begin{aligned} \frac{d}{dt}(R(t) - R^+_{*,\mu}) &\le -c_0 (R(t) - R^+_{*,\mu})_+ + A(\gamma + \vartheta) e^{-\beta_1 t} R(t) \\ &\le -c_0 (R(t) - R^+_{*,\mu}) + A(\gamma + \vartheta) e^{-\beta_1 t} \end{aligned}$$

whenever $R(t) > R^+_{*,\mu}$ ($R^\pm_{*,\mu}$ being the unique positive root of $G^\pm_\mu$), for some new constant A, so that for some $\beta_2 \in (0, \beta_1]$,

$$R(t) - R^+_{*,\mu} \le A(\gamma + \vartheta) e^{-\beta_2 t},$$

and then also

$$R(t) - R_* \le A(\gamma + \vartheta)(\mu + e^{-\beta_2 t}) + A\vartheta.$$

Similarly,

$$R(t) - R_* \ge -A(\gamma + \vartheta)(\mu + e^{-\beta_2 t}) - A\vartheta.$$

And the proof of (53) is complete. The proof of (54) follows from (55) and (56). □

Proof of Theorem 8.1. We take $\mu < \frac{1}{\bar{u} - \tilde{u}}$ so that by Theorem 4.1, $R(t)$ is uniformly bounded. By Proposition 6.1 and Remark 4.4, arguing as in Proof of Theorem 8.1, we may assume that

$$0 \le u_0(r) \le \bar{u} \quad \text{for all } r, \quad \frac{\delta_0}{2} \le R(t) \le B_2 + 1 \quad \text{for all } t \ge 0, \tag{59}$$

where $B_2 = \left(\frac{3\bar{u}\sup\alpha}{\tilde{u}}\right)\left[1+\frac{\mu(\bar{u}-\tilde{u})}{\beta}\right]^{\frac{1}{3}}$. We can now establish the stability of the stationary solution by repeated application of the Lemma 8.6. Indeed, combining (5) and Theorem 4.1 or Theorem 4.5, we know that for some μ_0 (depending on $\Gamma = B_2 + 1$ and $\delta_0 > 0$ as given in Proposition 6.1), the hypothesis of the lemma hold true. Taking μ small such that $2A\mu < 1$, and defining T_0 by $e^{-\beta T_0} = \mu$, we have (recall that A is a generic constant independent of γ and ϑ, and may change from one line to another)

$$|R(t) - R_*| \le A(\gamma+\vartheta)(\mu + e^{-\beta t}) + A\vartheta \le 2A\mu\gamma + A\vartheta \quad \text{for } t \ge T_0$$

Finally, if we define $\beta_3 > 0$ by

$$2A\mu = e^{-\beta_3 T_0}$$

and, given $t > 0$, let n be the largest integer that satisfies $nT_0 \le t < (n+1)T_0$, then we have

$$\begin{aligned}|R(t) - R_*| &\le \gamma(2A\mu)^n + \frac{A\vartheta}{1-2A\mu} = \gamma e^{-\beta_3 n T_0} + \frac{A\vartheta}{1-2A\mu} = \gamma e^{-\beta_3 t} e^{-\beta_3(nT_0 - t)} + \frac{A\vartheta}{1-2A\mu}\\ &\le \gamma e^{\beta_3 T_0} e^{-\beta_3 t} + \frac{A\vartheta}{1-2A\mu} = B_0 e^{-\beta_3 t} + \frac{A\vartheta}{1-2A\mu}, \quad \text{where } B_0 = \gamma e^{B_3 T_0}.\end{aligned}$$

If $\vartheta = 0$, i.e. $\alpha(t) = \alpha_*$ for all large positive t, then $|R(t) - R_*|$ decreases exponentially in t, and by [6, Theorem 5, Chapter 6], $\lim_{t\to\infty} u(r,t) = u_*(r)$ also exponentially.

Otherwise, $\limsup_{t\to\infty} |R(t) - R_*| \le \frac{A\sup_{t\ge T}|\alpha(t)-\alpha_*|}{1-\beta}$ for any $T > 0$, and taking $T \to \infty$, we deduce that $\lim_{t\to\infty} |R(t) - R_*| = 0$. Finally, as before, it follows similarly from [6, Theorem 5, Chapter 6] that $\lim_{t\to\infty} u(r,t) = u_*(r)$. $\square$

A Appendix

Proof of Lemma 2.1. From the identity $f''(s) + \frac{2}{s}f'(s) = f(s)$, we have

$$g'(s) = \frac{f''(s)}{f(s)} - \left(\frac{f'(s)}{f(s)}\right)^2 = -\frac{2}{s}\frac{f'(s)}{f(s)} + 1 - \left(\frac{f'(s)}{f(s)}\right)^2,$$

that is,

$$g'(s) = -\frac{2}{s}g(s) + 1 - g^2(s). \tag{60}$$

From the power series expansions

$$f(s) = \sum_{k=0}^{\infty} \frac{s^{2k}}{(2k+1)!}, \quad f'(s) = \sum_{k=1}^{\infty} \frac{2k}{(2k+1)!}s^{2k-1}, \quad g(s) = \frac{s}{3} - \frac{s^3}{45} + \frac{2}{945}s^5 + \dots$$

we deduce that

$$g(0) = 0, \quad g'(0) = \frac{1}{3}, \quad \text{and} \quad g'(s) > 0 \quad \text{for all small and positive } s. \tag{61}$$

Moreover, since $g(s) = \coth s - \frac{1}{s}$, we also have

$$\lim_{s\to+\infty} g(s) = 1. \tag{62}$$

Let $I_1 := \{\bar{s} \in (0, +\infty) : g'(s) > 0 \text{ for all } s \in (0, \bar{s})\}$. We claim that $I_1 = (0, \infty)$. Otherwise there is a bounded interval $I_1 = (0, s_0]$, with $g'(s_0) = 0$ and $g'(s) > 0$ for all $s \in (0, s_0)$. Then $g''(s_0) \leq 0$. But by differentiating (60) at $s = s_0$, we get (by the fact that for all $s > 0$, $g(s) > 0$ and hence $h(s) > 0$)

$$g''(s_0) = \frac{2}{s_0^2} g(s_0) > 0,$$

which is a contradiction. □

Proof of Lemma 2.2. First, we observe that by straightforward calculations, that

$$sh'(s) = 1 - 3h(s) - s^2 h(s). \tag{63}$$

Also, by power series expansion,

$$h(s) = \frac{\frac{s}{3} + \frac{s^3}{30} + \dots}{s + \frac{s^3}{6} + \dots} = \frac{1}{3} + \left(\frac{1}{30} - \frac{1}{18}\right) s^2 + \dots = \frac{1}{3} - \frac{s^2}{45} + \dots$$

Therefore, $h'(s) < 0$ for all s positive and sufficiently small. Let

$$I_1 = \{\bar{s} \in (0, +\infty) : h'(s) < 0 \text{ for all } s \in (0, \bar{s})\}.$$

It remains to show that $I_1 = (0, \infty)$. Suppose $I_1 = (0, s_0]$, then $h'(s_0) = 0$, $h'(s) < 0$ for all $s \in (0, s_0)$, and $h''(s) \geq 0$. Differentiating (63) at $s = s_0$, we get (using the fact that for $s > 0$, $g(s) > 0$ and hence $h(s) = g(s)/s > 0$)

$$s_0 h''(s_0) = (sh')'(s_0) = -2 s_0 h^2(s_0) < 0,$$

which is a contradiction. □

Proof of Lemma 2.4. For $a, R > 0$ and $0 < k < 1$,

$$\begin{aligned} \int_{kR}^{R} r^2 f\left(\frac{ar}{R}\right) dr &= \frac{R^3}{a^3} \int_{ak}^{a} s^2 f(s)\, ds \\ &= \frac{R^3}{a^3} \int_{ak}^{a} (s^2 f'(s))'\, ds \qquad \text{as } (s^2 f'(s))' = s^2 f(s), \\ &= \frac{R^3}{a} [f'(a) - k^2 f'(ka)]. \end{aligned}$$

□

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References

[1] J.A. Adam, *A simplified mathematical model of tumor growth*, Math. Biosciences, **81**, 229–244, 1986.

[2] J.A. Adam, *A mathematical model of tumor growth, II. Effect of geometry and spatial non-uniformity on stability*, Math. Biosciences, **86**, 183–211, 1987.

[3] H.M. Byrne, *The effect of time delays on the dynamics of avascular tumor growth*, Math. Biosciences, **144**, 83–117, 1997.

[4] H.M. Byrne and M.A.J. Chaplain, *Growth of nonnecrotic tumors in the presence and absence of inhibitors*, Math. Biosciences, **130**, 151–181, 1995.

[5] H.M. Byrne and M.A.J. Chaplain, *Growth of necrotic tumors in the presence and absence of inhibitors*, Math. Biosciences, **135**, 187–216, 1996.

[6] A. Friedman, Partial Differential Equations of Parabolic Type, Prentice-Hall, Englewood Cliffs, N.J., 1964. Preprinted by Dover Publications, Minnesota, N.Y., 2002.

[7] A. Friedman and F. Reitich, *Analysis of a mathematical model for the growth of tumors*, J. Math. Biol., **38**, 262–284, 1999.

[8] H.P. Greenspan, *Models for the growth of a solid tumor by diffusion*, Studies in Appl. Math., **52**, 317–340, 1972.

[9] C. Xue, A. Friedman and C.K. Sen, *A mathematical model of ischemic cutaneous wounds*, Proc. Natl. Acad. Sci. U.S.A., **106**, 16782–16787, 2009.